Perianal Tuberculosis

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Key Points

- The most frequent presentation of perianal tuberculosis (TB) is abscess and/or fistula.
- TB fistulas are significantly more complex than non-TB fistulas.
- Polymerase chain reaction (PCR) has a higher detection rate than histopathology.
- Pus has a higher microbiological positivity than tissue (fistula tract lining/wall) to detect TB.
- A single negative sample does not exclude the presence of TB and repeated samples should be considered in suspicious cases.
- The cure rate is excellent when TB is detected, and ATT is started before surgery or within 6 weeks of surgery.

9.1 Introduction

Every year, ten million new cases are diagnosed with tuberculosis (TB) and it is the world's top infectious killer [1]. Extrapulmonary TB accounts for 3–46% of all types of tuberculosis patients across the world [2]. It can involve any part of the

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gastrointestinal tract from mouth to anus. Gastrointestinal involvement accounts for 1% of all TB cases and, amongst these, TB of the perianal region accounts for only 0.7% of cases [3]. Though perianal TB is a miniscule proportion of the huge overall TB burden, yet the proportion of anal fistulas associated with TB is much higher [3]. This is especially true of TB endemic areas. Various studies have reported that TB can be detected in 2.3–16% cases of anal fistulas in developing countries (endemic regions) and 0.3–1.2% in developed countries [3–9].

9.2 Etiopathogenesis

There are two hypotheses regarding the involvement of the perianal region with TB. The first is ingestion of pulmonary secretions heavily laden with TB bacilli, and the second is reactivation of a latent focus [10]. Other mechanisms like hematogenous spread from pulmonary TB, lymphatic spread from regional lymph nodes, or direct extension from neighboring affected organs seem exceedingly rare [11]. However, most researchers believe the first hypotheses (ingestion of pulmonary secretions) is the most common mechanism [10]. Though the association of TB with anal fistulas and abscesses is undisputed, there is no evidence or clinical data available which can indicate as to whether TB has the potential to cause a new disease process (formation of anal fistula/abscess) or TB bacilli can only infect an already existing fistula-in-ano and complicate it [10, 12]. But it is likely that once a fistula is infected by TB, then this infection needs to be treated for the fistula to heal [12]. In the absence of anti-TB therapy, the fistula would either not heal after surgery or would recur a few weeks to months after clinical healing [12]. This is so because TB bacilli are very slow growing. Therefore, at times, they may not be able to prevent the fistula from healing temporarily but once they have slowly multiplied in sufficient numbers over a few weeks, they can cause recurrence of fistula/abscess [12].

There have been reports recently that non-tuberculous mycobacteria (NTM) can also be associated with perianal fistulas [13]. Though this is rare, it needs to be kept in mind because it can cause confusion in the diagnosis. Moreover, the treatment of most NTM is quite different from usual anti-TB treatment [13–15].

9.3 Clinical Manifestations

Perianal TB is commonly seen in males with a male: female ratio of 7:1 [12]. The age groups most frequently afflicted are the third and fourth decades of life [12]. The most common presentations of perianal TB are anal fistula and anorectal abscess [16]. Occasionally, it may present as a pilonidal sinus [17] or as an anal ulceration with inguinal lymphadenopathy [18]. Rarely, perianal TB may also present as a recurrent perianal mass [18], anal fissure, [19] anal stricture [20], hemorrhoids [21], or as a rectal submucosal tumor [22].

Anal fistulas associated with TB are much more complex than cryptoglandular non-TB fistulas [3] (Figs. 9.1, 9.2 and 9.3). In a recently published large study, the proportion of complex fistulas was significantly higher in TB fistula (69%-78/113) than in non-TB fistula cohort (44.3%-278/727) ($p < 0.00001$, significant, Fisher's exact test) [12]. As per St James's University Hospital (SJUH) classification [23] and the newly described Garg classification [24–27], the presence of fistulas of higher grade (III, IV & V) were significantly higher in the TB fistula group as compared to the non-TB fistula groups [12]. Garg classification has been shown to grade fistulas as per their severity much more accurately and also guides in the management of the disease [24, 25].

