Tuberculosis should not be ignored in patients with peripheral gangrene

Yuan Yao, MM, Bin Liu, MD, Ji-bo Wang, MD, Hua Li, MM, and **Hong Da Liang, MM,** *Shandong Province, China*

Peripheral gangrene, characterized by distal ischemia of the extremities, is a rare complication in patients with tuberculosis (TB). We diagnosed a female patient with gangrene of her left toe caused by TB infection. She presented with fever, lymphadenectasis, and peripheral gangrene of the left toe. Lymph node biopsy confirmed tuberculous lymphadenitis and the computer tomography angiography showed vasculitis. The patient underwent antituberculous therapy and her condition was gradually improved. Although it is rare, TB should be considered as a possible cause of peripheral gangrene. (J Vasc Surg 2010;52:1662-4.)

Tuberculosis (TB) is one of the important public health problems of China. China has the second largest TB epidemic of the world, with more than 1.3 million new cases of TB every year.[1] The clinical spectrum of TB is complicated, as various manifestations can present. Peripheral gangrene is characterized by distal ischemic damage in two or more extremities without large vessel obstruction. This syndrome has been reported in various conditions such as infections, diabetes mellitus, low cardiac output states, and rarely associated with TB.[2,3] We present here a patient with tuberculous lymphadenitis which induced medium-vessel vasculitis and caused peripheral gangrene.

CASE REPORT

A previously healthy 28-year-old woman came to our clinic with a history of fever, lymphadenectasis, and peripheral gangrene. Two years ago, she experienced recurrent episodes of fever. Her temperature was approximately 37.5°C, which presented mostly at night, and was accompanied with sweats. In addition, she complained of pain and swelling of the left side of her neck. Physical examination found that the lymph nodes were enlarged in the left cervical region (the largest one was 1.5 cm × 2 cm in size). Tuberculin skin test was strongly positive. Chest radiographs showed parenchymal opacity and small nodules in the left upper zone, which suggested possible pulmonary TB. The patient received standard antituberculosis therapy with isoniazid, rifampicin, ethambutol, and pyrazinamide. Forty-five days after the antituberculous treatment, her body temperature returned to normal and the enlarged lymph nodes shrank. Unfortunately, she stopped taking the medicine without consulting her physician. About 10 months ago, she had 1 to 3 swollen left toes with severe pain. The pain and swelling of her toes became progressively worse and they gradually turned blue. Ulcers with yellow secretions presented on her toes. There was no family history or any known history of contacting with TB patients.

The patient seemed to be in good general condition. Her weight was 40 kg. Her blood pressure in the right upper arm was 130/90 mm Hg, 132/84 mm Hg in the right lower extremity, 130/85 mm Hg in the left upper arm and 120/81 mm Hg in the lower extremity. The pulsations of her left posterior tibial and foot dorsum arteries were weak. Enlarged lymph nodes could be palpated in the left cervical region (the largest one was 1 cm × 1 cm in size). The temperature of her left foot was lower than that of the right one. Her second left toe was gangrenous and her first to third toes were purplish. A deep ulceration with thick elevated margins and purulent secretions was found in her left toe (Fig 1).

The complete blood cell count, urine analysis, erythrocyte sedimentation rate, and C-reactive protein were all in the normal range. Her serum urea nitrogen was 2.53 mmol/L (normal range, 2.14-7.14 mmol/L); creatinine was 77 μmol/L (31-132 μmol/L). Serum immunoglobulin A was 4.18 g/L (0.7-4.0 g/L), immunoglobulin G was 15.10 g/L (2.14-7.14 g/L), and immunoglobulin M was 1.65 g/L (0.4-2.3 g/L). Antiphospholipid antibody and Rheumatoid factor were positive but with low titre. D-dimer was 1164 ng/mL (0-300 ng/mL). Mantoux test with 5 tuberculin unit purified protein derivative was strongly positive. Anti-cyclic citrullinated peptide, anti-extractable nuclear antigens antibody, anti-ds-DNA antibody, and anti-neutrophil cytoplasmic antibody were negative. Serological markers for hepatitis B and C, human immunodeficiency virus (HIV), cytomegalovirus, Epstein-Barr virus, mycoplasma, and syphilis were all negative. Cultures of blood, stool, and urine were negative. Both abdomen and urinary system ultrasonography were normal. Chest computed tomography scan showed old tuberculosis on the upper left side of the lung. The lower limb angiography showed that the left posterior tibial and peroneal arteries were narrower and the lumina were anomalous, which indicated the presence of vasculitis (Fig 2). Histopathology of cervical lymph nodes revealed typical chronic granulomatous inflammation characterized by the cluster of Langerhans giant cells, the epithelioid histiocyte, lymphocytes,

From the Department of Rheumatology, The Affiliation Hospital of QingDao University Medical College, No.16 Jiang Su Lu, Shi Nan District, QingDao City, Shandong Province, China.

