Diagnostic Snapshot

Abdominal Bloating Following a Diagnosis of Aplastic Anemia: Correlation or Red Herring?

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Author's disclosures of conflicts of interest are found at the end of this article.

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Abstract

Aplastic anemia (AA) is a bone marrow failure disorder resulting in peripheral pancytopenia and marrow hypoplasia. An alternative diagnosis of hypoplastic myelodysplastic syndrome (MDS) can overlap this diagnosis but is differentiated by the presence of dysplastic progenitor cells. Since AA can be characterized as an autoimmune disease directed against hematopoietic stem cells, its presence can potentially increase susceptibility to alternate malignancies. Hypoplastic MDS, however, can present itself in an extramedullary fashion solely or as a relapse of acute myeloid leukemia resulting in symptoms similar to those described in this case study. Solid tumor malignancies may also result in abnormal blood counts, creating a wide differential diagnosis. This manuscript presents a case of untreated AA in a patient presenting later with severe abdominal bloating.

HISTORY

Mr. ER is a 48-year-old adopted African American male never-smoker with rare alcohol consumption and a past medical history of insulin-dependent type 2 diabetes mellitus (T2DM), hypertension, and gastroesophageal reflux disease, on daily esomeprazole. He presents with a reported 14-year history of pancytopenia following a diagnosis of herpes zoster. His wife noticed a more pronounced decline in his platelet count and made an appointment with the primary care provider (PCP).

His bloodwork at the time of his visit revealed a white blood cell (WBC) count of 2.6 × 10^9/L, hemoglobin (Hgb) of 12.3 g/dL, platelet count (PLT) of 81,000/µL, and absolute neutrophil count (ANC) of 1.13 × 10^9/L. He was referred to a local hematologist/oncologist for further evaluation. His performance status was 0. A bone marrow biopsy (BMBx) was performed, and results showed a hypocellular marrow with insufficient evidence to suggest leukemia or an alternate bone marrow disorder. After 2 months of testing without a confirmed etiology for his low blood counts, Mr. ER presented to an academic medical center for further evaluation.

The initial lab work showed a WBC count of 2.5 × 10^9/L, Hgb of 12.8 g/dL, PLT of 75,000/µL, and ANC of 1.15 × 10^9/L. A repeat BMBx revealed a 0% to 1% hypocellular marrow (normal bone marrow cellularity = 100 – age ± 10) with focal trilineage hematopoiesis and a diploid male karyotype (46,XY) consistent with aplastic anemia (AA). Molecular testing showed monoclonal T-cell receptor γ chain gene rearrangements indicating clonal rearrangements of receptor genes resulting from malignant transformation of a single cell. Despite severe bone marrow hypocellularity, Mr. ER's

blood counts remained stable with transfusion independence. He continued monthly complete blood counts (CBCs) at his local oncologist's office with close monitoring.

PRESENTATION

Four years following his initial presentation, Mr. ER reported 2.5 weeks of abdominal cramping with bloating, which worsened with oral intake (particularly fatty foods) and palpation, and improved with fasting. The pain was localized to the right upper quadrant with a negative Murphy's sign. He described unintentional weight loss of 5 to 6 pounds along with increased flatulence and diarrhea alternating with constipation. He denied nausea, vomiting, fever, chills, or changes in skin color. No scleral icterus was described. Mr. ER's family denied witnessing any mental status changes. A screening colonoscopy performed 2 years ago was within normal limits.

DIAGNOSTIC STUDIES

A liver ultrasound was performed and revealed multiple hepatic masses, the largest a homogeneous mass in the right hepatic lobe measuring 7.7 × 7.1 × 8.3 cm with an unknown primary source. Mr. ER transferred his care back to the academic medical center for further workup. Upon arrival, labs were drawn, including a CBC with a complete metabolic panel, liver function tests, amylase, and lipase. Mr. ER was referred to internal medicine consultation services for a suspected malignancy. Tumor markers and a hepatitis panel were ordered. Results are shown in Table 1.

A CT of the chest, abdomen, and pelvis was performed and confirmed multifocal bilobar heterogeneous hypodense hepatic enhancing masses (Figure 1), with a large discrete mass within hepatic segment VIII measuring 5.2 × 6.4 × 6.6 cm without extrahepatic biliary ductal dilatation (Figures 2A and 2B). A percutaneous liver biopsy was ordered.

Table 1. Patient Results

Indices	Result	Reference range
WBC	6.0 × 10^9/L	4–11 × 10^9/L
Hgb	11.8 g/dL	14–18 g/dL
PLT	51,000/µL	140–440/µL
ANC	4.31 K/µL	1.7–7.3 K/µL
Sodium	136 mEq/L	135–147 mEq/L
Potassium	4.2 mEq/L	3.5–5.0 mEq/L
BUN	9 mg/dL	8–20 mg/dL
Creatinine	0.71 mg/dL	0.7–1.3 mg/dL
Glucose	367 mg/dL	70–99 mg/dL
AST	52 U/L	15–46 U/L
ALT	48 U/L	7–56 U/L
Alk phos	149 U/L	38–126 U/L
Amylase	35 U/L	30–110 U/L
Lipase	101 U/L	23–300 U/L
Total bili	0.4 mg/dL	0.2–1.3 mg/dL
CEA	2.5 ng/mL	0.3 ng/mL
CA 19-9	34 U/mL	0–35 U/mL
AFP	18.3 ng/mL	1–5 ng/mL

Note. WBC = white blood count; Hgb = hemoglobin; PLT = platelets; ANC = absolute neutrophil count; BUN = blood urea nitrogen; AST = aspartate aminotransferase; ALT = alanine aminotransferase; Alk phos = alkaline phosphatase; bili = bilirubin; CEA = carcinoembryonic antigen; CA 19-9 = carbohydrate antigen 19-9; AFP = alpha-fetoprotein.

