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Case Report

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An Atypical Presentation of Tuberculosis in a Kidney Transplant Recipient with Tenosynovitis Attack

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ABSTRACT

The frequency of tuberculosis in organ transplant recipients has not been clearly determined and varies according to geographical distribution. However, the incidence has been considerably higher in organ transplant recipients than in the healthy population. Tuberculosis may have an atypical presentation in immunocompromised hosts, which can delay the diagnosis. Also, tuberculosis leads to alteration in immunosuppressive treatments, such as drug interaction or discontinuation. In this case, we present a kidney transplant recipient with joint pain in the right hand and wrist. Her pain was refractory to analgesics and steroid therapy. Tenosynovitis was detected by radiological examination. Subsequently, miliary tuberculosis diagnosis was established through the onset of respiratory symptoms during hospitalization. The diagnosis was based on thoracic tomographic findings and molecular tests. The arthralgias resolved after the administration of tuberculosis therapy.

Keywords: Kidney transplantation, tuberculosis, tenosynovitis

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INTRODUCTION

Mycobacterium tuberculosis complex bacilli cause tuberculosis (TB) disease. Tuberculosis disease is a clinical condition affecting all organs and systems, although it mainly involves the lungs. Tuberculosis disease occurs essentially due to the reactivation of latent infection in immunocompromised hosts. However, it can result from undetermined infection in the allograft or as the new onset disease after transplantation.[1] Tuberculosis may have atypical manifestations in this population, such as pyomyositis, cutaneous ulcer, abscess, or tenosynovitis.[2]

Miliary TB is a fatal form of TB and a consequence of lymphohematogeneous dissemination of bacillus. An increased and widespread application of immunosuppressive agents affects the epidemiology of miliary TB. Essentially, the disruption of cell-mediated immunity provokes the emergence of disease.[3] The clinical presentations are often not distinctive, and typical radiographic evidences may not be observed until an advanced stage of the disease. Therefore, the frequent establishment of diagnosis has been retarded.[3]

The musculoskeletal system is frequently involved among patients with extrapulmonary TB, accounting for 25%.[4] The hand and wrist have been frequently reported as the location for tenosynovitis in TB. The flexor tendon sheath of the hand and the radioulnar bursa is mostly influenced. Here we present a case of atypical tuberculosis and the unusual etiology of tenosynovitis.

CASE PRESENTATION

A 45-year-old female patient underwent preemptive kidney transplantation from a living donor 10 years

ago due to an unknown etiological chronic kidney disease. The immunosuppressive regimen included tacrolimus 2 × 1 mg, mycophenolic acid 2 × 720 mg, and prednisolone 1 × 5 mg. Additionally, she received insulin therapy for new-onset diabetes after transplantation. Last month, she complained about joint pain, especially in the hand, wrist, and elbow locations. Her other symptoms were malaise, fatigue, and poor appetite. Initially, the patient was examined in an orthopedic clinic, and an analgesic was prescribed. Subsequently, she presented to the rheumatology department due to increased complaints. Undifferentiated arthritis diagnosis was considered, and a methylprednisolone tablet (40 mg/day) was prescribed. The patient was referred to nephrology for worsening kidney functions after arthritis treatment. The patient was hospitalized at the nephrology clinic because of acute kidney injury and a malnourished state.

On physical examination, the general condition was poor: blood pressure was 100/70 mmHg, fever was 37.4°C, pulse was 78/minute, respiratory rate was 16/minute, and oxygen saturation was 98%. Respiratory and cardiac sounds were normal, the abdomen had the operational scar, and pulses were palpable on all extremities. Tenderness and swelling were detected in the right wrist joint and metacarpals. The initial laboratory tests were as follows: glucose 102 mg/dL, blood urea nitrogen 54 mg/dL; creatinine 1.7 mg/dL; sodium 129 mEq/L; potassium 4.2 mEq/L; calcium 8.5 mg/dL; phosphorus 3.9 mg/dL; protein 5.6 g/dL; albumin 2.8 g/dL; alanine aminotransferase 15 IU/L; aspartate aminotransferase 13 IU/L; lactate dehydrogenase 314 IU/L; total bilirubin 0.4 mg/dL; C-reactive protein (CRP) 158 mg/L; leukocyte 12.5 10^3/µL; hemoglobin 9.4 g/dL; platelet 357 10^3/µL; and tacrolimus trough level 7.3 ng/mL. Pyuria and proteinuria were detected in urine analysis. The urinary protein-to-creatinine ratio was 0.8 mg/g. No pathogen was isolated in 2 urine cultures.

