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Review Article

Bevacizumab – Why it is an effective biological agent and how to make it better?

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ABSTRACT

Cancer continues to be among the primary causes of demise worldwide. Medical research has witnessed a large wealth of knowledge gain, looking into therapeutic modalities available, including ones that target the specific hallmarks of cancer. Among these hallmarks is the induction of angiogenesis, regulated mainly by vascular endothelial growth factor (VEGF). Upregulated VEGF expression accompanying tumorigenesis has been showing significant correlation with disease progression and spread and thus is a vital component to target.

This report will discuss VEGF inhibitors, with particular attention to Bevacizumab, looking into its history, mechanism of action, uses and side-effects. It will also review ongoing trials looking into amalgam therapies, along with potential thoughts to augment its value and enhance effectiveness thereafter.

The rise of anti-VEGF therapy has been one of the most dramatic additions in the field. As some patients show transient or no response to therapy, it is vital to delve further into the modes by which response can be improved. Maintaining safety is another important aspect, where side-effect profile can be minimized without compromising efficacy. Despite the hurdles that hinder the path of angiogenesis, it remaining a vital component of tumour growth and sustainability ensures that drugs targeting it will always play a critical role in healing. A move towards a better understanding of the methods by which vascularization is attained, and means of resisting the effects of angiogenic inhibitors, will open new doors towards better and more enhanced means of inhibiting the angiogenic process of cancerous cells. With the continuance of innovating novel medications, merging targets and adopting innovative methods of drug delivery, the future will hold bigger hopes and aspirations for the care of ailed patients.

KEY WORDS: angiogenesis, anti-VEGF, bevacizumab, cancer hallmarks, VEGF

INTRODUCTION

Since the rise of tumorigenesis, research in the medical field has witnessed a large wealth of knowledge gain, as this hurdle continues to be among the primary causes of demise across the globe. A substantial level of work has been done, particularly focusing on the therapeutic modalities that target specific hallmarks of cancer, due to them playing a major part in enabling cancerous cells to survive, grow and spread within the human body. Among the main hallmarks of cancer is the induction of angiogenesis. Under normal circumstances, regulation of angiogenesis is achieved by upholding an equilibrium between activators and inhibitors. Agents working on the former encompass vascular endothelial growth factors (VEGF), interleukin 8 and angiogenin, whereas agents inducing the latter include interferon, interleukin 12 and angiostatin. The upregulated expression of VEGF that accompanies tumorigenesis shows a significant correlation with disease progression and spread, thus is a vital component to target by therapeutic agents. This report will discuss VEGF inhibitors, with particular attention to Bevacizumab, looking into its history, mechanism of action, clinical use and side effect profile. It will also highlight currently running trials looking into amalgam therapies, along with potential thoughts to augment its value and enhance its effectiveness in the future.

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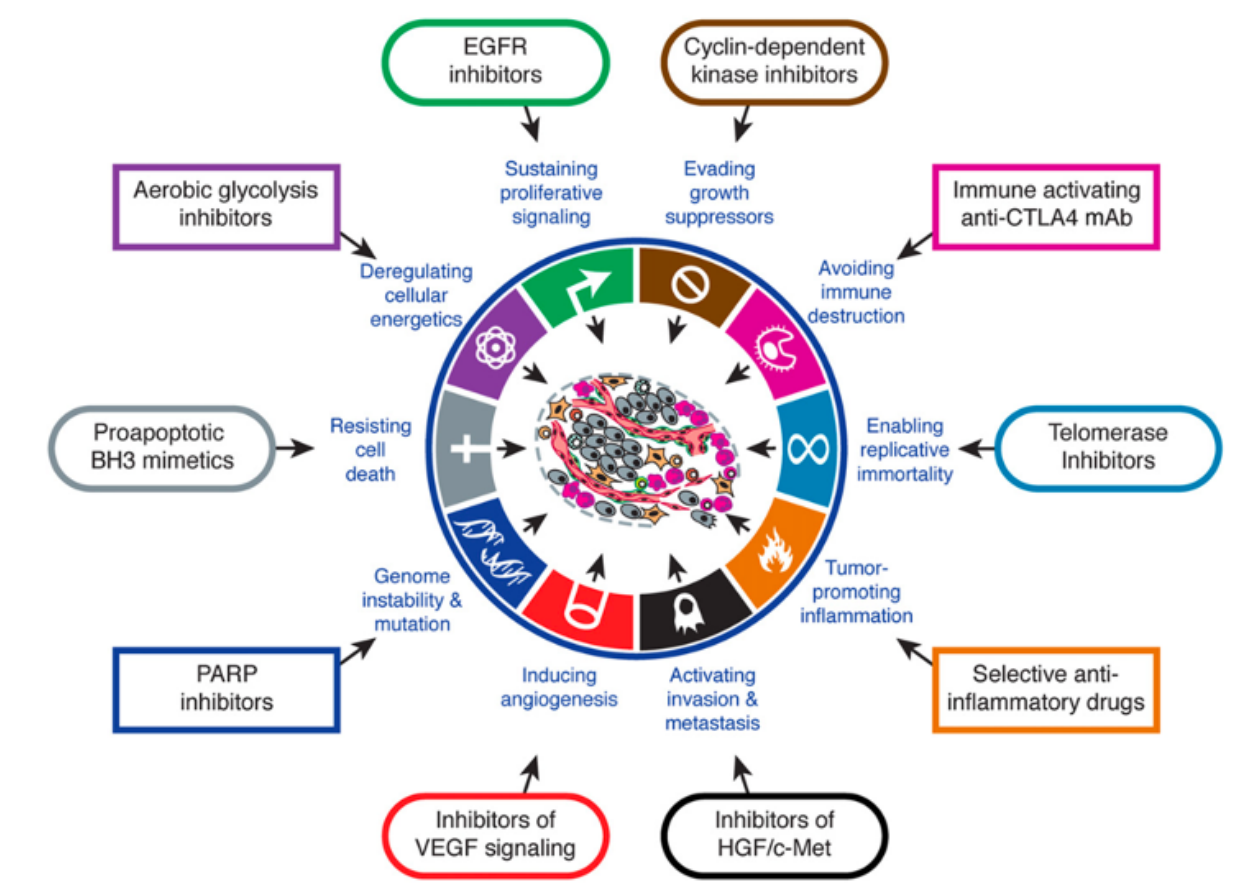

Figure 1: A summary of the eight cancer hallmarks and two enabling characteristics labelled by Hanahan and Weinberg, along with examples of treatment modalities targeting each component. (EGFR: epidermal growth factor receptor; CTLA4: cytotoxic T-lymphocyte-associated protein-4; HGF: hepatocyte growth factor; VEGF: vascular endothelial growth factor; PARP: poly ADP ribose polymerase; BH3: Bcl-homology domain 3)

LITERATURE REVIEW

Angiogenesis refers to the process of forming new blood vessels within the body. Yet being dynamic, this task remains closely controlled when occurring under physiological states, but under pathological settings, the scenario changes. With the former, angiogenesis ensues in tissues going through stress-induced transformation, but with the latter, it undergoes excessive abnormal activation in response to pathological triggers, including immune diseases, inflammatory conditions, cancer and diabetes[1,2]. Consequently, these vessels function in a disorganized manner, creating pockets of reduced blood supply, with consequent tissue hypoxia[2]. In the context of tumorigenesis, inducing angiogenesis is among the hallmarks of cancer, essential for its growth and sustainability, as described by Hanahan and Weinberg in the year 2000 (Figure 1)[3]. Activation of angiogenesis occurs through two main routes; angiopoietin and platelet-derived growth factor signaling, and regulating the process is primarily achieved through VEGF signaling[4].

VEGF, initially named vascular permeability factors, are glycoproteins critical to multiple steps that activate the process of angiogenesis[5]. Both genetic components and environmental factors regulate the expression of soluble VEGF, and upregulating expression down either line enhances VEGF stimulation, that ultimately triggers angiogenesis (Figure 2)[5]. VEGF have been shown to play a critical role within the tumour microenvironment. In the context of metastatic breast cancer, over-expression was correlated with bigger sizes of growth, higher levels of cancer differentiation, higher rates of p53 mutation as well as negative steroid-receptor states[6]. Other studies looking into the same correlation in patients with earlier stages of breast cancer concluded that higher levels of VEGF upregulation was also associated with lower rates of relapse-free and overall survival states[7]. In addition, several other reports looking into the role

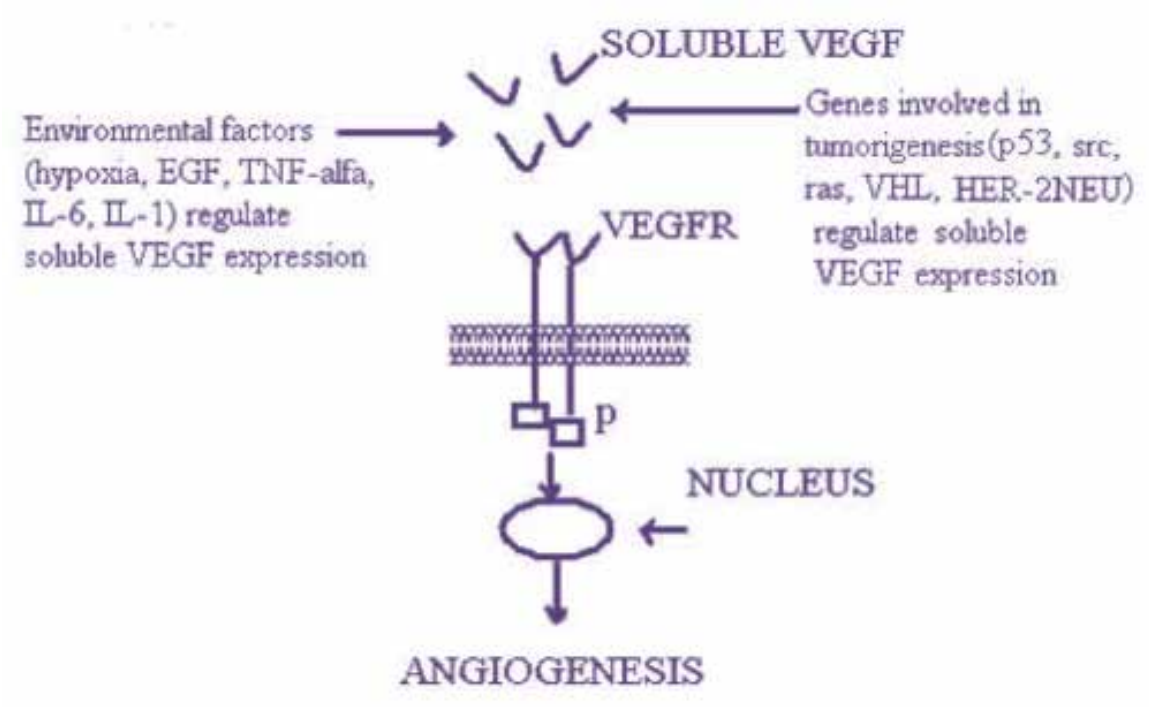

Figure 2: Factors that lead to upregulated expression of VEGF. The figure shows two groups of factors regulating the expression of VEGF: environmental factors and genetic factors. (EGF: epidermal growth factor; TNF: tumour necrosis factor alpha; IL: interleukin; src: sarcoma; ras: rat sarcoma virus; VHL: Von Hippel-Lindau)

of VEGF, in the context of non-small cell lung cancer (NSCLC), renal cell carcinoma, pancreatic, prostate, gynaecological and haematological cancers all yielded similar inferences[8-14]. An essential point to note is that deterring the action of VEGF not only hinders tumour growth through impeding angiogenesis, but also through the process of immunosuppression[15].

The first VEGF inhibitor that came to light was Bevacizumab, a recombinant, monoclonal IgG1 antibody, consisting mainly of human parts, with a minor component derived from mice. Figure 3 represents the molecular structure of bevacizumab[5]. Its' story began fifty years ago, when anti-angiogenic agents and their implications became first renowned to man. Angiogenesis was first labeled in 1794 by the anatomist John Hunter[16]. In 1971, Judah Folkman, the so called 'father of angiogenesis', postulated the theory that tumour growth is angiogenesis-dependent[16]. He labelled agents inducing angiogenesis within malignant growths and hypothesized that impeding angiogenesis halts tumour growth and survival[17]. From there onwards, VEGF gradually became renowned; they were identified for the first time in 1983 by Dr. Dvorak and officially recognized and labelled by Napoleone Ferrara and his colleagues at Genentech lab in 1989[18]. Ten years later, use of angiogenesis inhibitors in clinical trials ensued, and Bevacizumab received initial U.S. approval in 2004,

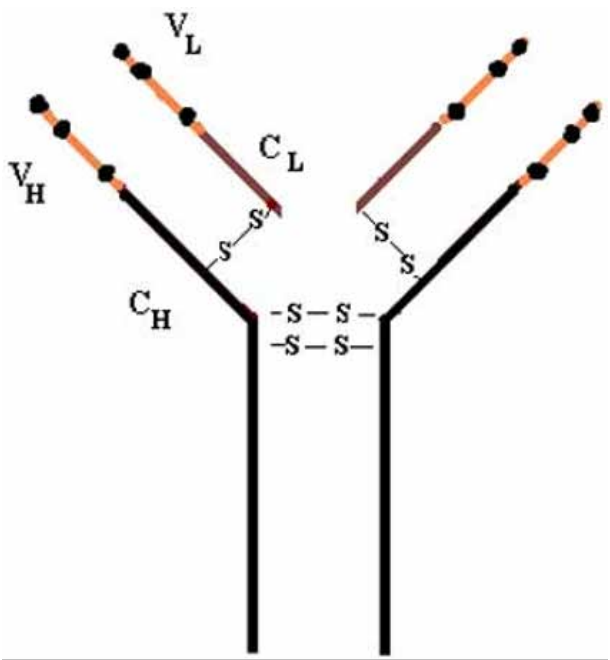

Figure 3: Molecular structure of Bevacizumab. Backbone consists of heavy & light chains, bridged via disulfide chains, with six specificity sequences, resembled as black dots. CH and CL resemble the constant regions on the chains, while VH and VL resemble the variable ones. (CH: constant heavy; CL: constant light; VH: variable heavy; VL: variable light)

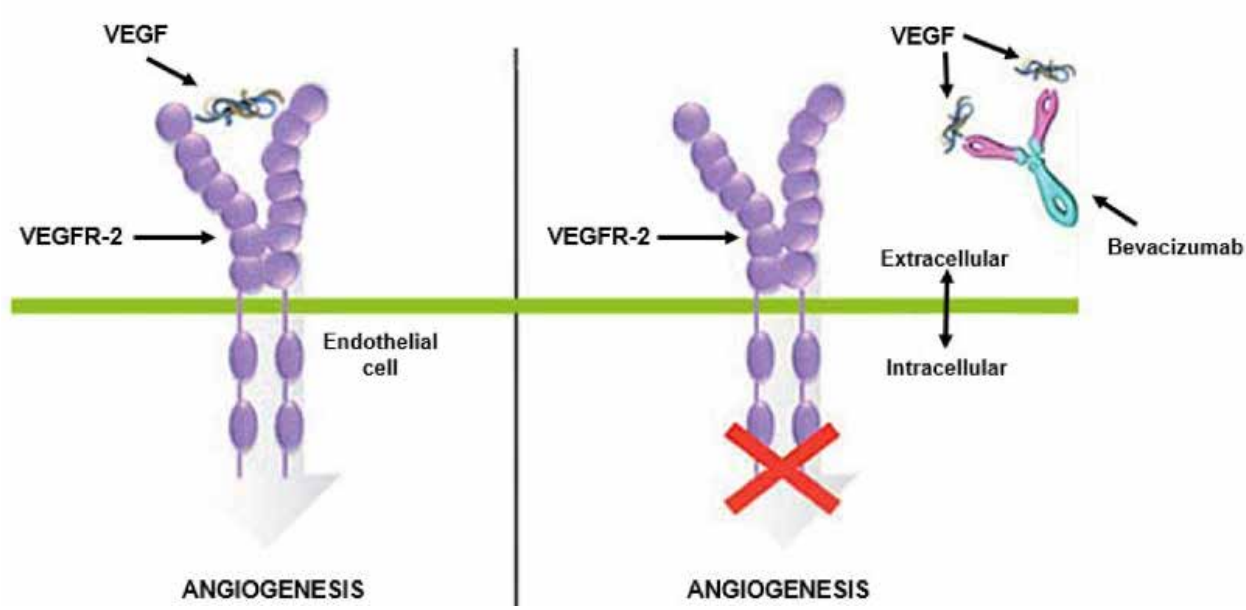

Figure 4: Mechanism of action of Bevacizumab. When VEGF binds to VEGFR-2, the signaling pathway for angiogenesis is activated. With the presence of Bevacizumab, Bevacizumab binds to VEGF and VEGFR-2 is neutralized extracellularly, thereby inhibiting the process of angiogenesis.

after the publication of the first article highlighting their clinical effectiveness in metastatic colorectal cancer[19]. At present, Bevacizumab is approved for use in multiple types of cancer[20].

At the cellular level, Bevacizumab exhibits its effect by neutralizing VEGF[21]. These factors are predominantly derived from platelets, but the malignant cells also release them to improve the efficiency of angiogenesis[22-23]. Bevacizumab selectively binds to the VEGF circulating within the system, to oppose their attachment with their membrane-based receptors. One study reported the ability of platelets to pick up Bevacizumab and deliver them directly to the tumour site, in an attempt to enhance their binding with the VEGF derived from tumour cells[24]. The binding represses the consequent downstream signaling, thereby inhibiting formation of new blood vessels and reducing blood supply to the cancerous growth[24]. Figure 4 shows a graphical representation of the mechanism of action of Bevacizumab[25].

Additional benefits to opposing VEGF effects extend to lowering pressure within the interstitium and enhancing permeability within the vascular system[24]. This has been proposed to improve flow of

Table 1: FDA approved indications for using bevacizumab

Type	Specifications
mCRC	-1st or 2nd line (+ IV FU). -2nd line for patients who progressed on 1st line (+ FP-oxaliplatin or FP-irinotecan).
Non-squamous NSCLC	1st line (+ carboplatin & paclitaxel). Metastatic, unresectable, locally advanced or recurrent.
Glioblastoma	Recurrent in adults
RCC	Metastatic (+ IFN-α).
Cervical cancer	Metastatic, persistent or recurrent (+ paclitaxel & cisplatin, or paclitaxel & topotecan).
Ovarian (epithelial), fallopian tube or primary peritoneal cancer	- Stage III - IV, after surgical resection (+ carboplatin-paclitaxel, followed by bevacizumab as single agent). - platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens (+ paclitaxel, pegylated liposomal doxorubicin, or topotecan). - platinum-sensitive recurrent disease (+ carboplatin-gemcitabine or carboplatin-paclitaxel, followed by bevacizumab as single agent).

mCRC: metastatic colorectal cancer; NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma; IV FU: intravenous fluorouracil; FP: fluoropyrimidine; IFN-α: interferon alpha.

Table 2: Currently running trials that are looking into the effect of anti-angiogenic agents along with immune-checkpoint inhibitors (ICIs) in solid cancers.

Trial number	Cancer type	Combination therapy arm	Comparison therapy arm	Primary endpoint
NCT04017455	Rectal cancer	Bevacizumab + Atezolizumab	-	Clinical complete and near-complete response rate
NCT04213170	Brain metastasis from NSCLC	Bevacizumab + Sintilimab	-	iPFS, OS, PFS
NCT04408118	BC, TNBC	Bevacizumab + Atezolizumab + paclitaxel	-	PFS
NCT04727307	Small HCC	Bevacizumab + Atezolizumab + RFA	RFA	RFS
NCT04732598	BC	Bevacizumab + Atezolizumab + paclitaxel	Bevacizumab + paclitaxel	PFS

NSCLC: Non-small cell lung cancer; iPFS: intracranial progression free survival; OS: overall survival; PFS: progression free survival; BC: breast cancer; TNBC: triple negative breast cancer; HCC: hepatocellular carcinoma; RFA: percutaneous radiofrequency ablation; RFS: recurrence free survival.

chemotherapeutic agents that destroy cells within the malignant growth and ultimately reduce their clinical effectiveness[26].

The efficiency of Bevacizumab stems from having well-defined targets[18]. In clinical practice, it has been approved by the Food and Drug Administration for the treatment of several types of cancer, as summarised in Table 1[20]. At present, it is the first line treatment modality for metastatic colorectal cancer (mCRC) and NSCLC. Studies showed substantial improvement in both overall survival and progression free survival in patients with mCRC receiving Bevacizumab as compared to chemotherapeutic agents alone ($p < 0.05$)[26]. From another perspective, approval for use in metastatic breast cancer was reverted due to lack of data verifying improved overall survival with its use[27].

VEGF play a part in multiple physiological pathways within the body. Inhibiting their effect could impede progression of the cancerous growth, but at the same time, could give rise to various untoward effects[20]. Documented adverse events include raised blood pressure, thromboembolic phenomena (arterial and venous), renal injury with symptom-free proteinuria, cardiac and ovarian failure, as well as hemorrhage[20]. Among the most serious adverse events reported with Bevacizumab is bleeding. A phase II trial on patients with NSCLC reported 9% of cases developing life-threatening pulmonary hemorrhage[28]. Through an alternative angiogenesis pathway, VEGF appear to have a protective effect on the body's vasculature. Accordingly, additional unpredicted side-effects can entail myocardial infarction (in patients with pre-existing vascular disease), arrhythmias as well as pericardial effusion[29].

VEGF appear to have an effect on both angiogenesis and the tumor immune microenvironment[15]. An important field that has been delved into addresses the combinatory effect of anti-angiogenic therapies with other therapeutic modalities, including immune checkpoint blockers. Several trials are currently ongoing to look into the effect of this cocktail of therapy. Table 2 summarizes the currently ongoing clinical trials in this domain, registered over the last five years on clinicaltrials.gov[30].

Utilizing angiogenic inhibitors in combination therapy has been showing more promise than monotherapy, however, limitations still exist. These include decreased delivery of chemotherapeutic agent to the tumour, increased levels of tissue hypoxia, as well as increased rates of metastasis[31]. Other hurdles that can be encountered relate to the process of vessel co-option, where certain tumours rely on pre-existing vessels as their primary supplier of blood, thereby hindering the process of tumour control down the angiogenesis route[32]. Besides, inhibiting the formation of new blood vessels does not achieve tumour control as was previously hypothesized. This was elucidated in 2006, where two studies published that year revolutionized our understanding of the topic. Ridgway *et al* and Noguera-Troise *et al* both concluded in their studies that blockage of the protein coding gene 'Dll4', despite being followed by abnormal vessel sprouting, resulted in decreased tumour perfusion and ultimately its growth[33,34]. This supported the deduction that tumour development primarily relies on vascular functionality and its level of maturation, rather than the quantity of new vessels being made[33].

CONCLUSION

The preceding era of research that looked into the pathogenesis of cancer generated a wealth of knowledge that has assisted in the analysis and understanding of cancer genomics, as well as advancing therapeutics, that label and halt steps preceding evolvement of cancer. Some therapeutic modalities have shown promising outcomes, and with the gradual expansion of our understanding towards the cellular and molecular background

of these ailments, preventative approaches will be feasible and effectual over the coming few years.

The rise of anti-VEGF therapy in the field of cancer has been one of the most dramatic additions to this field. As some patients show transient or no response to therapy, it is vital to delve further into the modes by which response can be improved. Another aspect that warrants further research is maintaining safety, where side-effect profile can be minimized without compromising efficacy. Despite the hurdles that hinder the path of angiogenesis, being a vital component of tumour growth and sustainability ensures that drugs targeting this component will always play a critical role in paving the route towards recovery and healing.

It is worth noting that therapeutics targeting blood vessels remain to play a vital role in cancer care, and a better understanding of the vascularization process of tumours and their untoward complexities will undoubtedly augment success rates of these agents. One approach to make these drugs better could be through targeted delivery, in addition to targeting angiogenic pathways independent of VEGF. Currently, the focus is moving towards the enhancement of function of these vessels, through methods that promote vascular function, to overcome the disorganized and abnormally functioning juvenile vessels. A move towards a better understanding of the methods by which vascularization is attained, as well as means of resisting effects of angiogenic inhibitors, will open new doors towards better and more enhanced means of inhibiting the angiogenic process of cancerous cells. Another component worth looking into includes developing drugs that target both angiogenesis as well as vessel co-option. With the continuance of innovating novel medications, merging targets as well as adopting innovative methods of drug delivery, the future will hold bigger hopes and aspirations for the care of patients ailing with cancer.

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Original Article

An assessment on the systemic immune-inflammatory index in children with Bell's Palsy

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ABSTRACT

Objective: This study aims to assess systemic immune-inflammatory index (SII) in children with Bell's Palsy (BP).
Design: This was a retrospective study.
Setting: Department of ear-nose-throat and pediatrics clinics, Konya Training and Research Hospital, Konya, Turkey
Subjects: Between January 2016 and August 2020, 66 patients with BP and 60 healthy children were included in the study.
Intervention: Clinical and laboratory parameters
Main outcome measures: Hematologic parameters, C-reactive protein (CRP), albumin, neutrophil-lymphocyte (NLR), platelet-to-lymphocyte, CRP-albumin ratio and SII were assessed.
Results: 68.2% of the children with BP were female. Their median age was 12.0 (4.0) years. Their distribution according to the House Brackmann (HB) grading system was as follows: grade 2 (16.7%), grade 3 (48.5%), grade 4 (27.3%) and grade 5 (7.6%). The BP group's white blood cell (WBC, $P<0.001$), neutrophil ($P<0.001$), CRP ($P<0.001$), NLR ($P=0.049$) and SII ($P=0.043$) values were statistically significantly higher than the control group.
Conclusions: The BP group exhibited high CRP, WBC, neutrophil, NLR and SII values; therefore supporting the hypothesis that they have inflammatory etiopathogenesis. There was no significant correlation between their SII and pre-treatment HB grade.

