

Review

Lobar and Segmental Atrophy of the Liver: Differential Diagnoses and Treatments

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Abstract: Segmental or lobar liver atrophy is a common but not well-understood clinical condition. Hepatic atrophy can be classified into hepatic atrophy secondary to other pathologies and primary segmental hepatic atrophy, which is a benign intrahepatic lesion (pseudotumor) not associated with any other pathology. The pathophysiological mechanisms underlying atrophy can be divided into three main situations: obstruction of biliary outflow, obstruction of the systemic venous outflow, and obstruction of incoming portal venous flow. For what may concern secondary hepatic atrophy, there are many pathologies that could underlie this condition, ranging from benign to intrahepatic malignancies, with particular reference to particularly hepatocellular carcinoma and biliary duct carcinoma. An accurate and prompt differential diagnosis between the various forms and causes of atrophy is important for early identification and adequate treatment of underlying pathologies. A comprehensive review of the literature on the etiology and the radiological and histological characteristics of different types of hepatic atrophy is currently unavailable. Therefore, the aim of this review is to summarize the primary and secondary causes of segmental or lobar liver atrophy (excluding forms involving the entire liver parenchyma) and to provide practical tools for clinical and radiological differential diagnosis.

Keywords: hepatic atrophy; segmental hepatic atrophy; lobar hepatic atrophy; biliary obstruction; portal obstruction; pseudotumor of the liver; intrahepatic lithiasis; cancer-associated hepatic atrophy



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1. Introduction

Segmental or lobar liver atrophy is a common but not well-understood clinical condition. Interest in this pathology is increasing as second-level radiological diagnostic exams become more capable of recognizing it and differentiating it from degenerative or neoplastic diagnoses [1–3].

Hepatic atrophy can be classified into hepatic atrophy secondary to other pathologies, extending to segmental or lobar areas and possibly involving the whole liver (as in cirrhosis), and primary segmental hepatic atrophy, which is a benign intrahepatic lesion (pseudotumor) not associated with any other pathology [4–6].

The current literature is limited to case reports or small case series, focusing on a single form of atrophy and, more recently, on the histologic and radiologic characterization of the benign pseudotumor [7]. No extensive literature review covering the aetiologic, radiologic, and histologic features of the different types of hepatic atrophy is currently available.

The aim of this literature review is to summarize the main causes of segmental or lobar liver atrophy (excluding forms involving the entire liver parenchyma) and to provide practical tools for clinical and radiological differential diagnosis.

2. Traditional Definitions

Historically, the past literature [5] has described two main forms of liver atrophy:

- Partial atrophy, described as a reduction in volume of at least 50% of the affected lobe or segment.
- Complete atrophy, described as a complete subversion of the affected lobe or segment; the volume is approximately one tenth of the initial volume, and the lobe or segment is severely shrunken, pinkish, and firm [1].

At a microscopic level, complete atrophy is characterized by a total absence of hepatocytes, disorganized proliferation of small dilated bile ducts extending close to the liver surface, advanced fibrosis, and infiltration of inflammatory cells [8].

In contrast, in cases of partial atrophy, aggregates of hepatocytes surrounded by bands of fibrous tissue or especially elastic fibers can still be observed [2].

3. Pathophysiology

Several conditions, which we will expand on in the next paragraphs, can lead to hepatic, segmental, or lobar atrophy [9].

However, the pathophysiological mechanisms underlying atrophy can be divided into three main situations:

- Obstruction of biliary outflow;
- Obstruction of the systemic venous outflow;
- Obstruction of incoming portal venous flow.

The molecular mechanisms of hepatocyte loss are similar, despite having different initial causes.

Obstruction of bile flow causes periductal inflammatory activation, which can damage the bile ducts themselves and induce their proliferation, in addition to damaging the periductal venous branches, widening the sinusoids, and determining the slow deposition of fibrotic septa. Obstruction of the systemic venous outflow leads to increased pressure in the sinusoids, resulting in sinusoidal portal hypertension, centrilobular necrosis, and subsequent fibrosis. Obstruction of the incoming portal venous flow causes hypoxia and, in severe cases, anoxia of the hepatocyte cells. Anoxic cells undergo necrosis, leading to the development of fibrosis to replace the damaged parenchyma [10].

