

Ghost Tumor: An Inflammatory Pseudotumor of the Liver

Bruno Rosa, MD¹
 Pedro Moutinho-Ribeiro, MD²
 José M. Pereira, MD³
 Daniel Fonseca, MD⁴
 Joanne Lopes, MD⁵
 Isabel Amendoeira, MD⁵
 José Cotter, MD¹

¹Department of Gastroenterology, Alto Ave Hospital Center, Guimarães, Portugal; ²Department of Gastroenterology, Arrábida Hospital, Vila Nova de Gaia, Portugal; ³Department of Radiology, São João University Hospital, Porto, Portugal; ⁴Department of Radiology, Arrábida Hospital, Vila Nova de Gaia, Portugal; ⁵Department of Pathology, São João University Hospital, Porto, Portugal

Inflammatory pseudotumors (IPTs) of the liver are uncommon benign lesions of unclear etiology and behavior that were first described in 1953 by Pack and Baker.^{1,2} Histologically, these lesions are composed of inflammatory cells, histiocytes, and fibroblasts, and IPTs have been described in the literature as plasma cell granulomas, xanthogranulomas, histiocytomas, myofibrohistiocytic proliferations, or inflammatory myofibroblastic lesions. In addition to the liver, IPTs may develop in diverse extrahepatic locations such as the lungs, central nervous system, major salivary glands, larynx, bladder, breasts, pancreas, spleen, lymph nodes, skin, and soft tissues.³⁻¹² Although uncommon, IPTs of the liver have been increasingly recognized in recent years, mainly in Asian countries. These lesions are often treated via hepatic resection because they are mistaken for malignant lesions.^{1,2}

Case Report

A 40-year-old white Portuguese man with no significant medical history presented with a 4-week history of asthenia, malaise, headache, sore throat, vague upper abdominal discomfort, and intermittent fever. The patient also reported a weight loss of less than 10% of his body weight. The patient had not travelled outside of Europe but had been to France on a vacation approximately 1 month prior to symptom onset. He reported a recent change in his alimentary pattern, with heavy daily consumption of a variety of French cheeses that he had brought from France and continued to consume upon his return to Portugal. Empiric treatment with beta-lactam antibiotics had

been attempted, with no clinical improvement. A physical examination did not reveal any stigmata of chronic liver disease or hepatomegaly. Laboratory tests revealed an aspartate aminotransferase level of 73 IU/L (normal, 10–37 IU/L), alanine aminotransferase level of 212 IU/L (normal, 10–37 IU/L), alkaline phosphatase (ALP) level of 550 IU/L (normal, 34–104 IU/L), gamma-glutamyl transpeptidase (GGT) level of 922 IU/L (normal, 10–55 IU/L), erythrocyte sedimentation rate (ESR) of 72 (normal, 1–7), and cancer antigen (CA) 19.9 level of 45 ng/mL (normal, <37 ng/mL). In addition, the patient had negative serologic results for hepatotropic viruses, cytomegalovirus, Epstein-Barr virus (EBV), and HIV 1 and 2.

An abdominal ultrasound (US) of the posterior segment of the right hepatic lobe revealed a heterogeneous, solid, mainly hypoechoic mass measuring 54 mm × 50 mm and presenting with intrinsic vascularization on Doppler study. An abdominal computed tomography (CT) scan revealed a hypodense lesion measuring 41 mm × 36 mm in liver segments VII/VIII, with a hypodense peripheral halo and no significant enhancement after endovenous iodine contrast (Figure 1). A magnetic resonance imaging (MRI) scan performed 1 week later revealed a well-circumscribed nodular lesion measuring 32 mm × 31 mm in the segment VII/VIII transition; findings included the nonspecific features of a hypointense T1 central area and a hyperintense T2 central area with no contrast uptake, a hypointense peripheral halo in T1-weighted and T2-weighted images with progressive contrast uptake, and no washout on the dynamic study. Fine-needle aspiration (FNA) of the lesion revealed a polymorphous inflammatory infiltrate with macrophages, lymphocytes, and plasmocytes in a prominent myxoid collagen stroma, with no atypical hepatocytes and rare bile ducts; these findings were suggestive of an IPT (Figure 2).

