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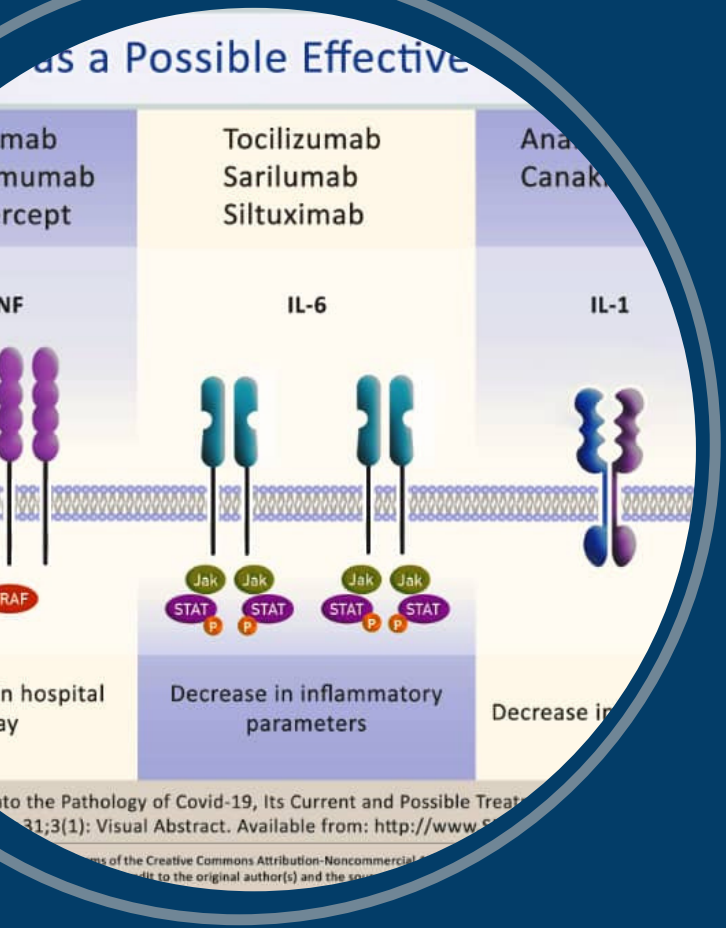

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A glance into the Pathology of Covid-19, Its Current and Possible Treatments; Interleukin Antagonists as an Effective Option; a Review

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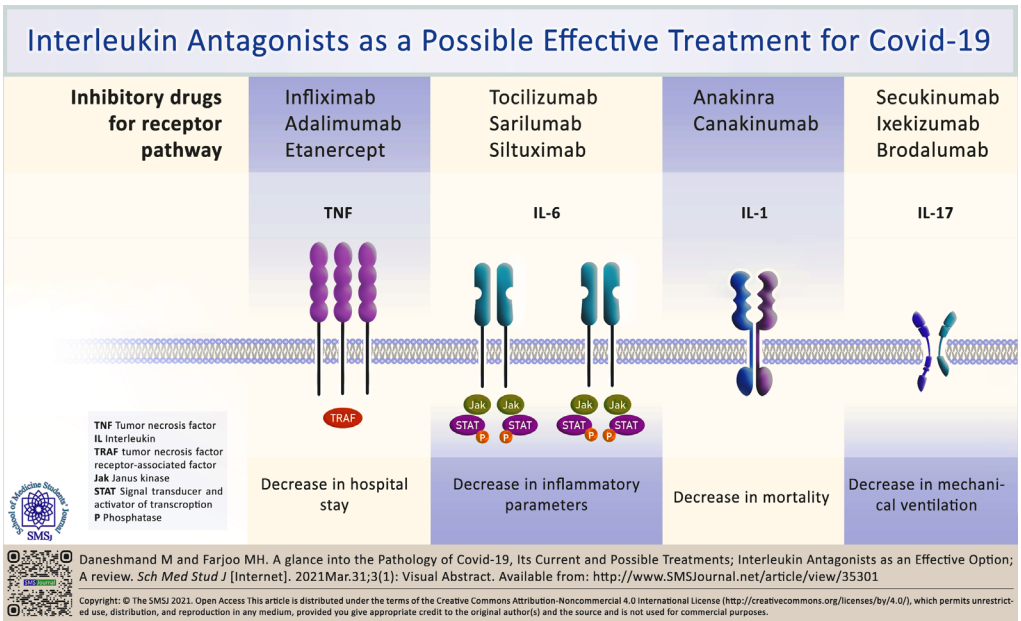
ABSTRACT

The outbreak of the novel SARS-COV-2 and its following complications has caused an almost unprecedented chaos throughout the world in recent years. Although a series of vaccines have been proposed recently in order to reduce the risk of mortality and morbidity of this disease, an ultimate and reliable cure has yet to be discovered. One of the major complications of Covid-19 is the outburst of a series of inflammatory responses in the respiratory system of the patients, which eventually causes a hypoxemic pneumonitis and accounts for most of the Covid-19 patients' mortality. It is suggested that a group of inflammatory cytokines such as different interleukins are responsible for this complication, therefore drugs which can influence this system may be useful in reducing this exaggerated inflammatory response which is dubbed the 'cytokine storm'. In this article we review potential treatment options for reducing the inflammatory response and discuss some clinical trials and case reports related to the drugs interfering with responsible interleukins in order to quench the cytokine storm.



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INTRODUCTION

The beginning of 2020 was heralded by an outbreak of a coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-COV-2). The current global pandemic of SARS-COV-2 has been spreading limitlessly throughout the world since December 2019. It primarily was observed in Wuhan city, China and to date, over 172 million confirmed cases and over 3 million deaths are reported by WHO [1]. Ever since there has been a significant effort for finding a treatment for this disease. Although a series of vaccines have been introduced among which some are FDA approved and are currently being injected, but a definitive cure is yet to be found [1, 2].

Various complications are attributed to this disease. Patients diagnosed with covid-19 often develop a hypoxemic pneumonitis with a profound inflammatory response which may be caused by elevated levels of inflammatory cytokines such as IL1 and IL6, interferon-γ inducible protein 10, and granulocyte-colony stimulating factor (GCSF) [3]. These cytokines increase the amount of cell adhesion molecules and vascular-endothelial growth factor (VEGF) in the lung and thereby increase the permeability in the lung epithelial cells and decrease barrier protection, which allows viral propagation and infiltration of neutrophils and inflammatory monocytes. These cytokines stimulate release of immature granulocytes from bone marrow which exacerbate the lung epithelium adherence and inflammation. This so called second loop in the lung leads to a series of systemic inflammations which culminate in what is known as cytokine storm syndrome [4]. This cytokine storm causes diffuse alveolar damage and acute respiratory distress syndrome and is the leading cause of mortality in the covid-19 patients (see below) [5].

A considerable amount of researches and trials have been carried out about Covid-19 treatment and drugs which antagonize IL1 and IL6 receptors may be a promising approach for this purpose [6-10].

COVID-19 and Its Pathologic Respiratory Features

Corona virus is a positive-sense, single-stranded RNA virus which belongs to the family Coronaviridae with a genome size of approximately 30 kilobases. The virus encodes multiple structural and non-structural proteins. The former consist of: spike, envelope, membrane, and nucleocapsid protein, and the latter are responsible for corona virus RNA synthesis and processing. This is done by nonstructural protein (NSP) 7 to 16, which are cleavage products of two large replicase polyproteins translated from the coronavirus genome. [11]. The virus apparently triggers both humoral and cellular immune responses which may notoriously affect respiratory system. The severe lung injury in patients with covid-19 results from both direct viral infection and immune system overreaction [12, 13]. The detrimental changes consist of a constellation of pathologic processes occurring both in macro- and microenvironment. Hyaline membrane formation may cause vast alveolar damage which may be accompanied by pulmonary edema, and exudates of fibrin with subsequent aggregation of proteins. A reactive hyperplasia of type II pneumocytes also occurs with accumulation of different types of white blood cells such as monocytes, macrophages, and other mononuclear cells within alveoli. [14, 15]. Covid-19 attacks the respiratory system via invading epithelial cells and type 2 pneumocytes by attachment of the virus spike protein to the angiotensin converting enzyme 2 (ACE2) receptors [16]. The regulator gene of this receptor has shown a dose-dependent expression concomitant with the higher levels of SARS-CoV-2 virus, and is upregulated by interferon regulating genes such as Interferon Alpha Inducible Protein (IFI) 27, and IFI 6 [17]. This is while SARS-COVID-2 decreases surface expression of ACE2 receptors [18]. ACE2 acts via converting Angiotensin 2 into Angiotensin 1-7, and therefore has a vasodilatory effect. Moreover, it has a reducing effect on bradykinin expression, hence with the blockade of ACE2 receptors, high amounts of bradykinins can stimulate inflammatory response [19].