In contrast, what we would properly call hepatic segmental atrophy (HSA), which is macroscopically characterized by a mass-forming appearance, is microscopically characterized by the stage of nodular elastosis. Elastic fibers, including elastins and microfibrils, are typically prominent in tissues such as the skin, in the lungs, and in walls of large vessels. In the liver parenchyma, elastic fibers can be found in the walls of the portal and centrilobular venous branches, as well as in the walls of the major vessels. Even if a tissue does not have a significant elastic component, it can still produce elastic fibers after injury. However, in hepatic atrophy, these newly formed elastic fibers are excessive in number and disorganized. Moreover, hepatic injury can trigger a sequence of reactions that lead to cell death. This, in turn, causes portal myofibroblasts to produce an excess of elastic fibers that are deposited in a disorganized pattern. The accumulation of elastic fibers is always accompanied by a slower and more gradual increase in fibrotic septa [8,11].

The obstruction of arterial inflow plays a minor role in the induction of liver atrophy due to the ratio between venous and arterial perfusion, which is clearly in favor of the former. In cases where parenchymal areas are exclusively supplied by arterial vascularization (such as hepatocarcinoma), however, the effect of arterial obstruction is comparable to that of portal obstruction in healthy parenchyma, the same mechanism that is employed by transarterial chemoembolization treatment—TACE [12–14].

However, it has been demonstrated that lobar atrophy is associated with a reduction in the number of arteries feeding the affected lobe. The arteries that can be observed are “crowded” and tortuous. In essence, the affected region is relatively avascular. It is challenging to discern the precise causal relationship between some of the histological alterations observed in areas of liver atrophy. The increase in arterial and venous vessels in areas unaffected by atrophy may, thus, be a consequence of biochemical and hormonal changes affecting regions undergoing atrophic involution [5].

Although this review is primarily concerned with the etiology, the pathological and clinical features, and the management of hepatic atrophy, it is essential to recognize that the underlying pathophysiological mechanisms of hepatic atrophy are the same, which will determine the compensatory hypertrophy in the unaffected parenchyma of the same patient. In the clinical setting, these identical mechanisms are employed to prompt targeted atrophy in specific regions while simultaneously stimulating compensatory liver hypertrophy in advance of major liver resections to minimize the risk of postoperative liver failure.

Liver atrophy and hypertrophy are two frequently associated clinical and anatomopathological entities, often brought together in the definition of the so-called atrophy-hypertrophy complex (AHC), which represents the hepatic regenerative response following loss of hepatocytes [10]. Although the term “hypertrophy” is typically used to describe this process, it is important to specify that the restoration process primarily involves hyperplasia, or an increase in the number of cells, rather than an increase in their size.

It is well established that the principal mechanisms of liver regeneration are driven by the following: hepatic hypoxia, an increase in portal blood flow that induces shear stress, and the involvement of various mediators, including cytokines, vaso-regulators, growth factors, eicosanoids, and hormones. Conversely, other factors are associated with impaired liver regeneration, including biliary obstruction, malnutrition, diabetes mellitus, male sex, age, and ethanol.

The complexity and multiplicity of the factors involved could justify the fact that hypertrophy is not always associated with segmental or lobar liver atrophy [15–18].

Nevertheless, to date, no comprehensive understanding of all the variables involved has been achieved, and they are not a primary focus of this review.

4. Diagnosis

The diagnosis of hepatic atrophy, whether segmental or lobar, is primarily based on radiological tools such as ultrasound, CT scan, and magnetic resonance imaging. However, in most cases it is an incidental diagnosis.

Laboratory tests can be either in the range of normality or show alterations of the underlying pathology of the liver. These alterations may include an increase in cholestasis indices (alkaline phosphatase, gamma-glutamyltransferase) with or without hyperbilirubinemia, an increase in liver transaminases (alanine transaminase and aspartate transaminase), and a secondary increase in tumor markers CA 19.9 [19].

Radiological examination is the first essential step in the diagnostic process.

