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Abstract

EXTRAPULMONARY TUBERCULOSIS IN A KAZAKH PATIENT WITH MIXED CONNECTIVE TISSUE DISEASE. CLINICAL CASE

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Patients with systemic autoimmune diseases have increased susceptibility to infections, including tuberculosis, partly due to immunosuppressive treatment. We describe a case of extrapulmonary tuberculosis (tuberculous osteomyelitis of the right foot) occurring a few months after a diagnosis and apparently successful treatment of abdominal TB in a Kazakh patient with mixed connective tissue disease. Abdominal tuberculosis had occurred while the patient was on high doses of corticosteroids, whereas bone tuberculosis was diagnosed when glucocorticoid doses had been reduced. The diagnosis of tuberculous osteomyelitis was unfortunately made months after the disease manifested. Screening for latent tuberculosis should be mandatory before starting immunosuppressive treatment in patients with autoimmune diseases, especially in countries with a considerable tuberculosis burden, and tuberculosis should be high in the list of possible etiologies of multiple clinical manifestations in these patients.

Key words: *Mycobacterium tuberculosis; Septic arthritis; Mixed connective tissue disease; Osteoarticular tuberculosis; Abdominal tuberculosis; Extrapulmonary tuberculosis.*

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Резюме

ВНЕЛЕГОЧНЫЙ ТУБЕРКУЛЕЗ У КАЗАХСКОГО ПАЦИЕНТА СО СМЕШАННЫМ ЗАБОЛЕВАНИЕМ СОЕДИНИТЕЛЬНОЙ ТКАНИ. КЛИНИЧЕСКИЙ СЛУЧАЙ.

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Пациенты с системными аутоиммунными заболеваниями имеют повышенную восприимчивость к инфекциям, включая туберкулез, отчасти из-за иммуносупрессивной терапии. Мы описываем случай внелегочного туберкулеза (туберкулезный остеомиелит правой стопы), возникший через несколько месяцев после постановки диагноза и, по-видимому, успешного лечения абдоминального туберкулеза у казахского пациента со смешанным заболеванием соединительной ткани. Абдоминальный туберкулез возник, когда пациент принимал высокие дозы кортикостероидов, тогда как костный туберкулез был диагностирован, когда дозы глюкокортикоидов были снижены. К сожалению, диагноз туберкулезного остеомиелита был поставлен через несколько месяцев после манифестации заболевания. Скрининг на латентный туберкулез должен быть обязательным перед началом иммуносупрессивной терапии у пациентов с аутоиммунными заболеваниями, особенно в странах со значительным бременем туберкулеза, и туберкулез должен быть одним из первых в списке возможных этиологий множественных клинических проявлений у этих пациентов.

Ключевые слова: *Микобактерии туберкулеза; Септический артрит; Смешанное заболевание соединительной ткани; Костно-суставной туберкулез; Абдоминальный туберкулез; Внелегочный туберкулез.*

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Түйіндеме

АРАЛАС ДӘНЕКЕР ТІН АУРУЫ БАР ҚАЗАҚСТАНДЫҚ НАУҚАСТА ӨКПЕДЕН ТЫС ТУБЕРКУЛЕЗ. КЛИНИКАЛЫҚ ЖАҒДАЙ.

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Жүйелік аутоиммунды аурулары бар емделушілерде ішінара иммуносупрессивті емге байланысты туберкулезді қоса, жұқпалы аурулардың қаупі жоғары. Біз дәнекер тінінің аралас ауруымен ауыратын қазақстандық науқаста абдоминальды туберкулез диагнозы қойылған және сәтті емделгеннен кейін бірнеше айдан кейін пайда болған өкпеден тыс туберкулез (оң аяқтың туберкулездік остеомиелиті) жағдайын сипаттаймыз. Құрсақ қуысының туберкулезі науқас кортикостероидтардың жоғары дозаларын қабылдаған кезде дамыған, ал сүйек туберкулезі глюкокортикоидтардың дозасын азайтқанда анықталған. Өкінішке орай, туберкулезді остеомиелит диагнозы ауру басталғаннан кейін бірнеше айдан кейін қойылды. Аутоиммунды аурулары бар емделушілерде, әсіресе туберкулездің айтарлықтай ауыртпалығы бар елдерде иммуносупрессивті терапияны бастамас бұрын жасырын туберкулезге скрининг міндетті болуы керек, ал туберкулез осы науқастардағы көптеген клиникалық көріністер үшін ықтимал этиологиялар тізімінде жоғары болуы керек.