Address correspondence to: Dr. Bruno Rosa, Department of Gastroenterology, Alto Ave Hospital Center, Rua dos Cutileiros, Creixomil, Guimarães, Portugal 4835; Tel: +351 914 155 893; E-mail: Bruno.joel.rosa@gmail.com

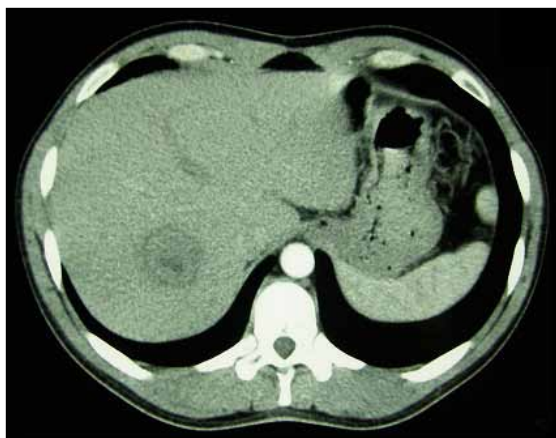


Figure 1. An abdominal computed tomography scan showing a hypodense lesion measuring 41 mm × 36 mm in liver segments VII/VIII, with a hypodense peripheral halo and no significant contrast enhancement.

Follow-up via clinical, analytic, and radiologic surveillance was adopted, and no empiric treatment was initiated. The patient became asymptomatic approximately 6 weeks after symptom onset. Laboratory test results 2 months after the patient's initial presentation showed significant improvement. An abdominal US performed 1 month later revealed a normal homogeneous hepatic parenchyma with no residual lesions. An MRI scan performed within 3 months revealed a small nodular area measuring 20 mm × 15 mm that was hypointense in both T1-weighted and T2-weighted images without contrast uptake; this finding was interpreted to be residual fibrosis in the location of the IPT (Figure 3). Findings from subsequent US abdominal imaging (performed at 6 months, 1 year, 2 years, and 3 years) were entirely normal. Laboratory test results at the same time points were also normal.

Discussion

The majority of hepatic IPTs occur in childhood and early adulthood.² In adults, the male-to-female ratio ranges from 1:1 to 3.5:1.² IPTs of the liver appear to be more common in non-European populations.¹³ Our patient was a white Portuguese man who had no significant medical history, no history of travelling outside of Europe, and who lived in good environmental salubrity conditions. As with our patient, most liver IPTs that have been reported in the literature have been solitary solid tumors, mainly arising in the right hepatic lobe.²

The etiology and pathogenesis of hepatic IPTs remain unknown, although they are thought to involve a reactive inflammatory process. Etiologic causes that have been hypothesized include infections, trauma, vascular causes,

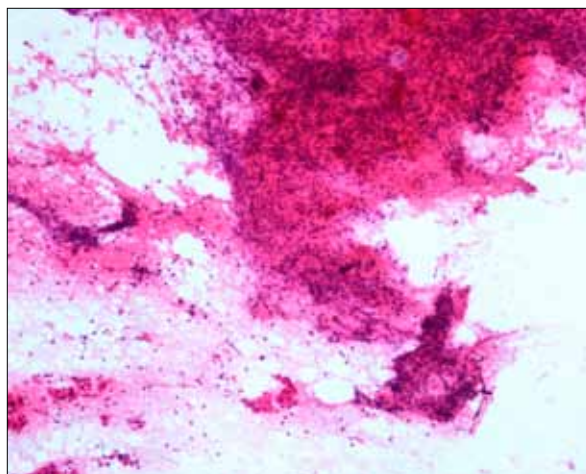


Figure 2. Fine-needle aspiration cytology showing a polymorphous inflammatory infiltrate in myxoid collagen stroma, with no atypical hepatocytes and rare bile ducts, compatible with an inflammatory pseudotumor (hematoxylin and eosin stain, 100× magnification).

