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Case Report

Scrofuloderma: report of two cases

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Abstract

Introduction: Tuberculosis (TB) is a chronic, granulomatous, infectious disease caused by the *Mycobacterium tuberculosis* complex. Cutaneous TB accounts for less than 1–2% of all TB cases. Scrofuloderma is a subcutaneous form of cutaneous TB, which results from direct spreading of infection from deeper tissues.

Case reports: We present two patients with scrofuloderma who exhibited typical clinical features but posed significant diagnostic challenges. In the first case, diagnosis was confirmed by polymerase chain reaction (PCR) of a tissue specimen which detected *M. tuberculosis*. All other microbiological tests, including direct microscopy, acid-fast bacilli smear, mycobacterial cultures, and TB-PCR of caseous discharge, were negative. In the second case, *M. tuberculosis* was identified via PCR of an ulcer swab, while other tests were negative. Histopathological findings were consistent with cutaneous TB. Both patients were treated with four first-line antitubercular drugs. The first patient developed progressive leukopenia and neutropenia and the treatment was adjusted to exclude ethambutol. Both the patients showed significant clinical improvement shortly after starting therapy.

Conclusions: Cutaneous TB is often misdiagnosed due to its rarity and the challenges of microbiological testing, especially in paucibacillary forms. Histopathological features, though suggestive, are not pathognomonic, contributing to diagnostic delays. Increased awareness among dermatologists can lead to earlier diagnosis and better outcomes.

Key words: scrofuloderma; *Mycobacetium tuberculosis*; cutaneous tuberculosis.

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Introduction

Tuberculosis (TB) is a chronic, granulomatous, infectious disease caused by bacteria belonging to the *Mycobacterium tuberculosis* complex. Despite being preventable and treatable, TB continues to be a global health priority with estimated 10 million cases and 1.3 million deaths annually [1]. The mortality rate from TB is very high (approximately 50%) without appropriate therapy. The standard treatment regimen recommended by the World Health Organization (WHO) is highly effective in almost 85% of patients, but the emergence of drug-resistant TB is a growing challenge for the global control and prevention of the disease [1].

TB is primarily a pulmonary disease, but it can potentially affect almost every organ in the body [2]. Extrapulmonary TB constitutes 15–20% of all active TB cases [3]. It produces a wide spectrum of clinical manifestations which can often mimic other diseases. Although it can occur regardless of a patient's immune status, some studies have suggested increased proportion of extrapulmonary TB among all TB cases in patients with compromised immune function, particularly in human immunodeficiency virus (HIV)-infected persons [4,5]. The most frequent form of extrapulmonary TB is lymphadenitis (50%), followed by pleural infection (18%), and bone and joint disease [6,7]. Extra pulmonary TB can exist alone, or can sometimes be accompanied by pulmonary or disseminated forms of TB.

Cutaneous TB is an extremely rare form of TB. It comprises only a small proportion of all TB cases (< 1–2%) [1,2]. The main etiological agent is *Mycobacterium tuberculosis*. Occasionally it is also caused by *Mycobacterium bovis*, and rarely by the bacillus Calmette-Guérin (BCG vaccine) [8]. The spectrum of cutaneous TB clinical manifestations is wide and depends on several factors, including the history of prior contact with microorganisms, inoculation site, host's immunity, and tissue response to the infection [9].

Scrofuloderma, also known as tuberculosis cutis colliquativa, represents the cutaneous form of TB that occurs by direct spreading of infection from an underlying infected focus, particularly lymph nodes,

bones, joints or epididymis. The most commonly affected sites are the chest, neck, and axilla. It manifests as livid, hard, painless, subcutaneous nodes that are prone to suppurate and form ulcers and sinus tracts in the overlying skin from which serous, purulent or caseous discharge is drained.

The prognosis is generally good in patients who are not immunocompromised [10]. Spontaneous regression is possible, followed by formation of irregular scars and retraction. However, since it is often accompanied by pulmonary or other extrapulmonary forms of TB disease, timely diagnosis and appropriate management of patients with scrofuloderma is necessary to avoid serious complications and even lethal outcome [10,11].