***Түйінді сөздер**: Туберкулез микобактериясы;Септикалық артрит; Аралас дәнекер тінінің ауруы; Сүйек және буын туберкулезі; Іштің туберкулезі; Өкпеден тыс туберкулез..*

Дәйексөз үшін:

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Introduction

Susceptibility to infections in patients with systemic autoimmune diseases is increased, partly due to immunosuppressive treatment, and mixed connective tissue disease (MCTD) is no exception. One case of pulmonary and cutaneous tuberculosis (TB), and one case of pulmonary tuberculosis following steroid therapy for MCTD were reported from Japan [14] and Germany [6] respectively. Another case of pulmonary tuberculosis in a patient on immunosuppressives occurred in Senegal [7], and one case of pulmonary tuberculosis prior to the start of immunosuppressive therapy in a patient with MCTD was described from India [11]. One case of knee joint tuberculosis in a patient with a 9-year history of MCTD on long-term immunosuppressive treatment was reported from Germany [4]. Finally, a female patient in Germany who had been treated with immunosuppressive drugs for five years for mixed connective tissue disease and whose symptoms had changed (increasing joint pains and loss of weight) five years later, leading to higher doses of steroids, developed a tuberculous meningoencephalitis, and at that point *Mycobacterium tuberculosis* was detected in urine, sputum and secretions of different joints [9]. In this latter case, the misinterpretation of the change of symptoms as worsening of the MCTD ultimately led to the death of the patient [9].

We report a case of tuberculous osteomyelitis of the right foot occurring few months after a diagnosis of abdominal TB in a patient with mixed connective tissue disease in Kazakhstan, a country with a considerable TB burden and a high occurrence of multidrug-resistant tuberculosis [12].

Case description

A 48-year-old Kazakh female patient (who gave informed consent for publication of her clinical data) presented in mid-November 2024 at the Department of Internal Medicine and Rheumatology of Semey Medical University complaining of pain and swelling in the right ankle and foot (increasing with walking) and in the left wrist joint, and of an ulcer in the dorsal area of the right foot.

The patient had Raynaud's syndrome since 2019 and was diagnosed with mixed connective tissue disease in May 2021, after complaining of fever, weight loss, polyarthralgia, dysphagia, alopecia, xerostomia. Antinuclear antibodies were then positive (1:640), as well as anti-ribonucleoprotein (+++) and anti-SS-A/Ro52 antibodies (++). She was initially treated with hydroxychloroquine (400mg daily), mycophenolate mofetil (2g per day) and corticosteroids. The highest dose of methylprednisolone was 32 mg daily per os, while the average doses were 12–16mg per day. In May 2023, the patient was admitted to a hospital with a diagnosis of acute appendicitis and peritonitis. Appendectomy was performed; during the surgery, a large amount of fluid was noted in the abdominal cavity, and small light-yellow tubercles were seen in areas of the intestine, parietal peritoneum and omentum. Tuberculosis was suspected and subsequently confirmed histologically. Treatment started with rifampicin, pyrazinamide, isoniazid and ethambutol and continued for nine months. The patient had never had symptoms of, or had been treated for, pulmonary tuberculosis, but had fibro-focal changes at chest X-ray. Following the diagnosis of tuberculosis, methylprednisolone was reduced to 8 mg/day.

In February 2024, a marginal fracture of the base of the 5th metatarsal bone of the right foot was found and a plaster cast applied. In June the patient discontinued hydroxychloroquine and mycophenolate mofetil while methylprednisolone was further reduced to 4 mg daily. Because of the persistence of severe pain in the right ankle joint, in July of the same year a CT scan of the feet and ankle joints was performed and revealed fractures of the cuboid and talus bones of the right foot without displacement, and synovitis of the right ankle joint. In September 2024, a whitish lump and swelling at the base of the 1st toe of the right foot appeared. Two days after squeezing the swollen area, a "cheesy" content came out, and new foci with a whitish center appeared. These foci were also squeezed and the contents evacuated. After some time, an open wound of 3 cm in diameter developed on the back of the right foot, was interpreted as a trophic ulcer, and was periodically dressed.