Areas of atrophy in liver ultrasound are characterized by an iso- or hypoechoic appearance compared to the surrounding parenchyma, with ill-defined margins and no Doppler flow signal. In contrast-enhanced abdominal CT scans, atrophic liver areas are hypodense compared to the adjacent parenchyma, and occasionally characterized by focal calcifications. In magnetic resonance imaging (MRI), either contrast-enhanced or not, these areas appear hypointense in the T1-weighted sequences, hyperintense in the diffusing sequences (DWI) and in the weighted T2 sequences, and hypointense in the cholangiographic sequences. Atrophic liver areas are isometabolic compared to the surrounding liver parenchyma in a fluorodeoxyglucose-positron emission tomography (FDG-PET). This technique can help differentiate benign from malignant disease; however, in case of lack of metabolic uptake, a malignant disease cannot be excluded with certainty.

since some primary liver malignancies can show a low or null uptake in an FDG-PET (especially hepatocellular carcinoma) [1]. Sometimes, in the case of development of a benign atrophic liver pseudotumor, its main radiological characteristic can be a clear transition between the atrophic and nonatrophic areas, known as the “step” sign [2]. Indirect radiologic signs of segmental or lobar atrophy can also become useful guides in the diagnostic process: in right hepatic atrophy, the atrophic lobe rotates superiorly and posteriorly; in left hepatic atrophy, however, there is no clear change in position. In both right and left hepatic atrophy, the nonatrophic parenchyma may undergo compensatory hyperplasia (more commonly referred to as hypertrophy, although histologically the increase in volume is due to hyperplasia) [2].

Whether it be for benign segmental atrophy or other underlying pathology, diagnosis confirmation requires an anatomopathological examination. Histological characteristics of segmental liver atrophy and underlying pathology can be observed on an operative piece or biopsy sample. Indeed, the development of hepatic atrophy, whether segmental or lobar, involves a histological progression through various stages.

5. Etiology and Treatment

According to the currently available literature, most cases of atrophy are associated with biliary obstruction (e.g., caused by intrahepatic lithiasis), development of proper well-defined hepatic segmental atrophy (HSA), or intrahepatic malignancies causing venous, biliary, or portal obstruction [4]. These causes of segmental atrophy will be more extensively addressed later.

Other conditions underlying segmental and lobar atrophy are noted in Table 1, while different management pathways related to diagnosis are reported in Figure 1.

Table 1. Conditions underlying hepatic atrophy.

Conditions Associated with Hepatic Atrophy	
Pseudotumor like	Hepatic segmental atrophy (HSA)
	IgG4-related sclerosing disease
	Syphilis
	Hydatid disease
	Zahn’s infarction
Cystic appearance	Simple hepatic cysts or bile duct cysts
	Caroli disease
	Mucinous cystic neoplasms
Benign neoplasms	Rare benign neoplasms (hepatic angiomyolipoma, mesenchymal hamartoma . . .)
	Hepatic vascular lesions (sclerosed hemangioma . . .)
Malignant neoplasms	Cancer-associated portal flow, venous outflow or biliary obstruction (hepatocellular carcinoma, cholangiocarcinoma . . .)
Iatrogenic	Post-surgical biliary occlusion
	Post-surgical arterial occlusion
	Post-surgical portal flow obstruction