In this report, we present two adult patients with scrofuloderma and discuss the difficulties associated with the diagnosis and treatment of this rare condition.

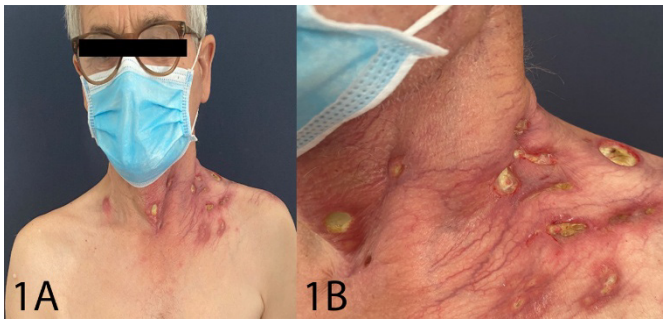
Case reports

Case 1

A 73-year-old male patient presented with a long-standing history of hypertension and angina pectoris, an 18-month history of numerous subcutaneous nodules of multiple non-healing ulcers, and suppuration of the left side of the neck. The initial changes were enlarged cervical lymph nodes with later formation of oval ulcerations. He also reported low grade fever, occasional night sweating, and a decreased appetite followed by mild weight loss. The patient was previously diagnosed as lymphadenitis of unknown etiology, and unsuccessfully treated with numerous antibiotics.

Physical examination revealed painless, enlarged, livid, nodules with multiple oval ulcerations covered by purulent and caseous discharge; as well as draining sinuses and atrophic, disfiguring scars on the left side of the neck and retro auricular region (Figure 1). This clinical presentation was highly suggestive of scrofuloderma; thus, microbiological analyses were performed in order to detect *M. tuberculosis*.

Figure 1. Enlarged livid nodules with multiple oval ulcerations covered by purulent and caseous discharge on the left side of the neck and retroauricular region.



The results of routine blood tests revealed elevated inflammatory parameters (erythrocyte sedimentation rate of 96 mm/h and C-reactive protein of 108.4 mg/L) and reduced hemoglobin level (101 g/L). All other results, including blood sugar, liver and renal function tests, and urinalysis were within the reference range. In order to exclude underlying immunodeficiency, enzyme-linked immunosorbent assay (ELISA) for HIV was done and the result was negative.

Tuberculin skin test was strongly reactive with > 20 mm induration, and the QuantiFERON-TB Gold (QFT-G) test was positive. Analysis of caseous discharge from the ulcerated lesions using the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA), acid-fast bacilli smear microscopy, and mycobacterial cultures turned out negative. The results of standard bacterial cultures were also negative. Tissue specimens were analyzed using Ziehl-Neelsen staining technique and cultivated on Löwenstein-Jenssen medium (Difco, BD, Franklin Lakes, NJ, USA); both results were negative. Only the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) of the biopsy specimen detected the traces of *M. tuberculosis*.

Cervical sonography detected multiple enlarged lymph nodes (up to 26 mm), suggestive for tuberculous lymphadenitis. Histopathological examination of ulcerated lymph nodes showed necrotizing granulomas with mixed inflammatory cell infiltrate which was highly suggestive of cutaneous tuberculosis, but could also be seen in other granulomatous diseases.

