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Cutaneous tuberculosis in Rio de Janeiro, Brazil: description of a series of 75 cases

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Abstract

Background Brazil is one of the highest tuberculosis (TB) burden countries of the world. Cutaneous tuberculosis (CTB) is a rare form of extrapulmonary manifestation of tuberculosis. This study aimed to describe the clinico-evolutive, laboratory and therapeutic aspects of CTB cases among patients from a cohort with TB in Rio de Janeiro, Brazil.

Methods Cases of diagnosed CTB with microbiologic confirmation or clinical response to anti-tuberculous treatment associated with positive smear or histopathological findings between the years 2000 and 2016 were selected.

Results Seventy-five patients with CTB were included, most were women (58.7%) with a median age of 42 years. CTB diagnosis was based on culture in only 42.7% of the cases. Scrofuloderma represented 50.7% of the cases, followed by erythema induratum of Bazin (EIB) (18.7%), tuberculous gumma (13.3%), lupus vulgaris (8%), TB verrucosa cutis (4%), orificial TB (2.7%) and associated forms (2.7%). Other TB presentations were pulmonary (22.7%), mammary (6.6%) and osteoarticular (4%). All patients who completed the treatment (97.3%) had their lesions healed. Only two patients (2.6%) needed to change the therapy due to adverse reactions. Fifty percent of EIB patients presented recurrence.

Conclusions These data highlight the diversity of CTB presentations and the importance of the skin to assist in early identification and treatment of TB. More studies are necessary to improve the knowledge on EIB for a better approach towards these patients, mainly in cases of recurrence.

Introduction

In the last decades, tuberculosis (TB) emerged as a serious public health problem, with a significant increase in the number of cases. Brazil ranks at the 20th position in the disease burden among countries that represent 87% of the world's cases of TB.[1] Cutaneous tuberculosis (CTB) is a rare extrapulmonary form of TB and remains one of the least studied. It is estimated that 14% of TB patients present the extrapulmonary form of the disease, and 1–2% of these have cutaneous presentation.[2]

There are multiple CTB manifestations that differ not only on clinical presentation but also by the way the infection reaches the skin, the load of *Mycobacterium tuberculosis* in the skin, patient's predisposing factors, and previous TB sensitization, among others.[3] It is most widely accepted to classify CTB into two primary categories: true CTB and tuberculids. In true CTB, the way that *M. tuberculosis* reaches the skin, and its morphological aspect, is used to subdivide the clinical variants. Tuberculous chancre, TB verrucosa cutis (TVC), and few cases of lupus vulgaris are related to direct inoculation of the *bacillus*; scrofuloderma corresponds to endogenous spread by a contiguous focus of TB to the skin, whereas orificial TB corresponds to autoinoculation of the *M. tuberculosis* in traumatized skin or mucosa from deep tissue. Lupus vulgaris, acute miliary TB, and tuberculous gumma correspond to hematogenous dissemination.[2,4,5] Tuberculids are immunologic reactions to *bacillus* or its products in a patient with high immunity and are classified by their clinical aspect as papulonecrotic tuberculid, lichen scrofulosorum, and erythema induratum of Bazin (EIB).[4]

This study describes 75 patients with CTB followed at a reference hospital for TB in the city of Rio de Janeiro, Brazil, for a period of 17 years. Case reports of 15 of these patients have already been published because of their particular characteristics, but they were maintained in the cohort.[6]

Materials and methods

We describe a series of 75 CTB cases based on secondary data from the electronic medical record (EMR) of a prospective ongoing cohort of 1,643 TB patients, monitored at the TB outpatient clinic of Evandro Chagas National Institute of Infectious Diseases (INI)/Oswaldo Cruz Foundation (Fiocruz), in the city of Rio de Janeiro, Brazil, between the years 2000 and 2016. INI/Fiocruz hospital is a reference in the city's public health system infectious diseases treatment. This study was approved by the Ethics Committee of INI/Fiocruz (CAAE: 57208016.9.0000.5262). An informed consent form was obtained from all patients who had entered the cohort study since 2016. Before that, a statement of responsibility by the lead investigator was signed, ensuring the confidentiality of the data.

