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Research article

Interest of First Laparoscopy in the Etiological Diagnosis of Isolated Exudative Ascites

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Abstract

The purpose of this research article was to determine the contribution of performing laparoscopy first in the etiological diagnosis of isolated exudative ascites. Our retrospective descriptive study had been performed over 15 years and included 46 patients who had undergone exploratory laparoscopy for exudative ascites. The average age of the patients was 52 years. Biological and morphological examinations contributed to making the etiological diagnosis. Therefore, diagnostic laparoscopy was indicated. Peritoneal carcinomatosis and tuberculosis were the most common causes seen in 34.2% and respectively 65.8% of cases. Visual laparoscopic diagnosis was peritoneal carcinomatosis in 16 cases and peritoneal tuberculosis in 28 cases, indecisive in one case and biliary ascites in one case. The histological diagnosis was peritoneal tuberculosis in 24 cases and peritoneal carcinomatosis in 12 cases and there were 9 cases of rare diagnoses. Peritoneal biopsies were negative in 2 cases for which the etiological diagnoses were kidney failure in one case and hypothyroidism in the other case. The postoperative recovery was simple in 42 cases (91.3%). The complications were: an accidental rupture of the left diaphragmatic dome in one case (2.1%), gastrointestinal bleeding in the immediate postoperative period in two cases (4.2%) and infected ascites in one case (2.1%). The post-operative scapular pain was reported in 4.2% of our patients. Operative mortality in our patients was nil. The overall care had an average cost of 1685.7 dinars for each of our patients, with extremes ranging from 1055.7 to 3605.7 dinars. For patients with isolated exudative ascites that should have been explored through laparoscopy first, the average cost would be 130.1 dinars, with a material gain for each of 1555.6 dinars. This attitude could also allow a reduction in the mean hospital stay (which was 27 days to few days) associated with early treatment. Our study confirms the interest in laparoscopy first with peritoneal biopsies as part of the etiological diagnosis of isolated exudative ascites.

Keywords : ascite, laparoscopy, peritoneal carcinomatosis, peritoneal tuberculosis

Highlights

- ✓ Literature data and our study confirms the feasibility and interest of laparoscopy with peritoneal biopsies in the etiological diagnosis of isolated exudative ascites.
- ✓ This methods still remains an invasive examination, so that it would be necessary to introduce the micro-laparoscopes in order to reduce possible complications.

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Introduction

Depending on the level of proteins, two types of ascites can be distinguished: transudative ascites defined by a protein content of less than 25g /l and exudative ascites defined by a protein content greater than 25g / l (1). Exudative ascites (EA) is a common clinical entity that has several etiologies. The usual EA diagnostic procedure involves physical examination, biological examinations (blood and ascites) and morphological examinations. This procedure may identify the cause of ascites in the majority of cases.

However, the origin of EA may remain unknown after a usual diagnostic procedure and further invasive explorations will be needed.

Isolated EA of indeterminate origin is dominated by tuberculosis and peritoneal carcinomatosis that require early diagnosis and management. Both diagnoses require histological confirmation. Biopsies can be obtained by several invasive means including classically interventional imaging, laparoscopy and laparotomy.

The purpose of this work was:

- to determine the interest in performing laparoscopy first in isolated EA of indeterminate origin
- to identify the different laparoscopic aspects and their possible complications
- to study the cost / benefit ratio of performing laparoscopy first in the case of isolated EA.

Materials and Methods

We report a descriptive retrospective study conducted in the Department of Hepato-Gastro-Enterology within "Fattouma Bourguiba Monastir" Hospital between January 2000 and December 2014 including all cases of EA of indeterminate etiology who underwent diagnostic laparoscopy in the surgical department of the same hospital.

The 46 patients included in the study were those whose definitive diagnosis had not been retained or remained doubtful after an exhaustive exploration including an interrogation with a complete examination, a tuberculosis assessment (tuberculin intra-dermal reaction (IDR), chest X-ray, search for Koch bacillus (KB) in the sputum, urine and ascites), an ascites paracentesis (biochemical tests, search of germs, cytology with search of neoplastic cells, culture of ascites fluid).

Additional blood tests (blood count, inflammatory and tumor markers) were endoscopic examinations (upper fibroscopy, colonoscopy) and radiological examinations (abdominal-pelvic ultrasound, thoracic-abdominal-pelvic computed tomography (CT)).

The data entry and the statistical analysis were performed using SPSS software version 20.0:

- For the descriptive study, we calculated simple and relative frequencies, averages and medians.
- For the analytical study, we used the Pearson chi-square test to compare percentages and the student test to compare averages.
- For all tests, a P value of < 0.05 was taken as statistically significant.