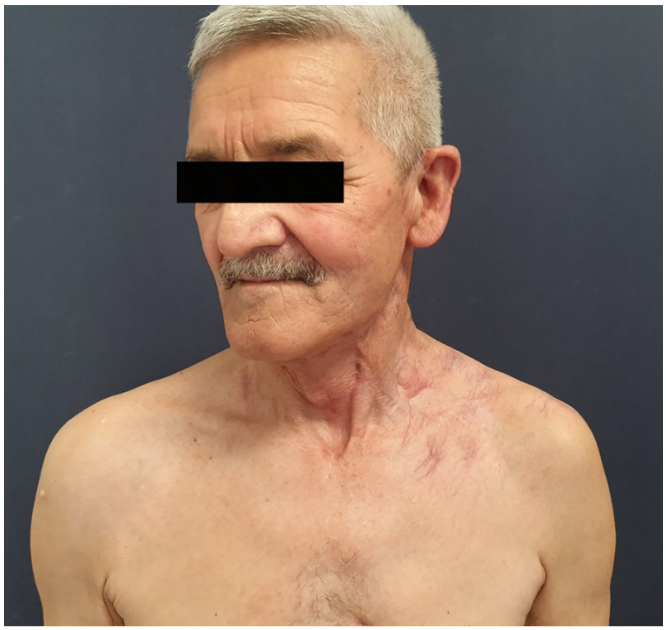
Multi-slice computed tomography (MSCT) of chest showed right infraclavicular 8 mm fibronodular change. In order to exclude systemic TB, sputum was analyzed using Ziehl-Neelsen staining, Löwenstein-Jenssen medium, and *Mycobacteria* Growth Indicator Tube (MGIT) system (BD Batec MGIT 960, Becton, Dickinson and Company, Franklin Lakes, NJ, USA). Urine was also cultivated on the Löwenstein-Jenssen medium. All the test results were negative.

Based on the history, typical clinical presentation, positive result of Xpert MTB/RIF assay of the tissue sample, and the finding of cervical sonography, a diagnosis of scrofuloderma with underlying TB lymphadenitis was made.

Standard antituberculosis therapy with isoniazid, rifampicin, pyrazinamide, and ethambutol was started. The drugs were gradually introduced, one at the time. Shortly upon the initiation of the therapy, progressive leukopenia (leucocyte dropped from 4.8 to 1.8 × 10^9/L), with neutropenia (neutrophils dropped from 4.2 to 1.2

× 10^9/L), and lymphopenia (up to 0.5 × 10^9/L) were detected. All medications were temporarily suspended due to progressive leukopenia caused by tuberculostatic agents. Blood count was carefully monitored and myelogram analysis was performed. After excluding myelodysplastic disorders, antituberculotic drugs were gradually re-introduced. The treatment was continued with rifampicin, isoniazid, and pyrazinamide; whereas ethambutol was excluded from the therapy, as it was suspected to be the most likely cause of leukopenia, based on available literature. Complete clinical regression was noted after 8 months of therapy (Figure 2).

Figure 2. Complete clinical regression after 8 months of therapy.



Case 2

Seven months after the recovery of the first patient, the second patient came to our department. He was a 73-year-old cachectic male patient, with no underlying comorbidities, and an 18-month history of numerous subcutaneous nodules and ulcers on the lateral sides of the neck and over the presternal and axillary region. He also reported chronic cough with yellowish sputum since several months along with intermittent low-grade fever, night sweating, and a decreased appetite followed by rapid weight loss. The patient had also been previously unsuccessfully treated with numerous antibiotics.

Physical examination revealed numerous deep ulcerations (up to 5 × 4 cm in diameter), with indurated, livid borders; as well as fistulous tracts with drainage of purulent and caseous content and scars on the lateral sides of the neck, chests, and axillary region (Figure 3). The patient was extremely malnourished, but vital signs were within normal ranges.

Complete blood count and biochemical blood analysis showed elevated inflammatory parameters (erythrocyte sedimentation rate of 82 mm/h and C-reactive protein of 67.4 mg/L), low hemoglobin level (102 g/L), and hypoalbuminemia (30 g/L). All other results, including blood sugar, liver and renal function tests, and urinalysis were within normal ranges. Serology testing on HIV antibody and antigen (ELISA) was negative.

Establishing a diagnosis was also challenging in this case. Tuberculin skin test and QuantiFERON-TB Gold (QFT-G) test were positive. *M. tuberculosis* was detected only by polymerase chain reaction (PCR) examination (Xpert MTB/RIF, Cepheid, Sunnyvale, CA, USA) of the ulcer swab. All other microbiological tests, including acid-fast bacilli smear microscopy, Ziehl-Neelsen staining, and mycobacterial cultures of the tissue specimens were negative.

Histopathological examination of affected skin revealed epithelioid cell granuloma accompanied by Langhans multinucleated giant cells and numerous neutrophils (Figure 4). Chest X-ray revealed irregular opacity (11 × 18 mm in dimeter), located in the left medial lobe of the lung, that indicated pulmonary

Figure 3. Numerous deep ulcerations with indurated livid borders, as well as fistulous tracts with drainage of purulent and caseous content and scars on the lateral sides of the neck, chests and axillary region.

