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Chapter 1 : Gallbladder and Biliary Tract Disease

Gallbladder and Bile Ducts (Gastroenterology and Hepatology: The Comprehensive Visual Reference, Vol 6).

What is the most effective initial therapy? Selecting the appropriate therapy for patients with HCC There are two considerations: Listing of usual initial therapeutic options, including guidelines for use, along with expected result of therapy. Resection in these patients is associated with a poor prognosis, frequent post-resection ascites, jaundice, and slow deterioration to death. The ideal tumor for resection is a single lesion in the periphery of the left or right lobe. Unfortunately, few tumors are ideal. The tumor must be removed with at least a 1-cm tumor-free margin. This method usually involves a right or left partial hepatectomy. Occasionally, with poorly situated tumors, a trisegmentectomy can be performed. This method requires excellent liver function. Instead of this, sometimes it is possible to perform a mesohepatectomy: Smaller, well-situated tumors can be removed by a segmentectomy: Laparoscopic hepatectomy is becoming more frequent, with the attendant decrease in post-operative complications. Not all HCCs are suitable for transplantation. Two major issues remain to be resolved. These are 1 criteria for listing for transplantation and 2 downstaging i. The Milan criteria were based on pretransplant radiological assessment of tumor extent. However, it is clear that some patients whose tumors exceed Milan criteria can be transplanted with good survival. This has led to the development of several additional criteria. None have yet gained wide acceptance. These include the San Francisco Criteria, the "Metroticket concept," and criteria based on tumor volume, rather than cross-sectional diameter. Most programs still use the Milan Criteria. Downstaging Downstaging is the process of treating an HCC that exceeds listing criteria to bring it within criteria. The literature on this topic is very confusing. There is no uniformity in maximum extent of tumor that can be treated, nor in the target size that is acceptable after downstaging so that transplantation has a reasonable survival. Assessment of downstaging relies largely on the anatomical extent of the tumor, rather than on its biology. Because larger tumors generally have worse prognoses, it is not clear if simply making the tumor smaller reduces the risk of recurrence to the same level as that for tumors within Milan criteria, to start with. Some clinicians have used the response to chemoembolization as a criterion to assess suitability for transplant. Tumors that respond by shrinkage and show no further growth for 3 months after chemoembolization have a much better prognosis than those tumors that do not respond to treatment. Contraindications to liver transplantation for HCC Vascular invasion on pretransplant radiology carries a very high risk of post-transplant recurrence, and is usually a contraindication to transplantation. Poorly differentiated tumor morphology is also an adverse prognostic sign. However, the importance of this criterion in patients whose tumors are within the Milan criteria is not clear. However, it is not clear whether this should be an absolute contraindication to transplantation. In addition to tumor-specific contraindications, there also are general medical contraindications to major surgery, such as significant heart or lung disease. There are also social contraindications. Patients have to be able to comply with the post-transplant follow-up and medical regimen. In patients who developed liver failure on the basis of alcoholic cirrhosis, most programs require a 6-month period of abstinence before considering transplant. Local ablation There are two commonly used forms of local ablation: Radiofrequency ablation is the preferred option because tumor destruction is more complete, and it takes fewer sessions to achieve this. Both can be performed as percutaneous outpatient procedures. The commonly used radiofrequency probes can successfully ablate a lesion of up to 4 cm in diameter. Larger lesions can be ablated using multiple probes, but the success rate for these probes is unknown, and there is also no data on survival. It is not certain that achieving a large ablation zone for a large tumor improves survival because the larger the tumor, the more likely that there is at least microvascular invasion, with the risk of metastases. RFA destroys a rim of normal liver surrounding the tumor, as well as the tumor itself. The

larger the tumor, the greater the amount of liver destroyed. The amount of damaged liver increases exponentially, so that for a 2-cm tumor, about 10 cc of normal liver is destroyed; for a 5-cm tumor, about 65 cc of normal liver is destroyed. Therefore, in patients with marginal liver function, ablation of larger tumors carries a risk of deterioration of liver function. Chemoembolization Chemoembolization involves inserting a catheter into a branch of the hepatic artery feeding the HCC via the femoral artery and injecting a chemotherapy agent mixed with lipiodol, an oily radiographic contrast agent. This procedure is usually followed by embolizing the artery feeding the tumor. The chemotherapy used is most commonly doxorubicin, cisplatin, or mitomycin C. Chemoembolization has been used for all but the most advanced stages of disease. Chemoembolization improves survival but at about 12 to 24 months. Complications of chemoembolization The most common complication is the post-embolization syndrome of fever, pain, and nausea. This lasts about 24 to 28 hours. The chemotherapy agent causes bone marrow depression, with a risk of infection during the neutropenic phase. Patients with biliary-enteric anastomoses are at particularly high risk for infection and should not be treated by chemoembolization. Patients usually develop alopecia. Peripheral biliary strictures are possible, as evidenced by the presence of dilated bile ducts on imaging follow-up. Patients with chronic hepatitis B may develop a recrudescence of viral replication and, subsequently, of acute or chronic hepatitis. Such patients need to be covered with an antiviral for the duration of the treatment and for up to 3 months subsequently. Chemobolization in patients with Child B cirrhosis In a randomized controlled trial that included patients with more advanced liver disease, chemoembolization failed to show any survival advantage. The post-procedure mortality in this study was high, suggesting that patients with more advanced liver disease do not tolerate the procedure well. Therefore, chemoembolization is not recommended for patients with Child B cirrhosis. These patients may do better with other forms of therapy, such as liver transplantation. Chemoembolization in patients with vascular invasion The randomized controlled trials showing a survival advantage of chemoembolization excluded patients with vascular invasion. Cohort studies have shown that patients with vascular invasion have a much shortened survival compared to those without vascular invasion. Therefore, it is not known whether chemoembolization in these patients confers a survival advantage. Nonetheless, chemoembolization has been given in such circumstances. Most clinicians would avoid chemoembolization in patients with main portal vein obstruction, for fear of infarcting the liver by embolizing the hepatic artery. However, many continue to give chemoembolization to patients with second-order branch portal vein invasion. This is not recommended in the guidelines. The improvement in survival is about 3 months compared with untreated patients. Sorafenib is a multikinase inhibitor that is thought to work by inhibiting angiogenesis and blocking signal transduction in a number of important intracellular pathways. Conventional chemotherapeutic agents have not been shown to enhance survival significantly and are associated with significant toxicity. Some trials have even demonstrated a decrease in survival in the treated group. This therapy is not recommended. Infusion chemotherapy, where drug is infused into the hepatic artery via a subcutaneous injection port, is popular in Japan. However, the results are not good. There are no randomized controlled trials of sufficient power to demonstrate a benefit. In some studies, the survival of the treated group is no different from that expected for that stage of disease. A listing of a subset of second-line therapies, including guidelines for choosing and using these salvage therapies Other forms of therapy for HCC There are several additional forms of treatment that have been devised for HCC. None, however, have been adequately tested. Radioembolization involves injecting radiolabelled particles glass beads or resin particles into the branch of the hepatic artery that feeds the tumor. This treatment has been associated with substantial tumor responses, but it remains to be demonstrated that radioembolization is superior to chemoembolization or other forms of treatment. Hepatic artery ligation now is seldom used. Bland embolization continues to be used, but there is no satisfactory evidence of efficacy in improving survival. Chemoembolization can be delivered using drug-eluting beads. These have been shown in a single trial to be approximately equivalent to standard