and autoimmune disorders.¹⁴ Most reported cases of hepatic IPTs have a possible antecedent cause, such as travel to the tropics, biliary disease, gastrointestinal infection, or ulcerating gastric carcinoma.¹ IPTs of the liver could represent an atypical or exaggerated response to microorganisms entering the liver through the portal circulation. However, no evidence of infectious organisms has been demonstrated in most of the reported case series. Nevertheless, some cases have reportedly involved EBV-positive tumors, and other liver IPTs have contained parasitic fragments or microorganisms such as Gram-positive cocci, *Klebsiella pneumoniae*, or *Escherichia coli*.¹⁵ These observations suggest that an infectious agent may be involved in the development of IPTs of the liver, although no single organism has been consistently implicated. We could speculate whether our patient's IPT was triggered by his recent ingestion of large amounts of cheese that had been kept under suboptimal storage conditions for several weeks; however, no common symptoms of gastrointestinal infection (such as vomiting or diarrhea) were observed, and a direct cause-effect relationship could not be firmly established.

Biologically, no specific laboratory markers are useful for diagnosing IPTs. As was seen in our patient, a high serum CA 19-9 level has been reported with IPTs.¹⁶ Serum analyses are usually normal or may reveal an acute-phase response with an elevated ESR and/or white blood cell count. Liver function tests may reveal elevated ALP and GGT levels; bilirubin levels are usually not elevated unless the patient has preexisting liver disease.¹⁵

The imaging features of liver IPTs have not been discussed much in the literature. On CT scans, these lesions may appear to be well-circumscribed or poorly marginated



Figure 3. An abdominal magnetic resonance imaging scan at 3 months showing a small area of residual fibrosis that was hypointense in both T1-weighted and T2-weighted images without contrast uptake.

heterogeneous lesions. Yoon and associates summarized CT findings suggestive of IPTs of the liver.¹⁷ Most importantly, the enhancement pattern of a hepatocellular carcinoma differs from that of an IPT, as the former pattern is hyperdense in the arterial phase and hypodense with capsule enhancement on a delayed-phase CT scan; in addition, the latter pattern has nonspecific features and (as with our patient) usually shows a hypoattenuating mass and a hypodense peripheral halo with no significant enhancement after endovenous contrast.

Tissue sampling is required for establishing the diagnosis of IPT. The histologic appearance of IPTs may be highly variable. Generally, there is a benign spindle-cell proliferation in a myxoid collagen stroma with an inflammatory component of lymphocytes, plasma cells, and histiocytes.² Ideally, the diagnosis of IPT should be made via a core biopsy. Nevertheless, as with our patient, FNA of the lesion can support the diagnosis of an IPT. However, when the lesion is highly fibrotic, FNA samples can be difficult to obtain and can lead to misdiagnosis.¹⁵

The natural history of liver IPTs is not often discussed in the literature because initial misdiagnoses and local complications often lead to surgical resection. However, as with our patient, spontaneous and complete regression of hepatic IPTs has been reported for intrahepatic tumors of the right lobe. In these cases, the average time between diagnosis and spontaneous regression was 4 months.² IPTs of the liver are often misdiagnosed as hepatocellular carcinomas, cholangiocarcinomas, secondary tumors, or abscesses because of their nonspecific clinical, radiologic, and biochemical presentations. Thus, management of IPTs ranges from conservative treatment to hepatic resection or even liver transplantation.^{1,2} Conservative treatment has included antibiotics or nonsteroidal anti-inflammatory drugs; if the patient has biliary obstruction, biliary stents may be placed.¹⁸⁻²⁰

Differentiating IPTs from malignant liver tumors has been assuming greater importance because hepatic surgery is being performed more frequently, due to its increased safety and the adoption of a more aggressive treatment approach via resection of liver masses. Thus, some doctors have advocated the use of hepatic resection for IPTs of the liver, taking into account the possible destructive nature of the lesions and the uncertainty of their potential for malignancy. However, immunohistochemical analysis has shown that IPTs are benign lesions with no evidence of malignant transformation. Moreover, a number of reports published in the literature suggest that the natural history of these lesions leads to complete resolution.¹⁵ These observations provide good evidence that progressive IPTs of the liver are exceedingly rare and typically resolve without treatment. Complete and sustained resolution was observed in our patient at 36 months.