KEY WORDS: Bell's palsy, children, CRP-albumin ratio, hematologic parameters, systemic immune-inflammatory index

INTRODUCTION

Bell's Palsy (BP) is a unilateral facial nerve palsy whose cause is unknown, and that can occur spontaneously. However, it appears that inflammation may play a key role in its pathogenesis[1]. BP accounts for approximately 70% of all forms of facial paralysis[2]. It displays an annual incidence rate of 20.2-53.3 cases per 100,000 people[2-4]. It is particularly common in people between the ages of 15 and 45 years. Furthermore, one study reported that it also occurred in roughly 18.8 out of 100,000 children under the age of 18 as well[5].

Several studies have looked at BP patients' white blood cell count (WBC), neutrophil lymphocyte ratio (NLR), and platelet lymphocyte ratio (PLR), alongside their c-reactive protein albumin ratio (CAR). However, researchers are now using systemic immune-inflammatory index (SII) as a new prognostic marker to diagnose malignant and inflammatory conditions – albeit the number of studies on it remains limited[6-10].

This study aims to assess SII in children with BP. A small handful of studies have looked at the WBC, NLR, PLR and CAR values of children with BP, however none of them include SII. We hope that this study helps researchers pinpoint the etiopathogenesis of BP in children so that they can find markers to diagnose it.

SUBJECTS AND METHODS

This was a retrospective study conducted on 135 children (under 18) at an ear-nose-throat and pediatrics clinic at a training and research hospital between January 2016 and August 2020. Based on the patient files, those who had any history of infection

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Table 1: The distribution of demographic data, hematologic parameters and inflammatory markers of both groups

Demographic and laboratory paramaters	Bell's palsy (n=66)	Control group (n=60)	*P*-value
Gender, n (%)			
Male	21 (31.8)	22 (36.7)	0.566
Female	45 (68.2)	38 (63.3)	
Age (year)	12.0 (4.0)	12.0 (5.0)	0.906
White blood cell (10^3/mm^3)	8.80 (3.69)	7.39 (1.87)	<0.001
Neutrophil (10^3/mm^3)	4.91 (3.03)	3.83 (1.74)	<0.001
Platelet (10^3/mm^3)	308.73 ±70.71	292.95 ±47.63	0.141
Lymphocyte (10^3/mm^3)	2.87 ±0.97	2.73 ±0.69	0.321
C-reactive protein (mg/L)	3.14 (0.20)	3.02 (0.00)	<0.001
Albumin (g/dL)	4.54 (0.57)	4.52 (0.29)	0.903
CAR	0.70 (0.10)	0.68 (0.09)	0.174
NLR	1.63 (1.68)	1.49 (0.89)	0.049
PLR	108.91 (52.36)	105.52 (30.02)	0.696
SII	466.85 (632.14)	409.25 (182.41)	0.043

CAR: C-reactive protein-to-albumin ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index
Note: Parameters were expressed as n (%), median (Interquartile Range) and mean ±standard deviation.

and trauma within the 15 days, suffered from tumor-based, neurological or otological diseases, Ramsay-Hunt syndrome, had a history of otological surgery, and had an incomplete whole blood count, C-reactive protein (CRP) and albumin counts were excluded from the study. The control group included healthy children of similar ages and genders as the BP group. They applied to the department of pediatrics for routine controls. The researchers recorded all the participants' age, gender, House Brackmann (HB) grade, seasonal distribution, hematologic parameters and inflammatory markers.

The blood tests of both groups were examined at the time of admission. The researchers recorded their WBC, neutrophil, lymphocyte and platelet count alongside CRP and albumin values, and then used these data to calculate their NLR, PLR, CAR and SII (neutrophil x platelet/lymphocyte) values.

The participants' complete blood counts were counted on an automated blood cell counter (Mindray BC-6000, Shenzhen, China). Their CRP and albumin levels were measured using nephelometry (AU5800 System; Beckman Coulter Inc, Brea, CA, USA) and an automatic photometric commercial kit (Abbott C8000i, Abbott Park, IL, USA), respectively.

Approval of the local ethics committee was obtained (Date:2021/ no:001). The study was carried out according to the Declaration of Helsinki.

Statistical analysis

The researchers used descriptive statistics to compare all the participants' general characteristics. Normality Kolmogorov-Smirnov and Shapiro-Wilk tests were used to analyze how the data was distributed. Mean ± standard deviation represented the normally distributed data; median (interquartile range) represented data without normal distribution. Categorical variables were expressed in numbers (n) and percentage (%). Both Student t and Mann-Whitney U tests – depending on the situation – were used to compare the numerical data between the groups. Chi-Square test was used to compare categorical variables. Receiver operating characteristic (ROC) analysis was used to specify the sensitivity and specificity values of hematologic and nephelometric parameters in order to diagnose BP. Correlation analysis was used to assess how the data were correlated with each other. SPSS (ver. 22; IBM, Chicago, USA) was used to analyze the

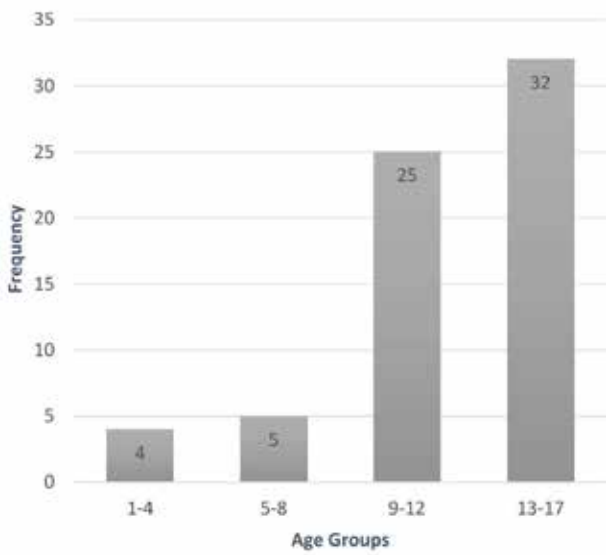

Figure 1: The distribution of the patients with BP according to the age groups.

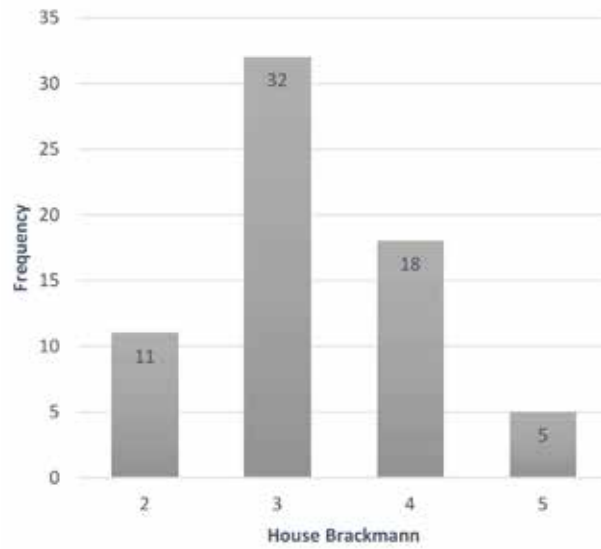

Figure 2: The distribution of the patients with BP according to House Brackmann grade.

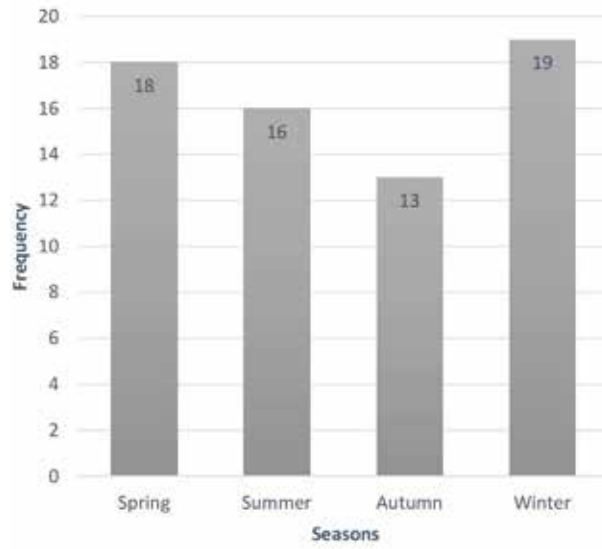

Figure 3: The distribution of the patients with BP according to seasons.

statistics. A *P*-value of <0.05 was deemed as statistically significant.

RESULTS

In the study, the researchers assessed 66 BP pediatric patients and 60 healthy children. 68.2% of the BP group were female and 31.8% were male. Likewise, 63.3% of the control group were female and 36.7% were male. The median age of the participants was 12.0 (4.0) years in the BP group and 12.0 (5.0) in the control group. No significant difference was observed between the groups in terms of age or gender (*P*>0.05). Table 1 shows the demographic data of both groups. Distribution of the patients according to their age groups was: 0-4 years (6.1%), 5-8 years (7.6%), 9-12 years (37.9%) and 13-17 years (48.5%) Figure 1 shows the distribution of the patients according to the age groups.

The distribution of the patients according to the HB grading system was: grade 2 (16.7%), grade 3 (48.5%), grade 4 (27.3%) and grade 5 (7.6%) Figure 2 shows the distribution of the patients according to the HB grading system.

The distribution of the patients according to each season was: spring (27.3%), summer (24.2%), autumn (19.7%) and winter (28.8%). Figure 3 shows the distribution of the patients according to seasons.

The BP group's WBC (*P*<0.001), neutrophil (*P*<0.001), CRP (*P*<0.001), NLR (*P*=0.049) and SII (*P*=0.043) values were statistically significantly higher than those of the control group. No significant difference was found between both groups in terms of albumin, platelet, lymphocyte, CAR and PLR values (*P*>0.05). Table 1 shows the distribution of hematologic parameters and inflammatory markers of both groups.

The researchers used ROC to analyze the area under the curve (AUC) values for the patients' CRP, WBC, neutrophil, NLR and SII. Their CRP values had the highest AUC at 0.789. For 3.03 cut-off value of CRP, sensitivity was 83.3% and specificity was 85%. Table 2 shows the ROC analysis results of patients with BP

Table 2: ROC analysis results of patients with BP

Laboratory paramaters	Value	AUC	P	95% CI		Sensitivity(%)	Specificity (%)
				Lower	Upper		
C-reactive protein (mg/L)	3.03	0.789	<0.001	0.698	0.880	83.3	85.0
Neutrophil (10^3/mm^3)	4.72	0.682	<0.001	0.588	0.775	51.5	86.7
White blood cell (10^3/mm^3)	9.20	0.699	<0.001	0.606	0.792	50.0	93.3
NLR	2.23	0.602	0.049	0.503	0.701	33.3	91.7
SII	513	0.605	0.043	0.505	0.704	48.5	83.3

NLR: neutrophil-to-lymphocyte ratio; SII: systemic immune-inflammation index; AUC: area under the curve; CI: confidence interval; ROC: receiver operator characteristic.
Receiver operator curve evaluating C-reactive protein, neutrophil, white blood cell, NLR and SII for BP. AUC >0.600 and P <0.05 were accepted as significant.

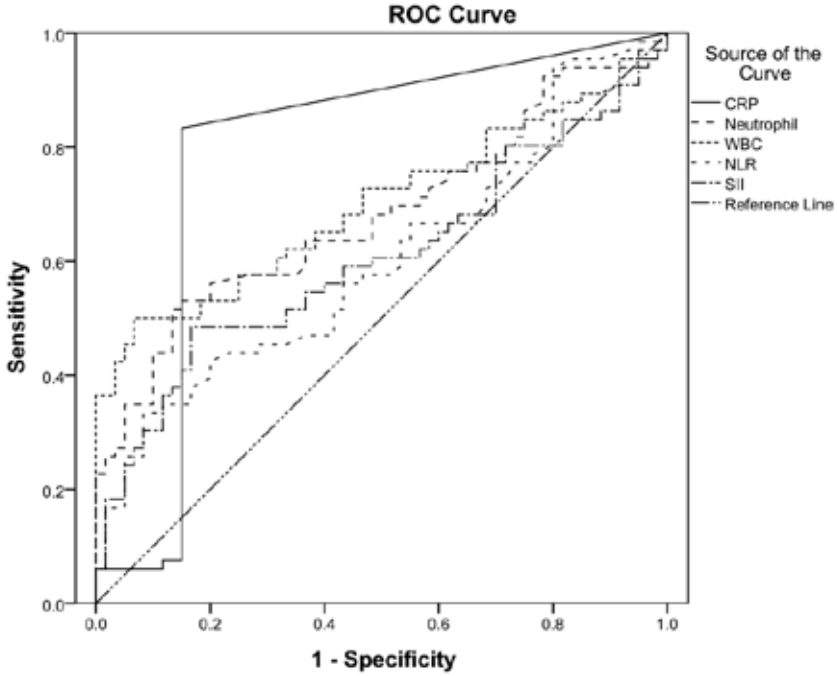

Figure 4: The ROC analysis graph of the patients with BP.

for CRP, neutrophil, WBC, NLR and SII and Figure 4 shows the relevant graph.

No significant correlation was found between the subjects' CRP, neutrophil, WBC, NLR, SII and pre-treatment HB grade (r = 0.817, 0.080, 0.154, 0.182, and 0.200, respectively, *P* >0.05 for all).

DISCUSSION

Inflammation is widely believed to play the most important role in the pathogenesis of BP. However, how this is the case remains unclear. Anatomical issues, viral infections, ischemia and cold exposure theories take place in its etiopathogenesis along with the immune-inflammatory theory[11,12]. Its unknown etiology causes differences in the treatment. Positive response to steroid therapy and high levels of inflammatory markers both support inflammatory pathogenesis[11].

Several studies have reported that children tend to contract BP between 9.9 and 12.0 years of age on average[5,13]. In this study, the median age of the patients was 12.0 years (4.0). In the BP group, the female to male ratio was relatively equal, but the rate of female patients in the pediatric age group was specified higher than most studies (58.2%-63.7%)[5,7,13]. In this study, more female patients had BP than males did (68.2%).

Different results have reported the seasonal distribution data of the patients with BP. Erdur *et al* found that there were significantly more BP patients in the winter than other seasons, and environmental factors associated with cold seasons may play a role in the disease's pathogenesis[14]. In the study of Zhao *et al* including all age groups, they found that BP occurred more frequently during the summer. Narci *et al* found that there were more patients in all the age groups during the spring and Aysel *et al* found that there were more patients in pediatric patients during the spring[15-17]. One study reported that there was no seasonal difference whatsoever[3]. In this study, it was found to be most common during the winter (28.8%). The results of these studies indicated that BP's incidence rate changes from one region to the other, and one population to the other by season.

Researchers frequently blame inflammation for causing BP[1]. Inflammatory markers are widely used to diagnose and follow-up inflammatory diseases. Such markers include biochemical values such as CRP and albumin, as well as hematologic parameters such as WBC, neutrophil and lymphocyte count. Researchers can also use these values to calculate inflammatory index values such as NLR, PLR, CAR and SII[6,9,10,18].

Acute phase reactants are commonly used to assess inflammatory response. CRP is an acute phase reactant and an acute inflammatory protein of a high level in correlation with the strength of inflammation as a response to the inflammation that develops primarily in the liver. It is capable of increase up to 1000-fold

during infections and in inflamed parts of the body[19]. Albumin is a negative acute phase reactant. CAR can also be used as an inflammatory marker[20]. Cayir and Kilicaslan found that pediatric BP patients exhibited high CAR values and such values could be a more valuable prognostic marker than NLR[6]. In this study, all of the children with BP had high CAR values, however they were not significant.

Neutrophils are the immune cells with cytotoxic functions that regulate the inflammatory processes of numerous infectious and inflammatory diseases giving primary response to acute inflammation[21]. Moreover, they are the primary host defense against various pathogens including bacteria, fungi and protozoa. They are produced daily in the bone marrow and their production may increase up to ten times in case of an infection[22]. A number of studies on BP patents have reported that they have significantly higher NLR values as well as the neutrophil counts than their control group counterparts[18,23,24]. Atan *et al* found that the WBC counts were higher alongside neutrophil and NLR values. In this study, the BP group's neutrophil and WBC count were significantly higher than those of the control group[23].

Whole blood count is a routine test in hospitals. One can use it to calculate NLR, PLR and SII inflammatory markers – and at no extra cost[23,25]. Some studies have shown that adult BP patients have high NLR values[23,24,26,27]. Other studies have found the same for pediatric BP patients as well[6,9]. A handful of studies have demonstrated that adult BP patients with NLR values have a worse recovery than those who do not[24,26]. Kim *et al* found that adult BP patients with high NLR levels had long recoveries[28]. One study involving pediatric BP patients also reported that those with high NLR levels may indicate a poor prognosis[6]. NLR values in this study were found to be significant in the patients with BP, which supports the studies investigating the NLR values.

PLR is another marker used to diagnose inflammatory diseases. A handful of studies state that PLR is high in adults and children with BP, and therefore can be used as a prognostic marker[9,23]. However, some studies have not found PLR to be particularly high in BP patients[10,27]. In one meta-analysis, researchers used PLR as an inflammatory marker for BP adult patients, to conclude that PLR was not a suitable prognostic marker at all[25]. In this study, it was found that PLR values in the children with BP were not significant.

SII is a new defined marker. The combination with NLR and PLR has been shown to be a superior prognostic factor that accurately reflects the state of inflammation[29,30]. One can calculate patients' SII from their peripheral neutrophil, platelet and lymphocyte counts. High SII values can stem from a high neutrophil and platelet count or from a low lymphocyte count and indicate inflammatory activity. SII can help researchers diagnose the prognosis of numerous malignancies. In fact, high SII values are superior to NLR and PLR for predicting the prognostic course and survival in people who suffer from pancreatic ductal adenocarcinoma[29]. SII is also better than NLR, PLR and CAR at predicting a person's chance of surviving bladder cancer[30]. One study addressing neutrophil, NLR and SII values in adult BP patients found that their SII values were extremely accurate as a predictive marker[10]. To date, no study has been published focusing on SII in pediatric BP patients. In this study, the BP group's SII values were significantly higher than the control group's values. This result was similar to the study conducted in adults.

Cayir and Kilicaslan found that CAR of children with BP was higher than their NLR for AUC value via ROC analysis and concluded that CAR can be a more valuable prognostic marker[6]. In this study, AUC value for CRP was found to be higher than WBC, neutrophil, NLR and SII values.

One study reported that there was no correlation between NLR value and pre-treatment HB grade of children with BP[18]. In contrast, a few studies have found a significant correlation between NLR values and HB grade[26,31]. This study could not identify any correlation between NLR, PLR, SII and HB grade.

The limitations of the present study were retrospective, single-center and relatively few patients. Another limitation of this study is that post-treatment SII values could not be included in the study because follow-up and post-treatment laboratory data were insufficient. Multicenter, prospective studies with a larger number of patients can provide more valuable results.

CONCLUSION

High CRP, WBC, neutrophil, NLR and SII values of children with BP support that BP's etiopathogenesis is rooted in inflammation. In addition, the high SII values in these patients support the accuracy of anti-inflammatory therapy in Bell's palsy. This study is the first attempt to find that pediatric BP patients have high SII values. However, no significant correlation was found between SII and pre-treatment HB grade. More studies are needed to investigate this relationship in greater detail.

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Original Article

Programmed cell death ligand 1 (PDL1) expression in classical Hodgkin lymphoma: clinicopathologic significance and relation with CD68+ tumour-associated macrophage (TAM) in tumour microenvironment

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ABSTRACT

Objectives: To explore the variable clinicopathological features of classical Hodgkin lymphoma (cHL) and to assess the significance of expression of both programmed cell death ligand 1 (PDL1) on tumour cells and CD68 on tumour-associated macrophages in the tumour microenvironment via immunohistochemistry (IHC).
Design: A retrospective cross-sectional study
Setting: Rizgary Teaching Hospital and Nanakaly hospital in Erbil city, Iraq
Subjects: One hundred and ten cases (110) of cHL patients were enrolled from January 2015 to July 2022.
Interventions: No interventions
Main outcome measures: Clinical data were obtained from the hospital's medical records. All specimens were revised for histopathological and immunohistochemical diagnosis of CD15 and CD30, followed by staining with PDL1 and CD68 using IHC, with an estimation of overall survival rates and outcome results regarding the PDL1 marker.
Results: The IHC showed 93% positivity for the PDL1 antibody. Regarding CD68, 56.36% of cases expressed intermediate staining scores, whereas 27.27% expressed high staining scores. A positive association was found between the staging of the patients and each of the PDL1 and CD68 immune expressions. In addition, a positive correlation was identified between PDL1 expression on Hodgkin and Reed-Sternberg (HRS) cells and CD68-positive TAM. The five-year overall survival was 65%, and PDL1 overexpression was significantly associated with an inferior outcome.
Conclusion: PDL1 immunohistochemical analysis on HRS cells in cHL has diagnostic and prognostic significance; together with CD68-positive TAM, their overexpression may predict cancer progression.

KEY WORDS: CD68, classical Hodgkin's lymphoma (cHL), PDL1, tumour associated macrophage (TAM)

INTRODUCTION

It is well known that there are two major types of Hodgkin lymphoma (HL): classical HL (cHL), which currently accounts for 95% of all HL cases, and nodular lymphocyte predominant HL. HL is distinguished histologically by a scanty number of neoplastic Hodgkin and Reed-Sternberg (HRS) cells immersed in a rich inflammatory infiltrate of immune cells, including lymphocytes, macrophages, eosinophils, mast cells, plasma cells and stromal cells. These cells participate in the microenvironment of the tumour[1].

Programmed cell death ligand 1 (PDL1) is expressed on the surface of tumour cells and stuck to programmed cell death one (PD-1) on T cells to withstand the lethal implementations of T cells, in time, resulting in tumour immune escape, the usage of anti-PD-1/PDL1 monoclonal antibodies to block the PD-1/PDL1 signalling pathway has shown matchless antitumour success in a diversity of cancers[2]. Generally, macrophages are an essential cell in tumour microenvironments, they are typically described using the M1/M2 model. It is commonly agreed that M1-

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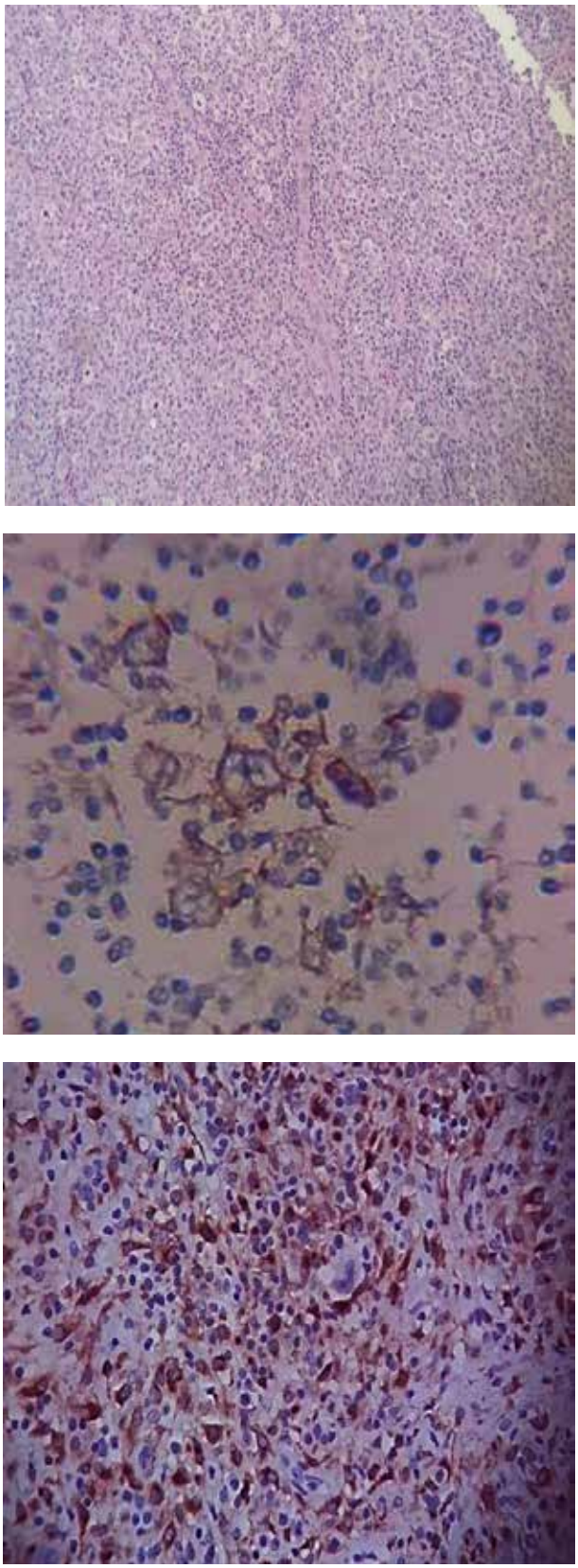

Figure 1: Classical Hodgkin lymphoma. **(A)** H&E stain; **(B)** Immunohistochemical expression of PDL1 on HRS cells; **(C)** Immunohistochemical expression of CD68 on macrophages.

polarised macrophages have anti-neoplastic impacts while M2 polarised macrophages are expected to accelerate tumourigenesis[3].

The current research aims to explore the diverse clinicopathological parameters of cHL and to assess the value of both PDL1 immunohistochemical expressions in HRS cells and CD68 in associated tumour-associated macrophages (TAM) as predictors for disease progression and outcome.

SUBJECTS AND METHODS

This study collected 110 FFPE blocks of cHL that had been surgically removed from January 2015 to July 2022 from Rizgary Teaching Hospital and Nanakaly Hospital in Erbil, Iraq.

Specimen collection and analysis

The ethical approval for handling human samples was obtained from the Ethics Committee at Hawler Medical University. The specimen was handled according to the Declaration of Helsinki criteria[4]. From the Nanakaly hospital's database, clinical data including age, gender, B symptoms, bulky disease, stage and bone marrow involvement were retrieved. The most relevant tissue block that was found to have the necessary elements was used to cut new sections, which were subsequently stained with haematoxylin and eosin (H&E) and histopathologically reviewed.

