Inflammatory pseudo-tumor of the liver: is pre-operative diagnosis possible?

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SUMMARY

Objectives — To specify the circumstances of detection and the clinical, biological, radiological and pathological features of inflammatory pseudo-tumors, in order to improve preoperative diagnosis.

Methods — Diagnosis of inflammatory pseudo-tumors of the liver was performed on surgical specimens in 8 patients from January 1987 to January 2001. We retrospectively analyzed the clinical, biological, radiological and pathological features of these 8 inflammatory pseudo-tumors.

Results — All the patients (5 females and 3 males) presented a chronic infectious syndrome and/or previous history of chronic inflammatory disease. The correlation between biological, radiological and pathological aspects showed two distinctive types of inflammatory pseudo-tumors: a type revealed by a biological inflammatory syndrome, with a non encapsulated, heterogeneous and hypervascular lesion at imaging, and a dense fibroblastic inflammatory pseudo-tumor with portal endophlebitis on histology (n = 5), and a type without inflammatory syndrome, with an encapsulated, homogeneous, hypovascular lesion at imaging and abundant necrosis on histology (n = 3).

Conclusion — The analysis of previous history, of clinical, biological and radiological presentations, specially MRI, could predict the diagnosis of inflammatory lesion which must be confirmed by transperial biopsy to avoid inappropriate radical hepatectomy.

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Introduction

According to the World Health Organization (WHO) definition [1], inflammatory pseudotumors of the liver are more or less fibrotic fibroblastic proliferative reactions infiltrated with polymorphous inflammatory cells (plasma cells, lymphocytes, histiocytes). Liver lesions described as inflammatory pseudotumors thus include very different clinical and morphological entities, which in some cases mimic chronic abscess formations or fibroblastic tumors in others. These lesions are rare. Since the first description of inflammatory pseudotumors of the liver by Pack and Baker [2] in 1953, about sixty cases have been reported in the literature. Authors have used different sometimes ambiguous terms: plasma cell granuloma, myofibroblastic inflammatory tumor, histiocytoma, fibroxanthoma, pseudolymphoma.

Dendritic follicular cell tumors of the liver, which are sometimes erroneously termed inflammatory pseudotumors in the literature, are currently recognized as authentic neoplastic proliferations with precise and distinct histological and immunohistological characteristics [3]. These tumors, which constitute one of the main differential diagnoses of inflammatory pseudotumors of the liver, are thus not included in this study.

In routine practice, preoperative diagnosis of inflammatory pseudotumor of the liver is a difficult task. Certain diagnosis is rarely made before surgery because the radiological presentation is often suggestive of a malignant process.

The purpose of this retrospective analysis was to study eight cases of inflammatory pseudotumors of the liver examined at the Beaujon hospital and to describe the circumstances of diagnosis as well as the characteristic biological and radiological features. We studied the macroscopic and microscopic aspects of the tumors and searched for correlations with the radiographic findings.

Material and methods

From January 1987 to January 2001, the diagnosis of inflammatory pseudotumor of the liver was established in eight patients who underwent surgery for a liver tumor: suspected malignancy N = 6, uncertain diagnosis N = 2. Case reports concerning patients n° 6, 7, and 8 have been published elsewhere [4]. During this same period, 858 patients underwent hepatectomy for hepatocellular carcinoma. The clinical files of these eight patients were examined retrospectively. We noted the medical and surgical history, the clinical presentation at the time of diagnosis (functional and general signs), and results of laboratory tests. The presence of a biological inflammatory syndrome, defined as significant elevation of erythrocyte sedimentation rate, C reactive protein (CRP) and white cell count as well as abnormal liver function tests, was noted.

The preoperative imaging data available for each patient were reviewed by a radiologist (VV). Ultrasonography had been performed in all patients and computed tomography (CT) with and without contrast injection was available for 7 of the 8. Magnetic resonance imaging (MRI) had been performed in three patients. The radiological analysis defined the size, localization and contours of the tumor. The presence or not of a capsule, the ecostructure, and any involvement of adjacent portal vessels on the CT and MRI documents was noted.

