Non-neoplastic hepatopancreatobiliary lesions simulating malignancy: can we differentiate?

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Abstract

Despite the success of cross-sectional imaging in evaluating hepatopancreatobiliary system malignancies, several non-malignant disease processes may closely mimic malignancy. Differentiating these benign diseases from malignancy may be difficult, or even impossible, even in the hands of experienced imagers. In this manuscript, we present benign mimics involving the hepatopancreatobiliary system and try to increase awareness of these potential pitfalls.

Keywords: Hepatobiliary, Pancreas, Neoplasm, Mimicker, Radiology

Key points

- Several infectious and inflammatory conditions may mimic neoplastic processes on imaging studies and differential diagnosis may be difficult.
- Clinical history and patient demographics are critical for correct diagnosis in addition to imaging findings.
- Image-guided biopsy may be used for definitive differential diagnosis in selected patients.

Introduction

Despite the success of cross-sectional imaging in evaluating hepatopancreatobiliary system malignancies, several non-malignant disease processes may closely mimic malignancy [1, 2]. Differentiating these benign diseases from malignancy may be difficult, or even impossible, even in the hands of experienced imagers. In this manuscript, we present benign mimics involving the hepatopancreatobiliary system and try to increase awareness of these potential pitfalls.

Liver

Liver is probably the most commonly affected organ in the abdomen in patients with malignancy. Secondary malignancies, in the form of metastases from different sources, far exceed the primary malignant diseases of the liver. The imaging diagnosis of primary hepatic tumors including hepatocellular carcinoma (HCC) and cholangiocellular carcinomas (CCC) is usually straightforward. Metastatic involvement of the liver is common and diagnosis is generally not problematic in patients with known primary malignancies outside the liver. The early detection of metastatic liver disease is important; as it is generally a sign of advanced disease and the patient’s treatment and prognostic expectations should be adjusted accordingly in the light of this finding. Both infectious and non-infectious tumor-like conditions mimic primary and secondary liver neoplasms. We will discuss the infectious mimics first, followed by non-infectious disease processes which may simulate a liver malignancy.

Infectious mimics

The liver is frequently affected in the course of various viral, bacterial, fungal, and parasitic infections. There are several predisposing local and systemic factors which may render liver more prone to infections, including, but not limited to, immunosuppression such as related to human immunodeficiency virus (HIV), several drugs, and surgery. The differential diagnosis may be difficult and a detailed patient history is critical for correct diagnosis.
**Candida albicans infection**

Fungal liver infections are most common in patients with compromised immune system or in cases of hematologic malignancies. It is a manifestation of systemic fungal infection [3]. Leukemia is the most commonly encountered predisposing factor for hepatic infection from *Candida albicans* [3].

Ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) may all be used for diagnosis. On US, the echogenicity of the parenchymal candida nodules vary significantly depending on the stage of the disease [4]. The most frequent patterns is detection of multiple hypoechoic subcentimeter lesions which may closely mimic lymphomatous or leukemic involvement as well as metastases from solid organ cancers [5].

CT is a very commonly used modality for diagnosis. The infectious parenchymal foci mostly appear as round low attenuation lesions with distinct margins (Fig. 1). The size generally ranges from 2 to 20 mm. Detection of a hyperattenuating rim surrounding a hypoattenuating center (“bull’s eye” appearance) in the arterial phase of the scan appears to be the most sensitive finding. In the portal-venous phase, lesions are often seen as subcentimeter hypoattenuating lesions [5–7].

On MRI, the nodules appear hypointense on pre-contrast T1-weighted (T1W) images with marked hyper-intensity on corresponding T2-weighted (T2W) images [8, 9]. Enhancement may be seen after contrast injection [9]. The signal intensities may evolve during the course of the disease. The T2 signal gradually fades away with the response to treatment [10]. MRI was reported to be superior to CT for detection of these fungal foci [8, 10].

**Fig. 1** A 61-year-old male with recently diagnosed AML undergoing chemotherapy now presenting with neutropenic fever. Axial plane postcontrast CT image demonstrates multiple well-defined hypodense liver lesions (arrows). Clinical and laboratory findings were consistent with candida infection. The findings almost completely resolved after antifungal treatment (not shown).

