Immune Thrombocytopenia Secondary Splenic Tuberculosis: A Case Report

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Abstract
Despite all the medical and scientific improvements over the past decades; tuberculosis still remains wide-spread and deadly serious. Splenic tuberculosis is a rare form of extra pulmonary tuberculosis. Immune thrombocytopenia is an auto-immune condition that results in isolated thrombocytopenia. Moreover, with its secondary form; it is scientifically proven that immune thrombocytopenia can be triggered with numerous infections or even non-infectious conditions. Although the symptoms and results can be severe, subordinate immune thrombocytopenia which is associated with splenic tuberculosis has not yet taken its crucial and much-needed place in the medical history; surprisingly this matter has not been profoundly covered and analysed yet. A report states that on a 63-year-old patient, diagnostic splenectomy was performed. This elderly patient suffers from purpura and petechial with the cause of immune-mediated thrombocytopenia which is secondary to splenic tuberculosis; and after the diagnostic splenectomy; splenic tuberculosis was pathologically detected in tests and microbiologic examinations. However, the treatment on patient worked and the medical experts treated the patient with splenectomy and antituberculous therapy. The crucial point here is that patients, who have immune thrombocytopenic purpura, should be exposed to relevant tests and the medical professionals should suspect the high-risk possibility of splenic tuberculosis especially in the endemic area in-patients who have higher risk. Regarding the diagnosis, histopathological examination remains as an ideal method, when it comes to a solid confirmation, executed with microbiological examination.

Keywords: Immune Thrombocytopenia, Splenic Tuberculosis, Splenectomy

Introduction
Although it was once believed that Tuberculosis (TB) is common in under-developed countries that this belief is a myth as TB predominantly progresses in the developing countries with morbidity and mortality. Simply due to the fact that the increasing prevalence of immunocompromised patients and human immunodeficiency virus (HIV) infections [1, 2]. As mentioned before that TB is a multi-system disease, 90% of which occurs primarily in the lung. Extra pulmonary tuberculosis accounts for 5–50% of all cases of tuberculosis. Another fact is that the diagnosis of extra pulmonary tuberculosis is usually delayed because after the specific symptoms show at a later stage and are not always evident. TB of the spleen is an extremely uncommon condition, particularly in the non-HIV patient population. One fact is to mention that the difficulty of the preoperative diagnosis of the condition due to it is being an uncommon and unanticipated post-op discovery as it’s usually diagnosed following an operation. The primary tuberculosis of the spleen was suggested by Coley in 1846 as disseminated TB occurrence [3,4]. The Splenic TB also was categorized by Winternitz in 1912 as “the primary or secondary form”; in which the primary form the disease was discovered to be limited to the spleen only, the original focus having healed. On the other hand, the other form, namely “the secondary splenic TB” had a different outcome as it occurred as part of disseminated TB [5].

There are of course hematological abnormalities such as, pancytopenia, anemia, thrombocytosis and leukocytosis which have connection with TB. There is another fact that the abnormality of thrombocytosis platelet is usually considered a reactive change [6]. It is discovered that the regular pattern for thrombocytopenia in TB is the cause of non-immune mechanisms which lies in the pancytopenia which is known for developing secondary to granulomatous infiltration of the bone marrow. However, as a consequence of the tuberculosis infection; the occurrence of the immune-mediated thrombocytopenia (ITP) is highly rare. ITP and TB were first linked during the mid-twentieth century. Therefore, the date refers to pathophysiological and epidemiological aspect of this matter still remains scarce [7,8]. In fact, there are only a few cases that can be linked with the immune thrombocytopenia and its connection with immune thrombocytopenia; it is common diagnose this as pulmonary tuberculosis [9].

It is known that ITP has a relationship with isolated splenic tuberculosis (splenic TB). However, this hasn’t been covered nor examined in the medical literature. Our intention is to demonstrate a case of immune thrombocytopenic purpura (ITP) associated with splenic tuberculosis in which thrombocytopenia and tuberculosis
Case Report

Approximately, over a month ago a patient who is 63 year-old-female was admitted to the clinic with the involuntary weight loss problem and the patient was generalized with purpuric lesions for the previous 3–4 days. The patient did not have any previous history of infection, tuberculosis, surgical interventions or any other significant past illnesses. She had a small family who had no history of tuberculosis. The physical examination was unremarkable except for diffuse purpuric lesions in both lower extremities. Allow us to point at the vitals! Which follows as; arterial blood pressure: 120/80 mmHg, temperature: 36.5°C and pulse: 80 per minute. Additionally, no organomegaly or lymphadenomegaly was detectable.