Immunohistochemistry

The diagnosis of cHL was made on the basis of H&E stains and the positivity of tumour cells for CD15 and CD30 by immunohistochemistry (IHC). In addition, two thin 4 mm sections were taken for further analysis. IHC for PDL1 was performed by Dako autostainer Link48 using the primary antibody for PDL1: DAKO, monoclonal mouse anti-human antibody, clone 22C3, Glostrup, Denmark. Staining for CD68 was done using the avidin-biotin-peroxidase complex and primarily monoclonal antibodies raised against CD68, as well as the Dako CytomationEnVisionR+Dual Link System-HRP (DAB+) staining protocol.

For the analysis of PDL1 immunohistochemical staining, only expression on unequivocal tumour cells was considered. The positively stained TAM was regarded as an internal positive control. Tumour cells were rated positive if higher than 5% show a distinct membranous staining of any intensity[5-7]. The percentage of CD68 positive macrophages was calculated in relation to the rate of negative HRS cells and reactive inflammatory cells in the background. It was scored as I (5%), II (5-25%), and III (> 25%)[8-10], internal positive controls (endothelial cells lining adjacent vascular spaces) and negative controls (slides not incubated with primary antibodies) were used for quality control.

Table 1: Clinicopathologic characteristics of cases.

Variables	No.	Percentage
Age		
Young	58	52.7
Young adult	43	39.1
Elderly	9	8.2
Gender		
Male	68	61.8
Female	42	38.2
Stage		
I	12	10.9
II	58	52.7
III	22	20
IV	18	16.4
B symptoms		
Present	57	51.8
Absent	53	48.2
BM involvement		
Involve	8	7.3
Not involve	102	92.7
Histological type		
Nodular Sclerosis	69	62.7
Mixed Cellularity	34	30.9
Others	7	6.4
Bulky disease		
Yes	13	11.8

Table 2: Association between some clinicopathologic variables and PDL1 immunoreactivity.

Variables	PDL1% >5% positive	*P* value
Age		0.748
Young (58)	54(93.1)	
Young adult (43)	41(95.3)	
Elderly (9)	8(88.9)	
Gender		0.729
Male (68)	63(92.6)	
Female (42)	38(90.5)	
Stage		0.012
I (12)	8(66.7)	
II (58)	53(91.4)	
III (22)	21(95.5)	
IV (18)	18(100)	
B symptoms		0.491
Present (57)	51(89.5)	
Absent (53)	50(94.3)	
BM involvement		0.999
Involve (8)	8(100)	
Not involve (102)	100(98)	
Histological type		0.666
Nodular sclerosis (69)	63(91.3)	
Mixed cellularity (34)	31(91.2)	
Others (7)	7(100)	
Bulky disease		0.316
Yes (13)	12(92.3)	
No (97)	95(99)	

Data analysis

Data entry, interpretation and graphing were performed using SPSS v22 and GraphPad Prism v8, The Chi-square and Fisher exact tests were used to examine the relationship between the categorical variables. The Kaplan-Meier method and Long- rank test were used for survival analysis. A *P*-value of ≤0.05 was considered significant. A *P*-value of ≤0.01 was considered highly significant.

RESULTS

This study included a total of 110 cases of cHL. One hundred sixty-eight (61.8%) of the cases were male, while forty-two (38.2%) were female. The age of the studied cases was grouped as young (patients aged 15-34 years), which were 58 (52.7%) cases; young-adult (patients aged 35-50 years), which were 43 (39.1%) cases; and elderly (patients older than 50 years), which were 9 (8.2%) cases. The age of the cases ranged between 15 and 82 years, with a mean of 34.77 years.

Histopathological diagnosis was revised, and histologically, the cases were divided as nodular sclerosis (169, 62.7% cases (Figure 1A)), mixed cellularity (34, 30.9% cases), and others (including lymphocyte-rich, lymphocyte-depleted, and unclassified), which were seven (6.4%) cases[11]. In addition, the staging of the studied cases was divided into four subtypes: 12 (10.9%) cases of stage one (stage I); 58 (52.7%) cases of stage two (stage II); 22 (20%) cases of stage three (stage III); and eighteen (16.4%) cases of stage four (stage IV)[11].

Fifty-seven (51.8%) cases presented with B symptoms at the time of diagnosis, while the remaining 53 (48.2%) patients were free of B symptoms at the original time of the disease diagnosis. Eight (7.3%) cases had involvement of the bone marrow by the disease process at diagnosis, compared to 102 (92.7%) cases whose bone marrow was tumour-free at diagnosis. According to the radiological investigation, 13 (11.8%) patients had Bulky disease at diagnosis, while 97 (88.2%) cases didn't have bulky disease at diagnosis. Table 1 shows the number and percentages of the patients studied.

IHC analyses for PDL1 were performed, and a distinct continuous membranous staining on 5% or more of HRS cells was identified in 102 (93%) cases (Figure 1B). A significant correlation was found between case staging and PDL1 immunostaining with a *P*-value of 0.012, while no significant relations were identified with other studied clinicopathologic parameters (Table 2).

CD68 immunohistochemical staining gives the following results: low (score I; <5% of macrophages were stained) that were detected in 18 (16.36%) cases; intermediate (score II; 5-25% of macrophages were stained) that were detected in 62 (56.36%) cases; and high (score III; >25% of macrophages were stained) that were detected in 30 (27.27%) cases (Figure 1C). There was no statistically significant correlation between CD68 expression and patient age, gender, bulky

Table 3: Association between PDL1 and CD68 immune expressions.

PDL1	CD68			*P* value
	Low (18 cases)	Intermediate (62 cases)	High (30 cases)	
>5% positive (102 cases)	12 cases	60 cases	30 cases	<0.0001
<5% positive (8 cases)	6 cases	2 cases	0 cases	

disease, bone marrow involvement, B symptoms, or histological type, whereas a significant relationship was achieved with disease staging with a *P*-value of 0.011.

A positive association was achieved between PDL1 and CD68 immune expression with a highly significant *P*-value (Table 3).

The 5-year overall survival was 65% and PDL1 overexpression was significantly associated with inferior outcome with a *P*-value of 0.04 and a 95% CI lower bound of 0.3094 to 1.209 and an upper bound of 0.8286 to 3.232 (Figure 2).

DISCUSSION

Compared to other lymphomas, the cellular background infiltration is more intimately associated with the lymphomagenesis of cHL. Histiocytes and CD4+ cells are drawn in and become activated as a result of the numerous cytokines and chemokines that HRSC produce. In turn, HRSC react to the chemokines and growth factors that these neighbouring cells produce, and these latter substances act as vital feedback signals to promote proliferation and prevent apoptosis in HRSC[12].

Concerning the clinicopathological outcomes of the current study, it showed that males made up 61.8% of the studied cases, which is in agreement with most other studies that showed male gender predilection[13,9], whereas few studies showed the reverse finding[8,14] that may be due to racial and geographical factors and population differences.

In terms of age, patients ranged from 15 to 82 years old with a mean of 34.77; this finding is consistent with a previous study conducted in the same centre as the current study by Lilan *et al* in Erbil, Iraq in 2019[15] and many other studies[14,8,13,9]. Cases younger than 14 years were excluded from the study as childhood cHL may have a different pathogenesis[16].

Many previous studies reported that most cases were presented without bone marrow involvement by the disease process. This is nearly similar to the results of the current study[14,8,13,9].

Regarding histological type, nodular sclerosis is the most frequent out of the other diverse types; it constitutes 62.7% of the total studied cases. Mixed cellularity type follows as the second most common; it constitutes 30.9% of the total involved cases[14,13,9]. We considered all other histological subtypes together because of small number of cases in each categories, so considering them together make the statistical analysis more reliable. A study done by Mona *et al* in Egypt showed a slightly more common mixed cellularity type over nodular sclerosis[8]. This minor discrepancy

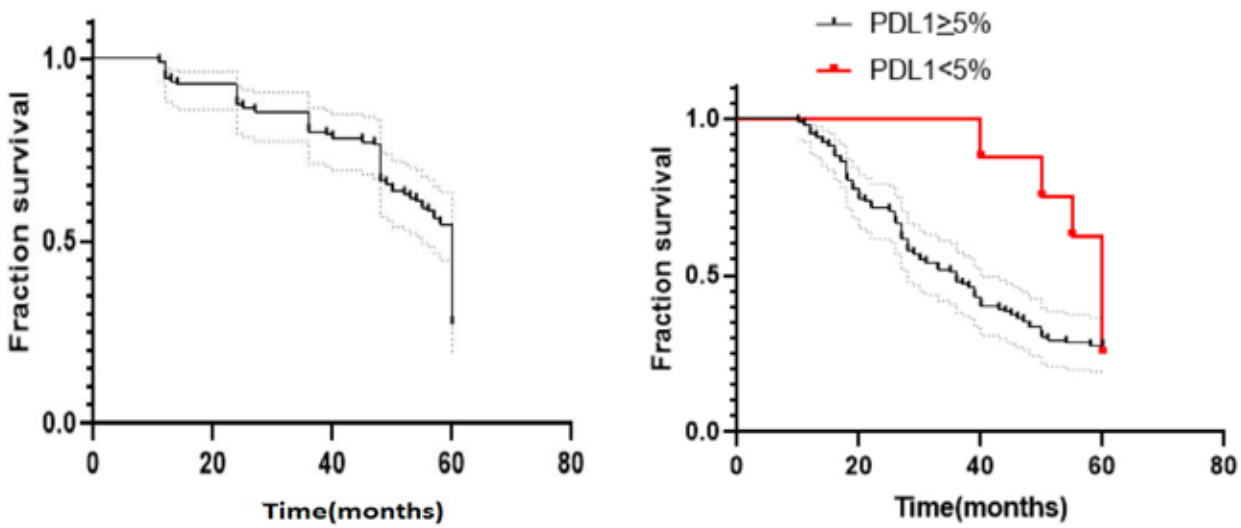

Figure 2: Survival analysis. (**a)** mean overall survival time; (**b)** mean overall survival time by PDL1 immune expression.

may be the result of a difference in sample size and case selection bias.

As for B symptoms at presentation, findings in this study showed a slightly larger number presented with B symptoms (51.8%); this result is in agreement with other studies[8,10], while another study showed that most cases of cHL were free of B symptoms at diagnosis[13]. A study done by Lilan *et al* in the same centre as this study (Nanakaly Centre, Erbil, Iraq) from the period of 2012-2016 also showed a larger number of cases presented with B symptoms (67.2%)[15] and this mild improvement in presentation may indicate better early diagnostic strategies.

Bulky disease was present in only 11.8% of the studied cases, a finding that is similar to nearly all recent studies done[14,8,13,9].

This study found that most of the cHL cases in this locality presented with stage II disease (52%), followed by stage III and stage IV, while the least presentation by stage was stage I, consisting of 10.9% of the studied cases, findings that were nearly similar to most others[14,8,13,9].

Overexpression of PDL1, modulated by genetic alterations and deregulated signalling pathways, has been recognized in HRS cells and mediates immune evasion of these cells[17]. In the current study, PDL1 was identified in 93% of cases when considering a 5% cutoff value. Other studies might have shown slightly, considerably similar, or different results due to different factors, among them the clone of antibody used and the different cutoff values determined. Many studies used 5% as the cutoff value for PDL1 expression on HRS cells, but others defined the cutoff as ranging from 1% to 50%, and still others used different interpretation methods, identifying the expression pattern as low, moderate and high percentages of expression[18-21].

Although many data achieved from solid tumours implied that PDL1 expression on tumour cells was the strongest determinant of response to treatment, the augment is more challenging in hemopoietic neoplasias, particularly in Hodgkin's lymphoma (HL) due to polymorphic infiltration so that we may need more standardized measures for interpretation.

The result of this study identified a statistically positive correlation between PDL1 immune expression and disease staging but not with other clinicopathological parameters. We caught a study that discovered a significant relationship between PDL1 expression in HL and case age[22]. Many other studies explored the diagnostic and prognostic roles of PDL1 in HL cases. One study found that increased expression of PDL1 on tumour cells has superior clinical responses[23], another stated that expression of PDL1 on HRS cells was upregulated in association with genetic alteration at the *9p24.1* locus[24], yet another identified that the significance of PDL1 is related to a high proportion on leukocytes but not HRS cells[25], while another study indicated that it is LMP1 that upregulates PDL1 expression and is a potential biomarker for predicting the effectiveness of immune checkpoint inhibitors[20]. A group of studies highlights the important role of PDL1 as a marker for the diagnosis of HL cases and, mainly, to differentiate it from other lymphoma subtypes[21,22]. Away from all these findings, others did not agree with the significance of the PDL1 marker in HL disease progression[18,26].

With the enormous evolution of immunotherapies, much effort has been centered on finding a convenient predictive marker for cases of HL. However, this is not a simple issue; false positives and negative results must be considered. The other critical aspect is the expression of PDL1 on infiltrating lymphocytes, monocytes and macrophages. This characteristic is critical in HL studies due to abundant cell infiltration around the HRS tumour cells.

Since macrophages are heterogeneous cells that play an important role in altering the tumour immune microenvironment and have been identified as a pan-macrophage biomarker by CD68, the relationship between TAM and the outcome of various malignancies has caught the attention of many researchers[2]. In the assessment of relationships between CD68 immunohistochemical expressions and studied clinicopathologic features, the current study reached to a significant correlation between disease stage and CD68 protein expression. Osama *et al* and Mona *et al* from Egypt and other recent studies had the same findings. However, Mona *et al* reached a significant association with bulky disease in addition[14,8,13,9].

Upon analyzing the relationship between PDL1 and CD68 markers, a statistically highly significant positive correlation was identified. A previous study discovered a significant relationship between both markers and disease progression, but when they were considered on TAM, the same study did not reach a conclusion on the prognostic value of analyzing PDL1 with regard to HRS cells[14]. Another study found a significant relationship between PDL1 reactivity on HRS cells and CD68 positivity on TAM[27]. There are various ways in which TAMs regulate the expression and function of PDL1. TAMs can release various cytokines to modulate the TME, such as TGF-b and PGE2. There are also homologous immune checkpoint ligands on the surface of TAMs that can block anti-PD-1/PDL1 immune efficacy. Many more clinical trials are being conducted to validate the relationship between macrophage infiltration or phenotype and the outcomes of patients receiving anti-PDL1 therapy.

Actually, it is important to specify macrophage subpopulations that have the potential to benefit from different targeted therapies. The difficulty comes from the dynamic nature of TME and the influences of other external factors.

CONCLUSION

Assessment of both PDL1 antibody on HRS cells and CD68 on TAM expressions by IHC may have an important role in identifying disease progression and outcome in cHL cases and, hence, in employing them in clinical practice.

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Author contribution statement: Tenya Tariq Abdulhameed collected the data and wrote, reviewed and edited the manuscript; Salah Abubakir Ali wrote the original draft of the manuscript; and Amin Aziz Bakir analyzed the data and wrote, reviewed, and edited the manuscript.

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Original Article

Could alpha-L-fucosidase be useful as a diagnostic and stage discriminative factor for lung cancer?

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ABSTRACT

Objective: To investigate the relationship between clinicopathological variables of patients with lung cancer and Alpha-L-fucosidase (AFU) serum levels and to examine AFU usability in distinguishing between early-stage and advanced-stage lung cancer.
Design: This was a prospective observational study.
Setting: Van Yuzuncu Yil University Department of Thoracic Surgery, between June 2020 and December 2020.
Subjects: Fifty healthy volunteers as the control group and seventy-five lung cancer patients confirmed and staged by imaging methods.
Interventions: The patients' demographic (age, gender) and clinicopathological characteristics were determined by physical examination, biochemical tests, pathological examination and imaging studies. The TNM staging system is used in cancer staging.
Main outcome measures: Serum AFU levels were measured in both the control and lung cancer groups.
Results: The mean AFU level of lung cancer patients was 13.35 ± 0.61 ng/mL, while the mean AFU level of the control group was 1.86 ± 0.35 ng/mL (P<0.001). AFU levels were significantly higher in the lung cancer group with increasing depth of invasion, lymph node metastasis, distant metastasis and TNM stages (P<0.001).
Conclusions: This study is the first to show that AFU can detect lung cancer early and predict the cancer stage. AFU can be an essential diagnostic and stage discriminative marker for lung cancer.

KEY WORDS: alpha-L-fucosidase, lung cancer, metastasis

INTRODUCTION

Cancer-related deaths are common in lung cancer. Lung cancer ranks second for both sexes of all cancer cases in terms of the estimated number of new cancer cases in the United States. For 2022, the estimated percentage of new cases in men was 12%, while the estimated percentage of new cases in women was 11%. On the other hand, the estimated mortality rate due to lung cancer in 2022 was 21% in the United States[1].

Lung cancer manifests itself, especially with wheezing, sudden weight loss, shortness of breath or various pains. Computed tomography (CT) is first performed on lung cancer patients with symptoms or a suspicious lung lesion on lung radiographs[2,3]. Nonetheless, despite its high sensitivity, the specificity of CT in lung cancer diagnosis is vulnerable[3]. A fine needle biopsy or bronchoscopy is the most appropriate way of reaching the mass. The diagnosis of lung cancer is made due to the examination of the biopsy material. If the disease has spread to other organs, the diagnosis can be made by taking samples from those organs. Lung cancer staging is done after the diagnosis is finalised[2,3].

Since lung cancer is a type that cannot be evaluated in cancer screening programs, it can rarely be detected in the early stage before it spreads from

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the lung to the lymphatics or other organs. The probability of catching the disease in the early period is around 15%. In cases that have not spread to the lymph nodes, the 5-year survival rate is 50%[3]. This rate falls below 15% when the disease has spread to nearby organs other than the lung. Due to the low detection of the disease in the early stages and the low 5-year survival, efficient and feasible serum markers are needed for early lung cancer diagnosis.

Serum markers are molecules consisting of blood or tissue produced by a tumour related to cancer or by a regimen in response to cancer. Ascertainment or establishment of tumour markers is available for clinical diagnosis or patient management. Previous studies have examined a range of serum tumour markers in lung cancer, including embryonic carcinoma antigen, CA-125, chromogranin A, α1-antitrypsin and retinol-binding protein (RBP)[4-7]. No exact serum test exists for lung cancer. Therefore, more effective and applicable markers are needed.

Alpha-L-fucosidase (AFU) is a sort of lysosomal enzyme in all mammalian cells and hydrolyzes sugars containing L-fucose[8]. Although it has been shown in previous studies that serum AFU activity can be used for the diagnosis of hepatocellular carcinoma[9], colorectal cancer[4,10] and ovarian tumours[11], there is no clear view of the primary mechanism yet. Although its mechanism is not fully proven, this prospective study was designed because of the potential of AFU as a serum marker that can also be used for lung cancer since previous studies have shown its prognostic value in some malignancies.

Because of both the need for a marker for the early diagnosis of lung cancer and proving that it is a useful serum marker in previous studies, the relationship between AFU serum levels and clinicopathological variables of patients with lung cancer was investigated, as well as its usability in distinguishing between early and advanced lung cancer.

SUBJECTS AND METHODS

Patients

This prospective observational study was initiated after obtaining ethical committee approval from a tertiary health centre (Decision Number: 2020/02-23). Written consent from the patients was obtained under the Ethical Principles stated in the Declaration of Helsinki. Between June 2020 and December 2020, 75 lung cancer patients (lung cancer group) diagnosed with radiological and pathological diagnosis and staged by imaging methods (positron emission tomography / CT) and 50 healthy volunteers (control group) were included in the study.

The patients' demographic (age, gender) and clinicopathological characteristics were determined by physical examination, biochemical tests, pathological examination and imaging studies. The TNM staging system is used in cancer staging. Serum AFU levels were measured in both the control and lung cancer groups.

Sample collection

After obtaining consent from the people included in the study, 4 mL of venous blood was obtained from the control group and newly detected lung cancer patients. Samples are allowed to clot for 2 hours at room temperature or overnight at 4 °C. The clot was centrifuged at 1000xg for 15 minutes, and the supernatant was collected. The supernatants were transferred to wells of plates pre-coated with primary antibodies. After the recommended incubation period and washing period, substrate solution was added. The wells were added colour-reagent and stop solution. Optical density was determined at a wavelength of 450 nm using automated optical densitometry. Each sample was run in duplicate, and the mean value was used for analysis.

ELISA for AFU (Alpha Fuca) was performed using commercially available kits according to the manufacturer's instructions (Biocompare, Catalog No: ABIN1113347; detection range= 0.313-20 ng/ml with a sensitivity of 0.188 ng/mL). This assay has high sensitivity and specificity for the detection of human AFU.

Table 1: The clinicopathological features of lung cancer patients

Clinicopathological features	Lung cancer group (n=75)
Age (mean±SD, year)	56.65 ± 5.89 (54-60)
Gender (M/F, %)	43/32 (57.3/42.7)
Tumour size (n, %)	
<40 mm	12 (16)
≥ 40 mm	63 (84)
TNM Stage (n, %)	
Stage I	9 (12)
Stage II	22 (29.3)
Stage III	17 (22.7)
Stage IV	27 (36)
Depth of invasion (n, %)	
T_1	12 (16)
T_2	19 (25.3)
T_3	21 (28)
T_4	23 (30.7)
Lymph node metastasis (n, %)	
N_0	17 (22.7)
N_1	13 (17.3)
N_2	45 (60)
Distant metastasis (n, %)	
Absent	9 (12)
Present	66 (88)

Table 2: Comparison of the control and lung cancer groups according to age, gender and Alpha-L-fucosidase levels

Characteristics	Control group (n=50)	Lung cancer group (n=75)	*P*-value
Age (mean±SD, year)	57.4 ± 2.28	56.65 ± 5.89	>0.05*
Min-Max (year)	50-60	54-60	
Gender (M/F)	28/22	43/32	>0.05**
(%)	(56/44)	(57.3/42.7)	
Alpha-L-fucosidase (ng/mL)	1.86 ± 0.35	13.35 ± 0.61	<0.001*
min-max (ng/mL)	1-2	11.9-14.5	

*Mann Whitney U test, **Chi-square test.

Statistical analysis

Statistical Packages for Social Sciences (SPSS) ver. 26.0 for Windows was used for statistical analysis. Data were given as a median, range (minimum-maximum), frequency and percentage. A Shapiro-Wilk test or Kolmogorov-Smirnov test evaluated the normal distribution of data. Mann Whitney U test (for two groups) or Kruskal Wallis test (for three or more groups) was used to evaluate the groups according to the normality test results. In addition, qualitative variables were compared with the chi-square test. Statistical results with a *P*-value less than 0.05 were considered significant.

RESULTS

This prospective observational study included 125 patients. The lung cancer group included 75 patients (male/female=43/32) with a mean age of 56.65 years (range from 54 to 60), control group included 50 people (male/female=28/22) with a mean age of 57.14 years (range from 50 to 60). Both groups showed similar age distribution (*P*>0.05). 84% of all patients with lung cancer had a tumour diameter of over 40 mm. Additionally, 58 patients had at least one metastatic lymph node, while 66 patients had distant metastasis. Clinicopathological features of the lung cancer group are given in Table 1.

The mean AFU level of the lung cancer group was 13.35 ± 0.61 (11.9-14.5) ng/mL, while the mean AFU level of the control group was 1.86 ± 0.35 (1-2) ng/mL. AFU levels were significantly higher in the lung cancer group (*P*<0.001). A comparison of the control group and lung cancer group according to age, gender, and AFU levels is shown in Figure 1 and Table 2. AFU levels were significantly higher in the lung cancer group with increasing depth of invasion, lymph node metastasis, distant metastasis and TNM stages (*P*<0.001). According to clinicopathological variables, AFU levels of patients with lung cancer are shown in Table 3.

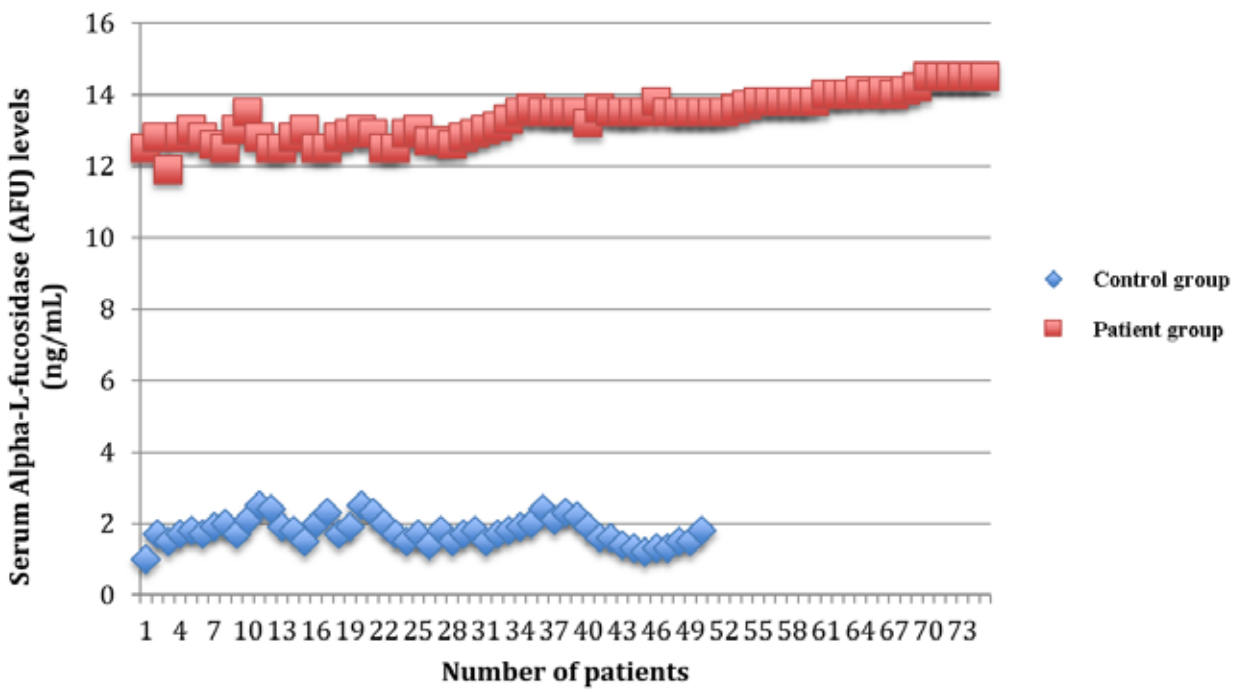

Figure 1: The histogram of Alpha-L-fucosidase levels of the control group and lung cancer patients.