Results

I-Patients' characteristics

Out of the 152 patients hospitalized with exudative ascites, 46 had an indeterminate origin and were included in our study. There were 25 women (54%) and 21 men (45%) with a sex ratio of 0.84. The mean age of the patients was 52 years with extremes ranging from 21 to 80 years. No patient had a family history of tuberculosis or neoplasia.

Abdominal pain, weight loss and asthenia were the most common symptoms seen in 23, 19 and 17 cases, respectively. Ascites was present in all patients. Fever (8 cases) and edema of the lower limbs (6 cases) were the two most common physical signs.

Fever and night sweats were significantly more common during peritoneal tuberculosis ($P = 0.02$). The main functional and physical signs are summarized in Table 1 according to the etiology.

II- Characteristics of ascites fluid

Ascites was lymphocytic in 44 cases (95.6%) and mixed in 2 cases (4.4%). The search for neoplastic cells was positive in 5 cases. A predominantly lymphocytic ascites fluid was significantly reported in tuberculosis and peritoneal carcinomatosis ($p < 0.001$). Direct examinations, research for KB and ascites culture were negative in all cases. The KB polymerase chain reaction (PCR) was not performed in any patient.

III- Biological explorations

The CA-125 level was high in 7 cases: 5 cases were peritoneal carcinomatosis (3 ovarian tumors, one biliary-pancreatic adenocarcinoma and 1 mammary tumor), one case of peritoneal tuberculosis and one case was kidney failure. IDR was positive only in 7 cases of tuberculosis. The search for KB in sputum and urine was negative in all cases. Quantiferon was requested once, but the result was not available. Five patients had pleurisies; the search for KB in the pleural fluid was negative.

Table 1. Comparison of the prevalence of functional and physical signs according to etiology

Functional signs	Peritoneal tuberculosis	Peritoneal carcinomatosis	Other diagnoses	Significance (p)
Asthenia	12	3	2	0.73
anorexia	5	4	1	0.62
Thinning	13	5	1	0.45
Abdominal pain	19	3	1	0.56
Night sweats	10	2	1	0.02
Fever	5	2	1	0.02
Transit disorders	6	4	2	0.42
Ascites	24	13	9	-
Abdominal mass	0	1	0	-
Axillar lymphadenopathy	2	1	0	-

IV - Morphological examinations

1- Chest X-ray was pathological in 5 cases, revealing pleurisy in 4 cases of peritoneal tuberculosis and in one case of peritoneal carcinomatosis.

2- The ultrasound abnormalities were: Peritoneal thickening in 9 cases, peritoneal nodules in one case, intra-abdominal lymphadenopathy in 3 cases and ovarian tissue mass in 2 cases.

3- The thoracic-abdominal-pelvic CT was performed in 45 patients. The radiological diagnosis was in favor of peritoneal carcinomatosis in 5 cases and not contributory in 40 cases (89.1%). The only predictive factor of CT peritoneal carcinomatosis was epiploic cake (P = 0.01). Table 2 summarizes the different CT aspects in the different groups.

4 – The upper fibroscopy was normal in all patients.

5 – Colonoscopy: It was normal in 40 cases. It revealed sigmoid polyps in 6 cases (biopsy concluded that there was low-grade dysplasia in 4 cases and high-grade dysplasia in 2 cases).

Table 2. Scanographic **Aspects**

Scanographic aspects	Peritoneal tuberculosis	Peritoneal carcinomatosis	Other diagnoses	Significance (P)
Thoracic nodules	5	3	0	0.27
Pleurisy	5	4	0	0.27
Mediastinal lymphadenopathy	6	0	0	0.2
Hepatic nodules	1	0	1	0.27
Peritoneal thickening	7	4	2	0.21
Peritoneal nodules	4	2	0	0.38
Intra-abdominal lymphadenopathy	4	2	1	0.74
Peritoneal cake	1	3	0	0.01
Visible ovaries	12	7	4	0.33
Tissular ovarian mass	0	2	0	0.23

V- Laparoscopy

The average time between hospitalization and laparoscopy was 27.3 days, with extremes ranging from 6 to 90 days. Laparoscopy was normal in one case. It was pathological in 45 cases. The main elementary lesions are summarized in Table 3.

Peritoneal nodules had a sensitivity and specificity in peritoneal carcinomatosis of 92.3% and 63.6% respectively, and had a Positive Predictive Value (PPV) and a Negative Predictive Value (NPV) of 50% and 95.4% respectively.

Peritoneal granules had a sensitivity and specificity in peritoneal tuberculosis of 29.1% and 90.9%, respectively, and had a PPV and a NPV respectively of 77.7% and 54%. Granules, peritoneal hyperemia, adhesions and agglutination of the digestive loops were significantly related to peritoneal tuberculosis (p varies between 0.01 and 0.04).