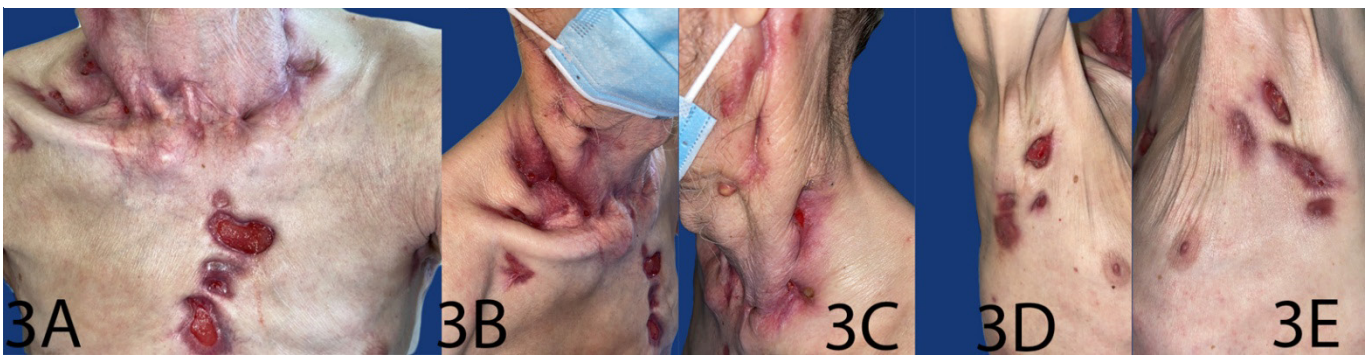
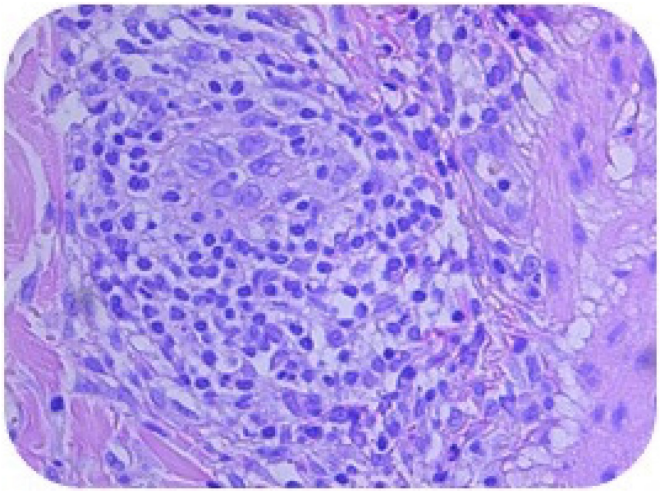


Figure 4. Epithelioid cell granuloma accompanied by Langhans multinucleated giant cells and numerous neutrophils.



tuberculosis (Figure 5). Additionally, visceral tuberculosis (pulmonary and genitourinary TB) was diagnosed by positive acid-fast bacilli sputum smear and positive urine mycobacterial culture.

Treatment with standard 6-month regiment composed of 4 first line tuberculostatics was initiated. No drug-related side effects were noticed during the hospitalization. Further treatment was continued at the Clinic of Pulmonology because of coexisting visceral tuberculosis. Clinical regression of cutaneous changes was noted after 3 months during follow-up visits (Figure 6).

Discussion

Cutaneous TB is an uncommon form of extrapulmonary TB, which comprises a wide spectrum of distinct clinical presentations. Two of the most prevalent forms of cutaneous TB are scrofuloderma and lupus vulgaris.

Scrofuloderma is the most common form of cutaneous TB in developing countries [12]. This rare variant of TB has a significantly higher incidence among children, but clinicians should be aware that it may be seen in any age group, especially in young adults and elderly people [8]. Furthermore, although cutaneous TB primarily affects the immunosuppressed, such as HIV infected patients, we report two cases of scrofuloderma in immunocompetent adults from Serbia, and highlight the importance of considering this rare condition in every patient who presents with slowly growing nodules that evolve into non-healing ulcers regardless of age and immune status, even in low-burden TB countries [13].