The inclusion criteria were: age $\geq$ 16 years and (i) isolation of *M. tuberculosis* in culture of the affected skin or contiguous focus; or (ii) clinical response to antituberculous treatment associated with a positive smear, or histopathological findings of the affected skin or contiguous focus showing chronic granulomatous infiltrate. In EIB cases, histopathological findings of lobular granulomatous panniculitis with or without necrosis and/or vasculitis were considered, when associated with a positive tuberculin skin test (TST) and response to treatment. The exclusion criterion was a lack of description of the clinical form and therapeutic information in the EMR.

All clinical specimens were submitted to a microbiologic examination, which included search for acid-fast bacilli (AFB) in Ziehl–Neelsen technique and culture in Löwenstein–Jensen medium and histopathological analysis with hematoxylin-eosin (H&E) and Wade stains.

Clinical evaluation was performed using a structured form with demographic, socioeconomic, clinical, and therapeutic data at baseline (TB diagnosis) and during the whole treatment period. Patients received the standard Brazilian 6-month treatment of three drugs (rifampicin, isoniazid, pyrazinamide; RHZ) for TB until 2009 and a four-drug (also with ethambutol; RHZE) regimen in a fixed-dose combination subsequently, according to the change in the national guideline for 6 months.[7] However, in case of persistence of activity of the disease after this period, the therapy was extended until clinical cure (no signs of clinical skin activity with healed lesions). TB recurrence was defined if new active lesions of TB occurred in a previously cured patient. Disseminated cutaneous lesions were established as two or more lesions in noncontiguous anatomical sites and disseminated TB the presentation in two noncontiguous organs.

Sociodemographic, clinical, and laboratory data were collected from the patient's EMR. The data obtained were stored in Microsoft Excel® version 2016, and R-Project version 3.3.3 was used for descriptive analysis, such as frequencies for categorical variables and summary measures (mean, median, and range) of continuous variables.[8]

Results

In this study, the diagnosis of CTB was based on the identification of *M. tuberculosis* in culture in 32 (42.6%) cases, on clinical response to antituberculous treatment associated with histopathological findings in 43 patients (57.3%) or with a positive smear in four (5.3%), or with positive smear combined with histopathological findings in two (2.7%). The clinical specimen for histopathological analysis ($n = 53$; 70.7%) was skin fragments in 41 (77.4%) and lymph node fragments in 12 (22.6%) patients. TST was performed in only 50 patients, because it was unavailable in Brazil during some periods, with a median induration of 20 mm (ranged: 10–51) in 45 TST-positive patients.

There was a predominance of women (58.7%) ranging in age from 16 to 87 years (median age 42 years) and white

individuals (58.7%). Forty-four patients (58.7%) were from the city of Rio de Janeiro and the other 31 (41.3%) from other cities in the state. Forty-eight patients (64%) had a monthly income up to USD 571, and six patients (8%) had an income above this value. Forty-seven (62.7%) completed at least 9 years of education, and 25 (33.3%) studied less than that. Information about monthly income (28%) and schooling (4%) of the remaining patients was not available in the EMR. Table 1 shows the clinical characteristics and diagnosis of patients with CTB in this study.

Thirty-seven patients (49.3%) presented underlying conditions characterized as metabolic and immunosuppressive diseases. The most frequent one was arterial hypertension (24%) followed by AIDS (20%). Thirteen (17.3%) were smokers, and two (2.7%) had a history of illicit drug use. The median time between the lesion appearance and treatment onset was 8 months (range: 0.6–360 months).