Differential diagnosis may be difficult and these lesions may easily be confused with metastatic disease. Clinical context and patient history are key factors for correct diagnosis. In patients who are undergoing an intensive chemotherapy for hematological malignancies, the acute emergence of fever, elevated serum CRP, and abnormal liver function tests are highly suggestive for hepatic candidiasis. Follow-up imaging after treatment may be helpful for confirming the diagnosis in some patients [11]. Sometimes, lesions paradoxically become more evident as the white count recovers and patient’s condition improves. Biopsy is typically not indicated for diagnosis in the setting of suggestive clinical history [1]. Despite all efforts, conclusive diagnosis may be impossible based on imaging findings and a percutaneous biopsy procedure may be needed for final diagnosis. Fungal micro-abscesses commonly involve the spleen as well. The spleen should be carefully scrutinized for coincident infection.

**Hepatic tuberculosis**

Tuberculosis (TB) is globally among the most common infectious diseases, with a variable distribution around the world. Liver involvement may be classified as either miliary form, where liver is involved in the course of systemic disease or as mass-forming localized form. The localized mass-forming (macronodular, >2 cm) hepatic TB lesions are typically seen as focal parenchymal lesions. Hepatic tuberculomas and tuberculous abscesses may be detected in this form [12–14].

As isolation of the slow-growing TB bacilli may be extremely difficult for definite diagnosis, imaging plays a crucial role in the diagnosis. Miliary lesions are typically observed as multiple subcentimeter lesions (generally less than 2 cm in size). These may be randomly distributed throughout the liver parenchyma but sometimes associated in clusters. These lesions may appear as solid or cystic, with minimal peripheral contrast enhancement. It may sometimes be difficult to differentiate them from metastases or lymphoma involvement [14].

Tuberculomas are usually detected as round lesions and may manifest as solitary or multiple lesions of varying sizes. This form is rare as compared to the miliary form and may closely mimic metastatic disease or a primary liver tumor. Tuberculomas are generally larger than 2 cm in size and are also referred to as macronodular or pseudotumoral TB [14]. Tuberculomas may be seen as hypoechoic solid masses on US; however, hyperechogenicity may also be occasionally seen [15–17]. On CT, the imaging findings are generally not conclusive and they are mostly observed as hypoattenuating lesions with ill-defined borders with surrounding edema. MRI findings are also not very specific and they are usually hypointense on T1W images and hypo, iso, or hyperintense on T2W images with a peripheral hypointense rim [18]. Postcontrast images typically
demonstrate peripheral rim-shaped enhancement with occasional heterogenous septal enhancement (Fig. 2) [13, 14]. The peripheral enhancement pattern may be useful for differentiating tuberculomas from neoplastic disease such as HCC and hypervascular metastases [13]. Cystic metastases from the ovaries and gastrointestinal system may look similar but detection of the perilesional edema, which is more conspicuous on T2W images, is more characteristic for a TB or pyogenic abscess over a cystic metastasis.

Hepatic TB should be considered in the differential diagnosis in patients with suggestive clinical findings such as documented TB elsewhere in the body or a history of prior TB. The demographics of the patient as well as the country of origin (in migrant and refugee patients) may also be other helpful clinical clues. However, percutaneous biopsy should be needed in certain clinical circumstances where noninvasive definitive diagnosis cannot be done.

**Hydatid disease**

Hydatid disease occurs in humans incidentally infected with *Echinococcus granulosus* and *Echinococcus multilocularis*. Right lobe is the most frequently involved part of the liver in patients infected with the cystic hydatid disease caused by *E. granulosus*. The imaging findings are highly variable depending on the stage of the disease. US primarily shows anechoic or multisepatated lesions with variable degree of calcification. CT typically demonstrates a hypodense, large lesion with walls having minimal or no enhancement (Fig. 3). In case of detaching endocyst, the detached wall appears as an undulating structure. Daughter cysts may also be visible at different stages of the disease and when present they are pathognomonic. The presence of hypointense wall...
on both T1- and T2-weighted images is characteristic for cystic hydatid disease. Contrast enhancement of the cyst is typically not detected on either CT or MR images, a finding that may serve as a helpful feature to differentiate degenerated hydatid cysts from cystic biliary cystadenomas/cystadenocarcinomas.

*E. multilocularis* infection, the alveolar form of hydatid disease, may be more difficult to differentiate from malignant lesions of the liver. The disease is biologically aggressive and typically presents as a solid, infiltrative heterogeneous mass with indistinct borders (Fig. 4). There may be small cysts. Nodular and dystrophic calcifications may be detected (Fig. 5) [1]. On CT, the mass also typically includes hypoattenuating areas corresponding to necrosis and parasitic tissue. In certain cases, *E. multilocularis* infection may simulate a large hemangiomma or a cholangiocellular carcinoma. There may be mild delayed peripheral enhancement, which corresponds to the fibroinflammatory peripheral rim, in both postcontrast CT and MRI studies (Fig. 6) [19]. On MRI, the lack of diffusion restriction in the mass is a helpful finding for differentiating alveolar echinococcosis from malignant neoplasms such as cholangiocarcinoma [19]. Familiarity with the characteristic imaging findings of alveolar echinococcosis with supportive serologic and clinical information is essential for diagnosis in patients from endemic regions.