There are several possible reasons for higher proportion of complex fistulas in setting of TB [12]. First, due to low prevalence or incidence of TB in anal fistulas, it is usually not suspected. Second, good diagnostic tests which can detect TB with reasonably high sensitivity and specificity are not available. Third, most first-line antibiotics commonly prescribed for pyogenic infections are not effective in TB. Therefore, underlying tubercular disease process continues to spread. Fourth, anti-TB therapy is quite long and cumbersome. Therefore, poor compliance of patients for completing treatment could lead to MDR-TB (multi-drug resistant TB) which further makes treatment difficult and fistulas become more complex [3]. Fifth, contrary to an acute pyogenic abscess, TB usually presents with a cold abscess with minimal symptoms, and it has a slow, indolent progressive course [3]. Therefore, patients tend to ignore the disease until it is well advanced. Sixth, due to above factors, TB fistulas have a higher recurrence rate requiring multiple operations [3]. Repeated surgery can lead to sphincter damage which makes the fistula more complex and treatment difficult [12].

9.3.1 Clinical Features Which Raise Suspicion of a Possible TB Infection [3]

Though there are no pathognomonic or specific clinical features of anal fistula or abscess due to TB [10], certain features raise the level of suspicion of a possible TB infection [3]. These features include the presence of a very complex fistula, non-healing fistula, development of new abscesses or tracts while the fistula is being treated and a relapse of fistula within 6 months after complete healing [12].

The samples (tissue or pus) should be tested for TB, especially in these scenarios. It is recommended that in endemic regions, routine TB testing of all pus and tissue samples from anal fistulas should be considered [3]. In countries where TB is not endemic, selective sample testing may be done (fistula associated with HIV/AIDS, fistula refractory to treatment, etc.) [5].

