Le Infezioni in Medicina, n. 1, 50-55, 2013

Caso clinico

Case report

Idiopathic thrombocytopenic purpura associated with splenic tuberculosis: case report

Porpora trombocitopenica idiopatica associata a tubercolosi splenica: un caso clinic

Mehmet Sinan Dal[1], Tuba Dal[2], Recep Tekin[3], Erdal Bodakçi[1], Yakup Düzköprü[1], Mehmet Orhan Ayyildiz[1]

[1]Department of Hematology;
[2]Department of Microbiology and Clinical Microbiology;
[3]Department of Infectious Diseases and Clinical Microbiology, Dicle University, Diyarbakir, Turkey

INTRODUCTION

Tuberculosis is a major health problem in developing countries because of the increasing prevalence of immunocompromised patients and human immunodeficiency virus (HIV) infections [1, 2]. The first lesion of tuberculosis develops in the lung and then in the regional lymph node. Sometimes bacilli spread through blood and lymphatic circulation to multiple distant organs.

This picture is known as miliary tuberculosis. In the large majority of tuberculosis cases the development of immunological reaction inhibits the growth of mycobacteria in all infected sites and granulomas are formed. Granulomas are composed of epithelioid cells and giant cells, and surround and limit the foci of caseous necrosis which contains disintegrated cells and tuberculosis bacilli.

Some bacilli located within granuloma may survive for a very long time and reactivate in favourable circumstances.

Extrapulmonary tuberculosis accounts for 5-50% of all tuberculosis cases. In humans with reduced immune function, in young children with immature immune systems and in the elderly people with poor immune system functioning, and in patients with HIV infection and kidney failure, extra pulmonary tuberculosis is encountered more common [3-6]. Abdominal tuberculosis is one of the common presentations of extrapulmonary tuberculosis and affects the gastrointestinal tract, peritoneum, mesentery, abdominal lymph nodes, liver, pancreas and spleen.

Diagnosis of extrapulmonary tuberculosis is often delayed due to a lack of specific symptoms. Therefore laboratory findings and radiologic detection are important for diagnosis. Abdominal tuberculosis often shares manifestations with lymphoproliferative disease, inflammatory bowel disease, tumorous conditions or other infectious diseases [1, 7-9].

Isolated splenic tuberculosis is a rare form of abdominal tuberculosis. Splenic tuberculosis generally develops secondary to miliary tuberculosis. Isolated splenic tuberculosis has no characteristic symptoms or abnormal imaging findings.

It can be misdiagnosed as carcinoma of the spleen, splenic abscess, lymphoma, rheumatic fever or other diseases. The misdiagnosis rate is high if there is no history of tuberculosis in other organs [1, 10].

In addition, many haematological abnormalities, such as pancytopenia, anaemia and leukocytosis, may be associated with tuberculosis. Thrombocytopenia is frequently caused by a

*Corresponding author
Tuba Dal
E-mail: tuba_dal@yahoo.com

non-immune mechanism in the setting of pancytopenia that develops secondary to granulomatous infiltration of the bone marrow. There are limited numbers of cases in which immune thrombocytopenia is associated with tuberculosis and all of the cases in the literature have pulmonary tuberculosis [11].

To our knowledge, there are no available data about immune thrombocytopenia related with splenic tuberculosis (splenic TB). We present a case of immune thrombocytopenic purpura (ITP) associated with splenic tuberculosis in which thrombocytopenia and tuberculosis were successfully treated with antituberculosis drugs and high-dose immunoglobulin therapy.

CASE REPORT

A 58-year-old female was admitted to our clinic with headache, gum bleeding, redness in legs the size of a pinhead, and ecchymoses on the arms for the previous 10 days.

There was no known history of infection, tuberculosis, surgical interventions or any other significant illness in the past.

She lived in a small family with no family history of tuberculosis. On admission to hospital, laboratory tests were as follows: platelet count 6.000/mm^3 (150.000-450.000), haemoglobin: 12 g/dl, WBC: 8000/mm^3, erythrocyte sedimentation rate (ESR): 58 mm/h, and C-reactive protein (CRP) in the normal range.

The patient was hospitalized in our hospital haematology clinic. Blood glucose, kidney function tests and liver function tests were unremarkable. Urine routine and microscopy revealed no abnormality.