Percutaneous treatment may be successfully used for treatment of *E. granulosus* infection but surgery is typically indicated for *E. multilocularis* infections. The most fearsome potential complication of percutaneous treatment of hydatid cyst is anaphylactic reaction. Despite the fact that it is rare, it can be fatal and therefore the interventionalist should take relevant precautionary measures before starting the procedure [20].

**Pyogenic and amebic liver abscesses**

Hepatic abscesses may be secondary to fungal, bacterial, or amebic infections. Pyogenic abscesses represent the
The vast majority of these abscesses with *Escherichia coli* and *Clostridium* species being the common causative agents [21]. Solitary hepatic abscesses are often cryptogenic with no clear-cut source to be identified [22, 23]. CT typically shows a hypoattenuating cystic lesion with surrounding parenchymal edema (Fig. 7). This parenchymal edema is a very useful sign for differentiating pyogenic abscesses from cystic metastases. However, it should also be noted that some solitary liver abscesses may present as mostly solid lesions with no identifiable underlying risk factor. Without perilesional edema and typical septations, liver abscess may be difficult to recognize (Fig. 8). Also, the presence of fever is not a universal feature of liver abscesses, further complicating diagnosis. The absence of centrally progressing contrast enhancement on delayed phase images and progressive enhancement in the outermost layer corresponding to the fibroinflammatory capsule of the abscess may be helpful for differentiating mostly solid appearing pyogenic abscesses from intrahepatic cholangiocarcinomas. It is also difficult to differentiate necrotic liver tumors from abscesses. Nodularity in the internal surface of the lesion wall, focal calcifications within the lesion, and the absence of perilesional edema favors necrotic neoplasm over an abscess [24]. Follow-up imaging after empirical treatment for liver abscess may also be

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**Fig. 6** A 33-year-old female with no known past medical history presented with gradually increasing right upper quadrant pain. Abdominal postcontrast CT demonstrates a hypoattenuating centrally necrotic massive mass lesion (arrows). There was no evidence of obvious enhancement after contrast injection. Percutaneous biopsy revealed alveolar hydatid cyst.

**Fig. 7** A 70-year-old male with known colon cancer under complete remission underwent a routine screening CT examination. Axial plane postcontrast CT image revealed 5 cm predominantly solid mass (arrows) within the left liver lobe. The patient was completely afebrile and free of any abdominal pain at the time of the CT scan. Percutaneous biopsy confirmed liver abscess with no evidence of neoplastic cells. Follow up CT scan (not shown) after IV antibiotics confirmed significant regression of the lesion.

**Fig. 8** A 64-year-old female with previously surgically treated pancreatic adenocarcinoma now presenting with a hypoechoic focal liver lesion detected in outside US. Clinically the patient was in complete remission for her tumor and her prior abdominal scan was normal. She was asymptomatic and had no fever. **a** Axial plane T2W MR image demonstrates a moderately hyperintense focal lesion (arrows) in the right liver lobe. **b** Axial plane postcontrast T1W MR image at the late arterial phase demonstrates marked ring enhancement in the periphery of the lesion (arrows) which was considered to be highly suspicious for an adenocarcinoma metastasis. Percutaneous biopsy did not demonstrate any neoplastic cells but was interpreted as an abscess. Follow up CT scan (not shown) after intense IV antibiotic treatment showed complete disappearance of the lesion.
implemented as an alternative approach for differential diagnosis. However, morphological changes may also be observed during the natural course of the disease without any therapeutic intervention. In patients where no diagnosis could be achieved in a noninvasive manner, percutaneous biopsy may be utilized for definitive treatment planning.

Amebic abscesses are caused by the protozoan Entamoeba histolytica [21]. In around 70% of the cases, a solitary abscess within the right liver lobe is detected. US typically shows a round or oval shaped, hypoechogenic lesion without any significant wall echoes [25]. On contrast enhanced CT, amebic abscess usually may appear as round shaped, hypodense lesions with ill-defined borders (Fig. 9). An enhancing wall and a peripheral edema are also a common feature. Also, septations may be seen within the abscess cavity [24, 26].