Figure 5. Irregular opacity located in the left medial lobe of the lung.

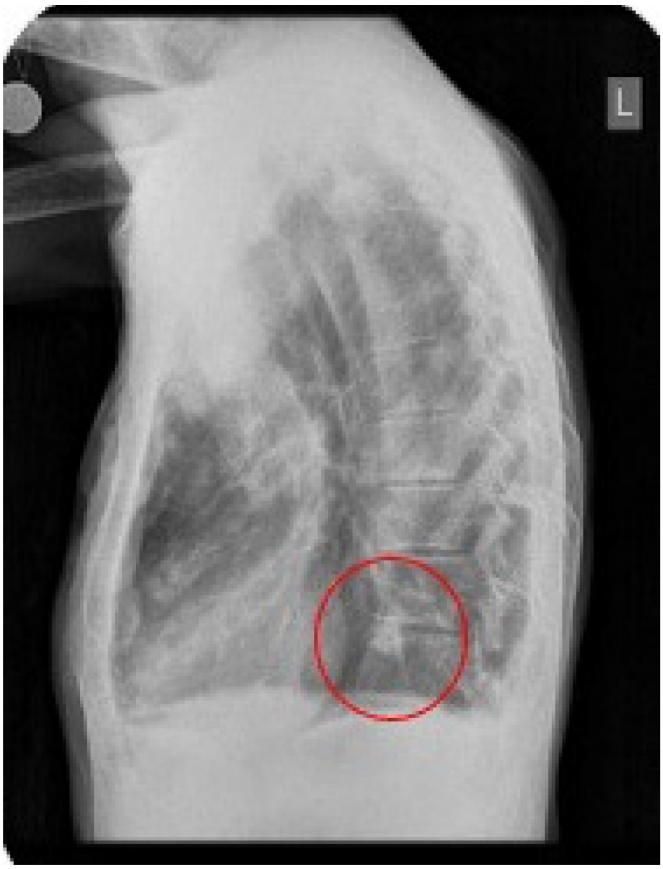
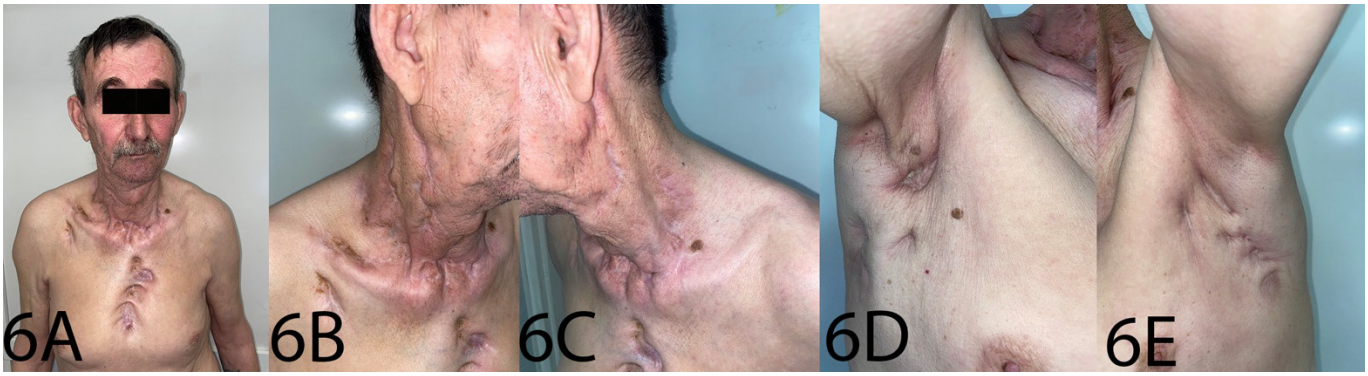


Figure 6. Clinical regression of skin changes.



