CONTINUING EDUCATION PROGRAM: FOCUS...

Infections of the right hypochondrium

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Keywords: Cholecystitis; Cholangitis; Abscess; Bile ducts

Abstract Among the infectious diseases of the right hypochondrium, cholecystitis, cholangitis, and liver abscesses predominate. These are frequently encountered diseases, but they can still raise questions in daily practice. In this elaboration, we will thus address and illustrate: the major infectious diseases of the liver and gallbladder, and their radiological features; the potential interpretation problems and differential diagnoses; the diagnostic and therapeutic strategies used in imaging to manage infections of the right hypochondrium.

Infections of the right hypochondrium include some common, well-known diseases: cholecystitis, cholangitis, and liver abscess. However, certain difficulties can arise in terms of etiologic or differential diagnosis and management. In this elaboration, we will thus focus on these issues by selecting and illustrating those that are most often seen in daily practice.

Cholecystitis

What is the role of ultrasound?

Studies comparing strategies for biliary disease that begin with either ultrasound or CT scan have confirmed the role of ultrasonography as the first-line examination [1]. This was also used in 2010 by the French National Gastroenterology Society Clinical Practice Recommendations for the management of cholelithiasis [2], which establish the following criteria for diagnosing cholecystitis:
- gallbladder calculus;
- Murphy’s sign on ultrasound;
- gallbladder wall greater or equal to 4 mm;
- fluid around gallbladder.

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doi:10.1016/j.diii.2012.04.005
A combination of the first two signs (presence of a calculus and Murphy’s sign on ultrasound) is a major criterion for clinical suspicion of cholecystitis, with a 92% positive predictive value for that diagnosis [3]. As several authors point out, a diagnosis of cholecystitis should also be made with caution in the absence of gallbladder distension (transverse diameter greater than 4 cm) [4].

What are the main limitations of these criteria?

The relationship between gallbladder calculus and cholecystitis is of course not a direct one: of all patients with a gallbladder calculus, fewer than 15% become symptomatic and fewer than 5% develop cholecystitis [5]. In contrast, in 5 to 10% of cases of cholecystitis, there is no lithiasis.

With respect to the criterion of gallbladder wall thickening, it is well known that a wall greater or equal to 4 mm is not specific to cholecystitis (Fig. 1a–b): it can be seen in cases of ascites, heart failure, hypoproteinemia, hepatitis, and other diseases in the vicinity (perforated ulcer, pancreatitis, pyelonephritis, etc.), especially if the gallbladder is empty, and in the differential diagnoses that we will see later. Finally, Murphy’s sign on the ultrasound can be absent in two-thirds of the serious forms [6]. In those forms, on the ultrasound, we should look for the potential presence of echogenic membranes floating in the gallbladder lumen (Fig. 2): this sign does not have much sensitivity, but does have very good specificity for the diagnosis of gangrenous cholecystitis [7].

Figure 1. Thickening of the gallbladder wall visible in the absence of any cholecystitis: a: related to the presence of ascites; b–c: in a context of acute viral hepatitis on the ultrasound (b) and CT scan (c).
What is the value of other procedures (CT scan, MRI)?

MRI
Some authors [8] have defended the value of the MRI as the first-line examination for biliary disease. This obviously raises the problems of device availability and feasibility in an emergency situation. Contrary to the CT scan, we would also point out the difficulty the MRI has with differentiating gas from calculi or calcification (for example, for identifying emphysematous cholecystitis or porcelain gallbladder). However, for recognizing gas, we can make use of the fact that it rises and that gas generates greater magnetic susceptibility artefacts than calculi in all MRI sequences except heavily T2-weighted sequences.

CT scan
We use the following criteria for CT scan diagnosis of cholecystitis (the first two are not specific to the CT scan, but shared with ultrasound):
• gallbladder calculus;
• wall thickening;
• fat stranding around gallbladder — best sign on a CT scan;
• transient pericholecystic hepatic enhancement (when an arterial phase acquisition was done): this sign of local inflammatory involvement can help in cases of diagnostic doubt.

It is particularly valuable to perform a CT scan to reveal serious gangrenous forms, for which the following signs each have between 97 and 100% specificity [9]:
• gas in the wall or lumen;
• intraluminal membranes;
• breach in the gallbladder wall;
• pericholecystic abscess.