Before we continue any further that it is essential to indicate the following lab result which as follows; platelet count 8.000/mm³ (150.000–450.000), hemoglobin: 12,6g/dl, WBC: 6900/mm³, erythrocyte sedimentation rate (ESR): 48 mm/h, and C-reactive protein (CRP) in the normal range. Patient was hospitalized in the hematology clinic. Blood glucose, kidney function tests and liver function tests were normal. Both tests of the urine routine and the microscopy showed no abnormality. We also conducted a test for paucity of platelets and the results of peripheral smear were remarkable. Furthermore, we discovered the following: Direct Coombs test was negative PT/PTT, fibrin degradation products (FDP), rheumatoid factor, lupus anticoagulant, anticardiolipin antibodies (IgM, IgG), antinuclear antibodies, dsDNA, HIV, HBsAg and anti-HCV were negative. Chest radiograph and electrocardiogram were also normal. We also performed the bone marrow aspiration and bone marrow biopsy tests which showed that bone marrow aspiration showed increased cellularity of all cell lines, and in particular an increase in the number of megakaryocytes. Further bone marrow biopsy indicated that mild hyper cellularity of all cell lines with normal maturation of myeloid and elytroid precursors. We also found out that the megakaryocytes were increased in number with normal morphology. However, we didn’t detect any sign of granulomas, leukemic infiltrate or metastatic deposits.

These were followed by computed tomography (CT) of the chest, abdomen, and pelvis. We found out that the thorax CT had a normal lung parenchyma and non-pathologic Para tracheal, bilateral hilar, submarine lymphadenopathies. The test we conducted for abdominal and pelvic CT showed no lesions or lymphadenopathies. Moreover, the size of the spleen was normal and parenchymal echogenicity of spleen was homogeneous. Based on the above clinical findings, provisional diagnosis was made as ITP. 1mg/per kg/ day oral steroid therapy was prescribed with a weekly follow up. However, the outcome was a failure as patient did not respond to steroid therapy. Due to the failed outcome, patient was referred for splenectomy. IVIG (Intravenous immunoglobulin) was chosen as treatment for patient with a fever, general malaise, weight loss, and runs a chronic course for a transient increase in the platelet count before splenectomy. Patient was stable a week after the splenectomy, having a count of platelet indicating 257000/ mm³. The pathology results also showed the splenectomy specimen as caseous necrotic granulomatous splenitis (Figure 1). The acid-fast bacilli on Ziehl-Neelsen staining were also seen in sample after the microbiological examinations. The histology report which was not proved macroscopically, confirmed the active splenic tuberculosis. As next course of treatment, patient was postoperatively given our antituberculous agents (isoniazid 300 mg/d, rifampin 600mg/d, ethambutol 1200 mg/d, pyrazinamide 1500 mg/d) for two months, followed by isoniazid and rifampin and pyridoxine. In conclusion, the treatment of patient was a success as we found no recurrence of thrombocytopenia in the follow-up two years.

Discussion

As mentioned before that tuberculosis is seen as an endemic in most of the developing nations in the world. Especially, after the AIDS epidemic, this disease also becomes prominent in the developed and advanced countries. A rare form of tuberculosis, called the isolated splenic tuberculosis, usually develops subordinate to military tuberculosis. Although Winternitz claims splenic TB with subordinate and primary forms, other experts believe that all splenic TB patients are secondary to the previous infection of tubercle bacillus in other organs. In contrary, in our patient, the case was different as the patient’s history had no sign of TB nor any other indication of other involvement in other organs when the patient was admitted [10].

Isolated splenic tuberculosis is an extremely rare form, particularly in the immunocompetent people. Many reports suggest that there is a strong link with HIV infection [1]. Moreover, medical reports indicate that the splenic abscess caused by tuberculosis is not a common case in immune-competent patients [11]. However, the patient was a very different case as the splenic tuberculosis patient was immunocompetent.

