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Proposed tuberculosis investigation and management protocol in complex and recurrent fistula-in-ano



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ABSTRACT

Background: Tuberculosis (TB) is an ancient disease, endemic in some regions, caused by *Mycobacterium tuberculosis*. Among 22 countries accounting for 90% of tuberculosis cases worldwide, Brazil occupies the 17th place. The gastrointestinal form ranks sixth (5%) of extrapulmonary cases, while anorectal represents 2–7% of cases of fistula-in-ano, more common in midlife men, from endemic regions. In our country epidemiological data and accumulated clinical evidence strongly suggest the need for a systematic TB research as a responsible co-factor for complex anal fistulas or also those immunosuppression associated, in an attempt to reduce the high rates of recurrence of anal fistula (>30%).

Purpose: The course from a complex anal tuberculosis associated fistula, confirmed after initial suspicion of Crohn's disease, is presented in order to emphasize the relevance of suspicion and a diagnosis protocol, as well as healing criteria in fistulas contaminated by the bacilli.

Discussion: Sphincter damage risk in repeated fistula-in-ano surgical approaches requires considering tuberculosis infection, an underdiagnosed condition, and a preoperative diagnostic routine should be suggested. In the absence of description in the literature, preliminary clinical protocols must be provided in order to reduce recurrence and sphincter damage rates, when indicating surgical treatment of the disease.

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Proposta de investigação e tratamento da tuberculose em fístulas anorretais complexas e recorrentes

R E S U M O

Palavras chave:

Tuberculose
Fístula anal
Canal anal
Recorrência
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Introdução: A tuberculose (TB) é uma doença ancestral, endêmica em algumas regiões, e causada pelo *Mycobacterium tuberculosis*. Entre 22 países responsáveis por 90% dos casos de tuberculose em todo o mundo, o Brasil ocupa o 17° lugar. A forma gastrointestinal está em sexto lugar (5%) dos casos extrapulmonares, enquanto a anorretal representa 2–7% dos casos de fístula anal, sendo mais comum em homens de meia-idade e de regiões endêmicas. Em nosso país, os dados epidemiológicos e evidência clínica acumulada sugerem fortemente a necessidade de uma investigação sistemática TB como um cofator responsável por fístulas anais complexas ou também associada à imunossupressão, na tentativa de reduzir as altas taxas de recorrência de fístula anal (> 30%).

Objetivo: O curso de uma fístula anal complexa associada à tuberculose, confirmada após suspeita inicial de doença de Crohn, é apresentada a fim de enfatizar a relevância da suspeita e de um protocolo de diagnóstico, bem como os critérios de cura em fístulas contaminadas pelo bacilo.

Discussão: O risco de danos no esfíncter nas abordagens cirúrgicas repetidas da fístula anal requer considerar a infecção por tuberculose como uma doença subdiagnosticada. Na ausência de dados da literatura, sugere-se uma rotina de diagnóstico pré-operatório e protocolos clínicos preliminares a fim de reduzir a recorrência da doença e a ocorrência de danos ao esfíncter.

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Introduction

Tuberculosis, an endemic worldwide condition, has its incidence aggravated by the AIDS epidemic, multidrug resistance pulmonary tuberculosis, high poverty rate and migration.^{1,2} According to the WHO up to a third population would be infected with *Mycobacterium tuberculosis*, reaching almost 9 million new cases and 1.4 million deaths in 2011 (990,000 among HIV-seronegative individuals and 430,000 HIV seropositive).³ In this context, Brazil occupies the 17th place among the 22 countries responsible for 90% of tuberculosis cases worldwide, therefore responsible for the higher incidence and mortality in 2012.³

Fistula-in-ano recognition is dated from ancient times,^{4,5} constituting a commonly benign disease found in surgical practice, revealing a high incidence – 2:10,000 inhabitants – and most often affecting males (2:1).⁶

Complex and recurrent anal fistulas may require repeated surgical interventions resulting in a high risk of incontinence.⁵ Most fistulas have cryptoglandular nonspecific origin. Less frequent, but not least, anal fistulas attributed to other causes, such as Crohn's disease and tuberculosis (TB),⁷ and this should be reminded.