chemoembolization but with fewer side effects. Listing of these, including any guidelines for monitoring side effects. Post-treatment monitoring of patients with HCC The post-treatment management of patients with HCC is directed at evaluating the response to treatment, presence or absence of recurrence, and progression of liver disease. Monitoring for response and recurrence is usually performed by imaging, usually with the same imaging method that was used in the initial diagnosis. The same diagnostic criteria are used: Recurrence is shown by a focus exhibiting these characteristics. However, because evaluation of the recurrence requires imaging even if AFP is rising, unless the lesion is visible on imaging, nothing can be done. It is therefore not clear that monitoring AFP adds anything. Liver disease should be monitored by regular blood tests. In addition, patients with cirrhosis should have a gastroscopy to look for esophageal varices and, if present, these should be treated by band ligation. If the underlying liver disease can be treated, the risk of recurrent disease may be reduced. This applies mainly to hepatitis B and hepatitis C.

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Chapter 2 : Nonalcoholic steatohepatitis and nonalcoholic fatty liver disease - Cancer Therapy Advisor

Gastroenterology Gastroenterology and Hepatology: The Comprehensive Visual Reference, vol 5: Esophagus and Pharynx, vol 6: Gallbladder and Bile Ducts Gastroenterology and Hepatology: The Comprehensive Visual Reference, vol 5: Esophagus and Pharynx, vol 6: Gallbladder and Bile Ducts Slide Atlas of Gastroenterology and Hepatology: The.

Carcinosarcomas of the bile ducts are very rare tumors consisting of both epithelial and mesenchymal elements. We report a case of bile duct carcinosarcoma and its clinical, radiological and pathological features and a brief review on this rare condition. Carcinosarcoma; sarcomatoid carcinoma; bile duct Submitted May 19, Accepted for publication Jun 04, These tumors have been reported in many different organs, including the pancreas, lung, uterus, ovary, esophagus, stomach and kidney 1 - 5. However, carcinosarcoma of the biliary tree is rare, with only a handful of cases reported in the bile ducts 6 - We report an interesting case of a bile duct carcinosarcoma and a brief literature review. Case presentation A year-old female patient was referred to the hepato-pancreato-biliary HPB service for further management of an intrabiliary mass near the biliary confluence detected on her CT scan Figure 1. She had elevated liver enzymes [aspartate aminotransferase AST: Figure 1 Computed tomography cross-sectional and coronal images. White arrows illustrate the hilar location and the intraductal papillaryâ€”like features of the bile duct carcinosarcoma distending the biliary confluence and causing proximal intrahepatic biliary dilatation. The consensus at a multi-disciplinary HPB tumor conference was an intraluminal soft tissue mass at the confluence of the left and right main bile ducts resulting in marked bilobar intrahepatic biliary dilatation, suspicious for a papillary hilar cholangiocarcinoma. Additionally, given the difficulties of palliating jaundice in the setting of a large intraductal tumor, even a limited resection was considered preferable to non-operative decompression. Intraoperatively, after exclusion of peritoneal metastases, a large papillary intrabiliary duct tumor arising from the biliary confluence was found and a complete gross resection was achieved by removing the biliary confluence and the tumor in-situ, and hepatojejunostomy was fashioned to the right, left and caudate ducts separately. The patient recovered uneventfully but the disease recurred after 2 months and she passed away soon after. Histological features On gross examination, the tumor was primarily exophytic with masses seen within both the right and left hepatic ducts. An area of mural invasion was noted involving the right hepatic duct wall Figure 2. Histologically, both the exophytic and murally invasive components were composed primarily of sarcomatoid elements, mostly in the form of spindle and pleomorphic tumor cells with prominent mitotic activity Figure 3A. A minor component of the tumor showed osteogenic differentiation with formation of malignant osteoid Figure 3B. Notably, the underlying bile duct epithelium showed foci of low and high grade dysplasia Figure 3D. Figure 2 Gross specimen. Arrows illustrate the areas of mural invasion involving the right hepatic duct wall near the resection margins when the tumor specimen was bivalved. Figure 3 Histological features illustrating the mixed components of the tumor. Hematoxylin and Eosin stain. Discussion Carcinosarcomas are pathologically characterized by the presence of both epithelial and mesenchymal components within the same tumor. The most common site for carcinosarcoma of the biliary tract is the gallbladder with fewer than cases reported in the literature; comparatively, there are only 7 cases of carcinosarcoma of the bile ducts reported in the English literature to date Table 1 6 - The pathogenesis of these rare tumors is uncertain but several hypotheses exist. It has been theorized that carcinosarcoma arises from totipotent stromal stem cells that are capable of divergent differentiation. Another postulation is the collision tumor theory that suggests the distinct and concurrent malignant proliferation of both the epithelial and mesenchymal components within the same tissue. It has also been suggested that a carcinoma can transform into a sarcoma by metaplastic transformation 14 - A distinguishing feature of a true carcinosarcoma is the biphasic nature of the tumor with a lack of transition between the two epithelial and sarcomatous