The visual diagnosis was peritoneal carcinomatosis in 16 cases, and peritoneal tuberculosis in 28 cases. The visual aspect was inconclusive in one case.

Peritoneal biopsies were systematic (46 cases). Hepatic biopsies were performed in 9 patients with suspicious laparoscopic lesions. Ovarian biopsy was performed in the four patients whose ovaries were considered pathological.

The average time between hospitalization and final diagnosis was 29.2 days, with extremes ranging from 9 to 97 days.

The histological diagnosis is summarized in Table 4.

Table 3. Laparoscopic aspects

Laparoscopic aspects	Peritoneal tuberculosis	Peritoneal carcinomatosis	Other diagnoses	Significance (p)
Peritoneal nodules	10	12	2	0.03
Peritoneal granules	7	1	1	0.03
Adhesiveness of digestive loops	12	4	3	0.03
Peritoneal hyperemia	3	4	0	0.01
Intestinal loops agglutination	5	2	1	0.04
False membranes	4	1	1	0.68

Table 4. Histological diagnoses

Histological diagnosis	Number of cases
Mesothelioma	**1**
Peritoneal carcinomatosis	**12**
Ovarian origin	4
Digestive origin	4
Pancreatic	2
Colic	1
Gastric	1
Mammary origin	2
Undetermined origin	2

Table 4. Histological diagnoses	
Peritoneal tuberculosis	**24**
Nonspecific inflammation	**3**
Steatonecrosis	**2**
Biliary ascites (biliary fistula)	**1**
Eosinophilic ascite	**1**
Normal biopsies	**2**
Hypothyroidism	**1**
Chronic renal failure	**1**

Postoperative consequences:

Postoperative follow-up was simple in 42 cases (91.3%).

An accidental rupture of the left diaphragmatic cupola was reported in one case (2.1%) that was sutured. Hemorrhagic complications were noted in two cases (4.2%). Ascites fluid infection was noted in one case (2.1%).

Postoperative scapular pain was reported in 4.2% of our patients. The average length of postoperative stay was 32.54 hours with extremes ranging from 24 to 96 hours. Operative mortality in our patients was nil and morbidity was 8.6%.

VI- Patients' care cost

Our patients were subjected to a range of biological, radiological and surgical explorations to determine the etiological diagnosis during a hospitalization period ranging from 9 to 94 days. The average cost was 1685.7 dinars for each patient with extremes ranging from 1055.7 to 3605.7 dinars.

For patients who had isolated EA without any call signs: if they underwent direct exploration through laparoscopy preceded by a general pre-anesthesia check-up, the average cost would be 130.1 dinars, with a material gain of 1555.6 dinars for each patient. This attitude would also allow a reduction in the hospitalization period associated with early management.

Discussions

EA of indeterminate origin is dominated by tuberculosis and peritoneal carcinomatosis seen in 34.2% and 65.8% of cases respectively (1). In our series, carcinomatosis and peritoneal tuberculosis were found in 28.2% and 52.1% of cases respectively.

In these different situations, several invasive means are used such as percutaneous peritoneal biopsy with or without radiologic guidance, laparoscopy and laparotomy.

Ascites is the most common finding of peritoneal carcinomatosis seen in 70% of cases (2).

The search for malignant cells in ascites is the first step in the etiological diagnosis. However, its sensitivity is low, varying between 40 and 60% even when examining a significant amount of fluid greater than 500 ml (3). In our series, the search for neoplastic cells was positive in 5 cases (38.4%).

Tumor markers in the blood are commonly requested in the diagnostic approach of ascites. Nevertheless, these markers lack specificity. CA-125 is frequently used as a marker for epithelial ovarian cancer. However, its specificity is weak. It can be elevated in many benign and malignant diseases such as endometriosis, pelvic inflammatory diseases, peritoneal tuberculosis, endometrial, pancreatic, colon, breast, liver and lung cancer (4).

Different means of imaging (ultrasound, CT, magnetic resonance imaging) have only a very limited place in the

etiological diagnosis of exudative neoplastic ascites (5). The sensitivity of imaging for peritoneal carcinomatosis diagnosis is mediocre. It only detects nodules whose size is greater than 5 mm (6, 7).

Peritoneal tuberculosis accounts for 1 to 2% of all cases of tuberculosis (8).

Morphologically, peritoneal tuberculosis can occur in three different forms: ascitic, fibro-adhesive and dry. The ascitic form is the most common (90% of cases) (9).

Peritoneal tuberculosis can occur at any age with a peak frequency between 35 and 45 years. The average age of our patients was within the limits of this interval (10).

Peritoneal tuberculosis can simulate advanced ovarian cancer (11). Clinically, pelvic pain, ascites and weight loss can predict these two pathologies (12). CA-125 can also be elevated in peritoneal tuberculosis (13).