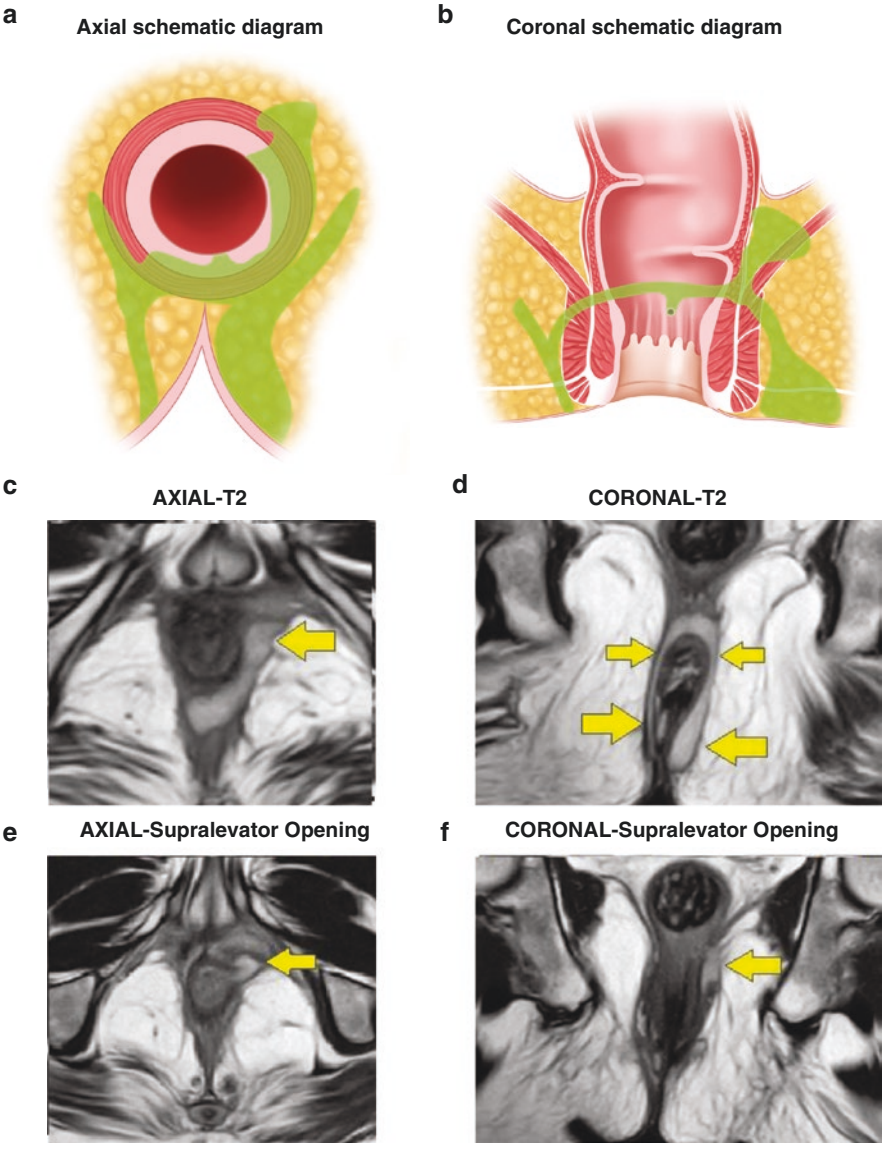

Fig. 9.1 A 55-year-old male patient with TB infected high recurrent transsphincteric horseshoe complex anal fistula with multiple tracts and supralevator extension with supralevator rectal opening at 2 o'clock (SJUH grade V). (yellow arrows show fistula tracts). (**a**) Schematic diagram—Axial section (**b**) Schematic diagram—Coronal section. (**c**) MRI—Axial Section-T2 sequence. (**d**) MRI—Coronal Section-T2 sequence. (**e**) MRI—Axial Section-T2 sequence: high level showing supralevator rectal opening at 2 o'clock. (**f**) MRI—Coronal Section-T2 sequence: showing supralevator rectal opening