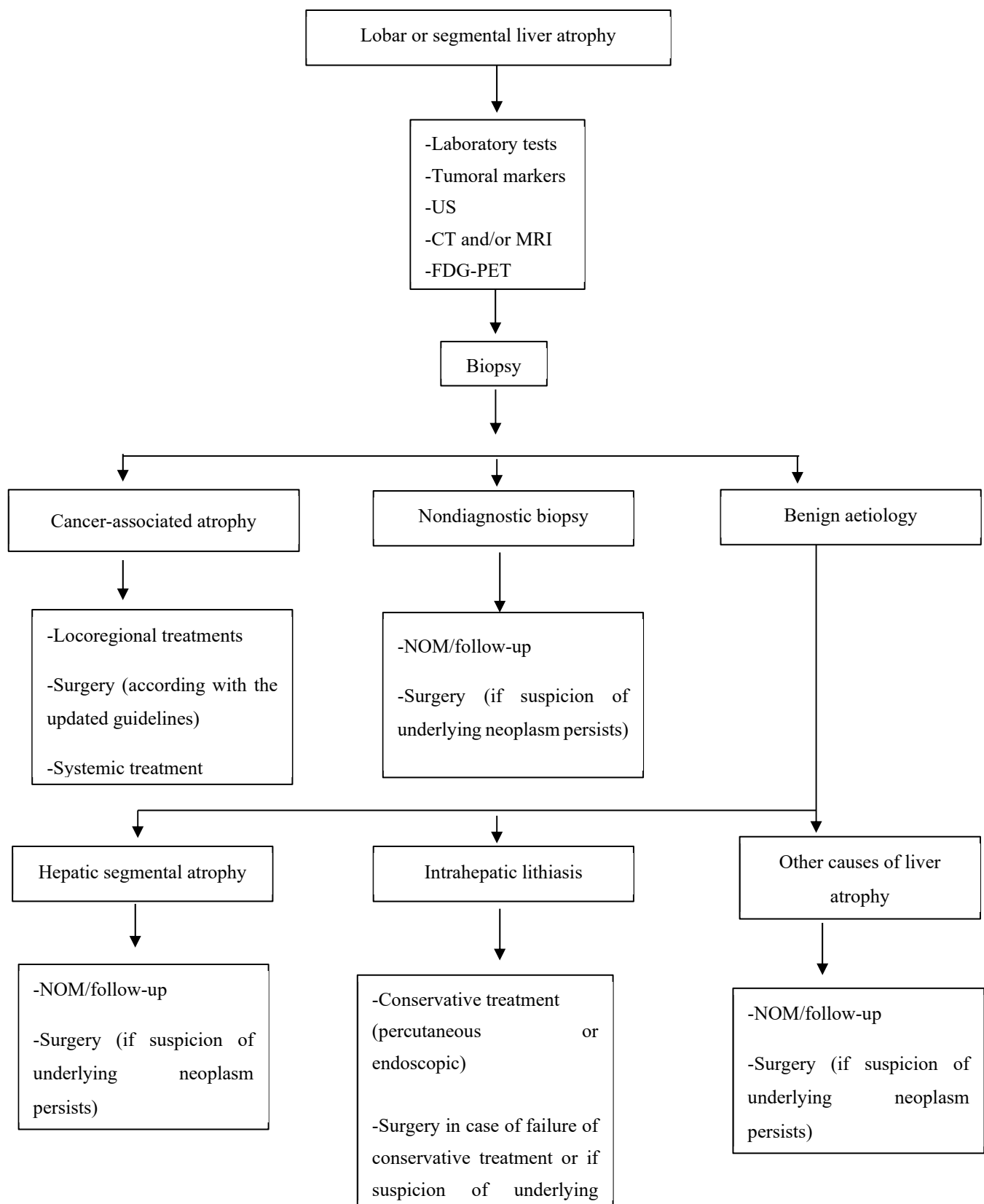


Figure 1. Flowchart of diagnosis and treatment pathways for lobar and segmental atrophy. US: ultrasound; CT: computed tomography; MRI: magnetic resonance imaging; FDG-PET: fluorodeoxyglucose-positron emission tomography; NOM: nonoperative management.

5.1. Differential Diagnosis

In addition to the primary etiologies of circumscribed liver atrophy outlined in this review, it is essential to consider the possibility of a multitude of other diseases, frequently benign, manifesting in radiological findings with areas of segmental or lobar atrophy, and rarely affecting the entire liver parenchyma.

While performing the differential diagnosis of segmental or lobar hepatic atrophy, the following benign conditions should be taken into account:

- Liver cysts, which can simulate biliary dilations observed in cases of hepatic segmental atrophy (HSA) [20];
- IgG4-related sclerosing disease. Liver lesions in this case can range from moderate and nonspecific periportal inflammation to sclerosing cholangitis and inflammatory pseudotumor [21,22];
- Syphilis, which may be associated with the development of intrahepatic inflammatory pseudotumor, potentially occurring at any stage of the disease [23];
- Hydatid disease (echinococcosis), which is the most common cause of liver cysts worldwide. The cysts often appear multilocular, and the cystic cavity contains dense and thick material [24,25];
- Caroli disease, characterized by segmental dilatation of the large intrahepatic bile ducts which is typically associated with congenital hepatic fibrosis [26];
- Post-ischemic parenchymal changes due to concomitant obstruction of portal and intrahepatic arterial flow, such as Zahn's infarction [27];
- Iatrogenic occlusion of arterial or portal flow, such as after surgical (Figure 2) or radiological accidents [28];
- Rare benign hepatic neoplasms such as intrahepatic angiomyolipoma, mesenchymal hamartoma, sclerosed hemangioma, anastomosing hemangioma, and sclerosing cavernous hemangioma [29].