Perforations may cause various complications depending on the duration of the problem:
• acute forms (10% of cases), responsible for peritonitis or hemorrhaging;
• subacute forms (60% of cases), responsible for abscesses;
• chronic forms (30% of cases), responsible for gallstone ileus (or Bouveret’s syndrome when the site of the occluding gallstone is the duodenum).

What are the possible pitfalls of a CT scan?

As with ultrasound, thickening of the gallbladder wall is not specific to cholecystitis, with the same etiologies as those reviewed above (Fig. 1c).

The important limitation of CT scanning for biliary exploration is due to its poor performance in detecting calculi (Fig. 3): as a reminder, one in five calculi is actually invisible on a CT scan [10]. Due to this fact, often unknown to referring physicians, caution should be used when writing CT scan reports: rather than “no calculi,” wording such as “no calculi that are dense enough to be visible on the CT scan” can remind physicians that CT is not the gold standard for this purpose. On the contrary, misleading images can, on rare occasions, result in an incorrect diagnosis of gallbladder calculus if slices without contrast are not obtained (Fig. 4). Finally, the presence of gallbladder gas can sometimes suggest the possibility of emphysematous cholecystitis (Fig. 5): but remember that it is not rare to see gas within calculi (sometimes invisible themselves), irrespective of any infectious complication [11].

What are the differential diagnoses for cholecystitis?

In 20% of patients clinically suspected of having cholecystitis, imaging makes it possible to discover another diagnosis that does not always require surgical treatment, hence the importance of the radiological study [5].

Gallbladder cancer
It is not always easy to differentiate between infectious and tumor disease (Fig. 6). While certain presentations are immediately identifiable as tumoral, many cases of gallbladder cancer are only discovered by surgery or biopsy. Thus, 1 to 3% of cholecystectomies lead to an incidental discovery of cancer. When there is an abnormality of the gallbladder wall, the following CT criteria point toward a neoplastic rather than an infectious condition [12]:
• asymmetrical thickening greater than 1 cm;
• early enhancement;
• irregular, poorly delimited external margins.

Adenomyomatosis of the gallbladder
One must be able to recognize a case of simple adenomyomatosis of the gallbladder, which requires no treatment if asymptomatic. Remember that this is a common disease, with 3 to 5% prevalence, combining parietal hyperplasia with cystic cavities corresponding to dilated Rokitansky-Aschoff sinuses. The possible forms are focal (most often at the
Figure 3. Poor sensitivity for detection of gallstone on the CT scan: a: in the same patient, the gallbladder appears to have no lithiasis on the CT scan; b–c: however, the gallstones are quite visible on the MRI (b) and ultrasound (c).

Figure 4. Gangrenous cholecystitis with extension of abscessing to the adjacent hepatic parenchyma. Note the presence of gas in the vesicular lumen (emphysematous form): a: a dense rounded image may suggest the presence of a calculus on this CT scan with contrast; b: the scan before injection of the contrast product does not show this image: this is actually a pseudoaneurysm of the cystic artery, complicating the infectious disease.
fundus of the gallbladder), diffuse, and rarely segmental, with circumferential thickening of the mid gallbladder wall. The diagnosis can be made by ultrasound when it shows mural images with “comet tail artifact” related to reverberations or cholesterol debris within dilated Rokitansky-Aschoff sinuses [7]. The CT scan is not very successful for diagnostic purposes. If in doubt, we suggest an MRI to look for cystic spaces filled with bile within the mural thickening on heavily T2-weighted sequences (Fig. 7); we can thus diagnose adenomyomatosis with 62% sensitivity and 92% specificity [13].

What is the treatment?

Acalculous cholecystitis

This particular important case requires special management and raises specific diagnostic problems since, by definition, it should be possible to diagnose even in the absence of calculi. A suggestive context (patient in CCU or ICU) can aid in making a diagnosis, but that renders the usual criteria ineffective: thus, even irrespective of any cholecystitis, gallbladder distention is present in 59% of ICU patients and mural thickening in 25% [14]. In these patients, if there is
a clinical suspicion, one must be able to suggest a percutaneous cholecystectomy, despite the absence of reliable imaging criteria. In fact, it is ultimately the favorable outcome after such an interventional radiological procedure that retrospectively confirms the initial suspicion of acalculous cholecystitis, while at the same time treating the patient.