Additionally, when it comes to establishing the splenic TB diagnosis, you notice that this form has no specific symptoms [10]. However, it is believed that a sign of a painful left upper quadrant mass linked with a fever, general malaise, weight loss, and runs a chronic course are associated with the likely symptoms [12]. However, our patient does not comply with the above nor the common description as it is difficult to establish the preoperative diagnosis of TB of spleen. One of the methods of categorizing splenic TB has been conducting the procedure radiologically into micronodular or macronodular forms which depend on the size whether it is smaller or larger than 10 mm. Macronodular form of splenic tuberculosis is rare and it is discovered that the macronodular splenic TB can manifest as a singular abscess or multiple large nodules [1]. The micronodular form of splenic TB is more common and the patients with this type of TB have multiple nodules. A CT (Computerized Tomography)
The important fact here is that TB preoperative diagnosis is not always possible and it is invariably and splenectomy is diagnostic. After the pathologic examination of splenectomy specimens of patient; we discovered granulomatous splenitis. However, CT showed preoperatively a normal result for spleen. As a result the TB was not suspected. This brings us to the fact that when it comes confirming the diagnosis, histopathological examination still remains as an ideal method. An essential quality here would be that the physician has to approach the matter with high degree of clinical suspicion and use the appropriate clinical equipment to conduct the procedure.

There are of course hematological abnormalities such as, pancytopenia, anemia, and leukocytosis which have connection with TB. Moreover, TB is associated with the changes in the bone marrow which scopes the marrow cellularity that manifests as myeloid hyperplasia where the occurrence rate is higher, especially with pulmonary tuberculosis, plasmaocytosis, megaloblastic changes in cell lineages, and marrow aplasia. It is also established in 60–70% cases that military tuberculosis is also linked with histiophagocytosis of all cell lineages and caseating granuloma formation. When you look at the association between TB and the other bone marrow changes, you will discover that they include marrow necrosis and myelofibrosis [16].

Another interesting fact is that more commonly thrombocytopenia in TB is the cause of non-immune mechanisms. A particularly discovery showed that in the setting of pancytopenia that develops secondary to granulomatous infiltration of the bone marrow. Thrombocytopenia in TB can also be existing due to a defect in platelet production (marrow suppression) or due to the side effects of anti-tuberculous therapy. Moreover, TB can be complicated by thrombotic thrombocytopenic purpura (TTP) or even disseminated intravascular coagulopathy (DIC), or due to immune-mediated platelet destruction. However, in our patient we discovered no sign of granulomatous infiltration and histiophagocytosis in the bone marrow. Also patient had no history of anti-tuberculous therapy and no laboratory findings which may have supported a diagnosis of DIC, TTP.

Another rare occurrence we must touch base is the immune-mediated thrombocytopenia (ITP) which subordinate to TB. The association between TB and the pathophysiological mechanisms of secondary ITP still remains unknown. However, it is discovered and claimed in the medical literature that the tuberculosis-induced thrombocytopenia has been supported by both the platelet antigen-specific antibodies and platelet surface membrane IgG or by response to immunomodulatory therapy [18–20]. It is believed that the immune thrombocytopenia which is caused by the pathogenesis of TB; is the generation of antiplatelet antibodies by lymphocytes borne as a result of clonal proliferation due to host’s immune response to the tuberculous pathogen[18]. It is also worth mentioning that we didn’t detect any antiplatelet antibodies in our patient which is not a routine procedure in Turkey. The American Society for Hematology’s guidelines in 2011 claims that for the diagnosis and management of ITP, the absence of anti-platelet antibodies in no way invalidates the diagnosis of ITP [21]. As a matter of fact, the antibodies of anti-platelet were classified as an “unnecessary” examination for the ITP patients’ routine evaluation.