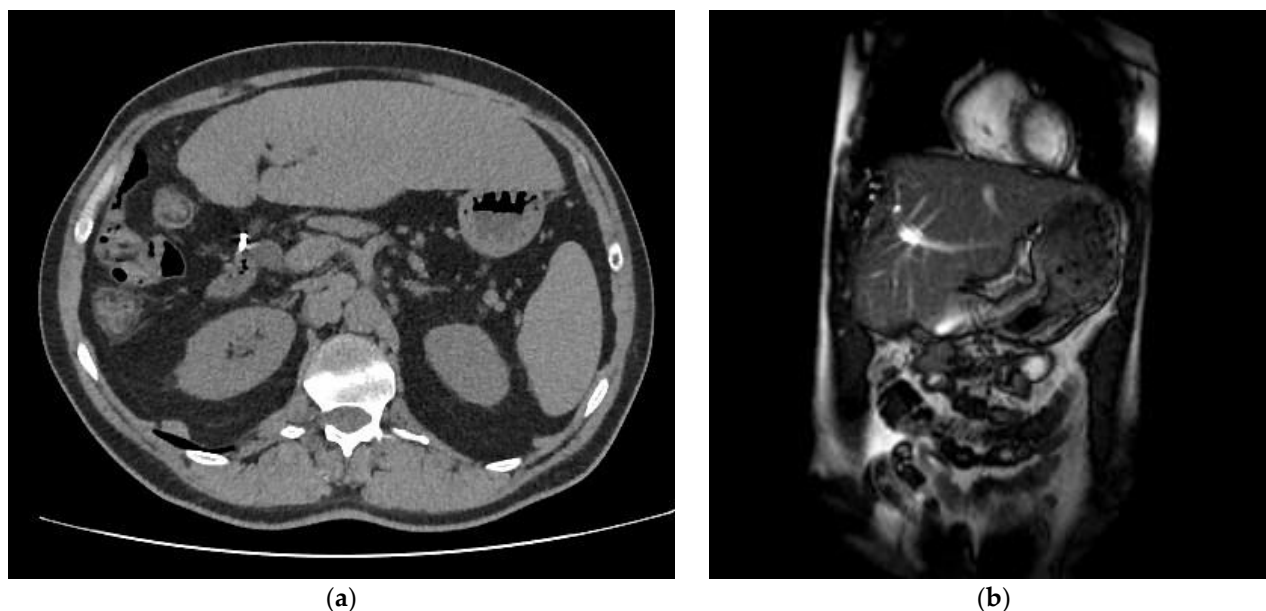


Figure 2. 73-year-old male with history of previous cholecystectomy (about 30 years ago), with accidental closure of right hepatic artery. Axial CT image (a) and coronal MRI image (b) of the liver, showing hypertrophic left lobe and complete atrophy of right liver. Patient underwent a nonoperative management, and he currently is under a yearly laboratory and diagnostic follow-up.

In both benign and malignant liver diseases, biliary or venous flow obstruction, whether it be portal or systemic, may be the cause of atrophy.

5.2. Intrahepatic Lithiasis

5.2.1. Clinical and Diagnostic Features

The incidence of intrahepatic lithiasis is increasing in parallel with the increase in biliary interventions [30] and this condition represents a risk factor for the development of intrahepatic cholangiocarcinoma [31].

Clinical manifestations range from complete absence of symptoms to recurrent episodes of abdominal pain, fever, and obstructive jaundice.