The pathology materials were reviewed retrospectively by two pathologists (AAAT, DCH) who noted the size, number, and gross aspect of the lesions, their limits and the presence of a capsule (complete or not). Six blocks on average were used for the microscopic analysis. Cell composition was assessed semiquantitatively (respective densities of each cell type: lymphocytes, plasma cells, polymorphonuclear neutrophils, histiocytes, fibroblasts). The presence of collagen fibrosis within the lesions was noted.

Vessel density in the center of the lesions was evaluated semiquantitatively using immunohistochemistry endothelial cell labeling. The presence of portal endophlebitis within the lesion or peripherally was noted. Steatosis in the adjacent hepatic tissue was expressed in percent hepatocytes involved and portal fibrosis was expressed using the METAVIR classification system for viral hepatitis. Periodic acid Schiff (PAS), Grocott, Gram and Ziehl stains were used to search for bacterial contamination.

An immunohistochemistry study on paraffin embedded slices was performed to confirm the benign nature of the tumor and describe the cell composition.

The following antibodies were used for the immunohistochemistry study: anti-cytokeratin (Immuneclone, clone KLI, dilution 1/1000) for epithelial cells, anti-vimentin ( Dako, clone V9, dilution 1/500) for connec-

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tive tissue components, anti-desmin (Dako, clone D33, dilution 1/500) for smooth and striated muscles, smooth muscle anti-actin (Dako, clone 1A4, dilution 1/500) for smooth muscle cells and myofibroblasts, anti-protein S100 (Immunotech, polyclonal, dilution 1/100) for nerve cells, anti-CNA42 (Dako, clone KION CNA42, dilution 1/400) and CD35 (Dako, clone Ber-MAC-DRC, dilution 1/100) for dendritic follicular cells, CD20 (Dako, clone L26, dilution 1/500) for B lymphocytes, anti-Kappa and Lambda (Chemical Credential, polyclonal, dilution 1/2000) for immunoglobulin secreting cells, CD3 (Dako, polyclonal, dilution 1/500) for T lymphocytes, CD68 (Dako, clone KP1, dilution 1/500) for histiocytes, CD34 (Immunotech, clone QBEND10, dilution 1/500) endothelial cells and anti-ALK 1 (Anaplastic Lymphoma Kinase) (Dako, clone ALK 1, dilution 1/50). Anti-LMP-1 (Dako, clone CS1, CS2, CS3, CS4, dilution 1/50). Anti-LMP-1 (Dako, clone CS1, CS2, CS3, CS4, dilution 1/50) and hybridation in situ with an EBER cold probe (routine paraffin block slice method) were used for the immunohistochemistry search for Epstein-Barr virus (EBV).

Results

The clinical and biological characteristics of the eight patients are presented in Table I. There were five women and three men, mean age 46 years (range 26–67). Seven patients were symptomatic: abdominal pain in six with low-grade fever in four of them, and isolated fever in one. A biological inflammatory syndrome was present in four patients associated with anicteric cholestasis in three. Anicteric cholestasis without an inflammatory syndrome was also observed in one patient (n° 3). Three patients had a history of chronic infection or inflammation: tuberculosis, pyelonephritis, and lower limb phlebitis in a context of disseminated lupus erythematosus. One patient had concomitant cancer of the colon with peritoneal carcinomatosis.

Imaging data are summarized in Table II. Briefly, all lesions were subcapsular, hypoechoogenic, and hypodense on CT without contrast injection. Peripheral contrast uptake was visible on six of the seven available contrast CTs, four of which revealed heterogeneous enhancement of the lesion. For the three patients who had an MRI, the lesion was hypointense on the T1 sequence and isointense on the T2 sequence. For five patients (n° 1-5), the lesion was heterogeneous and poorly limited with perfusion disorders in the adjacent portal vessels in three of them. For the other three patients (n° 6-8), the lesion was encapsulated, homogeneous, without clear vascular enhancement, and without any visible portal anomaly. The pre-operative radiographic diagnosis was suspected malignant tumor in six patients and possible inflammatory pseudotumor in one (patient n°7). Tranparietal biopsy was not attempted before liver resection in any of the patients.