components as opposed to a poorly differentiated carcinoma with spindle cell pattern 6 , The sarcomatous element commonly consists of undifferentiated spindle cells and a variety of heterogeneous components such as, chondro-, osteo-, leiomyo-, rhabdomyosarcoma cells Table 1. The epithelial element usually consists of adenocarcinoma and occasionally, components such as squamous-, small cell- and undifferentiated carcinomas 17 - Genetic analysis has been utilized to evaluate the pathogenesis of these tumors They have also been sub-classified into two sub-groups: The demographics of biliary carcinosarcoma are similar to that of gallbladder adenocarcinoma, with the majority occurring in elderly women and strongly associated with cholelithiasis The prognosis is dismal, largely extrapolated from the experience of gallbladder carcinosarcomas. The reported median survival time of patients with carcinosarcomas of the gallbladder after surgical resection was only 7 months with a 1-, 2-, and 3-year survival rates of The median time to recurrence for patients who died was less than 2 months The TNM staging system is a valuable prognostic tool in gallbladder carcinoma but has little role in gallbladder carcinosarcoma; a recent review demonstrated that the survival time is in matter of months regardless of their tumor stage 24 - In general, carcinosarcomas are locally aggressive tumors with a propensity to metastasize systemically even in early stages 7 , It been suggested that the aggressiveness of the tumor depends on the sarcomatoid component, as they metastasize to the lymph nodes and distant organs more readily. Interestingly, it is also the sarcomatoid component that forms the bulk of polypoidal element that leads to an earlier presentation as it obstructs the bile ducts, in contrast to gallbladder carcinosarcomas, where the carcinomatoid element forms the infiltrative component of the tumor 6 , 7 , 9 , 11 , This observation is consistent with other studies reporting that Ki has prognostic value in various types of carcinosarcoma and other malignant tumors as well 31 , Due to the rarity of bile duct carcinosarcoma, its true prognosis and clinicopathological features are not well established. Based on the reported cases, the survival time can vary widely, from 2 months to 5 years of disease-free survival Table 1. The strategy has largely been extrapolated from the experience in treating cholangiocarcinoma, with resection as the mainstay of treatment. As is also true for the more common biliary adenocarcinoma, there is no clear evidence that chemotherapy or radiotherapy confers any survival benefit, either as adjuvant treatment or in the palliative setting 20 , However, judging from the poor results, it is clear that surgery alone is inadequate. Adjuvant chemotherapy has been used in carcinosarcomas of the female genital tract but with disappointing results and the role of radiation is currently unclear as well 6 , 7 , 20 , This case report includes interesting radiologic and histologic features of carcinosarcoma of the bile duct. Carcinosarcomas often demonstrate unusual gross and radiographic features. Polypoid growth, which was also observed in this patient, was reported to be the characteristic gross feature of carcinosarcomas 5 , 7 , 8 , The features of intraductal expansion, distension of the biliary confluence by the polypoidal tumor and subsequent proximal biliary tree obstruction were noted in our patient and are illustrated in Figure 1. This growth pattern is also seen in papillary cholangiocarcinoma, which is often a more indolent disease. As the present cases illustrates, the radiographic features of carcinosarcoma and papillary cholangiocarcinoma may be indistinguishable. Conclusions We report a case of carcinosarcoma of the bile duct with biphasic areas of papillary adenocarcinoma, poorly differentiated carcinoma intermingled with spindle cell and pleomorphic sarcoma and a heterologous element of osteoid sarcoma. Acknowledgements Footnote Conflicts of Interest: The authors have no conflicts of interest to declare. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal. Carcinosarcoma of the gallbladder producing alpha-fetoprotein and manifesting as leukocytosis with elevated serum granulocyte colony-stimulating factor: Clinical features and outcomes of uterine and ovarian carcinosarcoma. Sarcomatoid carcinomas of the upper aerodigestive tracts. Adv Anat Pathol ;7: Spindle-cell carcinoma of the upper aerodigestive tract mucosa. An immunohistologic and ultrastructural study of 18 biphasic tumors and comparison with seven monophasic spindle-cell tumors. Am J

Surg Pathol ; Carcinosarcoma of the esophagus: Jpn J Clin Oncol ; Carcinosarcoma of the biliary tract: Eur J Gastroenterol Hepatol ; Carcinosarcoma of the extrahepatic bile duct. J Hepatobiliary Pancreat Surg ; Carcinosarcoma of the extrahepatic bile ducts: Sarcomatoid carcinoma of common bile duct: Korean J Pathol ; Synchronous carcinosarcoma of the intrapancreatic bile duct and carcinoma in situ of wirsung duct: Duodenal protrusion by carcinosarcoma of the extrahepatic bile duct. Semin Diagn Pathol ; Carcinosarcoma of the liver. Arch Pathol Lab Med ; Biphasic and monophasic sarcomatoid carcinomas of the lung. Am J Clin Pathol ; Carcinosarcoma of the gallbladder manifesting as cholangitis due to hemobilia. J Gastrointest Surg ; Sarcomatoid carcinoma of the gallbladder with a rhabdoid tumor component. Sarcomatoid carcinoma with components of small cell carcinoma and undifferentiated carcinoma of the gallbladder. Carcinosarcoma of the gallbladder with chondroid differentiation. Carcinosarcoma and carcinoma of the gallbladder. Surgical outcome of carcinosarcoma of the gall bladder: World J Gastroenterol ; BMJ Case Rep ; Surgical management of gallbladder sarcomatoid carcinoma. Carcinosarcoma of the gallbladder: Carcinosarcoma of the gallbladder. A case report and review of the literature. J Clin Gastroenterol ; Carcinosarcoma of the ovary.

Chapter 3 : New Insights in Genetic Cholestasis: From Molecular Mechanisms to Clinical Implications

- Gallbladder and Bile Ducts (Gastroenterology and Hepatology: the Complete Visual Reference, Vol 6) by M.D. Larusso Nicholas F.