Cholecystitis with lithiasis
The advent of laparoscopy led to a discussion of the respective roles of early surgery (fewer than 4 or 7 days after the onset of symptoms) and delayed surgery (6 to 8 weeks after the onset of symptoms): in the case of early laparoscopic cholecystectomy, the hospitalization time is actually shorter, but the operating time is longer [15]. Due to the risk of further complication from calculi with delayed surgery (17.5% to 36% of cases), we are currently recommending a laparoscopic cholecystectomy as soon as possible after the onset of symptoms [2]. Note that the rate of conversion to laparotomy, which is 13% in simple forms, increases to 36% in gangrenous and emphysematous forms. When there are signs of clinical severity (organ failure), there is increased risk of surgical complications: even if the radiologist will not be treating the causal lithiasic disease, he then plays an important therapeutic management role, since drainage by percutaneous cholecystectomy is generally suggested as an initial alternative in these difficult surgical patients. Prior to surgery, a search for lithiasis in the common bile duct (CBD) is not systematic, but only if suspected, based on clinical and laboratory criteria. If they are present, the patient can theoretically be explored directly by intraoperative cholangiography, or by endoscopic ultrasonography ± endoscopic retrograde cholangiopancreatography (especially when there is a strong clinical suspicion). But in practice, a biliary MRI is increasingly requested in these patients to noninvasively facilitate their ongoing management [16]. Note that the biliary MRI is unnecessary if the ultrasound has already revealed a calculus in the common bile duct: ultrasound has low sensitivity but is very specific, as long as care is taken to avoid the trap of false images of CBD lithiasis associated with pancreatic calcifications or juxtapapillary duodenal diverticula.

Cholangitis

Etiological workup: what are the difficulties?
In more than 85% of cases, cholangitis is related to a lithiasic obstruction of the common bile duct. The most common causal organism is *Escherichia coli*, which has the property of producing glucuronidase, which is responsible for the deconjugation of bilirubin and, therefore, the formation of calculi [5]. Thus, there is a relationship between obstruction, biliary stasis, infection, and production of calculi, which themselves cause obstruction. The discovery of calculi therefore raises the question of whether they are truly the cause, or simply the consequence of another obstructive disease: in cases of intrahepatic calculi or recurrent calculi of the common bile duct in a cholecystectomized patient, there should be a systematic search for the underlying cause. The etiologies of obstructions of the common bile duct are classic [16]: lithiasis of the common bile duct, obstructions caused by tumors (pancreatic cancer, ampulloma, cholangiocarcinoma, extrinsic compression by malignant lymph nodes) and much more rarely parasitic (ascaris, distomatosis, hydatidosis).

Fig. 8 illustrates different cases of cholangitis related to obstructions in the intrahepatic bile ducts.

Low phospholipid associated cholelithiasis syndrome
We should mention low phospholipid associated cholelithiasis (LPAC) syndrome. An intrahepatic lithiasis recurrence in a young patient who already as a history of cholecystectomy due to lithiasis or lithiasis of the CBD should indicate a search for an underlying genetic abnormality (MDR3 deficiency due to mutation of the *ABCB4* gene) [17].

Hepatic abscess

Is it really an infectious lesion?
Perilesional edema is present in 50% of abscesses, but also in 20 to 30% of tumors. This is thus a sign of an infectious etiology with very low specificity. A sign more suggestive of abscess is the presence of a capsule with extended enhancement both in thickness and intensity (Fig. 9). The presence of multiple peripheral microabscesses (cluster sign) (Fig. 10) is also very suggestive of an infectious condition [18].

The clinical context and history are of course very helpful with the diagnosis. Several studies have examined the value of MRI diffusion sequences for differentiating between abscess and tumor; as in brain disease, it was shown that purulent content is associated with significantly lower apparent diffusion coefficient (ADC) values for an abscess than for a tumor with necrotic content [19]. However, the number of patients was small and the variability of the diffusion values as a function of the stage of maturation of the abscess has since been pointed out [20]: the true impact of diffusion has, in fact, not yet been firmly established and a biopsy is still essential for decision-making in difficult cases (Fig. 11).

What is the cause?
Cholangitis is the main cause of hepatic abscesses, which are, in this case, of biliary origin. The origin may also be arterial, in the case of sepsisemia, or direct, in the case of trauma or surgery, or portal in relation to a gastrointestinal focus of infection [18]. In the latter case, a search for the cause must be very careful (appendical or sigmoid focus, diverticular in particular). These are often chronic foci, progressing silently and easily missed on imaging studies.