Due to its rarity, the diagnosis of scrofuloderma is often delayed. Although the presented patients had typical clinical findings, the time from initial lesions to clinical suspicion of scrofuloderma was longer than 6 months in both cases. As a concomitant bacterial infection often occurs, scrofuloderma is most frequently misdiagnosed as a bacterial abscess and treated with systemic antibiotics. Other important differential diagnoses include pyoderma gangrenosum, tumor metastasis, hidradenitis suppurativa. sporotrichosis, gummatous syphilis, and actinomycosis [9].

The two presented cases also highlight the difficulties associated with microbiological confirmation of cutaneous TB. Although scrofuloderma is traditionally classified as a multibacillary form of TB (high load of pathogen), establishing the correct diagnosis was quite challenging in both patients. The first patient was diagnosed by PCR of the tissue specimen, where traces of *M. tuberculosis* were detected. All other microbiological tests, including acid-fast bacilli smear microscopy, mycobacterial cultures, and TB-PCR of caseous discharge were negative. In the second patient, *M. tuberculosis* has been detected by PCR examination of the caseous discharge. All other microbiological results, including PCR of biopted tissue, were negative. In both patients, the tuberculin test was strongly positive and the histopathological features were suggestive of cutaneous tuberculosis, but with negative Ziehl-Neelsen staining. Our findings confirm that direct microscopy and culture often have low sensitivity in cutaneous tuberculosis, and although PCR assay has significantly improved diagnostic accuracy, it is not always reliable [14]. Therefore, combining multiple diagnostic examinations is necessary to avoid misdiagnosis and delay in treatment [15].

In the presented cases, the first patient had an isolated form of the disease; but in the second patient, acid-fast bacilli positive sputum smear, and positive urine mycobacterial culture detected coexisting pulmonary and genitourinary TB. This case emphasizes the need for a thorough examination to rule out systemic involvement, particularly pulmonary disease, since concomitant extracutaneous TB has been reported in 12.4% of adults [11]. Additionally, HIV screening test is also recommended for all patients with presumptive or confirmed TB [16].

Herein, we also describe the difficulties associated with the therapy of cutaneous TB. Following WHO treatment guidelines, both patients started the standard regimen with first-line anti-tuberculosis therapy comprising of isoniazid, rifampicin, ethambutol, and pyrazinamide. Shortly after treatment initiation, progressive severe leukopenia with neutropenia was detected in the first case. All medications were temporarily suspended and gradually re-introduced afterwards. Although it is not always necessary to stop the anti TB-chemotherapy when leukopenia appears, in this case the total white blood cell (WBC) count and the number of neutrophils rapidly decreased and reached extremely low levels; so, we were forced to discontinue all potential leukopenia inducers [17]. Following suggestions of previous reports, we gradually re-introduced the drugs, one-by-one, starting with the potentially less harmful ones [18]. The treatment was continued with rifampicin, isoniazid, and pyrazinamide; whereas ethambutol was excluded from the therapy.

Conclusions

The diagnosis of scrofuloderma is often delayed in low-burden TB regions mostly because it is not routinely considered in the differential diagnosis of non-healing skin ulcers. Additionally, considering that the routine microbiological techniques, such as direct microscopy and mycobacterial cultures, often have low sensitivity in cutaneous tuberculosis, and molecular biology diagnostic tools are not always readily available, laboratory confirmation of TB is frequently challenging. Moreover, histopathological finding is characteristic, but not pathognomonic; and this additionally impacts the diagnostic delay.

Thus, increased awareness of this condition among dermatologists, and combining all available diagnostic methods, presents key steps to avoid misdiagnosis and treatment delay.

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Conflict of interests

No conflict of interests is declared.