Chest radiograph and electrocardiogram were normal. On physical examination, the patient was conscious and was found to be actively cooperating. Vital signs were as follows: arterial blood pressure: 110/70 mmHg, temparature: 38.5°C and pulse: 80 per minute. The patient had 2x2 cm haemorrhagic bullae in the upper palate, a 3x4 cm ecchymosis around the left arm, and petechial purpuric rashes on both lower extremities.

No organomegaly or lymphadenomegaly or evidence of another disease such as chronic liver disease was detectable. As the patient's temperature was 38.5°C on admission, her blood and urine cultures were taken and piperacillin-tazobactam treatment was started. In addition cranial computed tomography (CT) scans were obtained for suffering headaches and platelet value was low. Cranial CT findings were as follows: epidural haemorrhagic areas were determined in the right frontal convex and an unclear separation of epidural, subdural or parenchymal hemorrhagic areas containing blood elements in different phases were determined in left parietal convex. Apheresis platelet suspension was given to the patient.

Bone marrow aspiration and bone marrow biopsy were also performed. In bone marrow aspiration, no pathological findings were detected other than an increase of megakaryocytes. With the suspicion of ITP, 1 g/kg intravenous immunoglobulin (IVIG) was initiated for the patient for 2 days. The patient was scanned by abdominal ultrasound. Abdominal ultrasonography findings were as follows: a few pieces of enlarged lymphadenopathies (LAPs), the largest being 34x12 mm, were found in the peripancreatic and paracaval regions.

By contrast, in abdominal USG spleen showed normal parenchymal echogenicity and the size of spleen was observed in the normal range. Due to continuing fever, thrombocytopeni and enlarged abdominal lymphadenopathies, the patient was suspected with the lymphoma, and thoracic, abdominal and pelvic CT scans were obtained.

Thorax CT showed normal lung parenchyma and mediastinal, paratracheal, bilateral hilar, subcarinal lymphadenopathies. In abdominal and pelvic CT there was no lesion in the liver parenchyma. Spleen size was normal, and parenchymal echogenicity of spleen was homogeneous. In addition, enlarged lymph nodes were detected in the paracaval, para-aortic, peripancreatic regions.

The patient's platelet count rose to 100.000 with IVIG, a presumptive diagnosis of lymphoma was posed and diagnostic laparotomy and splenectomy and lymph node excision were performed.

The samples obtained were sent to the pathology laboratory for histopathological examination and to the microbiology laboratory. In the pathology examination, the splenectomy specimen revealed caseous necrotic granulomatous splenitis; excisional biopsy revealed granulomatous lymphadenitis.

Under microbiological examination acid-fast bacilli on Ziehl-Neelsen staining were seen in both samples. Identification and susceptibility to anti-tuberculosis drugs were performed by

the MGIT 960™ TB automated system. In bone marrow biopsy, cellularity of bone marrow was observed in 70% and there was no granulomatous formation.

The patient was started on four antituberculous agents (isoniazid 300 mg/d, rifampin 600 mg/d, ethambutol 1200 mg/d, pyrazinamide 1500 mg/d) for two months, followed by isoniazid and rifampin and pyridoxine. No side effects of antituberculous drugs were encountered during the therapy. The patient was successfully treated and thrombocytopenia did not recur in the follow-up.

DISCUSSION

Tuberculosis is a multi-system disease, 90% of which locates primarily in the lung. Extrapulmonary tuberculosis accounts for 5–50% of all cases of tuberculosis. It is encountered in subjects with reduced immune function such as HIV infection, with kidney failure and in patients receiving immunosuppressive therapy. Splenic tuberculosis is a rare form of extrapulmonary tuberculosis.

While Winternitz categorized splenic TB as a primary or secondary form, some scholars insist that all patients with splenic TB are secondary to the previous infection of tubercle bacillus in other organs.

In our case, the patient had no history of TB and there was no indication of any other involvement in other sites or organs at the time of admission [3]. Isolated splenic TB is rare and has been reported to be more associated with HIV infection in literature [1]. Our patient was an immunocompetent patient with splenic tuberculosis.

Many haematological abnormalities, such as pancytopenia, anaemia, and leukocytosis, can be associated with tuberculosis. Immune thrombocytopenic purpura (ITP) is an extremely rare event in TB.

Thrombocytopenia is frequently caused by a non-immune mechanism in the setting of pancytopenia that develops secondary to granulomatous infiltration of the bone marrow [11, 12]. In our patient there was no granulomatous infiltration in the bone marrow.