Table 3: Comparison of serum Alpha-L-fucosidase levels of the clinicopathological variables of the patients

Evaluated parameters	Alpha-L-fucosidase levels (ng/mL) (Mean SD)	*P*-value
Tumour size		<0.001*
<40 mm	12.72 ± 0.38	
≥ 40 mm	13.46 ± 0.57	
TNM Stage		<0.001**
Stage I	12.65 ± 0.33	
Stage II	12.78 ± 0.24	
Stage III	13.47 ± 0.15	
Stage IV	13.98 ± 0.34	
Depth of invasion		<0.001**
T_1	12.72 ±0.38	
T_2	12.76 ± 0.38	
T_3	13.48 ± 0.14	
T_4	14.07 ± 0.29	
Lymph node metastasis		<0.001**
N_0	12.70 ± 0.34	
N_1	12.78 ± 0.17	
N_2	13.77 ± 0.39	
Distant metastasis		<0.001*
Absent	12.65 ± 0.33	
Present	13.45 ± 0.58	

*Mann-Whitney U test, **Kruskal Wallis test.

DISCUSSION

Lung cancer, a significant health problem globally and in our country, is the second most common cancer after breast cancer in women and prostate cancer in men[1]. Lung cancer, the most important cause of which is smoking, manifests itself, especially with wheezing, sudden weight loss, shortness of breath or various pains. Since lung cancer is a type that cannot be evaluated in cancer screening programs, it can rarely be detected in the early stage before it spreads from the lung to the lymphatics or other organs. The probability of catching the disease in the early period is around 15%. In cases that have not spread to the lymph nodes, the 5-year survival rate is 50%[3]. This rate falls below 15% when the disease has spread to nearby organs other than the lung. Because the diagnosis cannot be made early, the patients apply in the advanced stages. The life expectancy of patients increases with early diagnosis and treatment. Therefore, specific serum markers are needed for early diagnosis.

Carcinoembryonic antigen (CEA), one of the first oncofetal antigens, was first detected in colon cancer. However, the clinical utility of serum CEA in lung cancer has also been seriously investigated recently[12]. However, CEA had low sensitivity levels (50-60%) for lung cancer, despite high specificities (90%) and cannot meet the essentiality of clinical execution[13]. Although CA-125 is a marker thought useful in staging lung cancer, it is not a specific marker for lung cancer[14]. In previous studies, neuron-specific enolase levels in squamous cell lung cancer are specific at diagnosis, although their predictive value remains controversial[6]. On the other hand, α1-antitrypsin, RBP and squamous cell carcinoma antigen are valuable markers in the early diagnosis of lung cancer[15]. Although many markers are helpful in early lung cancer diagnosis, there is no specific marker for lung cancer diagnosis. Because of both the need for a marker for the early diagnosis of lung cancer and proving that it is a useful serum marker in previous studies, the relationship between AFU serum levels and clinicopathological variables of patients with lung cancer was investigated, as well as its usability in distinguishing between early and advanced lung cancer.

As a result of malignant transformation, normal cells lose many of their properties and gain new properties. This process depends on various changes in cell membranes, and due to this feature, tumour marker studies have been directed to plasma membrane components such as glycoproteins and glycolipids. On the other hand, qualitative and quantitative increases in serum glycoprotein and glycolipid fractions were observed in many malignancies[16]. AFU is a lysosomal acid hydrolase found in all cells in the organism. AFU liberates alpha-L-fucose in fucose-containing glycoproteins and glycolipids in oligosaccharides[8]. In conclusion, the balance of alpha-1-fucose and AFU affects the prognosis of malignancies. Because AFU is consumed during the degradation of alpha-1-fucose, the survival of patients with low AFU levels is better[5,17]. Studies showed that hepatocellular carcinoma and colorectal carcinoma patients with high AFU levels are more likely to die from cancer[4,18]. As another theory, AFUs not only contribute to the development of numerous malignant tumours but are also involved in the regulation of pathological processes, including immune escape, invasion and metastasis of cancers[19]. The change in the activity of AFUs in serum or tissues can be used as an indicator of tumour burden, metastasis and response to anti-cancer therapy[20].

AFU as a tumour marker was first described in diagnosing hepatocellular carcinoma[1]. The predictive value of AFU was also found for the survival of patients after surgery with hepatocellular carcinoma, intrahepatic cholangiocarcinoma, cervical cancer and endometrial cancer[4,5,7]. In Yu *et al*'s study, AFU demonstrated a better predictive value for long-term survival in patients with early-stage oesophagal carcinoma[21]. In another study by Shah *et al*, serum AFU levels were significantly higher in patients with untreated oral cancer compared to the normal population[22]. A previous study determined that AFU upregulation is required for *Helicobacter pylori* adhesion, a predisposing factor for gastric cancer.

Additionally, AFU may help their defence strategy to escape host surveillance[23]. On the other hand, a decrease in AFU expression and activity was observed in triple-negative breast cancer and neuroblastoma[5,24].

Since no study shows that AFU level can be used in lung cancer, this study is beneficial to the literature. This study showed that serum AFU levels could be an important marker for lung cancer. According to statistical comparisons, serum AFU levels were higher in patients with lung cancer than in the average population. In addition, overexpression was considered in patients with high AFU levels, which may be associated with advanced TNM stages and poor differentiation. Since it has been shown that elevated serum AFU levels may be associated with vascular invasion and lymph node metastasis, we think it may have a role in the diagnosis and follow-up of lung cancer during treatment (oncological or surgical treatment) and the early diagnosis of relapse cases. The study shows that tumour markers such as AFU in the serum of lung cancer patients may be helpful for marker-based studies and lung cancer diagnosis.

CONCLUSION

Lung cancer is the second most common type after breast cancer in women and prostate cancer in men. As with every disease, early diagnosis and treatment positively affect the prognosis of lung cancer. Therefore, markers are needed for early diagnosis.

This study is the first to show that AFU can be used in the early detection of lung cancer and predicting the cancer stage. Serum AFU levels in healthy people are in the normal range. However, serum AFU levels were higher in patients with lung cancer. Therefore, higher AFU levels may indicate lung cancer.

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Contribution: Duygu Mergan Iliklerden contributed to designing the study and preparation of the manuscript. She also contributed to data collection and conduction of the study. Tolga Kalayci and Buket Mermit Cilingir contributed to the data analysis, writing, and design of this study.

Ethical Approval: Ethical Committee at Van Yuzuncu Yil University Faculty of Medicine, Van, Turkey (Decision Number: 2020/02-23).

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Original Article

Is the preoperative thyroid-stimulating hormone associated with cancer in cytologically indeterminate thyroid nodules?

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ABSTRACT

Objective: We aimed to examine the association between pre-operative thyroid-stimulating hormone (TSH) and thyroid cancer in patients with indeterminate thyroid nodules.
Design: Retrospective cohort study
Setting: Single tertiary hospital.
Subjects: Fifty patients who underwent thyroidectomies
Interventions: We analyzed 50 resected indeterminate thyroid nodules in 50 patients from our previous study. Patients were divided into two groups according to TSH levels.
Main outcome measures: The association between the TSH level and type of pathology (benign vs. malignant) and whether this biomarker predicts thyroid cancer were investigated.
Results: Fifty patients with atypia/follicular lesion of undetermined significance and follicular neoplasm/ suspicious for a follicular neoplasm were enrolled. The median TSH levels for men and women were 1.35 (with an interquartile range [IQR] of 12.64) and 1.41 (IQR: 2.1) respectively with no statistically significant difference between the two groups (z=-0.676, *P*=0.499). Furthermore, the median (IQR) TSH levels for malignant and benign pathologies were 1.2 (2.5) and 1.5 (2.09) respectively with no significant difference between the two groups (z=-1.131, *P*=0.258). Overall, no association was found between TSH levels and the pathology type. Considering TSH levels <1 and ≥1 mIU/L, there was a significant association between TSH levels and the pathology type among female patients, and in the presence of TR4 nodules (*P*= 0.02 and *P*=0.049, respectively). When dividing patients based on normal TSH levels, there was no significant association between TSH levels and the pathology type.
Conclusion: TSH can represent an effective biomarker of malignancy in indeterminate thyroid nodules, especially when combined with certain demographic and ultrasound features. Further research is necessary to examine and address these findings.

KEY WORDS: thyroidectomy, thyroid neoplasms, thyroid nodule, thyrotropin

INTRODUCTION

A thyroid nodule (TN) is a common surgical condition that necessitates exclusion of malignancy[1]. Cytologically indeterminate thyroid nodules (CITNs) refer to Bethesda III (atypia of undetermined significance [AUS] or follicular lesion of undetermined significance [FLUS]) and IV nodules (follicular neoplasm [FN] or suspicious for a follicular neoplasm [SFN]). These account for approximately 25% of all TNs and are clinically challenging[2].

Although the clinical management of CITNs remains a significant challenge for clinicians, the implementation of molecular markers, repeat fine-needle aspiration cytology (FNAC) or diagnostic lobectomy is recommended[2]. Repeating FNAC in indeterminate thyroid nodules yields more definite categories. However, some reports have found that 76% of cases had the same cytological diagnosis[3]. Unilateral lobectomy has been recommended in CITN with a diameter of ≤10 mm, while other

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authors have recommended total thyroidectomy as the appropriate treatment for CITNs. The latter treatment aids in assessing the presence of extrathyroidal extension and multifocality, as well as allowing histologic variant verification[4]. Conversely, molecular testing is an ideal tool, but its lack of availability in most centers limits its use. Therefore, research to determine the appropriate approaches and management for these indeterminate nodules is ongoing. The role of anti-thyroid antibodies and thyroid-stimulating hormone (TSH) in predicting cancer has been investigated in all cytological categories of TNs[5-10]. However, very few studies have examined these markers in CITNs[4,8,11,12].

TSH, a thyrocyte growth factor, is secreted by the pituitary gland. Its role is primarily focused on the regulation of thyroid hormone production and thyroid function. Furthermore, high TSH levels have been implicated in the initiation and development of papillary thyroid cancer (PTC), even if they are within the normal range[5,9-16].

Our research group previously studied the clinical and radiological features of CITNs and concluded that none could predict the risk of malignancy (ROM)[1]. However, we did not investigate the relationship between preoperative TSH levels and the ROM. Therefore, in the current study we aimed to investigate the association between preoperative TSH and thyroid cancer in Bethesda III and IV TNs. To the best of our knowledge, this is the first study in the Gulf region to investigate the relationship between the TSH level and ROM in CITNs (Bethesda III and IV TNs).

SUBJECTS AND METHODS

Ethics statements

This study was approved by the Research Ethical Committee at King Salman Armed Forces Hospital Northwestern Region, Tabuk, Saudi Arabia. The requirement for informed consent was waived due to the retrospective nature of the study and lack of direct communication with the patients.

Study design and population

This retrospective cohort study used the data collected in our previous study[1], which was performed at a single tertiary hospital. It included all surgical patients with cytological diagnoses of AUS/FLUS and FN/SFN from January 2014 to January 2020. In our previous study[1], 1595 thyroid FNACs were performed during the study period. The cytological diagnoses were AUS/FLUS for 102 (6.4%) patients and FN/SFN for 57 (3.6%). Of these patients, 50 (29 with AUS/FLUS and 21 with FN/SFN) who underwent thyroidectomies were included as subjects in the present study. The dataset contained demographic features, preoperative TSH levels, ultrasonography (US) features, Thyroid Imaging Reporting & Data System (TI-RADS) scores and final pathological diagnoses.

TSH

Serum TSH levels were measured by chemiluminescence using an ATELLICA machine, with a normal range of 0.5–5 mIU/L. TSH levels were categorized using two methods: the first one (TSH group 1) split the participants into two groups: <1 and ≥1 mIU/L, which is similar to the methods of several studies that considered a TSH level of 1 mIU/L as the threshold above which the ROM increases[9-11,13-16]. The second method (based on the normal TSH level in our hospital) categorized the participants into three groups: <0.5, 0.5-5, and >5 mIU/L.

Statistical analysis

Descriptive statistics are provided for demographic characteristics, Bethesda categories and pathology types. The number of observations, percentages and median (interquartile range (IQR)) are used to express quantitative and qualitative data. Categorical data are presented as frequencies and percentages, whereas continuous variables are presented as median (IQR). Data normality was evaluated by conducting both the Shapiro-Wilk and Kolmogorov-Smirnov tests. The results of these tests gave *P*-values <0.05, which led us to reject the null hypothesis and conclude that the data were not normally distributed. Therefore, non-parametric methods were utilized to determine the correlation between the categorical variables included in our study. This approach is more appropriate for abnormal data, as non-parametric tests do not depend on assumptions about the underlying distribution and can provide more accurate and reliable results. The correlation between categorical variables was estimated using the Pearson chi-square test and Fisher

Table 1: TSH level by different variables

Parameter	TSH level (mIU/L) Median (IQR)	Mann-Whitney U	
		Z	*P*-value
Sex		-0.676	0.499
Male	1.35 (12.08)		
Female	1.41 (2.1)		
Bethesda category		-1.66	0.096
AUS/FLUS	1.07 (1.48)		
FN/SFN	1.9 (3.67)		
Pathology		1.131	0.258
Benign	1.5 (2.09)		
Malignant	1.2 (2.5)		

TSH: thyroid-stimulating hormone; IQR: interquartile range; AUS: atypia of undetermined significance; FLUS: follicular lesion of undetermined significance; FN: follicular neoplasm; SFN: suspicious for a follicular neoplasm

Table 2: Association between TSH levels (group 1) and the final pathology by different variables

Variable	TSH level, MIU/L	Pathology		CHI-square *P*-value	FISHER TEST *P*-value
		Benign n (%)	Malignant n (%)		
TSH	<1	7 (43.75)	9 (56.25)	0.068	0.117
	≥1	24 (70.59)	10 (29.41)		
SEX				0.013*	
Male	<1	2 (100)	0 (0)		0.464
	≥1	3 (50)	3 (50)		
Female	<1	5 (35.71)	9 (64.29)		0.02*
	≥1	21 (75)	7 (25)		
BETHESDA category					
AUS/FLUS	<1	4 (36.36)	7 (63.64)		0.143
	≥1	12 (66.67)	6 (33.33)		
FN/SFN	<1	3 (60)	2 (40)		0.598
	≥1	12 (75)	4 (25)		
AGE				0.122	
≤45 years	<1	5 (45.45)	6 (54.55)		0.238
	≥1	14 (73.68)	5 (26.32)		
>45 years	<1	2 (40)	3 (60)		0.347
	≥1	10 (66.67)	5 (33.33)		
TI-RADS score					
TR2	<1	1 (50)	1 (50)		1
	≥1	3 (75)	1(25)		
TR3	<1	2 (50)	2 (50)		1
	≥1	12 (63.16)	7 (36.84)		
TR4	<1	3 (37.5)	5 (62.5)		0.049*
	≥1	8 (88.89)	1 (11.11)		
TR5	<1	1 (50)	1 (50)		1
	≥1	1 (50)	1 (50)		
Composition					
Mixed cystic and solid	<1	3 (60)	2 (40)		0.56
	≥1	8 (80)	2 (20)		
Solid	<1	4 (36.36)	7 (63.64)		0.144
	≥1	16 (66.67)	8 (33.33)		
Echogenicity					
Hypoechoic	<1	5 (45.45)	6 (54.55)		0.097
	≥1	13 (81.25)	3 (18.75)		
Hyper or iso	<1	2 (40)	3 (60)		0.618
	≥1	11 (61.11)	7 (38.89)		
Margin				0.1465	
Smooth	<1	7 (46.67)	8 (53.33)		0.202
	≥1	22 (68.75)	10 (31.25)		
Ill-defined	<1	0 (0)	1 (100)		0.333
	≥1	2 (100)	0 (0)		
Echogenic foci				0.25	
Macrocalcification	<1	0 (0)	3 (100)		0.250
	≥1	1 (100)	0 (0)		
Punctate echogenic foci	<1	2 (66.67)	1 (33.33)		1
	≥1	2 (66.67)	1 (33.33)		
None	<1	5 (50)	5 (50)		0.278
	≥1	21 (70)	9 (30)		

TSH: thyroid-stimulating hormone; AUS: atypia of undetermined significance; FLUS: follicular lesion of undetermined significance; FN: follicular neoplasm; SFN: suspicious for a follicular neoplasm; TI-RADS: Thyroid Imaging Reporting & Data System
*Significant at P <0.05

exact test, as appropriate. SPSS (version 27.0; IBM Corp.) for Windows was used to perform data analysis. Statistical significance was set at P <0.05 with a 95% confidence interval.

RESULTS

In total, 50 resected nodules from 50 patients with cytological diagnoses of AUS/FLUS (n=29, 58%) and FN/SFN (n=21, 42%) were included. Women represented the majority of the patients (n=42, 84%). Overall, 60% of patients were aged ≤45 years and 40% were aged >45 years. A total of 31 patients (62%) had benign pathology. As stated in the "Subjects and methods" section, we used two methods to categorize TSH levels. Based on the first method, 68% of the participants had TSH levels ≥1 mIU/L, whereas 32% had TSH levels <1 mIU/L. Similarly, using the second method, most patients (78%) had TSH levels from 0.5-5

Table 3: Association between TSH levels (group 2) and the final pathology by different variables

Variable	TSH level, MIU/L	Pathology		FISHER TEST *P*-value
		Benign n (%)	Malignant n (%)	
TSH	<0.5	1 (25)	3 (75)	0.262
	0.5–5	26 (66.67)	13 (33.33)	
	>5	4 (57.14)	3 (42.86)	
SEX				
Male	0.5–5	4 (80)	1 (20)	0.464
	>5	1 (33.33)	2 (66.67)	
Female	<0.5	1 (25)	3 (75)	0.480
	0.5–5	22 (64.71)	12 (35.29)	
	>5	3 (75)	1 (25)	
BETHESDA category				
AUS/FLUS	<0.5	1 (33.33)	2 (66.67)	0.210
	0.5–5	15 (62.5)	9 (37.5)	
	>5	0 (0)	2 (100)	
FN/SFN	<0.5	0 (0)	1 (100)	0.472
	0.5–5	11 (73.33)	4 (26.67)	
	>5	4 (80)	1 (20)	
AGE				
≤45 years	<0.5	1 (50)	1 (50)	1
	0.5–5	15 (62.5)	9 (37.5)	
	>5	3 (75)	1 (25)	
>45 years	<0.5	0 (0)	2 (100)	0.082
	0.5–5	11 (73.33)	4 (26.67)	
	>5	1 (33.33)	2 (66.67)	
TI-RADS score				
TR2	0.5–5	2 (50)	2 (50)	0.467
	>5	2 (100)	0 (0)	
	<0.5	1 (100)	0 (0)	
TR3	0.5–5	13 (65)	7 (35)	0.142
	>5	0 (0)	2 (100)	
	<0.5	0 (0)	2 (100)	
TR4	0.5–5	9 (69.23)	4 (30.77)	0.214
	>5	2 (100)	0 (0)	
	<0.5	0 (0)	1 (100)	
TR5	0.5–5	2 (100)	0 (0)	0.333
	>5	0 (0)	1 (100)	
Composition				
Mixed cystic and solid	0.5–5	9 (69.23)	4 (30.77)	1
	>5	2 (100)	0 (0)	
	<0.5	1 (25)	3 (75)	
Solid	0.5–5	17 (65.38)	9 (34.62)	0.279
	>5	2 (40)	3 (60)	
	<0.5	0 (0)	2 (100)	
Echogenicity				
Hypoechoic	0.5–5	16 (72.73)	6 (27.27)	0.130
	>5	2 (66.67)	1 (33.33)	
	<0.5	1 (50)	1 (50)	
Hyper or iso	0.5–5	10 (58.82)	7 (41.18)	1
	>5	2 (50)	2 (50)	
	<0.5	1 (25)	3 (75)	
Margin				
Smooth	0.5–5	24 (66.67)	12 (33.33)	0.261
	>5	4 (57.14)	3 (42.86)	
Ill-defined	0.5–5	2 (66.67)	1 (33.33)	1a
	<0.5	0 (0)	2 (100)	
Echogenic foci		1 (50)	1 (50)	
Macrocalcification	0.5–5			1
	<0.5	0 (0)	1 (100)	
Punctate echogenic foci	0.5–5	4 (100)	0 (0)	0.666
	>5	0 (0)	1 (100)	
	<0.5	1 (100)	0 (0)	
None	0.5–5	21 (63.64)	12 (36.36)	1
	>5	4 (66.67)	2 (33.33)	

TSH: thyroid-stimulating hormone; AUS: atypia of undetermined significance; FLUS: follicular lesion of undetermined significance; FN: follicular neoplasm; SFN: suspicious for a follicular neoplasm; TI-RADS: Thyroid Imaging Reporting & Data System

*Significant at $P < 0.05$

[a] No statistics are computed because the TSH is constant.

mIU/L, 14% had TSH levels >5 mIU/L, and 8% had TSH levels <0.5 mIU/L.

Median TSH levels according to sex, the Bethesda category and pathology type are shown in Table 1 with no significant associations.

Although the ROM was higher in patients with TSH levels ≥1 mIU/L than in those with TSH levels <1 mIU/L, the difference was not statistically significant (X^2 P=0.068 and Fisher exact P=0.117). Furthermore, there was no significant correlation between the ROM and TSH levels when splitting data according to the Bethesda category and age. Notably, when splitting the data according to sex, the TSH level was significantly associated with the type of pathology only in females (X^2 P= 0.013 and Fisher exact P=0.02). Except for TR4 nodules (P=0.049), there were no significant associations between the TSH level and final pathology in other TI-RADS scores and US features (Table 2).

Table 3 shows that the type of pathology was not significantly correlated with the TSH level (P=0.262). Furthermore, there was no significant difference between the two variables when splitting data according to sex, Bethesda category, TI-RADS score or US features. Interestingly, when considering age (≤45 or >45 years), the ROM was higher if the TSH level was within the normal range. However, no significant association was observed.

DISCUSSION

CITNs are clinically challenging to treat. In our previous cohort study, we reported ROMs of 44.8% in the AUS/FLUS and 28.6% in the FN/SFN groups; these aloes are in accordance with the actual ROMs in surgically excised nodules in a previous study[1]. Furthermore, clinical and radiological variables did not help predict the ROM in either group[1]. Hence, we explored the potential role of biochemical tests such as TSH as markers for thyroid cancer in Bethesda III and IV TNs.

Certain biochemical tests (e.g., high anti-thyroid antibodies and high TSH levels) were found to be predictors of thyroid carcinoma occurrence and aggressive biology in patients with CITNs, showing that they can be used for diagnostic and prognostic purposes[11]. Similarly, Boi *et al* found that increased TSH levels and thyroid autoimmunity were independent risk factors for TN malignancy[10]. This finding contradicts our results, except for the results of female sex, as well as TR4 nodules in the first TSH group.

Our data showed that the ROM was higher among female patients than that among male patients, which is in line with another study's findings[12]. Interestingly, there was a significant association between TSH levels and the type of pathology in female sex when the data were divided according to the TSH level (< or ≥1 mIU/L; P=0.02). High TSH levels, even within the normal range, are associated with thyroid cancer occurrence[5]. Likewise, Fiore *et al* found a significantly lower rate of PTC (1.9%) in patients with TSH levels <0.4 mlU/L than in those with TSH levels >3.4 mlU/L (16.5%)[17]. In contrast, Castro *et al* concluded that TSH levels did not increase the ROM in cytologically suspicious TNs[18]. This finding is also in agreement with those of other studies[19,20]. Moreover, in a retrospective study of AUS/FLUS TNs, there was no significant relationship between the TSH levels and ROM[21]. However, low TSH levels cause less differentiation of thyroid epithelial cells and may increase the risk of malignant cell transformation in only three variants[22].

According to Al Dawish *et al*, a TSH level of >4.5 mIU/L with certain US features was associated with a higher ROM. However, the difference was not statistically significant[23]. This finding was also confirmed by other studies[19,20]. Our results showed no association between the TSH level and ROM when splitting the data according to TI-RADS scores and US features, except for TR4 nodules in the first group.

Patients older than 55 years of age with high TSH levels have a higher ROM and advanced stage than younger patients[12]. This finding was also supported by the study of Haymart *et al*[5]. Furthermore, a high TSH level (>2.615 mlU/L) is associated with poor disease-free survival in patients with PTC[24]. Our results showed no statistically significant relationship between TSH levels and the type of pathology when splitting data according to age.

Strengths and limitations

Our study has several strengths. First, this is the first study in the Gulf region to investigate the effects of the TSH level on the ROM in both AUS/FLUS and FN/SFN nodules. Second, all patients had a final pathological diagnosis (benign vs. malignant). Nevertheless, this study has limitations, including the small sample size and retrospective nature. Furthermore, the nodule size and anti-thyroid antibodies were not included in the analysis.

CONCLUSION

Our study has provided insights into the efficacy of TSH levels in conjunction with specific demographic and US features for the prognostication of malignancy in indeterminate thyroid nodules. To provide a comprehensive understanding, a large, longitudinal, prospective multicentre study is warranted. Such a future study should encompass not only TSH levels but also integrate a comprehensive array of

biochemical markers, including anti-thyroid antibodies, to refine the management strategies for these challenging groups.

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Case Report

Non-puerperal uterine inversion due to endometrial stromal sarcoma: A case report

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ABSTRACT

Non-puerperal uterine inversion is an uncommon clinical condition, which has been reported. The management was difficult for most gynecologists because of the rare nature of the condition. We present a rare case of non-puerperal uterine inversion due to endometrial stromal sarcoma. A 62-year-old postmenopausal female was admitted with irregular vaginal bleeding for one month. Vaginal examination showed the presence of a large red mass of size 9 × 9 × 8 cm protruding into the vagina with no obvious pedicle. A mass biopsy was done and histology revealed a endometrial stromal sarcoma. At the time of surgery, the patient was placed at supine position and an inverted uterus was observed at laparotomy. Total hysterectomy with bilateral adnexectomy was performed. Histopathological evaluation showed endometrial stromal sarcoma. Uterine inversion rarely occurs outside the puerperal period; however, when it does occur, the possibility of an underlying malignancy should not be neglected.

