Disseminated tuberculosis in an immunocompetent 15-year-old adolescent

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Abstract

Tuberculosis is one of the oldest known diseases and it remains one of the main causes of morbidity and mortality, especially in developing countries. It is associated with social inequalities and affects different age groups. Tuberculosis in children and adolescents should be considered a sentinel event, since it is linked to a recent infection through contact with bacilliferous adults. We report an immunocompetent 15-year-old adolescent with tuberculosis, exhibiting pulmonary, osteoarticular, and cutaneous involvement. Conventional treatment with tuberculostatic drugs for a year had satisfactory results without sequelae.

Keywords: adolescent, disseminated, immunocompetent, Mycobacterium tuberculosis, tuberculosis

Introduction

Tuberculosis (TB) is a contagious bacterial disease caused by *Mycobacterium tuberculosis*. The lung is the main organ affected, but the infection can manifest itself in multiple organs and systems, constituting a disseminated form. According to the World Health Organization (WHO), it is estimated that 850,000 people between 10 and 19 years of age are diagnosed with tuberculosis each year [1]. Tuberculosis represents a serious public health problem and records considerable death rates of children worldwide. Adequate treatment of infected children and adolescents is employed to prevent the progression of the infection and to prevent them from becoming reservoirs for the transmission of tuberculosis [2].

Adolescents, in the process of growth, have dynamic physical, psychological, emotional, cognitive, and social development. Thus, a rapid diagnosis and adequate treatment of tuberculosis is essential to avoid negative impacts [3]. Most studies on tuberculosis group their patients with a focus on children (0 to 14 years) and adults (≥15 years), overlooking adolescents, which leads to a lack of data for this age group of patients. Nevertheless, it is unanimous that health services need to improve the quality of care for adolescents with complex health problems, for example by actively engaging in the prevention, diagnosis, and effective treatment of tuberculosis [4].

Tuberculosis is responsible for a third of the causes of mortality among patients infected with the human immunodeficiency virus and it can also affect immunocompetent patients [5]. Cases of disseminated forms of tuberculosis in adolescents have been reported for individuals with compromised immunity [6,7]. It is considered

disseminated when at least two extra-pulmonary sites are involved, with or without pulmonary involvement. This manuscript describes a rare case of disseminated tuberculosis in a 15-year-old boy, with involvement of the skin, joints, bones, and lungs.

Case Synopsis

An otherwise healthy 15-year-old-male student, born in the city of Itaboraí (Rio de Janeiro), an urban area of the state of Rio de Janeiro (city of São Gonçalo) presented to physicians in February of 2022. His illness started in November 2021 with evening fever, moderate weight loss, and a lack of appetite; it later progressed and additional symptoms of increased abdominal volume and edema in the lower limbs were noted from February 2022 (three months after the onset of symptoms). Examination and laboratory testing confirmed moderate ascites, hepatomegaly, moderate anemia, and a mild abnormalities in liver function.

In May of 2022 (seven months after the onset of symptoms), persistent productive cough, pain and swelling of the left wrist, and skin lesions that appeared on various segments of the body (scalp, chest, and lower limbs) brought him again to seek medical help. Nine months after the onset of symptoms (August, 2022), the patient was admitted to the Department of Infectious Diseases at the Hospital Universitario Antonio Pedro of Universidade Federal Fluminense. Hospital Universitario Antonio Pedro is a quaternary hospital, responsible for the care of patients with complex health conditions and is located in the second largest metropolitan area of the State of Rio de Janeiro.

