Peritoneal tuberculosis in the Fes University Hospital (Morocco)

Report of 123 cases

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SUMMARY

Aims — Peritoneal tuberculosis is an important public health issue in Morocco. Our aim was to describe the clinical, biological, and therapeutic features of peritoneal tuberculosis treated in a University Hospital in Morocco.

Patients and methods — We retrospectively included 123 patients with peritoneal tuberculosis diagnosed at the gastroenterology unit of the Fes University Hospital between January 2001 and August 2003.

Results — The mean age was 28 years with a clear female predominance (sex ratio 2.61). Ascites associated with fever were the most frequent signs found in 80.5% of patients. The ascitic fluid was exudative in 90% of cases and lymphocytic in 88%. The diagnosis was based on laparoscopy or laparotomy with peritoneal biopsy demonstrating caseating granulomatous lesions in 92.4% of patients. Patients were given antituberculous therapy for 6 months, and the outcome was favourable in 90%.

Conclusion — Peritoneal tuberculosis is very frequent in Morocco, where the diagnosis is based exclusively on peritoneal biopsies obtained during laparoscopy. With an adapted treatment, the course of the disease is favourable in most cases.

Introduction

While tuberculosis has become uncommon in developed countries despite the recent rise due to the AIDS epidemic, the disease is endemic in Morocco, causing a serious public health problem.

Peritoneal tuberculosis is the most frequent abdominal form, raising diagnostic difficulties related to polymorphic clinical presentations, nonspecific biological markers, minimally contributive bacteriology, and nonspecific radiographic signs.

In our country, a definite diagnosis of tuberculosis is established on examination of a laparoscopic peritoneal biopsy which allows ruling out other differential diagnoses, particularly peritoneal carcinomatosis. Treatment, which is entirely financed by the state, is part of a national anti-tuberculosis campaign designed to reduce significantly the incidence of tuberculosis in Morocco.

The purpose of this study was to assess the incidence of tuberculosis in the Hassan II University Hospital in Fes and to describe its clinical presentations, as well as management practices and difficulties.

Material and methods

This retrospective study included all cases of peritoneal tuberculosis diagnosed in the gastroenterology unit of the Hassan II University Hospital in Fes, Morocco, during a 32 month period from January 2001 to August 2003.

The diagnosis of peritoneal tuberculosis was established on the basis of epidemiological, clinical, biological, morphological and histological findings. History taking included a search for familial and personal history of tuberculosis, general signs of chronic disease (fever, nocturnal sweating, anemia, weight loss, and anorexia) and functional problems such as abdominal pain, transit disorders, and pathological amenorrhea. Presence of ascites, abdominal masses, and local signs of tuberculosis were noted.

A chest x-ray was obtained to search for pulmonary involvement and a bacteriological examination of sputum was requested in all patients with respiratory signs.

Laboratory tests included erythrocyte sedimentation rate, blood cell counts, transaminases, prothrombin time, and renal function tests.
An abdomen and pelvis ultrasound was performed in nearly all patients to verify the presence or absence of ascites and/or partitioning and to rule out potential ovarian disease.

In patients with ascites, an aspiration was performed for chemistry and cytobacteriology tests. Laparoscopy, or laparotomy in patients in whom laparoscopy was contraindicated, was performed to explore the abdominal cavity and obtain peritoneal biopsies to achieve a definite diagnosis.

In the event of pleural effusion, an aspiration biopsy was performed to avoid the need for laparoscopy or laparotomy.

The diagnosis of peritoneal tuberculosis was considered to be formally established when histological proof could be obtained from peritoneal samples (or pleural samples in the event of associated pleurisy: epithelioid and giant-cell granuloma with caseous necrosis). The diagnosis was considered very probable in the presence of a granuloma without caseous necrosis.

Once the diagnosis was established, patients were referred to specialized centers to receive free treatment.

The response to antimicrobial chemotherapy and clinical tolerance to treatment were followed up with clinical and biological parameters:

- None of the patients was removed from the analysis because of missing data, but the exact frequency of peritoneal tuberculosis associated with other localizations (pulmonary and extra-pulmonary) could not be established.
- Epi-Info was used to establish the data spread sheet where epidemiological, clinical, biological, radiological, endoscopic, histological, and therapeutic parameters were recorded.

