Thrombocytopenic Purpura Associated with Miliary Tuberculosis†

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Abstract

The authors report a case of thrombocytopenia associated with miliary tuberculosis. The patient was a 28-year-old woman who was admitted because of massive upper gastrointestinal hemorrhage and acute respiratory failure. Chest radiographs revealed diffuse bilateral reticulonodular infiltration and complete blood count was significant for severe thrombocytopenia. Bone marrow biopsy was performed to investigate the cause of thrombocytopenia and demonstrated multiple tiny caseating granulomas suggesting miliary tuberculosis (TB). She received anti-TB therapy and a short course of steroid with good response. Platelet count returned to normal limit within 10 days. Although isolated thrombocytopenia is uncommon in TB, it is still important to consider TB in the differential diagnosis of thrombocytopenia, particularly in patients with abnormal chest radiographs. Bone marrow examination is very helpful in this situation.

Key word : Miliary Tuberculosis, Thrombocytopenia, Hemorrhage

TONGYOO S, VILAICHONE W, SUKPANICHNANT S, et al
J Med Assoc Thai 2003; 86: 976-980

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† Presented as interesting case discussion at an inter-hospital conference of critical care in August, 2002

Tuberculosis (TB) remains a significant public health problem in Thailand and can present in many forms. Hematological abnormalities such as monocytosis, basophilia, leukocytosis, anemia, or pancytopenia have been reported, especially when the bone marrow is involved by TB; but pure thrombocytopenia is exceedingly rare[1]. Until now, there have been few case reports of thrombocytopenia associated with TB[2-5]. The authors, hereby, report a case of thrombocytopenia presenting with massive mucosal bleeding and abnormal chest radiographs; the patient responded well to anti-TB therapy given after the discovery of multiple tiny caseating granulomas, consistent with miliary TB, in the bone marrow biopsy.

CASE REPORT

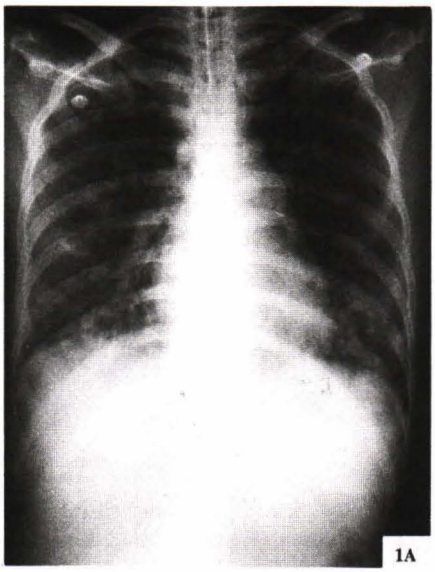
A 28-year-old Thai woman presented at Siriraj hospital because of massive upper gastrointestinal bleeding. She had been in good health until 3 weeks prior to this hospitalization when she started to lose her appetite and body weight. She subsequently observed some petechiae on her trunk and extremities and black tarry stools. On the day of admission she started to cough up red blood and had shortness of breath. She was then taken to the hospital.

On physical examination, she was febrile, dyspneic, hypotensive and tachycardic. Some amounts of blood clots were seen in the oral cavity. She had neither superficial lymphadenopathy nor hepatosplenomegaly. Generalized petechiae and ecchymoses were found on her trunk and all extremities. Fine to medium crepitation was detected at both lungs. Cardiovascular and nervous system examination were unremarkable.

Complete blood count revealed hematocrit 24 per cent, white blood cell 9,500/mm^3. and platelet count 15,000/mm^3. Peripheral blood smear showed normochromic normocytic anemia without spherocyte or fragmented red blood cells. Coagulation tests, including prothrombin time and partial thromboplastin time, were normal. Anti-HIV antibody, antinuclear antibody, anti-double stranded DNA and Coombs' test were negative.

A chest radiography showed diffuse bilateral reticulonodular infiltration (Fig. 1A). No organisms were demonstrated in the sputum by either Gram's or acid fast stain. Subsequently, sputum culture for bacteria and mycobacteria and blood culture results were also negative.