The pathology findings are reported in Table III. For patients n°1-5, the lesions were macroscopically poorly limited, non-encapsulated and showed a whitsch aspect on the cut surface. Histologically, they were rich in cells without necrosis (figure 1). There was a more or less dense collagen network. Mitoses were rare and normal. Portal veinules situated in the periphery of the lesion exhibited zones of endophlebitis (figure 1e, f). For patients n°6-8, the lesions were well limited, encapsulated with necrosis of three-quarters of the lesion (figure 2). The portal vessels examined in the immediate proximity were healthy. The adjacent hepatic tissue more distant from the lesion was subnormal in seven cases with fibrosis in one (alcoholic liver disease) and no vascular anomaly. Immunohistochemistry confirmed the reactive nature of the cell population in all cases with a predomination of T lymphocytes (CD3+), polytrophic plasma cells and macrophages (CD68+), which were present in variable numbers depending on the zone. The fibroblastic component was negative for cytokeratin, desmin, smooth muscle actin, PS100, CD34 and ALK1. Inversely, all lesions were vimentin-positive. Search for bacterial contamination was negative in all lesions.

Immunohistochemistry and hybridation in situ failed to detect EBV in all lesions and dendritic follicular cell labelings were negative, ruling out dendritic follicular cell tumors.

The pathology findings were found to be in agreement with the radiological characteristics of the tumors. Two anatomic

Table I – Clinical and biological data.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender /age (years)</th>
<th>History</th>
<th>Reason for consultation</th>
<th>Inflammatory syndrome</th>
<th>Liver tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F 47</td>
<td>0</td>
<td>Fever, abdominal pain</td>
<td>Yes</td>
<td>Cholestasis, elevated enzymes</td>
</tr>
<tr>
<td>2</td>
<td>M 40</td>
<td>0</td>
<td>Fever, abdominal pain</td>
<td>Yes</td>
<td>Cholestasis</td>
</tr>
<tr>
<td>3</td>
<td>M 62</td>
<td>Chronic alcoholism, tuberculosis, non-treated IDDM</td>
<td>Fever, abdominal pain</td>
<td>No</td>
<td>Cholestasis</td>
</tr>
<tr>
<td>4</td>
<td>F 67</td>
<td>na</td>
<td>Fever, cough</td>
<td>Yes</td>
<td>Cholestasis</td>
</tr>
<tr>
<td>5</td>
<td>M 49</td>
<td>Cancer of the ascending colon, peritoneal carcinomatosis</td>
<td>Fever, abdominal pain</td>
<td>Yes</td>
<td>na</td>
</tr>
<tr>
<td>6</td>
<td>F 45</td>
<td>Pyelonephritis, Cholesystectomy</td>
<td>Abdominal pain</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>F 26</td>
<td>Splenectomy for ITP, pulmonary embolism, lower limb phlebitis, lupus</td>
<td>Fortuitous discovery</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>F 26</td>
<td>0</td>
<td>Abdominal pain</td>
<td>No</td>
<td>Normal</td>
</tr>
</tbody>
</table>

IDDM: insulin-dependent diabetes mellitus; ITP: idiopathic thrombocytopenic purpura.

* significantly elevated erythrocyte sedimentation rate and/or white cell count.
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Discussion

This analysis of a series of eight inflammatory pseudotumors of the liver revealed several points which were common with
cases reported in the literature. We focused on the clinical and biological context at diagnosis. These tumors are discovered in patients presenting abdominal pain with fever, associated in half of the cases with a biological inflammatory syndrome. More rarely, patients present weight loss (20%), nausea, vomiting, or jaundice [6-9]. Tumor markers are generally normal and the biological inflammatory syndrome is not constant [10, 11]. In this context, systematic ultrasonography discloses the presence of a liver nodule in these young adults free of known chronic liver disease. In about one half of the patients, a history of chronic local
or general inflammatory disease can be identified, sometimes in association with factors favoring infections (diabetes, chronic alcoholism, splenectomy).