Anoperineal tuberculosis commonly coexists with anal fistula presentation, representing 90% of cases.² Complex fistulas in patients with human immunodeficiency virus (HIV) and active pulmonary TB should be evaluated with a high level of suspicion for tuberculosis etiology.^{1,8,9} However, diagnosis is difficult in healthy patients. Data have suggested TB as a relevant factor responsible in recurrence.¹⁰

The lack of consensus, regarding diagnostic investigation routines for TB infection in the treatment of anal fistula,^{5,10} allows rekindling this debate. To exclude the persistence of TB as a causal agent of recurrence is suggesting a systematic routine laboratory research, based on clinical data of this case, which featured a totally atypical profile in a female patient.

Case report

A single 24-year-old woman was admitted presenting anovulvar abscess and fistulous holes in the left gluteal and perianal region.

Symptoms started 12 months earlier with a painful gluteus bulging which drained spontaneously. On clinical examination were found four fistulous orifices (left gluteous, root of the left thigh, right of the vaginal fourchette and right perianal region), posterior edematous fibrotic anal plicoma, sphincter hypertonia and anoscopy undermined by pain. A month before admission, fistulography at another institution showed complex high supralelevator horseshoe fistula, and secondary tracks to perianal right left gluteus. Another track ending blindly, on the right, goes toward vulva (Fig. 1A and B). A MRI (magnetic resonance imaging) and ERUS (endorectal ultrasound) confirmed the tracks (Fig. 1C–F).

Patient underwent surgical exploration, fistulous tracks and sinus curettage, partial fistulotomy shortening the gluteus track, and seton application in all fistula tracks (Fig. 2). Histopathology using hematoxylin–eosin staining showed “chronic granulomatous inflammatory process” (Fig. 3A and B). Alcohol-acid-fast bacilli and fungi tests were negative