Bone marrow aspiration was performed to investigate the cause of thrombocytopenia. Normal erythroid and myeloid series with an increase in megakaryocytes were found. Bone marrow biopsy revealed multiple tiny granulomas, some of which had Langhans giant cells and occasional central caseous



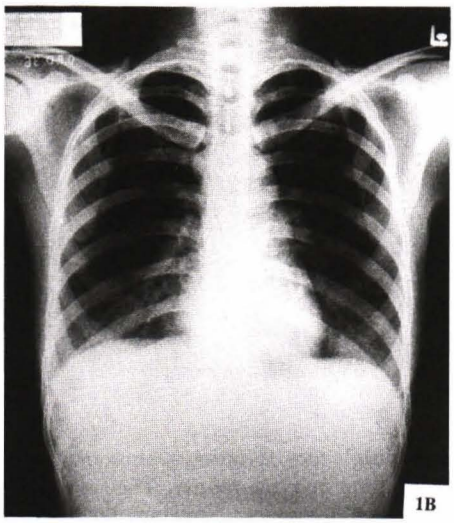


Fig. 1. Improvement of miliary infiltration at presentation A) to post- treatment B) four weeks later.

necrosis (Fig. 2). Special stains of the bone marrow for acid fast bacilli and fungi were negative. The paraffin block of bone marrow tissue was sent to the Division of Medical Mycology and Mycobacteriology for detection of *Mycobacterium tuberculosis* complex DNA. The block was serially cut into 5 μm thick tissue sections and collected into a sterile Eppendorf tube (about 20 sections per tube). Deparaffinization was performed according to Bascunana and Belak[6] with some modification and the tissue-pellet was subjected to DNA extraction using Qiagen-kit (QIAamp® DNA Mini Kit, Germany, Lot No.1099184). Purified DNA was resuspended in 50 μl Buffer AE (Elution buffer) and 5 μl of DNA solution were employed in one-tube nested polymerase chain reaction (PCR) as previously described[7]. The method was specific for detection of *M. tuberculosis* complex DNA and revealed the least detected DNA concentration of 100 fg (equal to DNA from 20 mycobacterial cells). No *M. tuberculosis* complex DNA was detected in this case. However, clinical, chest X-ray and bone marrow findings in the absence of fungal infection were consistent with miliary TB.

During the first day of admission she developed acute respiratory acidosis and required ventilatory support in the intensive care unit (ICU). She was resuscitated by intravenous fluid, packed red blood cell and platelet transfusion to maintain hemodynamic and control bleeding. Initially dexamethasone 5 mg intravenous injection was given every 6 hours because immune thrombocytopenic purpura was suspected. Anti-TB drugs (isoniazid 5 mg/kg/day, rifampicin 10 mg/kg/day, ethambutol 25 mg/kg/day, pyrazinamide 30 mg/kg/day) were started one day later, when the bone marrow biopsy revealed caseous granulomas. The patient responded well to anti-TB therapy. She could be extubated and transferred from the ICU to the medical floor within one week. Dexamethasone was administered intravenously for ten days and changed to prednisolone 60 mg/day for two days.

After platelet count returned to normal range on the 12th day of anti-TB therapy, prednisolone was discontinued. She has not experienced any more bleeding episodes. Since pyrazinamide and ethambutol were stopped after two months, isoniazid and rifampicin were continued to complete six months. There was improvement of the chest radiographic findings (Fig. 1B). Her general condition and body weight increased from 42 kg to 45 kg in 3 months after starting the anti-TB therapy.

DISCUSSION

In the present case, immune thrombocytopenic purpura was suspected due to low platelet count in peripheral blood smear without evidence of microangiopathic hemolytic blood picture. Peripheral

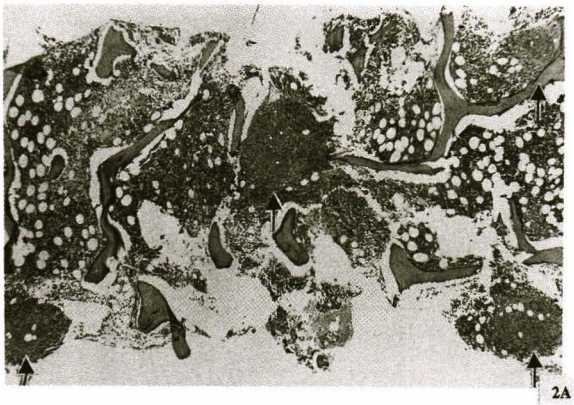


Fig. 2A. Multiple tiny caseating granulomas (arrows) in bone marrow biopsy. Their sizes do not exceed 2 mm in diameter. The remaining marrow shows an increase in mature megakaryocytes and normal erythroid and myeloid series. (Hematoxylin & Eosin, x20).