Competition of interest: none.

Reprint requests: Bin Liu, MD, Department of Rheumatology, The Affiliation Hospital of QingDao University Medical College, No. 16 Jiang Su Lu, Shi Nan District, QingDao city, Shandong Province, 266003, China (e-mail: binliupumc@hotmail.com).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a competition of interest.

0741-5214/$36.00

doi:10.1016/j.jvs.2010.07.017

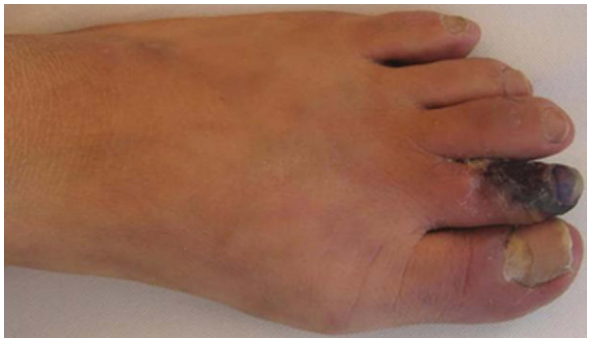

Fig 1. The second left toe was gangrenous and first to third toes were purplish. Deep ulceration in the left toe with thick elevated margin and purulent secretions was found.

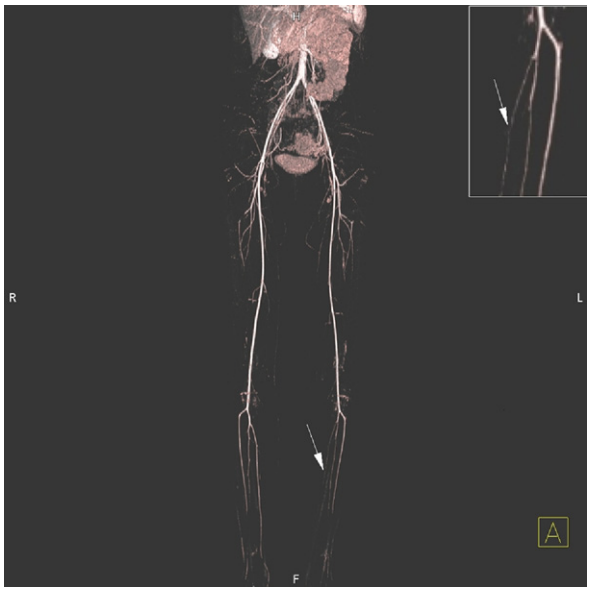

Fig 2. The lower limb computed tomographic angiography showed that the left posterior tibial and peroneal arteries were narrower and the lumina were anomalous (*arrow*), which indicated the presence of vasculitis.

and caseous necrosis, which was consistent with the caseous tuberculosis (Fig 3).

We diagnosed the patient with tuberculosis and secondary vasculitis based on her clinical manifestations, laboratory, histopathology, and image studies. Her symptoms were markedly improved after treated with classic antituberculous treatment during hospitalization and the patient was discharged with prednisone 10 mg/day, levofloxacin 0.5 g/day, isoniazid 0.3 g/day, rifampicin 0.45 g/day, ethambutol 0.75 g/day, cardoverine 60 mg/day, and aspirin. Her gangrenous foot dried up and a definite line of demarcation formed on the edge of the ulcer became crusted. The surrounding skin returned to normal color. The pain in her toes was relieved and the lymph nodes were softened. After 3 months of treatment, her symptoms disappeared completely. Repeated chest