The kidney functions improved, and the creatinine level decreased to baseline (1.2 mg/dL) after parenteral hydration with isotonic fluid. However, arthralgia and the high CRP level were sustained. Asymmetrical thickness in the tendons with hyperechogenic alterations in the adjacent soft tissue was observed by ultrasonographic examination of the right wrist. Tenosynovitis was confirmed with magnetic resonance imaging of the joint, and the images are shown in Figures 1 and 2.

MAIN POINTS

- Kidney transplant recipients are prone to atypical infections.
- Miliary tuberculosis presents with unexpected clinics like musculoskeletal symptoms in immunocompromised individuals.
- Unexplained symptoms in kidney transplant recipients should be carefully considered.

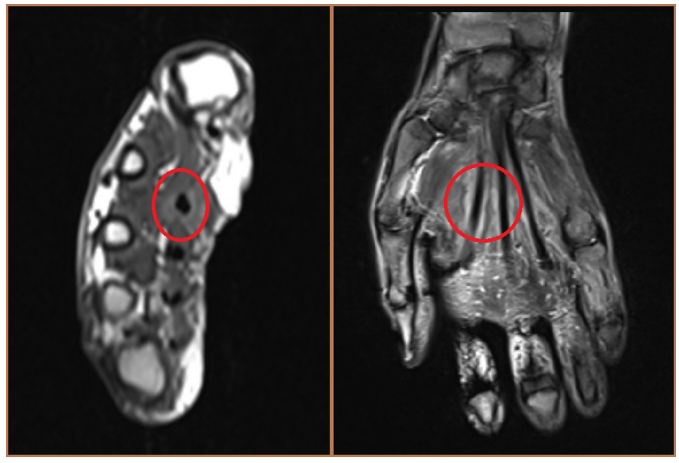

Figure 1. Magnetic resonance images showing minimal effusion around the flexor tendons (flexor digitorum superficialis and profundus) and minimal edematous signal changes in the surrounding soft tissues at the wrist level.

The results of subsequent laboratory tests for tenosynovitis etiology were as follows: erythrocyte sedimentation rate 98 mm/h, CRP 200 mg/L, rheumatoid factor was negative, anticyclic citrullinated peptides was negative, antinuclear antibody was low positive (1/100), and Brucella agglutination test was negative. No pathogen was isolated in the bloodstream and urine samples.

Hospitalization was extended for palliation of pain and improving nutrition. Even narcotic analgesics were utilized for tenosynovitis-related pains. There was onset of chest pain, tachypnea, and fever on the seventh day of hospitalization. Bilateral spreading infiltration was detected on chest radiography, and then computerized thoracic tomography, and the image is shown in Figures 3 and 4. Polymerase chain reaction

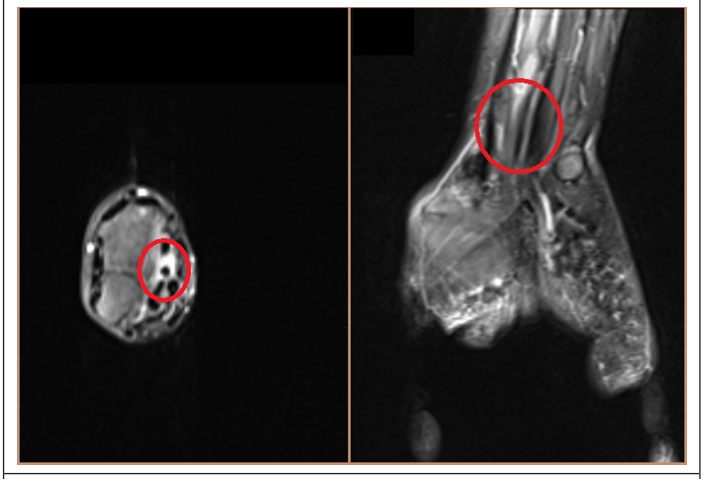

Figure 2. Magnetic resonance images showing alterations consistent with tenosynovitis.