In the case of true CTB, scrofuloderma was the predominant clinical form, followed by gumma (Figs. 1 and 2). Scrofuloderma was associated with cervical ($n = 29$), axillary ($n = 6$), supraclavicular ($n = 5$), submandibular ($n = 4$), and inguinal ($n = 2$) lymph node injury. Both cutaneous variants were associated with extracutaneous focus in some cases: lung ($n = 12$), breast ($n = 5$), and osteoarticular ($n = 3$). Breast TB was characterized by females, all but one was above 40 years old, with unilateral lesions. Three cases presented small solitary gumma and two other scrofuloderma. These last cases were referred from a mastology outpatient clinic with multiple ulcerated lesions and scars with fistulas on the breast (Fig. 3). Among the patients with osteoarticular TB involvement, the diagnosis took from 9 to 12 months. Scrofuloderma presentation was associated with paravertebral abscess, another case with fistulized tumor lesion after an ankle fracture, and disseminated gumma with lumbosacral osteomyelitis in the third case. Another patient with cutaneous disseminated gumma was diagnosed also with paracoccidioidomycosis in oral mucosa during follow-up.

Orificial TB ($n = 2$) presented as a painful ulcer in the oral mucosa (lip and gum mucosa) and perianal region, respectively (Fig. 4). The first case had undergone laryngectomy for malignant laryngeal neoplasia 2 years before and had previous pulmonary TB treatment. The second one had a history of smoking, alcohol abuse, and illicit drug use, including previous hospitalization for detoxification. Scrofuloderma, gumma, and orificial TB were associated with immunosuppressive conditions, disseminated TB, a greater presence of constitutional symptoms ($P = 0.003$), and isolation of *M. tuberculosis* in culture of skin or adjacent site ($P = 0.001$).

Lupus vulgaris presented as a single lesion in three cases (scalp, left inguinal area, and right flank region) and as disseminated lesions in four cases. The lesions were large (4–30 cm) (Fig. 5). TVC presented as a single lesion in the lower limbs (knee, heel, leg) ($n = 3$) (Fig. 6). Two of them had a history of previous contact with soil, and the third one had a limitation in the right leg because of previous poliomyelitis. Two patients

Table 1 Clinical and laboratory features of patients with cutaneous tuberculosis (CTB) treated at the Evandro Chagas National Institute of Infectious Diseases/Oswaldo Cruz Foundation, Rio de Janeiro, Brazil, from 2000 to 2016

Variables	Scrofuloderma ($n = 38$)	TB gumma ($n = 10$)	Orificial TB ($n = 2$)	Lupus vulgaris ($n = 6$)	Verrucous TB ($n = 3$)	Erythema induratum ($n = 14$)	Associated forms[a] ($n = 2$)	$N = 75$
Men	17	2	2	3	3	2	2	31
Median age (years)	37	44.5	56	48	19	45.5	16	42
Comorbidity/ immunosuppression	HIV (11) HBP (4) Diabetes (1) Alcohol (1)	HBP (4) HIV (3) CO (1) Alcohol (1)	Alcohol (1)	HBP (2) Diabetes (1)	Alcohol (1)	HBP (8) Diabetes (2)	HIV (1) Alcohol (1)	19
Site	Lymph node (35) Breast (2) Spine (1) Knee (1)	Single lesion (6) Disseminated lesions (4)	Oral mucosa (1) Perianal (1)	Single lesion (3) Disseminated lesions (3)	LL (100%)	LL (13) UL (1) Abdomen (1)	Cervical lymph node + back (1) LLL (1)	—
Concomitant site of TB	Lung (9)	Lung (3) Spine (1)	Lung (2)	Lung (1)	Lung (1)	Lung (1)	0	17
CTB microbiology								
AFB+/total	12/32	6/10	1/1	0/5	0/3	0/10	0/2	19/63
Culture+/total	21/31	6/9	2/2	1/5	2/3	0/10	0/2	32/62
TST (+/–)	18/3	6/2	0/0	5/0	1/0	14/0	1/0	45/5
Histopathology	25	4	2	6	2	14	2	53

N, number; UL, upper limbs; LL, lower limbs; LLL, left lower limb; TB, tuberculosis; AFB, acid-fast bacillus; HBP, high blood pressure; CO, corticosteroid; TST, tuberculin skin test.

[a]1 scrofuloderma + papulonecrotic tuberculid and 1 TB gumma + verrucous TB.