Cytokine Storm and Its Effects on Lung Pathology

Following entrance of SARS-COV2 into the respiratory epithelial cells, the virus provokes an immune response which leads to the production of plentiful amounts of inflammatory cytokines. Pathogenic T helper 1 (Th1) cells and intermediate CD14+, and CD16+ monocytes ignite a series of inflammatory immune responses which happen by the interaction between the membrane-bound immune receptors with antigens and the subsequent signaling pathways. This is followed by infiltration of macrophages and neutrophils into the epithelial cells of the lungs which provokes cytokine storm [12]. This happens when SARS-COV-2 stimulates Th1 cells to produce inflammatory mediators for instance different kinds of interleukins (e.g., IL1 and IL6), granulocyte-macrophage colony stimulating factor (GM-CSF) which stimulates CD14+, CD16+ monocytes to secrete massive amounts of other cytokines such as tumor necrosis factor α (TNFα) [12, 20]. The release of these types of cytokines is associated with a series of manifestations such as flu like symptoms, fatigue, cardio -myopathy and lung injury. IL6 can cause vascular leakage which activates complement and coagulation pathways that could cause diffuse intravascular coagulation. These clinical features are mostly seen in COVID-19 patients in severe condition and are major contributing factors to the mortality of this disease [21, 22].

Medications Effective in the Modulation of the Cytokine Storm

Considering the fundamental role of cytokine storm in severity of the COVID-19, anti-inflammatory drugs may be a potential therapy for reducing morbidity and mortality of this disease. The time period in which the anti-inflammatory drugs are used is of great importance, since there is a seven-day critical time between the onset of the symptoms and worsening of the patient's condition towards critical status [21]. This type of treatment has its own disadvan-

tages, for instance a number of cytokines such as interleukins 1, 6, 10, 12 and 17 are necessary in the process of virus clearance and therefore anti-interleukin drugs could cause some complications. Furthermore, immune system deficiencies occurs in some patients suffering from COVID-19 and utilization of anti-inflammatory drugs such as glucocorticoids may exacerbate their situation [23]. Another option for COVID-19 treatment is administration of human immunoglobulin for intravenous use (IVIG). These molecules are natural antibodies with poly reactive properties with the ability to recognize and neutralize exogenous antigens of viral and bacterial origin, toxins and super antigens, or endogenous antigens like cytokines, chemokines and metalloproteases. IVIG molecules also depend on their Fc region interaction with the Fcγ receptors (FcγRs) to induce anti-inflammatory / immune-regulatory responses. Since FcγRs are expressed on cells involved in natural immunity (phagocytes), adaptive immunity (T cells, B cells), and also on antigen presenting-cells which connect both types of immunities, this interaction acts as a modifier for signaling through FcγRs and eventually may lead to strong anti-inflammatory responses [24]. Many studies have suggested that complement system becomes active during body exposure to SARS-CoV in humans and animals. It appears that a large amount of complement residues are dispersed throughout the bodies of patients, so finding a molecule with antagonistic potential against complement receptors could be promising in reducing the inflammatory response in these patients. Studies show that a humanized monoclonal antibody that works against complement receptor, C5a could reduce SARS-CoV-induced lung injury in mice and monkeys, therefore drugs with this mechanism such as [Eculizumab] might play a functional role [25]. Another important factor in inflammatory response is TNFα. It is mainly produced by macrophages and to a lesser extent by monocytes and B cells. TNFα stimulates IL1 and IL6 production and is vastly observed in the blood and tissues of COVID-19 patients. Therefore, anti TNFα drugs such as [Adalimumab] and [Infliximab] can be a logical option in the modulation of cytokine storm [26]. Calcitonin gene-related peptide (CGRP) is a potent vasoactive peptide and potential cardio-protective mediator. CGRP has also been found in pulmonary afferent nerve fibers and contributes to the vasodilation of pulmonary vasculature. Studies show that CGRP has an inducing effect on IL6 production; therefore, CGRP antagonists could have effects in treating cytokine storm [27].

Drugs in statin group are also considered potentially effective. Statins can be effective in the modulation of lipids, induction of autophagy, modulation of coagulation process, and regulation of NLRP3 inflammasome mediated inflammation. NLRP3 is a molecule belonging to NLR protein family and has a tripartite structure. It provokes immune system via activation of caspase-1 and IL1ß and IL18 [28, 29]. In another study, it was reported that Haloperidol decreased rate of mortality in patients on mechanical ventilation which might be due to its effect on lowering cytokine levels, therefore it can be potentially useful in combating the inflammatory response in COVID-19 [30, 31].

Role of Interleukin Antagonists in the Modulation of the Cytokine Storm

Several interleukins are involved in the inflammatory response of the cytokine storm such as IL-1β, IL-2, IL-4, IL-6, IL-8, IL-12, IL-13, and IL-17 [32]. One of the major interleukins responsible for the cytokine storm is interleukin 6 which is activated by leukocytes and promotes differentiation of B lymphocytes and secretion of acute phase proteins [33]. Interleukin 6 has an important role in the dendritic cell -T cell interaction which is crucial for the synthesis of T helper 17 cells along with other factors such as TGF-ß and IL-23. The T helper 17 cells secrete interleukin 17 which is responsible for the apoptosis of alveolar epithelial cells and progression to pulmonary fibrosis which compromises normal alveolar architecture, alveolar-capillary gas exchange, and eventually normal oxygenation in the lungs leading to the respiratory symptoms of the disease [32]. It seems that following the increase of IL-6 synthesis in COVID-19 patients, the number of T helper 17 cells escalates noticeably. There are various ways to inhibit IL-17 related pathways such as direct inhibitors, receptor antagonists, and direct pathway blockers [34, 32]. To date, there are three IL-17 blockers available: [Secukinumab]; an IgG 1, which directly binds to IL17A, [Ixekizumab]; an IgG4, which also directly binds to IL17A, and [Brodalumab]; an IgG 2, which binds selectively to IL17A receptor and inhibits its interaction with IL17A [35]. On the other hand, IL-6 acts through the Janus kinase-Signal Transducer and Activator of Transcription (JAK-STAT) signaling pathway to implement various immunological effects such as immune regulation, lymphocyte growth and secretion, and oxidative stress; consequently, finding a way to block the JAK-STAT pathways could actually have a role in reducing the cytokine storm severity [36], and [Ruxolitinib] and [Baricitinib] are drugs with JAK/STAT inhibition potency which could be helpful in this setting [36].

IL-6 effect can also be restricted through IL-6 receptor antagonists such as [Tocilizumab] and [Sarilumab], or by [Siltuximab] which binds directly to IL6 [37]. Tocilizumab has a long half-life and it is not easily available in clinic, therefore there is still a high demand for other potentially effective immunomodulatory drugs [10]. IL1 also plays a noticeable role, for example [Anakinra], a drug with antagonistic effect on IL-1 receptor, is commonly used in rheumatologic conditions and is of great importance in COVID-19 [38]. This is because IL1 is involved considerably in thrombotic complications and venous thromboembolism caused by COVD-19, and also induces the secretion of TNF which itself is a pro inflammatory cytokine. Both IL1 and TNF molecules are involved in the COVID-19 cytokine storm. When an inflammation happens, thromboxane A2, which is released by IL1, causes platelet vascular thrombogenicity both on endothelial and on non-endothelial cells. IL-1 is the most important immune molecule in inducing fever, since it has a role in the metabolism of arachidonic acid which is released from vascular

endothelial organs of the hypothalamus which function as a center for temperature control of the body. [Canakinumab] is another antagonist in this group which is a human monoclonal antibody against IL-1β and is used in the treatment of inflammatory diseases such as Familial Mediterranean Fever, and can have possible effects on COVID-19 related inflammatory response [39]. Hence, blockade or synthesis inhibition of IL-1 blocks all the pathological events, which can lead to death of the COVID-19 patient [40, 41].

Clinical Trials and Case Reports

Tocilizumab

Several studies are performed concerning the effectiveness of interleukin antagonists, among them Tocilizumab and Anakinra are the most worked on.

A clinical trial was performed among 255 COVID-19 patients. The patients were randomly given Sarilumab or Tocilizumab, an IL6 antagonist. Patients were divided into two groups: those requiring ≤45% fraction of inspired oxygen (FiO2) (termed stage IIB, 106 patients) and those requiring >45% FiO2 (termed stage III, 149 patients). Only one patient needed ventilation in group IIB, while 16 patients of group III required mechanical ventilation. Patients treated in stage IIB had lower mortality than those treated in stage III and also had shorter length of stay (mean days of stay 11.3 for IIB versus 15 for III). Hence, IL6 receptor inhibitor administration prior to entering stage III, was associated with improved COVID-19 outcomes [42].

Tocilizumab effects was assessed on 80 COVID-19 patients in a clinical trial. More than 88% of patients who were given IL-6 inhibitor did not need mechanical ventilator (MV). Moreover, Tocilizumab reduced the cytokine storm and inflammatory response in the majority of patients. This reduction in cytokine release appeared to be the cause of decrease in requiring mechanical ventilation of these patients and reduced the mortality and morbidity [6].

A comparative analysis was done on 74 recipients of Tocilizumab and 148 controls who were treated with hydroxychloroquine plus [Lopinavir/ritonavir] or [Remdesivir] as standard of care. In patients with severe disease, Tocilizumab did not seem to have any beneficial effect, while it exerted an obvious improvement in critical patients. A severe case was defined as the presence of respiratory distress, oxygen saturation in room air ≤93% at rest or P/F (arterial pO2 divided by the FIO2) ≤300 mmHg. A critical case was defined as the presence of respiratory failure which needs ventilation (either invasive or not), septic shock or any other organ dysfunction requiring ICU monitoring and treatment. Tocilizumab use was accompanied with a better overall survival compared to controls, but with a longer hospital stay mainly due to biochemical, respiratory and infectious adverse events. It is recommended to use Tocilizumab cautiously regarding its adverse effects, remarkable worsening of respiratory conditions, and bacterial infections. Shortly after Tocilizumab administration, the patients needed a transient ventilation, but they recovered. Since ventilation might compromise drug benefits and patients could proceed to critical state immediately after drug receiving, respiratory monitoring after drug administration is needed [43].