**Eosinophilic liver abscess**

Eosinophilic liver abscess (ELA) consists of focal eosinophil-related parenchymal liver necrosis. Hepatic eosinophilia and hepatic eosinophilic granuloma are alternative terms for this clinical entity. Most cases are incidentally diagnosed in asymptomatic patients who also typically have peripheral eosinophilia. The disease usually runs a benign course. Hepatic migration of parasitic larvae has been implicated in the etiology; however, medications, allergic, and neoplastic diseases have also been considered in the pathogenesis [27]. This is a rare clinical condition and may mimic liver metastases on imaging studies (Fig. 10) [28].

Typically, ELAs are seen as multiple small, hypodense, and oval-shaped lesions on CT [27]. Multifocality and a history of parasitic disease may be helpful for differential diagnosis. Follow-up imaging may also show regression of the liver lesions which may be helpful for differential diagnosis. However, definitive diagnosis almost always requires histopathologic confirmation [29].

**Fascioliasis of the liver**

Fascioliasis is an infection caused by Fasciola hepatica flatworm. The larvae are acquired by ingesting infected water. The parasites may stay dormant within the liver parenchyma for years and this chronic presence typically leads to chronic parenchymal inflammation [30]. The typical imaging findings include tunnel-shaped microabscesses and necrotic parenchymal cavities along the migration tract of the larva. These tunnels often extend from Glisson’s capsule to the central portions of the liver [30]. Peripheral eosinophilia is a common finding in fascioliasis and may be helpful to reach a correct diagnosis [31]. Imaging presentation may mimic malignant processes in some patients (Fig. 11). Histopathologic diagnosis may be necessary in these patients for correct diagnosis, particularly without antecedent imaging findings that show tunneling tracts.

**Rare granulomatous liver infections**

Spirochetal infections of the liver are rare in the postantibiotic era [32]. Spirochetal hepatitis can lead to cirrhosis, and the detection of gummas, caseating, and non-caseating granulomas and focal necrosis around the hepatic veins are characteristic histologic findings [33, 34]. Liver involvement may be seen in secondary and tertiary stages of syphilis. Focal gumma may develop in the liver typically 1–10 years after the original infection [35]. There is not much information in the imaging
literature due to the rarity of hepatic involvement. However, it appears that low attenuation lesions with peripheral enhancement on CT (Fig. 12) are a potential finding. Calcification may also be rarely present [36, 37].

*Francisella tularensis* is a Gram-negative coccobacillus endemic to many parts of North America. The most common presentation is the ulceroglandular form. Untreated disease can spread to multiple organs. Liver involvement is common and may be observed in 75% of cases with extralymphatic organ involvement [38]. The spectrum of findings in tularemia is considered to be in the spectrum of granulomatous hepatitis [39]. Visible hepatic abscess can form, which in our experience can appear quite solid on CT (Fig. 13).
Bartonellosis is among the causes of fever of unknown origin and unusual presentations may happen in 0.3–10% of cases [40]. In cases with hepatic and splenic involvement, granulomatous inflammatory process is typically the hallmark pathologic finding. Imaging findings are non-specific but hypoenhancing or non-enhancing focal parenchymal lesions may be observed (Fig. 14a). MR imaging features are not well described, with only anecdotal case reports. T2 hyperintensity and postcontrast enhancement on T1W images are among the reported findings (Fig. 14b). Calcifications may appear within these nodules on long-term follow-up [3, 41]. The nodules may easily be confused on CT and MR with hypoenhancing metastases. It should also be noted that the disease may appear as a single mass within the liver parenchyma mimicking a primary hypoenhancing cholangiocellular carcinoma.

**Actinomycosis of the liver**

Actinomyces are slow growing, Gram-positive, branching bacilli. They are most frequently associated with infections in the cervicofacial region. Abdominal involvement is rare, where iliocecal area is the most frequently affected region. Hepatic infection has been reported to be seen in 15% of those with abdominal infection and, overall, represents 5% of all cases with actinomycosis [42]. Imaging studies may reveal multiple or solitary lesions, a single hypointensuating mass the most common presentation (Fig. 15) [43]. T1 hypointensity, with variable contrast enhancement, and associated T2 hyperintensity are the commonly encountered findings on MRI studies (Fig. 16) [44].

**Pneumocystis jirovecii infection of the liver**

*Pneumocystis jirovecii* is a common opportunistic infection in immunocompromised and HIV-infected patients and lung is the most commonly involved organ. Liver involvement is not common, but when present, hypodense lesions within the liver and spleen may be seen on CT (Fig. 17). The differential diagnosis from a neoplastic process is even more difficult when infection is the presenting symptom of unrecognized retroviral infection. In our limited experience, lesions are almost always multiple rather than solitary. Clinical and medication history as well as the immune status of the patient are key factors.
for the correct diagnosis. The presence of associated lung findings may also be helpful.