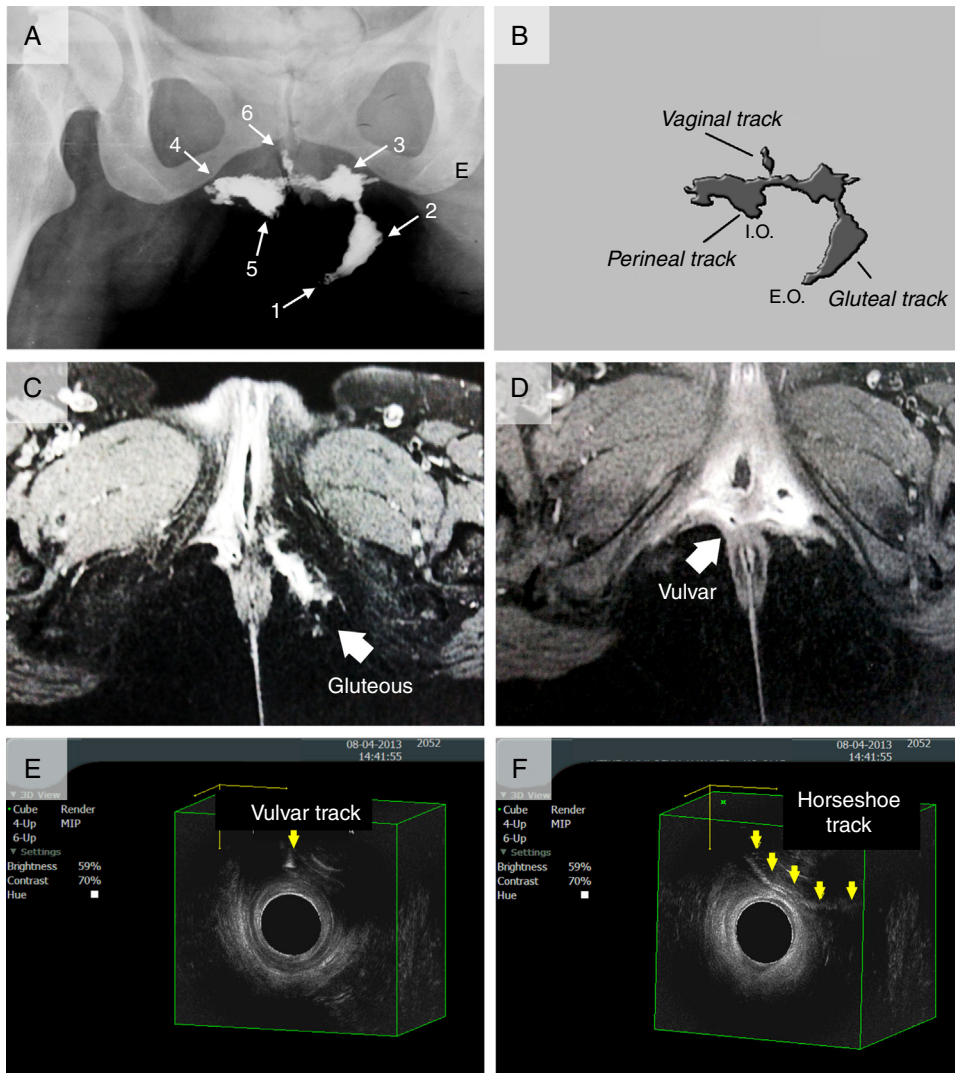


Fig. 1 – Fistulography images of horseshoe track in antero-posterior fistulography (A) showing left gluteal external orifices [1,2], left horseshoe track communicating left ischiorectal fossa track and hole [3], right horseshoe track next to levator ani, which communicates with the internal hole in anterior position [4], perianal ipsilateral external orifice [5] and the superficial blindly branch in right large labia [6] that evolves into new external orifice, observed on admission; and its schematic superposition (B). MRI image showing the ischiopubic track and left perineal oval fistula extending to the gluteal region (C) and perianal track and vulvar compromise (D). Endoanal 3D ultrasonography (ERUS) confirmed a horseshoe multiple and complex tracks fistula (E and F).

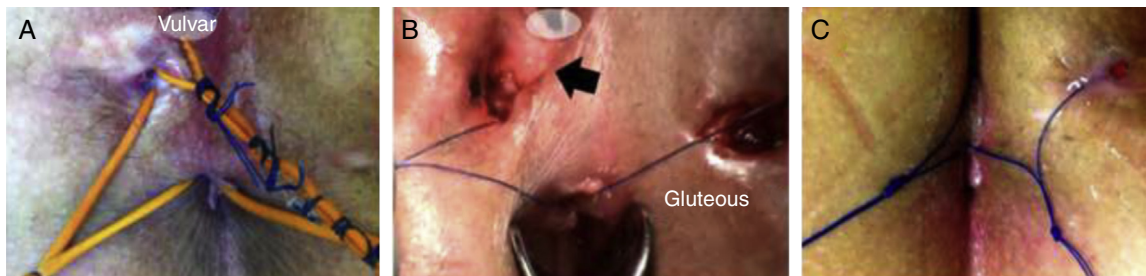


Fig. 2 – Perianal region appearance. Initial Foley seton drainage (A) changed to polypropylene seton at the second surgical exploration (B). The vulvar track was treated by cutting seton technique (black arrow). Finally, 12 months after anti-TB treatment before definitive surgical treatment (C).