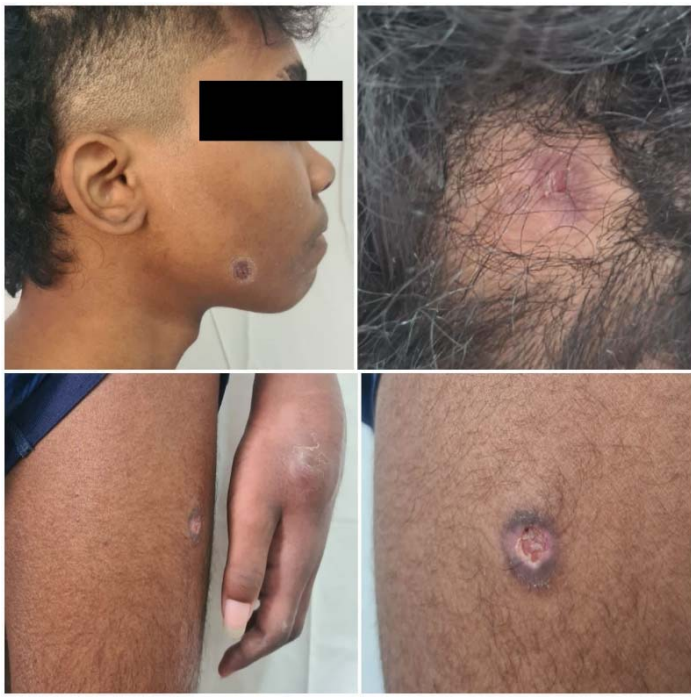

Figure 1. *Primary cutaneous and joint tuberculous lesions observed in the patient upon admission. The patient presented with ulcerations on face, scalp, left hand, and left thigh. The skin lesion on the left hand was associated with an intense inflammatory response on the left wrist.*

Upon admission, the patient´s presentation on physical examination was as follows: lucid, oriented, eupneic, afebrile, anicteric, pale, and sarcopenic. Lung and heart auscultation showed no significant alterations. The abdomen was flaccid, peristaltic, and with moderate pain on palpation in the right upper quadrant. The liver was palpable four centimeters from the right costal margin. The patient also had edema, pain, warmth and functional limitation of the left wrist. Several skin lesions were identified on the body, most notably a small ulceration on the left thigh as shown in **Figure 1**.

Imaging performed on August 2, 2022, including a chest CT exhibited multiple lytic lesions of the ribs and thoracic vertebrae, in addition to clusters of lymph nodes in the mediastinum. An abdominal CT showed mild ascites, hepatomegaly, and splenomegaly. The skin lesions and imaging strongly suggested the diagnosis of disseminated tuberculosis (**Figure 2**). MRI of the left wrist carried out on August 4, 2022, showed periarthritis, myositis, and reactive osteitis in the carpal and metacarpal bones, confirming the diagnosis of osteomyelitis.

The diagnosis of tuberculosis was confirmed by the isolation of *M. tuberculosis* on microbiological culture and a positive acid-fast bacilli sputum smear. In addition, the diagnosis of osteoarticular tuberculosis was confirmed by the detection of the *Mycobacterium tuberculosis* complex (very low, rifampicin resistance not detected) in a fragment of synovium from the left wrist performed by Xpert MTB/RIF® assay. The diagnosis of cutaneous tuberculosis was confirmed by histopathological examination of a fragment of the left thigh lesion,