Sarcoidosis
Sarcoidosis is a systemic granulomatous disease. The exact etiology is obscure and the detection of non-caseating granulomas on pathology specimens is characteristic for this disease. Lungs are the most commonly involved organs but virtually any organ can be affected in the course of the disease [45]. Liver is the third most commonly affected organ after lung and lymph nodes and in most cases hepatic involvement occurs in the course of systemic disease. However, isolated liver involvement had also been reported [45]. The detection of liver involvement may be delayed as most of the affected patients are asymptomatic [46]. Although the liver is commonly involved, in only 5% of sarcoid cases will liver lesions be detected with CT [47]. Liver involvement in sarcoidosis may present in diffuse or focal nodular patterns [46]. Focal lesions are typically small and randomly scattered throughout the liver parenchyma. On CT, the lesions are mostly hypoattenuating without significant contrast enhancement (Fig. 18). MR imaging may also be helpful for lesion detection. Concurrent splenic lesions should be sought, as these are often more readily detected than sarcoid in the liver. From an imaging standpoint, differentiation from metastatic disease, lymphomatous involvement, or other infectious processes may be difficult without relevant clinical and serologic information.

Elevated serum ACE levels are a relatively common finding which may act as a supportive information to reach the diagnosis. Despite best efforts, image-guided percutaneous biopsy may be necessary for definitive diagnosis [45].

IgG4-related focal liver disease
IgG4-related disease commonly affects the liver and the biliary system. Histopathologically IgG4-related hepatic disease is characterized as a fibroinflammatory condition with dense lymphoplasmocytic infiltrate rich in IgG4-positive plasma cells with or without elevated serum IgG4 levels [48]. Focal parenchymal mass with well-defined borders is relatively rare in patients with liver involvement [49]. Differentiation from liver malignancy
may be extremely difficult without proper history and pathological analysis (Figs. 19 and 20) [48, 50].

**Inflammatory pseudotumor of the liver**

Inflammatory pseudotumor of the liver was first described in 1953 and more than 200 patients have since been reported [51, 52]. The etiology remains largely unknown but autoimmune reactions, infectious hepatitis, and bacterial infections have all been implicated in the etiology [53]. In certain patients, differential diagnosis from neoplastic liver lesions may necessitate percutaneous biopsy and histopathologic confirmation. Inflammatory pseudotumors have been reported to simulate HCC in patients with viral hepatitis [53].

On US, lesions generally appear hypoechoic in the right liver lobe [54]. CT findings are highly variable. Early arterial phase enhancement mimicking an HCC or hypervascular metastasis, peripheral enhancement mimicking a cholangiocellular carcinoma or metastasis, and wash-out in the venous phase suggesting an HCC have all been reported [54, 55]. On MRI, these lesions appear hypointense on pre-contrast T1W images and iso-hyperintense on T2W images. Heterogenous or peripheral enhancement is common after contrast injection (Fig. 21) [56, 57].

**Dropped gallstones**

Dropped gallstones (DS) may be seen after approximately 7% of laparoscopic cholecystectomies as a result of the rupture of gallbladder wall during dissection and removal of the gallbladder [58]. These DSs may become symptomatic in rare instances. Correct diagnosis might be extremely challenging and delayed due to atypical modes of clinical presentation and unexpected locations of these DSs [59]. Meticulous dissection and aspiration of the gallbladder during surgery comprise important factors to prevent this complication [60]. These DSs may become symptomatic with a median time interval of 5 months after the surgery, but symptoms were reported to appear even 20 years after the procedure [58].

Focal inflammation with abscess and fistula tract formation are relatively common complications. The detection of hyperdense structures within necrotic abscesses (in cases with dropped calcified gallstones) may be an important diagnostic clue. The location of the collection/inflammation adjacent to the liver capsule may also be regarded as a suggestive finding. Other rare complications include erosion into large bowel and bowel obstruction due to adhesion formation [58]. In patients with known malignant tumors, inflammation in hepatorenal fossa due to dropped gallstones may mimic an implant and histopathologic evaluation may be necessary (Fig. 22). Dropped gallstones may also be seen in the gallbladder fossa and differentiation from a primary focal liver malignancy may again be extremely difficult (Fig. 23).

