Peritoneal tuberculosis

K. Mimidis, K. Ritis, G. Kartalis

SUMMARY
Tuberculosis (TB) can involve any part of the gastrointestinal tract and is the sixth most frequent site of extrapulmonary involvement. Both the incidence and severity of abdominal tuberculosis (AT) are expected to increase with increasing incidence of HIV infection. Peritoneal tuberculosis (PT), a form of AT, occurs in three forms: wet type with ascites, dry type with adhesions, and fibrotic type with omental thickening and loculated ascites. Clinically, PT is characterized by fever, abdominal pain, anorexia, weight loss, and ascites. However, none of these symptoms is specific for the disease, so it is commonly misdiagnosed, especially as carcinomatous peritonitis in the elderly. Early diagnosis of PT is of major importance in the control of the disease. Chest X-rays show evidence of concomitant pulmonary lesions in less than 25 per cent of cases. Laparoscopy with direct biopsy is an excellent diagnostic method and must be considered for every patient with unexplained ascites. A definitive diagnosis requires identification of bacilli in ascitic fluid or peritoneum tissue. However, acid-fast staining is usually negative and cultures are positive in 30-40% of cases, making bacteriological confirmation of the disease very difficult. Recently, advances in molecular techniques have provided a new approach to the rapid diagnosis of tuberculosis by nucleic acid probes and polymerase chain reaction (PCR). Management is with conventional antitubercular therapy for at least six months.

Key words: PCR, ascites, peritoneal tuberculosis

INTRODUCTION
Tuberculosis was a prevalent infection even in Ancient Greece and Egypt. The disease was put under control only after the advent of antimicrobial therapy in 1946. Autopsies conducted on patients with pulmonary tuberculosis before the era of effective antitubercular drugs revealed intestinal involvement in 55-90 per cent of cases, with the frequency related to the extent of pulmonary involvement. Pimparkar et al. found evidence of AT (bowel, peritoneum and liver) in 3.72 per cent of 11,746 autopsies carried out in K.E.M. Hospital, Mumbai between 1964 to 1974. After a few decades of decreasing incidence of tuberculosis, during the last 10 years there has been a worldwide reemergence of the disease. This may be due to several reasons such as the HIV epidemic, an increase in the number of immigrants and the primary resistance to first-line drugs. One-third of the world population is in risk of acquiring TB according to WHO and more than 30 million deaths due to TB were expected in the nineties, especially in Africa and Asia. Not surprisingly, there is also an increase in the percentage of patients with atypical presentations and atypical extra-pulmonary forms of TB. Extra-pulmonary organ involvement of TB is estimated as 10-15% of patients not infected with HIV whereas the frequency is about 50-70% in patients infected with HIV.

AT is one of the most prevalent forms of extrapulmonary disease. Peritoneal tuberculosis is a form of abdominal TB that involves the omentum, intestinal tract, liver, spleen, or female genital tract in addition to the parietal and visceral peritoneum. It accounts for about 1-2% of all cases of tuberculosis. Due to the non-specific course of the disease there are great difficulties in its diagnosis. Various methods of investigation have been reported as gold standards; however, there are great difficulties in clinical practice. As a result, the diagnosis of PT is still a challenge to the clinician.
PATHOGENESIS

PT is usually associated with a primary focus of tuberculosis elsewhere. This primary focus is usually the lung; however only about one third of cases have clinical or radiographic evidence of pulmonary tuberculosis. As in other forms of extra-pulmonary TB, fewer bacilli than those found in pulmonary disease are responsible for much greater damage. In addition, the paucity of bacilli may be combined with a relatively inaccessible or unknown site of extra-pulmonary TB infection, making laboratory confirmation very difficult.

The postulated mechanisms by which the tubercle bacilli can gain entry to the peritoneal cavity are: transmurally from diseased bowel, through lymph channels from infected abdominal lymph nodes, from tuberculous salpingitis, or, more commonly, by hematogenous spread from a pulmonary focus.

In PT, the peritoneum is studded with multiple yellow-white tubercles. It is thick and hyperemic with a loss of its shiny luster. The omentum is also thickened. Strictures may result from cicatrical healing of circumferential tubercular ulcers. Occlusive arterial changes may produce ischemia and also contribute to the development of strictures.

Mesenteric lymph nodes may be enlarged, matted and may caseate. Characteristic granulomas may be seen only in the mesenteric lymph nodes. This is especially common in patients who have taken antitubercular therapy for some time. The reverse, i.e., the presence of granulomas in the intestine and no granulomas in the draining lymph nodes is rare.

PT occurs in three forms: (1) wet type with ascites, (2) encysted (loculated) type with a localized abdominal swelling; and (3) fibrotic type with abdominal masses composed of mesenteric and omental thickening, with matted bowel loops felt as lumps in the abdomen. A combination of these types is also common.