In conclusion, if an atypical solid mass is found in the liver, IPT should be considered as a diagnosis, particularly if the mass is accompanied by a clinical inflammatory process. In addition, liver needle biopsy should be performed to prevent unnecessary surgery. Conservative management is appropriate if the diagnosis is confirmed via the biopsy specimen and the patient is followed with clinical examinations and imaging until resolution of the lesion.

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Review

Inflammatory Pseudotumor of the Liver: A Rare But Distinct Tumor-Like Lesion

Charles Balabaud, MD¹
 Paulette Bioulac-Sage, MD²
 Zachary D. Goodman, MD, PhD³
 Hala R. Makhlof, MD, PhD⁴

¹Hepatology Department, ²Pathology Department, University of Bordeaux Segalen, Bordeaux, France; ³Liver Pathology Research and Consultation, Inova Fairfax Hospital, Falls Church, Virginia; ⁴Pathology Department, Ein Shams University, Severn, Maryland

Rosa and colleagues present a case of a hepatic inflammatory pseudotumor that was correctly diagnosed via fine-needle biopsy and that spontaneously resolved without treatment.¹ The patient was a white Portuguese man who had no significant medical history and had never traveled outside of Europe. He presented with a 4-week history of intermittent fever, malaise, and abdominal discomfort. A thorough examination revealed a heterogeneous, solid, right hepatic lobe mass that was determined via biopsy to be an inflammatory pseudotumor. This well-documented case raises a number of important points.

Given the lack of uniform criteria for diagnosing inflammatory pseudotumors, it is difficult to obtain clear data from the literature regarding the incidence, anatomic distribution, natural history, and malignant potential of these lesions.¹⁻³ Not surprisingly, this difficulty has an impact on the understanding of the natural history of this condition as well as its prognosis and treatment.

The term “inflammatory pseudotumor” describes a heterogeneous group of mass-forming lesions that can involve many organs and that are characterized by a prominent inflammatory infiltrate as the predominant cellular component. There has long been confusion over the nature of these lesions, particularly since the term “inflammatory pseudotumor” has been synonymous with “inflammatory myofibroblastic tumor” in the literature when referring to pediatric soft tissue tumors.

Several lesions previously considered to be variants of inflammatory pseudotumors have recently been identified as different entities. The neoplastic variants of inflammatory pseudotumors include inflammatory myofibroblastic tumors associated with anaplastic lymphoma kinase (ALK-1) translocation, as well as inflammatory pseudotumor-like follicular dendritic cell tumors of the liver and spleen that are related to clonal Epstein-Barr virus infection.^{4,5} Some of these lesions represent true neoplasms. In addition, mycobacterial spindle-cell inflammatory pseudotumors of lymph nodes and tumefactive lesions associated with immunoglobulin (Ig) G4 are examples of infectious and autoimmune-induced inflammatory pseudotumors, respectively.⁶⁻⁸ The etiology and pathogenesis of inflammatory pseudotumors remain unclear for a variety of tumorous inflammatory lesions that lack the features of the entities listed above (inflammatory pseudotumors, not otherwise specified).

An inflammatory pseudotumor of the liver is an uncommon, benign, tumor-like lesion that sometimes mimics a malignant tumor, particularly metastatic disease or cholangiocarcinoma.⁹ In the majority of cases, including the case presented by Rosa and associates, these inflammatory pseudotumors are most likely inflammatory or infectious in origin.¹ The lesions often appear to develop from a healing abscess or an inflammatory condition resulting from rupture of the bile duct and extravasation of bile into the tissue, which provokes a xanthogranulomatous inflammatory response that heals with scarring.