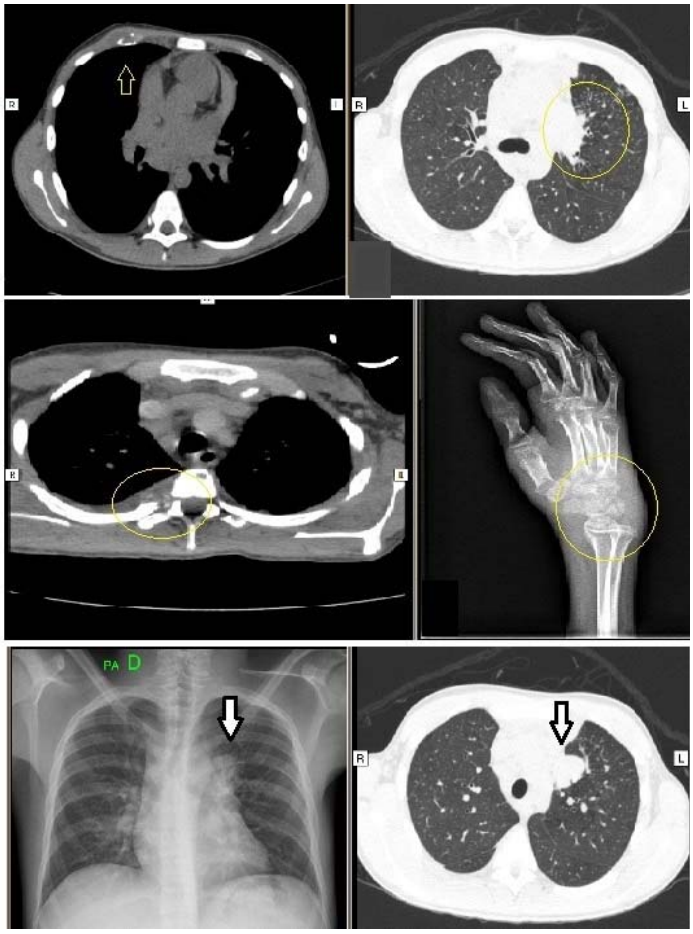

Figure 2. *The main radiological examinations performed during hospitalization: osteochondral lesion in the anterior thoracic region (upper right image), tree-in-bud lung lesion (upper left image), lytic lesion in the rib (right medial image), bone destruction in the left wrist (left medial image), and involvement of mediastinal lymph nodes (lower images).*

showing a chronic suppurative inflammatory process, compatible with pathologies that produce verrucous tuberculosis skin lesions (**Figure 3**).

Laboratory screening was performed on admission to the hospital. The serological, biochemical, and hematological parameters were performed. Serological parameters for investigation of human immunodeficiency virus, syphilis, cytomegalovirus and rubella were negative. Hematological and biochemical parameters showed decrease in hemoglobin value (11.8g/dl, normal 12.0-15.5g/dl) and increased levels of alanine aminotransferase (109.0UI/l, normal 0-38UI/l), alkaline phosphatase (121.0UI/l, normal 7-56UI/l), and C-reactive protein (13.10mg/dl, normal 0-0.30mg/dl). These biomarkers remained altered during the hospitalization period.

On August 6 of 2022 (nine months after the onset of symptoms), treatment with rifampicin (450mg/day), isoniazid (225mg/day), pyrazinamide (1,200mg/day) and ethambutol (825mg/day) was initiated for the treatment of disseminated tuberculosis (patient weight 45kg) and was expected to continue for one year (the first two months with all four drugs, followed by 10 months with rifampicin and isoniazid). For osteomyelitis, intravenous oxacillin (6mg/day) was used for 25 days, followed by cephalexin (500mg four times a day) for 21 days.

The patient was discharged after 28 days of hospitalization in an asymptomatic state with general clinical improvement and considerable weight gain; he was to continue treatment with anti-tuberculosis drugs through outpatient appointments. Outpatient consultation in May 2023 indicated that the patient progressed satisfactorily. He gained considerable weight (15kg), was asymptomatic, and was performing academic tasks without any psychological repercussions. Treatment was scheduled to be completed in August 2023 and the patient has demonstrated adherence to treatment.

Case Discussion

This case presented an unusual evolution of pulmonary tuberculosis, with rapid dissemination of skin lesions and joint involvement in an immunocompetent adolescent with no comorbidities. It demonstrates that the clinical evolution of this disease has varied presentations and can be a challenge for the adequate diagnosis and success of medical treatment.

A study carried out by Sant'Anna et al. [8] in Brazil from 1996 to 2003 with 1,781 adolescents diagnosed with tuberculosis found that most participants were male (52.1%) with a median age of 16 years (ranging from 10 to 19). The main clinical forms reported by the study were pulmonary tuberculosis (83.0%), Pleural tuberculosis (10.3%), and ganglionic tuberculosis (4.6%), [8]. The adolescent patient in our report fits within the demographic profile of the study by Sant'Anna et al. [8], but had rare extra-pulmonary involvement (cutaneous, bone and joint),

