Calcaneal Osteomyelitis Presenting as a Paradoxical Reaction during Treatment of Multidrug-Resistant Tuberculosis

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Tuberculosis in the foot progresses gradually; thus, diagnosis is usually delayed, and early treatment is rarely provided. If osteomyelitis occurs due to delayed diagnosis and treatment, surgical treatment should be considered. We report the case of a 46-year-old man with osteomyelitis of the calcaneus who was diagnosed with multidrug-resistant pulmonary tuberculosis and he was treated with anti-tuberculosis drugs. Bilateral adrenal masses, abscess of both testes and a small wound in the left plantar heel were observed. Both adrenal masses and abscess were regarded as paradoxical reaction of anti-tuberculosis treatment. After 1 month, he developed a pain in the left plantar heel that was compatible with calcaneal osteomyelitis in radiological features. He underwent right orchiectomy for right scrotal abscess aggravation and surgical treatment for left calcaneal osteomyelitis. *Mycobacterium tuberculosis* was confirmed by polymerase chain reaction. The patient was immobilized by cast for 8 weeks and the heel pain gradually improved. (Clinical Pain 2019;18:102-106)

Key Words: Tuberculous osteomyelitis, Heel pain, Calcaneal tuberculosis

INTRODUCTION

The prevalence of tuberculosis (TB) in Korea was 70.4 per 100,000 people in 2017. About 85% of TB develops in the lungs; it rarely (1%~3%) occurs in the skeletal system. TB in foot accounts for 8%~10% of skeletal TB, with talus being the most common site, followed by the calcaneus. 1 It is more difficult to diagnose skeletal TB than pulmonary tuberculosis (PTB) due to the former’s rare incidence, ambiguous symptoms, and characteristics of radiologically mimicking other diseases. Delayed diagnosis increases morbidity and mortality.

In outpatient or inpatient settings, physicians can encounter patients with plantar heel pain, which is usually benign and self-limiting. 2 However, TB that develops in the foot tends to progress gradually. Thus, diagnosis is usually delayed, and early treatment is rarely provided. If osteomyelitis develops due to delayed diagnosis and treatment, surgical treatment should be considered. Here, we report the case of a patient who developed plantar heel pain during PTB treatment and needed surgical approach.

CASE REPORT

A 46-year-old man presented with cough, night sweats, and weight loss for 6 months and was diagnosed with active PTB (Fig. 1-A). Since resistance to rifampin was confirmed by polymerase chain reaction for *Mycobacterium tuberculosis* (TB-PCR), moxifloxacin, pyrazinamide, cycloserine, prothionamide, and kanamycin were administered for multidrug-resistant PTB. Respiratory isolation was discontinued after three consecutive negative smears in acid-fast bacilli (AFB) stain. Two months after TB treatment, he developed fever, and blood test showed electrolyte imbalance. Computed tomography was performed to determine the cause of the electrolyte imbalance, and bi-
lateral adrenal masses were observed. In addition, an abscess developed in both scrotal sacs and a small wound was observed in the left plantar heel. Incision and drainage was performed in the left scrotum to drain excess pus. The AFB stain results of the pus were negative, but histopathological examination showed chronic active inflammation. At that time, there was no history of minor trauma in the left heel that caused the wound, and because there were no particular symptoms, simple dressing was performed. His unfavorable economic status prevented further examination. Bilateral adrenal masses and scrotal abscess were regarded as paradoxical reaction of anti-TB treatment. He was initially scheduled for multidrug-resistant TB treatment for 12 months. However, we were unable to exclude the possibility that extrapulmonary TB was caused by a hematogenic spread, so the duration of anti-TB therapy was modified to 18 months. Thereafter, there was delayed recovery of the right scrotal abscess. However, since the left testis failed to function due to testicular atrophy during recovery, dressing alone was done, without orchiectomy. After 1 month, he complained of local pain with numeric rating scale (NRS) of 4 in the left plantar heel (Fig. 1-B).

On physical examination, mild heat and soft tissue swelling were observed in the posterolateral heel. Radiographic findings showed no bony erosion or destructive lesion (Fig. 2-A). Laboratory tests revealed white blood cell count of 9,200 cells/mm³ and C-reactive protein level of 0.91 mg/L. The AFB stain and culture of the brownish pus came out negative so the only dressing treatment was continued. Initially, the wound appeared to heal. However, after 1

Fig. 1. (A) Chest radiograph shows ill defined increased opacities in both upper and mid lung zone. (B, C) Wounds are observed in the left heel (arrow) and right scrotum (arrowhead).