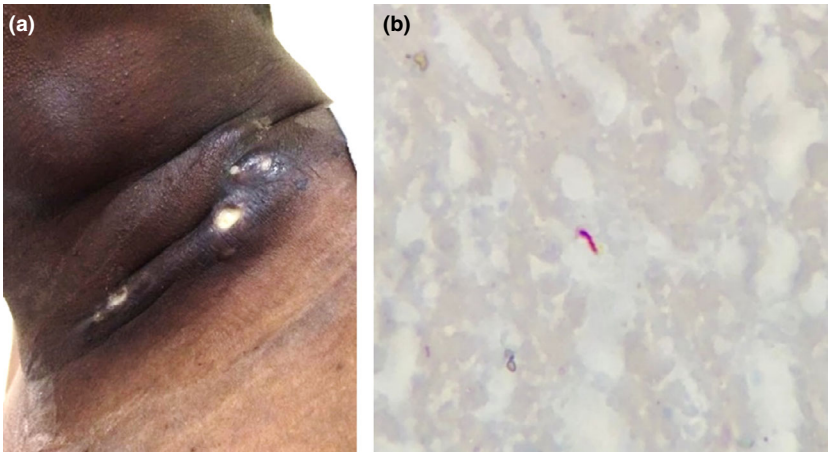

Figure 1 (a) Scrofuloderma associated with cervical lymph node tuberculosis. (b) Acid-fast bacillus in lymph node fragment (Histopathology, Wade, ×1000)

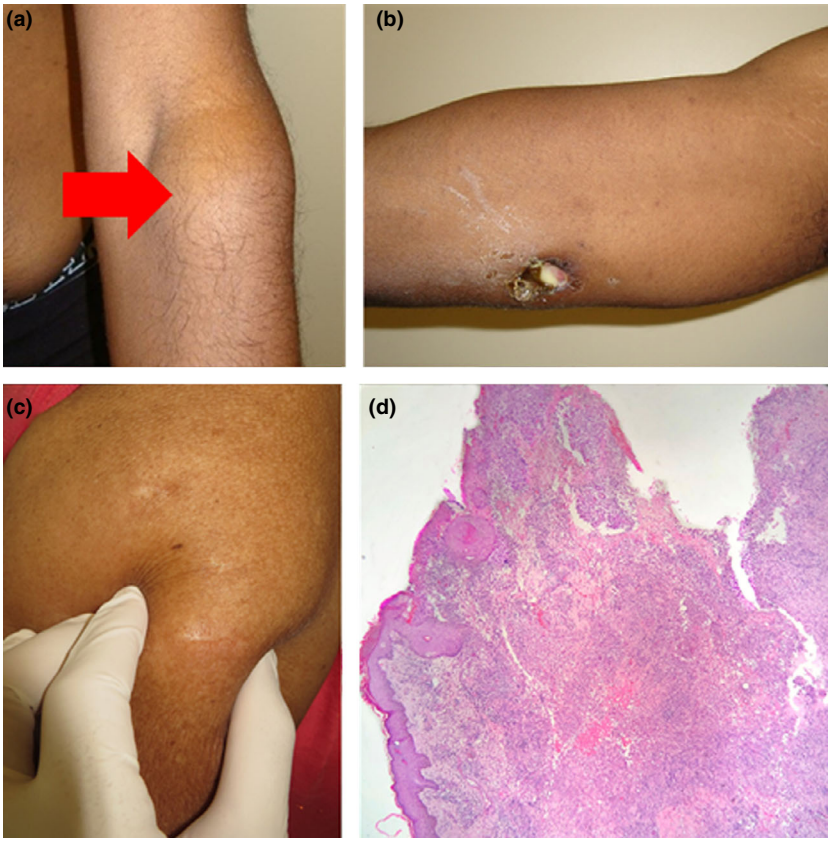

Figure 2 (a) Gumma (red arrow) on the left forearm. (b) Ulcerated gumma on the right forearm in a male patient. (c) Gumma on the right arm in a female patient. (d) Histopathology of skin fragment with an ulcer area and diffuse dermal inflammation that was categorized as granulomatous with caseous necrosis (hematoxylin & eosin, ×40)

with lupus vulgaris and one with TVC had the longest evolution time in this study: 120, 300, and 360 months, respectively.