In a case of thrombocytopenia associated with TB infection developed concurrently in a mother and son; antiplatelet antibodies were observed in the serum of both patients. It was suggested that this and possibly other haematologic complications associated with tuberculosis were immune mediated [13].

There are no specific symptoms for establishing the diagnosis of splenic TB [3]. Fever was the only symptom in our case, and helpful laboratory data include anaemia and elevated ESR.

There are five types of pathomorphological classifications for splenic TB including miliary TB, nodular TB, tuberculous spleen abscess, calcific TB and mixed type TB [3]. In addition, splenic tuberculosis has been categorized radiologically into micronodular or macronodular forms, depending on whether it is smaller or larger than 10 mm. Micronodular tuberculosis is more common and the patients with this type of TB have multiple nodules.

Micronodular TB is usually encountered in disseminated systemic tuberculosis. If the nodules are below the resolution capability of imaging techniques, they could manifest as simple splenomegaly.

Macronodular splenic tuberculosis is rare and could manifest as a singular abscess or multiple large nodules [1]. In our patient pathologic examination of splenectomy specimens revealed granulomatous splenitis while excisional biopsy revealed a granulomatous lymphadenitis. Radiological diagnostic methods are also helpful in the diagnosis of splenic tuberculosis. However, they have their limitations.

On the one hand, there are many situations that may have presentations of multiple, hypodense splenic lesions on CT such as malignant lymphoma, metastatic cancer, echinococcal cysts, haemangioma or even infectious diseases due to frequent fever and splenic abcess. However, CT may not be able to suggest the nature of lesions in spleen.

On the other hand, typical nodules on the splenic capsule are usually too small to be detected by CT scan [3]. In our case CT scan was also helpful in our diagnosis but we suspected lymphoma according to the CT findings. Our study revealed that histopathological examination is still an ideal method to confirm the diagnosis. Many patients are reluctant to accept invasive procedures, which leads to misdiagnosed or delayed diagnosis. We believe that laparoscopy might be an alternative method in the diagnosis of splenic TB, and it has proved to be a minimally invasive approach avoiding unnecessary splenectomy. In addition, in the light of TB experiments in the literature, microbiological and molecular examinations may be helpful in aetiological diagnosis [3, 14].

Our case could be confused by coincidental presentation of adult idiopathic thrombocytopenic purpura and tuberculosis, by drug-induced thrombocytopenia, thrombotic thrombocytopenic purpura (TTP), haemolytic uraemic syndrome (HUS), haemophagocytic syndrome and disseminated intravascular coagulation (DIC) associated with TB [10]. Idiopathic thrombocytopenic purpura is an acquired disease of children and adults. Patients with isolated thrombocytopenia have no clinically apparent associated conditions or other causes of thrombocytopenia.

Chronic ITP typically has an insidious onset with long-lasting histories of purpura (thrombocytopenia for >6 months): spontaneous remission is uncommon and is likely to be incomplete. Steroids are the conventional first line therapy for adult ITP.

Also in adults, IVIG is used when clinical situations require 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 pretreatment level within several weeks [15]. Due to the patient's fever and LAPs, we did not give steroid treatment to our patient.

In our case, we excluded chronic adult ITP not only based on standard criteria, but after response to IVIG therapy since thrombocytopenia did not recur after withdrawal of IVIG therapy. We also excluded other causes of thrombocytopenia with history, clinical and laboratory findings, and examination of bone marrow aspiration.

There are few reported cases where ITP is related to tuberculosis in the literature [11-13, 15, 16]. Boots et al. reported the first case of ITP with pulmonary tuberculosis in a 20-year-old Thai man [16]. Tsuro *et al.* reported an ITP case associated with pulmonary tuberculosis in a 22-year-old woman [11]. In Turkey Ursava *et al.* reported a 46-year-old male patient with ITP due to pulmonary tuberculosis [17].

In all studies related to this issue, extrapulmonary tuberculosis was found to be significantly more common in females. However, pleural tuberculosis occurs more often in males. Extrapulmonary tuberculosis is more prevalent in certain ethnic groups. In the United States, extrapulmonary tuberculosis is particularly common in people originating from South Asia in the absence of HIV infection or other immunosuppressive factors [10].

Low incidence of extrapulmonary tuberculosis reported in national registers may result from poor identification and from atypical symptoms, while detection rates also depend on the quality of medical services in a particular country. In many countries 20-50% of cases of extrapulmonary tuberculosis are diagnosed postmortem.