In a clinical trial, effectiveness of Tocilizumab was assessed on 64 COVID-19 patients. Since other factors affect survival rate as well, such as patients' comorbidities and the rate of demand for respiratory support, the study could not support effectiveness of Tocilizumab in modifying mortality of COVID-19 patients with hyper inflammation in 5 days, however, the study showed that it was effective on the survival of patients who stayed alive after 5 days and reduced the rate of mortality between days 6 and 30 on the second outcome, defined as incidence of invasive ventilation, thrombosis and hemorrhage [9].

A series of controversial results were observed in another study. In a retrospective case control study on 45 COVID-19 patients, 20 were treated with Tocilizumab, and 25 treated with standard care. Charlson comorbidity index (19 specific conditions like diabetes, MI, COPD, dementia, etc.) was higher than normal among Tocilizumab group, presented with more severe symptoms such as higher oxygen demand, and had poorer biological findings like severe lymphopenia and higher CRP level than patients without Tocilizumab (5.3 [±2.4] vs 3.4 [±2.6], p=0.014). However, Tocilizumab group accounted for less number of ICU admissions and/or death in comparison with the standard group. Despite the small sample size and the retrospective nature of the work, the study suggests that Tocilizumab may improve the conditions of the patients with severe SARS-CoV2 pneumonia [44]. In contrast, a retrospective study was performed among 224 patients hospitalized with COVID-19. Tocilizumab was administered to two groups of 57 non ICU and 167 ICU patients, and then the rate of fungal infections and in hospital mortality rates were assessed. Tocilizumab was administered to 28.1% of ICU patients and 4.2% of non ICU patients. Rate of fungal infections was significantly higher in patients who received Tocilizumab irrespective of being in ICU or non ICU group. Among the non ICU patients, Tocilizumab was accompanied with higher ratio of later ICU admission. Also in both groups, demand for invasive mechanical ventilation increased, and relatively higher in-hospital mortality rates were observed after Tocilizumab administration. Therefore Tocilizumab did not decrease in-hospital mortality in this cohort [45].

Effects of Tocilizumab was also assessed in a clinical trial among 42 COVID-19 patients in severe and critical stage. Severe stage is defined as chronic obstructive pulmonary disease and lower CRP levels, and critical status is defined as hypertension, diabetes, and higher CRP levels. Among 20 patients in severe conditions, only one patient died, and out of 22 critical patients, 6 patients died, and in general, conditions of 35 patients improved after Tocilizumab administration. Lung images related to the patients before and after receiving Tocilizumab were compared, and seven patients showed worsening pulmonary conditions in imaging, the same number did not represent considerable improvement,

and images of the remaining 28 patients showed noticeable changes in favor of healing. In this study, the mortality rate among patients receiving Tocilizumab in severe or critical status was reported to be 16% with a 6% reduction from 22% mortality rate observed in previous studies [46].

A retrospective analysis was done on 40 patients treated with Tocilizumab, most of whom had several comorbidities, and all had a series of biological abnormalities such as lymphopenia, increased CRP, ferritin, fibrinogen, D-dimer, and liver enzymes. Clinical state in 30 patients improved with Tocilizumab, but 10 patients died. Among the survivors, CRP levels dropped sharply as early as day 4 after Tocilizumab administration, and reached normal levels on day 6. Fibrinogen and lymphocyte count also returned to normal on day 6. Ferritin levels decreased significantly as well. The death of 10 patients a few days after Tocilizumab administration, may suggest that the treatment was too late, therefore it raised the notion "window of opportunity" for Tocilizumab. The dramatic reduction of serum CRP levels were observed both in patients successfully treated with Tocilizumab and in those who died after Tocilizumab administration. further investigations is needed on larger groups of patients for a more definite result [47].

In a multicenter observational study, the association between Tocilizumab exposure and hospital-related mortality among patients requiring intensive care unit (ICU) support for COVID-19 was checked in 13 hospitals. Tocilizumab decreased hospital-related mortality in patients who had CRP levels higher than 15 mg/dL. Additionally, a noticeable decline in mortality was found among patients who required mechanical ventilation and also in patients less than 65 years of age. It could be concluded that Tocilizumab has a suppressing effect on inflammatory stage of COVID-19 patients [8].

In another study the difference between single and multiple doses of Tocilizumab were compared as a single center experience. It appears that a single dose of Tocilizumab may have positive outcomes in critical patients even in those receiving glucocorticoids. Besides, repeated doses (even in lower doses) of Tocilizumab is also beneficial for critically ill patients. It is proven that repeated dosing of Tocilizumab at a frequency of daily, every other day, or every 3 days in various doses would be useful in critical patients, or even in patients whose IL6 levels are exceptionally high (90 times of normal levels). Tocilizumab has a long duration of action and its receptors have saturable binding properties, therefore the dose of Tocilizumab could be reduced with repeated use. Tocilizumab might be effective in the prevention or treatment of cytokine storms. After administration of Tocilizumab most patients recovered from acute phase and were stabilized following a later gradual fall in IL-6 levels [48].

A systematic review was performed on studies about treating COVID-19 patients with Tocilizumab. Total number of 29 patients were enrolled in these studies. IL-6 levels in these patients were elevated initially after Tocilizumab therapy which is in favor of cytokine storm and may persist in a number of patients which was seen among 2 of these patients. However, after initiation of Tocilizumab, C reactive protein levels declined sharply, which shows that this drug is capable of reducing hyper-inflammation but due to the mentioned complications, further investigation is required [7].

Two cases of patients with COVID-19, who received Tocilizumab, complicated with cytokine release syndrome and its fatal correlate, secondary hemophagocytic lymphohistiocytosis (sHLH), were studied. In spite of the medication, they both progressed to sHLH and one of them developed viral myocarditis. Therefore the safety of this drug and the timing for its use should be taken into consideration [49].

Anakinra

In a retrospective cohort study, the effectiveness of Anakinra was evaluated among 36 COVID-19 patients with acute respiratory syndrome. Patients were divided into two groups receiving high dose and low dose of Anakinra and results were compared with a group of patients with standard treatment. Prior to study, 16 patients had received only mechanical ventilation and standard therapy and comprised the study's control group. 29 patients formed the high dose Anakinra group and 7 patients received low dose of Anakinra. In Anakinra group, low dose of Anakinra was not associated with a significant difference in CRP levels or changes in clinical status. However, high-dose drug on 21 patients were associated with reduction in serum CRP and progressive improvement in respiratory function, five patients required mechanical ventilation and the remaining three died. Totally 90% of patients survived in the high dose Anakinra group and 56% in the standard treatment group. Rate of survival without mechanical ventilation was 72% in the high dose Anakinra group versus 50% in the standard treatment group. This study showed that treatment with high-dose Anakinra was safe and associated with better clinical outcomes [10].

A clinical trial was done on nine COVID-19 patients who were all older than 18 years old and their chest CT scans were compatible with COVID-19-pneumonia. After initiation of Anakinra, only one out of nine patients showed acute respiratory failure after 6 hours of drug initiation which demanded discontinuation of therapy. All of the other eight patients showed good clinical and biological outcomes after three days of Anakinra administration. CRP levels decreased steadily during six days of therapy and was normalized on day 11. In all patients, an early chest CT scan between days 5 to 8 showed no more abnormalities. All nine patients were alive at the last follow-up [50].

The efficacy of Anakinra on preventing mechanical ventilation was assessed in a case series among 11 patients with severe COVID-19. Seven of the patients did not require mechanical ventilation, and all of them were discharged. Four patients who received Anakinra in more than 4 days after onset of acute hypoxemic respiratory failure required mechanical ventilation, three of whom were eventually ex-

tubated (2 discharged and 1 remained hospitalized), and 1 died. All 3 patients who were eligible for Anakinra administration (such as documented SARS-CoV-2, fever, and ferritin >1,000 ng/mL with one additional laboratory marker of hyper-inflammation) but did not receive the drug, required mechanical ventilation. Ultimately this study suggests that Anakinra may be a potential option in treating COVID-19 patients with cytokine storm syndrome [51].

Effectiveness of Anakinra; an interleukin 1 inhibitor; was assessed in a case report study among 5 patients with hematological diseases, severe SARS-CoV-2 infection and hyper-inflammation following Tocilizumab treatment. Despite the previous use of Tocilizumab, all patients showed minimal improvement, as they needed higher oxygen aid with progressive elevation of inflammatory markers. After administration of Anakinra, patients' clinical condition continued to deteriorate, as predicted by progressive worsening of radiology images accompanied by continuous rise in inflammatory markers. Moreover, an increase in IL-10, the most immunosuppressive cytokine, was observed after the administration of Anakinra. It seems that Anakinra could not improve clinical status of these patients [52].