KEY WORDS: endometrial stromal sarcoma, non-puerperal, uterine inversion

INTRODUCTION

Uterine inversion is a condition in which the fundus collapses into the endometrial cavity, which can turn the uterus partially or completely inside out[1]. Uterine inversion can be puerperal or non-puerperal. Puerperal inversion is usually a complication of pregnancy occurring in the post-partum period. Non-puerperal uterine inversion is extremely rare and the most common cause is submucous myoma. However, other causes may also be involved, such as malignant uterine tumors or idiopathic causes[2]. The majority of patients describe gynaecological symptoms as vaginal bleeding or shock, lower abdominal pain or bowel or bladder difficulties. This is the third case of inversion reported due to endometrial stromal sarcoma. We present a rare case with uterine inversion caused by an uncommon tumour.

CASE REPORT

A 62-year-old postmenopausal female was admitted with irregular vaginal bleeding for one month. Vaginal examination showed the presence of a large red mass of size 9 × 9 × 8 cm protruding into the vagina with no obvious pedicle. The mass showed surface with hemorrhage by touch. The cervix could not be seen or felt due to the large size of the mass filling the upper 2/3 part of the vagina. A mass biopsy was done and histology revealed an endometrial stromal sarcoma.

Laboratory tests revealed serum CA 125 levels of 22.7 U/ml and CEA levels of 2.43 U/ml, all of which remained in the normal range. Hemoglobin was 8.1 g/dl suggesting anemia. A transvaginal ultrasound showed a heterogeneous nodular lesion in the cervix with 80 mm, the uterine fundus was not identified. The magnetic resonance imaging observed a large mass of 94 mm located at the fundus and protruding to the vagina (Fig 1).

At the time of surgery, the patient was placed at supine position and an inverted uterus was observed at laparotomy. The round and the ovarian ligaments, as well as the tubes were pulled into the uterus (Fig 2). At first, it was attempted to treat the inversion by applying

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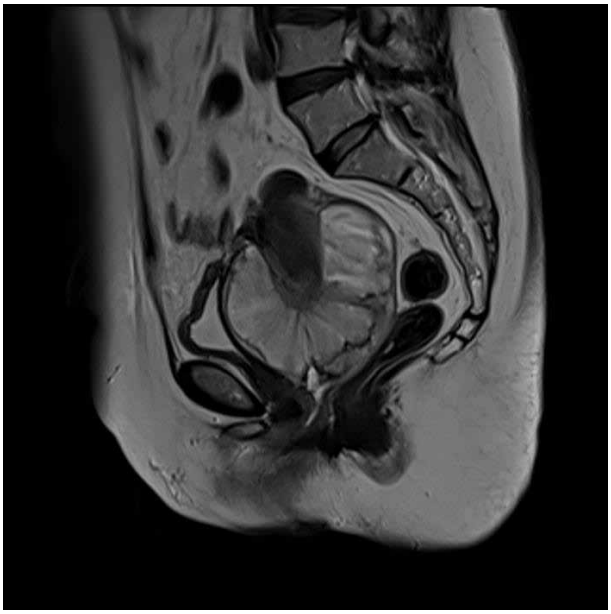

Fig 1: Magnetic resonance imaging (MRI) shows a large mass located in the fundus and protruding towards the vagina.

tension on the ligament, which was not successful due to the extent of the inversion. Total hysterectomy with bilateral adnexectomy was performed (Fig 2). No complications were reported during procedure and postoperative course. The patient was discharged after day 3. Histology confirmed an endometrial stromal sarcoma.

DISCUSSION

Uterine inversion is an uncommon condition characterized by the invagination of the uterine fundus through the uterine cavity, reaching the cervix or beyond the cervix. Uterine inversion can be puerperal or non-puerperal. The puerperal type is a life-threatening emergency that occurs in the third stage of labour; it has a 15% mortality rate due to bleeding and shock[3]. The non-puerperal type is typically associated with a mass in the vagina. The prominent symptoms are vaginal discharge, irregular uterine bleeding and pelvic discomfort[4].

Non-puerperal uterine inversion represents a very rare event with no reliable estimate of frequency in the literature, and may be idiopathic or occur in association with a tumor, almost always with polypoid uterine tumors. Of these, approximately 85% are benign leiomyomas[5], while the remaining are mostly uterine leiomyosarcomas. Signs and symptoms of uterine sarcoma typically include abnormal uterine bleeding, pelvic pain/pressure, and/or a uterine mass, although some women are asymptomatic. In rare cases, the sarcoma prolapses through the cervix. Some studies have reported bleeding accompanied by a foul smelling vaginal discharge as part of the clinical presentation[6]. Constipation has also been reported, likely due to pelvic pressure.

To date, 33 cases of uterine inversion due to sarcoma have been reported with only three cases of endometrial stromal sarcoma, including our case since 1887[7]. Sarcoma-associated uterine inversion may be related to the softening of the uterine wall, due to tumor enlargement into the uterine cavity[8]. Nulliparity and menopause may also play a role in the reduction of the thickness of the uterine wall[9].

A preoperative diagnosis of inversion is not always possible, and even if the clinical suspicion is high, definitive diagnosis would be known at the time of

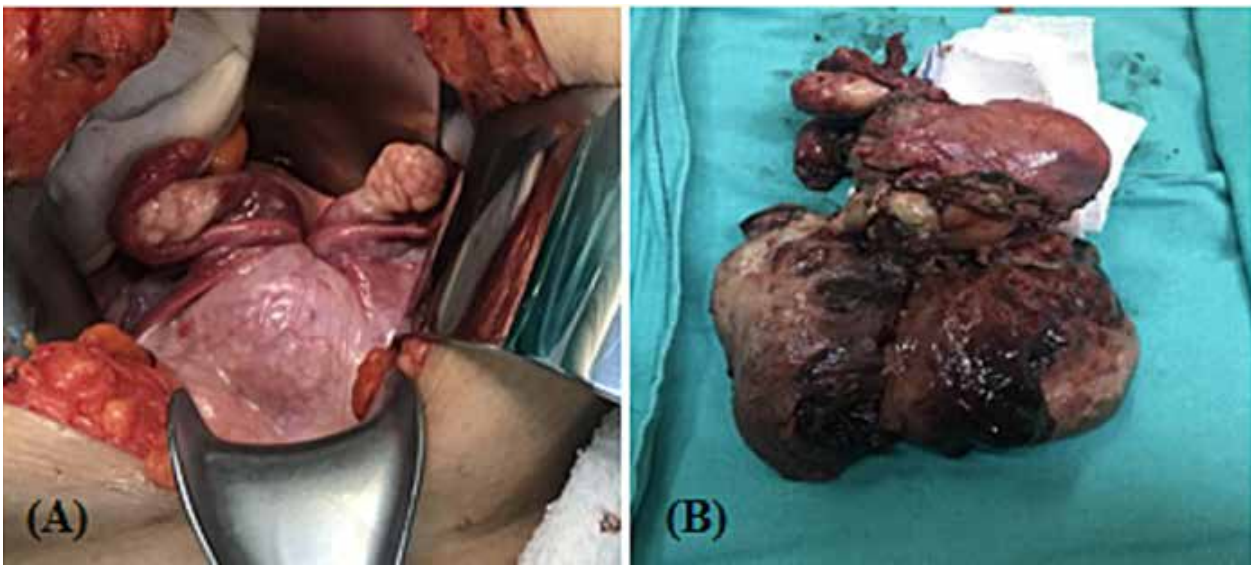

Fig 2: (A) Both tubes and ovaries were completely draw in through the fundus. (B) The uterus maintained its appearance postoperatively and a large endometrial stromal sarcoma is identified.

the surgery. The gold standard practice for diagnosing the disease is ultrasound and magnetic resonance imaging. During a magnetic resonance imaging scan, the physician looks for a U-shaped uterine cavity with a thickened, inverted uterine fundus on a sagittal image. Such a signature is considered to be a sign of uterine inversion. However, in emergency cases, the diagnosis is clinical.

This condition is treated surgically. In younger patients, fertility sparing surgery is the optimal treatment, after removing the cause for the uterine inversion (myoma, polyp) and reducing the inversion, under antibiotics cover. However, according to most reported cases, hysterectomy is routinely performed. Vaginal, abdominal or combined vaginal-abdominal laparoscopy approaches are valid options, depending on the patient conditions and surgeon skills. Several surgical techniques have been described for reduction of uterine inversion: Huntington and Hultain procedures are common abdominal approaches and Spinelli and Kustner procedures are vaginal approaches[10].

The reposition of the uterus and correcting the anatomy is vital before proceeding to hysterectomy. It would not be possible to separate and push down the bladder or clamp the uterine vessels for hysterectomy before repositing the uterus to its proper position. Reposition is difficult in view of the bulky malignancy invading the uterus. Patients with suspected endometrial stromal sarcoma confined to the uterus should undergo staging surgery, including a total extrafascial hysterectomy with or without bilateral salpingo-oophorectomy. Whether systematic lymphadenectomy is needed is unclear.

CONCLUSION

Uterine inversion rarely occurs outside the puerperal period; however, when it does occur, the possibility of an underlying malignancy should not be neglected.

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Case Report

Meningococcemia and COVID-19 co-infection in a child: a case report

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ABSTRACT

Introduction: COVID-19 could be accompanied by gram-positive, negative bacteria or other viruses. Additionally, COVID-19 and meningococcemia co-infection have not been reported in a child by this time.
Case report: We report a new COVID-19 co-infection due to Neisseria meningitidis occurring in a 5-month-old girl. She had a fever, rashes and hypotension. She was admitted to the pediatric intensive care unit. SARS-CoV-2 real-time polymerase chain reaction on nasopharyngeal swab was positive and Neisseria meningitidis type B was isolated in cerebrospinal fluid on admission.
Conclusion: We aimed to contribute to the literature by reporting that meningococcemia infection can be accompanied by COVID-19 infection.

KEY WORDS: child, COVID-19, meningococcemia

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a viral respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which significantly affects global healthcare and social systems. COVID-19-positive patients may have a higher risk of secondary viral, bacterial or fungal infections, which usually leads to a worse prognosis[1-2]. Neisseria meningitidis is a gram-negative coccus that can manifest as life-threatening meningitis and/or septicemia (meningococcemia)[3-4]. We aimed to describe meningococcemia coinfection in a pediatric patient with COVID-19. To our knowledge, this is the first pediatric case of meningococcemia in the context of COVID-19 co-infection.

CASE REPORT

A 5-month-old previously healthy girl presented with a two-day fever. She was admitted to the pediatric ward to investigate a fever of unknown origin. Her immunization status was appropriate according to the patient's age. She was fed breastmilk. She had no family history of immunodeficiency disorder. She was administered cefotaxime, ampicillin and paracetamol on admission. Laboratory findings revealed elevated levels of inflammatory markers (Table 1). In the first 24 hours, her fever was >38°C, unresponsive to paracetamol, a mild purpuric rash was evident on her trunk and thighs, and her blood pressure was 68/32 mmHg. She was admitted to the pediatric intensive care unit with a presumptive diagnosis of meningococcaemia.

On PICU admission, her fever was 38.3 °C, heart rate was 208 beats/min, blood pressure was 34/72 mmHg, respiratory rate was 40 breaths/min and oxygen saturation was 88% on room air. She had sleepiness, hypotonia and a bulging anterior fontanelle. Both pupils were reactive to light. She had petechial and purpuric rashes localized to her trunk and lower extremities (Figure 1). Other physical examination findings did not show any pathological signs. A diagnostic lumbar puncture was performed. Cerebrospinal fluid (CSF) analysis showed 540 neutrophils/mm, a protein level of 43 mg/dl and a

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Table 1: Changes in biochemical and hematologic findings of the patient

Variables	Inpatient clinic	PICU admission	24th hour	48th hour	72nd hour
WBC count, $\times 10^3/\mu L$	19.11	23.42	8.66	7.86	6.19
Neutrophil, $\times 10^3/\mu L$	13.20	12.98	5.50	4.27	2.87
Lymphocyte, $\times 10^3/\mu L$	3.82	8.05	2.69	3.08	2.44
Hemoglobin, g/dl	9.6	8.4	8.1	8.5	8.8
Platelets, $\times 10^3/\mu L$	159	168	139	219	320
Glucose, mg/dl	133	111	-	-	113
Urea, mg/dl	23	11.1	-	-	19.5
Creatinine, mg/dl	0.21	0.24	-	-	0.33
Total bilirubin, mg/dl	0.84	0.4	-	-	0.23
AST, U/L	30	22	-	-	19.6
ALT, U/L	16	9.6	-	-	11
Uric acid, mg/dl	5.6	3.63	-	-	3.12
CK, U/L	84	38	-	-	-
LDH, U/L	224	250	-	-	-
Sodium, mmol/L	134	135	-	-	139
Potassium, mmol/L	4.3	4.9	-	-	4.87
Total protein, g/dl	5.28	4.74	-	-	54.7
Albumin, g/dl	3.94	3.68	-	-	41
CRP, mg/L		159	120	44	12
Pro-calcitonin, ng/mL	20.5	19.3	18.5	11.4	3.94
PT, s	18.2	17.6	14.7	-	11.7
PT INR	1.4	1.35	1.09	-	0.88
aPTT, s	35.9	30	26.8	-	25.6
D-dimer, µg/mL (FEU)	0.74	2.21	0.53	-	0.35
Fibrinogen, mg/dl	476	536	560	-	388
Ferritin, µg/L	-	73	-	97	80

PICU: pediatric intensive care unit; ALT: alanine aminotransferase; AST: aspartate aminotransferase; aPTT: activated partial thromboplastin time; CK: creatine kinase; CRP: C-reactive protein; FEU: fibrinogen equivalent units; INR: international normalized ratio; LDH: lactate dehydrogenase; PT: prothrombin time; WBC: white blood cell.

glucose level of 88 mg/dl when the serum glucose level was 114 mg/dl. SARS-CoV-2 real-time polymerase chain reaction (PCR) of a nasopharyngeal swab was positive upon admission. Two weeks previously, the patient's family tested positive for COVID-19. The SARS-CoV-2 antibody level was 237 U/ml in the serum and 1.39 U/ml in the CSF, both were positive. The immunoglobulin G (IgG) was 1.95 g/L, IgM was 0.48 g/L and IgA was 0.05 g/L. The patient was treated with cefotaxime, vancomycin and dexamethasone. The CSF culture was sterile. The meningitis/encephalitis panel revealed the presence of Neisseria meningitidis DNA in the CSF sample by PCR. Our patient had COVID-19 and meningococcemia; therefore, antibody levels were checked to rule out any underlying immunodeficiency concerns. The patient didn't need intubation and inotropes. Fluid resuscitation therapy and meticulous vital sign monitoring had been performed. On PICU day 2, her body temperature was within the normal range and her rashes became paler. On PICU day 3,

Figure 1: At admission, the patient presented with purpuric lesions.

the patient was transferred to the pediatric ward. The patient was discharged 10 days later.

DISCUSSION

We present the case of a 5-month-old girl who developed meningococcemia coinfection with COVID-19. Coinfections and superinfections have been reported to be associated with COVID-19. Garcia-Vidal *et al*[5] described the epidemiology and outcome of co-infections and superinfections accompanying hospitalized patients with COVID-19. In this study, co-infection with COVID-19 was rare and mostly associated with bacterial infections in hospitalized patients[5]. The most commonly isolated bacteria were S. pneumoniae and S. aureus. Although superinfections are rare, they have poor outcomes. The most frequently isolated bacteria are *Pseudomonas aeruginosa* and *Escherichia coli*[2,5]. Bacterial and viral coinfection seems to have a devastating effect on the risk of mortality and critical illness of COVID-19[2]. Our patient received antibiotic therapy at PICU admission, and we isolated the Neisseria meningitidis type B in the CSF. Clinical findings of meningococcemia include fever, generalized malaise, weakness, cold extremities and skin pallor, leukocytosis or leukopenia, rash, headache and/or drowsiness, and hypotension[4]. Our patient had a fever, rash, hypotension, cold extremities and drowsiness. The literature also shows a 22-year-old patient, with a meningococcal infection along with COVID-19 coinfection[6].

CONCLUSION

In conclusion, this case is the first meningococcemia with COVID-19 coinfection in children. This case revealed that meningococcemia as a coinfection could occur in COVID-19-infected children who have no comorbidities. It also showed that children's immunity could defeat both illnesses, resulting in a speedy and complete recovery. Further study is needed to understand the phenomena of bacterial co-infection with COVID-19.

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Case Report

Rare case of situs inversus totalis associated with sepsis

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ABSTRACT

Situs inversus totalis (SIT) is a rare autosomal recessive genetic disease in which the major visceral organs of the thoracic and abdominal cavities are inverted like a mirror image. We present a rare case of a patient with SIT and sepsis.

A 55-year-old man was hospitalized because of suffocation, wheezing, coughing, fever and general weakness. He was normotensive, tachycardic, tachy-dyspnoeic and acyanotic. Auscultatory weakened respiratory sound, prolonged exhaling, diffuse polyphonic whistling. He had congenital dextrocardia and ventricular septal defect. Electrocardiogram, lung X-ray, echocardiogram of the heart and abdomen, multislice computed tomography chest were undertaken in accordance with the diagnosis of SIT. Positive quick sequential organ failure assessment criteria for sepsis on admission, positive Systemic Inflammatory Response Syndrome criteria during hospitalization, and laboratory results of slightly elevated inflammatory markers caused by isolated *Staphylococcus epidermidis* confirmed the diagnosis of sepsis.

Early suspicion of the association of SIT and infective endocarditis or sepsis with urgent targeted diagnostic and laboratory analyzes is of paramount importance, as well as the application of adequate therapeutic measures in the first hours afterwards, in order to increase the chance of a positive treatment outcome.

KEY WORDS: sepsis, situs inversus totalis, Staphylococcus epidermidis

INTRODUCTION

Situs inversus totalis (SIT) is an autosomal recessive genetic disease in which the major visceral organs of the thoracic and abdominal cavities are inverted like a mirror image. It is a rare anomaly with an incidence rate of 1 / 10,000 live births[1].

As far back as 1789, a complete reversal of the position of the organs was described. Since then, numerous cases of SIT have been reported, but without an explained cause until 1995, when immobility of cilia was observed[2] in patients diagnosed with Kartagener's syndrome. Kartagener's syndrome is a clinical manifestation of primary ciliary which includes chronic sinusitis, bronchiectasis and SIT[3].

In recent years, there has been a noticeable increase in the number of published papers in which SIT is associated with certain diseases such as: congenital heart defects[4], Klippel-Feil syndrome[5], transplantation of the liver[6] and lung cancer[7]. This genetic anomaly is most often diagnosed as an accidental finding[8] on an X-ray or computed tomography (CT) scan of the chest or abdomen.

Here we report as a rarity a patient with SIT and sepsis caused by *Staphylococcus epidermidis*.

CASE REPORT

A 55-year-old man was hospitalized due to suffocation, wheezing, cough, fever up to 38.5 °C and general weakness for several days. On admission, he was conscious, of average build, oriented, normotensive (120/100 mmHg), tachycardic (100/min), tachy-dyspneic (26/min), acyanotic, with normal skin color without peripheral lymphadenopathy and hemorrhagic syndrome. Auscultatory on the lungs weakened respiratory sound, prolonged exhaling, polyphonic diffused whizzing. The heart is auscultated on the right side of the chest. Rhythmic heartbeat, clear tones, rough systolic murmur 6/6 over the entire precordium. No organomegaly and peripheral oedema.

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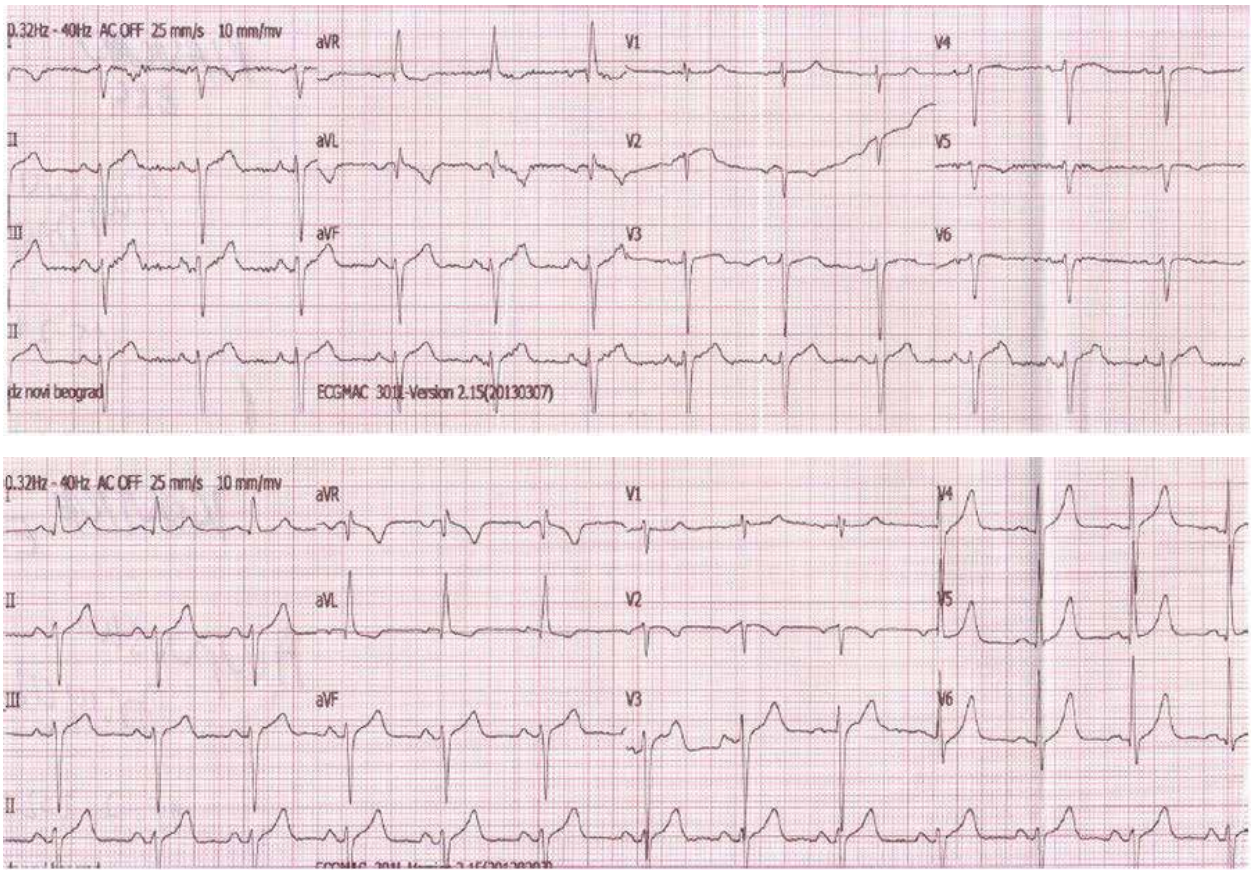

Figure 1: 12-lead ECG finding in standard (A) and right-sided chest leads (B). **A**: Sinus rhythm 76/min, right axis deviation, negative QRS complex and inverted P and T waves in lead I, rS in D3, aVF, V2, VR, increase ST in D2, D3, aVF, V4 - V6, biphasic T waves in aVL; **B**: Marked right axis deviation, global negativity in lead I and global positivity in aVR, absent R wave progression in precordial leads.

Anamnestic: married, has children, denies drug allergy, smoker (20 years, ≥20 cigarettes / day), is being treated for asthma and deep vein thrombosis and hospitalized several times. He knows about congenital dextrocardia and ventricular septal defect (VSD). He was not operated on VSD. He denies a family linked predisposition to the disease. Under oral therapy with verapamil, theophylline, fixed combination long-acting beta antagonists with inhaled corticosteroids, long-acting muscarinic antagonists, long-acting beta2 agonist and anticoagulant drugs. Negative epidemiological survey for H1N1 and COVID-19 virus infection.

An electrocardiogram (ECG) diagnosis of dextrocardia was made. Figure 1 demonstrated 12-lead ECG finding in standard and right-sided chest leads. Chest X-ray showed dextrocardia and a right-sided "stomach bubble" (Fig 2).

Cardiac echo revealed dextrocardia, situs inversus. Left atrium 39 mm, EF 60%, without regional asynergy, diastole neat, aorta at root 25mm, in ascending part 31 mm, left ventricle 54 mm without contractility disorders, normal global systolic functions, interventricular septum defect 6 mm in diameter with left-to-right (L-D) shunt, through which Vmax is registered up to 4.7m / sec with a max gradient of 88 mmHg corresponding to VSD. There was no pericardial effusion. Aorta had normal dimensions and appearance with a three-leafed aortic valve, subvalvularly smaller ridge starting from the muscular septum with turbulent flow in the left ventricular outflow tract obstruction, without significant gradients. Right ventricular systolic pressure was about 40 mm; right ventricle had normal dimensions and function.

Echo abdomen: liver in the left, spleen in the right hemiabdomen without pathological changes. Gallbladder, bile ducts, abdominal aorta, pancreas and kidneys b.o.

Multislice computed tomography chest (MSCT) thorax examination (Fig 3): situs inversus viscerum; diffuse confluent centrilobular emphysema; in the right upper pulmonary lobe posterior segment, cavities of thin walls up to 2 mm, diameter 7 x 6 mm and 13 x 10 mm are present.

In laboratory analysis, slightly elevated markers of the acute phase of inflammation, negative markers of systemic inflammation, a normal hemogram and thrombocythemia (Table 1).