### Results

During the study period from January 2001 to August 2003, 123 cases of peritoneal tuberculosis were identified, representing 6.1% of hospitalizations. Mean patient age was 28 years (range 2-66) with a significant female predominance (sex ratio 2.61). Contact with a contagious person was identified in 10.56% of patients and 3.25% had a personal history of tuberculosis involving lymph nodes (N = 2), the lung (N = 1), or the pleura (N = 1). None of the patients was considered to be immunodepressed due to immunosuppressive therapy, malignant hematological disease, or underlying neoplasia. Mean time from symptom onset to first visit for care was three months (range 20 days – 16 months). Mean delay to diagnosis (time from first visit to diagnosis) was 15 days (range 1 day – 1 month). These delays resulted to a large degree from difficulties in access to medical care in the Moroccan population.

Ascites with fever were the predominant signs (Table I). Non-specific biological findings are presented in Table II. C-reactive protein assay was not available in our center. Serum CA-125 assay was not performed in any of the patients and pelvic ultrasound alone was performed to rule out ovarian tumors. Exploratory ascites aspiration was a basic element of the etiological search but was performed in only 53 patients because of an availability problem in our hospital laboratory. Exsudative effusion was observed in 90% of cases and cytology was reported with a lymphocytic predominance in 88.67%. Search for tuberculus bacilli was not performed in any of the patients and adenosine desaminase assay was not available in Morocco at the time of this study.

A chest x-ray was obtained in all patients and was pathological in 34%. A pleural effusion was noted in 26 patients; and pleural biopsy was performed in six, which provided positive diagnosis in four. Lung parenchymal anomalies were found in 14% of patients and led to the search for tuberculosis bacilli in sputum, which was negative in all cases. Abdominal ultrasound was performed in 119 patients and demonstrated peritoneal effusion in all, free in 78% and partitioned in 22%.

Laparoscopy was performed in 76 patients, under local anesthesia in all, and visualized different aspects of the disease. Peritoneal biopsies were obtained in all patients. Pinhead peritoneal nodules were scattered throughout the peritoneum in 94.7% of patients; large nodules were unevenly distributed and found in 5.3% of patients. Intestinal perforations occurred in four patients who had a partitioned ascites not recognized on the abdominal ultrasound.

Exploratory laparotomy was performed in 39 patients, mainly in patients with a contraindication for laparoscopy (distended abdomen, history of abdominal surgery, partitioned ascites or agglutination visualized on ultrasound). Nodules were identified in 80% of patients, adherences in 90%, and loop agglutination in 28%.

Histological examination of the biopsy specimens (laparoscopy and laparotomy) confirmed the diagnosis, revealing caseating granulomas in 106 patients. An aspect compatible with peritoneal tuberculosis (giant cell and epithelioid granuloma without caseous necrosis) was noted in six patients while the histological examination was non conclusive in three.

Among patients who had undergone neither procedures (laparoscopy or laparotomy), the diagnosis of peritoneal tuberculosis was established on the basis of the pleural biopsy (N = 4) or concordant clinical findings (N = 4). These were cases where it was not possible to explore the peritoneal cavity.

In total, the diagnosis of peritoneal tuberculosis was formally established in 110 patients (granuloma with caseous necrosis on peritoneal or pleural specimens) and very probable in six (granuloma without caseous necrosis). In seven patients, the diagnosis was retained on the basis of epidemiological, clinical (fever, abdominal pain, abnormal liver tests), and therapeutic parameters.

### Table I – Main symptoms of peritoneal tuberculosis (N = 123).

<table>
<thead>
<tr>
<th>Clinical signs</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>99</td>
<td>80.5</td>
</tr>
<tr>
<td>Fever</td>
<td>61</td>
<td>50</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>95</td>
<td>77.2</td>
</tr>
<tr>
<td>Poor general health</td>
<td>89</td>
<td>72.4</td>
</tr>
<tr>
<td>Abdominal mass</td>
<td>5</td>
<td>4.1</td>
</tr>
<tr>
<td>Transit disorders</td>
<td>27</td>
<td>22</td>
</tr>
<tr>
<td>Menstrual disorders</td>
<td>9</td>
<td>7.3</td>
</tr>
</tbody>
</table>

### Table II – Main biological signs of peritoneal tuberculosis (N = 123).

<table>
<thead>
<tr>
<th>Biological signs</th>
<th>Number of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accelerated erythrocyte sedimentation rate</td>
<td>31/77</td>
<td>40</td>
</tr>
<tr>
<td>Hypochromic microcytic anemia</td>
<td>44/119</td>
<td>37</td>
</tr>
<tr>
<td>Hyperleukocytosis</td>
<td>13/119</td>
<td>11</td>
</tr>
<tr>
<td>Normal blood counts</td>
<td>62/119</td>
<td>52</td>
</tr>
<tr>
<td>Elevated transaminases</td>
<td>0/50</td>
<td>0</td>
</tr>
<tr>
<td>HIV positive</td>
<td>0/123</td>
<td>0</td>
</tr>
<tr>
<td>Exsudative peritoneal fluid</td>
<td>48/53</td>
<td>90</td>
</tr>
<tr>
<td>Lymphocytic ascitic fluid</td>
<td>47/53</td>
<td>88.7</td>
</tr>
</tbody>
</table>
amplification by polymerase chain reaction (PCR), can detect