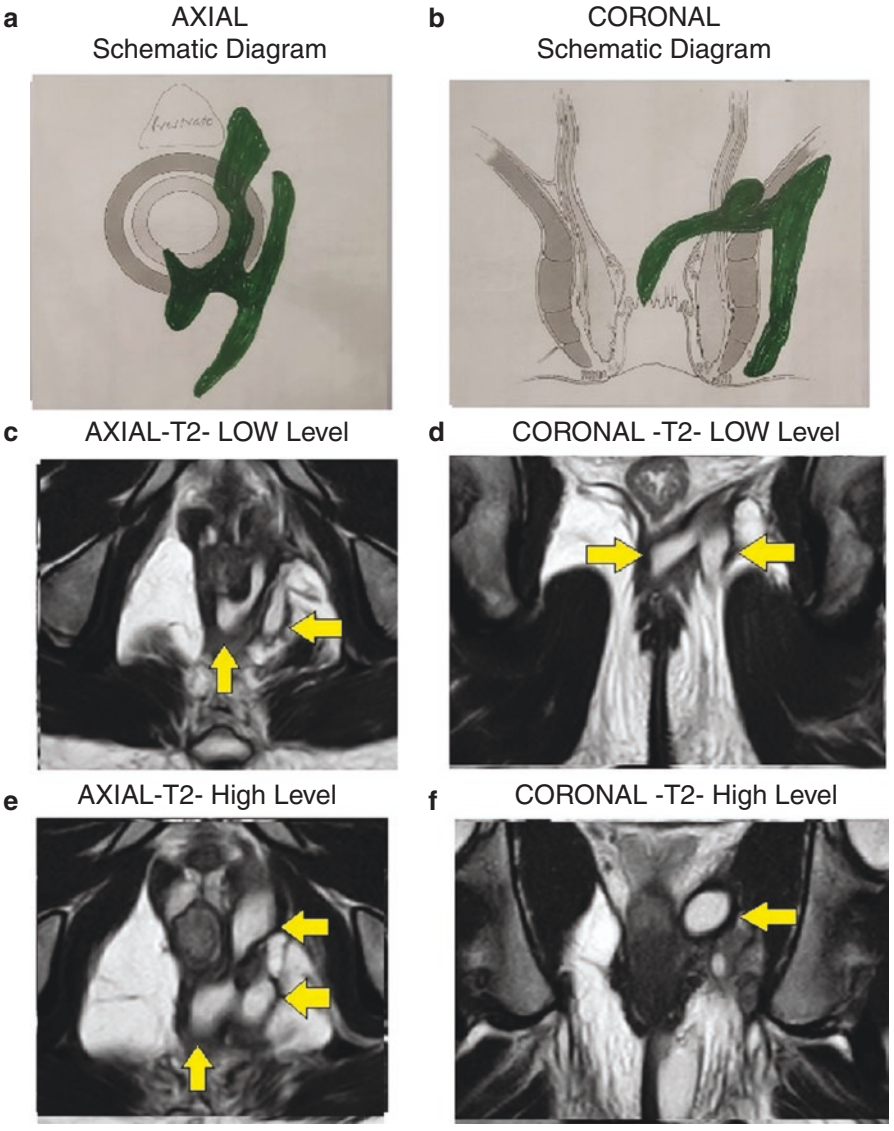

Fig. 9.2 A 17-year-old male patient with TB infected high recurrent transsphincteric horseshoe complex anal fistula with multiple tracts and supralevator extension (SJUH grade V). The fistula is extending up to the left lateral aspect of the prostrate (yellow arrows show fistula tracts). (**a**) Schematic diagram—Axial section (**b**) Schematic diagram—Coronal section (**c**) MRI—Axial Section-T2 sequence (**d**) MRI—Coronal Section-T2 sequence (**e**) MRI—Axial Section-T2 sequence: high level showing supralevator extension (**f**) MRI- Coronal Section-T2 sequence: showing supralevator extension

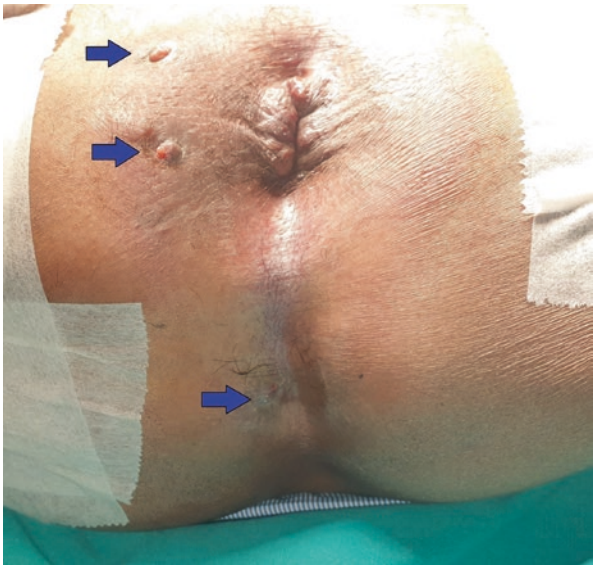

Fig. 9.3 A 52-year-old male patient with TB infected highly complex anal fistula associated with an abscess and multiple tracts. The three external openings can be seen (marked by dark blue arrows)

9.4 Diagnosis

The diagnosis of perineal tuberculosis is difficult due to lack of a satisfactory test that has reasonably high sensitivity and specificity [10]. TB bacilli are slow-growing and ubiquitous, leading to difficulty in culture and the problem of contamination [28]. Several tests have been utilized to detect TB, which include culture, histopathology (HPE), Acid-fast bacilli (AFB) stain, tuberculin test, ELISA, polymerase chain reaction (PCR), GeneXpert or CBNAAT (cartridge-based nucleic acid amplification test), rapid immunochromatographic assay, etc. [10, 29] However, the commonly used tests amongst these are AFB stain, culture, HPE, PCR, and GeneXpert [28]. These tests can be done on either pus (from anorectal abscess or discharge oozing out from fistula tracts) or tissue (fistula tract lining epithelium or fistula tract wall) or both [29].