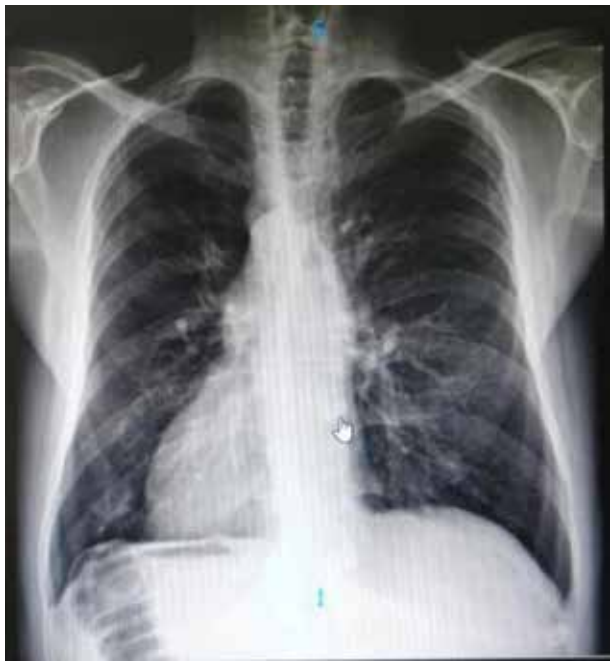

Figure 2: Chest X-ray showed dextrocardia and a right-sided "stomach bubble"; in the lungs bilaterally, chronic deforming changes in the central lung area on the right in exacerbation, costophrenic sinuses free.

Urine culture and sputum culture are sterile (acid-alcohol-resistant bacilli and Candida species were negative). Blood culture was done once (two days after admission) and was positive for *Staphylococcus epidermidis*.

Pulmonary function tests: gas analysis without pulmonary dysfunction (pH: 7.44; PO_2: 111 mmHg; PCO_2: 40 mmHg; SO_2: 99%; HCO_3: 27.2 mmol/l), spirogram: mixed ventilation disturbances of predominantly obstructive type, reduced forced expiratory flows at lower lung volumes (FVC: 45%; FEV1: 24% / 0.76L / min; FEV1 / FVC: 42%; MMEF: 25/75 10%, FEV: 30%).

During the nine-day hospitalization, he was treated with bronchodilators, infusion solutions, antibiotics according to the antibiogram (ceftriaxone and ciprofloxacin i.v.) with probiotics, calcium antagonists, antioxidants with oral anticoagulant therapy, oxygen therapy and other symptomatic therapy.

On prescribing antibiotic therapy, the clinical picture improved and the inflammatory factor decreased. The patient was released for home treatment due to the stabilization of his health condition and the newly emerging epidemiological situation. The patient was monitored on an outpatient basis. Since then, the patient is well. There was no recurrence.

Written informed consent was obtained from the patient for publication. All procedures described in this paper were in accordance with the institutional ethical standards and with the 1964 Helsinki declaration.

DISCUSSION

Dextrocardia with situs inversus (SIT)[9] is a very rare congenital defect characterized by reversal of the position of the heart to the right side of the

Table 1: Laboratory analysis

Analysis	Value	Reference value	Analysis	Value	Reference value
ESR	52	2-12 mm/h	Glucose	7.0	3.5-6.1 mmol/l
CRP	29.8	<10 mg/l	Direct bilirubin	0.9	< 5 μmol/L
Fibrinogen	3.4	2-4 g/l	Total bilirubin	5.0	2-21 μmol/l
LDH	459	<241 U/l	Total protein	65.0	64-83 g/L
WBC	16	3.9-10x109/l	Albumin	36.0	41–51 g/L
Neutrophils	87	40-70%	Tryglicerides	1.9	0.46-2.28 mmol/l
RDW	4.55	4.34-5.72x1012/l	Cholesterol	3.03	3.1-5.5 mmol/l
Iron	10.3	8.9-30 μmol/l	Urea	5.2	2.8-7.2 mmol/l
Hemoglobin	137	110-180 g/l	Creatinine	58	53-124 μmol/l
Hematocrit	42.2	0.41-0.53 l/l	AST	27	7-38 IJ/l
MCV	91.6	81-89 fl	ALT	34	8-41 IJ/l
MCH	29.8	29-32.9 pg	GGT	22	8-40 IJ/l
MCHC	325	310 - 350 g/l	Sodium	141	135-145 mmol/l
Platelets	731	140-450 x 109/l	Potassium	45	3.5-5.1 mmol/l
PT	19.6	2-4,5 INR	Chloride	99	98 - 106 mmol/L
APTT	30.6	25-42 s	Calcium	2.19	1.18-1.29 mmol/L
d-DIMER	176	cut-off<160 μg/l			
INR	4.3	2-4			
Procalcitonin	1.8	<0.5 i >2.0 ng/ml			
Presepsin	141	< 200 pg/mL Exclude sepsis			

ALT: alanine transaminase; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; CRP: C reactive protein; ESR: erythrocyte sedimentation rate; GGT: gamma-glutamyl transferase; INR: international normalized ratio; LDH: lactate dehydrogenase; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; PT: prothrombin time; WBC: white blood cells; RDW: red blood cell distribution width

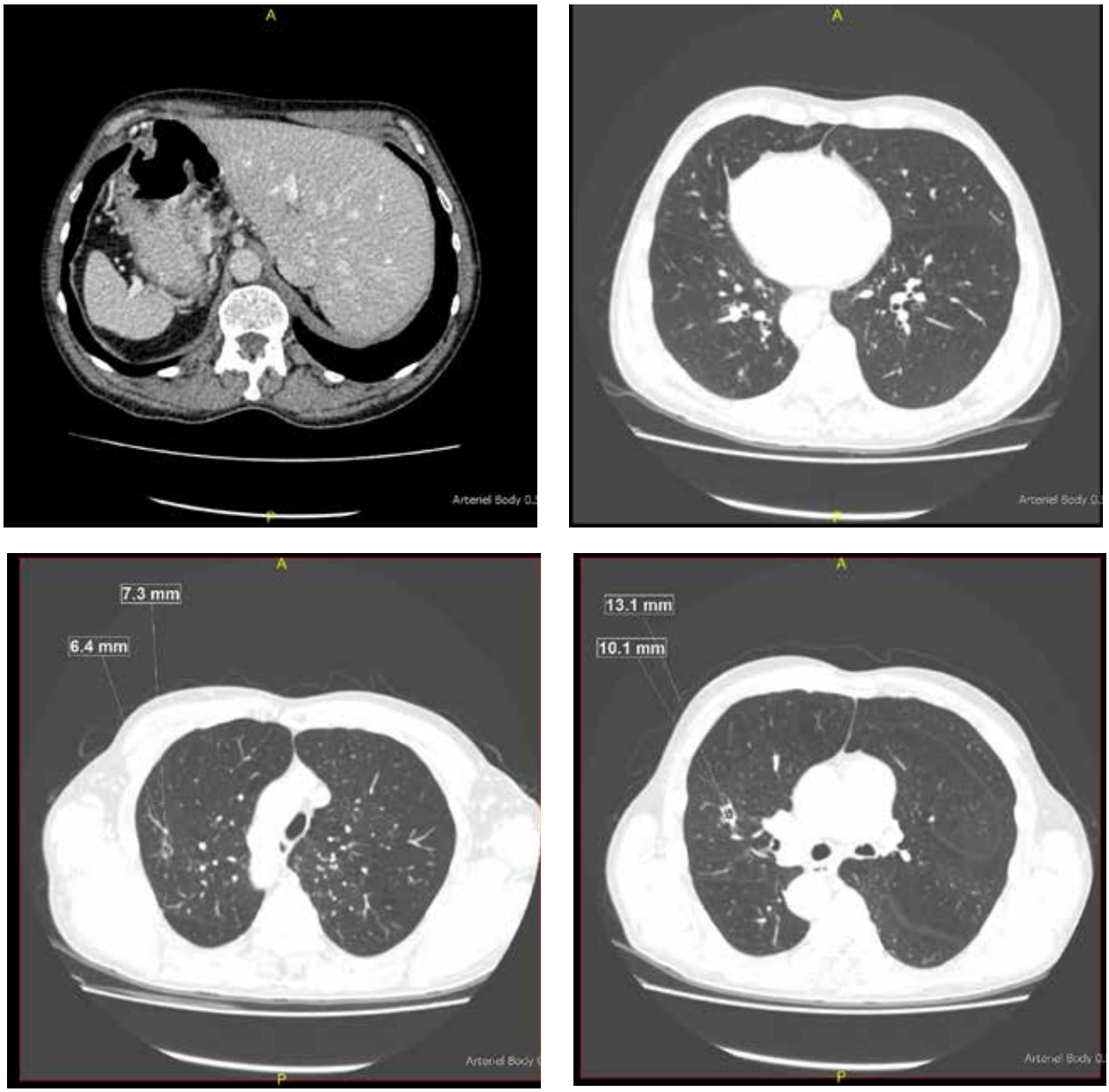

Figure 3: MSCT thorax examination showed: situs inversus viscerum (**a**); diffuse confluent centrilobular emphysema (**b**); in the right upper pulmonary lobe posterior segment, cavities of thin walls up to 2 mm, 7 x 6 mm (**c**) and 13 x 10 mm (**d**) are present. Trachea and large bronchi of normal diameter without signs of obstruction and external compression. There is no free fluid in the pleural spaces. Enlarged lymph nodes present in group VII up to 13 mm. Significantly enlarged lymph nodes in the axillary region are not observed. Thoracic aorta and pulmonary arteries are of normal diameter. A low-density hypovascular lesion 7 mm in diameter is present subcapsularly in the liver (resembling a cyst).

thoracic cavity along with all inversely rotated visceral organs (mirror image). The physical finding in patients with dextrocardia is the presence of right-sided heart sounds on auscultation, with the maximum cardiac impulse located on the right side of the chest[10]. Electrocardiogram can raise suspicion on dextrocardia and can also show inversion of the electrical waves. Chest radiography can aid in confirming the diagnosis of SIT, in which case the cardiac apex and aortic arch will be located in the right side of the chest, with the gastric air bubble located in the right upper abdomen[9]. CT remains the best imaging procedure for the definitive diagnosis of SIT as CT scan provides an excellent anatomic detail. In addition to SIT and VSD, centrilobular emphysema and lung abscess of the right upper lung lobe were detected in our patient with MSCT findings.

Infectious endocarditis (IE) was first suspected during the examination. However, although the

diagnosis of IE according to the modified Duke criteria[11] initially seemed possible, due to the existence of only two minor criteria (predisposition - VSD and temperature> 38 °C) it was not set. For the definitive diagnosis of IE, either one minor criterion was missing (eg: rheumatism factor, which is not performed in this hospital) or at least one major criterion. Our patient had one incomplete major criterion, i.e., only one positive blood culture was performed and obtained. The explanation is that the patient was already given antibiotics according to the antibiogram after the first positive blood culture, after which there was a rapid improvement in the clinical condition.

The three major echocardiographic findings as defined by the modified Duke criteria[11] suggesting direct evidence of endocardial involvement are vegetation, abscess and new partial dehiscence of a prosthetic valve. Ultrasound of the heart was done due to predisposition. The window was excellent and the finding was neat, except for the already mentioned congenital malformations. In our patient, echocardiography findings and microbiological data excluded endocarditis and tuberculosis.

The association of SIT with sepsis has been proven by a comprehensive diagnosis (positive blood cultures, high inflammatory factors and manifested clinical picture).

Sepsis is not a disease but a clinical syndrome. Year 2018 guidelines provide a new definition for sepsis: a life-threatening organ dysfunction caused by a dysregulated host response to infection[12]. This guideline includes quick sequential organ failure assessment (quick SOFA) to aid in diagnosis. Although the Systemic Inflammatory Response Syndrome (SIRS) criteria are no longer endorsed in the guidelines, they still have a role in the identification of acute infection. Our patient had two (number of respirations ≥ 22/min and systolic pressure ≤100 mmHg) of three signs of the qSOFA criteria on emergency admission and was positive for all SIRS criteria during hospitalization (temperature >38 °C, heart rate >90 /min, and leukocyte count >12,000/mm^3)[13]. Markers of the acute phase of inflammation and negative markers of systemic inflammation were in both cases slightly elevated in the laboratory findings of our patient, and *Staphylococcus epidermidis* was isolated by blood culture as a cause of the sepsis.

Biomarkers that are most widely used for diagnosing sepsis are C-reactive protein (CRP) and procalcitonin[14]. Another biomarker, frequently used over the last decade, is the soluble CD14 subtype (sCD14-ST), known as presepsin[15]. Only one of these biomarkers (CRP) was elevated in our patient. After successful initial resuscitation (infusion solution therapy), according to new recommendations[16], a selection of broad-spectrum antibiotics according to the antibiogram was performed, which act on blood culture-isolated *Staphylococcus epidermidis* as a cause of sepsis.

The patient was released for home treatment due to the stabilization of his health condition and the newly emerging epidemiological situation. The patient was monitored on an outpatient basis. Since then, the patient is well. There was no recurrence.

CONCLUSION

In conclusion, for clinicians, early suspicion of the association of SIT and IE or sepsis with urgent targeted diagnostic and laboratory analyzes is of paramount importance, as well as the application of adequate therapeutic measures in the first hours afterwards, in order to increase the chance of a positive treatment outcome.

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Author contributions: Tatjana Mladenovic: design of the work and performed the medical report analysis with interpretation results; Sladjana Andjelic: drafting the work and approved the final version; Goran Colakovic: preparation of the first draft and revisions of the manuscript**.** All authors critically reviewed the manuscript and approved the final version of the manuscript.

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Informed consent: Written patient consent was obtained from the patient for being included in the study and use of medical data and clinical pictures.

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Case Report

Coexistence of patellar tendon avulsion and a tibial tubercle fracture in an adolescent male weightlifter

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ABSTRACT

Isolated patellar tendon avulsion fractures are prevalent among athletic adolescents. Patellar tendon avulsion with tibial tubercle fracture occurs when the extensor mechanism of the knee is subjected to trauma in two different directions simultaneously. Physical examination and routine imaging can be used to diagnose a tibial tubercle fracture. However, in cases wherein a tibial tubercle fracture coexists with patellar tendon avulsion, further care and additional radiological examination is required to prevent diagnosis failure. Although different surgical treatment techniques have been described, open reduction and internal fixation is thought to be an appropriate treatment option for this clinical condition.

KEY WORDS: avulsion, fractures, patellar tendon, rupture, surgery

INTRODUCTION

Tibial tubercle fractures constitute less than 1% of all pediatric physical injuries and less than 3% of all proximal tibial fractures[1]. The proximal tibia has two centers of ossification, i.e., the proximal tibial physis and the tibial tubercle. Physical closure occurs from the posterior aspect towards the anterior aspect and from the proximal aspect towards the distal aspect. The tibial tubercle is the last site of closure[2]. Tibial tubercle fractures generally occur as a result of eccentric contraction of the quadriceps muscle when the knee is flexed or concentric contraction of the quadriceps during jumping when the knee is in full extension[3]. Coexistence of patellar tendon avulsion with a tibial tubercle fracture is a rare condition encountered by surgeons, and there are limited publications regarding it in the relevant literature in the form of sporadic case reports. In this case report, avulsion fracture of the tibial tubercle of an adolescent male weightlifter was presented.

CASE REPORT

A 14-year-old male patient actively engaged in weightlifting fell down with a feeling of rupture and pain in the knee during training. Thereafter, the patient could not bear weight on that knee and presented to the emergency department with pain and swelling in the front of his knee.

Physical examination indicated an intense effusion in the knee joint and pain on palpation of the tibial tubercle and patellar tendon attachment site. The patient was unable to perform active knee extension. The patient received negative results for Lachman, anterior drawer, and varus and valgus stress tests, which was performed under analgesic sedation in the emergency department. During radiological examination, a comminuted avulsion fracture of the tibial tubercle was observed on X-ray (Figure 1a) and computed tomography images (Figure 1b).

Under regional anesthesia, an incision of approximately 5 cm was made beginning from the inferior pole of the patella towards the tibial tubercle. Upon careful dissection of the soft tissue, the fracture line was exposed and irrigated by saline solution. The patellar tendon was found to be avulsed from the enthesis (Figure 2 a,b). At this stage, open reduction was performed and the diagnosis of Ogden type 3b fracture was confirmed using a C-arm. After the open reduction procedure, the fracture was fixed using two cannulated compression headless screws. Upon

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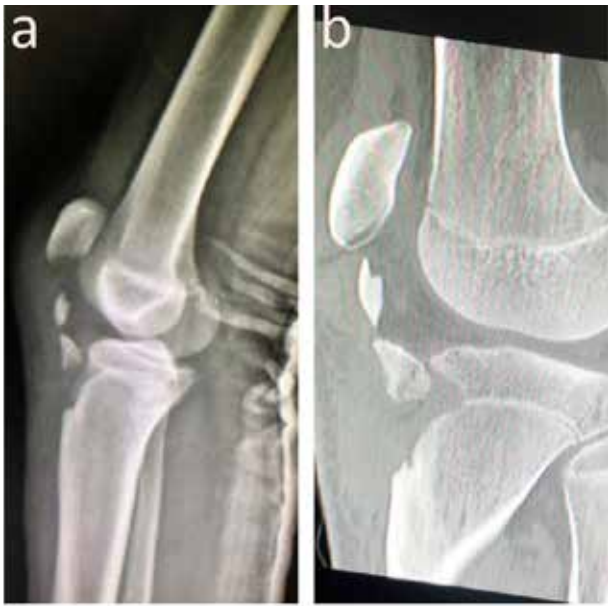

Figure 1a-b: Bone avulsion of the tibial tubercle.

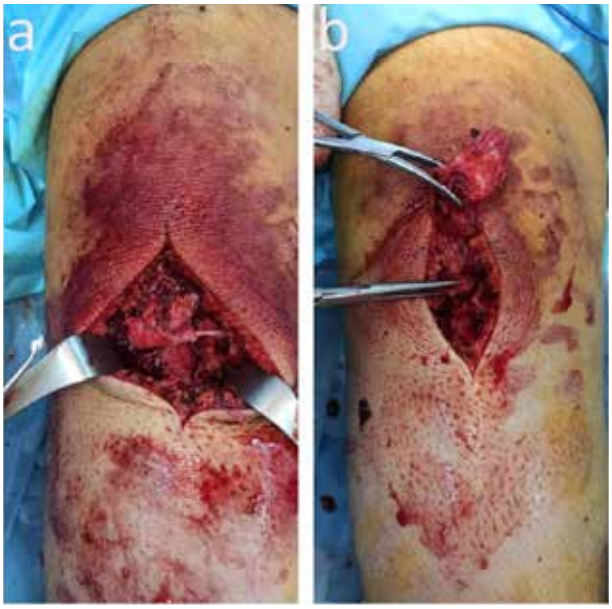

Figure 2a-b: Intraoperative view of the patellar tendon avulsion from the enthesis.

confirmation of the absence of displacement and step-offs using C-arm, the patellar tendon was fixed to the original enthesis region using No. 2 Ethibond Excel® Polyester Suture via the transosseous technique. Long leg splinting was performed postoperatively with the knee in extension. Passive rehabilitation of the knee joint was initiated after retaining the splint for 4 weeks. At postoperative week 12, complete recovery of the fracture line was confirmed on X-ray and computed tomography (Figure 3 a-d) and full range of motion of the knee joint was achieved clinically (Figure 4).

DISCUSSION

Although tibial tubercle fractures are rare, its incidence has started to increase in the last two decades due to the increasing number of children professionally engaged in sports. However, the occurrence of patellar tendon avulsion with tibial tubercle fracture is still rare[4]. It is the most prevalent in individuals aged between 13 and 17, when the proximal tibial physis starts to close[5].

Patients usually present with pain in the knee as well as failure to bear weight on and move the knee as a result of a sudden movement. They have sensitivity in the tibial tubercle and tibial plateau[6]. It is seen that 85% of tibial tubercle avulsion fractures occur during athletic activities[7]. Most of the injuries are seen in children who are engaged in sports activities, including basketball, skateboarding, hurdling and soccer[8]. There are publications suggesting that this type of injury might also be encountered in children engaged in wrestling[9]. This is the first case report describing this type of injury among weightlifters in the literature.

During physical examination, it should be considered whether the patient is able to perform active extension. Additionally, a detailed neurological examination of the lower extremity should be performed. Anteroposterior and lateral X-rays of the

Figure 3a-d: Twelve months after the operation, the X-ray and CT revealed complete bone union.

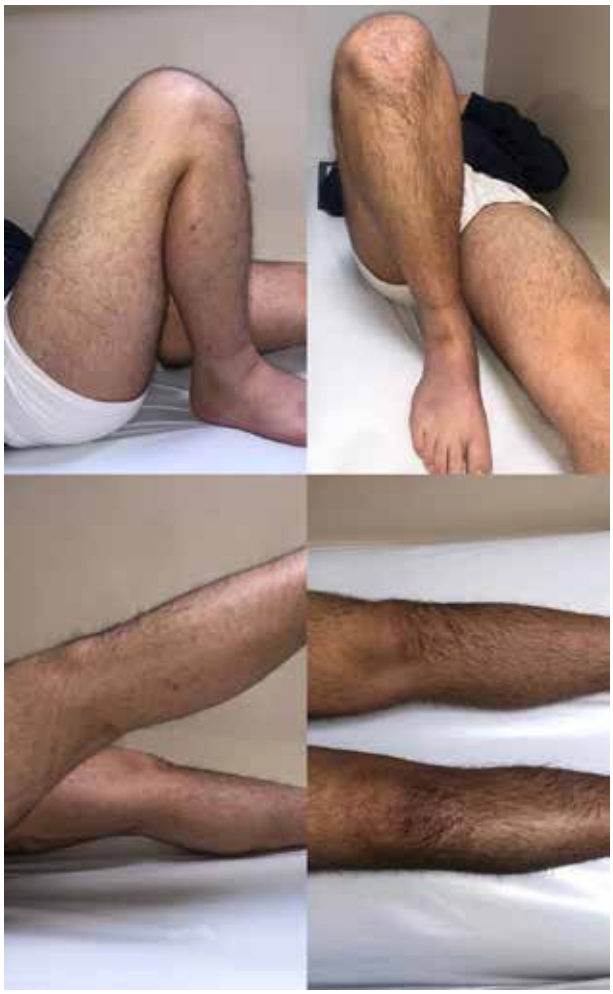

Figure 4: Twelve weeks after the surgery the patient achieved full range of motion of the injured knee without any pain or flexion or extension lag.

knee should be obtained. Computed tomography is recommended to gain a better understanding of the fracture preoperatively and identify the presence of any intraarticular fractures[6]. Additional meniscal and cruciate ligament injuries may also coexist with these types of injuries. Therefore, pathologies other than fractures in the knee should be identified using magnetic resonance imaging during the early postoperative period[10].

These fractures are classified using the Ogden classification. Classification is based on the amount of displacement and comminution[11]. In cases of a displacement of <2 mm upon closed reduction, a 6-week splint treatment is recommended[5]. In a previous study, conservative treatment was recommended for Ogden type 1 and 2a fractures in which the extensor mechanism was preserved[12]. However, open reduction is required in patients with patellar tendon avulsion as seen in this report, wherein a detailed evaluation is a must during preoperative planning.

Frankel *et al* showed that an increased distance between the distal patellar pole and avulsed tibial tubercle due to knee flexion might be suggestive of patellar tendon avulsion[13].

Open reduction with an incision over the fracture line and fixation is recommended as the surgical approach[14]. Staples, tension band and transosseous techniques are used for patellar tendon repair[8]. A long leg splint is used while the knee is maintained in extension for 4-6 weeks postoperatively, followed by rehabilitation after 6 weeks wherein patients can ultimately return to their usual sports activities with quadriceps strengthening and joint range of motion exercises[15].

The most common complication in the early postoperative period is anterior knee pain associated with bursitis. Refractures, limited range of motion, growth defects due to epiphyseal irritation and transient epiphyseal arrest may be seen in a minority of cases[14]. Therefore, these patients should be followed up at regular intervals until the completion of their growth.

CONCLUSION

This report described a case of patellar tendon avulsion coexisting with a tibial tubercle avulsion fracture and its treatment in a semi-professional weightlifter, which has not been previously reported in the literature. Although rare, patellar tendon avulsion coexisting with a tibial tubercle avulsion fracture is still encountered. Therefore, it is important to identify the presence of patellar tendon avulsion using imaging methods and the support of appropriate and adequate clinical examination. Particularly, superior displacement of the patella on X-rays and an increased distance between the distal patellar pole and tibial tubercle during knee flexion upon clinical examination should raise the suspicion of patellar tendon avulsion. The presence of patellar tendon avulsion is a definite surgical indication. With this report, we showed that it is possible to achieve successful outcomes using open reduction and internal fixation. Another condition to consider in these cases is compartment syndrome in the early postoperative period. For early intervention and surgery, it is necessary to be aware of this complication and conduct long-term follow-ups.

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Informed consent: The authors certify that they have obtained all appropriate patient consent forms. The patients and/or their families were informed that data from the case would be submitted for publication and gave their consent. The patient understands that his name and initials will not be published and due efforts will be made to conceal their identity; however, anonymity cannot be guaranteed.

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2025; 57 (3): 198 - 199

The Outcome of Non-surgical Root Canal Treatment using Sealer-based Obturation versus Warm Vertical Compaction: A Randomized Controlled Trial

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INTRODUCTION
Calcium silicate sealer (CSS) based obturation (SBO) has gained wide popularity for its relative simplicity and material biocompatibility. Limited information exists how its treatment outcome compares to warm-vertical compaction (WVC). The primary aim of this randomized controlled clinical trial was to compare the outcome of non-surgical root canal treatment (NSRCT) using SBO with CSS versus WVC with a resin-based sealer (RBS). The secondary aim was to assess differences in the obturation time between SBO and WVC.

METHODS
A total of 195 participants with 212 teeth took part in this study and randomly allocated to either SBO or WVC after completion of the bio-mechanical instrumentation. The time required to complete the obturation was recorded. Participants were followed-up after a minimum of 12 months for clinical and radiographic assessment using periapical radiographs with the periapical index (PAI) and CBCT scans using the CBCT-PAI. Statistical evaluation involved descriptive analysis and binary logistic regression.

