

Acute and Chronic Inflammation of the Biliary System

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Question 1: What is your diagnostic approach to a patient with biliary strictures of unknown origin?

Dechêne: In patients with jaundice, ultrasound gives an overview of the presence and location of biliary obstruction, whereas magnetic resonance imaging (MRI) is much more accurate. As treatment is mainly guided by the distinction between benign and malignant origin of the stricture, tissue retrieval is an important issue in stricture management. I use endoscopic retrograde cholangiography (ERC) to characterize stricture location and extension of the stricture. Regarding imaging-guided tissue sampling, cholangioscopy offers the best results. Histological workup shows typical features of autoimmune diseases as well, and immunohistological staining of biliary samples can reveal immunoglobulin (Ig) G4-associated disease.

Ehlken/Schramm: In case of a clinical suspicion for a new biliary stricture, firstly we take a careful history including information on previous imaging studies that helps establishing a reference for comparison. Secondly, we recommend imaging studies with abdominal ultrasound as well as liver MRI plus magnetic resonance cholangiopancreatography (MRCP) to detect a mass lesion and to specify where the stricture is localized. Our approach to verify malignancy would then be an endoscopic retrograde cholangiopancreatography (ERCP) with brush cytology and, if needed, biopsy – also repeatedly and in conjunction with cholangioscopy. In patients with primary sclerosing cholangitis (PSC), additional fluorescence in situ hybridization (FISH) of biliary brushings could enhance the sensitivity of brush cytology by around 20%.

Kirchner: In my opinion, the medical history of the patient is important. Total serum IgG, serum IgG4, and pANCA should be determined. If cholestatic parameters are increased, ERC is indicated to search for significant and treatable biliary strictures. In addition, brush cytology and biopsy is recommended in patients with a suspect biliary stricture or positive serum IgG4. In case of intraluminal material like biliary casts, a removal of this material is mandatory, and bile collection for microbiological analysis is needed. In some cases the performance of a liver biopsy is helpful.

Question 2: Secondary sclerosing cholangitis (SSC) in critically ill patients is an underdiagnosed emerging disease. What do you think is the best way to diagnose SSC in critically ill patients?

Dechêne: The typical history of pre-existing critical illness and/or previous severe disease including polytrauma as well as cardiovascular and infectious events guides the presumptive diagnosis in patients with clinical and serological signs of cholestasis. Septic cholestasis can be excluded in most cases by the typical patterns of the laboratory results. Transcutaneous ultrasound often does not show major pathology, given the rarefication of the biliary tract, and MRI is precluded by the critical state the patients are in. We found that ERCP offers a sensitivity towards SSC but is invasive and requires a considerable number of resources and staff to care for the critically ill patient.

Ehlken/Schramm: Due to the absence of early markers, suspicion for SSC usually arises when the critically ill patient develops strongly elevated cholestasis parameters; thus, especially serum AP levels and SSC should always be on the list of differentials when the patient becomes jaundiced after around 10–14 days in the absence of overt sepsis. To ascertain the diagnosis of SSC of the critically ill patient, MRCP and ERCP are the most sensitive modalities. ERCP might have a better sensitivity to detect early changes of the biliary tree, and it offers the possibility to remove biliary casts and to obtain bile fluid for microbiology.

Kirchner: The best way to diagnose sclerosing cholangitis in critically ill patients (SC-CIP) is an ERC. If ERC is not possible, liver biopsy is the second best diagnostic tool, as reported in the literature. In patients with SCC the sensitivity and specificity of MRCP or ultrasound is low.

Question 3: The optimal therapy of SSC in critical patients remains unknown. How do you treat such patients?

Dechène: To be honest, treatment options are sparse – partly because the triggering event has happened weeks or months before the onset of symptoms and cannot be controlled any more. The aim is therefore to prevent or slow down progressive biliary destruction. Repeated ERCs enable the removal of biliary casts and the dilatation of strictures in a proportion of patients but carries the risk of inducing infectious cholangitis. As mortality in SSC arises mainly from septic complications, antibiotic treatment is frequently necessary, and endoscopic bile sampling can help to identify biliary bacterial flora.

One of the most important treatment measures that should be offered to patients with progressive disease is orthotopic liver transplantation (OLT). However, many patients are suffering from severe comorbidities and are not eligible for OLT.

Ehlken/Schramm: In the critically ill patient with SSC, we would recommend an ERCP for collection of bile for microbiology testing and subsequent antibiotic treatment, sphincterotomy, and removal of biliary casts. The use of ursodeoxycholic acid seems a reasonable option, although there are no controlled studies to recommend its use. Most importantly, however, depending on the dynamics and prognosis of the underlying disease, SSC of the critically ill progresses to end-stage liver disease in a large proportion of patients, and liver transplantation is an option for some of these patients.

Kirchner: In patients with SSC, ERC with removal of biliary casts and bile collection for microbiological investigation is needed. Resistogram-based antibiotic therapy should be performed for 14 days. Due to the poor outcome of SSC, patients should be evaluated early for liver transplantation.

Question 4: Cancer surveillance is critical and difficult in patients with PSC. What is your surveillance strategy?

Dechène: I encourage every patient to find a specialized gastroenterologist and see her or him at least twice a year. In PSC patients with dominant biliary strictures and/or cholangitis, sampling of suspicious strictured biliary segments either by brush cytology or, if possible, by forceps biopsy is possible during ERC performed for decompression. A recently introduced digital cholangioscopy system enables differentiation of vascular patterns in inflammatory versus malignant biliary lesions and shows promising first results towards image-guided tissue sampling. Patients without indications for endoscopy will be sent for MRCP every 12 months. It is important to keep in mind that most PSC patients suffer from chronic inflammatory bowel disease (IBD) and should therefore undergo colon cancer screening at least as often as IBD patients without PSC.