EIB (18.7%) was the most common manifestation of hypersensitivity found (Fig. 7). EIB affected more women ($P = 0.03$) and patients with arterial hypertension ($P = 0.003$) than the other forms of CTB. Eight (57.2%) patients were classified as overweight or obese. All of the patients had lesions in lower extremities. No microbiological evidence of *M. tuberculosis* was found in the laboratory analyses of cutaneous fragments.

Associated forms of CTB were seen in two patients (Table 1): scrofuloderma (with cervical lymph node disease) and concomitant papulonecrotic tuberculid; TVC lesion in the left foot and a single gumma lesion in the ipsilateral lower limb.

Fifty-three (70.7%) patients presented adverse reactions, mainly gastrointestinal intolerance ($n = 31$), skin changes such as rash and/or pruritus ($n = 25$), flu-like symptoms ($n = 11$), hepatotoxicity ($n = 6$), and hyperuricemia ($n = 6$). In four patients (7.6%), treatment had to be suspended: two required only temporary withdrawal of the drugs (because of

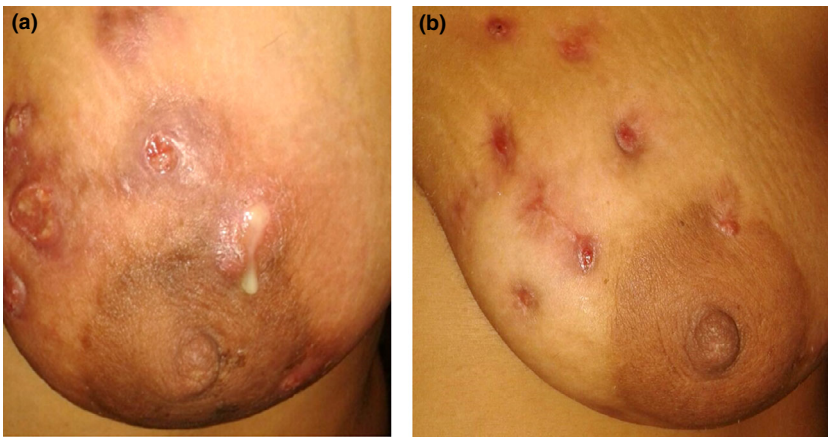

Figure 3 (a) Scrofuloderma associated with breast tuberculosis at the beginning of the treatment. (b) At the end of the treatment

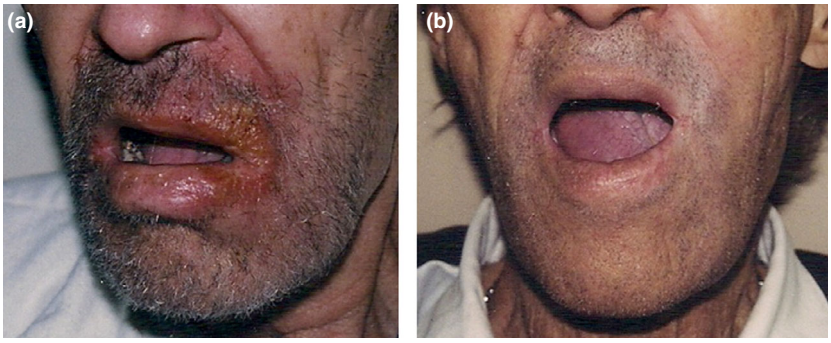

Figure 4 (a) Orificial tuberculosis in the oral mucosa and lips at the beginning of the treatment. (b) At the end of the treatment