RESULTS
181 teeth in 167 participants were followed-up (85.4%) after 12-22 months (mean 12.9 months). Using strict criteria, success rates were 76.6% for SBO and 80.5% for WVC based on PAI, and 71.3% for SBO and 65.5% for WVC using CBCT-PAI. The overall success was 78.5% assessed using PA radiographs and 68.5% using CBCT with no significant differences in outcomes. SBO required significantly less time (85.4±44.0s) to complete the root filling compared to WVC (159.7±71.0s)($p<0.001$).

CONCLUSIONS
Given comparable clinical outcomes to WVC yet demonstrating faster obturation time, SBO with CSS may be a suitable clinical alternative.

Empowering Residents Through the Kuwait Family Medicine Review Course

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Empowerment plays a crucial role in advancing innovation within medical education. Research demonstrates that fostering autonomy and leadership among residents in medical residency programs significantly benefits both trainees and the healthcare system. The Kuwait Family Medicine Review Course has emerged as a pioneering initiative that has transformed the Kuwait Family Medicine Residency Program (KFMRP), serving as a model for educational advancement. This paper examines the role of empowerment in medical education, with a particular focus on the Kuwait Family Medicine Review Course. It explores how resident-led teaching, leadership development, and academic collaboration contribute to enhancing residency training and strengthening Kuwait's healthcare infrastructure. Resident empowerment fosters leadership, autonomy, and innovation within medical education. The Kuwait Family Medicine Review Course exemplifies how structured initiatives can improve residency training, ultimately benefiting healthcare systems through better-prepared physicians. This model underscores the importance of empowerment-driven approaches in shaping the future of medical education.

Impact of media use on oral health, parafunctional habits, and nutritional status in preschoolers: a cross-sectional study

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BMC Oral Health. 2025 Jul 11;25(1):1143. doi: 10.1186/s12903-025-06536-8.

OBJECTIVES
This study investigated the potential correlation between problematic media use (PMU) and poor oral health, increased parafunctional habits, and poor nutritional status in preschool children.

METHODS
Participants were healthy preschool children aged 3 to 5 who presented to a pediatric dentistry clinic. Clinical examinations were performed to evaluate children's caries experience and oral hygiene. The weight and height of each child were recorded. Structured questionnaires were administered to obtain children's demographic information, oral hygiene practices, dietary habits, oral parafunctional habits, and their daily use of screen-based media devices. Problematic media use was assessed using the Arabic version of the Problematic Media Use Measure-Short Form (PMUM-SF).

RESULTS
A total of 388 children completed the study. The majority (69%) were categorized as underweight, with a mean body mass index of 13.3. Children with moderate to high PMU exhibited significantly more bruxism and nail biting than those with low PMU ($p < 0.05$). The prevalence of dental caries was extremely high (99.2%), with no significant difference across PMU groups. Poor oral hygiene was more evident in children with high PMU (38.3%, $p < 0.05$).

CONCLUSIONS
Problematic media use (PMU) in preschool children was associated with some parafunctional oral habits and a trend toward poorer oral hygiene. No significant impact of PMU on children's nutritional status was determined.

Forthcoming Conferences and Meetings

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Vineetha Elizabeth Mammen

Kuwait Medical Journal 2025; 57 (3): 200 - 207

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International Conference on **Medical Health Science, Pharmacology and Bio Technology**
Oct 06, 2025
Singapore, Singapore
Organized by: ISSRD
Email ID: papers.issrd@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Oct 07, 2025
United States, Santa Clara, California
Organized by: Wrfer
Email ID: contact.wrfer@gmail.com

International World Research Congress on **Dentistry and Oral Health**
Oct 10, 2025
Switzerland, Geneva
Organized by: Biofora
Email ID: papers.biofora@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences**
Oct 10, 2025
Russia, Moscow
Organized by: Academics world
Email ID: info@academicsworld.org

International Congress on **Physical Activity and Public Health**
Oct 10, 2025
Saudi Arabia, Al Khobar
Organized by: Meeting fora
Email ID: info@meetingfora.com

1st **GCC Pediatric Associations** Conference
Oct 11-13, 2025
Kuwait, Kuwait city
Organized by: GCC Pediatric Associations

International Conference on Recent Advances in **Medical and Health Sciences**
Oct 12, 2025
Morocco, Rabat
Organized by: Academics world
Email ID: info@academicsworld.org

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Oct 13, 2025
France, Paris
Organized by: Wrfer
Email ID: contact.wrfer@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences**
Oct 14, 2025
China, Shanghai
Organized by: Academics world
Email ID: info@academicsworld.org

International Conference on **Urology and Renal Health**
Oct 14, 2025
United Arab Emirates, Ras Al Khaimah
Organized by: the United Science Research Society
Email ID: info.usrsociety@gmail.com

World Congress on **Women's Health Reproduction and Fertility**
Oct 14, 2025
Greenland, Ilulissat
Organized by: United Research
Email ID: info.unitedresearch@gmail.com

International Conference on **Mental Health and Treatment**
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Saudi Arabia, Khamis Mushait
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Email ID: info.allconferenceseries@gmail.com

2nd International Conference on **Women's Health and Breast Cancer**
Oct 16, 2025
Italy, Rome
Organized by: Prezentis
Email ID: womenshealth@prezentismeetings.org

International Conference on **Medical and Health Sciences**
Oct 17, 2025
United States, Hawaii
Organized by: Scienceplus
Email ID: papers.scienceplus@gmail.com

International Conference on Advanced Research in **Health Science and Medicine**
Oct 18, 2025
United States, New York
Organized by: Biofora
Email ID: papers.biofora@gmail.com

International Conference on **Physical Education, Health and Sports**
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Turkey, Edirne
Organized by: Academic Research Network
Email ID: info.academicresearchnetwork@gmail.com

International Conference on Recent Advancement in **Medical Education, Nursing and Health Sciences**
Oct 22, 2025
Australia, Sydney
Organized by: IRF conference
Email ID: info.irfconference@gmail.com

International Conference on **Gynecology, Obstetrics and Women's Health**
Oct 24, 2025
United Kingdom, Newcastle
Organized by: Academic Research Network
Email ID: info.academicresearchnetwork@gmail.com

International Conference on **Pediatrics, Perinatology and Child Health**
Oct 24, 2025
Italy, Genoa
Organized by: Academic Research Network
Email ID: info.academicresearchnetwork@gmail.com

International Conference on **Community Psychology and Mental Health**
Oct 24, 2025
Qatar, Al Rayyan
Organized by: Meeting fora
Email ID: info@meetingfora.com

World Congress on **Women's Health Reproduction and Fertility**
Oct 25, 2025
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Organized by: United Science Research Society
Email ID: info.usrsociety@gmail.com

International Conferences on Advances in **Nursing Science, Medical and Health Care**
Oct 26, 2025
United Arab Emirates, Dubai
Organized by: Theires
Email ID: info@theires.org

International Conference on **Nutrition and Health**
Oct 27, 2025
United Arab Emirates, Dubai
Organized by: Conference Online
Email ID: info.conferenceonline@gmail.com

International Research Conference on **COVID-19** and its Impact on Mental Health
Oct 30, 2025
Indonesia, Bali
Organized by: Research Conferences
Email ID: info.researchconferences@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Nov 01, 2025
Australia, Sydney
Organized by: Wrfer
Email ID: contact.wrfer@gmail.com

International Conference on **Medical and Health Sciences**
Nov 01, 2025
Malaysia, Kuala Lumpur
Organized by: Academics conference
Email ID: papers.academicsconference@gmail.com

International Conference on **Medical, Medicine and Health Sciences**
Nov 01, 2025
United States, Boston, Massachusetts
Organized by: International Institute of Engineers Researchers and Doctors
Email ID: contact.iierd@gmail.com

3rd Kuwait **Obesity** Conference
Nov 3-4, 2025
Kuwait, Kuwait city
Organized by: Kuwait Association of Surgeons

International Conference on **Medical and Health Sciences**
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Qatar, Doha
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Email ID: info.inderscience@gmail.com

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Organized by: Meeting fora
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Nov 08, 2025
Saudi Arabia, Riyadh
Organized by: Academic Research Network
Email ID: info.academicresearchnetwork@gmail.com

International Conference on **Medical and Health Sciences**
Nov 12, 2025
France, Paris
Organized by: ISERD
Email ID: info@iserd.co

International Conference on **Epidemiology and Public Health**
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Organized by: Meetingvfora
Email ID: info@meetingfora.com

World Conference on **Bioethics, Medical Ethics and Health Law**
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Organized by: Academic Research Network
Email ID: info.academicresearchnetwork@gmail.com

2nd European Congress on **Public Health and Epidemiology**
Nov 17, 2025
Italy, Rome, Lazio
Organized by: C2P Forum
Email ID: publichealth@c2presearch.org

International Conference on **Medical and Health Sciences**
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United Kingdom, Manchester
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International Research Conference on **COVID-19** and its Impact on Mental Health
Nov 19, 2025
Japan, Kyoto
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Research International Conference on **Medical, Medicine and Health Science**
Nov 21, 2025
Australia, Melbourne
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International Research Conference on **COVID-19** and its Impact on Mental Health
Nov 22, 2025
India, Mumbai, Maharashtra
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International Experts Summit on **Women Health and Breast Cancer**
Nov 24, 2025
Portugal, Lisbon
Organized by: The Iconic Meetings
Email ID: womenhealthsummit-2025@iconicmeetings.org

International Conference on Advances in **Medical Science and Health care**
Nov 26, 2025
United Arab Emirates, Dubai
Organized by: Academics era
Email ID: info@academicsera.com

19th Congress of the **Asian Society of Transplantation**
Nov 26-29, 2025
Kuwait, Kuwait city
Organized by: CAST 2025
Email ID: info@cast2025.org

International Conference on **Gynecology, Obstetrics and Women's Health**
Nov 27, 2025
Turkey, Edirne
Organized by: Global Science Networks
Email ID: info.globalsciencenetworks@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Nov 27, 2025
Canada, Toronto
Organized by: Wrfer
Email ID: contact.wrfer@gmail.com

7th Kuwait **Mental Health** Conference
Nov 29-30, 2025
Kuwait, Kuwait city
Organized by: Kuwait Centre for Mental Health

International Conference on Recent Advances in **Medical and Health Sciences**
Nov 30, 2025
Indonesia, Bali
Organized by: Academics world
Email ID: info@academicsworld.org

International Conference on **Food, Nutrition, Health and Lifestyle**
Dec 01, 2025
Qatar, Doha
Organized by: Biofora
Email ID: papers.biofora@gmail.com

International Conference on **Physical Education, Health and Sports**
Dec 02, 2025
China, Dongguan
Organized by: Academic Research Network
Email ID: info.academicresearchnetwork@gmail.com

International Conference on **Psychology and Mental Health**
Dec 03, 2025
Italy, Milan
Organized by: Global Science Networks
Email ID: info.globalsciencenetworks@gmail.com

Kuwait **Dermatology** Council Conference 2025
Dec 5-6, 2025
Kuwait, Kuwait city
Organized by: Ministry of Health, Kuwait

International Conference on **Mental Health and Psychiatry**
Dec 05, 2025
United States, Denver, Colorado
Organized by: Japanese Society for Academic Research and Publication
Email ID: info.jsarap@gmail.com

World Congress on **Women's Health, Reproduction and Fertility**
Dec 05, 2025
Italy, Verona
Organized by: Research Era
Email ID: info.researcheraconference@gmail.com

International Conference on **Mental Health and Wellbeing**
Dec 05, 2025
Russia, Novosibirsk
Organized by: Research Era
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International Conference on **Medical, Pharmaceutical and Health Sciences**
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International Congress on **Physical Activity and Public Health**
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International Conference on **Epidemiology and Public Health**
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Organized by: Japanese Society for Academic Research and Publication
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International Conference on **Women's Health and Breast Cancer**
Dec 09, 2025
Bahrain, Muharraq
Organized by: Science and research
Email ID: summit.scienceandresearch@gmail.com

International Conference on **Psychological, Educational, Health and Social Sciences**
Dec 10, 2025
Cyprus, Nicosia
Organized by: Meeting fora
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3rd Global Research Conference and Expo on **Public Health and Preventive Medicine**
Dec 11, 2025
United States, Las Vegas
Organized by: Foster research
Email ID: grcpublichealth@fosterresearch.org

International Conference on **Urology and Renal Health**
Dec 11, 2025
Hong Kong, Kowloon City
Organized by: Science and research
Email ID: summit.scienceandresearch@gmail.com

International Congress on **Obesity and Nutritional Health**
Dec 14, 2025
South Korea, Seoul
Organized by: The International Society for Researchers and Doctors
Email ID: info.theisrd@gmail.com

International Conference on **Sexual and Reproductive Health**
Dec 15, 2025
United States, Los Angeles, California
Organized by: Canadian Association for Scientific Research and Publication
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Dec 15, 2025
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International Conference on **Pediatrics, Perinatology and Child Health**
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International Conference on **Gynecology, Obstetrics and Women's Health**
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International Conference on Recent Advances in **Medical and Health Sciences**
Dec 28, 2025
Kuwait, Kuwait City
Organized by: Academics world
Email ID: info@academicsworld.org

International Conference on **Smart Living and Public Health**
Dec 30, 2025
Sweden, Stockholm
Organized by: Canadian Association for Scientific Research and Publication
Email ID: info@casrp.org

International Conference on **Psychology and Mental Health**
Dec 31, 2025
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WHO-Facts Sheet

1. Childhood cancer
2. Fragility fractures
3. Immunization coverage
4. Oropouche virus disease
5. Schistosomiasis

Compiled and edited by
Vineetha E Mammen

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1. Childhood cancer

KEY FACTS

- Each year, an estimated 000 400 children and adolescents of 19–0 years old develop cancer *(1)*.
- The most common types of childhood cancer include leukemias, brain tumours, lymphomas, and solid tumours such as neuroblastoma and Wilms tumour.
- In high-income countries, where comprehensive services are generally accessible, more than 80% of children with cancer are cured. In low- and middle-income countries (LMICs), less than 30% are cured *(2)*.
- Avoidable deaths from childhood cancers in LMICs result from lack of diagnosis, misdiagnosis or delayed diagnosis, obstacles to accessing care, abandonment of treatment, death from toxicity and relapse *(2)*.
- Only 29% of low-income countries report that cancer medicines are generally available to their populations compared to %96 of high-income countries.

Overview

Cancer is a leading cause of death for children and adolescents. The likelihood of surviving a diagnosis of childhood cancer depends on the country in which the child lives; in high-income countries, more than 80% of children with cancer are cured, but in many LMICs less than 30% are cured *(2)*.

Although childhood cancer cannot generally be prevented or identified through screening, most types of childhood cancer can be cured with generic medicines and other forms of treatment, including surgery and radiotherapy.

The reasons for lower survival rates in LMICs include delay in diagnosis, an inability to obtain an accurate diagnosis, inaccessible therapy, abandonment of treatment, death from toxicity (side effects) and avoidable relapse. Improving access to childhood cancer care, including to essential medicines and technologies, is highly cost-effective, feasible and can improve survival in all income settings.

Childhood cancer data systems are needed to drive continuous improvements in the quality of care, and to inform policy decisions.

Causes

Cancer occurs in people of all ages and can affect any part of the body. It begins with genetic change in single cells, that can then grow into a mass (or tumour), invade other parts of the body and cause harm and death if left untreated. Unlike cancer in adults, most childhood cancers do not have a known cause. Many studies have sought to identify the causes of childhood cancer, but very few cancers in children are caused by environmental or lifestyle factors. Cancer prevention efforts in children should focus on behaviours that will prevent the child from developing preventable cancer as an adult.

Some chronic infections, such as HIV, Epstein-Barr virus and malaria, are risk factors for childhood cancer. They are particularly relevant in LMICs. Other infections can increase a child's risk of developing cancer as an adult, so it is important to be vaccinated (against hepatitis B to help prevent liver cancer and against human papillomavirus to help prevent cervical cancer) and to other pursue other methods such as early detection and treatment of chronic infections that can lead to cancer.

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Current data suggest that approximately 10% of all children with cancer have a predisposition because of genetic factors *(3)*. Further research is needed to identify factors impacting cancer development in children.

Improving outcomes of childhood cancer

Because it is generally not possible to prevent cancer in children, the most effective strategy to reduce the burden of cancer in children and improve outcomes is to focus on a prompt, correct diagnosis followed by effective, evidence-based therapy with tailored supportive care.

Early diagnosis

When identified early, cancer is more likely to respond to effective treatment and result in a greater probability of survival, less suffering, and often less expensive and less intensive treatment. Significant improvements can be made in the lives of children with cancer by detecting cancer early and avoiding delays in care. A correct diagnosis is essential to treat children with cancer because each cancer requires a specific treatment regimen that may include surgery, radiotherapy, and chemotherapy.

Early diagnosis consists of 3 components:

- awareness of symptoms by families and primary care providers;
- accurate and timely clinical evaluation, diagnosis, and staging (determining the extent to which a cancer has spread); and
- access to prompt treatment.

Early diagnosis is relevant in all settings and improves survival for many cancers. Programmes to promote early and correct diagnosis have been successfully implemented in countries of all income levels, often through the collaborative efforts of governments, civil society and nongovernmental organizations, with vital roles played by parent groups. Childhood cancer is associated with a range of warning symptoms, such as fever, severe and persistent headaches, bone pain and weight loss, that can be detected by families and by trained primary health-care providers.

Screening is generally not helpful for childhood cancers. In some select cases, it can be considered in high-risk populations. For example, some eye cancers in children can be caused by a mutation that is inherited, so if that mutation or disease is identified in the family of a child with retinoblastoma, genetic counselling can be offered and siblings monitored with regular eye examinations early in life. Genetic causes of childhood cancers are relevant in only a small proportion children with cancer. There is no high-quality evidence to support population-based screening programmes in children.

Treatment

A correct diagnosis is essential to prescribe appropriate therapy for the type and extent of the disease. Standard therapies include chemotherapy, surgery and/or radiotherapy. Children also need special attention to their continued physical and cognitive growth and nutritional status, which requires a dedicated, multi-disciplinary team. Access to effective diagnosis, essential medicines, pathology, blood products, radiation therapy, technology and psychosocial and supportive care are variable and inequitable around the world.

However, cure is possible for more than 80% of children with cancer when childhood cancer services are accessible. Pharmacological treatment, for example, includes inexpensive generic medications included on the WHO List of essential medicines for children. Children who complete treatment require ongoing care to monitor for cancer recurrence and to manage any possible long-term impact of treatment.

Palliative care

Palliative care relieves symptoms caused by cancer and improves the quality of life of patients and their families. Not all children with cancer can be cured, but relief of suffering is possible for everyone. Paediatric palliative care is considered a core component of comprehensive care, starting when the disease is diagnosed and continuing throughout treatment and care, regardless of whether a child receives treatment with curative intent.

Palliative care programmes can be delivered through community and home-based care, providing pain relief and psychosocial support to patients and their families. Adequate access to oral morphine and other pain medicines should be provided for the treatment of moderate to severe cancer pain, which affects more than 80% of cancer patients in the terminal phase.

WHO response

In 2018, WHO launched, with the support of St. Jude Children's Research Hospital, the Global Initiative for Childhood Cancer (Global Initiative), to provide leadership and technical assistance to governments to support them in building and sustaining high-quality childhood cancer programmes. The goal is to achieve at least 60% survival for all children with cancer by 2030. This represents an approximate doubling of the current cure rate and will save an additional 1 million lives over the next decade.

The CureAll framework and its accompanying technical package have been developed to support implementation of the Initiative. The package helps governments and other stakeholders assess current capacity, set priorities, generate investment cases, develop evidence-based standards of care and monitor progress. An information-sharing portal has been created to facilitate sharing of expertise between countries and partners.

The Global Initiative is part of the response to the World Health Assembly resolution Cancer Prevention and Control through an Integrated Approach (WHA70.12), focused on the reduction of premature mortality from NCDs and the achievement of universal health coverage.

In December 2021, WHO and St Jude Children's Research Hospital launched the Global Platform for Access to Childhood Cancer Medicines (Global Platform), the first of its kind, to provide an uninterrupted supply of quality-assured childhood cancer medicines with end-to-end support from selecting to dispensing medicines according to best possible care standards. The Global Platform synergizes with the Global Initiative, with activities implemented through this new effort expected to contribute substantially to the achievement of the initiative's goals.

WHO and the International Agency for Research on Cancer (IARC) collaborate with the International Atomic Energy Agency (IAEA) and other UN organizations and partners, to:

- increase political commitment for childhood cancer control;
- support governments to develop high-quality cancer centres and regional satellites to ensure early and accurate diagnosis and effective treatment;
- develop standards and tools to guide the planning and implementation of interventions for early diagnosis, treatment and palliative and survivorship care,
- improve access to essential medicines and technologies; and
- support governments to safeguard families of children with cancer from financial harm and social isolation as a result of cancer care.

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2. Fragility fractures

KEY FACTS

- In 2019, there were 178 million new fractures globally, an increase of 33.4% of the absolute number of new fractures since 1990, partly driven by population growth and ageing.
- The same year, there were 455 million prevalent cases of acute or long-term symptoms of a fracture, an increase of 70.1% of the absolute prevalence since 1990.
- Globally in 2019, fractures accounted for 25.8 million years lived with disability (YLDs), an increase of 65.3% of the absolute YLDs since 1990.
- Fractures are more likely to occur in older people, especially older women.
- Most fractures in older people are due to bone fragility (fragility fractures) and result from mechanical forces quantified as equivalent to a fall from standing height or less (known as low energy trauma).
- Owing to the global population growth and ageing, the annual incidence of total fractures worldwide is expected to continue to increase, driven by fragility fractures. However, an individual's risk of fragility fracture can be predicted, and these fractures are preventable using effective interventions.

Overview

Bone fractures are partial or complete breaks in a bone, which may spontaneously occur (due to diseases such as osteoporosis and associated chronic conditions) or result from a fall or a trauma (due to road traffic accidents, sports, etc.). Fractures are a global public health concern and are associated with significant morbidity, mortality and healthcare costs.

Due to worldwide population growth and ageing, the number of people sustaining a fracture each year has been increasing. Currently, there are no global estimates on fragility fractures, and available data include all fractures combined. According to data from the Global Burden of Disease Study, the absolute incidence, prevalence and years lived with disability for fractures have significantly increased from 1990 to 2019, with highest age-specific incidence rates in the oldest age groups *(1)* in which most fractures are due to bone fragility (fragility fractures). These substantial increases have been associated with increased healthcare costs globally.

In the largest five countries of the European Union plus Sweden, the annual costs of fragility fractures are expected to increase by 27% by 2030 *(2)*. The same trend is reported in other parts of the world. Therefore, preventing fragility fractures through early assessment of risk factors and treatment of osteoporosis is essential for good health and well-being for all adults, and particularly so for older people.

Types of fragility fractures

Fragility fractures result from low-energy trauma (a mechanical force that would not ordinarily cause a fracture), such as a fall from standing height or less. These fractures are the main clinical consequence of osteoporosis, although they may occur in postmenopausal women even in the absence of osteoporosis.

The most common sites of fragility fractures are the:

- spine
- hip
- distal forearm (wrist)
- proximal humerus (upper arm).

Other fragility fracture sites include the pelvis, ribs, and proximal tibia. Hip and vertebral (spine) fractures are considered the most serious fragility fractures.

Risk factors

Risk factors are lifestyle, genetic, social or environmental factors that increase an individual's risk or propensity of developing a disease or sustaining a health-related problem and are generally categorized into modifiable and non-modifiable factors. Modifiable risk factors can be changed by modifying one's lifestyle or environment, so that the probability of occurrence of a disease or a health condition may be reduced.

Modifiable risk factors for fragility fractures include:

- smoking
- alcohol consumption
- sedentary behaviour/physical inactivity
- low body weight
- nutrient-poor diet
- vitamin D and calcium deficiency
- eating disorders (for example anorexia nervosa and bulimia)
- malabsorption
- medications (including glucocorticoids, antidepressants, anticonvulsants, androgen deprivation therapy, etc.)
- falls.

Non-modifiable risk factors include:

- older age
- sex (women have a higher risk)
- ethnicity (Caucasian people have a higher risk)
- history of prior fractures
- history of parental fractures
- menopause.

Although non-modifiable risk factors cannot be altered by lifestyle or environmental changes, knowledge of these factors is fundamental for health workers and patients for optimal prevention strategies. In fact, as with many age-related conditions, fragility fractures can result from multiple causes and risk factors.

Osteoporosis and low bone mineral density

Osteoporosis is a disease characterized by low bone density and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture. Aside from the factors listed above, osteoporosis itself is a risk factor for fracture the same way hypertension is for stroke, for example.

Can an individual's risk of fragility fracture be predicted?

Many tools have been developed to predict the probability of a fracture, most of which use combinations of clinical risk factors (for example, age, sex, history of previous fractures), with or without bone mineral density (BMD) measurement. These tools are used to calculate the individuals' risk of fracture over a certain number of years (for example, five or ten years), which supports the clinical decision-making process. However, there is no global consensus on which fracture risk assessment tools have the best prediction performance.

WHO is currently assessing all available fracture risk prediction tools to determine which tools could be recommended for use globally.

Strategies for primary prevention

Primary prevention refers to actions, strategies or interventions for preventing or avoiding the initial occurrence of diseases or health conditions. These include actions to identify risk factors in individuals or populations, and actions to mitigate or eliminate these risk factors.

Primary prevention strategies for fragility fractures mainly aim at promoting or maintaining bone density and strength. These include:

- improvement of diet and nutrition
- regular exercise and physical activity
- smoking cessation
- limitation of alcohol consumption
- treatment of osteoporosis
- prevention of falls.

Whereas there is some consensus on basic principles for primary prevention of fragility fractures (for example, nutrition/healthy diet, physical activity), controversies still exist over the effectiveness of some specific interventions, as well as treatment duration.

WHO has initiated a reassessment of the effectiveness and safety of key interventions for fracture prevention in adults, based on systematic reviews of available evidence.

Treatment and management

Early detection of fragility fractures and treatment (secondary prevention) is fundamental, as delayed treatment may lead to complications and compromise optimal treatment outcomes. In fact, although they are common in postmenopausal women and older men, most vertebral fractures are undiagnosed.