If intrahepatic lithiasis is clinically suspected, stepwise diagnosis shall include blood chemistry, abdominal ultrasound, and confirmation using second-level diagnostics (CT, MRI or MRCP) [31]. Given the high risk of cholangiocarcinoma in the presence of intrahepatic lithiasis, a quantitative analysis of tumor markers values (carcinoembryonic antigen and Ca 19.9) is recommended at the time of diagnosis [30]. The probability of an underlying cholangiocarcinoma will also determine the choice of second-level diagnostics.

5.2.2. Treatment

The management of intrahepatic lithiasis can include both surgical and conservative options [32]. Nonsurgical treatments include extracorporeal lithotripsy (ESWL) [33], percutaneous transhepatic cholangioscopic lithotripsy (Figure 3) [33], ultrasound-guided hepaticogastrostomy [34], operative endoscopic retrograde cholangiography (ERCP) [35], and operative transoral cholangioscopy (POC) [36].



Figure 3. 81-year-old female with history of main bile duct lithiasis and cholangitis, associated with intrahepatic lithiasis of left bile duct. She was firstly treated with operative endoscopic retrograde cholangiography (ERCP), with evacuation of main duct lithiasis. After that, the patient underwent a rendezvous procedure, combining percutaneous transhepatic cholangioscopic lithotripsy and ERCP and obtaining a complete clearing of intrahepatic and extrahepatic bile ducts. Post-procedural axial CT image of the liver showed atrophy of left lobe of the liver and residual aerobilia (white arrow). Patient is under follow-up, but no more infectious episodes occurred.

Surgical treatments include hepatectomy, choledochenterostomy, choledochotomy with mechanical removal of displaced stones and with or without T-tube placement, and papilla plasty surgery [37,38].

When technically feasible, radical resection is recommended in all patients with a confirmed diagnosis of cholangiocarcinoma. Also, intrahepatic lithiasis with concomitant segmental or lobar atrophy represents an indication to liver resection [31]. Surgery is indicated when the abovementioned conservative treatments fail [39,40].

Nonoperative management is indicated only in the case of asymptomatic patients, with no evidence of cholangiocarcinoma, liver atrophy, biliary stenosis, or biliary dilatation [31].

5.3. Hepatic Segmental Atrophy (HSA) and Nodular Elastosis

5.3.1. Clinical and Diagnostic Features

HSA, which in this form is not normally associated with other intrahepatic disease, is usually diagnosed incidentally. Typically, it manifests with the formation of a subcapsular benign pseudotumor characterized by a well-defined histological evolution.

In the early stage, liver parenchyma collapses, leaving few residual hepatocytes surrounded by chronic inflammation, prominent bile duct proliferation, and mild elastosis (1–10%). Stage two shows reduced inflammation, little or no ductal proliferation, and increased elastosis (11–80%). The third stage consists of nodular elastosis with marked elastin deposit (>90%), mild cellularity with small bland cells, and few portal tracts. In the final stage, nodular lesions consist of elastosis with dense fibrosis, scattered islands of hepatocytes, biliary cysts, thick-walled thrombosed vessels with fibrotic change, and recanalization [8,41,42].

The specific initiating factor, identified as the start of the well-documented histopathological changes typically observed in cases of segmental liver atrophy, has yet to be accurately determined. The histological evolution of this lesion suggests that there may be a microvascular alteration at its origin, such as local thrombosis of a vessel feeding a smaller subsegment of the liver, which could in turn be responsible for triggering the chain of events [1].

The clinical picture is almost always silent and the physical examination of the abdomen is negative.

In the absence of altered blood chemistry, negative tumor markers, and other visible masses, ultrasound or radiological evidence by CT or MRI of a well-defined intrahepatic atrophic area with a clear transition between healthy and atrophic parenchyma should suggest the diagnosis of HSA [6].

5.3.2. Treatment

The risk of progression of a segmental liver atrophy lesion to a malignant neoplastic lesion is currently unknown. Few cases of HSA have been described in the literature, all confirmed by histological examination of the surgical specimen [8]. However, no study including higher level of evidence is available to further describe the link between segmental liver atrophy and liver malignancy development, and there is no strong indication to follow-up, which remains up to clinician personal experience [9].

Surgical resection is only recommended when atrophy is suspected to be secondary to other conditions.

5.4. Cancer-Associated Atrophy

5.4.1. Clinical and Diagnostic Features

Areas of focal atrophy may be associated with various intrahepatic neoplastic lesions.