Once the diagnosis was retained, anti-tuberculosis treatment was instituted in all patients. 94% of patients were given a three-drug regimen for six months combining rifampicin (R) 10 mg/kg/d, isoniazide (H) 5 mg/kg/d, and pyrazinamide (Z) 30 mg/kg/d. According to the protocol RHZ was given for two months, then RH for four months. The other patients were given three-drug regimens using other combinations with streptomycin or ethambutol (in the event of associated pleuropulmonary tuberculosis).

Outcome was favourable in 90% of patients. The clinical condition (weight, temperature, physical examination) was assessed at two and six months of treatment. In one patient, transaminase levels increased 20 fold on day 15 of treatment then regressed spontaneously, returning to normal within one month.

Discussion

Peritoneal tuberculosis is a common disease in underdeveloped countries and is the cause of 20-50% of all cases of ascites [1-3]. In Morocco, peritoneal tuberculosis is a major public health issue because of its prevalence and the expenditures required for the diagnosis and treatment. In industrialized countries, a revival of tuberculosis has been observed in recent years in parallel with the HIV epidemic [3-7], unfavorable living conditions of immigrants and expatriates [2, 8, 9] and use of anti-TNF for broader and broader indications [7]. Peritoneal tuberculosis is the most frequent form of abdominal involvement [2, 7] and in Morocco, is the second leading localization of extra-pulmonary disease after lymph node involvement. Peritoneal tuberculosis is observed predominantly in women [1, 10] as was noted in our series. This is in contrast with the situation in developed countries where male predominance resulting from the presence of immigrants in the workforce [11]. The disease is generally observed in young adults in the third or fourth decade [12]. In our series, mean age was 28 years. Clinicians should search for a personal history of tuberculosis and a contagious context, particularly in Morocco and in other endemic areas.

The clinical presentation was generally with ascites and fever associated with abdominal pain and poor general health [11-17]. In our center, tuberculosis is the second leading cause of ascites after cirrhosis. It should be noted that certain misleading clinical presentations [1, 10, 18] can be limited to abdominal pain, persistent fever and unexplained poor health. Other "pseudo" surgical forms can mimic appendicitis, cholecystitis, intestinal obstruction or acute peritonitis [1, 10].

There is no specific biological marker for peritoneal tuberculosis. An inflammatory syndrome, with hyperleukocytosis, accelerated erythrocyte sedimentation rate, and elevated C-reactive protein with hypochromic microcytic anemia is common. The tuberculin skin test, which was not performed in our patients, is positive in 40 to 85% of patients, depending on reports [1-4], and does not contribute to diagnosis. Study of the ascitic fluid can be helpful; this is usually an exudative effusion with predominantly lymphocytes [3, 8]. In our series, 90.5% of patients presented with an exudate and 88.67% showed hyperleukocytosis. The tuberculosis bacillus is identified on direct examination of the ascitic fluid in only 5% of patients [2, 19] and culture on Lowenstein medium is crucial for diagnosis if positive but cultures require several weeks to grow, retarding the diagnosis and treatment [19]. We did not search for tuberculosis bacillus. More recently developed techniques, such as genetic amplification by polymerase chain reaction (PCR), can detect

Mycobacterium tuberculosis in peritoneal fluid in 24 to 48 hours but routine application is a topic of debate due to its cost considerations and its low sensitivity, to the order of 60-80% [20-23]. At the present time, several studies have emphasized the importance of assaying adenosine deaminase (ADA) activity in ascitic fluid using a simple noninvasive technique. The diagnostic values are excellent (98% specificity, 96% sensitivity, 95% positive predictive value and 98% negative predictive value) [19, 24, 25]. Diagnostic yield is also excellent with interferon-γ assay, for which Sathar et al. have reported 93% sensitivity, 96% specificity, 93% positive predictive value and 96% negative predictive value [24]. LDH assay in ascitic fluid is a sensitive test (90% for > 90 IU/L) but poorly specific (14%) [26]. Serum CA-125 is often elevated, raising the question of the differential diagnosis with ovarian cancer [27, 28]. Unfortunately, all of these new noninvasive methods are currently unavailable in Morocco where laparoscopy remains the principal diagnostic tool for diagnosing peritoneal tuberculosis.