In populations living in South Asia and United States, extrapulmonary tuberculosis was diagnosed in 50% of cases, whereas in southern Asia, only in 21-28% of cases [10]. In a study from Turkey the incidence of extrapulmonary tuberculosis was found to be 17.1% and isolated splenic involvement 0.1% in patient without HIV [19]. Our case was also an immunocompetent patient and to our knowledge it was the first case with ITP associated with splenic tuberculosis described in the literature with normal size of spleen.

Splenic TB treatment must be carried out in accordance with the following principles-timely treatment in combination, regularly treatment like pulmonary TB.

Treatment for tuberculosis should last more than six months. Standard anti-tuberculosis treatment should be taken preoperatively and postoperatively if an operation is carried out [10]. Standard anti-tuberculosis medication was also successful in our patient. If the patient receives an early diagnosis, he/she may be healed with anti-tuberculosis treatment, without a surgical procedure.

In conclusion, we suggest that splenic tuberculosis must be suspected in patients who have fever, abdominal lymphadenopathy and thrombocytopenia. With the timely antituberculosis therapy and IVIG treatment, the patient may be recovered without the need for surgical treatment. In the light of our reported case, we can say that histopathological examination is still an ideal method to confirm the diagnosis of splenic and that microbiological examination is also helpful in diagnosis.

Keywords: extrapulmonary tuberculosis, immune thrombocytopenic purpura, splenic tuberculosis.

SUMMARY

Tuberculosis is still one of the most prevalent and fatal infectious diseases in spite of considerable improvements in medical science. Splenic tuberculosis is a rare form of extrapulmonary tuberculosis. There are limited numbers of cases in which immune thrombocytopenia is associated with splenic tuberculosis. We report a case of immune thrombocytopenic purpura due to splenic tuberculosis. Our case was a 58-year-old female with headache, gum bleeding, redness in legs, and ecchymoses on the arms for 10 days. On admission to hospital, laboratory tests were as follows: platelet count 6.000/mm³ (150 000-450 000), haemoglobin: 12 g/dl, WBC: 8000/mm³, erythrocyte sedimentation rate: 58 mm/h and C-reactive protein was in normal ranges. After standard laboratory tests, the patient was diagnosed with idiopathic thrombocytopenic purpura. The patient presented abdominal lymphadenopathies and spleen in normal size in radiological examinations. Diagnostic laparotomy and splenectomy and lymph node excision was performed and splenic tuberculosis was detected in pathologic and microbiologic examination. The patient was successfully treated with apheresis platelets suspension, intravenous immunoglobulin and antituberculous therapy. In conclusion, splenic tuberculosis should be suspected in patients who have fever, abdominal lymphadenopathies and immune thrombocytopenic purpura. Histopathological examination is still an ideal method to confirm the diagnosis, suitably aided by microbiological examination.

RİASSUNTO

La tubercolosi rappresenta ancora oggi, nonostante i considerevoli progressi compiuti in medicina, una delle malattie infettive gravate dalle maggiori prevalenza e letalità. La tubercolosi splenica è una forma rara di tubercolosi extrapolmonare. In letteratura, i casi descritti di trombocitopenia immune associata a tubercolosi splenica sono pochi. In questo articolo gli autori riportano un caso di porpora trombocitopenica immune dovuta a tubercolosi splenica.

Donna di 58 anni con cefalea, sanguinamento gengivale, arrossamento della gambe ed ecchimosi alle braccia da 10 giorni. I test di laboratorio eseguiti al ricovero in ospedale evidenziavano i seguenti valori: piastrine 6.000/mm³ (150.000-450.000), emoglobina 12 g/dl, globuli bianchi 8000/mm³, VES 58 mm/h e proteina C reattiva nel range di normalità. Alla paziente veniva diagnosticata porpora trombocitopenica idiopatica. La paziente, che all'esame radiografico presentava linfoadenopatia addominale e milza di dimensioni normali, veniva sottoposta a laparatomia e splenectomia diagnostiche ed escissione linfonodale. L'esame microbiologico e istopatologico evidenziava tubercolosi splenica.

La paziente è stata trattata con successo con sospensione piastrinica ottenuta in aferesi, immunoglobuline per via endovenosa e terapia antitubercolare.