References

1. World Health Organization (2022) Global tuberculosis report 2022, 1st edition. World Health Organization, Geneva. Available: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022. Accessed: 23 May 2022.
2. Gopalaswamy R, Dusthackeer VNA, Kannayan S, Subbian S (2021) Extrapulmonary tuberculosis-an update on the diagnosis, treatment and drug resistance. J Respir 1: 141–164. doi: 10.3390/jor1020015.
3. Das S (2016) Head and neck tuberculosis: scenario in a tertiary care hospital of north eastern India. J Clin Diagn Res 10: MC04-7. doi: 10.7860/JCDR/2016/17171.7076.
4. Sterling TR, Dorman SE, Chaisson RE, Ding L, Hackman J, Moore K, Holland SM (2001) Human immunodeficiency virus-seronegative adults with extrapulmonary tuberculosis have abnormal innate immune responses. Clin Infect Dis 33: 976–982. doi: 10.1086/322670.
5. Naing C, Mak JW, Maung M, Wong SF, Kassim AIBM (2013) Meta-analysis: the association between HIV infection and extrapulmonary tuberculosis. Lung 191: 27–34. doi: 10.1007/s00408-012-9440-6.
6. Baykan A, Sayiner H, Aydin E, Koc M, Inan I and Erturk S (2022) Extrapulmonary tuberculosis: an old but resurgent problem. Insights Imaging 13: 39. doi: 10.1186/s13244-022-01172-0.
7. Rodriguez-Takeuchi SY, Renjifo ME, Medina FJ (2019) Extrapulmonary tuberculosis: pathophysiology and imaging findings. RadioGraphics 39: 2023–2037. doi: 10.1148/rg.2019190109.
8. Santos JBD, Figueiredo AR, Ferraz CE, Oliveira MHD, Silva PGD, Medeiros VLSD (2014) Cutaneous tuberculosis: epidemiologic, etiopathogenic and clinical aspects - Part I. An Bras Dermatol 89: 219–228. doi: 10.1590/abd1806-4841.20142334.
9. Mello RBD, Vale ECSD, Baeta IGR (2019) Scrofuloderma: a diagnostic challenge. An Bras Dermatol 94: 102–104. doi: 10.1590/abd1806-4841.20188560.
10. Charifa A, Mangat R, Oakley AM (2024) Cutaneous tuberculosis. StatPearls. StatPearls Publishing, Treasure Island (FL).
11. Centers for Disease Control and Prevention (2023) Reported TB in the United States, 2022 surveillance report. Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention. Available: https://www.cdc.gov/mmwr/volumes/73/wr/mm7312a4.htm. Accessed: 1 April 2024.
12. Brito ACD, Oliveira CMMD, Unger DA-A, Bittencourt MDJS (2022) Cutaneous tuberculosis: epidemiological, clinical, diagnostic and therapeutic update. An Bras Dermatol 97: 129–144. doi: 10.1016/j.abd.2021.07.004.
13. Adzic-Vukicevic T, Stosic M, Antonijevic G, Jevtic M, Radovanovic-Spurnic A, Velickovic J (2022) Tuberculosis and COVID-19 co-infection in Serbia: pandemic challenge in a low-burden country. Front Med 9: 971008. doi: 10.3389/fmed.2022.971008.
14. Khadka P, Koirala S, Thapaliya J (2018) Cutaneous tuberculosis: clinicopathologic arrays and diagnostic challenges. Dermatol Res Pract 2018: 1–9. doi: 10.1155/2018/7201973.
15. Ueno E, Murase C, Fukaura R, Adachi R, Mori S, Suzuki Y, Tetsuka N, Akiyama M (2023) Multiple diagnostic examinations are effective for the early diagnosis of scrofuloderma. Clin Med 23: 179–181. doi: 10.7861/clinmed.2022-0557.
16. World Health Organization. WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders. Geneva: World Health Organization; 2012. Available: https://apps.who.int/iris/handle/10665/44789. Accessed: 24 May 2024.
17. Nagayama N, Shishido Y, Masuda K, Baba M, Tamura A, Nagai H, Akagawa S, Kawabe Y, Machida K, Kurashima A, Komatsu H, Yotsumoto H (2004) Leukopenia due to anti-tuberculous chemotherapy including rifampicin and isoniazid. Kekkaku 79: 341–348.
18. Belloumi N, Ben Bdira B, Bachouche I, Kacem M, Chermiti Ben Abdallah F, Fenniche S (2018) Leukopenia induced by anti-tuberculosis treatment. Int J Respir Pulm Med 5: 093. doi: 10.23937/2378-3516/1410093.