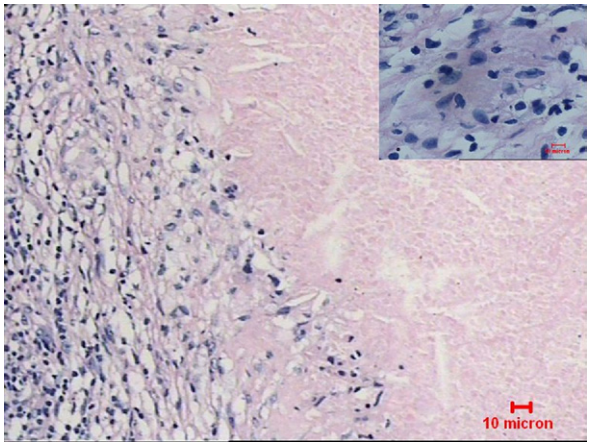

Fig 3. Histopathology of cervical lymph nodes. These features characterize a well-formed granuloma, formed as a response to *M. tuberculosis* in the patient. (Hematoxylin and eosin stain, bar 10 um.)

computed tomography scans showed that the lesions were improved.

DISCUSSION

Although the bacillus Calmette-Guérin vaccines can substantially reduce the incidence of TB, this disease still occurs throughout the world. Poverty, HIV, and drug resistance are major contributors to the global resurging of the TB epidemic. The clinical presentations of TB are highly variable. When the disease becomes active, 75% of the cases are pulmonary TB. Tuberculous lymphadenitis continues to be a common cause of extrapulmonary TB. In the developing world, up to 43% of all peripheral lymphadenopathy are caused by TB.[4] For non-HIV infected patients, the occurrence of isolated peripheral TB lymphadenopathy is very likely due to reactivation of disease at the sites which were initially seeded by hematogenous dissemination during primary TB infection. However, some authors considered that cervical TB lymphadenitis might be due to infection of the tonsils, adenoids, and Waldeyer's ring resulting in cervical node involvement.[4] Tuberculous lymphadenitis is a chronic specific granulomatous inflammation with caseous necrosis of the lymph node. The characteristic morphological presentations are the tuberculous granuloma, giant multinucleated cells surrounded by epithelioid cells aggregates, T cell lymphocytes, and few fibroblasts. Granulomatous tubercules evolve to central caseous necrosis and tend to become confluent, replacing the lymphoid tissue.

Peripheral gangrene refers to situations that induce diminishing of the blood supply, nutrient, or oxygen to the tissues or organs for a prolonged period of time and lead to death of the tissues or organs. There are usually two types of gangrene – dry and wet. Dry gangrene is mainly a vascular gangrene. Malnourishment, diabetes mellitus, serious vascular impairment, and old age are predisposing factors.

Gangrene resulting from TB is uncommon.[3] Our patient experienced fever, lymphadenectasis, and confirmed pulmonary TB by radiograph and therapeutic efficacy. After she withdrew from the medication, the symptoms relapsed and deteriorated. Based on the pathological presentations and image changes, we considered that her gangrene resulted from vasculitis secondary to TB.

Vasculitis is a clinicopathologic process characterized by blood vessel wall inflammation, which can be primary or secondary to other systemic diseases. Vasculitis can affect blood vessels of all sizes in any organ, and these result in a wide variety of signs and symptoms in clinical presentation. Vasculitis secondary to TB was first described by Parish and Rhodes in 1967.[5] TB could result in granulomatous arteritis and affect the aorta and its branches, thereby mimicking large-vessel vasculitis. Moreover, vasculitis might be seen at histopathology in the region of tuberculous granulomas. Involvement of the descending aorta or renal artery might resemble Takayasu's arteritis, especially in clinical settings where this pattern of aortic involvement from Takayasu's arteritis was common.[6] TB also was considered a cause of small-vessel vasculitis, such as leukocytoclastic vasculitis.[7-10] Leukocytoclastic vasculitis was a small-vessel vasculitis. The major clinical manifestations included palpable purpura and petechiae. Leukocytoclastic vasculitis could be caused by the deposition of immune complexes formed by antibodies against *M. tuberculosis* proteins in the small vessel walls. The mechanism of injury proposed for vasculitis is deposition of immune complexes in the vascular wall rather than direct aggression of *M. tuberculosis.*[11] The existence of circulating immune complexes has been demonstrated in 56% of patients with active TB, and that their levels are related to disease activity.[12] To our knowledge, TB had no association with medium-vessel vasculitis. The symptoms and angiography in the case reported here supports that vasculitis can involve medium-sized arteries such as the left posterior tibial artery and peroneal artery. The exact pathogenic mechanism remains uncertain. Stratta et al[13] proposed that *M. tuberculosis* could result in granulomatous arteritis leading to vessel wall thickening, aneurysm formation, and stenoses that could affect the large vessel and its branches. They suggested that *M. tuberculosis* was a chronic stimulus for an immunogenic reaction which could induce vasculitis process and might have a immunological mechanism characterized by the activation of cell-mediated immunity and by granulomatosis reaction. Moreover, some studies showed that hyperaggregation of platelets participated in the chronic tuberculous process. In addition, the presence of gangrene with peripheral pulses was always associated with abnormal platelet aggregation and platelet suppressive therapy was of therapeutic value in this situation.[14-16] Therefore, according to the character of the case, we presumed that cervical TB lymphadenitis might be due to pulmonary TB infection, and chronic *M. tuberculosis* stimulation induced the vasculitis process, ultimately causing gangrene.