**Gallbladder and the biliary system**

Biliary dilatation and asymmetric gallbladder (GB) wall thickening are fearsome imaging findings, often indicating a pancreatobiliary system cancer or biliary stone disease. Despite these common entities, several non-neoplastic diseases may also affect the biliary system and may cause biliary system abnormalities. Primary adenocarcinoma of the gallbladder is a highly aggressive malignancy with grave prognosis. In certain patients, the gallbladder may be completely replaced by the tumor, a finding that makes difficult to conclude the source organ. However, the diagnosis may be generally made based on imaging findings. Despite this relative ease of diagnosis, one should keep in mind the several non-neoplastic mimickers of this cancer including xanthogranulomatous cholecystitis [61].

**Gallbladder-associated pseudomasses**

Adenocarcinoma of the gallbladder is one of the deadliest hepatobiliary cancers. Some small cancers are incidental discoveries at cholecystectomy. When diagnosed with GB cancer by imaging, most patients are at an advanced stage with local lymph node metastases and parenchymal liver invasion. For these reasons, correct diagnosis is of critical importance and potential mimics should be considered.

Xanthogranulomatous cholecystitis (XGC) is a rare variant of chronic cholecystitis. Despite the fact that it is a benign disease, the inflammatory process may be infiltrative and locally destructive. There is asymmetrical
thickening of the gallbladder wall, with the inflammatory process extending into liver parenchyma, omentum, and duodenum (Fig. 24) [62]. Because of close resemblance of the imaging findings, patients with XGC might undergo radical surgical procedures with a misdiagnosis of primary gallbladder adenocarcinoma. The adjacent liver parenchyma may also show abnormal enhancement.

**Fig. 18** A 60-year-old male with previously treated lymphoma, in complete clinical and imaging remission, now presents with fatigue, fever, and malaise. **a** Abdominal US image demonstrated several hardly discernible subcentimeter lesions throughout the liver parenchyma. Only one lesion was larger than a centimeter (arrows). **b** Axial plane postcontrast CT image demonstrates innumerable hypodense lesions (arrows). **c** On PET-CT, these lesions were found to be metabolically active with intense FDG uptake (arrows). Chest and neck CT studies were unremarkable (not shown). Percutaneous biopsy surprisingly showed noncaseating granulomas consistent with sarcoidosis. Symptoms and imaging findings promptly resolved after corticosteroid treatment.

**Fig. 19** A 70-year-old male with no significant past medical history presenting with focal hypoechoic liver mass on an US exam performed for new onset right upper quadrant pain. **a** Axial plane T2W image demonstrates moderately hypointense mass (arrows) in the right liver lobe. **b** Same lesion demonstrates mild peripheral enhancement with no significant central contrast filling (arrows). The putative diagnosis was cholangiocellular carcinoma. Post biopsy pathologic examination confirmed IgG4-related focal liver pseudomass with no evidence of neoplastic cells.
which may falsely suggest parenchymal invasion. Enlarged lymph nodes may be seen in both gallbladder cancer and XGC, and cholelithiasis is common in both. Intramural hypoattenuating nodules on CT in the thickened gallbladder wall may serve as a helpful finding for diagnosing XGC over gallbladder adenocarcinoma. On MRI, the detection of the fatty content in these nodules could be detected by chemical-shift MR imaging [63]. Cholecystectomy may be necessary for definitive diagnosis in certain patients [62].

**Tuberculous cholangitis**
Clinical presentation of biliary involvement in patients with tuberculous cholangitis is usually insidious. Among the commonly reported symptoms are abdominal pain, fever, weight loss, and jaundice [64]. Imaging findings may mimic neoplastic disorders especially in patients with significant mural contrast enhancement and sclerosing biliary obstruction (Fig. 25). Endoscopic retrograde cholangiopancreatography (ERCP) findings may mimic primary sclerosing cholangitis with alternating stenotic and dilated biliary radicals and associated wall irregularities within bile duct walls. These ERCP findings may be seen in other conditions such as leukemia, lymphoma, solid tumor metastases, and hepatic amyloidosis [65].

**IgG4-related sclerosing cholangitis**
IgG4-related sclerosing cholangitis is frequently associated with autoimmune pancreatitis (AIP). Bile ducts are the most commonly involved body part aside from the pancreas in IgG4-related disease. However, isolated biliary involvement may also be seen without obvious pancreatic involvement [66, 67]. Histopathologically, biliary involvement is characterized with infiltration of bile ducts with IgG4-positive plasma cells and associated extensive fibrosis. Both intrahepatic and extrahepatic bile ducts may be involved in IgG4-related sclerosing
cholangitis in diffuse or isolated patterns. Intrapancreatic distal portion of the common bile duct is the most commonly affected biliary segment [66, 68]. Wall thickening and irregularity with associated contrast enhancement and luminal stenosis are typical imaging findings. Focal involvement of distal common bile duct or hilar hepatic involvement with upstream dilation of biliary system may closely mimic a hepatic cholangiocarcinoma or a pancreatic head mass (Fig. 26) [66, 68].