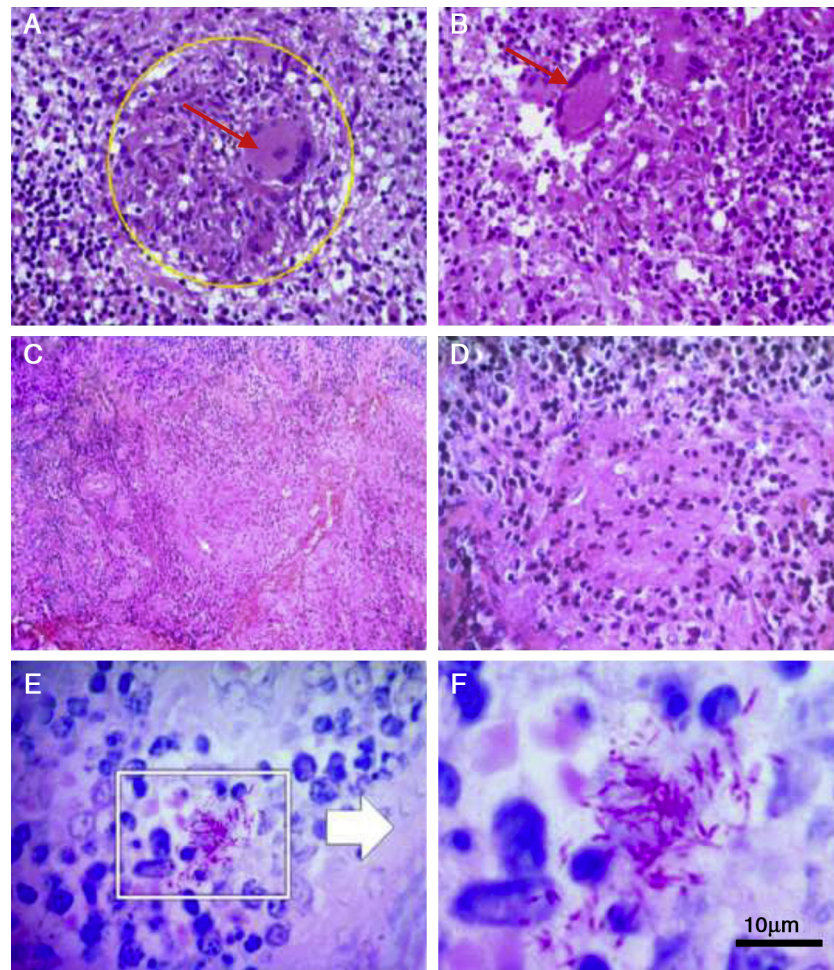


Fig. 3 – Photomicrographs of histological sections of fistula. (A) and (B) Area with giant cell granuloma (Langerhans cells) technique using hematoxylin–eosin; note the characteristic alignment of nuclei in the vicinity of the giant cell, characteristic of fusion of macrophages (400×). (C) and (D) Hematoxylin–eosin staining in an outbreak of liquefaction necrosis amid chronic inflammatory infiltrate (10× and 40× magnification). (E) and (F) A niche of alcohol-acid-fast bacilli, some within histiocytes, in Wade staining technique (40× and 100× magnification).

and therefore Crohn's disease was strongly suspected. In ileocolonoscopy mild erosive lesions in terminal ileum were found, reinforcing the initial suspicion, but biopsies showed "chronic granulomatous ileitis with necrosis". After discharge, drainage persisted, with reappearing fever and vaginal phlegmon, and the patient was readmitted for new surgical exploration and seton change was carried out. Secretions were collected revealing *Escherichia coli* growing in culture, "a chronic granulomatous process" and the presence of alcohol-acid-fast bacilli, observed in hematoxylin–eosin and Wade staining paraffin sections (Fig. 3C–F). The intradermal test with purified protein derivative (PPD) was 7 mm. Serologic tests for HIV, hepatitis and Lues were negative.

When referred to a tuberculosis control program, patient reported weight loss and vespertine fever, and specific treatment was started. A chest radiographic reevaluation revealed streaks and dense nodules in the apical segment at the right lung. Induced sputum bacilloscopy was negative but a mycobacterial culture was positive on the 34th day and a

scheme with Rifampicin, Isoniazid, Pyrazinamide and Ethambutol (RIPE) was started. Five months after the beginning of RIPE scheme, she was asymptomatic and there was a significant improvement of fistulas suppuration; so drug schema was reduced to Rifampicin and Isoniazid at fourth month. Two induced sputum bacilloscopy were negative. Mycobacterial culture (induced sputum) was negative in the sixth month of treatment.

Medical treatment was terminated in the seventh month and the patient remained comfortable with draining setons without pain complaints, fever or secretion through outer holes. Two months after completing anti-TB treatment, the vulvar track was opened by a cutting seton and a new surgical exploration was done for changing setons (Fig. 2B). However, analysis of material obtained in this last surgical exploration showed persistent bacilli, requiring drug treatment return and suspension of planned definitive surgery. Ten months after admission, fistula was dry (Fig. 2C) and definitive surgical treatment was in progress.