With global resurgence of *M. tuberculosis* infection, cases of extrapulmonary TB have also shown an increase. Some situations are extremely rare and difficult to diagnose just like our case. Although peripheral gangrene and vasculitis are seldomly associated with TB, it should not be ignored.

REFERENCES

1. WHO. Global tuberculosis control. WHO report. WHO/HTM/TB/2006.362. Geneva: World Health Organization 2006.
2. Davis MD. Peripheral symmetrical gangrene. Mayo Clin Proc 2004;79:914.
3. Dubey AP, Sudha S, Parakh A. Peripheral gangrene: an uncommon manifestation of disseminated tuberculosis. Indian Pediatr 2006;43:255-7.
4. Dandapat MC, Mishra BM, Dash SP, Kar PK. Peripheral lymph node tuberculosis: a review of 80 cases. Br J Surg 1990;77:911-2.
5. Parish WE, Rhodes EL. Bacterial antigens and aggregated gamma globulin in the lesions of nodular vasculitis. Br J Dermatol 1967;79:131-47.
6. Muranjan MN, Bavdekar SB, More V, Deshmukh H, Tripathi M, Vaswani R. Study of Takayasu's arteritis in children: clinical profile and management. J Postgrad Med 2000;46:3-8.
7. Carvalho M, Dominoni RL, Senchechen D, Fernandes AF, Burigo IP, Doubrawa E. Cutaneous leukocytoclastic vasculitis accompanied by pulmonary tuberculosis. [Article in English and Portuguese] J Bras Pneumol 2008;34:745-8.
8. Kim HM, Park YB, Maeng HY, Lee SK. Cutaneous leukocytoclastic vasculitis with cervical tuberculous lymphadenitis: a case report and literature review. Rheumatol Int 2006;26:1154-7.
9. Kitamura H, Shimizu K, Takeda H, Tai H, Ito Y, Fukunaga M. A case of henoch-schönlein purpura nephritis in pulmonary tuberculosis. Am J Med Sci 2007;333:117-21.
10. Stavropoulos PG, Boubouka DC, Anyfantakis NV, Panagiotopoulos KA, Kostakis GP, Georgala S, et al. Cutaneous small vessel vasculitis and pulmonary tuberculosis: an unusual association. Int J Dermatol 2006;45:996-8.
11. Minguez P, Pintor E, Burón R, Díaz-Pollán B, Puche JJ, Pontes JC. Pulmonary tuberculosis presenting with cutaneous leukocytoclastic vasculitis. Infection 2000;28:55-7.
12. Johnson NM, McNicol MW, Burton-Kee EJ, Mowbray JF. Circulating immune complexes in tuberculosis. Thorax 1981;36:610-7.
13. Stratta P, Messuerotti A, Canavese C, Coen M, Luccoli L, Bussolati B, et al. The role of metals in autoimmune vasculitis: epidemiological and pathogenic study. Sci Total Environ 2001;270:179-90.
14. Khechinashvili GN, Khvitiya NG. Protective characteristics of platelets in tuberculosis. Bull Exp Biol Med 2004;138:513-4.
15. Sarode R, Bhasin D, Marwaha N, Roy P, Singh K, Panigrahi D, et al. Hyperaggregation of platelets in intestinal tuberculosis: role of platelets in chronic inflammation. Am J Hematol 1995;48:52-4.
16. Morris-Jones W, Preston FE, Greaney M, Chatterjee DK. Gangrene of the toes with palpable peripheral pulses. Ann Surg 1981;193:462-6.

Submitted May 6, 2010; accepted Jul 9, 2010.