In conclusione, gli autori suggeriscono che la tubercolosi splenica debba essere sospettata nei pazienti con febbre, linfoadenopatia addominale e porpora trombocitopenica immune. L'esame istopatologico rappresenta ancora oggi un metodo di riferimento per la conferma della diagnosi. L'esame microbiologico si è rivelato utile per porre la diagnosi.

REFERENCES

[1] Lim J., Yu J.S., Hong S.W., Chung J.J., Kim J.H., Kim K.W. A case of mass-forming splenic tuberculosis: MRI findings with emphasis of diffusion-weighted ımaging characteristics. *J. Korean Med. Sci.* 26, 457-460, 2011.

[2] Santori D., Fabbiani M., Zanelli G., et al. Retrospective study on tuberculosis in Siena province. *Infezioni in Medicina* 3, 175-181, 2005.

[3] Rowi ska-Zakrzewska E. Extrapulmonary tuberculosis, risk factors and incidence. Pneumonol. *Alergol. Pol.* 79, 377-378, 2011.

[4] Salazar A., Carratalá J., Santín M., Meco F., Rufi G. Splenic abscesses caused by Mycobacterium tuberculosis in AIDS. *Enferm. Infecc. Microbiol. Clin.* 12, 146-149, 1994.

[5] Sandoval Gutiérrez J.L., Arcos Zamora M., Bautista E. Splenic tuberculosis in HIV patient. *Med. Intensiva* 36, 4, 318, 2012.

[6] Titone L., Romano A., Abbagnato L., Mazzola A., Di Carlo P. Epidemiology of paediatric tuberculosis today. *Infezioni in Medicina* 3, 127-132, 2003.

[7] Akhan O., Pringot J. Imaging of abdominal tuberculosis. *Eur. Radiol.* 12, 312-323, 2012.

[8] Sabbatani S., Legnani G., Baldoni C., Danielli A. Tuberculosis in Italian and Non-EU patients. Review of case mix (1996-2001). *Infezioni in Medicina* 1, 37-44, 2002.

[9] Carniato A., Fuser R., Giobbia M., et al. Tuberculous peritonitis: experience in Treviso from 2000 to 2010. *Infezioni in Medicina* 3, 195-199, 2012.

[10] Zhan F., Wang C.J., Lin J.Z., Zhong P.J., Qiu W.Z., Lin H.H., et al. Isolated splenic tuberculosis: A

case report. *World J. Gastrointest. Pathophysiol.* 15, 9-11, 2010.
[11] Tsuro K., Kojima H., Mitoro A., et al. Immune thrombocytopenic purpura associated with pulmonary tuberculosis. *Intern. Med.* 45, 739-742, 2006.
[12] Maejima H., Arai S., Ebata T., Takeda H., Kusunoki M., Katsuoka K. Tuberculous gumma associated with idiopathic thrombocytopenic purpura: report of a Japanese female patient. *J. Dermatol.* 34, 86-91, 2007.
[13] Jurak S.S., Aster R., Sawaf H. Immune thrombocytopenia associated with tuberculosis. *Clin. Pediatr.* 1, 318-319, 1983.
[14] Guglielmetti L., Michela Conti M., Cazzadori A., Lo Cascio G., Sorrentino A., Concia E. Diagnostic sensitivity of quantiFERON-TB gold in-tube and tuberculin skin test in active tuberculosis: influence of immunocompromission and radiological extent of disease. *Infezioni in Medicina* 1, 16-24, 2012.
[15] Ozkalemkas F., Ali R., Ozkan A., et al. Tuberculosis presenting as immune thrombocytopenic purpura. *Ann. Clin. Microbiol. Antimicrob.* 6, 16, 2004.
[16] Boots R.J., Roberts A.W., McEvoy D. Immune thrombocytopenia complicating pulmonary tuberculosis: case report and investigation of mechanisms. *Thorax* 47, 396-397, 1994.
[18] Ursavas A., Ediger D., Ali R., et al. Immune thrombocytopenia associated with pulmonary tuberculosis. *J. Infect. Chemother.* 16, 42-44, 2010.
[19] Sinha N., Gupta N., Jhamb R. Idiopathic thrombocytopenic purpura with isolated tuberculous splenic abscess. *Singapore Med. J.* 50, 41-43, 2009.
[20] Özvaran M.K., Baran R., Tor M., et al. Extrapulmonary tuberculosis in non-human immunodeficiency virus-infected adults in an endemic region. *Ann. Thorac. Med.* 2, 118-121, 2007.