On CT, biliary involvement is typically seen as focal or diffuse wall thickening with contrast enhancement. Biliary stricture with associated enhancing soft tissue mass may also be seen on postcontrast studies which can simulate a cholangiocarcinoma [66, 68].

In IgG4-related sclerosing cholangitis, CT and MRI typically demonstrates concentric soft-tissue thickening of the bile duct wall with homogeneous enhancement in the delayed phase. Associated luminal irregularities are found not only in stenotic segments or in the vicinity of the soft tissue mass but also in areas without any sign of stenosis [68]. Although a thick, annular rind of soft-tissue encasing the affected duct suggests IgG4-related sclerosing cholangitis, this finding may also be seen, to a milder degree, in patients with primary sclerosing cholangitis or infectious...
cholangitis [66]. Although elevated serum IgG4 levels and associated extrabiliary disease (especially the involvement of the pancreas or the kidneys) may act as a supportive finding, in some patients percutaneous or endoscopic biopsy may be necessary.

Pancreas
Pancreatic malignancies have significant morbidity and mortality. Pancreatic adenocarcinoma has dismal survival rates which have not changed significantly over the last few decades, despite advances in medical and surgical oncology. Around 90% of patients who were diagnosed with pancreatic cancer are expected to die eventually from the disease [69]. Acute or chronic pancreatitis are common pancreatic diseases that may sometimes be confused with pancreatic cancers.

IgG4-related autoimmune pancreatitis
AIP is the most common manifestation of IgG4-related systemic disease. AIP type 1 (also known as lymphoplasmacytic sclerosing pancreatitis) is seen mostly in middle aged men, whereas AIP type 2 is frequently a disease of a younger population [67]. Type 1 AIP represents the pancreatic manifestation of systemic IgG4-related disease and type 2 AIP is typically a pancreas-specific disorder with no extrapancreatic involvement (e.g., proximal biliary stricture, submandibular gland involvement, or retroperitoneal fibrosis) [70]. Imaging-based differentiation between these two subtypes is currently not possible and differentiation is based mainly on histopathological evaluation [71].

From an imaging standpoint, diffuse enlargement of the pancreas is a commonly encountered finding but focal or
mass-like enlargement is not unusual. Diffuse enlargement was reported in between 11 and 56% of patients, whereas focal or mass-like enlargement was observed in 28–59% of the cases (Fig. 27) [72]. Irregular narrowing of the main pancreatic duct is another important feature [67]. Peripancreatic fat planes are typically preserved with no evidence of fluid collection or peripancreatic inflammation, which are commonly seen in acute pancreatitis.

Given the overlap of clinical and imaging features between focal AIP and pancreatic cancer, several studies have sought to differentiate AIP from pancreatic malignancies. Dilation of the main pancreatic duct is mild in patients with AIP as compared to pancreatic adenocarcinoma. Indeed, upstream dilatation of the main pancreatic duct is rarely greater than 4 mm in patients with AIP [73]. The pancreatic duct penetrating through the pseudomass, also known as the duct-penetrating sign, is considered to be a helpful sign for differentiating AIP from pancreatic cancer [67].

**Focal pancreatitis mimicking pancreatic neoplasm**

Mass forming focal pancreatitis, by definition, refers to a focal inflammatory process which can sometimes closely mimic pancreatic cancer. Imaging differentiation between a cancer and mass forming focal pancreatitis can sometimes be extremely difficult or impossible [74].

Several studies based on either CT or MRI found no meaningful difference between these two entities in signal characteristics or contrast enhancement patterns [75]. Both are hypo- or isoattenuating to pancreatic parenchyma on CT and are hypointense or isointense on T1-weighted MRI images (Fig. 28). Gradual progressive enhancement is common after contrast injection. The differentiation from a primary adenocarcinoma may be particularly difficult when the clinical presentation does not suggest acute pancreatitis. The abundance of fibrosis in both conditions is probably the underlying reason for these similar imaging features [76]. Histopathologic evaluation or close follow-up imaging is almost always indicated for diagnosis.
Pancreatic tuberculosis

Isolated pancreatic tuberculosis (TB) is an extremely rare clinical entity, even in parts of the world where TB is prevalent. Clinical and imaging findings may closely mimic pancreatic cancer and differential diagnosis may be difficult [77]. Abdominal pain, jaundice, and weight loss are the most common presenting symptoms in both clinical situations [78]. The disease may focally or

**Fig. 28** A 54-year-old female with known alcohol induced chronic pancreatitis and chronic pain now presenting with unusually intense epigastric pain. **a** T2W MRI demonstrates a hypointense ill-defined 3-cm-diameter solid mass (arrows) in the pancreatic body/tail with downstream ductal dilatation, likely related to patient’s known chronic pancreatitis. **b** Axial plane postcontrast T1W image demonstrates heterogeneous enhancement of this lesion (arrows). The patient was scheduled for surgical excision. **c** Two weeks after the initial MRI scan, immediately before the planned surgery, the CT scan showed that the mass had almost completely resolved without any treatment. Based on these findings, the mass was considered to represent a pseudomass due to focal pancreatitis.