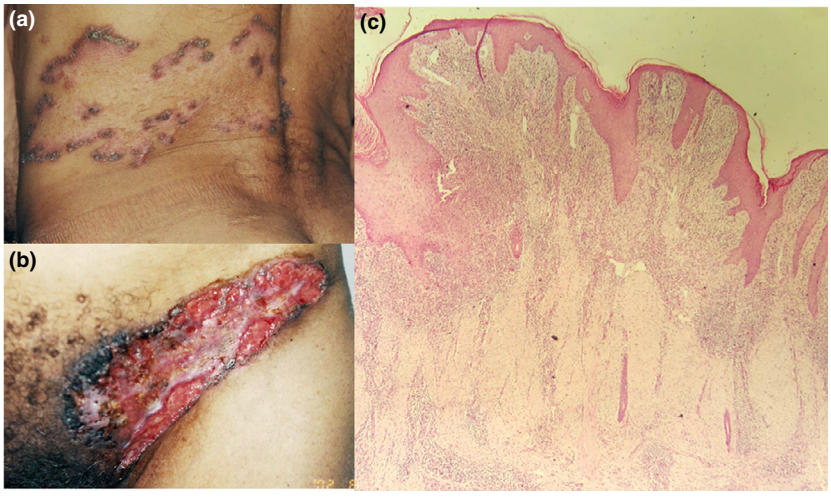

Figure 5 (a) Lupus vulgaris plaque in the posterior thorax of a male patient with 25 years of evolution. (b) Ulcerated lupus vulgaris in the inguinal region of a female patient. (c) Histopathology of skin fragment with irregular acanthosis, superficial inflammatory infiltrate categorized as granulomatous, and deeper fibrosis (hematoxylin & eosin, ×40)

hepatotoxicity and cutaneous alteration, respectively), and the remaining needed to change rifampicin to ofloxacin (because of hepatotoxicity) and pyrazinamide to levofloxacin (because of hepatotoxicity, visual turbidity, and paresthesia). Only one patient with clinical resistance to isoniazid switched to levofloxacin. All patients who completed the treatment (97.3%; $n = 73$) were cured. Forty-four (58.7%) patients were treated for 6 months, and the remaining (37.3%; $n = 28$) needed a median of 9 (7–19) months to achieve inactivity of the lesions. Two patients abandoned treatment, both with TVC. One (1.3%) patient with lupus vulgaris stopped treatment at 5 months but was considered cured in the follow-up. There were recurrences only in patients with EIB ($n = 7$; 50%), and these occurred at a median of 6 (1–72) months. Two were treated again for TB and

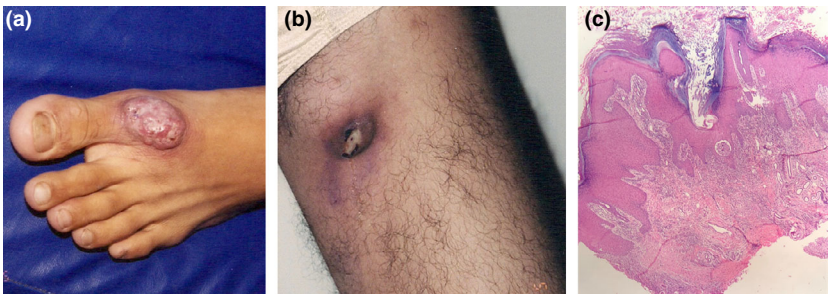

Figure 6 (a) Verrucous tuberculosis. (b) Associated with gumma on the left limb in the same male patient. (c) Histopathology of skin fragment presenting hyperkeratosis, acanthosis, papillomatosis, chronic dermal inflammatory infiltrate categorized as granulomatous, and fibrosis (hematoxylin & eosin, ×40)