Discussion

Fistula-in-ano is known since Hippocrates and has been described over the centuries. In 1835, Frederick Salmon inaugurated the Fistula Infirmary – a clinical precursor of St. Mark's Hospital for Fistula and other Diseases of the Rectum – where he treated fistula of several authorities.¹¹ Good-sall (1900) became popular describing fistula-in-ano details and later Parks (1976) named the world's most widely used classification.⁶ This cryptoglandular nonspecific infection surgical condition is responsible for 90% of all anorectal abscesses focusing on 5.6/100,000 women and 12.3/100,000 men.^{1,10} The tuberculosis origin is uncommon and possibly underdiagnosed. Among the anorectal manifestations commonly associated with tuberculosis (TB), fistula is the most frequent complication.^{1,7} Pathogenesis of perianal fistulas in patients with TB is still controversial. Authors consider the tropism of Koch's bacillus into lymphatic tissues.¹² However, other mechanisms may explain the presence of Koch's bacillus in the perianal region, such as: (a) hematogenous,^{1,2,9} (b) lymphatic, originating from infected lymph nodes,^{2,9} (c) ingestion of contaminated milk¹ or swallowing infected bacilli sputum from active pulmonary foci^{1,2,9} or even (d) direct dissemination from infected adjacent organs.^{2,9}

European studies show a strong association of anal fistula and pulmonary TB, although Indian data are not convinced of this association.^{1,13} Sexual transmission of *M. tuberculosis* during anal intercourse has been suspected, but not yet proven.²

On tuberculosis, this accompanied mankind since prehistoric times. Its characteristic lesions were found in mummies, and in Inca and American Indians before Columbus. In Brazil, it is an endemic infectious disease caused by *M. tuberculosis*, the principal etiologic agent, identified by Robert Koch (1882), who named the bacillus.¹⁴ *M. bovis* may be involved sometimes, and rarely other mycobacteria. It remains a serious global health infectious condition, causing pulmonary disease in most cases.¹ The World Health Organization (WHO) estimates that one-third of the population could be infected with *M. tuberculosis* in 2012. The increasing incidence worldwide is due to the AIDS epidemic, TB with standard multidrug resistance, high levels of poverty and migration.^{1,15} Brazil still remains in the 22 countries group responsible for 82% of TB cases in the world.¹⁶

Anoperineal TB is considered an uncommon event¹ and anorectal fistula is the most frequent presentation (up to 90% of cases) indistinguishable from those of cryptoglandular origin. TB incidence in complex fistulae is above 60%.¹⁷ Low

incidence has been reported, such as in the United Kingdom (6 cases in the last 25 years)¹ as well as in endemic regions such as Morocco, which does not exceed 1%.⁸ However, these numbers are higher in India which highlights Shukla et al. series¹⁸ confirming tuberculosis origin in almost 16% of cases of anal fistula. The typical case of fistula TB origin would be an immigrant man, middle aged and belonging to a low socioeconomic class.^{17,19} We summarize the studies reviewed (Table 1).

Clinical suspicion of TB in anal fistula is extremely difficult due to the absence of a typical, local or systemic pattern. Furthermore, pulmonary lesions occurrence may not precede the fistula tuberculosis infection. The case presented in this article has an atypical profile, and the radiologic diagnosis of pulmonary lesion came later, leading to another granulomatous diseases suspicion, such as Crohn's disease, also supported by the presence of ileitis in which ileal biopsies also collaborated for not including TB as initial suspicion, since they showed nonspecific changes. The clinical presentation of TB in anal fistula recorded in the literature is diverse, but a high degree of suspicion should be considered when evaluating a patient with recurrent complex anal fistula, in immunosuppressed patients, or when there is an initial suspicion of Crohn's disease.

Laboratory diagnosis of Koch's bacillus from collected secretions depends on the use of specific stains such as Ziehl-Neelsen or bacteriological studies. These tests should be performed routinely in all patients with cases of complex fistulas, especially in patients from endemic regions. Even so, the diagnosis may be limited, as in the present case in which etiologic agent identification occurred casually in the first sample (rare bacilli in histologic sections). Even though TB tests sensitivity is still limited, as already indicated by the majority of authors who study the subject, molecular detection methods, such as PCR (protein chain reaction), are now available.