In our experience, most cases that have been thought to be inflammatory myofibroblastic tumors in the liver are better classified as inflammatory pseudotumors and

Address correspondence to:

Dr. Charles Balabaud, Inserm U1053, University of Bordeaux Segalen, 146 Rue Léo Saïgnat, Bordeaux, France 33076; Tel: 33 5 57 57 17 12; Fax: 33 5 56 51 40 77; E-mail: Charles.balabaud@u-bordeaux2.fr

represent a resolving inflammatory process. All 145 cases in a study we conducted at the Armed Forces Institute of Pathology had features of inflammatory pseudotumors rather than inflammatory myofibroblastic tumors.¹⁰ It is well recognized that inflammatory pseudotumors have a wide variability in histologic features that may be reflected in different areas of the same lesion. Therefore, adequate sampling in multiple sections is essential for establishing an accurate diagnosis. Our study identified 5 main histologic subgroups: a plasma cell–rich subgroup with aggregates of or diffuse lymphocytes, a mixed inflammatory cell subgroup, a granulomatous subgroup, a granulomatous subgroup with eosinophils, and a predominantly purulent subgroup.¹⁰ None of the cases in our study stained positive for infectious organisms, and immunostaining found no evidence of lymphomas, Langerhans cell histiocytosis, IgG4-related sclerosing disease, or ALK-1–positive inflammatory myofibroblastic tumors, unlike reported cases of inflammatory pseudotumors in the lungs.¹¹ Follow-up data revealed no patients with subsequent neoplasms, recurrences, or metastases.

Since inflammatory pseudotumors are so rare, they are usually surprising when found in a biopsy or resection specimen. However, astute clinicians should consider this diagnosis whenever the following findings are present: a recent history of asthenia, malaise, vague upper abdominal discomfort, and/or intermittent fever; absence of stigmata of chronic liver disease or splenomegaly; abnormal liver function test results (such as elevated levels of transaminases, gamma-glutamyl transpeptidase, and alkaline phosphatase); and a lack of specific imaging findings.

Imaging studies of inflammatory pseudotumors have revealed hypoechoic, as well as hyperechoic, masses on ultrasound. Unenhanced computed tomography images show the tumor's hypoattenuating liver parenchyma, and contrast administration reveals variable patterns of enhancement. On magnetic resonance imaging, the lesions are typically hypointense on T1-weighted images and hyperintense on T2-weighted images, with variable enhancement patterns.

A definitive diagnosis of inflammatory pseudotumor can be made via needle biopsy findings and, occasionally, fine-needle aspiration, as long as the pathologist is aware of this possibility. In such cases, antibiotic treatment may be curative, and hepatic resection can be avoided. Corticosteroids have been successfully used in some cases and constitute another treatment option.¹¹ Occasionally, the

pseudotumor spontaneously regresses, as with the patient treated by Rosa and colleagues.¹

More data should be collected to better classify inflammatory pseudotumors and further understanding of their natural history; specific areas of future research should involve culturing the infectious agents, testing for aberrant expression of ALK-1 and its gene translocation, and testing for the expression of IgG4-positive plasma cells.

It is common practice to excise a resectable liver tumor in the absence of a firm diagnosis. However, if a preoperative diagnosis of an inflammatory pseudotumor can be made, there is no reason to advocate hepatic resection (as noted by Rosa and coworkers), as long as appropriate consideration has been given to the possible destructive nature of the lesion and the uncertainty of its potential for malignancy.¹ The case report by Rosa and associates is a good illustration of the necessity of considering the diagnosis of inflammatory pseudotumor if an atypical mass is found in the liver, particularly when it is accompanied by a clinical inflammatory process.¹ A liver biopsy is recommended to avoid unnecessary liver resection.

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