CLINICAL FEATURES

Generally the onset is quite insidious, with more than 70% of patients having had symptoms for more than 4 months before definitive diagnosis. The most common symptoms are constitutional and include fever, anorexia, weakness, malaise, and weight loss. Abdominal distention caused either by ascites or by partial obstruction may be present. On examination, the abdomen is diffusely tender in the majority of patients; however, the classic doughy abdomen is rarely found. PT should be suspected in high-risk or immunocompromised patients with ascites, fever, unexplained generalized symptoms, and diffuse abdominal pain or tenderness.

DIAGNOSIS

Routine laboratory and radiographic studies are rarely diagnostic. A normal leukocyte count is present in most patients, and anemia is only variably found. Tuberculin skin tests are usually positive in patients with tuberculous peritonitis; however a negative result is of no help in excluding the disease. Radiographs of the abdomen are seldom of benefit; however, a CT-scan may be useful in identifying thickened bowel and ascites.

The diagnosis of tuberculous peritonitis is often suggested by findings at laparoscopy or laparotomy. Tuberculous peritonitis is characterized by stalactite-like fibrinous masses from the parietal peritoneum and, in addition, may be studded with small granulomas.

The differential diagnosis of tuberculous peritonitis is variable, depending on the acuteness of the symptoms. In patients with a prolonged history, tuberculous peritonitis is most commonly confused with Crohn’s disease or carcinoma. In patients presenting acutely, the differential diagnosis must include such entities as acute appendicitis, cholecystitis, perforated ulcer, and salpingitis.

Ascitic fluid examination

Conventional techniques

Examination of the peritoneal fluid may prove useful. In patients with tuberculous peritonitis, the ascitic fluid is straw colored with protein >3g/dl, and total cell count of 150-4000/µl, consisting predominantly of lymphocytes (>70%). The ascites to blood glucose ratio is less than 0.96 and serum ascites albumin gradient is less than 1.1 g/dl.

The yield of organisms on smear and culture is low. Staining for acid fast bacilli is positive in less than 3% of cases. A positive culture is obtained in less than 20% of cases, and it takes 6-8 wk for the mycobacterial colonies to appear. However, in an earlier study, cultures set after centrifugation of 1 liter of ascitic fluid showed 83% positivity.

Adenosine deaminase (ADA) is an aminohydrolase that converts adenosine to inosine and is thus involved in the catabolism of purine bases. The enzyme activity is more in T than in B lymphocytes, and is proportional to the degree of T cell differentiation. ADA is increased in tuberculous ascitic fluid due to stimulation of T-cells by
mycobacterial antigens. ADA levels were determined in the ascitic fluid of 49 patients by Dwivedi et al. the levels in tuberculous ascites were significantly higher than those in cirrhotic or malignant ascites. Taking a cut off level of 33 U/l, the sensitivity, specificity and diagnostic accuracy were 100, 97 and 98% respectively. In coinfection with HIV the ADA values can be normal or low. Falsely high values can occur in malignant ascites. High interferon-γ levels in tubercular ascites have been reported to be useful diagnostically. Combining both ADA and interferon estimations may further increase sensitivity.

Molecular techniques

In recent years, advances in molecular techniques have provided a new approach to the rapid diagnosis of tuberculosis by nucleic acid probes and PCR. The insertion sequence IS6110 has been successfully used as a target for PCR amplification in clinical samples by many investigators. The sensitivity and specificity of IS6110 amplification is variable in different laboratories and depends on the source of the clinical sample, the localization of the tuberculosis, the coexistence of HIV infection, and other technical parameters. DNA amplification of M. tuberculosis does not always mean viable bacilli, and the PCR result has to be evaluated in combination with other clinical and laboratory findings. Finally, response to therapy constitutes the definitive criterion for the diagnosis of PT and confirms the results of molecular analysis.

The nested PCR protocol used by our group can briefly be outlined as follows:

**DNA extraction:** Cells lysis and DNA extraction protocol is an important first step in obtaining PCR copies of M. Tuberculosis. We suggest a protocol that is based on Lysozyme, it is applicable for all human tissues suspected for TB infection and is efficient even when a paucity of bacilli are responsible for Tuberculosis manifestations.

**PCR protocols:** Among different PCR protocols and primers sets we suggest two protocols (one in-house “classic” nested PCR protocol and a second based on LightCycler technology) with high sensitivity and specificity. Both protocols amplify the same IS6110 sequence of M. Tuberculosis complex (GenBank X17348) and have similar sensitivity performing in DNA, extracted from the suspected M. Tuberculosis infected tissue (e.g. ascetic fluid, urine, pleural, pericardial or cerebrospinal fluid). However, in bone marrow aspiration material, the LightCycler assay is superior from the in-house amplification system, indicating thus 98% sensitivity.

**Ultrasonography**

Ultrasonography can be very useful for imaging PT. The following features may be seen, usually in combination.