The efficacy of Anakinra was studied as a sole treatment on a 47-year-old man with no history of smoking and no noticeable medical history except for well-controlled and untreated asthma, and possible allergy to glucocorticoids. He was primarily treated with hydroxychloroquine, azithromycin, and oxygen but no significant change was observed in the patient symptoms. Following Anakinra administration, an abrupt and progressive improvement occurred in respiratory condition, the patient's fever faded, clinical stabilization was achieved and inflammatory parameters were normalized after 10 days. Also the chest x-ray at this time showed noticeable improvement of the pulmonary infiltrates. Therefore this study reported a well-tolerated case of COVID-19 treated with Anakinra [53].

The effectiveness of Anakinra on a 37 year old male with COVID-19 was studied in a case report. The drug was started with a dose of 100 mg/day. After 7 days of treatment, the patient's retrosternal chest pain was relieved, CRP and D-dimer values, as well as echocardiogram normalized. Anakinra was discontinued 7 days later and the patient was discharged in good clinical condition. He had no problem in his follow-up visit 2 weeks after the hospital discharge, while other treatment options like colchicine and indomethacin did not affect the patient's symptoms considerably prior to the administration of Anakinra. This study suggested that Anakinra may be effective in alleviating COVID-19 inflammatory symptoms [54].

In another case report, the effect of Anakinra on a 57 year old man with COVID-19 was assessed for reducing inflammatory responses caused by the disease. The patient received Anakinra for 7 days along with Tocilizumab and a group of antibiotics. During the follow up, inflammation was diminished and body temperature became normal. By day 16, the patient faced noticeable improvement in respiratory system, in which the oxygen saturation rose to 92% using Venturi mask, but a series of adverse reactions were reported following this study like elevation of procalcitonin, and lung consolidation which was detected on day 10 and could probably be due to persistent viral infection and inflammation. Since Anakinra has a short duration of action, its administration could be discontinued as soon as adverse reactions appear, a property in contrast to long acting medications such as Tocilizumab [38].

Canakinumab

In a prospective study, effectiveness of Canakinumab was evaluated among 150 Covid-19 patients, out of whom 88 patients received Canakinumab. Patients were compared according to changes in oxygen support, duration of hospitalization, and blood factors. In 61.4% of patients, Canakinumab significantly decreased oxygen support requirement. Median range of hospitalization was 24 days in the entire population and 6 days following Canakinumab administration. Also a significant increase in lymphocyte count and decrease in CRP levels were observed among patients who received Canakinumab. [55]

In a study among 48 patients, effects of Canakinumab was assessed on hospitalization duration, survival rate, and oxygen status in a clinical trial. 33 patients received Canakinumab and the rest received standard therapy (antivirals, antibiotics and Hydroxychloroquine). Median age, comorbidities and presenting symptoms were relatively similar between two groups. On day 10 after Canakinumab administration, a 63.2% decrease in supplemental oxygen was observed and ventilation improved significantly. Regarding survival rate, Canakinumab group outnumbered the standard group with 90% survival rate versus 73.3%. The hospitalization rate for less than 21 days was 63% in Canakinumab group, whilst in the standard group all patients were hospitalized more than 21 days [56].

In a study 34 patients were enrolled in a clinical trial to observe the effectiveness of Canakinumab on ICU patients with Covid-19. Effectiveness of this drug was evaluated monitoring inflammation indices and oxygen demand. Patients were divided into two groups of 17 individuals. One group received Canakinumab and the other group received the standard therapy for Covid-19 (Hydroxychloroquine or Lopinavir/Ritonavir). The groups were observed on day zero (before drug administration), day 3 and day 7 of drug administration. Inflammation indices such as D-dimer and fibrinogen dropped significantly, P/F (arterial pO2 divided by the FIO2) ratio increased, and oxygen flow decreased in Canakinumab group on day 3 and 7 versus day zero. On the other hand, supply of oxygen increased in the standard group on day 3 versus day zero, but decreased in day 7 versus day zero. Another finding was the reduction in the lactate levels in Canakinumab group which is a solid sign of reduced respiratory fatigue in this group of patients.[57]

Effects of Canakinumab was evaluated among ten hospitalized COVID-19 patients as a clinical trial and the results were compared with another ten hospitalized COVID-19

patients who did not receive this drug. There were no recorded adverse reactions such as site injection reactions. Following its administration, serum CRP was decreased rapidly and lung oxygenation improved. 45 days after hospitalization, all ten patients in Canakinumab group were discharged from the hospital with no need for oxygen or physical complications related to COVID-19 and no neutropenia or bacterial sepsis was seen. By contrast, the patients on the control group had slower improvements in serum CRP and oxygenation. After 45 days of hospitalization, in non-Canakinumab group, one patient deceased and the others were discharged, among whom one patient required oxygen therapy [58].

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The evaluation of of surface expression of platelet markers and left ventricle ejection fraction in patients with coronary artery disease

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ABSTRACT

Background and Aims: Surface expression of platelet markers enhanced during ischemic events and appear to play an important role in myocardial repair. Stromal cell-derived factor-1 (SDF-1) is one of these factors which its effects Mediated through CXCR4 and CXCR7 receptors. In our study we are going to determine the surface expressions of platelet markers and the changes of left ventricle ejection fraction in patients with coronary artery disease.

Materials and Methods: This descriptive cross-sectional study measured the superficial expression of platelet indices (SDF-1R, CXCR4, and CXCR7) and its association with the changes of the left ventricle ejection fraction in patients with coronary artery disease who have referred to Taleghani Hospital, Tehran in 2017-2018.

Results: Among all patients referred to Taleghani Hospital with symptoms of coronary artery disease, 57 patient had inclusion criteria. this study demonstrated that mean SDF1 and CXCR4 level were respectively 1.1 and 2.3 which there were significant difference between those with severe EF reduction comparing to the rest of the groups (respectively P<0.002 & P<0.004). The mean CXCR7 value of all patients was 3.5 (SD= 0.27) and showed a significant difference in patients with severe (6) and low (4.7) ejection fraction reductions compared to those with moderate (2.5) and normal (2.8) ejection fraction reductions (P<0.009).

Conclusion: Results from this study suggest that the level of surface expression of platelet markers (SDF-1, CXCR4, CXCR7) in patients with coronary artery disease who had severe LV dysfunction rise sharply compared to those with normal ejection fraction, and it can be, therefore, used as a factor to evaluate the level of damage caused by the coronary artery disease.

INTRODUCTION

This descriptive cross-sectional study measured the superficial expression of platelet indices (SDF–1R, CXCR4, CXCR7) and the left ventricle EF changes in patients with coronary heart disease who were referred to Taleghani Hospital during the years 2017-2018. Patients aged 18-60 years of age, who have referred to the hospital with symptoms of coronary heart disease and were admitted for angiography were included. The exclusion criteria were any history of revascularization, cancer and chemotherapy, platelet disorders and acute and chronic bleeding, and the consumption of medications with hematologic complication. Those who with history of receiving blood and platelet products during the last three months also were excluded as well. The consent forms were taken from the patients in case of a willingness to participate in this study. We get our ethical approval from shahid Beheshti University of medical sciences ethical center with ethical code 1398,12 .To measure the precise function of left ventricle and EF changes, Echocardiography were used after the angiography. In this

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regard, the EF > 55% was an indicator of normal function, EF 40-50% was a sign of mild LV dysfunction, EF 30-40% showed a modeate Lv dysfunction, and EF <30% suggested a severe reduction of left ventricle function [11].

The blood platelet indices count (SDF – 1R, CXCR4, CXCR7) was estimated by a 10 cc fasting blood sample that was taken from all patients, and the level of SDF – 1R, CXCR4, and CXCR7 factors was measured by flow cytometry analysis.

The collected data were analyzed by SPSS version 25, and the normality of the data was assessed by the Kolmogorov-Smirnov test. Normal distribution of the data for the ECG-based comparison of platelet factor, the AVONA test was used, and values below 0.05 were considered significant. Also, a post hoc analysis (in our study, Scheffe post hoc test) was used in order to investigate the association between subgroups. In this study, participants' information remained confidential, and participation was not compulsory. Written consent was taken from all participants, and the ethical regulations were based on the provision of the Helsinki convention and acquiesced from the ethical committee.

MATERIALS and METHODS

This descriptive cross-sectional study measured the superficial expression of platelet indices (SDF – 1R, CXCR4, CXCR7) and the left ventricle EF changes in patients with coronary heart disease who were referred to Taleghani Hospital during the years 2017-2018.. Patients aged 18-60 years of age, who have referred to the hospital with symptoms of coronary heart disease and were admitted for angiography were included. The exclusion criteria were any history of revascularization, cancer and chemotherapy, platelet disorders and acute and chronic bleeding, and the consumption of medications with hematologic complication. Those who with history of receiving blood and platelet products during the last three months also were excluded as well. The consent forms were taken from the patients in case of a willingness to participate in this study. We get our ethical approval from shahid Beheshti University of medical sciences ethical center with ethical code 1398,12 .To measure the precise function of left ventricle and EF changes, Echocardiography were used after the angiography. In this regard, the EF > 55% was an indicator of normal function, EF 40-50% was a sign of mild LV dysfunction, EF 30-40% showed a modeate Lv dysfunction, and EF <30% suggested a severe reduction of left ventricle function [11].