ITP as known as immune thrombocytopenia is previously stated as an auto-immune condition which results in isolated thrombocytopenia (platelet count <100x10³/µl) due to various defects in immune tolerance against platelet antigens. It is fair to say that out of many cases 50% was classified with the fact that ITP has no underlying etiology. When we looked at the subordinate forms of TB we discovered that the disease is usually triggered by other infections or diseases that are classified auto-immune diseases. ITP also has two major diagnostics criteria which are thrombocytopenia in the context of an otherwise normal blood count and a normal peripheral smear and the exclusion of conditions capable of inducing thrombocytopenia; the detection of anti-platelet antibodies is not considered necessary [23]. This way of treatment intends to reduce bleeding risk. Therefore first line treatment is corticosteroids, intravenous immunoglobulin (IVIG) or anti-D antibodies; second-line treatment may include splenectomy or thrombopoietin agonists [22]. Furthermore, as a method IVIG is particularly chosen if a transient increase in the platelet count, and a typical response is an increase in platelet count several days after the infusions are initiated and return to the pre-treatment level within several weeks.

Our case of patient excluded the reasons for thrombocytopenia with history, clinical and laboratory findings, and examination of bone marrow aspiration. And was started steroid therapy as a first line. However, as patient responded negatively to the steroid therapy we conducted a course of IVIG for a transient increase in the platelet count preoperatively and then the patient was referred for splenectomy.

We now can declare that the immune modulatory treatment and its effects remain unidentified in the TB-associated ITP. Purely based on the fact that, platelet count recovery shows an achievable result which is by ant tuberculosis treatment alone [24]. We discovered that usually there is one thing common in most cases, as the treatment for ITP (steroids or other immune-modulating agents) was started prior to ant tuberculosis treatment, as the diagnosis of TB was only established later. However, as a result we achieved a very minor increase in platelet count which under exclusive immune-modulatory medication; therapy extension or switching to antituberculosis treatment, however, the significant increase in platelet count was the inevitable result. It is also important to say that TB of spleen and the role of splenectomy should be considered as a vexed problem. It is proven that when TB is strongly suspected as the cause of the splenomegaly and attendant haematological disorders antituberculous therapy is effective in normalize the hematological profile [18,25]. What we discovered with our patient was that the splenectomy is diagnostic and it is rather difficult to establish a preoperative TB diagnosis. Another fact which was established was when TB is diagnosed serendipitously following splenectomy, in a case like this that it is suggested that standard anti-tuberculosis treatment should be taken preoperatively and postoperatively if an operation is carried out [26]. Which means that by conducting so this procedure is performed, is likely to cure the condition in some
cases [27]. That brings us to the point that if our patient’s diagnosis happened at an early stage, she could recover with anti-tuberculosis therapy without surgical intervention.

Up until now there is no reported clinical research about the prevalence of ITP secondary to TB which has never been investigated. However, there is a published study in 1995 which evaluated the incidence of ITP secondary to TB [28]. According to this study which was conducted in Saudi Arabia, out of 846 patients who were primarily diagnosed with TB, only 9 patients (1%) had initially shown ITP in their results. Which means that in this series of TB, the clear point was following the commencement of high dose steroid therapy and minimal improvement in the platelet count. It is claimed that there are also several cases in the medical literature that indicates ITP is related to tuberculosis [17,18,29,30]. The first case of ITP with pulmonary tuberculosis was reported by Boots et al; about a 28 years old Thai man [17]. As far as we know around 50 similar reports have been shown during the period between 1964 and 2016. In 2001, 21 of these cases were summarized by Ghobrial et al [31]. Moreover, 50 cases were summarized by Weber at al. In 2017 Pulmonary TB represented the most common clinical presentation with occurrences of 41% of in all cases which was followed equally at 21% by disseminated TB and the remaining patients had extra-pulmonary TB (EPTB) at various sites [32].

A study which was conducted in Turkey showed that the incidence of extra pulmonary tuberculosis was found to be 17.1% and isolated splenic involvement 0.1% in patient without HIV [33]. When we look at our case which was also an immunocompetent patient, we see that it was the third case with ITP associated with splenic tuberculosis described in the literature with normal size of spleen.

In conclusion, our immunocompetent patient’s thrombocytopenia was very likely to be subordinate to splenic tuberculosis as the main features of this case were isole thrombocytopenia, failure of first-line ITP treatment, prompt response to anti-tuberculosis treatment and the exclusion of other aetiologies. We would like to state that TB must always be suspected as an underlying cause of ITP, particularly in patients from endemic areas.

References