We report a case of a year-old Caucasian male presenting with an exfoliative skin rash all over his body. The patient was also found to have a huge gall bladder mass extending into the liver that turned out to be adenocarcinoma of the gall bladder on biopsy. Gall bladder cancer usually presents with abdominal pain, swelling or jaundice. We report only the second case in literature of a gall bladder adenocarcinoma presenting with exfoliative erythroderma as its paraneoplastic presentation. Exfoliative erythroderma; gall bladder carcinoma GBC ; paraneoplastic syndrome; skin rash Submitted Sep 20, Accepted for publication Sep 28, Worldwide, there is a prominent geographic variability in GBC incidence that correlates with the prevalence of cholelithiasis. We are presenting a case of gall bladder adenocarcinoma presenting with a paraneoplastic syndrome in the form of exfoliative erythroderma. This is a very rare presentation of gall bladder malignancy, which by itself is an uncommon malignancy. North America is considered a low incidence area. Estimates from the surveillance, epidemiology and end results SEER database reveal an incidence of 1 to 2 cases per , populations in the US 3. The only medications that the patient was taking were iron supplements for iron deficiency anemia and afzulosin for prostatic hypertrophy. Both these medications were stopped on appearance of the rash without any resolution. The patient as an outpatient also went to a dermatologist who prescribed him a course of oral prednisone without any improvement. The patient thus decided to come to the emergency room for further management. Interestingly, on further looking back the medical records it was seen that the patient had presented to the hospital 6 months ago after an episode of fall from a ladder. At that time, he had an evaluation in the emergency department where a CAT scan of chest and abdomen Figure 2 was performed which showed a comminuted displaced fracture of the left clavicular head that was treated with a sling and also compression fracture of the L2 vertebral body that was treated conservatively with pain medications. Co-incidentally at that time a liver mass was also seen on the CT scan described as a 5. High attenuation with nodularity was seen in the gallbladder fundus. The common bile duct was dilated, measuring 1. The patient was instructed to follow up for that mass at that time but was lost to follow up. The patient also noted a 25 pound weight loss in the 3 months prior to presentation. No abdominal pain or any other symptoms suggestive of the presence of intra-abdominal mass or obstructive jaundice were noted apart from the rash and itching. Family history was significant for colon cancer. Figure 1 A Rash over chest and abdomen; B rash over the knees; C rash over the hand. Figure 2 CAT scan of abdomen: On admission the routine labs showed microcytic hypochromic anemia with hemoglobin of 8. Liver, kidney function tests were found to be normal. Alfa-fetoprotein and CEA levels were not elevated. C-reactive protein was Hepatitis viral panel was found to be negative. ANA and anti-smooth muscle antibody were weakly positive. The patient then had an MRI of the abdomen Figure 3 that showed interval enlargement of that heterogeneously enhancing large soft tissue mass originating from the gallbladder wall and into the surrounding hepatic parenchyma measuring approximately 9. This likely represented a gallbladder carcinoma, infiltrating the surrounding hepatic parenchyma. Cholelithiasis, abdominal ascites and Splenomegaly were also noted on the MRI. Figure 3 MRI of the abdomen with and without contrast: This mass appears to originate from the gallbladder wall, with infiltration into the surrounding hepatic parenchy. Patient had a biopsy from the gallbladder mass via a trans-hepatic route under ultrasound guidance. Skin biopsy Figure 5 was taken from the right elbow that came back with non-specific finding in the form of benign skin with marked solar elastosis and mild perivascular lymphocytic infiltrate. The lesion shows poorly differentiated adenocarcinoma. The tumor cells have increased nuclear-cytoplasmic ratio, vesicular nuclei, prominent nucleoli, and increased mitotic activity. Marked

desmoplastic reaction is present. Figure 5 Skin biopsy of the rash: The patient was then transferred to another facility and underwent resection of the gall bladder mass. Two weeks after the removal of the mass, complete resolution of the skin rash was observed. The patient was then advised to follow up with the oncology clinic as an outpatient for further management. Discussion Gallbladder cancer is a rare disease that often arises in the setting of chronic inflammation. The American Cancer Society estimates that approximately 10, new cases of gallbladder cancer and other biliary cancers will be diagnosed in 4. Gallbladder cancer arises in the setting of chronic inflammation. The presence of gallstones increases the risk of gallbladder cancer 4- to 5-fold 5. Other more unusual causes of chronic inflammation are also associated with gallbladder cancer. These causes include primary sclerosing cholangitis, ulcerative colitis 6 , liver flukes, chronic Salmonella typhi and paratyphi infections 7 , and Helicobacter infection 8. Usual clinical presentations are steady pain in the upper right abdomen, weakness, loss of appetite, weight loss, jaundice and vomiting due to obstruction. We report a case of gall bladder adenocarcinoma with the only presenting symptom of exfoliative erythroderma all over the body associated with itching. Erythroderma was considered as a paraneoplastic syndrome secondary to the gall bladder malignancy. The only case with a similar presentation was seen in reported by Kameyama et al. While Kameyama reported the case in a Japanese male, our case is reported in a Caucasian male in whom the incidence of GBC is rare as compared to the Japanese. The lowest incidence rate for gallbladder cancer is among non-Hispanic white males and is 0. The rates for gallbladder cancer are higher among women than men in all age groups Erythroderma secondary to malignancies in general has been reported. A study was performed on cases with erythroderma found that about one fifth of the patients had lymphomas and mycosis fungoides Exfoliative erythroderma is rare secondary to GI malignancy In the case reported by Kameyama et al. In previous cases of other gastrointestinal malignancies like gastric cancer, similar resolution of the eruption was seen following curative gastrectomy 13 , Recurrence of the rash was seen with the recurrence of dysplasia Similar resolution of the rash was seen in our patient after surgical resection of the tumor. Thus, it indicates that resolution of the erythroderma can be seen with curative resection of the tumor and its recurrence might indicate recurrence. Thus while uncommon, it is important to keep gastrointestinal malignancies and specifically GBCs in the list if differentials when working up a patient for unexplained dermatological findings like exfoliative erythroderma. The authors declare no conflict of interest. Risk factors for gallbladder cancer. An international collaborative case-control study. Int J Cancer ; Liver, gallbladder, extrahepatic bile ducts, and pancreas. Epidemiology of gallbladder cancer. Cancer risk in patients with inflammatory bowel disease: Association between Helicobacter bilis in bile and biliary tract malignancies: Jpn J Cancer Res ; Int J Gastrointest Cancer ; Cancer Epidemiology and Prevention. Oxford University Press, Cutaneous manifestations of systemic malignancies: A clinicopathologic study of cases. An unusual association between erythroderma and an occult gastric carcinoma. Am J Gastroenterol ; Papuloerythroderma associated with gastric cancer; report of a case. Nihon Shokakibyo Gakkai Zasshi ; Exfoliative erythroderma as a paraneoplastic presentation of adenocarcinoma of the gallbladder. J Gastrointest Oncol ;6 2:

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Chapter 4 : Malignant tumors of the liver - Cancer Therapy Advisor

Type of Book: A multiauthored, visually focused teaching tool that includes an illustrated text, a loose-leaf book containing slides of each illustration, and a CD-ROM disk that allows grouping of the illustrations and tables by key words.

Choledocholithiasis Definition and Causes One of the most common causes of extrahepatic biliary obstruction is choledocholithiasis, with one or more stones in the common bile duct or common hepatic duct causing biliary obstruction. Pathophysiology and Natural History Stones in the bile duct can cause biliary obstruction and cholestasis. This can lead to infection in the bile duct bacterial cholangitis , which requires urgent medical therapy. The long-standing presence of stones in the bile duct can lead to secondary biliary cirrhosis. Choledocholithiasis can also lead to gallstone pancreatitis. Signs and Symptoms Most patients with choledocholithiasis report upper abdominal pain, although some patients may remain asymptomatic. Because complete obstruction of the bile duct by the stone may be intermittent, patients may report episodic jaundice. The initial manifestation of choledocholithiasis can also be heralded by an episode of cholangitis. Gallstone pancreatitis manifests with typical features of pancreatitis, including epigastric pain, nausea, and vomiting. Diagnosis Several diagnostic tools can be used when evaluating patients suspected of having choledocholithiasis. Ultrasound is the preferred initial screening test because it is usually less expensive than CT or magnetic resonance imaging MRI , does not use ionizing radiation, and is highly accurate in detecting gallbladder stones and bile duct dilation. Its accuracy in detecting bile duct stones approaches that of endoscopic retrograde cholangiography. It is as accurate as ultrasound in detecting common duct stones and may help localize the level of obstruction in the biliary tree. Once biliary dilation or the presence of a common duct stone is noted on an imaging study, or biliary obstruction is strongly suspected on clinical grounds despite negative imaging studies, endoscopic retrograde cholangiopancreatography ERCP is recommended. ERCP provides a means of visualizing the biliary tree and the opportunity for therapy. Percutaneous transhepatic cholangiography can be a useful alternative when ERCP is not successful, although it is sometimes not successful in the absence of dilated bile ducts. Practice guidelines from the Society for Surgery of the Alimentary Tract for the treatment of gallstone and gallbladder diseases can be found online www. Treatment The goals of therapy for choledocholithiasis are to remove the stones from the biliary tree and to decompress the biliary tree urgently if bacterial cholangitis is present. Stone extraction can be accomplished with ERCP, often preceded by an endoscopic sphincterotomy. In the presence of bacterial cholangitis, when a stone cannot be removed for technical reasonsâ€”for example, because of its large sizeâ€”an endoscopically placed biliary stent can be useful for decompressing the biliary tree. PTHC can be used for emergent drainage of the biliary tree in the presence of cholangitis. Passage of a wire into the duodenum via a percutaneous approach can also help guide an endoscopist when performing an ERCP with stone extraction if ERCP had previously failed because of technical factors. Cholangiocarcinoma Cholangiocarcinoma is an adenocarcinoma of the intrahepatic or extrahepatic bile duct. Primary sclerosing cholangitis PSC is a major risk factor for the development of cholangiocarcinoma. Other diseases associated with the development of cholangiocarcinoma include choledochal cysts and infection with liver flukes, including Opisthorchis formerly Clonorchis sinensis, O. Pathophysiology and Natural History Cholangiocarcinoma is a malignant transformation of the bile ducts, including the ducts in the intrahepatic, perihilar, or extrahepatic biliary tree. A commonly used classification system for cholangiocarcinoma is based on the anatomic location of the tumor. A tissue diagnosis is often difficult to obtain and, in the absence of obviously metastatic disease or extensive local spread, surgical exploration is the only way to determine resectability. Signs and Symptoms Patients typically present with jaundice and pruritus and more generalized symptoms, such as weight loss, anorexia, and fatigue.