Should we drain, and how?
With respect to pyogenic abscesses, antibiotic therapy alone may be sufficient to treat abscesses that do not exceed 3 cm (or even 5 cm). Otherwise, the choice between
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Figure 8. Examples of etiologies of cholangitis due to intrahepatic lithiasis: a: obstruction appearing to be related to intrahepatic calculi visible on the MRI; the biliary cytologic brushing revealed an underlying cause, i.e., the presence of cholangiocarcinoma; b: ultrasound showing the presence of intrahepatic lithiasis in a young cholecystectomized patient; the genetic testing confirmed low phospholipid associated cholelithiasis syndrome; c: cholangiography after biliary drainage, revealing calculi related to stenosis of a biliary-digestive anastomosis; d: this biliary MRI shows multiple calculi and an appearance of cholangitis of ischemic origin, due to thrombosis of the arterial anastomosis in a liver transplant patient.

Percutaneous radiological drainage or surgery will be made based on the size, number, and plurilocular nature of the lesions. A single, unilocular lesion of 5 cm is typically a good candidate for percutaneous drainage [21]. Coordinated multidisciplinary management is the key to success; but recent studies show that radiologists can effectively manage abscesses, even if they are multiple or plurilocular, with success rates higher than 90% [22]. Amoebic abscesses are a special case due to the very good efficacy of medical therapy, rendering drainage less often necessary. The diagnosis can be made based on the serology, which is positive in more than 90% of cases (but sometimes only when repeated 1 week later). On the imaging, an abscess with a thick wall (3–15 mm) accompanied by edema may suggest an amoebic origin [23].

What are the other possible etiologies?

Certain imaging presentations may be more specifically suggestive of a particular type of infection [23].

Infections in immunodepressed patients
Candidiasis, aspergillosis, pneumocystosis, and mycobacterial infections generally lead to multiple, disseminated,
Figure 9. Hepatic abscess due to cholangitis on the MRI: a: abscess with hypersignal on T2-weighted images; b: the lesion has an enhancing capsule on T1-weighted images after gadolinium injection; c: that enhancement is even more intense on a later acquisition.

Figure 10. Hepatic abscess due to Klebsiella pneumoniae: a: in the absence of any suggestive clinical or laboratory context, the initial presentation raised the hypothesis of a neoplastic or hydatid lesion; b: the progression at 1 week and the appearance of coalescent peripheral microabscesses (cluster sign) confirms its infectious nature.
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Figure 11. Sepsis with purulent meningoencephalitis on returning from Madagascar, in a patient with a history of adenocarcinoma of the colon in remission: a: on the CT scan, there is a doubt between the infectious or neoplastic nature of this single hepatic lesion; b: the ultrasound argues for a metastasis due to the hyperechoic nature of the lesion. The biopsy revealed that this is actually a metastasis of adenocarcinoma, of the colloid mucinous subtype.

small (2–20 mm) abscesses, possibly with central enhancement (Fig. 12).

Alveolar echinococcosis

In France, the northeastern regions are especially affected. Echinococcus multilocularis is responsible for parenchymal hepatic, vascular, and biliary invasion by nonencapsulated vesicles, and leads to pseudotumoral masses (in patients whose general health is not impaired) that may contain calcifications or areas of fibrosis and necrosis (Fig. 13). The diagnosis is aided by the serology, which is positive in 95% of cases.

Hydatid cysts

Echinococcus granulosus is at cause here; the serology used to be positive only in 25% of cases [23]; the sensitivity of the current techniques is now 70 to 100% (false negatives especially affect calcified cysts, but also young cysts) [24] (Fig. 14). Of the five types of conditions usually reported [25], the second and third types are pathognomonic, while the other types are nonspecific:
- type 1: cystic form (may be differentiated from simple cysts by the presence of a wall that is more or less thick);
- type 2: presence of a floating membrane (related to detachment of the geminal membrane from the hyaline membrane due to a drop in pressure within the cyst);

Figure 12. Patient examined after induction chemotherapy for acute leukemia. Multiple hypodense hepatic nodules, for which biopsy specimens revealed aspergillar lesions. We also note a splenic localization.