AFB staining is done by Ziehl–Neelsen stain. This method has a low detection rate [30]. Therefore, the clinical utility of this test is low [28]. TB culture with Lowenstein–Jensen medium has a high specificity, and the drug sensitivity profile can also be assessed at the same time [31]. However, the sensitivity of culture is quite low and culture takes a long time (6 weeks to 6 months) due to which the clinical utility of culture especially in perianal TB becomes very limited [31]. Moreover, culture cannot differentiate between infection and contamination [30]. BACTEC 460 TB system is a new technique for culture-based diagnosis that works on the principle of early specific detection of mycobacterial growth [32]. It provides results

within 3 weeks [32]. It has been reported that 76% of patients with abdominal TB showed positive BACTEC 460 TB cultures [33]. But this test has not been studied in perianal TB.

HPE is one of the commonest tests done around the globe [3, 28, 29]. HPE utilizes HE (hematoxylin and eosin) stain [29]. The features which suggest mycobacterial disease on HPE are confluent granulomas, a lymphoid cuff around granulomas, granulomas larger than 400 μm in diameter, five or more granulomas in biopsies from 1 segment, granulomas located in the submucosa, granulation tissue (often as palisaded epithelioid histiocytes), excessive submucosal inflammation and/or Langerhans giant cells [13, 34]. Amongst these, the caseation of granulomas is one of the most specific features of TB [35, 36]. However, these features can also be present in Crohn's disease or other chronic granulomatous diseases [34, 36]. As the specificity as well as the sensitivity of HPE is not very high, therefore, HPE is not a reliable method to detect TB [3, 12, 28].

Real time-*Polymerase Chain Reaction (PCR)* has a high sensitivity to diagnose TB [15]. TB PCR is rapid (can detect bacterial DNA within 48 h) as well as an accurate diagnostic method [37, 38]. Apart from tissue, PCR can also be done on pus from the abscess or fistula tracts [3, 12, 28]. Specific PCR can also differentiate between TB and NTM (non-tuberculous mycobacteria) [3, 12, 28]. Several studies had recommended that PCR should be employed routinely to detect TB [6, 15, 39, 40]. However, most of the studies utilized HPE [4, 5, 7–9, 41, 42], and very few studies in the literature have used PCR for testing [3, 6, 28]. A recent study analyzed 1336 samples in 776 patients of anal fistula and highlighted that PCR of tissue was significantly more sensitive than HPE to detect TB (7.4% vs 1.5%) [12]. The same study also demonstrated that PCR of pus was significantly better to detect TB than PCR of tissue (23.2% vs 7.4%) [12]. In this study, the rpobF and rpobF primers targeting the gene, rpobB were used [43, 44]. The limitation of PCR is that it can lead to false-positives as PCR cannot distinguish between dead and viable mycobacteria [3, 28]. Therefore, it is recommended that a positive PCR test should always be correlated with clinical features [3, 12, 28].

GeneXpert MTB/RIF assay (CBNAAT) uses a disposable cartridge. The advantage of this test is that it simultaneously detects TB as well as resistance to rifampin (RIF) and can be done in less than 2 h [12]. In 2010, the WHO recommended the use of the GeneXpert as a preliminary test for TB detection and improve diagnosis of rifampicin (RIF) resistance in pulmonary and extrapulmonary TB (EPTB) specimens [45]. However, this test has low sensitivity in EPTB cases and false-positives in strains that contain synonymous mutations [46, 47]. The only study which utilized GeneXpert in perianal TB found the sensitivity of GeneXpert to be quite low as compared to PCR (0.9% vs. 7.4%) [12].