Cholangiocarcinoma should always be suspected in a previously stable patient with PSC who has a rapid clinical decline. Diagnosis Initial diagnostic testing for cholangiocarcinoma is similar to that used for other causes of cholestasis. Laboratory testing typically shows an elevated level of alkaline phosphatase of liver origin, with or without an elevation of the bilirubin level. MRI is the optimal imaging study when cholangiocarcinoma is suspected. Some centers have had a more favorable outcome with radiation and chemotherapy followed by liver transplantation in patients with early-stage disease. Photodynamic therapy has also been used with some success. These include papillomas, adenomas, and cystadenomas. Either can result in biliary obstruction and can be confused with cholangiocarcinoma and pancreatic adenocarcinoma. At presentation, patients are often jaundiced and may have a palpable gallbladder because of bile duct obstruction distal to the cystic duct. Laboratory findings typically show an elevation of alkaline phosphatase and bilirubin levels. Imaging studies of the biliary tree will often show dilation, suggesting a distal bile duct obstruction. Further investigation with a side-viewing duodenoscope will reveal the presence of the ampullary tumor. Ampullary adenomas, often seen with familial adenomatous polyposis, can be treated with surgical excision of the ampulla. Pancreatic Disorders Carcinoma of the head of the pancreas can manifest with painless jaundice caused by obstruction of the bile duct as it passes through the head of the pancreas. Weight loss, fatigue, and other constitutional symptoms often accompany the cholestasis. CT scanning or ultrasound typically reveal biliary ductal dilation to the level of the pancreatic head and a pancreatic mass. Cholestasis can also result from benign pancreatic disorders such as chronic pancreatitis resulting in pancreatic fibrosis leading to common duct narrowing and cholestasis or a pancreatic pseudocyst causing compression of the biliary tree. Occasionally, the gallstone erodes into the common hepatic duct, producing a cholecystocholedochal fistula. Ultrasound or CT scanning reveals biliary dilation above the cystic duct. ERCP may reveal the obstructing stone, which can occasionally be removed, but the definitive treatment is usually surgical, consisting of cholecystectomy with surgical repair of the bile duct, if necessary. The ductal strictures are believed to be caused by infections, including Cryptosporidium spp, cytomegalovirus, microsporidian, and Cyclospora spp. Initial evaluation should include ultrasound and ERCP if the ultrasound is abnormal. Endoscopic therapy is useful in certain circumstances. Endoscopic sphincterotomy is useful for those patients with symptoms of papillary stenosis e. Endoscopic stenting of the dominant structure of the biliary may also be helpful. Parasites Extrahepatic biliary obstruction has been seen with various parasitic infections, such as Strongyloides and Ascaris spp, and liver flukes, such as Opisthorchis sinensis and Fasciola hepatica. Prevalence and ethnic differences in gallbladder disease in the United States. Prospective evaluation of endoscopic ultrasonography and microscopic examination of duodenal bile in the diagnosis of cholecystolithiasis in 45 patients with normal conventional ultrasonography. Prophylactic cholecystectomy or expectant management for silent gallstones. Polypoid lesions of the gallbladder: Report of cases with special reference to operative indications. How should polypoid lesions of the gallbladder be treated in the era of laparoscopic cholecystectomy?. Drainage of the gallbladder in patients with acute acalculous cholecystitis by transpapillary endoscopic cholecystoxeransis. Barie PS, Fischer E. J Am Coll Surg. The spectrum of biliary stone disease. Imaging strategies in the initial evaluation of the jaundiced patient. American College of Radiology. Diagnostic accuracy of magnetic resonance cholangiopancreatography and ultrasound compared with direct cholangiography in the detection of choledocholithiasis. Torok N, Gores GJ. Natural history and prognostic factors in Swedish patients with primary sclerosing cholangitis. N Engl J Med. Guidelines for the diagnosis and treatment of cholangiocarcinoma: Comparison of flow cytometry for DNA content and brush cytology for detection of malignancy in pancreaticobiliary strictures. Serum tumor markers for the diagnosis of cholangiocarcinoma in primary sclerosing cholangitis. Cholangiocarcinoma in patients with primary sclerosing cholangitis: A multicenter case-control study. The value of serum CA in predicting cholangiocarcinomas in patients with primary sclerosing cholangitis. Outcomes after curative resections of

cholangiocarcinoma. Aggressive surgical resection for cholangiocarcinoma. Prolonged disease-free survival after orthotopic liver transplantation plus adjuvant chemoirradiation for cholangiocarcinoma. Liver transplantation for unresectable perihilar cholangiocarcinoma. Photodynamic therapy of nonresectable cholangiocarcinoma. Tumors of the hepatobiliary system. Diagnostic Histopathology of Tumors. Churchill Livingstone, , pp Indications for local excision of ampullary lesions associated with familial adenomatous polyposis. Indications, surgical technique, and results. Results of pancreaticoduodenectomy for ampullary carcinoma and analysis of prognostic factors for survival. A new classification of Mirizzi syndrome from diagnostic and therapeutic viewpoints. The liver in AIDS.

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This is an open access article distributed under the Creative Commons Attribution License , which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Abstract Cholestasis is characterised by impaired bile secretion and accumulation of bile salts in the organism. Hereditary cholestasis is a heterogeneous group of rare autosomal recessive liver disorders, which are characterised by intrahepatic cholestasis, pruritus, and jaundice and caused by defects in genes related to the secretion and transport of bile salts and lipids. Phenotypic manifestation is highly variable, ranging from progressive familial intrahepatic cholestasis PFIC â€"with onset in early infancy and progression to end-stage liver diseaseâ€"to a milder intermittent mostly nonprogressive form known as benign recurrent intrahepatic cholestasis BRIC. Cases have been reported of initially benign episodic cholestasis that subsequently transitions to a persistent progressive form of the disease. This review summarises the current knowledge of the clinical manifestations, genetics, and molecular mechanisms of these diseases and briefly outlines the therapeutic options, both conservative and invasive, with an outlook for future personalised therapeutic strategies. Introduction Cholestasis is characterised by an impairment of bile secretion and transport, leading to the subsequent accumulation of toxic bile components in the organism. Bile salts BS , the main organic solutes in bile, are physiological detergents that facilitate the absorption and transport of lipids, vitamins, and nutrients. BS also play an important role in cell signalling as part of key metabolic processes. Bile Salt Synthesis BS are synthesised from cholesterol in the liver. The size of the total BS pool in human adults is g [1 , 2]. There are two main pathways of BS synthesis. The first and rate-limiting enzyme in this pathway is microsomal cholesterol 7 alpha-hydroxylase CYP7A1. In the alternative acidic pathway of BS synthesis, side chain oxidation precedes modification of the sterol ring. The first enzyme in the alternative pathway is mitochondrial sterol hydroxylase encoded by CYP27A1. Primary BS are conjugated at the side chain either with taurine or glycine, while water soluble conjugates are excreted into bile where they are rapidly incorporated in mixed micelles containing phospholipids predominantly phosphatidylcholine and cholesterol. Thereafter, they are transported into the intestinal tract where they are deconjugated, oxidised, and dehydroxylated to form 7-deoxycholic and lithocholic acid as part of a reaction catalysed by bacterial 7 alpha-dehydroxylases. The BS pool is recycled times a day. BS lost in the faeces 0. Bile Salt and Lipid Transporters Bile acids form dissociated sodium or potassium salts in body fluids with neutral pH. Therefore, BS transporters are designed as anion transporters. Enterohepatic circulation of BS is driven by several specific transport systems expressed predominantly in hepatocytes and biliary and intestinal epithelia Figure 1. Bile salt and lipid transporters and their regulatory pathways. NTCP deficiency has recently been shown to cause severe familial predominantly conjugated hypercholanemia with no cholestatic jaundice, pruritus, and liver disease [6]. In the liver, MRP3 is expressed predominantly in the centrilobular hepatocytes, and its expression is low under physiological conditions. MRP3 expression rate is upregulated during cholestasis and independently of any cholestatic manifestation, in individuals with Dubin-Johnson syndrome or after repeated administration of ethinylestradiol [11 , 14 , 15]. As well as in hepatocytes, Northern blotting of various human tissues indicates the presence of MRP3 in the bile duct epithelium, gallbladder, intestine, pancreas, and kidney [16]. MRP4 gene ABCC4 is an inducible basolateral transporter that cotransports taurine and glycine conjugates of cholic acid with glutathione. It is also a high-affinity transporter of sulphated BS, dehydroepiandrosterone sulphate, eicosanoids, and uric acid, as well as signalling molecules such as cAMP