The most common are primary biliary tract tumors (cholangiocarcinoma) and metastatic lesions [43]. Among the less common are primary hepatocellular tumors such as hepatocellular carcinoma (Figure 4). Biliary neoplasms also include biliary intraductal papillary mucinous neoplasms. These are often associated with benign chronic liver diseases such as intrahepatic lithiasis or clonorchiasis [30,44].

Although the majority of these neoplasms manifest as mass-forming intrahepatic lesions, the early stages of such neoplastic lesions may only occur with the development of circumscribed areas of parenchymal atrophy attributable to a pathophysiological mechanism previously described.

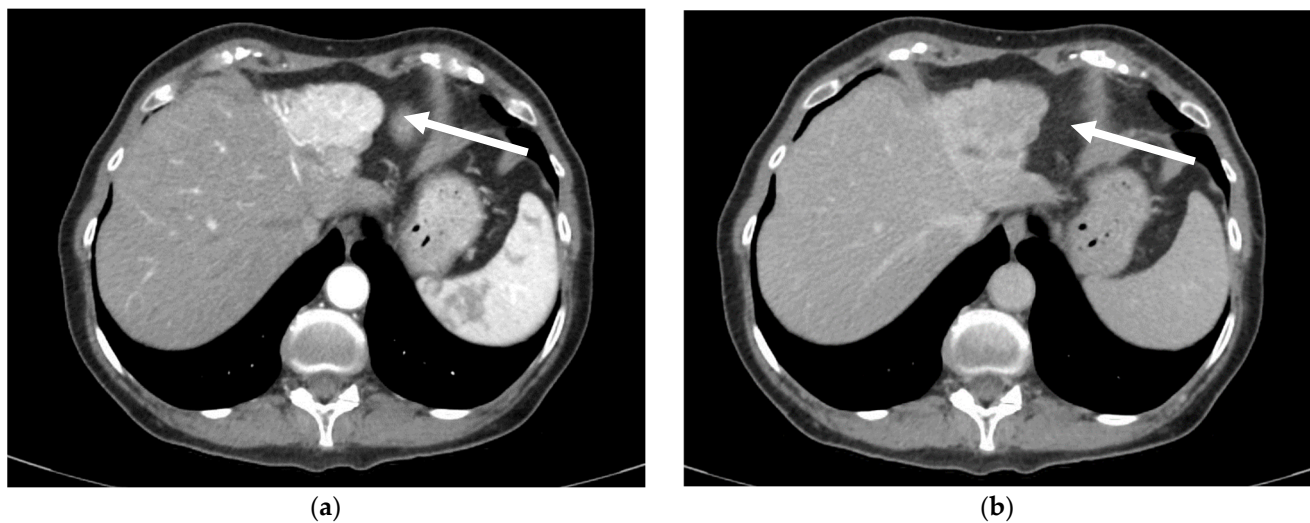


Figure 4. 77-year-old female with incidental diagnosis of left lobe atrophy of the liver, with an underlying suspicion of hepatocellular carcinoma. Axial CT image shows hyperenhancement in the arterial phase (a) and a rapid wash-out in portal phase (b); cancer is indicated by arrows. Biopsy was not feasible because of position and high risk of bleeding of the lesion. After multidisciplinary evaluation, the patient underwent a laparoscopic left hepatectomy. Diagnosis of hepatocellular carcinoma well-differentiated (G1) was confirmed at histological examination. No recurrence was observed after 48 months of follow-up.

Intraductal mucinous neoplasms are characterized by pathological dilatation of the segmental or lobar bile ducts and associated with atrophy of the surrounding parenchyma [45]. The growing mass of the tumor results in obstruction of the bile ducts. When tumor proliferation occludes a segmental or lobar biliary branch, atrophy develops long before jaundice, while jaundice occurs earlier when the tumor involves the confluence of the main biliary ducts [2].

The main mechanism of atrophy associated with intrahepatic malignancies appears to be neoplastic invasion of the portal vein at the segmental or lobar level [43]. However, it is now recognized that biliary strictures, even in the absence of portal vein obstruction, can be associated with parenchymal atrophy [7,11,43].