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RESULTS

A total of 57 patients who have referred to Taleghani Hospital with coronary artery disease symptoms were included in this study. All participants underwent echocardiography; 33 patients were in normal group and 10 patients have mild LV systolic dysfunction , 7 patients were diagnosed with moderate LV systolic dysfunction, and 7 patients were categorized as having severe LV function reduction.

Table 1 presents the mean values of SDF-1R, CXCR4, and CXCR7 in the groups. The mean SDF-1R value in all patients was 1.11, and there was only a significant difference in patients with severe EF reduction comparing to the rest of the people ($p < 0.002$).

The mean level of CXCR4 in all patients was 2.3, which showed only a significant difference between patients with severe reduction in ejection fraction (3.2) compared to other groups (moderate LV systolic dysfunction (2.1) and Mild Dysfunction (2.3) and patients with normal LV Function (2/2)) ($P = 0.004$).

The mean measure of CXCR7 among all patients was 3.5, and it had significant differences in groups of severe (6) and low (4.7) EF reductions compared to patients with moderate LV systolic dysfunction (2.5) and normal LV fuction (2.8) EF reductions ($P<0.009$), as illustrated in table 1.

Table 1. Patients' distribution based on the platelet indices count and EF reduction (LV= Left ventricle, SD= Standard deviation)

Platelet Marker	LV systolic function	Mean	SD
SDF1	Normal	1.07	0.24
	Mild Dysfunction	1.00	0.22
	Moderate Dysfunction	1.07	0.08
	Sever Dysfunction	1.5	0.51
	Total	1.11	0.3
CXCR4	Normal	2.21	0.47
	Mild Dysfunction	2.29	0.7
	Moderate Dysfunction	2.14	0.55
	Sever Dysfunction	3.16	1.06
	Total	2.33	0.68
CXCR7	Normal	2.85	0.13
	Mild Dysfunction	4.68	0.44
	Moderate Dysfunction	2.49	0.05
	Sever Dysfunction	6.04	0.38
	Total	3.52	0.27

DISCUSSION

This study suggest that the surface expressions of platelet markers (SDF-1, CXCR4, CXCR7) was increased in patients with coronary artery disease and severe left ventricle dysfunction compared to patients with normal EF and, therefore, can be used as an indicator to evaluate the level of damage caused by the coronary artery disease.

The expression of stromal cell-derived factor-1 (SDF-1) on the outer surface of platelets in ischemia plays an essential role in the myocardial damage recovery, leading to the migration of progenitor cells from the bone marrow to the site of injury. The CXCR4 and CXCR7 factors mediate the effect of SDF-1 and increase after injury or severe ischemia. Our results were in agreement with the 2017 study of Kiani and colleagues [12], who have suggested that any damages to the heart tissue lead to the inflammatory chemical secretion of SDF – 1, and subsequently, the increase of CXCR7 and CXCR4 expression in blood cells. In another study by Mayorga and colleagues in 2018 [13], the mesenchymal stem cells (MSC) isolated from the green fluorescent proteins (GFP) were induced to increase the expression of SDF-1 expression. In this study, the administration of MSC significantly improved the EF in control and diabetic rats 21 days after acute myocardial infarction, an outcome that was in line with our findings.

Based on a 2014 study by Rath and colleagues, the clinical potential of the CXCR7 platelet expression level is an influential factor in mediating the beneficial role of SDF-1 on improving performance in patients with acute coronary disease. Surprisingly, in our study the rate of CXCR7 in the group with mild LV systolic dysfunction was more than that of patients with moderate left ventricle dysfunction, which can be partly explained by the small study population in our study; therefore, inadequate power for statistical analyses. However, Schiller and colleagues [14] have neither reported a significant correlation with platelet expression level of CXCR4 and CXCR7 after assessing serum SDF-1 levels among 160 patients with coronary heart disease, as a result, further investigation of this factor will be recommended in future studies. Another limitation of our study is to conduct this study with small sample size from a single health center; therefore, broader multi-central studies with larger sample sizes might be required for the adaptation of the results to the general population.

CONCLUSION

In conclusion, based on the results of this study, it can be said that the level of surface expression of platelet markers (SDF-1, CXCR4, CXCR7) in patients with coronary artery disease who had severe left ventricle ejection fraction reduction rise sharply compared to those with normal ejection fraction, therefore, these platelet markers can be used as an index for the assessment of myocardial damage and left ventricular severe EF reduction.

CONFLICT OF INTERESTS

Authors declare that they have no conflict of interest.

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Evaluation of HER2 cell surface protein expression in differentiated thyroid cancers and its relationship with tumor size and stage

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ABSTRACT

Background and Aims: We aimed to evaluate the expression of HER2 marker in differentiated thyroid cancers and its correlation with tumor size and stage.

Materials and Methods: This is a cross-sectional study that was performed at Tehran Shohada-E-Tajrish hospital from 2015 to 2019. Patients with differentiated thyroid cancer were enrolled in the study. Patients' baseline characteristics and tumor properties were recorded. Expression of tumor marker testing was conducted with IHC. Analysis was performed with SPSS version 20.

Results: Fifty cases of thyroid cancer with a mean age of 46.6 years (78% females) were evaluated. 86% of cases were PTC, 10% FTC, and 4% hurthle cell carcinoma. HER2 positivity rate was 34% totally. HER2 positivity in FTC and PTC patients was 40% and 34.9%, respectively. 84% of patients had a sporadic tumor. HER2 positivity rate in sporadic tumors was 28.6% and 62.5% in familial cases (p=0.063). HER2 status did not association with clinicopathologic factors, significantly.

Conclusion: With the findings of our study, HER2 can't be considered a prognostic factor associated with clinicopathologic parameters.

INTRODUCTION

Thyroid cancer is the greatest prevalent endocrine system cancer. Medullary, anaplastic, and differentiated including papillary, follicular, and hurtle are the three major histologic forms.[1-3] Ionizing radiation exposures and a few rare familial syndromes are among the few known risk factors for thyroid cancer. Thyroid cancer is more common in women, according to epidemiological findings.[4, 5] The fact that thyroid cancer is more common in women during their menstrual years indicates that estrogen and progesterone may play important roles in thyroid cancer pathogenesis. Thyroid cancer risk was found to be lower in women after menopause. [6, 7] Several human epithelial tumors, including breast, ovarian, gastric, and colorectal cancers, have the human epidermal growth factor receptor 2 (HER2) gene enhanced and the protein overexpressed. [8-10] Overexpression and amplification of HER2 have been related to a poor outcome and a poorly differentiated phenotype in these tumors. [8, 11] The HER2 is of special interest in tumor biology since it is both a powerful predictive factor in a variety of tumor types and a very useful therapeutic target in breast and stomach cancer. There isn't enough evidence to determine that HER2 has an effect in thyroid cancer. In some studies it was observed that in involving thyroid patients, reported HER2 overexpression rates range from 0% to 79.5 percent. [12-16] In the recent literature, there is very little general agreement on this marker's possible prognostic and therapeutic importance in thyroid cancer. [17, 18] Due to there is a low consensus about the effect of HER2 on thyroid cancer and its relationship with size and stage of tumors, in this study, we aimed to investigate the expression of HER2 surface protein in differentiated thyroid cancer and evaluation of its relationship with stage and size of tumors.

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MATERIALS and METHODS

This study was approved by ethical committee of medical university of Shahid Beheshti and it took ethical code from this committee (IR.SBMU.MSP.REC.1398.870). In this descriptive cross-sectional study, patients who were referred to Shohada-e-Tajrish Hospital (Tehran-Iran) for thyroid cancer surgery from 2015 to 2018 with thyroid cancers, were studied. All patients in this duration were studied. The inclusion criterion was having differentiated thyroid cancer and exclusion criteria were patients with other concomitant malignancies, patients who did not consent to study, patients whose samples were not available for HER2 testing, and undifferentiated cancers in pathology. Five hundred and fifty-eight patients were evaluated and finally, 50 patients were enrolled in the study according to inclusion and exclusion criteria.

Written informed consent was obtained from all patients to participate in the study and no costs were imposed on patients. Patient's data including age, sex, and family history were asked from them. Tumor characteristics including pathology type, tumor size, tumor invasion status were determined by preoperative and postoperative pathological examination and evaluation of surface protein expression. HER2 tumor cells were analyzed by IHC. All histopathologic specimens were studied by a specific expert pathologist during the study.

Follow-ups of patients (one week, six months, and one year after surgery) were performed over time, and recovery status, recurrence, or mortality was recorded. Whole-exon mutation data were extracted from the Thyroid Cancer Genomic Data Analysis Center (GDAC) for genetic analysis. HER2-related information was obtained from this center and their mutations were assessed in patient samples.

Statistical analysis

SPSS software version 20 was used for data analysis. Absolute and relative abundance of markers was reported in the subgroups. In non-parametric data, the Mann-Whitney U test was used to compare patients age and tumor size between groups and used Chi-square test to compare difference between percent's in each categorical factors. Statistically significant limit (p-value) was considered lower than 0.05.