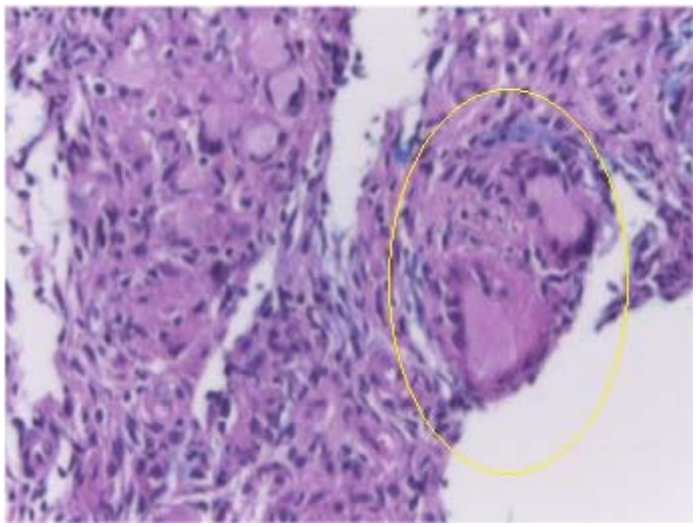

Figure 3. *Histopathological examination of a fragment from the left thigh skin lesion reveals a chronic suppurative inflammatory process with a central necrotic area (suppurative form). Highlighted within the image are tuberculoid granulomas characterized by the presence of epithelioid cells and multinucleated giant cells. H&E, 400×.*

demonstrating relevance in determining the length of treatment to be instituted.

Osteoarticular involvement has been described in a proportion of 1–5% of all tuberculous infections, with the spine and lower limb weight-bearing joints being more common. The wrist joint is an uncommon site for diagnosing skeletal tuberculosis [9]. A definitive diagnosis of joint tuberculosis requires confirmation with a microbiological identification of *Mycobacterium tuberculosis* bacilli and/or histopathological sample of involved tissue [9]. For the osteoarticular form of tuberculosis, treatment lasting at least one year is recommended and prolonged follow-up of these patients after completion of treatment is necessary to recognize early recurrence and the result of long-term therapy [10]. Our patient's left wrist joint disease significantly regressed in less than three months. However, the affected wrist has sequelae of decreased strength in the left hand, slight intention tremor, and moderate muscle atrophy.

Cutaneous tuberculosis is commonly the result of hematogenous spread or spread from underlying foci. Skin and soft tissue infection with *Mycobacterium tuberculosis* complex is rare but remains a potential threat in developing regions. Cutaneous tuberculosis must be differentiated from tuberculids, based on the demonstration in cutaneous tuberculosis, of vital mycobacterial bacilli in biopsies [11]. The type of cutaneous tuberculosis presented by our patient matches tuberculous gumma, also called metastatic tuberculous abscess, an unusual form of tuberculosis accounting for 1%–2% of all cutaneous tuberculosis cases.

Tuberculous gumma occurs owing to hematogenous spread of *M. tuberculosis* originating from a primary tuberculous focus. It affects poorly nourished children and immunocompromised adults and is rarely reported in immunocompetent patients [12]. The initial lesions are firm nodules, which evolve into abscesses with subsequent ulceration and drainage of necrotic material. They are usually located on the trunk and upper and lower limbs. The differential diagnosis includes syphilitic gumma, pyoderma gangrenosum, atypical mycobacterial infections, and subcutaneous fungal infections [13]. Despite being a multibacillary form, tuberculosis skin staining is positive in <50% of cases but culture is positive in 85% of cases. Giant epithelioid cell granuloma with widespread caseation necrosis is present in 82.4% of cases [14]. In our case, the histopathological examination was compatible, showing tuberculoid granuloma with caseous necrosis, but the specific stains did not demonstrate the presence of *M. tuberculosis* as it can occur in this form.

Snow et al. [4] listed important factors that can interfere with the adequate treatment of adolescents, including adherence to medical consultation appointments and medication, the effect of health-compromising behaviors (including substance use), interruption of education and employment, and the effects of social (and medical) isolation and stigma. Medication adherence and loss of follow-up are serious concerns during tuberculosis treatment owing to the risk of resistance emerging [4]. Our patient had a moderate state of depression during the first three months of the illness but managed to recover, and practices physical activities regularly. The period of absence from school did not affect the patient´s academic progression.

The present case fits into multifocal tuberculosis, which usually occurs in immunocompromised people, but can also affect the immunocompetent. To explain cases in immunocompetent people, the intensity of community transmission of tuberculosis, malnutrition, and genetic susceptibility have been considered [15,16].