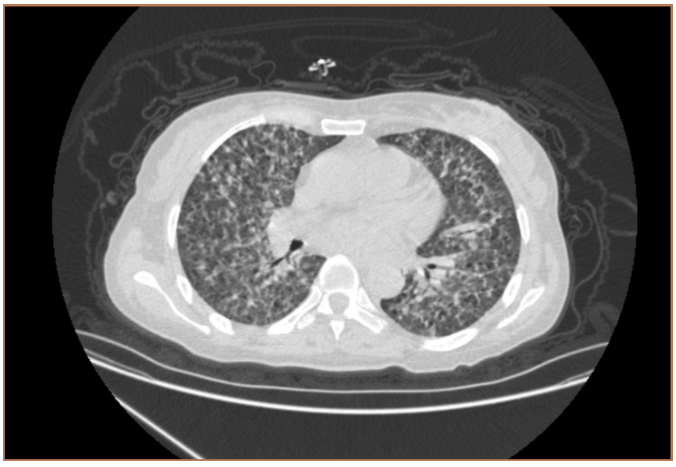

Figure 3. Chest radiography image. The view shows bilateral pulmonary parenchymal infiltration.

tests for SARS-CoV-2 with cytomegalovirus were performed, the results of which were negative. Radiological findings were primarily considered as miliary TB. Bronchoscopic examination did not reveal endobronchial formation. Polymerase chain reaction test result for *Mycobacterium* complex positive in the bronchoalveolar lavage sample.

Quadruple TB treatment (*isoniazid*, *rifampin*, *pyrazinamide*, and *ethambutol*) was initiated, and mycophenolic acid was discontinued for abating immunosuppression. Constitutional symptoms and joint pain resolved in the outpatient follow-up over time. Also, lung involvement has been regressed in subsequent radiological examinations.

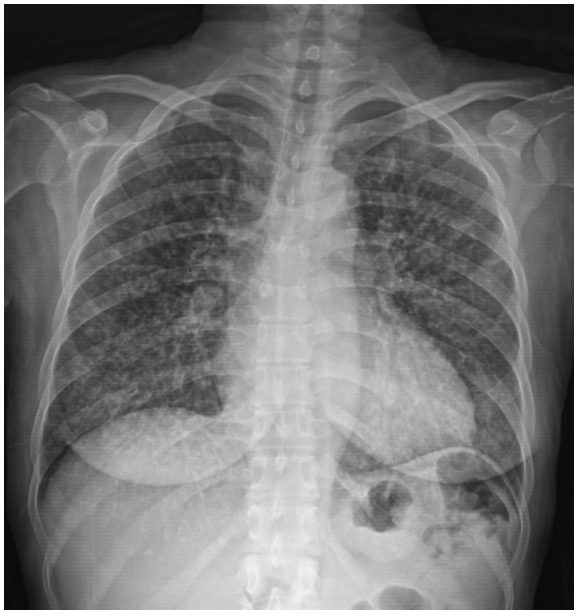

Figure 4. Computed tomography image. The view shows bilateral pulmonary parenchymal infiltration.

DISCUSSION

We have presented atypical TB and the unusual etiology of tenosynovitis together. It is well known that the occurrence of TB increases in kidney transplant recipients. However, this reported case is attractive owing to the order of symptoms. At the onset of the disease, severe rheumatologic symptoms were not accompanied by typical TB findings. Joint pain can be ignored since it is a widespread non-spesific symptom in the general population. More specific symptoms for TB, such as fever, cough, and shortness of breath, occurred much later. We have already established the TB diagnosis by investigating respiratory symptoms. Sterile pyuria was observed in the first evaluation; however, acid-fast bacilli was not stained in urine samples.

Infections are significant reasons for mortality after kidney transplantation.[5] Both standard and opportunistic infections occur in transplant recipients. Several factors, including immunosuppression, are associated with susceptibility to infection. Actually, this patient did not receive any intensive immunosuppression recently, but it is known that chronic maintenance immunosuppression can also trigger TB reactivation.