RESULTS

In this study, 50 differentiated thyroid cancers were studied with a mean age of 46.60 ± 13.96 years. Thirty-nine patients were female (78%) and 11 (22%) were male. Histologically, 5 cases (10%) had follicular thyroid carcinoma, 2 cases (4%) had hurthle cell cancer and 43 cases (86%) had papillary thyroid carcinoma. The HER2 marker was negative in 33 cases (66%) and overexpressed in 17 cases (34%). In terms of family distribution pattern, 42 cases (84%) had a sporadic pattern and 8 cases (16%) had cancer with a familial distribution pattern. The mean of the largest tumor diameters in this study was 2.32 ± 2.33 cm. In terms of staging, 35 patients (70%) had stage I and 15 patients (30%) stage II. In terms of tumor invasion depth (T), 33 cases (66%) were T1, 11 cases (22%) were T2, and 6 cases (12%) were T3. In terms of lymph node involvement, 39 patients (78%) did not have lymph node involvement and 11 patients (22%) had lymph node involvement.

The patient's gender composition was measured by HER-2 status. In females, 25 patients (64.1%) were negative and 14 patients (35.9%) were positive for HER2. Among males, 8 cases (72.7%) were negative and 3 cases (27.3%) were positive for HER2 ($p = 0.594$ -based on chi square.) The age of patients in the HER2 positive group was 45.88 ± 16.73 years and in the HER-2 negative group was 47.06 ± 12.57 years ($p = 0.780$). There was no statistically significant difference between HER2 positive and negative groups in the terms of age and sex.

In follicular thyroid carcinoma cases, 3 patients were HER2 negative (60%) and 2 patients were HER2 positive (40%). In Hurthle cell cases, 2 patients (100%) were HER2 negative. In PTC cases, 28 patients (65.1%) were HER2 negative and 15 patients (34.9%) were HER2 positive ($p = 0.570$ -based on chi square).

Between sporadic cases, 30 patients (71.4%) were HER2 negative and 12 patients (28.6%) were HER2 positive and in familial cases, 3 patients (37.3%) were HER2 negative and 5 patients (62.5%) were HER2 positive ($p = 0.063$-based on chi square).

The mean tumor size in the HER2 positive group was 2.63 ± 2.49 cm and in the HER2 negative group was 2.16 ± 2.26 cm ($p = 0.509$). In terms of disease stage, in stage-1 cases, 23 patients (65.7%) were HER2 negative and 12 patients (34.3%) were HER2 positive. In stage-2, 10 patients (66.7%) were HER2 negative and 5 patients (33.3%) were HER2 positive ($p = 0.948$-based on chi square).

In T1 cases, 24 patients (72.7%) were HER2 negative and 9 patients (27.3%) were HER2 positive. In T2 cases, 5 patients (45.5%) were HER2 negative and 6 patients (54.5%) were HER2 positive. In T3 cases, 4 patients (66.7%) were HER2 negative and 2 patients (33.3%) were HER2 positive ($p = 0.255$-based on chi square). In cases with N0, 27 patients (69.2%) were HER2 negative and 12 patients (30.8%) were HER2 positive. In N1 cases, 6 patients (54.5%) were HER2 negative and 5 patients (45.5%) were HER2 positive ($p = 0.364$-based on chi square).

In the following, we have analyzed the parameters based on the histological type of cancer and due to the very small number of Hurthle cases, we excluded them from the analysis.

The gender compositions were: in follicular cases, 4 patients were female (80%) and 1 was male (20%) and in the PTC cases, 33 patients (76.7%) were female and 10 patients (23.3%) were male ($p = 0.735$-based on chi square). The patient's age in the follicular group was 45.20 ±12.93 years and in the PTC group was 47.11 ±14.43 years ($p = 0.778$-based on Mann-Whitney U-test). In the follicular group, all cases (100%) were sporadic, and in the PTC group, 36 cases were sporadic (83.7%) and 7 cases (16.3%) were familial

(p = 0.262- based on chi square). Tumor size in the follicular group was 5.70 ± 3.09 cm and in the PTC group was 1.89 ± 1.95 cm (p <0.001- based on Mann-Whitney U-test).

In terms of disease stage, in the follicular group, 2 patients (40%) were in stage 1 and 3 patients (60%) were in stage 2. In PTC cases, 31 patients (72.1%) were in stage 1 and 12 patients (27.9%) were in stage 2 (p = 0.213- based on chi square).

In terms of tumor invasion depth, in the follicular group, 3 cases (60%) were T2 and 2 cases (40%) were T3. In the PTC group, 32 cases (74.4%) were in T1 stage, 7 patients (16.3%) were in T2 stage and 4 patients (9.3%) were in T3 stage (p = 0.016- based on chi square).

In terms of lymph node involvement in the follicular group, N0 in 4 patients (80%) and N1 in 1 patient (20%) were seen. In the case of PTC, 33 patients (76.7%) were N0 and 10 patients (23.3%) were N1 (p = 0.735- based on chi square).

The status of the parameters was analyzed based on the sporadic/familial distribution of the tumors. Among females, 32 cases (82.1%) were sporadic and 7 cases (17.9%) were familial and in the males, 10 cases (90.9%) were sporadic and 1 case (9.1%) was familial (p = 0.479- based on chi square). the mean patient's age was 45.61± 13.70 years in sporadic cases and 52.12 ± 14.98 years in familial cases (p = 0.231). Tumor size in sporadic cases was 2.17 ± 2.38 cm and in familial cases was 3.15 ± 1.94 cm (p = 0.281). About staging, in sporadic cases, tumor stages were stage 1 in 30 cases (71.4%) and stage 2 in 12 cases (28.6%) and in familial cases, in 5 cases (62.5%) were in the stage 1 and 3 cases (37.5%) were in the stage 2 (p = 0.614- based on chi square). About the depth of tumor invasion in sporadic cases, 31 cases were (73.8%) T1, 7 cases (16.7%) were T2 and in 4 cases (9.5%) were T3 and in familial cases, 2 cases (25%) were T1, 4 cases (50%) were T2 and 2 cases (25%) were T3 (p = 0.028- based on chi square).

In sporadic cases, 33 cases (78.6%) were N0 and 9 cases (21.4%) were N1 and in familial cases, 6 cases (75%) were N0 and 2 cases (25%) were N1 (p = 0.823- based on chi square).

There was no mortality in all patients during the study.

DISCUSSION

In the current study that was performed on 50 patients with thyroid cancers including PTC, FTC, and hurthle cell, 78% were female and 22% were male. About subtypes of carcinomas, FTC in 10%, hurthle cell in 4%, and PTC in 86% was seen. HER2 was negative in 33 cases (66%) and overexpressed in 17 cases (34%), overall. In the Ruggeri et al study, it was found HER2 overexpression was discovered in 20/45 (44%) FTC and 8/45 (18%) PTC, and it had a significant difference. We found that HER2 was positive in 40% of cases with FTC. In PTC cases, HER2 was positive in 34.9% of cases. Our findings were similar to Ruggeri et al study, approximately. In fact, about the relationship between FTC and HER2, these findings were similar but about HER2 relationship with PTC, there was a contrast between these two studies. This difference may be coming from the understudy population because, in the present study, 50 patients were studied but in the Ruggeri et al study, it was 90 patients.[19]

In the Dai et al study, it was demonstrated that there was a significant correlation between HER2 and PTC. In fact, there was a positive correlation between HER2 and PTC, and overexpression of HER2 can increase the risk of PTC occurrence. In the present study, we observed HER2 positive cells were seen in about 35% of patients with PTC. We saw HER2 had more correlation with FTC. In the Dai et al study HER2 relationship with FTC did not assess. About the relationship between PTC andHER2, it seems these studies are similar. [20]

In the Wei et al study, it was concluded that HER2 is a potential biomarker for anaplastic thyroid cancer. In the current study, we found that HER2 could be found in PTC and MTC but we didn't evaluate this relation with anaplastic thyroid cancer.[21]

In the Kavanagh et al study it was found that HER2 was associated with poorly differentiated tumors, tumor invasion, and disease relapse. In the current study, although we observed invasion mount of HER2 positive carcinomas were not statistically significant and HER2 negative carcinomas had a higher amount of invasion than HER2 positive, HER2 positive carcinomas had considerable rates of invasion, and some studies should be performed in the future. Also, in the present study, 34.3% of HER2 positive carcinomas were stage1, 33.3% of them were in stage2 and all of them didn't have a statistically significant difference. In fact, HER2 did not correlate with types of differentiation. These studies are different in findings . [22]

In the Zhang et al study, it was found that there was a significant relationship between differentiated thyroid carcinomas size and mortality, especially about PTC. Higher tumor size had a higher hazard ratio for mortality. In the current study, we saw there was no relation between mortality rate and size of tumors and follicular type had higher size than PTC. These findings are very different. One of the reasons for this difference could be the difference in follow-up duration in the two studies. In the current study, all patients were followed up for one year but in the Zhang et al study, it was about 2 years. This could be the cause of mortality in Zhang et al study. Also, in the Zhang et al study, all patients were in stage4 for differentiated carcinomas and it could be another reason for the difference. In the current study, FTCs had a higher size than PTCs and it was another difference between these studies. [23]

In our study, the sporadic or familial distribution of thyroid cancer in HER2 positive patients in 28.6% of cases, and in 62.5% of cases it was familial, but this difference was not significant. A study by Caria et al found a significant relationship of HER2 with familial type in PTC. These findings in these two studies were different. Also, these studies were different in terms of method of study because our study was performed on all differentiated thyroid cancer but Caria et al

study was performed on PTC. [24] In the Jiwang et al study it was mentioned that there was a significant relationship between T and N stage between the familial and sporadic PTC. These findings were approximately similar to our results because in the current study we found that higher sporadic pattern in PTC but this difference was not statistically significant [25].