Figure 13. Alveolar echinococcus with a hypodense mass infiltrating the right liver, containing calcifications, invading the right adrenal gland, and responsible for dilatation of the bile ducts.
Figure 14. Different forms of hydatidosis in three patients: a: on the ultrasound, the cyst contains floating membranes and a sediment of hydatid sand; b: on the CT scan, the cyst contains a gallbladder daughter cyst and fine peripheral calcifications; c: on the CT scan, voluminous hydatid cysts completely filled with daughter hydatid cysts. These cysts are responsible for biliary compression (dilated intrahepatic bile ducts) and compression of the inferior vena cava (with azygos collateral flow).

- type 3: presence of easily recognizable hydatid daughter cysts, forming peripheral vesicles;
- type 4: pseudo-solid form (related to the presence of hydatid sand, compressed hydatids, or calcifications);
- type 5: massively calcified form (indicating a lesion that has become inactive).

Conclusion
Imaging is currently an essential step in the management of infections of the right hypochondrium. The radiologist is thus called upon to intervene at all stages, from diagnosis to etiological search, to monitoring, and even to treatment when percutaneous drainage is indicated.
**TAKE-HOME MESSAGES**

- Ultrasound is still the first-line examination for biliary disease. Its performance is very good for the diagnosis of cholecystitis, but specific cases may make it more difficult: gangrenous forms with no Murphy’s sign on the ultrasound, non-infectious causes of mural thickening.
- The CT scan is particularly valuable for serious cases of cholecystitis, searching for gas in the vesical wall or lumen, intraluminal membranes, a breach in the gallbladder wall, or a perivesicular abscess.
- Asymmetrical thickening greater than 1 cm of the gallbladder wall, early enhancement, or irregular and poorly delimited external margins are suggestive of a neoplastic rather than an infectious gallbladder condition.
- Asymptomatic adenomyomatosis requires no treatment; but strict criteria are required if this diagnosis is to be made without risk of overlooking cancer: typical parietal images with “comet tail artifact” on the ultrasound, and visualization of cystic spaces filled with bile in the parietal thickening on the MRI.
- If there is a clinical suspicion of acalculous cholecystitis, given the absence of reliable imaging criteria, a percutaneous cholecystectomy is indicated for diagnostic and therapeutic purposes. This procedure is also suggested in cases of severe cholecystitis with lithiasis when organ failure constitutes a contraindication to the MRI.
- In cases of intrahepatic calculi or recurrent calculi of the common bile duct in a cholecystectomized patient, there should be a systematic search for the underlying cause, and particularly a neoplastic or genetic (LPAC syndrome) cause.
- If in doubt between a hepatic abscess and a neoplastic lesion, a diffusion MRI may provide evidence, but a biopsy is often necessary.
- Appendical or sigmoid foci of infection responsible for hepatic abscesses of portal origin often progress silently and require a particularly careful search.
- Contrary to amebic abscesses, which respond well to medical treatment, percutaneous drainage may be suggested as first-line therapy for most pyogenic abscesses of a significant size (> 3–5 cm).
- Infections in immunodepressed patients, alveolar echinococcosis, and hydatid cysts have radiological presentations that are often sufficiently specific to allow the radiologist to suggest an etiological diagnosis.

**Clinical case**

**Case study**

This 69-year-old patient with no remarkable history was referred to the emergency room for fever with chills and right hypochondrial pain. The laboratory workup showed a full-blown inflammatory syndrome. An abdominal CT scan was done with contrast injection (Fig. 15).

**Questions**

1. What are your findings at the abdominal level?
2. What are the two main etiologies to look for?
3. Which one do you choose in this patient?

**Answers**

1. We note the presence of several heterogeneous hypo-dense hepatic lesions (Fig. 15a): the coalescent appearance of these lesions (cluster sign) is very suggestive, in this context, of a pyogenic abscess. Associated with it (Fig. 15b) is thrombosis of the portal trunk and right portal branch (septic pylephlebitis).
2. In cases of hepatic abscess suspected to be of portal hematogenous origin, the two main causes of infection to be looked for are appendicitis and sigmoiditis.
3. The sagittal CT slice (Fig. 15c) shows the presence of a heterogeneous extra-digestive formation located between the sigmoid colon and the posterior face of the bladder. This is a chronic abscess of sigmoid diverticular origin that progressed silently and is responsible for portal dissemination of hepatic infection.
Figure 15. An abdominal CT scan was done with contrast injection: a: heterogeneous hypodense hepatic lesions; b: thrombosis of the portal trunk and right portal branch; c: the sagittal CT slice shows the presence of a heterogeneous extra-digestive formation located between the sigmoid colon and the posterior face of the bladder.

References