Conclusion

The differential diagnosis for nodules progressing to ulceration is extensive and includes conditions such as syphilitic gumma, pyoderma gangrenosum, atypical mycobacterial lesions, common pyoderma such as furuncles, and subcutaneous fungal infections. However, tuberculosis gumma should be considered, particularly when accompanied by symptoms like fever, weight loss, and cough, especially in endemic areas. Multifocal cutaneous tuberculosis typically occurs in immunosuppressed individuals. In the present case, malnutrition and possible genetic susceptibility could be predisposing factors.

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Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. World Health Organization. Global Accelerated Action for the Health of Adolescents (AA-HA!): Guidance to Support Country Implementation.World Health Organization; Geneva, Switzerland: 2017. https://www.perlego.com/book/1670781/global-accelerated-action-for-the-health-of-adolescents-aaha-guidance-to-support-country-implementation-pdf? Accessed on April 7, 2024.
2. Jaganath D, Beaudry J, Salazar-Austin N. Tuberculosis in Children. *Infect Dis Clin North Am*. 2022;36:49-71. [PMID: 35168714].
3. Moscibrodzki P, Enane LA, Hoddinott G, et al. The Impact of Tuberculosis on the Well-Being of Adolescents and Young Adults. *Pathogens*. 2021;10:1591. [PMID: 34959546].
4. Snow KJ, Cruz AT, Seddon JA, et al. Adolescent Tuberculosis. *Lancet Child Adolesc Health*. 2020;4:68–79. [PMID: 31753806].
5. Calado JOA, Miola AC, Silvares MRC, et al. Disseminated tuberculosis associated with reactive arthritis of Poncet in immunocompetent patient. *An Bras Dermatol*. 2020;95:343–6. [PMID: 32303434].
6. Gobir AA, Ariyibi SO, Ibraheem RM, et al. Disseminated Tuberculosis in a Nigerian Adolescent with Linear IgA Bullous Dermatosis: A Case Report and Review of Literature. *West Afr J Med*. 2022;39:646-650. [PMID: 35752975].
7. Kay AW, Rabie H, Maleche-Obimbo E, et al. HIV-Associated Tuberculosis in Children and Adolescents: Evolving Epidemiology, Screening, Prevention and Management Strategies. *Pathogens*. 2021;11:33. [PMID: 35055981].
8. Sant'Anna CC, Schmidt CM, Pombo March MFB, et al. Tuberculosis among adolescents in two Brazilian State capitals. *Cad Saude Publica*. 2013;29:111-6. [PMID: 23370030].
9. Jain VK, Iyengar KP, Botchu R, et al. Sacroiliac joint tuberculosis revisited - A clinico-radiological review. *J Clin Orthop Trauma*. 2021;24:101707. [PMID: 34853775].
10. Agashe VM, Rodrigues C, Soman R, et al. Diagnosis and management of osteoarticular tuberculosis: a drastic change in mind set needed-it is not enough to simply diagnose TB. *Indian J Orthop*. 2020;54:60–70. [PMID: 32952911].
11. Gardini G, Gregori N, Matteelli A, et al. Mycobacterial skin infection. *Curr Opin Infect Dis*. 2022;35:79-87. [PMID: 35067521].
12. Machan A, Hanafi T, Hjira N, et al. Tuberculous gummas: Epidemiological, clinical, bacteriological, immunological, and therapeutic features. *Int J Mycobacteriol*. 2018;7:203-211. [PMID: 30198497].
13. Santos JB, Figueiredo AR, Ferraz CE, et al. Cutaneous tuberculosis: epidemiologic, etiopathogenic and clinical aspects - Part I. *An Bras Dermatol*. 2014;89:219-28. [PMID: 24770496].
14. Brito AC, Oliveira CM, Unger DAA, et al. Cutaneous tuberculosis: epidemiological, clinical, diagnostic and therapeutic update. *An Bras Dermatol*. 2022;97:129-44. [PMID: 34996655].
15. Rezgui A, Fredj FB, Mzabi A, et al. Multifocal tuberculosis in immunocompetent patients. *Pan Afr Med J*. 2016;24:13. [PMID: 27583077].
16. Ghanavi J, Farnia P, Farnia P, et al. Human genetic background in susceptibility to tuberculosis. *Int J Mycobacteriol*. 2020;9:239-247. [PMID: 32862155].