Considering the high sensitivity of PCR, it has been recommended that PCR should be done in every fistula patient especially in endemic regions [3, 12, 28]. In cases where a pus sample is available, it should also be tested as the detection rate in pus is quite high [3, 12]. It has also been highlighted that TB may not be always detected in the first sample tested [3, 12, 28]. Therefore, repeated samples should be sent for testing in patients with high level of clinical suspicion of having TB as

mentioned above (a very complex fistula, a fistula in which the healing is not occurring in the usual expected course, development of new abscesses or tracts while the fistula is being treated or relapse of fistula within 6 months after complete healing) [3, 12]. In a large study of 740 operated fistula patients with a long-term follow-up, it was noted that TB was detected by repeat samples (sent in the postoperative period) in 15.9% (18/113) patients [12]. This diagnosis would have been missed if repeat samples had not been sent. Therefore, the importance of maintaining a high index of suspicion for TB before and after surgery and promptly sending samples (pus or tissue) as per the clinical picture plays a pivotal role in increasing the detection rate of TB [3, 28].

9.4.1 Tubercular vs. Crohn Disease-Related Perianal Disease

It is important to discuss the ways to differentiate TB from Crohn's disease (CD) since both these diseases can cause or present as anal fistulas or an anorectal abscesses. While the CD is more common in the developed world, TB is more common in low-income countries, though this differentiation is getting diluted in the last few years [48]. CD fistulas tend to occur in younger age group [median-23 years] as compared to TB fistulas [median-37 years] [49]. The type of fistulas (intersphincteric, transsphincteric, or suprasphincteric), presence of multiple tracts or number of recurrences seem to be comparable in both types of fistulas [49]. In comparing histopathological findings, TB fistulas are associated with much higher proportion of caseating granulomas (62% in TB vs. 0 in CD), while CD fistulas have significantly higher number of non-caseating granulomas (34% in TB vs. 58% in CD) [49]. On colonoscopy, the mucosal inflammation is much more common in CD (97%, along with aphthous ulcers, longitudinal ulcers and cobblestone appearance) than in TB patients (33%, along with transverse ulcers and aphthous ulcers) [49]. However, the site of involvement was similar in both the diseases (the most common sites being ileocecal region, ascending colon, transverse colon and other areas in decreasing order) [49]. The differentiating features between TB and CD are tabulated (Table 9.1)

Table 9.1 Features differentiating between Tuberculosis and Crohn's disease

	Tuberculosis	Crohn's Disease
Clinical features	Fever/night sweats	Diarrhea/hematochezia/perianal disease
Endoscopic features	Transverse ulcers/patulous ileocecal valve	Longitudinal/aphthous ulcers
Histologic features	Caseating/confluent/large granuloma	Micrograniuloma
Microbiologic features	Positive stain/culture for acid fast-bacillus	
Radiological features	Necrotic lymph node/contiguous ileocecal involvement	Long segment involvement/comb sign/skip lesions
Anti-TB therapy (ATT) trial	Improvement	No improvement

[48]. However, it is important to realize that these features have more suggestive value as the specificity of these features is not very high [48]. The only features with very high specificity are the presence of caseation granulomas and positive AFB smear and culture for TB [48].

9.5 Radiology

The commonly used modalities employed to assess anal fistulas are fistulography, transrectal ultrasound (TRUS) and MRI. With the advent of advanced modalities (MRI and TRUS), the utility of fistulography has markedly diminished as it does not show any relevant soft tissue structures (anorectum, anal sphincters, etc.). MRI is considered the gold-standard to evaluate anal fistulas as it has a slight edge over TRUS. There are no specific features on MRI or TRUS that can help in the diagnosis of TB in anal fistulas.

As discussed above, TB fistulas are more often complex and are more commonly associated with multiple tracts [4, 5, 7, 9, 41]. MRI and TRUS can help in accurately identifying multiple tracts and other features which make the fistula complex like horseshoe tract, supralevator extension, associated high abscess, etc. (Figs. 9.1 and 9.2) [50]. Secondly, MRI and TRUS are highly sensitive to detect non-healing of fistulas in postoperative period [51]. Thus, these advanced radiological modalities are extremely helpful in identifying features that raise suspicion of a possible TB infection. Thus, these modalities are an integral part of armamentarium available with physicians to combat TB fistulas.