and cGMP [17]. It is exclusively expressed in the liver and localised predominantly in the canalicular microvillar but not the intermicrovillar membrane and to a lesser extent in subcanalicular subapical vesicles [23]. Multidrug resistance protein 3 MDR3, gene ABCB4 is understood to act as a floppase, which translocates phospholipids from the inner to the outer leaflet of the lipid bilayer of the canalicular membrane [24]. Mutations in ABCB4 cause cholestasis, which is characterised by the decreased biliary lecithin output, impaired formation of mixed micelles, and the production of more hydrophilic bile with potent detergent properties, resulting in membrane damage [25 , 26]. Familial intrahepatic cholestasis type 1 transporter FIC1, gene ATP8B1 , a member of the type 4 subfamily of P-type ATPases P4 ATPase , is a flippase that mediates the translocation of aminophospholipids from the outer exoplasmic to the inner cytoplasmic leaflet of the plasma membrane [27]. In most eukaryotic cells, phosphatidylcholine and sphingolipids are concentrated in the exoplasmic leaflet, whereas the aminophospholipids phosphatidylserine and phosphatidylethanolamine are largely confined to the cytoplasmic leaflet. FIC1 thus helps in maintaining asymmetry and fluidity characteristics of plasma membranes, the essential prerequisites for proper function of transmembrane embedded pumps [27]. Cholangiocytes are important modifiers of bile composition. Under physiological conditions, BS transporters in cholangiocytes can play a major role in the regulation of intracellular concentrations of BS as signalling molecules. In obstructive cholestasis, cholangiocellular BS receptors may facilitate the removal of BS from stagnant bile [3 , 28 , 29]. An important step in maintaining BS homeostasis is the reabsorption of BS in the intestinal lumen, predominantly in the ileum. Intestinal epithelial cells reabsorb the majority of secreted BS through ASBT, localised in the brush border membrane of enterocytes. Human ASBT, also called ileal bile acid transporter or ileal sodium-dependent bile acid transporter, consists of amino acids. It transports conjugated and unconjugated BS with a higher affinity for chenodeoxycholic and deoxycholic acid than for taurocholate [30]. Furthermore, MRP3 may also participate in the basolateral transport of BS in human enterocytes, although its overall contribution is small [10]. Regulation of Bile Salt Synthesis and Trafficking The BS biosynthesis and enterohepatic circulation are tightly regulated at many levels but particularly by transcriptional and posttranscriptional mechanisms [2 , 3]. A key regulator of BS synthesis and enterohepatic flow is the nuclear farnesoid X receptor FXR , a major BS-responsive ligand-activated transcription factor with a high affinity for several major endogenous BS [2 , 31 , 32]. Expression levels of the FXR gene also known as the NR1H4 geneâ€”nuclear receptor subfamily 1, group H, member 4 are highest in the intestine, predominantly in the ileal epithelium, liver, and kidneys [31 , 32]. FXR acts as an agonist-dependent transcriptional activator of its direct target genes. FXR can also downregulate the transcription of specific target genes indirectly via another nuclear receptor, the small heterodimer partner SHP, the NR0B2 gene. It acts as a repressor of nuclear receptors, as well as of transcription factors belonging to other protein families [2 , 31 , 33]. FXR plays a key role in controlling the enterohepatic circulation of BS, largely by directly regulating the expression of several hepatobiliary transporters Figure 1. Furthermore, the FGF19 autocrine pathway exists in the human liver [2 , 31 , 37 , 38]. These factors activate signalling pathways, which play roles in protecting against BS toxicity during cholestatic liver injury [2 , 31 , 32 , 37]. Familial Intrahepatic Cholestasis Up- and downregulation of transport systems involved in bile formation can explain the impaired liver uptake and excretion of biliary constituents, which result in cholestasis and jaundice in some hereditary and many common acquired liver disorders. Hereditary diseases characterised by hepatocanalicular cholestasis, which is caused by defects in hepatobiliary transporters, their regulator FXR, and in tightness of the liver epithelium, include progressive familial intrahepatic cholestasis PFIC types 1 to 5, benign recurrent intrahepatic cholestasis BRIC 1 and 2, familial cholelithiasis caused by a lack of biliary secretion of phospholipids Low Phospholipid-Associated Cholelithiasis or Gallbladder Disease-1 , intrahepatic cholestasis of pregnancy ICP , and several other rare disorders. Hereditary predisposition also plays an important role in drug-induced intrahepatic cholestasis, including cholestasis induced by hormonal