In the natural history of these intrahepatic lesions, atrophy occurs before jaundice and other symptoms such as abdominal pain due to distension of the Glissonian capsule, abdominal distension, or weight loss, helping in early diagnosis.

In these cases, the diagnostic process employs a combination of laboratory investigations, radiological instruments, and, when necessary, invasive procedures to obtain histological samples.

The dosage of specific tumor markers like alpha-fetoprotein in hepatocarcinoma, Ca 19.9, and carcinoembryonic antigen in cholangiocarcinoma in high-risk patients can provide guidance in the diagnosis, but cannot serve as confirmation. In fact, it is known that even biliary obstruction alone can cause Ca 19.9 elevation [19].

The clinical–radiological presentation also depends on the type of neoplastic lesion and pre-existing risk conditions. For instance, hepatocellular carcinoma typically occurs in high-risk patients with chronic liver disease. In these cases, the liver may be affected by fibrosis in different stages up to cirrhosis of the liver.

Radiologic features are fundamental to characterize incidental liver nodules.

Most incidental liver lesions measuring less than 1 cm with smooth margins are benign. In addition, the absence of lesion growth over a one-year period suggests that the lesion is more likely to be benign [46].

Contrast enhancement is also used to aid in differentiation. Hepatocellular carcinoma typically shows nonbordered hyperenhancement in the arterial phase relative to the liver

parenchyma, coupled to a rapid wash-out [47]. Intrahepatic cholangiocarcinoma shows enhancement of the peripheral rim in both the arterial and venous phases after administration contrast agent [48]. The enhancement pattern of liver metastases varies depending on the primary malignancy. The most common metastatic liver lesions arise from neoplasms of the colon, stomach, and pancreas. These typically show less attenuation in contrast to the surrounding liver parenchyma appearing brighter on multiphase liver CT [49]. Other hypervascular metastases appear as rapidly enhancing lesions visible on arterial phase enhancement, such as those from neuroendocrine tumors, renal cell carcinoma, breast cancer, melanoma, and thyroid cancer [50].

The presence of an area of lobar or segmental atrophy with suspicion of an underlying neoplastic lesion but without any radiology diagnostic confirmation represents a complex clinical situation without standardized management recommendations backed by evidence-based indications.

Depending on the tumor's location, endoscopic ultrasonography (EUS) is useful in characterizing the extension of the lesion and its nodal involvement, and in case of diagnostic uncertainty it can be leveraged to perform an EUS-guided needle-biopsy [48].

5.4.2. Treatment

Surgical resection could be recommended for areas of lobar or segmental atrophy when clinical, radiological, and laboratory findings suggest a malignant lesion; however, we recommend referring to guidelines specific for each type of malignancy for a more exhaustive study of this topic.

For hepatocellular carcinoma, the reference text is the recently updated (2022) BCLC guidelines for hepatocellular carcinoma [47]. The BCLC guidelines differentiate treatment options based on the extent of the cancer and underlying liver disease, categorizing them as locoregional (surgical and nonsurgical) or systemic treatments, also taking into account the presence of concomitant portal thrombosis or biliary obstruction.

Regarding biliary tract cancer, surgery remains the primary treatment according to current guidelines [51], since the role of perioperative chemotherapy is still unclear.

6. Conclusions

Segmental or lobar hepatic atrophy may present as an isolated, completely benign intrahepatic lesion in the absence of underlying pathology (neoplastic or non-neoplastic).

However, when atrophy is observed, whether lobar or segmental, it is important to consider the possibility of underlying malignant pathology. Radiologic and laboratory findings can help detect these conditions, and increased awareness of the significance of these findings can assist in early differential diagnosis.

A conservative approach, based on close radiology and laboratory follow-up, may be justified in the absence of symptoms and lacking any founded suspicion of an underlying neoplasm. In all the other cases, surgery should be considered as a diagnostic and therapeutic tool.

A greater understanding of the clinical significance of circumscribed hepatic atrophy would facilitate a more accurate diagnosis of this condition. This understanding would also enhance the precision of subsequent follow-up assessments. Ultimately, this would enable a more comprehensive delineation of the potential natural history of those apparently primitive forms of segmental or lobar atrophy.

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