CONCLUSION

There is no significant difference between age, sex, type on differentiated thyroid cancer, sporadic/familial type, TMN scoring with HER2 positivity or negativity. Also, between PTC and FTC there were no statistically significant differences in sex, age, familial/sporadic type, staging, and lymph node involvement. But there were significant differences between FTC and PTC in terms of size and depth of tumor invasion of the tumor. Overall, there was a significant difference between the depth of tumor invasion in the sporadic and familial types of tumors.

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The Late presenting Bochdalek hernia; A Case report and review of literature

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ABSTRACT

We report a 22-month-old boy who referred due to nausea, vomiting, abdominal pain and watery non-bloody diarrhea and after thorough evaluation, a large defect in the left postero-lateral side of diaphragm and presence of bowel loops, spleen, stomach and left lobe of liver in the left hemi-thorax were detected. So, he was operated and managed with the impression of Bochdalek hernia. We have also reviewed the similar case reports in the past 10 years, briefly, in order to map the presentations and clinical course of cases with Bochdalek hernia which were diagnosed late, for giving physicians a better insight on this issue.

INTRODUCTION

Congenital Diaphragmatic hernia (CDH) is characterized by a defect in the integrity of diaphragm which leads to the herniation of abdominal components into the thoracic cavity. Genetic, environmental and nutritional factors are suggested as basic etiologic components of this congenital defect. Bochdalek hernias are referred to postero-lateral CHDs which are the most common type of them. CHDs are associated with life threatening health issues including lung hypoplasia and immaturity, pulmonary hypertension and ventricular dysfunction, hence the early diagnosis would be favorable. More than 50% of cases are diagnosed prenatally by ultrasound at a mean gestational age of 24 weeks, however, diagnosis of some cases may be delayed due to non-specific or late presentations of the herniation [1]. Here in, we intend to present a case of Bochdalek hernia in a 22-month-old boy with late presentations.

CASE PRESENTATION

A 22-month-old male (First born child of a non-consanguineous marriage, full term normal delivery) presented to our tertiary hospital with recurrent episodes of vomiting and nausea, abdominal pain and watery non-bloody diarrhea. The patient was ill but not toxic. He was also dehydrated (no tears, sunken eye). In physical examination, there was no abdominal tenderness. Also, a chest CT scan was requested and performed confirming diagnosis of hiatal hernia. After clinical stabilization, this patient was operated on. During the surgery a wide diaphragmatic defect into the left thorax was seen and bowel loops, spleen, stomach and left lobe of liver were placed ectopically. Herniated viscera were returned to the abdominal cavity. He had been discharged after 1 week with a stable condition. During about one year of post operation follow up except one episode of

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early partial bowel obstruction that cured with conservative management, he was in good condition with good weight gain and his developmental milestones were appropriate to his age.

DISCUSSION

Bochdalek hernia may be lately diagnosed due to its unspecific or late presentations. Many CDHs are diagnosed prenatally through ultrasound or other prenatal diagnostic modalities [1]. Moreover, after birth, as a result of herniation of different abdominal organs into the thoracic cavity, problems associated with the malfunctioning of organs in the thorax or that of the herniated organs, may present as pulmonary, cardiac or gastrointestinal sign and symptoms leading to early diagnosis of hernia [1]. However, some cases remain undiagnosed until older ages. We have reviewed the case reports of delayed diagnosis of Bochdalek hernias in pediatrics in the last 10 years (table1) and the most common presentations of these cases are as following: Irritability [2], dyspnea [2-4], tachypnea [4-6], cough [7, 8], fever [7-9], cyanosis [2, 4, 10] and gastrointestinal symptoms such as abdominal pain [10-15], nausea [13, 16] and vomiting [10, 14, 16-18]. In our case, 22-month-old male was presented with recurrent episodes of vomiting and nausea, abdominal pain and watery non-bloody diarrhea. To the best of our knowledge, this is the first report of delayed diagnosis of Bochdalek hernia in a patient with a defect large enough for the left lobe of liver to be herniated.

Since the mentioned symptoms are nonspecific, physicians usually evaluate other differential diagnosis prior to CDHs. Therefore, CHD diagnosis may be delayed which increases the possibility of further complications subsequent to the hernia. We intend to attract physicians' attention to this di-

Table 1. A review of the delayed diagnosis of Bochdalek hernia in pediatrics during the last 10 years. (yo: Year old, mo: Month old, do: Day old, CPAM: Congenital Pulmonary Airway Malformation)

Age/sex	Symptoms	Physical examination	Hernia site and Organs inside the thorax	Other findings	Ref and year
19yo / female	Distention pain, vomiting, nausea	normal	pancreas	In the 3 rd semester of pregnancy	[16]/ 2020
12yo / female	abdominal pain	air entry was reduced in lower lobe of left lung with no adventitious sounds.	A defect of size 8.2cm was noted in posterior 2/3rd of left hemidiaphragm / stomach, spleen, splenic flexure of colon, left kidney, left adrenal gland	collapse consolidation of left lung parenchyma with mild to moderate left sided pleural effusion (post-surgery)	[11]/ 2020
3mo / female	irritability, dyspnea, and feed refusal	Cyanosis / reduced left lung breath sounds / barrel-shaped chest / scaphoid-like abdomen. apex of the heart displaced to the right / O2sat=44% / respiratory rate= 60/min / heart rate =160/min	defect at the posteriolateral part of the left diaphragm spleen, stomach, transverse colon, and greater omentum.	No other findings	[2]/ 2020
10mo / male	Recurrence Anemia	normal	spleen	RPS 19 mutation	[19]/ 2019
9yo / female	Weight loss, vomiting, epigastric pain	Dullness in stomach	Colon, spleen	No other finding	[12]/ 2019
3yo / male	upper respiratory tract infection / progressing respiratory distress and retching/ dyspnea	temperature of 39.5°C and tachycardia of 200/min	left-sided Bochdalek hernia / small intestine, spleen, and stomach into the chest	Gastric perforation at the lesser curvature / Bile-stained fluid in the thorax and abdomen	[3]/ 2018
2yo / male	fever of low to moderate grade and dry, non-productive cough of ten days	decreased movements on left side of chest / Breath sounds decreased in left infrascapular, interscapular and infraaxillary regions.	left postero-lateral aspect - Congenital diaphranatic hernia / part of stomach, spleen, splenic flexure and part of transverse and descending colon	No other findings	[7]/ 2017
6mo / male	Respiratory distress and vomiting	Tachypenic and crepitant rales were heard in the basal segment of the hemithorax	kidney	No other finding	[17]/ 2017

Table 1. *(cont.)*

1yo / male	fever, cough, hurried breathing	severe acute malnutrition, tacyhpnea, retractions, absent air entry on left axillary, infrascapular areas with coarse crepitation	bowel loops	No other findings	[7]/ 2017
10yo/ male	Fever, cough	No related finding to hernia	Left colon	No other finding	[8]/ 2016
12yo / female	(recurrent) abdominal pain and nausea	unremarkable	Bochdalek hernia / stomach, spleen, and transverse colon	No other findings	[13]/ 2016
21do / female	Mild tachypnea and failure to thrive on day 20 of life	mild tachypnea / decreased air entry on right side / O2sat=90%	defect in posterior part of diaphragm / right kidney, adrenal gland, small bowel loops	No other findings	[6]/ 2015
17yo / female	Vomiting and abdominal pain, cyanosis	Abdominal distention	2 cm diameter defect in the central part of the diaphragm	No other finding	[10]/ 2015
6.5yo / female	Spastic tetraparesis, vomiting	Absence of respiratory sound	Small intestinal and colon segments in thorax	No other finding	[18]/ 2015
5yo/ female	Dyspnea and tachypnea, cyanosis	Decrease sound of the left side of the chest	Dilated Colonic loop in thorax	No other finding	[4]/ 2015
3mo / female	worsening tachypnea and fatigue	No related findings to hernia, presented for cardiac surgery	Undergone heart surgery and discharged after 6days, Bochdalek diagnosis was made during postmortem evaluation	defect in the left posterior hemidiaphragm / stomach	[5]/ 2015
1yo / male	Occasional chills and rigor in past 4 months	normal	Left kidney in thorax beside hearth	No other finding	[20]/ 2014
2yo / male	Gastric volvulus	Abdominal tenderness	kidney	No other finding	[21]/ 2013
3yo / male	Abdominal pain and vomiting	Cardiac arrest and death	Transverse colon and upper pole of the spleen	No other finding	[14]/ 2013

agnosis, in spite of its unspecific or late presentations even in the patients with large diaphragmatic defects.

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

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LETTER to EDITOR
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Slides with English text that are explained in Persian

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The common pattern of presentation in the Iranian medical community is lengthy English text in slides that are presented orally in Farsi, both in conferences and classrooms. In this paper, we aim to further explore this phenomenon based on a theory in the domain of cognitive science named the cognitive load theory (CLT).