Apart from radiological examinations, other non-invasive exams are used for diagnostic purposes such as: the positivity of the IDR is not specific for active tuberculosis, but demonstrates prior contact with KB.

Its interpretation varies according to the immune state of the patients, the history of vaccination, contagion or primary infection. IDR has a sensitivity that is often low, but ranges widely from 24 to 100% and has false negative values ranging from 15 to 60% (10).

In our series, the sensitivity of the IDR is 41% and has a NPV of 56%.

The direct examination of KB in ascites is disappointing with a sensitivity of less than 10% in most series. Ascites cultivation demonstrates KB in less than 20% of cases, mycobacterial colonies appear after 6 to 8 weeks (10, 14). This diagnostic delay increases mortality in this group of patients (15, 16). In our series, direct examination and culture of ascites to search for KB were negative in all cases. The Quantiferon test is not contributory to tuberculosis diagnosis in an immune-compromised patient. The specificity and sensitivity of Quantiferon ranged respectively from 73 to 97% and from 63 to 91%. (17, 18). Other tests (dosage of adenosine deaminase activity in ascites, PCR of BK in the ascites fluid, the gene amplification reaction by Ligase Chain Reaction in ascites) are not available in our country.

There are 3 invasive ways to access the peritoneal cavity: radiologically guided biopsy, laparotomy and laparoscopy.

1-Biopsies under radiological control:

In the Vardareli et al series (19) comprising 19 patients with peritoneal tuberculosis, radiologically controlled biopsies showed caseous granulomas in 17 cases (89%) and non-caseous granulomas in 2 cases. There were no complications in this series.

In the series of Nouira, 11 patients had peritoneal nodules greater than 0.5 cm with abundant ascites. These patients had a biopsy of peritoneal nodules under ultrasound control. The sensitivity was 81%. Out of the 11 cases, 7 cases had peritoneal tuberculosis, 2 cases had peritoneal carcinomatosis, and in 2 other cases the biopsy was not conclusive and laparoscopy was indicated (20).

2- Laparotomy

In peritoneal tuberculosis, laparotomy was once the only means to confirm the diagnosis. However, it is accompanied by high morbidity and mortality (11, 21). Several postoperative complications are possible, such as hemorrhage, infection, adhesions and postoperative disemboweling (22).

3- Laparoscopy

It has a sensitivity of 92 to 100% and a specificity of 84 to 100% (10).

Peritoneal biopsies are the gold standard for the definitive diagnosis by revealing a tuberculoid granuloma or giant-cell granuloma associated with caseous necrosis (10, 20). Zhiel Nelson Staining and culturing of the biopsy fragments should always be performed in search of KB (23). Caseous necrosis is not a constant histological sign; it is absent in 10% of the cases (24).

In our series, caseous necrosis was present in 17 patients only (70.8 %).

Isolated giant-cell granuloma is nonspecific. It can be observed in other pathologies such as sarcoidosis and vasculitis. However, because of the rarity of these conditions, the clinical context and the macroscopic aspect, it is possible to indicate tuberculosis at first; this diagnosis will be retained after the therapeutic test (24). Culture is positive in more than 90% of the cases (25).

Laparoscopy has a PPV in the diagnosis of peritoneal carcinomatosis of 100% and a NPV of 86% (26).

In our series, visual diagnosis was in accordance with the histological diagnosis (69%) in 9 cases of peritoneal carcinomatosis. Visual diagnosis had a sensitivity and specificity of 69.2 and 81.8%, respectively. It had a PPV of 60% and a NPV of 87%.

Conclusions

EA often has a problem of etiological diagnosis. The purpose of our work was to determine the contribution of performing laparoscopy first in the diagnosis of isolated EA of indeterminate origin.

Our patients were subjected to a range of biological, radiologic and surgical explorations to determine the etiological diagnosis of EA during a period of hospitalization ranging from 9 to 94 days with an average cost of 1685.7 dinars for each patient.

Our study confirms the feasibility and interest in performing laparoscopy first with peritoneal biopsies in the etiological diagnosis. However, it remains an invasive examination, hence it is interesting to introduce micro-laparoscopes in our centers in order to reduce the complications and make its realization possible on an outpatient basis under local anesthesia.

In our series, tuberculosis was a frequent cause of EA. Additional efforts must be made to fight this disease which has been on the rise lately.

Abbreviations

CA 125: cancer antigen 125
CT: computed tomography
EA: Exudative Ascites
G/l: gram per liter
IDR: tuberculin intra-dermal-reaction
KB: Koch Bacillus
NPV: Negative Predictive Value
PCR: Polymerase Chain Reaction
PPV: Positive Predictive Value

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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