It is also important that surgeons and endoscopists be alert for the high degree of suspicion cases, requiring bacilloscopy with appropriate staining and culture, from all collected materials such as samples of mucosa, skin or excised fistulous tract. In negative cases, when suspected diagnostic suspicion persists, the PCR should be indicated.

Finally, it is worth emphasizing the absence of cure criteria definition for TB associated to complex fistula-in-ano in literature data.^{9,14} Unlikely ulcerative anorectal and perianal TB forms, where it is easy to determine clinical cure (clinical healing findings in response to treatment), anal fistulas, with multiple/meandering paths and complex presentation, may have local TB cure difficult to determine, raising the

Table 1 – Fistula-in-ano TB incidence worldwide.

Author	Year	Country	Incidence
Sainio et al. ²⁰	1984	Finland	0.2% (10 years)
Shukla et al. ¹⁸	1988	India	16% (5 years)
Sultan et al. ¹⁸	2002	France	0.3% (17 years)
Favuzza ¹³	2008	USA	1 case (16 years)
Stupard et al. ²¹	2009	South Africa	7.3% (3 years)
Wijekoon ⁵	2010	Ireland	2.4% (3 years)
Chourak et al. ⁸	2010	Morocco	Less than 1%
Barker et al. ¹	2011	UK	6 cases (25 years)

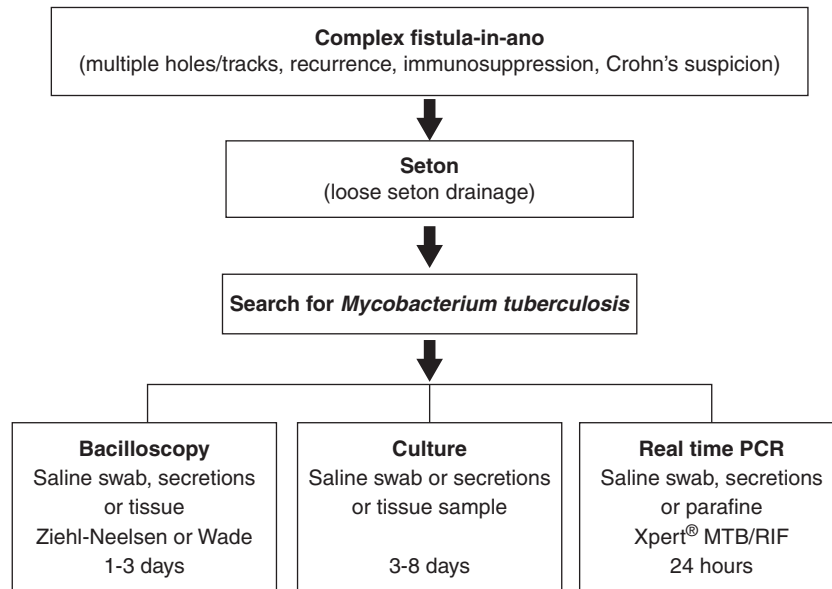


Fig. 4 – Diagnosis and management of fistula-in-ano in high degree of suspicion for TB infection scheme.

risk of failure of definitive surgical treatment, and the consequent unfortunate recurrence. Authors correlate surgical fistula recurrence to TB as a co-responsible factor.⁹ Based on these data we can affirm that the definitive surgical treatment should only be performed after excluding TB or confirmed healing of local TB infection. Therefore, curing lung focus should not be enough to determine the healing of perineal TB focus infection. In the diagram below, the steps for proper research are suggested (Fig. 4).

Conclusion

In those strong initial TB suspicion cases, as well as those confirmed TB fistulas, curettage of the tracks and biopsies should be performed. Samples should be sent for bacilloscopy and TB culture. Diagnostic confirmation may include histological analysis by Ziehl–Neelsen or Wade stain, mycobacterial culture and polymerase chain reaction (PCR). PCR may be indicated with a great cost-effective method currently available, which has greatly helped the confirmation of cure. While this confirmation does not occur, keeping the tracks drained and repaired with seton may be the best approach. Definitive fistula surgery before confirming TB focus elimination may result in disease recurrence.

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