According to Atkinson and Shiffrin's model introduced in 1968, human memory consists of three parts: sensory memory, working memory, and long-term memory. Information first enters the sensory memory, and if received adequate attention and reaches the level of consciousness, it enters the working memory, which, unlike the other two memories, i.e, sensory and long-term memory, has a limited capacity [1]. Interestingly, working memory has two separate and independent channels for processing visual and auditory information with a limited and predetermined capacity (dual-channel theory). As a result, the speed of learning in humans restricts [2].

In 1988, Sweller proposed a theory of learning called the CLT, in which the three key components of the cognitive structure, i.e. memory systems, learning processes, and types of the cognitive load imposed on the working memory, were merged. According to this theory, because of the limited capacity of the working memory, any factor that imposes an excessive load on this memory will disrupt the learning process [2]. Here three types of loads are introduced:

1. Intrinsic load is related to the task. The more complex the information that must be processed by the working memory, the greater the load imposes.

2. Germane load refers to the situations when some instructional formats could increase cognitive load and improve learning as well.

3. Extraneous load is the load resulting from the learner's use of the working memory to focus on something other than the task or learning [3]. When the teacher talks about the anatomy of the stomach and the related slide has a long text, the learner has to look for a picture about the stomach's anatomy in another source to understand. As a result, she is using her working memory for something other than learning which in turn reduces learning.

Now let's get back to our main question about long English text slides that are presented orally in Farsi. There are two issues here; the first is that the text is long, and the second is that it is in English.

Studies by Kayuga and colleagues in 1999 showed it is more effective to present the text orally than is presented visually. But in simultaneous oral and visual presentation, because of image processing, an additional external load leads to reduce learning. Therefore, considering the limited and independent capacity of dual channels of sensory memory, the text of the slides should not be too long [4].

On the other hand, English text slides for non-English speaking audiences and for those who have not read the text in English before can impose an additional cognitive load. This is because the audience has to think about the meaning of words and even search for their meaning. Conversely, for those who are familiar with both English texts and terms, reading and understanding the Persian translation of the terms may lead to additional load. Therefore, it is recommended to use short English text in the slides and to use language that imposes the least extraneous cognitive load on the audience.

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Several foreign bodies throughout the torso following a shotgun injury

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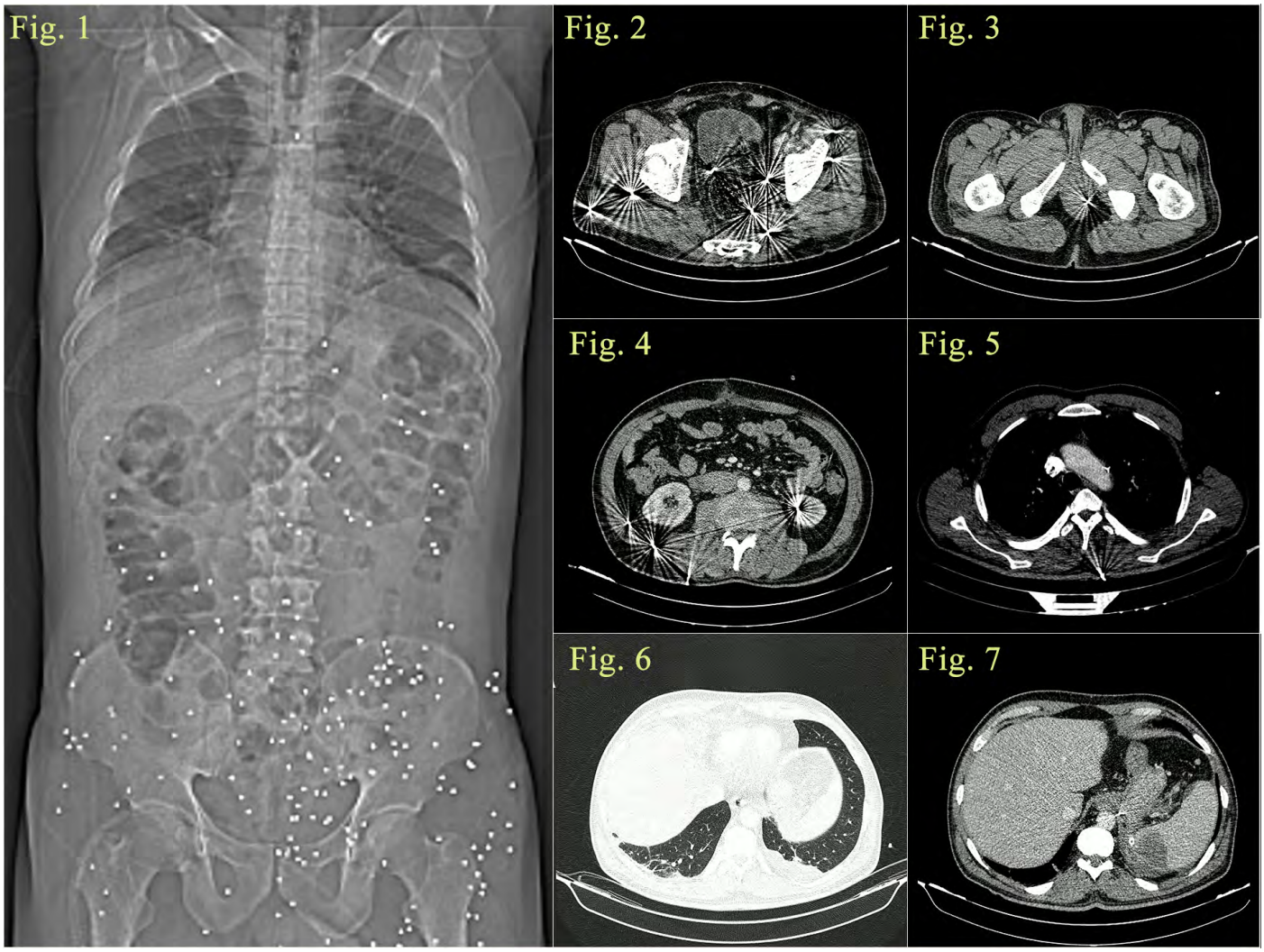

A 50 year old man with a history of posterior bullet shot with a shotgun was presented to the hospital 18 hours after the accident complaining of abdominal and gluteal pain. He had stable vital signs, no respiratory distress, and no active bleeding. Physical examination revealed abdominal tenderness and generalized abdominal guarding. After a primary survey, a complete abdominopelvic ultrasonography and whole body computed tomography (CT) scan were performed (Figure 1) and revealing several bullet fragments (confirmed with Hounsfield scale) in paraspinal and abdominal wall, mesenteric fossa, pererectal and prenephric area, intestinal surroundings and illiac fossa (Figure 2 and 3).

Keywords
Shotgun, Lead Poisoning, Firearms, Magnetic Resonance Imaging, Computed, Computed tomography, Pancreatic Pseudocyst, Multiple Retain fragments, Ballistic Debris, Gunshot wounds

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One of the bullet fragments was observed in left inferior renal calyx (Figure 4). Moreover another fragment was touching aortic arch (Figure 5).

Afterwards, the patient underwent explorative laparatomy. About two liters of blood clot was observed in pelvic fossa. Also evidences of spleen injury and pancreas tail and rectum hematoma with no active bleeding was observed. The patient was evaluated for damage to the mocusal layer and the ischemi of rectum due to the rectal injury; that, fortunately, was normal. All four quadrants were packed and drainage was applied for pancreas. Since there was no fragment in aortic intima, no intervention was needed. After post-operative antibiotic therapy and other follow-ups such as urologic assessments, the patient was discharged.

After two weeks, the patient was again referred to the hospital with pain in the site of drainage tubes. In laboratory tests amylase levels was 162 (U/L) and lipase levels was 83 (U/L). Plural effusion and atelectasis were observed in left lung CT scan (Figure 6) which did not need invasive intervention. Accumulation of spleen subcapsular fluid was observed in abdominopelvic CT scan. Loculated fluid collection was observed in pancreaticosplenic and paracolic areas (Figure 7) which led to diagnosis of pancreas drainage infection. The patient was treated with wide spectrum antibiotics and the symptoms were resolved. Also, there was the possibility for lead poisoning with lead bullet fragments, therefore serum levels of lead were examined after two months. The results showed a high level of lead concentration in serum (29 µg/dL). The patient was treated with antioxidant and vitamin C and asked to refer to the hospital every 2 months to check the lead level and have it under control [1, 2]. Administrating chelating agents such as dimercaptosuccinic acid and calcium disodium EDTA should be considered if the serum lead level is increased in the follow-up. Moreover, with the possibility for secondary adverse effects due to retained fragments, such as fistula formation, visceral adhesion, recurrent infection, et Cetra, the patient was advised to do frequent imaging checkups.

According to similar cases and new studies, the presence of the lead in the bullet fragments won't be causing any contraindications for magnetic resonance imaging but may cause some artifacts thus the alternative imaging tests such as CT or X-ray graphy are suggested. There's also no evidence for the pellets movements and visceral organs injury after MRI in shotgun injury cases [3, 4].

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