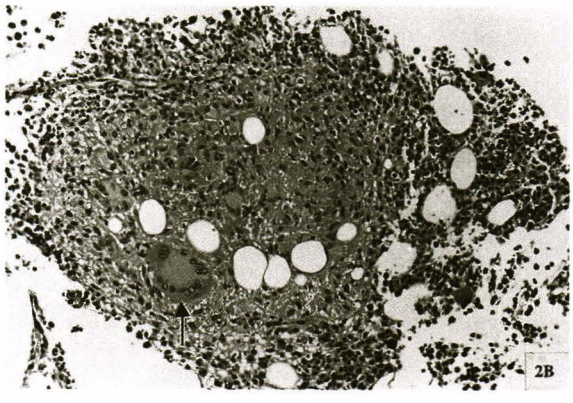


Fig. 2B. Typical Langhans giant cell (arrow) in one granuloma. (Hematoxylin & Eosin, x20).

destruction of platelets was confirmed by the increased number of megakaryocytes in the bone marrow. There were no abnormalities in the erythroid and myeloid cell lines. However, bone marrow biopsy revealed multiple tiny caseating granulomas consistent with miliary TB. Other causes of thrombocytopenia such as connective tissue disease and HIV infection were excluded. The patient responded well to anti-TB therapy. Despite failure to identify the organism by acid fast bacilli (AFB) staining and PCR, the clinical findings including abnormal chest radiographs, bone marrow biopsy findings, and clinical improvement after anti-TB therapy strongly suggested that the patient had thrombocytopenia associated with miliary TB.

Hematologic manifestations including leukocytosis, leukopenia, anemia, leukemoid reaction, and pancytopenia are usually associated with disseminated TB[1]. Isolated thrombocytopenia associated with TB is an uncommon complication and only 11 cases to the best of our knowledge have been previously reported in the literature[2-5]. The mechanism of TB-associated thrombocytopenia is unclear; however, there is some evidence to suggest that the immune process may play a role in the pathophysiology. Boots et al[2] demonstrated IgG deposits on the platelet membrane and suggested that the immune process was the main pathophysiology of isolated thrombocytopenia associated tuberculosis. Al Majed et al[3] reviewed 9 cases of thrombocytopenia associated with TB and found that thrombocytopenia associated with TB did not respond to neither steroid nor intravenous immunoglobulin therapy but thrombocytopenia responded well to anti-TB therapy. The present case recovered from thrombocytopenic bleeding following anti-TB therapy and a short course of corticosteroid administration. Platelet count has been within normal limits since and did not decrease after the discontinuation of corticosteroid.

In any area where TB remains an important public health problem, patients presenting with thrombocytopenia and abnormal chest radiography should, therefore, be evaluated for the possibility of TB. A complete hematologic work-up especially a complete bone marrow examination including bone marrow biopsy is mandatory. It may be difficult to obtain or identify granuloma in the marrow aspirate. If the diagnosis of TB is missed and only corticosteroid without anti-TB therapy is given to the patient for immune thrombocytopenic purpura for an extended period of time, it can accelerate the disease process and, without proper treatment for TB, a fatal outcome may ensue.

SUMMARY

Thrombocytopenia associated with tuberculosis is a unique condition. Missed diagnosis may lead to a fatal result. The immune process is thought to be the main mechanism of this condition; however, the benefit of corticosteroid and intravenous immunoglobulin are not clear. The authors reported a case of tuberculosis associated with thrombocytopenia who responded well to anti-tuberculous therapy.

(Received for publication on December 21, 2002)

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ภาวะเกร็ดเลือดต่ำที่พบร่วมกับวัณโรคชนิดแพร่กระจาย†

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รายงานผู้ป่วยหญิงไทยอายุ 28 ปี มีอาการอาเจียนเป็นเลือดและการหายใจล้มเหลว ภาพถ่ายรังสีทรวงอกพบรอยโรคลักษณะเป็นจุดขนาดเล็กจำนวนมากกระจายทั่วปอดทั้งสองข้าง จากการตรวจเลือดพบภาวะเกร็ดเลือดต่ำอย่างรุนแรง ผลการตรวจไขกระดูกพบความผิดปกติลักษณะเข้าได้กับการติดเชื้อวัณโรค ผู้ป่วยได้รับการรักษาด้วยยาในกลุ่มสเตียรอยด์เป็นช่วงสั้น ๆ ร่วมกับยาต้านวัณโรคตามสูตรมาตรฐาน พบว่าจำนวนเกร็ดเลือดสูงขึ้นจนอยู่ในเกณฑ์ปกติภายในระยะเวลาสิบวัน ตลอดจนอาการโดยรวมของผู้ป่วยดีขึ้นเรื่อยๆจนปกติหลังได้รับการรักษาด้วยยาต้านวัณโรค

คำสำคัญ : วัณโรคแพร่กระจาย, ภาวะเกร็ดเลือดต่ำ, เลือดออกผิดปกติ

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จดหมายเหตุทางแพทย์ ฯ 2546; 86: 976-980

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† ได้นำเสนอเพื่ออภิปรายในการประชุมระหว่างโรงพยาบาลของหน่วยเวชบำบัดวิกฤตประจำเดือนสิงหาคมปี พ.ศ. 2544