The radiopathology analysis of our cases enabled a more precise characterization of inflammatory pseudotumors of the liver. We identified two distinct forms. The first form is seen as a large poorly delimited heterogeneous tumor. Imaging reveals tumor vascularization seen as a central enhancement after contrast injection. Histologically, this form exhibits a network of regular spindle-shaped cells in a dense polymorphous cellular background. Associated anomalies of adjacent portal veins are visualized radiographically by images of vessel compression and stretching and

Fig. 2 – *Inflammatory pseudo-tumor of the liver: sharply limited form, encapsulated.*

(a) scanner: hypodense lesion of 2 cm in the right liver; (b) post contrast scanner: no intra tumor enhancement; hyperdense rim around the lesion; (c) magnetic resonance imaging: iso intense lesion surrounded by a hyperintense rim on T2 weighted (arrow); (d) lesion limited by thickened capsule (HE × 100); (e) some inflammatory cells in the capsule (HE × 200); (f) no vascular lesion in adjacent liver (HE × 400).
histologically by the presence of fibrous portal endophlebitis. The second form is a smaller encapsulated hypodense tumor with few vessels. Histologically, central necrosis is abundant. This encapsulated form is similar to what certain authors have described as solitary necrotic nodule of the liver [12].

At MRI, performed in three of our patients (one poorly delimited tumor and two encapsulated tumors) the lesion was isointense with surrounding tissue on the T2 sequence. A hyperintense rim was seen around the two encapsulated tumors. This type of presentation is unusual for a malignant tumor suggesting the lesion might be benign.

All of the poorly delimited pseudotumors in this series were histologically “active” with portal endophlebitis and biological signs of inflammation.

For both forms, the lesion is usually unique, predominantly in the right liver (53%), 24% of patients have lesions in the left liver and 13% in both lobes [13]. Multiple lesions are exceptional, 10 cases in the series reported by Shek et al. [14] and one in our series.

The pathophysiological mechanisms put forward to explain inflammatory pseudotumors of the liver suggest these lesions are secondary to microbial infection leading to a chronic lesion in a particular immunological background. The germs would come from the gut (appendix, sigmoid diverticle) and migrate via the portal vein to the liver [15]. Portal anomalies close to the lesions identical to those presented by our patients have been described previously by Horihuchi et al. [15]. In certain patients, local pyelonephritis can be associated with more or less extensive hepatic infarcts and a chronic inflammatory reaction sustained by persistence of the bacterial colonization. Different germs have been isolated from inflammatory pseudotumors of the liver (Escherichia coli, Gram-positive bacilli, Klebsiella pneumoniae) [2, 16, 17]. Parasite particles are exceptionally found [18]. Conversely, the encapsulated form can be clinically and histologically silent, corresponding to chronic sequelae of an old partially healed inflammatory process circumscribed by a fibrous shell.

Positive diagnosis of inflammatory pseudotumors is provided by pathology and in all cases requires a sufficiently large tissue sample to confirm the benign nature of the lesion. Immunohistochemistry confirms that the presence of plasma cells and lymphocytes, mainly T cells [19, 20], corresponds to a reactive process and not lymphoma. For these authors, the spindle-shaped phocytes, mainly T cells [19, 20], corresponds to a reactive process and not lymphoma. For these authors, the spindle-shaped phocytes, mainly T cells [19, 20], correspond to a reactive process and not lymphoma.

Immunohistochemistry eliminated all of these differential diagnoses in our tumors.

The diagnosis of inflammatory pseudotumors of the liver was established on the surgical specimen in all eight of our patients. Biopsy was not attempted preoperatively. This illustrates the problem of the preoperative diagnosis of these lesions. Imaging techniques usually suggest, wrongly, a malignant tumor. The histological examination of a first-intention biopsy can be difficult to interpret or non-contributive if the lesion is poorly accessible. Antibiotic and anti-inflammatory treatments have been used in cases where certain diagnosis was established successfully on a biopsy specimen [4, 9, 18, 27, 28]. Total or partial regression has been reported with these treatments [19, 29, 30]. Other authors have also reported total spontaneous regression [6, 31].

Certain diagnosis of these rare inflammatory pseudotumors of the liver is difficult to establish without surgical resection. A meticulous analysis of the patient’s medical history, rigorous search for a chronic infection, and MRI together with systematic transparietal biopsy should enable a tentative diagnosis. We describe two distinct pathoclinical forms with different radiographic expression which probably correspond to different times in the inflammatory process and/or the more or less effective host immune reaction to infection. Preoperative diagnosis of inflammatory pseudotumors of the liver should enable conservative medical treatment, or if necessary, adapted surgery.

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REFERENCES