1. Intra-abdominal fluid, which may be free or loculated; and clear or complex (with debris and septae). Fluid collections in the pelvis may have thick septa and can mimic ovarian cyst.
2. “Club sandwich” or “sliced bread” sign is due to localized fluid between radially oriented bowel loops, due to local exudation from the inflamed bowel (interloop ascitis).
3. Lymphadenopathy may be discrete or conglomerated (matted). The echotexture is mixed heterogeneous, in contrast to the homogenously hypoechoic nodes of lymphoma. Small discrete anechoic areas representing zones of caseation may be seen within the nodes. With treatment the nodes show a transient increase in size for 3-4 wk and then gradually reduce in size. Calcification in healing lesions is seen as discrete reflexive lines. Both caseation and calcification are highly suggestive of a tubercular etiology, neither being common in malignancy related lymphadenopathy.
4. Bowel wall thickening, best appreciated in the ileocaecal region.

**Computed tomographic scan**

Tubercular ascitic fluid is of high attenuation value (25-45HU) due to its high protein content. Strands, fine septae and debris within the fluid are characteristic, but are better appreciated on ultrasonography. Thickened peritoneum and enhancing peritoneal nodules may be seen.

Mesenteric disease on CT scan is seen as a patchy or diffuse increase in density, strands within the mesentery, and a stellate appearance. Lymph nodes may be interspersed. Omental thickening is often seen as an omental cake appearance. A fibrous wall, called the omental line, can cover the omentum, developing from long standing inflammation. An omental line is less common in malignant infiltration.

Caseating lymph nodes are seen as having hypodense centers and peripheral rim enhancement. Along with calcification, these findings are highly suggestive of tuberculosis. In tuberculosis the mesenteric, mesenteric root, celiac, porta hepatitis and peripancreatic nodes are characteristically involved, reflecting the lymphatic dran-
age of the small bowel. The retroperitoneal nodes are relatively spared, and are almost never seen in isolation, unlike lymphoma.29

**Laparoscopic findings**

Bhargava et al studied 87 patients with high protein ascites, of which 38 were diagnosed as having tuberculosis.30 They found visual appearances to be more helpful (95% accurate) than either histology, culture or guinea pig inoculation (82, 3 and 37.5% sensitivity respectively). Caseating granulomas may be found in 85-90% of the biopsies. The laparoscopic findings in peritoneal tuberculosis can be grouped into three categories:

1. **Thickened peritoneum with tubercles:** multiple, yellowish white, uniform sized (about 4-5mm) tubercles diffusely distributed on the parietal peritoneum. The peritoneum is thickened, hyperemic and lacks its usual shiny luster. The omentum, liver and spleen can also be studded with tubercles.

2. **Thickened peritoneum without tubercles.**

3. **Fibroadhesive peritonitis with markedly thickened peritoneum and multiple thick adhesions fixing the viscera.**

**TREATMENT**

Before the advent of chemotherapy, the mortality of tuberculous peritonitis was as high as 60%; now, the disease is, for the most part, readily curable with the available agents. All patients should receive conventional antitubercular therapy for at least 6 months including initial 2 months of rifampicin, isoniazid, pyrazinamide and ethambutol. A randomized comparison of a six-month short course chemotherapy with a 12-month course of ethambutol and isoniazid (supplement with streptomycin for the initial 2 wk) was conducted at the Tuberculosis Research Center, Chennai, in 193 adult patients. Cure rate was 99 and 94% in patients given short-course and the 12 month regimen respectively. However many physicians extend the treatment duration from 12 to 18 months.31

The recommended surgical treatment today is conservative.1 A period of pre-operative drug therapy is controversial. Strictures, which reduce the lumen by half or more and which cause proximal hypertrophy or dilatation, are treated by strictureplasty. This involves a 5-6 cm long incision along the anti-mesenteric side, which is closed transversely in two layers. A segment of bowel bearing multiple strictures or a single long tubular stricture may merit resection. Resection is segmental with a 5 cm margin.

Two reports suggest that obstructing intestinal lesions may relieve with antitubercular drugs alone without surgery. Anand et al reported clinical and radiological resolution of tuberculous strictures with drug therapy even in patients with subacute intestinal obstruction.32 They treated 39 patients with obstructive symptoms using medical therapy. At the end of one year 91% showed clinical improvement, 70% had complete radiological resolution and surgery was needed in only 3 cases (8%). Predictors of need for surgery were long strictures (>12cm) and multiple areas of involvement. Similar observations were made by Balasubramanian et al.33 The mean time required for the relief of obstructive symptoms was 6 months.

The most worrisome feature of the resurgence of tuberculosis has been the outbreaks of multidrug-resistant isolates that often fail to respond to both isoniazid and rifampicin, the two cornerstone antituberculosis drugs.34 However, data from a recent study indicate that multidrug-resistant tuberculosis is a curable disease, provided that an appropriate approach to control is implemented and that appropriate treatment protocols with second-line drugs are used.35

**REFERENCES**