**Fig. 29** A 62-year-old male with no prior significant medical history presented with gradually increasing epigastric pain and weight loss. **a** Axial plane postcontrast late arterial phase CT image demonstrates diffusely thickened and heterogeneously enhancing pancreas (arrows) with ductal dilatation. **b** There was abrupt cessation of the pancreatic ductal dilatation (arrows) at the location of the pancreatic head mass. Image-guided percutaneous biopsy of the head lesion demonstrated TBC bacillus. The patient was then placed on multidrug antituberculosis treatment. Head, neck, and chest CT scans did not reveal any evidence of disease elsewhere. **c** Axial plane fat-suppressed T2W image 28 months after the initial scan showed significant regression of the pancreatic findings. At the time of this MRI scan, the patient was asymptomatic.
diffusely involve the pancreas. Focal involvement typically presents as a hypoattenuating mass on CT (Fig. 29) and histopathologic examination is almost always necessary for diagnosis. Enlarged peripancreatic lymph nodes with central necrosis may be seen as an associating finding in some patients [79]. Diffuse involvement, a rare presentation of pancreatic adenocarcinoma, may also be difficult to differentiate from primary pancreatic malignancy.

Pancreatic septic embolus

Septic embolism (SE) is a potentially mortal cause of infection. It can appear in both the early and late phases of infectious diseases. Septic emboli to the brain and the lung have been most extensively studied. Embolic infarcts within pancreatic parenchyma have been reported in patients with multi-organ embolization where brain, spleen and myocardium are also affected [80]. Abdominal pain is a common symptom with associated leukocytosis and elevated amylase levels [81, 82].

There is limited information in the literature regarding the imaging findings of pancreatic SE. The embolic foci appeared as hypoattenuating focal lesion within the pancreatic parenchyma, thus mimicking a neoplastic process (Fig. 30). Multifocal hypodense foci may also mimic lymphomatous infiltration or metastases to the pancreas. Despite the fact that multifocal pancreatic adenocarcinoma is rare, that diagnosis should also be considered in the differential diagnosis. Close imaging follow-up after antibiotic treatment is advisable both for confirming diagnosis and for evaluating the response to treatment. Involvement of different organs due to septic emboli, in addition to pancreas, may be a helpful finding for correct differential diagnosis.

Conclusion

Several non-neoplastic abnormalities may simulate malignant disease and differential diagnosis may be difficult by imaging alone. However, the imaging characteristics and enhancement pattern of the lesion with the assessment of vascular involvement may be very helpful. Co-involvement of the spleen should raise the possibility of an infectious or inflammatory process, as should discrete cystic foci in a solid lesion. Multimodality imaging in relevant cases may also be extremely useful by delineating the different imaging aspects of the same lesion. Besides all these parameters, patient demographics, clinical symptoms, and signs such as fever, laboratory data, tumor markers, short-term changes of imaging findings, and imaging findings of diffusion-weighted imaging (DWI) should all be taken into account for correct diagnosis. Close communication with the referring physician is another important point to be considered. It should be borne in mind that many unusual infectious and non-infectious inflammatory lesions may be sampled for diagnosis with imaging guidance and that this approach is safe in experienced hands and should be liberally used as a tool for early diagnosis.

Abbreviations

ADC: Apparent diffusion coefficient; AIP: Autoimmune pancreatitis; AML: Acute myeloid leukemia; CCC: Cholangiocellular carcinoma; CT: Computed tomography; DS: Dropped gallstones; DWI: Diffusion-weighted imaging; ELA: Eosinophilic liver abscess; ERCP: Endoscopic retrograde cholangiopancreatography; HCC: Hepatocellular carcinoma; HIV: Human immunodeficiency virus; MRI: Magnetic resonance imaging; PET-CT: Positron emission tomography-computed tomography; SE: Septic embolism; T1W: T1-weighted; T2W: T2-weighted; TB: Tuberculosis; US: Ultrasound; XGC: Xanthogranulomatous cholecystitis
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