9.6 Treatment

The treatment of anal fistulas especially complex ones is an uphill task [3], and when TB is associated with such fistulas, the management becomes even more challenging [10]. The management of such fistulas is in two steps [3]. First, the internal opening is the culprit which needs to heal properly for the fistula to be cured completely [12]. If the internal opening does not heal within few weeks after surgery, it gets epithelialized, and the chance of fistula healing becomes remote [12]. Second, the main challenge in TB fistulas is accurate detection of associated TB infection and timely initiation of anti-TB therapy [3, 12]. This step, in itself, is also not straightforward as the timely detection of TB is not easy. An algorithm has been suggested to diagnose and manage TB associated with anal fistulas [3].

Recent studies conducted in large samples have demonstrated that anti-TB therapy should be started within 6 weeks (preferably 3 weeks) of surgery for anal fistula [3, 12]. If anti-TB therapy is initiated after 6 weeks, then the chances of non-healing and recurrence of fistula are quite high [3, 12]. In most surgical procedures, the fistula tracts and the internal opening are thoroughly debrided and cleaned due to which the microorganism load is reduced drastically. Therefore, in the postoperative period, the TB bacilli do not hinder the healing process during the first 6 weeks as

these bacilli are quite slow growing. So, if the TB is detected and anti-TB therapy is started within that time, then the infection can be eradicated and chances of fistula healing are quite high [3, 12]. On the other hand, if the detection of TB is missed, then bacilli would keep on multiplying to a considerable number and would lead to