Ultrasonographic and computed tomographic explorations of the abdomen and pelvis are non specific and contribute little to the diagnosis. These imaging methods can demonstrate the presence of more or less partitioned peritoneal effusion, lumboaortic and peritoneal nodal enlargement and infiltration of the bowel loops [29-32]. Association of ascites, adherences, peritoneal deposits and thickening is highly suggestive of tuberculosis [31]. A chest x-ray should be performed in all patients to search for active pleuropulmonary lesions or sequelae which could provide diagnostic clues since active pulmonary tuberculosis is associated with peritoneal tuberculosis in 4 to 50% of patients [2, 11].

Peritoneal tuberculosis remains, in our country, a difficult differential diagnosis, mainly with peritoneal carcinomatosis. Thus in Morocco, laparoscopy remains an indispensable tool for establishing a definite diagnosis. This method has the advantage of providing an immediate diagnosis in the majority of patients with a doubtful presentation, well before the results of bacteriological samples are known. A review of the literature shows that peritoneal deposits are the characteristic gross aspect, observed in 66 to 100% of patients. Adherences are seen in 13 to 80% and an inflammatory peritonitis in 21 to 79% [7, 33-36]. Such aspects are highly suggestive but are not specific since pseudo tuberculosis forms of peritoneal carcinoma and pseudo carcinomatous forms of peritoneal tuberculosis are described [34, 37]. This is why laparoscopic biopsies are required to confirm the diagnosis when a tuberculoid or giant-cell granuloma is associated with caseous necrosis or when the tuberculosis bacillus is demonstrated by the Ziehl-Nelson test on histological sections [34]. The risk of complications of laparoscopy, generally less than 3% [38], is related to intestinal perforations and bleeding due to injury of the great vessels [16, 17]. Fatal cases have been reported in the literature [39]; the current mortality is to the order of 1.25%. Thus to minimize risks and complications, we recently opted for open laparoscopy in patients with partitioned ascites recognized ultrasonographically, especially in patients with adherences which can jeopardize insertion of the laparoscope. Certain authors however prefer to resort to exploratory laparotomy for fibro-adhesive forms since the risk of perforation is high [7, 34]. In our series, we used laparotomy for 31% of patients; compared to Hammad et al. [10] for 13% and Piéron et al. [15] for 4.5%. More recently certain authors have proposed radioguided peritoneal biopsies using ultrasound or computed tomography. This would enable histological proof with a method much less invasive than laparoscopy [19, 40]. The indications are however limited and include very large peritoneal lymph node, peritoneal thickening, and an abdominal mass.

In Morocco, treatment of tuberculosis is part of a national anti-tuberculosis campaign [41]. A standardized treatment is provided free of charge for outpatients not requiring hospitalization. Five drugs are used: rifampicin (R), isoniazide (H), pyrazinamid...
namicid (Z), ethambutol and streptomycin. The therapeutic scheme currently advocated in two months of RHZ followed by four months of RH; 94% of our patients were given this regimen. If bacteriological samples are positive or if the presentation is particularly serious or life threatening (miliary tuberculosis, multifocal tuberculosis, immune deficiency), four anti-tuberculosis drugs may be associated (streptomycin, rifampicin, isoniazide and pyrazinamide) 6 to 7 days for eight weeks, then two drugs (rifampicin and isoniazide) for seven months for the severe forms and four months for patients with Mycobacterium tuberculosis positive sample. In our series, none of the patients were given corticotosteroids. The efficacy of corticosteroid therapy is a matter of debate [42]. The clinical course is generally favourable in treated patients and cure is obtained in the vast majority [13]. Death is generally due to disseminated disease in patients seen at an advanced stage. Late complications, particularly if diagnosis and treatment are delayed, include peritoneal fibrosis and adherences which can lead to ureteral stenosis, intestinal obstruction, ectopic pregnancy and sterility in women [7, 13].

In conclusion, despite an ongoing national anti-tuberculosis campaign, peritoneal tuberculosis remains a common disease in Morocco. It is generally observed in young subjects and is favored by poor socioeconomic conditions independently of the subject’s immune status. The clinical polymorphism, with the dominant symptom of ascites, raises the problem of a difficult differential diagnosis with peritoneal carcinomatosis. Classical biological and radiographic tests are not specific and contribute little to the diagnosis. Laparoscopy with peritoneal biopsies remains the indispensable method for establishing a definite diagnosis of peritoneal tuberculosis in our country where new diagnostic tools (adenosine deaminase, interferon-γ, LDH) are not available.

In Morocco, the state provides anti-tuberculosis treatment free of charge for all patients and the delay to diagnosis is relatively short. Outcome is generally favourable. Peritoneal tuberculosis can thus be considered as a benign condition despite its frequency and the high cost of treatment.

REFERENCES