Management of clinical fragility fractures and of complications secondary to fractures is also key. Treatment of fragility fractures can be surgical or non-surgical, with orthopaedic surgeons playing a central role.

Prevention of refracture (usually called secondary fracture prevention) is also essential, and counts as tertiary prevention strategies, which include effective rehabilitation and improvement of quality of life.

Timely rehabilitation provided by a skilled rehabilitation workforce following treatment is crucial to support people to recover from the fracture and related functioning loss. Ensuring access to assistive products (e.g. walking aids, orthoses) and providing associated training is a crucial component of rehabilitation.

Comorbidities

Comorbidities are diseases or conditions that coexist with a specific disease or condition of interest. Besides well-established risk factors for fragility fractures, several concomitant conditions have been reported, including diabetes, hypertension, cardiovascular diseases, kidney disease, liver disease, depression, dementia and HIV infection.

The presence of comorbidities has been reported as increasing the risk of negative post-fracture health outcomes (for example infections or stroke) and impairing functional outcomes after fracture surgery.

It is therefore important to identify comorbidities in people at risk of fragility fractures or in those who sustained a fragility fracture to take adequate co-management strategies to prevent potential surgery-related complications, improve treatment outcome, and ensure good post-fracture prognosis.

WHO response

WHO Rehabilitation 2030 Initiative

WHO's definition of universal health coverage includes rehabilitation as an essential health service, and as such, rehabilitation is a critical part of care for people with fragility fractures. The WHO Package of interventions for rehabilitation provides information on essential interventions, and human and material resources for 20 health conditions, including fractures.

The UN Decade of Healthy Ageing

The United Nations Decade of Healthy Ageing (2021–2030) is a global collaboration to improve the lives of older people, their families, and the communities in which they live, with implementation led by WHO in collaboration with other UN agencies. In the framework of the decade's areas for action, the WHO Integrated Care for Older People (ICOPE) approach provides specific recommendations to prevent, slow or reverse declines in intrinsic capacity of older people, including recommendations for those at risk of falls.

WHO Bone Health and Ageing Initiative

In 2023, as part of the UN Decade of Healthy Ageing, WHO launched a new Bone Health and Ageing initiative. This initiative is led by the WHO Department of Maternal, Newborn, Child and Adolescent Health and Ageing. The primary goals of the initiative are to develop a strategic roadmap for optimizing bone health to promote healthy ageing and to advocate for a public health strategy to prevent fractures among older people.

To follow the progress of the WHO Bone Health and Ageing initiative, please subscribe here to the newsletter.

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3. Immunization coverage

KEY FACTS

- Globally in 2024, there were 14.3 million children missing out on any vaccination – so-called zero-dose children.
- Coverage of a third dose of vaccine protecting against diphtheria, tetanus, and pertussis (DTP3) was 85% in 2024.
- The proportion of children receiving a first dose of measles vaccine was 84% in 2024, still not at the 2019 level of 86%.
- Global coverage for the first dose of HPV vaccine in girls grew from 27% in 2023 to 31% in 2024.
- Coverage of yellow fever vaccine in the countries at risk of it is 50%, well below the recommended 80%.

Overview

While immunization is one of the most successful public health interventions, coverage coverage has held steady since 2023, but data highlight a troubling trajectory in progress toward key targets of the global Immunization Agenda 2030 (IA2030).

During 2024, about 85% of infants worldwide (109 million) received 3 doses of diphtheria-tetanus-pertussis (DTP3) vaccine, protecting them against infectious diseases that can cause serious illness and disability or be fatal. However, these global figures hide significant disparity among countries of different income strata, with low-income countries lagging behind.

Measles, because of its high transmissibility, acts as an early warning system, quickly exposing immunity gaps in the population. Still, 20.6 million children missed their routine first dose of measles, far from the 2019 level of 19.3 million.

Global immunization coverage 2024

A summary of global vaccination coverage in 2024 follows.

Haemophilus influenzae type b (Hib) causes meningitis and pneumonia. The Hib vaccine had been introduced in 193 Member States by the end of 2024. Global coverage with 3 doses of Hib vaccine is estimated at 78%. There is great variation between regions. The WHO European Region is estimated to have 93% coverage, while it is only 34% in the WHO Western Pacific Region.

Hepatitis B is a viral infection that attacks the liver. Hepatitis B vaccine for infants had been introduced nationwide in 190 Member States by the end of 2024. Global coverage with 3 doses of hepatitis B vaccine is estimated at %84. In addition, 117 Member States introduced 1 dose of hepatitis B vaccine to newborns within the first 24 hours of life. Global coverage is %45 and is as high as %79 in the WHO Western Pacific Region, while it is estimated at only %17 in the WHO African Region.

Human papillomavirus (HPV) is the most common viral infection affecting the reproductive tract and can cause cervical cancer in women, other types of cancer, and genital warts in both men and women. The HPV vaccine was provided in national immunization programmes and services in 147 countries in 2024, including new introductions in four countries. In 2024, 67 countries – representing more than 80% of girls aged 9–14 years old vaccinated in that year – used a 1-dose schedule. Global coverage with the first dose of HPV among girls is now estimated at 31%. While far from the 90% target by 2030, it represents a large increase from the 17% coverage in 2019. The 4% increase in global coverage since last year was driven by new introductions and scale up in several large countries and by a widespread improvement in existing programmes, including in countries using the 1-dose schedule.

Malaria is a life-threatening disease caused by parasites transmitted to people through the bites of infected anopheline mosquitoes. It remains one of the leading causes of death among children in sub-Saharan Africa. The Malaria Vaccine Implementation Programme (MVIP), coordinated by WHO and conducted in Ghana, Kenya and Malawi from 2019 to 2023 demonstrated high public impact with a vaccine-attributable 13% reduction in all-cause mortality among children age-eligible for vaccination and substantial reduction in hospitalizations for severe malaria. Since 2024, malaria vaccines have been further introduced in national immunization schedules and scaled-up across Africa as part of integrated malaria control activities. At least 30 countries in Africa plan to introduce malaria vaccines into their childhood immunization programmes.

Measles is a highly contagious disease caused by a virus, which usually results in a high fever and rash, and can lead to blindness, encephalitis or death. By the end of %84 ,2024 of children had received 1 dose of measles-containing vaccine by their second birthday, and %76 of children received 2 doses of measles vaccine. By the end of 191 ,2024 Member States had included a second dose of measles vaccine in their national immunization schedules.

Mumps is a highly contagious virus that causes painful swelling at the side of the face under the ears (the parotid glands), fever, headache and muscle aches. It can lead to viral meningitis. Mumps vaccine had been introduced nationwide in 124 Member States by the end of 2024.

Pneumococcal diseases include pneumonia, meningitis and febrile bacteraemia, as well as otitis

media, sinusitis and bronchitis. Pneumococcal vaccine had been introduced in 163 Member States by the end of 2024 and global third dose coverage was estimated at 67%. There is great variation between regions. The WHO South-East Asia Region is estimated to have 88% coverage, while it is only 23% in the WHO Western Pacific Region.

Polio is a highly infectious viral disease that can cause irreversible paralysis. In %84 ,2024 of infants around the world received 3 doses of polio vaccine. In 2024, the coverage of infants receiving their first dose of inactivated polio vaccine (IPV) in countries that are still using oral polio vaccine (OPV) is estimated at %85 as well. In these same countries, the coverage of infants receiving their second dose of IPV is estimated at %68, which represents a huge increase from the %43 estimated in 2023. Targeted for global eradication, polio has been stopped in all countries except for Afghanistan and Pakistan. Until poliovirus transmission is interrupted in these countries, all countries remain at risk of importation of polio, especially vulnerable countries with weak public health and immunization services and travel or trade links to endemic countries.

Rotaviruses are the most common cause of severe diarrhoeal disease in young children throughout the world. Rotavirus vaccine was introduced in 131 countries by the end of 2024. Global coverage was estimated at 59%.

Rubella is a viral disease which is usually mild in children, but infection during early pregnancy may cause fetal death or congenital rubella syndrome, which can lead to defects of the brain, heart, eyes and ears. Rubella vaccine was introduced nationwide in 178 Member States by the end of 2024, and global coverage was estimated at %73.

Tetanus is caused by a bacterium which grows in the absence of oxygen, for example in dirty wounds or the umbilical cord if it is not kept clean. The spores of *C. tetani* are present in the environment irrespective of geographical location. It produces a toxin which can cause serious complications or death. Maternal and neonatal tetanus persist as public health problems in 10 countries, Afghanistan, Angola, Central African Republic, Nigeria, Pakistan, Papua New Guinea, Somalia, Sudan, South Sudan and Yemen.

Yellow fever is an acute viral haemorrhagic disease transmitted by infected mosquitoes. As of 2024, yellow fever vaccine had been introduced in routine infant immunization programmes in 38 of the 40 countries and territories at risk for yellow fever in Africa and the Americas. In these 40 countries and territories, coverage is estimated at 52%.

Key challenges

In 2024, 14.3 million infants did not receive an initial dose of DTP vaccine, pointing to a lack of access to immunization and other health services, and an additional 5.6 million are partially vaccinated. Of the 19.9 million, around 55% of these children live in 10 countries: Afghanistan, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Nigeria, Pakistan, the Philippines, Sudan and Yemen.

Monitoring data at subnational levels is critical to helping countries prioritize and tailor vaccination strategies and operational plans to address immunization gaps and reach every person with life-saving vaccines.

WHO response

WHO is working with countries and partners to improve global vaccination coverage, including through these initiatives adopted by the World Health Assembly in August 2020.

Immunization Agenda 2030

IA2030 sets an ambitious, overarching global vision and strategy for vaccines and immunization for the decade 2021–2030. It was co-created with thousands of contributions from countries and organizations around the world. It draws on lessons from the past decade and acknowledges continuing and new challenges posed by infectious diseases (e.g. Ebola, COVID-19).

The strategy has been designed to respond to the interests of every country and intends to inspire and align the activities of community, national, regional and global stakeholders towards achieving a world where everyone, everywhere fully benefits from vaccines for good health and well-being. IA2030 is operationalized through regional and national strategies and mechanisms to ensure ownership and accountability and a monitoring and evaluation framework to guide country implementation.

- Immunization Agenda 2030: A Global Strategy to Leave No One Behind
- Implementing the Immunization Agenda 2030: A Framework for Action
- The global strategy towards eliminating cervical cancer as a public health problem

In 2020, the World Health Assembly adopted the global strategy towards eliminating cervical cancer. In this strategy, the first of the 3 pillars require the introduction of the HPV vaccine in all countries and has set a target of reaching 90% coverage. With introduction currently in 76% of Member States, large investments towards introduction in low- and middle-income countries will be required in the next 10 years as well as programme improvements to reach the 90%

coverage targets in low- and high-income settings alike will be required to reach the 2030 targets.

4. Oropouche virus disease

KEY FACTS

- Oropouche virus disease (also known as Oropouche fever) is a febrile illness, from which patients typically recover quickly, that is caused by the Oropouche virus, which is spread to humans through the bites of infected biting midges, and possibly of some mosquitoes.
- The Oropouche virus is present mostly in South America and the Caribbean, but since December 2023 more cases were reported, totalling over 10 000 cases in 2024, including from areas in the region where it was not previously detected.
- Symptoms of Oropouche virus disease are similar to those that occur in other diseases, such as dengue and chikungunya, and the cause of infection is often misdiagnosed.
- In 2024 concerns arose about possible complications of Oropouche virus infection including two deaths in previously healthy infected adults, and of possible negative outcomes of infection during pregnancy with associated fetal death, miscarriage, and microcephaly in newborns, that requires further investigation and research.
- No specific treatments or vaccines are available for Oropouche virus disease, and patients should receive supportive care.
- Infections can be prevented mainly through vector control and personal protective measures against insect bites, including use of meshed bed nets, chemical insecticides, protective clothing, and insect repellents is recommended.

Overview

Oropouche virus disease is caused by the Oropouche virus (OROV) that can cause fever, headache, joint pain, muscle pain, chills, nausea, vomiting and rash. Most people recover on their own, but the disease can cause severe symptoms in some patients.

OROV is a segmented single-stranded RNA virus belonging to the family *Peribunyaviridae*, genus *Orthobunyavirus*, which was first identified in 1955 in Vega de Oropouche, Trinidad and Tobago *(1)*.

The virus is transmitted to people through the bite of an infected insect, usually biting midges but also possibly by mosquitoes. It is thus referred to as an arthropod-borne virus (arbovirus). Prior to late 2023, reported cases of Oropouche virus disease were limited to South America, mostly near the Amazon rainforest, and the Caribbean. However, since December 2023, cases have been detected in other areas and have become more severe. In 2024, outbreaks have been documented outbreaks in nonendemic areas, two fatal cases with confirmed infection, and the possibility of mothers transmitting the disease to their babies while pregnant.

Distribution and outbreaks

Oropouche virus disease was the second most common arboviral disease in South America (after dengue) before the emergence of chikungunya and Zika viruses in 2013 and 2015.

Prior to late 2023, Oropouche virus disease was reported in Brazil, Bolivia, Colombia, Ecuador, Haiti, Panama, Peru, Trinidad and Tobago, French Guiana and Venezuela; most cases were reported near the Amazon rainforest area. However, since December 2023, there has been an increase in the number of cases reported, including in areas where transmission had not been previously documented.

In 2024, locally transmitted Oropouche virus disease was reported in seven countries in Latin America and the Caribbean: Brazil, Bolivia, Colombia, Cuba, Guyana, Peru and the Dominican Republic *(2–5)*. Additionally, Oropouche virus disease cases were reported among travellers returning from countries with local transmission to the United States, Canada, Spain, Italy and Germany *(6,7)*.

Transmission

The Oropouche virus is primarily transmitted to humans through the bite of *Culicoides paraensis* midges. *Culex quinquefasciatus, Coquillettidia venezuelensis* and *Aedes serratus* mosquitoes can also act as possible vectors *(8)*. The virus is believed to circulate in both a sylvatic cycle in forested areas, and in an urban epidemic cycle between insects and people. In the sylvatic cycle, non-human primates, sloths and perhaps birds serve as vertebrate hosts, although a definitive arthropod vector has not been identified.

Further studies are underway to better understand the insect vectors and transmission cycles in the current outbreaks.

Previously, there had been no confirmed reports of human-to-human transmission. However, there were reports in Brazil in 2024 of possible fetal infection with Oropouche virus, transmitted from mothers infected during pregnancy.

Symptoms

The incubation period (the time from the bite of an infected insect to first symptoms) of the Oropouche virus is typically 3 to 10 days. Symptoms of disease

include fever, headache, joint pain (arthralgia), muscle pain (myalgia), chills, nausea, vomiting and rash.

Most cases recover completely within 7 days after the onset of symptoms. However, recovery can take weeks in some patients, and severe complications like aseptic meningitis may occasionally occur. Though deaths from OROV infection were not previously described, in 2024 there were two reports of deaths in previously healthy young adults with Oropouche virus infection.

Diagnosis

Given the similar clinical presentation to other arboviruses like dengue and chikungunya, Oropouche virus disease is often unrecognized or misdiagnosed.

Diagnosis of Oropouche virus disease is made by reverse transcription polymerase chain reaction (RT-PCR) and real-time RT-PCR *(9)*. Serologic assays can be used to aid diagnosis; however, they should be conducted by highly trained personnel and in laboratories equipped with appropriate containment facilities. There are no available commercial diagnostic or rapid tests based on antigens or immunoassays (e.g. ELISA, immunochromatography) available.

Treatment

There is no specific treatment available for Oropouche virus disease. Treatment is primarily supportive and focuses on relieving symptoms.

Complications

The understanding of complications from Oropouche virus disease is limited. Occasionally, aseptic meningitis may occur.

Recently, there were reports from Brazil describing five cases of possible Oropouche virus transmission during pregnancy (four stillbirth and one spontaneous miscarriage) as well as four cases of newborns with microcephaly detected via retrospective investigations. Despite the detection of viral RNA by reverse transcription polymerase chain reaction (RT-PCR) testing of fetal tissues, it cannot be concluded that OROV infection was the cause of fetal deaths, and investigations are still ongoing.

Prevention and control

There is no vaccine available to prevent Oropouche virus disease. Vector control and personal protective measures are key in reducing the spread of the virus.

Standard bed nets are less effective against the biting midge, as these insects are small and can pass through the netting. In contrast, fine mesh bed nets and chemical insecticides used as residual spray on internal and external walls of infested premises have been shown to be effective.

Personal protective measures, such as wearing protective clothing and using insect repellents containing DEET, IR3535 or icaridin, are recommended to minimize the risk of infection.

WHO response

The Pan American Health Organization (PAHO) – the World Health Organization Regional Office for the Americas – in collaboration with WHO Member States, is actively monitoring the epidemiological situation of Oropouche virus disease.

PAHO conducted a rapid risk assessment (RRA) which indicated a high regional risk due to the increasing number of cases, their expansion into new areas, recently reported fatal cases, and the possible risk of vertical transmission *(10)*. WHO Member States have been alerted by PAHO and have been provided recommendation to in terms of diagnosis and clinical management, laboratory diagnosis and surveillance, and prevention and control of Oropouche virus disease.

Learn more about the PAHO response.

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5. Schistosomiasis

KEY FACTS

- Lack of hygiene and certain play habits of school-aged children such as swimming or fishing in infested water make them especially vulnerable to infection.
- In 2021, the COVID-19 pandemic and work to mitigate its impacts decreased the provision of neglected tropical disease (NTD) interventions and the treatment coverage for schistosomiasis.
- Schistosomiasis is an acute and chronic disease caused by parasitic worms.
- People are infected during routine agricultural, domestic, occupational and recreational activities which expose them to infested water.
- Estimates show that at least 251.4 million people required preventive treatment for schistosomiasis in 2021, out of which more than 75.3 million people were reported to have been treated.
- Schistosomiasis control focuses on reducing disease through periodic, large-scale population treatment with praziquantel; a more comprehensive approach including potable water, adequate sanitation, and snail control would also reduce transmission.

Overview

Schistosomiasis is an acute and chronic parasitic disease caused by blood flukes (trematode worms) of the genus *Schistosoma*. Estimates show that at least 251.4 million people required preventive treatment in 2021. Preventive treatment, which should be repeated over a number of years, will reduce and prevent morbidity. Schistosomiasis transmission has been reported from 78 countries. However, preventive chemotherapy for schistosomiasis, where people and communities are targeted for large-scale treatment, is only required in 51 endemic countries with moderate-to-high transmission.

Infection and transmission

People become infected when larval forms of the parasite – released by freshwater snails – penetrate the skin during contact with infested water.

Transmission occurs when people suffering from schistosomiasis contaminate freshwater sources with faeces or urine containing parasite eggs, which hatch in water.

In the body, the larvae develop into adult schistosomes. Adult worms live in the blood vessels where the females release eggs. Some of the eggs are passed out of the body in the faeces or urine to continue the parasite's lifecycle. Others become trapped in body tissues, causing immune reactions and progressive damage to organs.

Epidemiology

Schistosomiasis is prevalent in tropical and subtropical areas, especially in poor communities without access to safe drinking water and adequate

Table: Parasite species and geographical distribution of schistosomiasis

	Species	Geographical distribution
Intestinal schistosomiasis	Schistosoma mansoni	Africa, the Middle East, the Caribbean, Brazil, Venezuela and Suriname
	Schistosoma japonicum	China, Indonesia, the Philippines
	Schistosoma mekongi	Several districts of Cambodia and the Lao People's Democratic Republic
	Schistosoma guineensis and related S. intercalatum	Rain forest areas of central Africa
Urogenital schistosomiasis	Schistosoma haematobium	Africa, the Middle East, Corsica (France)

sanitation. It is estimated that at least 90% of those requiring treatment for schistosomiasis live in Africa.

There are 2 major forms of schistosomiasis – intestinal and urogenital – caused by 5 main species of blood fluke.

Schistosomiasis mostly affects poor and rural communities, particularly agricultural and fishing populations. Women doing domestic chores in infested water, such as washing clothes, are also at risk and can develop female genital schistosomiasis. Inadequate hygiene and contact with infected water make children especially vulnerable to infection.

Migration to urban areas and population movements are introducing the disease to new areas. Increasing population size and the corresponding needs for power and water often result in development schemes, and environmental modifications facilitate transmission.

With the rise in eco-tourism and travel to remote areas, increasing numbers of tourists are contracting schistosomiasis. At times, tourists present severe acute infection and unusual problems including paralysis.

Urogenital schistosomiasis is also considered to be a risk factor for HIV infection, especially in women.

Symptoms

Symptoms of schistosomiasis are caused mainly by the body's reaction to the worms' eggs.

Intestinal schistosomiasis can result in abdominal pain, diarrhoea, and blood in the stool. Liver enlargement is common in advanced cases and is frequently associated with an accumulation of fluid in the peritoneal cavity and hypertension of the abdominal blood vessels. In such cases there may also be enlargement of the spleen.

The classic sign of urogenital schistosomiasis is haematuria (blood in urine). Kidney damage and fibrosis of the bladder and ureter are sometimes diagnosed in advanced cases. Bladder cancer is another possible complication in the later stages. In women, urogenital schistosomiasis may present with genital lesions, vaginal bleeding, pain during sexual intercourse and nodules in the vulva. In men, urogenital schistosomiasis can induce pathology of the seminal vesicles, prostate and other organs. This disease may also have other long-term irreversible consequences, including infertility.

The economic and health effects of schistosomiasis are considerable and the disease disables more than it kills. In children, schistosomiasis can cause anaemia, stunting and a reduced ability to learn, although the effects are usually reversible with treatment. Chronic schistosomiasis may affect people's ability to work and in some cases can result in death. The number of deaths due to schistosomiasis is difficult to estimate because of hidden pathologies such as liver and kidney failure, bladder cancer and ectopic pregnancies due to female genital schistosomiasis.

Deaths due to schistosomiasis are currently estimated at 11 792 globally per year. However, these figures are likely underestimated and need to be reassessed.

Diagnosis

Schistosomiasis is diagnosed through the detection of parasite eggs in stool or urine specimens. Antibodies and/or antigens detected in blood or urine samples are also indications of infection.

For urogenital schistosomiasis, a filtration technique using nylon, paper or polycarbonate filters is the standard diagnostic technique. Children with *S. haematobium* almost always have microscopic blood in their urine which can be detected by chemical reagent strips.

The eggs of intestinal schistosomiasis can be detected in faecal specimens through a technique using methylene blue-stained cellophane soaked in glycerin or glass slides, known as the Kato-Katz technique. In *S. mansoni* transmission areas, the circulating cathodic antigen (CCA) test can also be used.

For people living in non-endemic or low-transmission areas, serological and immunological tests may be useful in showing exposure to infection and the need for thorough examination, treatment and follow-up.

Prevention and control

The control of schistosomiasis is based on large-scale treatment of at-risk population groups, access to safe water, improved sanitation, hygiene education and behaviour change, and snail control and environmental management.

The new neglected tropical diseases road map 2021–2030, adopted by the World Health Assembly, set as global goals the elimination of schistosomiasis as a public health problem in all endemic countries and the interruption of its transmission (absence of infection in humans) in selected countries.

The WHO strategy for schistosomiasis control focuses on reducing disease through periodic, targeted treatment with praziquantel through the large-scale treatment (preventive chemotherapy) of affected populations. It involves regular treatment of all at-risk groups. In a few countries, where there is low transmission, the interruption of the transmission of the disease should be aimed for.

Groups targeted for treatment are:

- pre-school-aged children;
- school-aged children;
- adults considered to be at risk in endemic areas

and people with occupations involving contact with infested water, such as fishermen, farmers, irrigation workers and women whose domestic tasks bring them in contact with infested water; and
- entire communities living in highly endemic areas.

WHO recommends treatment of infected preschool aged children based on diagnostic and clinical judgment and their inclusion in large-scale treatment using the paediatric praziquantel formulation.

The frequency of treatment is determined by the prevalence of infection in school-age children. In high-transmission areas, treatment may have to be repeated every year for several years. Monitoring is essential to determine the impact of control interventions.

The aim is to reduce disease morbidity and transmission towards the elimination of the disease as public health problem. Periodic treatment of at-risk populations will cure mild symptoms and prevent infected people from developing severe, late-stage chronic disease. However, a major limitation to schistosomiasis control has been the limited availability of praziquantel, particularly for the treatment of adults. Data for 2021 show that 29.9% of people requiring treatment were reached globally, with a proportion of 43.3% of school-aged children requiring preventive chemotherapy for schistosomiasis being treated. A drop of 38% compared to 2019, due to the COVID-19 pandemic which suspended treatment campaigns in many endemic areas.

Praziquantel is the recommended treatment against all forms of schistosomiasis. It is effective, safe and low-cost. Even though re-infection may occur after treatment, the risk of developing severe disease is diminished and even reversed when treatment is initiated and repeated in childhood.

Schistosomiasis control has been successfully implemented over the past 40 years in several countries, including Brazil, Cambodia, China, Egypt, Mauritius, Islamic Republic of Iran, Oman, Jordan, Saudi Arabia, Morocco, Tunisia and others. In many countries it has been possible to scale-up schistosomiasis treatment to the national level and have an impact on the disease in a few years. An assessment of the status of transmission is required in several countries.

Over the past 10 years there has been scale-up of treatment campaigns in a number of sub-Saharan countries, where most of those at risk live. These treatments campaigns resulted in the decrease of prevalence of schistosomiasis in school age children by almost 60% *(1)*.

WHO response

WHO's work on schistosomiasis is part of an integrated approach to the control of neglected tropical diseases. Although medically diverse, neglected tropical diseases share features that allow them to persist in conditions of poverty, where they cluster and frequently overlap.

WHO coordinates the strategy of preventive chemotherapy in consultation with collaborating centres and partners from academic and research institutions, the private sector, nongovernmental organizations, international development agencies and other United Nations organizations. WHO develops technical guidelines and tools for use by national control programmes.

Working with partners and the private sector, WHO has advocated for increased access to praziquantel and resources for implementation. A significant amount of praziquantel – enough to treat more than 100 million children of the school age per year – has been pledged by the private sector and development partners.

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