In November 2024, in the absence of activity of mixed connective tissue disease, antibacterial therapy (ceftriaxone 2 mg/day intramuscularly for ten days, followed by azithromycin 250 mg twice daily for an additional ten days) was prescribed.

When the patient was seen for the first time at the Department of Internal Medicine and Rheumatology of Semey Medical University in January 2025, inflammatory arthritis of the left wrist joint with pain during palpation and movement was noted. The right ankle joint was severely deformed with edema, and pain was present at palpation and movement. A trophic ulcer of 3 cm in diameter with calloused edges was present in the 1st metatarsophalangeal and interdigital region on the dorsum of the right foot (Figure 1).

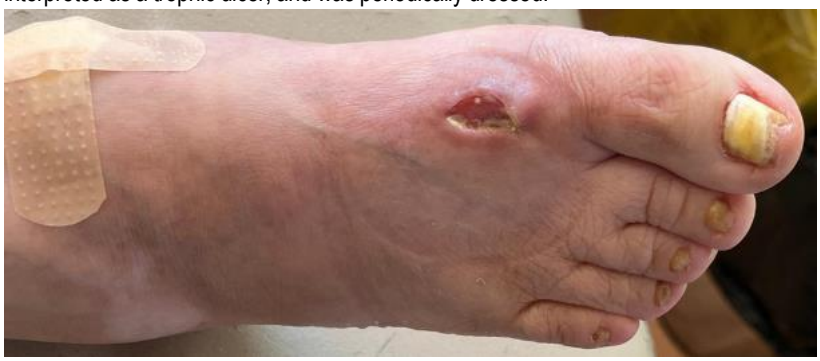

Figure 1. Right foot of the patient: swelling of the ankle joint and metatarsus, fistula on the dorsum of the foot.

Given the history of abdominal tuberculosis, a tuberculous abscess with ensuing fistula was suspected. An X-ray of the right ankle joint was done and showed destructive arthritis of the tarsal bones with predominant damage to the talonavicular and calcaneocuboid joints (Figure 2).

Gene-Xpert testing of the material from the ulcer on the right foot was positive and showed resistance to rifampicin. A diagnosis of tuberculous osteomyelitis with abscess formation was made in January 2025.

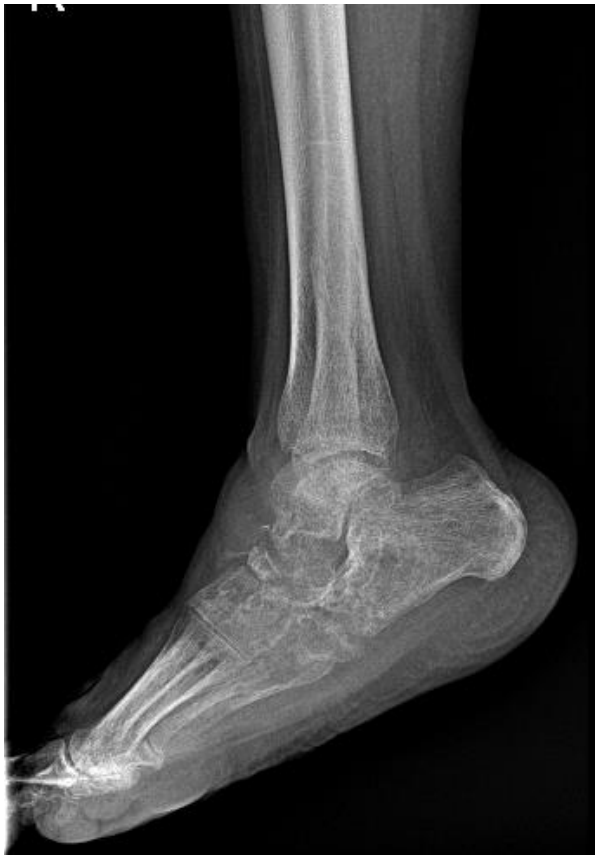

Figure 2. X-ray of the right foot (lateral projection): destructive arthritis of the tarsal bones with predominant damage to the talonavicular and calcaneocuboid joints.