Ehlken/Schramm: Unfortunately, we still lack prospective data on this important problem. Concerning cholangiocarcinoma and gallbladder cancer, we would counsel the patient to undergo abdominal ultrasound in 6-monthly intervals. Additionally, we would argue for liver MRI plus MRCP every year. Given the increased risk of colon cancer that comes with PSC-associated colitis, our patients are advised to have colonoscopy with mapping biopsies every 1 (–2) years. The PSC patient without clinical or histological signs of colitis would be counseled to undergo colonoscopy every 5 years.

Kirchner: Cholangiocarcinoma often occurs within the first year of PSC diagnosis. In patients with dominant biliary strictures, ERC with biliary brush cytology, biopsy, and cholangioscopy should be performed. Intraductal sonography may also be helpful, if available. In patients with dominant bile duct strictures and increased cholestatic parameters, ERC should be repeated every 3–6 months. FISH analyses for detection of chromosome abnormalities could give additional hints regarding cholangiocarcinoma. In patients with mild PSC, MRCP should be performed once a year.

Question 5: According to your experience, what is you approach to diagnose IgG4 cholangiopathy in patients with biliary strictures of unknown origin?

Dechène: The initial workup of biliary strictures potentially arising from autoimmunity in our center includes cross-sectional imaging (where pancreatic lesions typical for IgG4-related disease would be found), tissue sampling of biliary strictures and the major papilla (with immunohistological staining for IgG4), and measurement of IgG4 levels in aspirated bile samples as well as in serum.

In a number of patients with equivocal results and no evidence of malignant disease, I use a 4-week course of steroid treatment before re-evaluation of treatment response as a diagnostic criterion.

Ehlken/Schramm: Many if not most cases of IgG4 cholangiopathy come along with autoimmune pancreatitis. If autoimmune pancreatitis is already proven, biliary strictures on MRCP should raise a high level of suspicion for the diagnosis of IgG4 cholangiopathy. For a definitive diagnosis, compatible findings on imaging studies should be complemented by increased levels of serum IgG4 and plasma cell infiltrates upon bile duct histology. However, it is difficult and sometimes impossible to differentiate IgG4-associated strictures from PSC and sometimes cholangiocarcinoma (CCA); therefore, a trial of steroids is warranted in many patients which may not have a significant impact on the patient's course with a final diagnosis of CCA or PSC.

Kirchner: In patients with biliary strictures of unknown origin, detection of serum IgG4 and histology of the distal biliary duct and the papilla Vateri is recommended.

Question 6: In acute cholecystitis the timing of surgery is crucial. What is the maximal time interval you allow between the onset of symptoms and surgery? And why?

Bektas: The timing of surgery in acute cholecystitis is crucial. According to the current data, acute cholecystitis should be treated just like an acute appendicitis. If you want to operate in an interval, however, an interval of about 4–5 weeks after acute cholecystitis should be adhered to.

Ehlken/Schramm: Early cholecystectomy is the treatment of choice. There are data and theoretical considerations on the grade of inflammation suggesting that surgery within 72 h after the onset of symptoms or also within the first 7 days comes with a benefit for the patient since hospitalization time was shorter, risk of bile duct injury was found to be lower, and conversion from laparoscopy to open surgery was also less frequent.

In a patient with worsening symptoms despite adequate medical treatment and signs or symptoms of sepsis, such as hemodynamic instability, emergency cholecystectomy must be evaluated irrespective of the above considerations.

Lang: In acute cholecystitis we try to perform surgery early, usually laparoscopic cholecystectomy.

We aim to perform surgery within 24 h after the onset of symptoms; however, this is not a fixed rule. Depending on signs of inflammations (laboratory data as well as clinical signs), we usually also accept 48 h or sometimes even longer. The decision for operation is always made on an individual basis. In cases with longer onset of symptoms and danger for critical, serious condition, we prefer conservative treatment and cholecystectomy in the later period.

Question 7: Preoperative staging in patients with bile duct cancer is of great importance prior to surgical resection. In some patients, however, the diagnosis and staging remains inconclusive. When do you perform explorative surgery?

Bektas: If there are no contraindications, we always recommend an exploratory laparotomy because in most cases this is the only way of assessing the operability.

Ehlken/Schramm: In any case of doubt regarding the suitability for surgical resection, we would recommend laparoscopy to exclude peritoneal seeding or intrahepatic spread of CCA. Cross-sectional imaging cannot detect small intrahepatic lesions and early peritoneal carcinosis. At our center, we prefer mini-laparoscopy which is minimally invasive and can be performed even on an outpatient basis.

Lang: We perform explorative laparotomy in all patients in whom preoperative diagnostic tools do not show a contraindication for resection. Contraindications are:

- distant metastases;
- extensive bilateral tumor growth far into both liver lobes; this means 'extended' Bismuth type IV (early type IV is often resectable);
- ipsilateral extended biliary tumor growth and contralateral liver atrophy, usually due to vascular invasion (typically in Bismuth type IIIA and contralateral portal vein infiltration);
- ipsilateral extended tumor growth and contralateral vascular invasion which cannot be managed by resection and reconstruction of vessels.

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