Fig. 2. (A) Lateral view of the foot shows a well-marginated focal radiolucent lesion of irregular shape with a size of 2 × 2 cm (arrow). (B) Six-month follow-up radiograph after surgery shows that the surgical site is filled with bone grafts (arrowhead).
months, the pus increased in volume and the patient was observed an antalgic gait pattern. As the pain deteriorated to NRS of 6 and the right scrotal abscess worsened (Fig. 1-C), the patient was referred to the orthopedist and urologist in a tertiary-care hospital. Orchiectomy was performed for radical treatment of right scrotal abscess. Magnetic resonance imaging (MRI) by the orthopedist showed peripherally enhancing intraosseous lesions (Fig. 3) and three-phase bone scan showed mildly increased uptake in the left calcaneus in all three phases of the scan (Fig. 4). Both radiologic findings were compatible with calcaneal osteomyelitis. Surgical drainage and curettage of bone grafts of calcaneus were performed for diagnosis and treatment, and *M. tuberculosis* was confirmed by TB-PCR using bone specimens. The patient was immobilized by cast for 8 weeks. After 8 weeks, the cast was removed and he started toe touch weight bearing using crutch and gradually increased to full load. Heel pain also improved (NRS reduction > 70%). Six months after the surgery, follow-up radiographs showed bone remineralization (Fig. 2-B). He could walk normally without pain and could perform activities of daily living as before surgery.

**DISCUSSION**

A paradoxical reaction is defined as a clinical or radiological worsening of pre-existing tuberculous lesion or development of a new lesion in patients receiving appropriate anti-TB treatment. Drug discontinuation, drug resistance, secondary infections and side effect of anti-TB treatment should be excluded for the diagnosis of paradoxical reactions. Since our patient adhered to the medication; was treated with anti-TB drugs based on drug susceptibility test and the PTB, which was initially diagnosed; had negative
sputum culture results; and showed improvement in radiological findings, the current case is considered to be of a paradoxical reaction rather than of treatment failure. The fact that the CT findings at the beginning of PTB showed no abnormalities other than pulmonary lesions supported this point. Studies have suggested that paradoxical reactions should be considered within 3 months after anti-TB therapy and the possibility of treatment failure should be considered after 4 months.6 In our case, since the fact that a new lesion was observed 2 months after treatment initiation also increased the likelihood of paradoxical reaction. Paradoxical reactions occur in approximately 15% of TB patients, and the pathogenesis is generally accepted as a late hypersensitivity reaction to tuberculoproteins derived from dead bacilli, although the pathogenesis is unclear.7 These findings can also explain the rare occurrence of positive AFB stain and PCR test results.

Treatment of a paradoxical reaction has not been established yet, but 2~4 weeks of steroid use followed by tapering for 6~8 weeks is common. In our case, the initial heel symptoms were nonspecific, so we could not predict the possibility of the paradoxical reaction. In addition, the diagnosis of the paradoxical reaction was delayed because the patient’s low economic status limited the active examination. The failure to control this rapid progress of the lesion with the proper steroid therapy is thought to be a factor that ultimately led to the decision of surgery.

TB in the foot and ankle occurs mainly in immunocompromised individuals and mimics the characteristics of other diseases.8 To our best knowledge, paradoxical reactions in the calcaneus during anti-TB treatment in a non-HIV patient has not been reported before. In one study, 15 patients with TB in foot and ankle were analyzed; only 7 patients were correctly diagnosed by clinical symptoms and imaging studies.9 It was suggested that TB osteomyelitis should always be considered when localized and painful swelling and persistent draining sinus of foot and ankle are present.

Our patient had no history of any particular diseases and never received immunosuppressive therapy. However, he underwent anti-HIV-1/HIV-2 screening tests due to the possibility of immunosuppression, considering that he was a heavy smoker (25-pack-year). The screening tests were negative. Further tests were needed when considering the occurrence of multidrug-resistant TB in young age, but these could not be performed because of his poor economic status. However, as the pus was continuously draining from the calcaneus, additional tests should have been performed earlier for checking the possibility of TB osteomyelitis.

There was a case of calcaneal osteomyelitis associated with nontuberculous mycobacteria;10 this case was similar to our case in that surgical treatment of calcaneus was performed for chronic osteomyelitis and abscess formation. However, it was assumed to be contiguous osteomyelitis of nontuberculous mycobacteria caused by repeated steroid injections, while in our case, it was considered to be osteomyelitis due to paradoxical reaction of anti-TB treatment. In addition, in the above case, repeated steroid injection appears to have altered the hypothalamic-pituitary-adrenal (HPA) axis, whereas in our case, adrenal masses formation by M. tuberculosis might have affected the HPA axis. Moreover, our patient had rare bilateral anorchia due to the progression of testicular TB.

In the current case, the patient showed a significant improvement in pain after surgery and was able to walk without pain. However, delayed diagnosis and treatment due to financial constraints resulted in unexpected operation. It is thus important that in patients with progressive diseases, such as TB, prompt action is taken upon observing abnormal findings and tests are appropriately conducted. In particular, if heel pain is currently present in a patient who is recently treated for TB, the possibility that paradoxical reaction is the cause should be considered. Notably, the present case occurred even after appropriate anti-TB therapy. Therefore, the current case could be a reference in identifying the cause of plantar heel pain in a patient treated with the anti-TB drugs in the outpatient clinic.

REFERENCES

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