Treatment was prescribed with levofloxacin, cycloserine, bedaquiline, clofazimine and linezolid and is planned for twenty months. Methylprednisolone has been gradually reduced to 1 mg every other day. Three months after starting anti-tuberculosis treatment, the ulcer on the dorsum of the right foot healed and a fistula appeared on the medial and lateral sides of the right ankle joint (Figures 3 and 4).

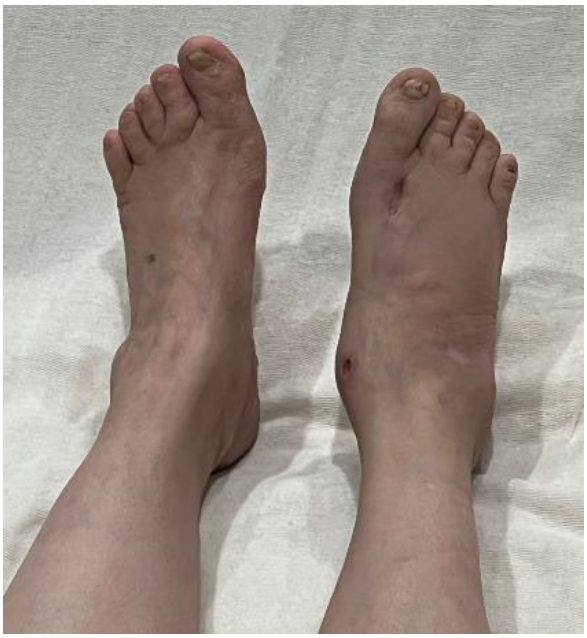

Figure 3. Formation of new fistulas on the medial and lateral surface of the right ankle joint.

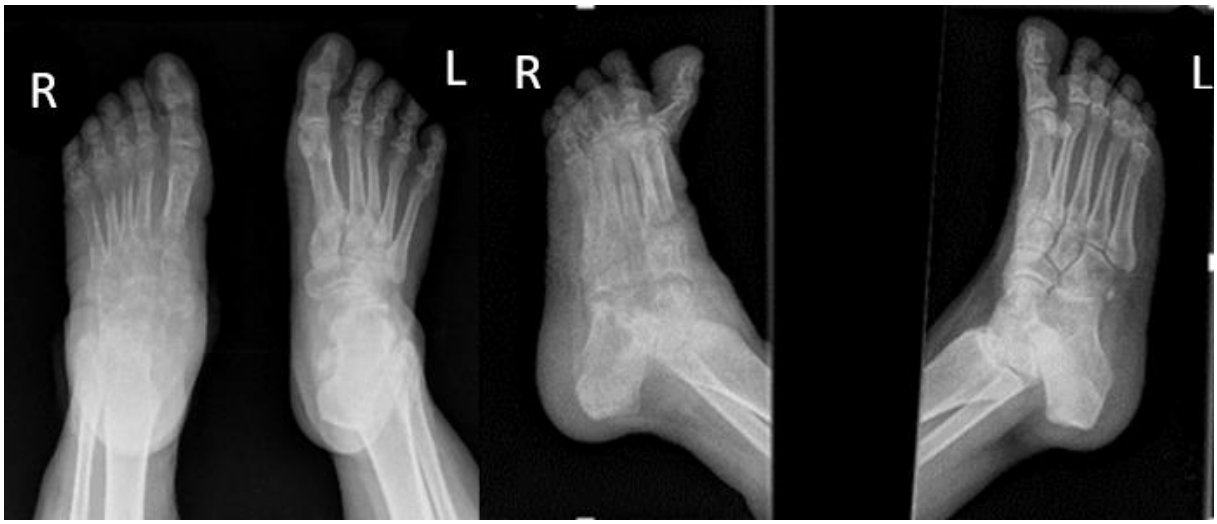

Figure 4. X-ray of the right and left foot (direct and lateral projections). Destructive arthritis of the tarsal bones with predominant damage to talonavicular and calcaneocuboid joints of the right foot. Osteoporosis of the right foot.