contraceptives [39 , 40]. Progressive Familial Intrahepatic Cholestasis PFIC, first described in [41], is a genetically heterogeneous group of autosomal recessive disorders caused by mutations in genes that encode hepatocanalicular transporters of BS and phospholipids, their regulator FXR, and TJP2 which is essential for tightness of cell junctions between the epithelial cells lining the bile ducts. Both genders are equally affected [42]. Clinically, PFIC usually manifests in the first year of life and is characterised by jaundice, severe pruritus, hepatosplenomegaly, steatorrhoea, and retardation of growth and mental development. Further symptoms caused by a deficit of fat-soluble vitamins include coagulopathy, osteopaenia, and neuromuscular disorders. Without adequate treatment, the disease progresses to liver fibrosis and cirrhosis and usually ends in death due to liver failure in the first or, more rarely, in the second decade of life [40 , 42]. GGT is considered a cholestatic enzyme and, when elevated, is associated with damage to the apical membranes of bile ducts and the disruption of intercellular connections due to high concentrations of BS in bile. However, in some cholestatic diseases, synthesis or canalicular secretion of BS is virtually absent and there are no conditions that predispose either to the release of membrane GGT from damaged cholangiocytes or to leakage of bile into the extracellular space and subsequently the blood. ATP8B1 deficiency, which causes membrane phospholipid asymmetry of the canalicular membrane, reduces the capacity of the liver to secrete bile [45 , 46]. These symptoms often persist, while diarrhoea even tends to worsen after liver transplantation LTX. Liver allografts in PFIC1 patients may display diffuse steatosis with a variable necroinflammatory component, with subsequent fibrosis [48]. Laboratory findings with regard to PFIC1 have reported cholestasis with low serum levels of GGT, increased serum concentrations of primary BS, and normal levels of cholesterol. Aminotransferases are initially within the reference range, but during disease progression they gradually increase by up to tenfold [41]. Histopathological changes predominantly involve canalicular cholestasis accentuated around the central veins. The interlobular ducts can be hypoplastic due to subnormal bile flow. Giant-cell changes of hepatocytes are generally not observed in biopsies. Liver fibrosis progression corresponds with the respective stage of the disease and can terminate in cirrhosis. A typical ultrastructural finding is the presence of Byler-type coarsely granular bile in the bile canaliculi [50]. Molecular diagnosis is based on the detection of pathogenic mutations in both alleles of the ATP8B1 gene. Additionally, in PFIC2 the formation of gallstones and the early elevation of serum aminotransferase activity can occur. The development of hepatobiliary malignancies, both hepatocellular carcinoma and cholangiocarcinoma, can be a serious complication of PFIC2, which is not observed in PFIC1 [52 , 53]. Screening for liver tumours is recommended from the first year of life in PFIC2 patients. Histologically, the typical findings in the liver biopsies of PFIC2 patients are giant-cell syncycial hepatitis with hepatocanalicular cholestasis, while extramedullary haemopoiesis is frequently discernible within lobules. Interlobular bile ducts can be hypoplastic, and ductular proliferation at the peripheries of portal triads is commonly observed. Ultrastructurally, canalicular bile can be either amorphous or filamentous but is not coarsely granular [51]. Histopathology of ABCB11 disease. It has been shown that canalicular immunostaining of the BSEP, MDR3, and MRP2 proteins is preserved in the liver graft biopsies and no discernible changes in BSEP immunoreactivity distribution between the apical membrane and the cytoplasm have been reported; nonetheless, de novo polyclonal inhibitory antibodies directed against the first extracellular loop of BSEP have been observed in the posttransplant serum of patients, a condition known as Autoimmune BSEP Disease AIBD [56 , 57]. The causal relationship between recurrent cholestasis in the liver grafts of PFIC2 patients and the occurrence of de novo antibodies directed against BSEP is further supported by observations that plasmapheresis and the administration of anti-CD20 antibodies rituximab may alleviate symptoms of cholestasis [54 â€” 57]. Clinical and laboratory findings associated with PFIC3 correspond to the other two forms of PFIC, but are characterised by the absence of extrahepatic symptoms except for cholelithiasis. Histopathological findings in connection with ABCB4 disease are variable. Syncytial giant-cell changes,

cholestasis, portal inflammatory infiltrate, and periportal ductular proliferation accompanied by various stages of fibrosis have been observed in liver tissue. Lipid crystals within bile ducts and fibroobliterative bile duct lesions can be seen. Immunohistochemistry has indicated the absence of the canalicular MDR3 protein, predominantly in early onset forms; however, its use is limited compared to PFIC2. Ultrastructurally, bile is dense and amorphous in PFIC3 [26 , 61]. Prolonged cholestasis in PFIC3 is associated with significant accumulation of copper in liver tissue and with increased urine copper excretion, i. Tight junction protein 2 TJP2, also zona occludens-2 is a cytoplasmic component of cell-cell junctional complexes expressed in most epithelia and creates a link between transmembrane tight junction proteins and the actin cytoskeleton. Complete TJP2 deficiency is associated with a significant reduction in an integral tight junction protein, claudin-1, predominantly in the canalicular membranes of liver cells, which subsequently leads to the disruption of intercellular connections and the leakage of bile through the paracellular space into the liver parenchyma [65 , 66]. Patients with TJP2 deficiency display severe progressive cholestatic liver disease in early childhood, which puts them at increased risk of developing hepatocellular carcinoma [67]. In addition to liver impairment, extrahepatic features have been identified in PFIC4 patients, including neurological and respiratory disorders [66]. A single homozygous missense mutation in TJP2 has been previously described as causing benign familial hypercholanemia, a rare disorder of oligogenic inheritance, which usually manifests in elevated serum BS concentrations, pruritus, and fat malabsorption, but which does not lead to the development of liver disease [68]. Homozygous loss of FXR function is associated with severe neonatal cholestasis and early onset vitamin K-independent coagulopathy, which rapidly progresses to end-stage liver disease. The nonresponsiveness of coagulopathy to vitamin K treatment is likely a direct consequence of the loss of FXR function, representing an important distinguishing diagnostic feature of NR1H4-related cholestasis. In addition to low or normal GGT activity, serum levels of alpha-fetoprotein are typically elevated [69]. Liver biopsies have shown diffuse giant-cell transformation of hepatocytes with hepatocellular cholestasis and ductular proliferation. Progressive fibrosis and even micronodular cirrhosis are evident at later stages.