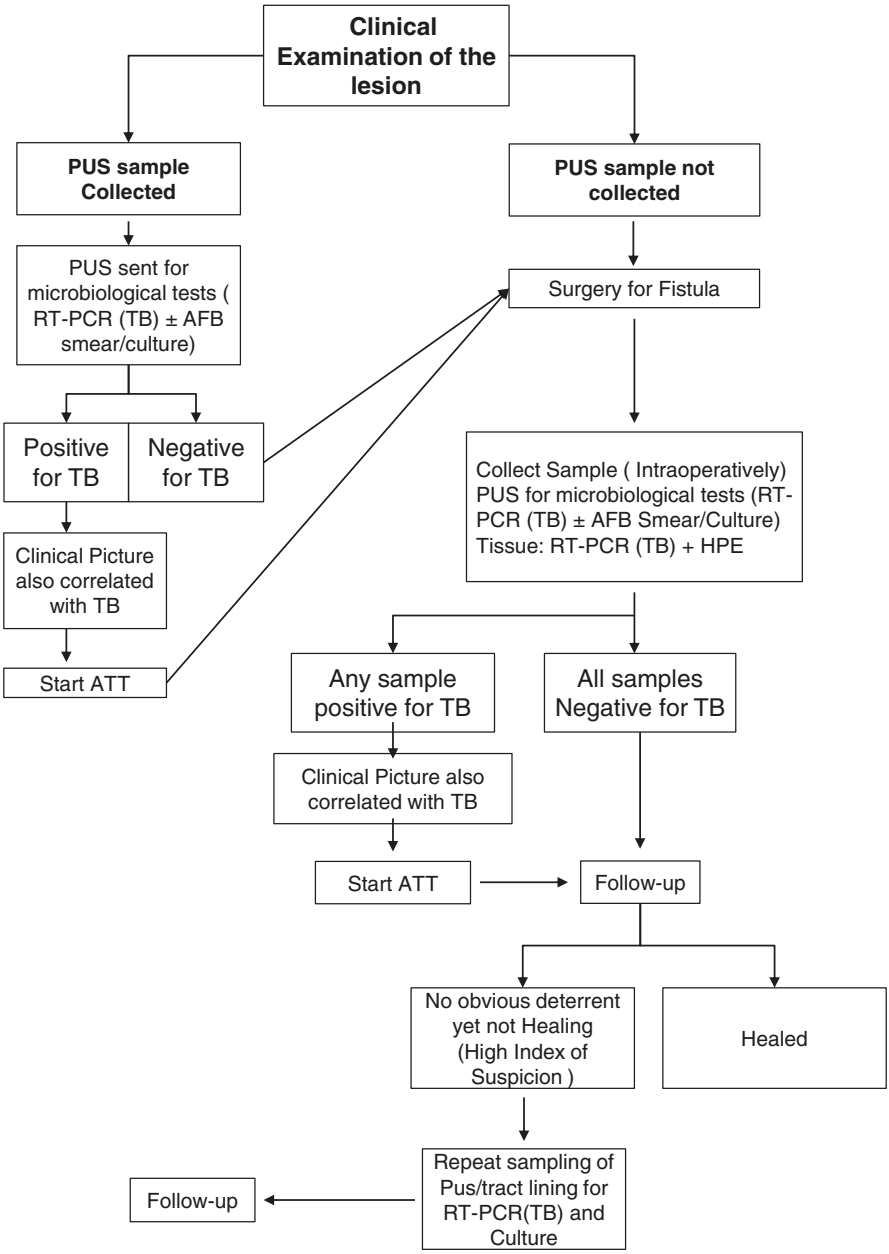

Fig. 9.4 Algorithm recommended to diagnose and manage tuberculosis in anal fistulas [3]

non-healing of internal opening or an abscess formation [12]. Thus, the importance of timely detection of TB infection present in anal fistulas/abscesses cannot be understated [3, 12].

In pursuance of the same goal, it is recommended that in the patients with high suspicion levels for having TB but with initial (first) negative report, repeat samples (pus or tissue) should be tested to detect missed TB infection (Fig. 9.4). In studies (cited above), the TB infection in up to 16% TB patients was detected on repeat samples [12].

As mentioned above, PCR tests cannot differentiate between viable and dead mycobacteria [3]. Therefore, it is recommended that a positive PCR test should always be correlated with clinical features [3]. A patient with a low simple fistula can be given the option of not starting anti-TB therapy, whereas therapy should be started in patients with complex fistulas or with high level of suspicion of TB clinically [3, 12].

9.7 Anti-TB Therapy

The patients scheduled to get anti-TB treatment are recommended the standard four-drug anti-TB regimen for first 2 months (intensive phase). This should be followed by the three-drug regimen (Isoniazid-5 mg/kg, Rifampicin and Ethambutol) for the next 4 months (maintenance phase) [3, 10]. It has been recommended that in patients who test positive for TB and have complex fistulas, injection Streptomycin (15 mg/kg, maximum of 750 mg/day, intramuscular) may also be administered during the first 2 months of the intensive four-drug regimen. The reason behind this is that Streptomycin penetrates well into most body tissues [3]. Conventionally, there has been a ceiling on the standard TB drugs (Isoniazid-300 mg, Rifampicin-600 mg, Pyrazinamide-1500 mg and Ethambutol-1000 mg). There have been recommendations that higher dosage of anti-TB drugs may be given as per body weight, unrestricted by the ceiling [1]. But there is no experience or data as to whether the recommended higher dosage of anti-TB drugs is better than conventional dosage (with the ceiling). However, existing data highlights high cure rates with conventional dosage (with the ceiling) [3, 12].

It has been also been recommended that anti-TB therapy may be extended for 9–18 months in complicated cases [41] but there is no consensus on that. The treatment in multi drug-resistant TB (MDR-TB) patients can be quite challenging. In MDR-TB patients, second-line drugs are recommended. In these patients, the intensive phase involves 6–9 months of second-line drugs like Kanamycin, Levofloxacin, Ethambutol, Pyrazinamide, Ethionamide and Cycloserine and 18 months of maintenance phase with Levofloxacin, Ethambutol, Ethionamide, and Cycloserine [45].

To conclude, TB associated with anal fistulas and anorectal abscesses poses a plethora of diagnostic and management challenges. Though TB is associated with more complex fistulas, a high level of suspicion especially in endemic regions, timely detection, and meticulous treatment lead to reasonably high cure rates that are similar to non-TB fistulas.

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