Discussion

Our case reinforces the notion that patients with autoimmune diseases under immunosuppressive treatment are at risk for tuberculosis, which should always be considered in the differential diagnosis of compatible pulmonary and extrapulmonary lesions. In particular, our patient had two manifestations (abdominal and bone tuberculosis) of extrapulmonary TB (indicating the reactivation of past infection) in just 13 months, and, in spite of a recent diagnosis of abdominal TB, the subsequent fractures of bones of the right foot, synovitis of the right ankle joint, and swelling at the base of the first toe of the right foot were not suspected to be TB-related for months, and a quite large open wound on the back of the right foot was interpreted as a trophic ulcer. The delay in diagnosis of tuberculosis seems unfortunately not uncommon in patients with MCTD[6] or other systemic autoimmune diseases [5, 10]. Screening for latent tuberculosis should be mandatory clinical practice before starting immunosuppressive treatment in patients with autoimmune diseases. However, for patients already on corticosteroids, the risk of false negative results with both tuberculin skin test (TST) and interferon-gamma release assays (IGRA) increases [1]. Thus, a combination of IGRA and TST to increase sensitivity could be used in immunosuppressed patients, where these tests should be done sequentially, with the second test done only if the first test was negative [3].

An additional issue is the dosage of corticosteroids in patients with autoimmune diseases with a TB diagnosis, considering that other immunosuppressive drugs do not appear to be significantly associated with tuberculosis [2]. A systematic review and meta-analysis of tuberculosis disease and infection in patients with systemic lupus erythematosus (SLE) found that TB prevalence in SLE was quite high and associated with glucocorticoids, and lowering their dose was essential to reduce the risk [2]. The 1-year cumulative corticosteroid dose in patients with SLE contracting TB was significantly higher than in those without TB, with a mean difference of 2.56 (95% CI: 0.22-4.91) [2]. In another systematic review and meta-analysis, the incidence and of TB in SLE patients was 1.16 per 100 person-years (95% confidence interval 0.69-1.93) and the prevalence was 3.59% (95% CI: 2.57%-5.02%) [13]. The pooled prevalence of SLE-pulmonary TB and SLE-extrapulmonary was 2.46% (95% CI 1.73%-3.51%) and 1.42% (95% CI 0.98%-2.06%), respectively.[13] The incidence of SLE-TB was higher in countries with a high TB burden and the prevalence of SLE-TB was elevated in Asia and in patients taking a mean daily dose of corticosteroids ≥20 mg [13].

Hence, it is advisable to keep the dose of glucocorticoids as low as possible in patients with tuberculosis. In a study including 1,618 treatment episodes of prolonged (≥4 weeks), high-dose steroids (≥30mg/day of prednisone, approximately equivalent to ≥24mg methylprednisolone) in 1,160 patients with rheumatic diseases, a high-risk subgroup for TB was defined as patients with incomplete adherence to treatment of previous TB, positive interferon-γ release assay, and/or linear/reticular fibrotic lesions on chest radiographs [8]. To evaluate the preventive effect of isoniazid (INH), the drug was given in 152 (9.4%) treatment episodes [8]. During 1,579.8 person-years, there were 21 cases of TB, with a significantly higher TB incidence in the high-risk subgroup (incidence rate ratio 8.29). INH reduced the 1-year TB incidence in the high-risk subgroup [adjusted hazards ratio 0.37 (95% CI, 0.002-5.10)] [13]; there was an important risk of adverse drug reactions [8]. On the basis of this study, it seems that an eventual isoniazid prophylaxis should be carefully balanced in patients treated with high dose corticosteroids.

Study Limitations: *The single-center nature of the study may limit its generalizability, and the absence of long-term follow-up data restricts the assessment of post-discharge outcomes.*

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Conflict of Interest: *The authors declare no conflicts of interest. This material has not been submitted to other journals and is not under consideration elsewhere.*

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