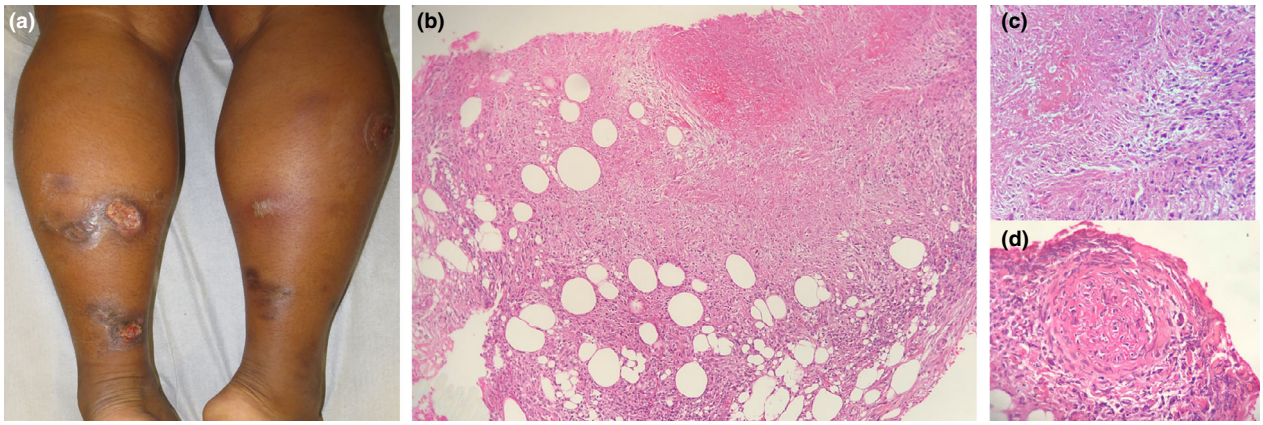

Figure 7 (a) Patient with erythema induratum presenting nodules and ulcers on the calves. (b, c) Histopathology of skin fragment with lobular panniculitis and necrotic area surrounded by palisade of epithelioid cells, forming a chronic granulomatous process (hematoxylin & eosin, ×40 and ×100, respectively). (d) Vessel with lumen obstructed by thrombus (hematoxylin & eosin, ×100)

the remaining with different anti-inflammatory drugs (prednisone, dapsone, potassium iodide, and ibuprofen), with total or partial control.

Discussion

Our cohort showed a greater number of CTB cases (4.5%, 16 times) as well as disseminated TB cases (16.2%, eight times) (the latter calculated only for the last 10 years), contrasting the estimative described in Brazilian literature.[9,10] This difference is most likely explained by the fact that we are a TB reference hospital in Rio de Janeiro state, which has the second highest TB incidence rate in Brazil.[11] Women predominated in our case series, as described in other studies of CTB.[9,12–15] The situation is different when compared to all TB forms, since men predominate in 65% of the cases. Men are also more common in small series of CTB cases in countries such as Spain, India, China, Hong Kong, and Mali.[1,16–19] In general, our patients had low purchasing power and technical qualification compatible with low schooling.

Scrofuloderma, gumma, and perioricial TB were related to conditions of immunosuppression, as well as disseminated disease. These clinical forms are associated with low immune response to the *M. tuberculosis* and a more frequent isolation of *M. tuberculosis* on the skin.[2,4,20,21] Scrofuloderma from lymph node is the most common presentation of CTB described in the literature in some developing countries.[22–24] Similarly, gumma, known as cutaneous abscesses, is also found in large case series of CTB.[13,24–26] Breast TB is a rare form of extrapulmonary TB, even in endemic areas, but it was present in this study.[27–29] It usually occurs secondary to a centripetal lymphatic spread of *M. tuberculosis* from the lungs to the mammary tissue through the lymph nodes of these areas.[30] Gumma, nodules, and draining sinus are usually unilateral, as were in our cases.[31] Scrofuloderma and gumma were associated with skeletal system involvement.[31–33] The diagnosis in these cases took a long time, making the disease much worse, causing us to always consider the possibility of concomitant subclinical bone disease upon the diagnosis of CTB in this localization. In Brazil, paracoccidioidomycosis is the most frequent endemic mycosis, and the association with TB, as seen in one patient in our cohort, occurs in 10% of the cases.[34] Orificial TB is a rare manifestation of CTB. Lesions in the oral mucosa and tongue are the most common presentations, whereas perianal ulcer is less frequent, as seen in two of the patients.[35] TB in internal organs (22.6%) was similar to that found in other studies (between 9 and 38%), and pulmonary and lymph node TB are the most frequent forms described in the literature.[13,24–26,36]