The prevalence of TB among transplant recipients in developed countries has varied from 1.2% to 6.4%; however, it has been highly reported (10%-15%) in endemic territories.[6] Also, TB disease can lead to morbidity and mortality in organ transplant recipients. Disseminated or extrapulmonary TB is determined more frequently in immunocompromised hosts. Approximately one-third to one-half of active TB after transplantation has been manifested with disseminated or extrapulmonary forms. Tuberculosis can emerge due to the reactivation of bacillus, originating from undetected infection in the allograft, or as a new infection after transplantation in the recipients.[7]

Miliary TB is severe and fatal formation outcome of the disease due to the spillover of bacillus to several organs through a hematogenous route. It occurs via tuberculous foci organization in seed-sized millets (1-2 mm). John Jacobus Manget first defined the term *miliary tuberculosis* in 1700 due to tiny tubercles-like millet seeds on the pathological specimen. Symptoms are not distinctive, and classical radiological alterations may be detected in the advanced stage of the disease. Furthermore, unusual manifestations of the disease commonly lead to the tardiness of diagnosis.[3]

The musculoskeletal system is among the frequently involved sites of extrapulmonary TB and is affected by approximately 25% frequency.[4,8] However, tenosynovitis is an uncommon location of extrapulmonary TB involvement and accounts for 5% of musculoskeletal TB cases, such as the hand and wrist. The flexor tendon sheath of the hand and the radioulnar bursa are reported as the affected sites. Bacillus spreads to the tendon sheath either by hematogenous spread or by direct inoculation. The clinical symptoms are often non-specific, with

patients suffering from pain in the wrist, swelling around the wrist or hand, and limited ability to move.[9,10] The thick synovial tissue and large rice bodies can envelop the median nerve, causing carpal tunnel syndrome.[11] The swelling of soft tissue along the involved tendon sheaths or tissue calcification can be detected on radiographs.[12] Joint pain was the first symptom in this patient. Although she complained of particular pain with limited motion in bilateral wrists, she had arthralgia in various sites. Due to the typical arthritis appearance in the patient's joints and the increase in acute phase reactants, rheumatological diseases were considered in the etiology. However, the diagnosis of miliary TB led us to conclude that this tenosynovitis was due to infectious causes.

The guidelines have all recommended that the approach to the treatment of TB in solid organ transplantation recipients be similar to immunocompetent hosts.[13] Rifampicin is preferred in classical antituberculosis therapy and induces the cytochrome P450 microsomal enzyme system.[14] If rifampicin is used, the calcineurin inhibitors or rapamycin dose should be increased approximately 3- to 5-fold, and serum concentrations should be monitored.[15] In our case, we acted proactive for tacrolimus dosing, and drug dosage was increased synchronously with the initiation of tuberculosis therapy. The dosage was increased to ≥1.5 times the previous tacrolimus dosage. The trough level of tacrolimus was targeted at 3-5 ng/mL in the follow-up. Despite increased dosage, tacrolimus levels were reduced in the early period of TB therapy, such as 2 ng/mL. Therefore, we increased the drug dosage again and measured the tacrolimus trough level twice a week. A stable drug level target was achieved when the drug dose was increased approximately 5 times. The patient did not undergo an allograft rejection attack during TB treatment due to a decreased tacrolimus level. Afterward, we followed the patient closely every month for drug-level and liver function test monitoring. The same antimicrobial agents are generally used both in the military and in pulmonary forms of TB.[13] Likewise, we administered standard HRZE (isoniazid, rifampin, pyrazinamide, and ethambutol) protocol to the reported patient consistent with guidelines recommendations. The duration of total TB treatment was 9 months; quadruple therapy was administered in the first 2 months, and then dual therapy was continued.

The treatment of Latent Tuberculosis Infection (LTBI) considerably decreases TB reactivation in the period of after organ transplantation.[16] Prophylactic isoniazid therapy should be administered for 9 months for all transplant recipients who have inadequate treatment for LTBI prior to transplantation. Also, preventive treatment should be initiated before transplantation in kidney transplant candidates due to the increased risk of TB reactivation in dialysis patients.[13] In the reported patient's medical history, clinical features of TB were not detected in the transplantation preparation period 10 years ago. For example, the radiological clues of TB were not observed in thoracic CT. The tuberculin skin test was performed, and the induration size was 7 mm. Prophylactic isoniazid prophylaxis was administered 9 months after kidney transplantation. Therefore, we have considered the reactivation of latent infection in this patient.

CONCLUSION

In this case, we want to emphasize opportunistic infections and their various clinical presentations in immunocompromised individuals, such as kidney transplantation recipients. In conclusion, physicians should be alert regarding TB in unexplained systemic symptoms in endemic countries.

Informed Consent: Written informed consent was obtained from the patients/patient who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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