Lupus vulgaris and TVC are chronic and progressive forms and presented the longest evolution in the study. An average of 25 years of evolution was described by Sellami et al. in 29 patients with lupus vulgaris.[37] Patients with these TB forms are generally paucibacillary and considered to have a moderate to high degree of immunity against the *bacillus*. The association with extracutaneous TB is rare[38–42] but occurred in our cohort (one patient in each group). When these clinical variants are on extremities, they may confound each other. However, the morphological aspects of lupus vulgaris and TVC should be evaluated to be told apart from each other. Lupus vulgaris is the most common clinical form of CTB in studies conducted in Spain, China, India, Japan, and Pakistan.[14,25,38,41] Large plaques are the main characteristics, as found in our cases, but we also had an ulcerative one (Fig. 5). Other lesions described are vegetative, tumor, and papulonodular lesions.[3,4] Squamous and basal carcinoma may develop in up to 10.5% of patients, usually after 25–30 years of the infection.[43,44] The lesions of verrucous TB are single, painless, and in areas that are prone to traumas, as occurred in our patients with leg or foot injury background (Fig. 6).[45–48] Historically, they are related to handling infectious material, especially in some professional groups, and also attributed to walking barefoot.[2,36,49]

Our group tend to regard a granulomatous lobular or septolobular panniculitis (with or without vasculitis) in the setting of a clinical, epidemiological, and/or microbiological diagnosis of tuberculosis as EIB, which was an important clinical form in our study. It is the most frequent clinical form of CTB in China, Hong Kong, Japan, and even in Rio de Janeiro, Brazil.[10,15,18,50] Another reference hospital also in the city of Rio de Janeiro found 26 cases of CTB in 14 years.[10] Overall, the studies highlight the predominance of women in this form of presentation.[10,15,18,50] The detection of mycobacteria can be based on identification of genetic material by PCR technique, searching for mycobacterial antigens or fragments, with a positivity of 14–80%.[51–59] In our center, this technique is not standardized to CTB. Only one patient with EIB presented concomitant pulmonary TB, less than in other studies (from 13.95 to 45.5%).[59,60] These lesions tend to respond to antituberculous treatment, although they may progress with relapse after the treatment. Their pathogenesis suggests a subclinical activity of a latent focus elsewhere, which releases mycobacterial antigens, leading to vasculitis with hypersensitivity reaction types III and IV.[61–64] Arterial hypertension was higher in this group, and most of these patients were women, overweight or obese, with venous stasis, factors already associated with EIB.[63,65] Papulonecrotic tuberculid associated with scrofuloderma is uncommon.[66] It is more associated with other tuberculids, but we have found one case here.[67–69]

Other forms of CTB such as tuberculous chancre, acute miliary TB, and lichen scrofulosorum were not observed, probably because they mainly occur in children, in regions with low BCG vaccination coverage.[70,71]

We emphasize the importance of the histopathology (52.0%) as a diagnostic tool in CTB, since in a significant proportion of cases the cultures are negative, mainly in cases of EIB. In these cases, it is important to perform a deep biopsy, with a representative sample of hypodermis, for an adequate histopathological study.[55,59]

Cure was achieved in all patients who completed the treatment (97.3%). Although the majority (70.7%) of the patients presented adverse reactions, only four (5.3%) presented major adverse reactions that caused them to stop the treatment, and a smaller proportion (2.6%) needed to change the antituberculous scheme. There was a higher frequency of EIB recurrence than in other studies.[55,72–74] Perhaps our period of follow-up was also longer. Recurrence of EIB could be associated with persistence of latent extracutaneous focus or not completely sterilized or persistence of antigens after treatment in combination with obesity and hemodynamic conditions such as vascular stasis in the lower limbs, which can be favorable situations for EIB lesions to reactivate.[75–78] The therapeutic approach to these recurrences was variable, but they showed complete or partial satisfactory results. We consider it important to carry out new studies in the field so as to improve the knowledge on EIB for a better approach toward these patients.

In this study, CTB predominantly affected female white patients and presented itself as scrofuloderma, TB gumma, lupus vulgaris, TVC, orificial TB, and tuberculids such as EIB papulonecrotic tuberculid. Injury of other sites such as lung, bone, joints, and breast also occurred. Histopathology becomes an important diagnostic tool in cases without isolation of *M. tuberculosis* in CTB. Treatment was generally well tolerated, and even cases with major adverse reactions progressed with cure. Relapses occurred only and in half of cases of EIB. These data highlight the diversity of CTB presentations and the importance of the skin to early identify and treat TB.

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