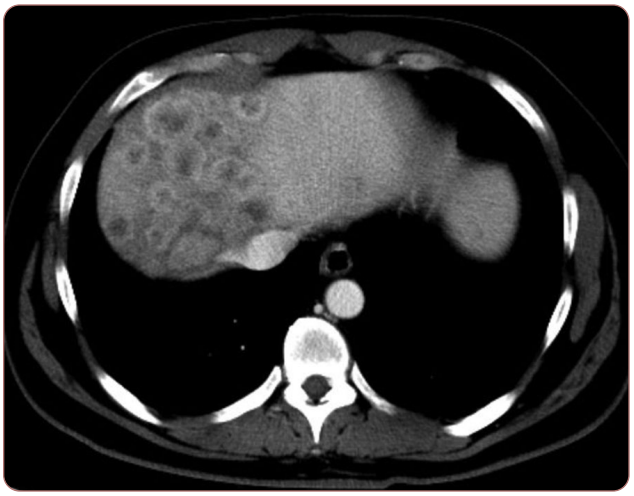

Figure 1. CT of the chest, abdomen, and pelvis.

DIFFERENTIAL DIAGNOSIS

WHAT IS THE CORRECT DIAGNOSIS FOR MR. ER'S PRESENTATION?

A ☐ Hepatocellular adenoma

B ☐ Extramedullary leukemia (myeloid sarcoma)

C ☐ Metastatic cholangiocarcinoma

SEE BACK FOR ANSWER ▶

THE CORRECT DIAGNOSIS FOR MR. ER'S PRESENTATION IS:

A Hepatocellular adenoma

B Extramedullary leukemia (myeloid sarcoma)

C Metastatic cholangiocarcinoma (correct answer)

DISCUSSION

A Hepatocellular adenoma. Hepatocellular adenoma (HCA) is a benign epithelial tumor consisting of a proliferation of hepatocytes generally found in young women with a history of long-term estrogen exposure due to oral contraceptive use (Choi & Nguyen, 2005; Grazioli et al., 2001; Krause & Tanabe, 2020). They are often found incidentally as patients are typically asymptomatic. Macroscopically, HCAs are usually solitary (70%–80%), well-circumscribed, round, encapsulated lesions ranging from 5 to 15 cm with associated intratumoral fat, necrosis, hemorrhage, or the presence of large subcapsular vessels (Choi & Nguyen, 2005; Figure 3).

Hepatocellular adenomas can occur spontaneously in individuals with underlying metabolic disease such as type 1 glycogen storage disease, iron overload, and diabetes mellitus (Brancatelli et al., 2006). They are the third most common benign liver lesion and classified based on mutations causing disruption in hepatocyte cell signaling patterns resulting in a change in the histologic pattern (Krause & Tanabe, 2020).

On multiphasic CT and MRI, HCAs are often heterogeneous due to intertumoral hemorrhage, necrosis, and fat components or with isoattenuation to normal liver in the unenhanced phase (Choi & Nguyen, 2005). Biopsy is not frequently indicated unless there are atypical features on imaging or a concern for abnormal mutations, as biopsy confirmation would unlikely change the management, and invasive procedures should be avoided in otherwise young, healthy patients (Krause & Tanabe, 2020).

In the case of Mr. ER, the CT displayed innumerable heterogeneous hypodense enhancing masses rather than one solitary lesion. Although the size of the dominant lesion still met criteria, the presence of numerous lesions throughout the liver along with multiple systemic systems rendered this diagnosis unlikely.

B Extramedullary leukemia (myeloid sarcoma). Myeloid sarcoma (MS), also called granulocytic sarcoma or chloroma, is a rare extramedullary proliferation of malignant immature myeloid cells outside of the bone marrow (extramedullary) described in 2% to 10% of patients with acute myeloid leukemia (AML) and those harboring a diagnosis of myelodysplastic syndrome (MDS; Norsworthy et al., 2016). The most common sites of involvement include the bones, lymph nodes, soft tissues, skin, and breasts (Tomasian et al., 2015), with the spleen and liver as the most common sites in adults at 95% (Malla et al., 2020). In the event of hepatic involvement of leukemia, patients generally present with nonspecific signs and symptoms such as obstructive jaundice, nausea, vomiting and/or right upper quadrant pain (Norsworthy et al., 2016).

Hepatic involvement seems to be a common extranodal manifestation of some rare hematologic malignancies; however, imaging features reveal heterogeneously enhancing lesions with diffuse hepatic sinusoidal infiltration of leukemic cells resulting in intrahepatic or extrahepatic biliary duct obstruction (Figure 4; Tomasian et al., 2015). On nonenhanced CT images, newer lesions are typically hypoattenuating with mild to moderate homogenous enhancement (Figure 5), while older lesions show attenuation comparable to skeletal muscle with absent or minimal enhancement (Malla et al., 2020). Fine-needle aspiration or biopsy is needed for definitive diagnosis and shows red and yellow elements with hyperplastic hematopoietic elements of all lineages between fat globules (Malla et al., 2020).

Marrow infiltrative disorders, such as leukemia, often result in directed differentiation and displacement of hematopoietic cell lines into the peripheral circulation resulting in passive extramedullary hematopoiesis (EMH), which is not the same as MS (Malla et al., 2020). The phenomenon

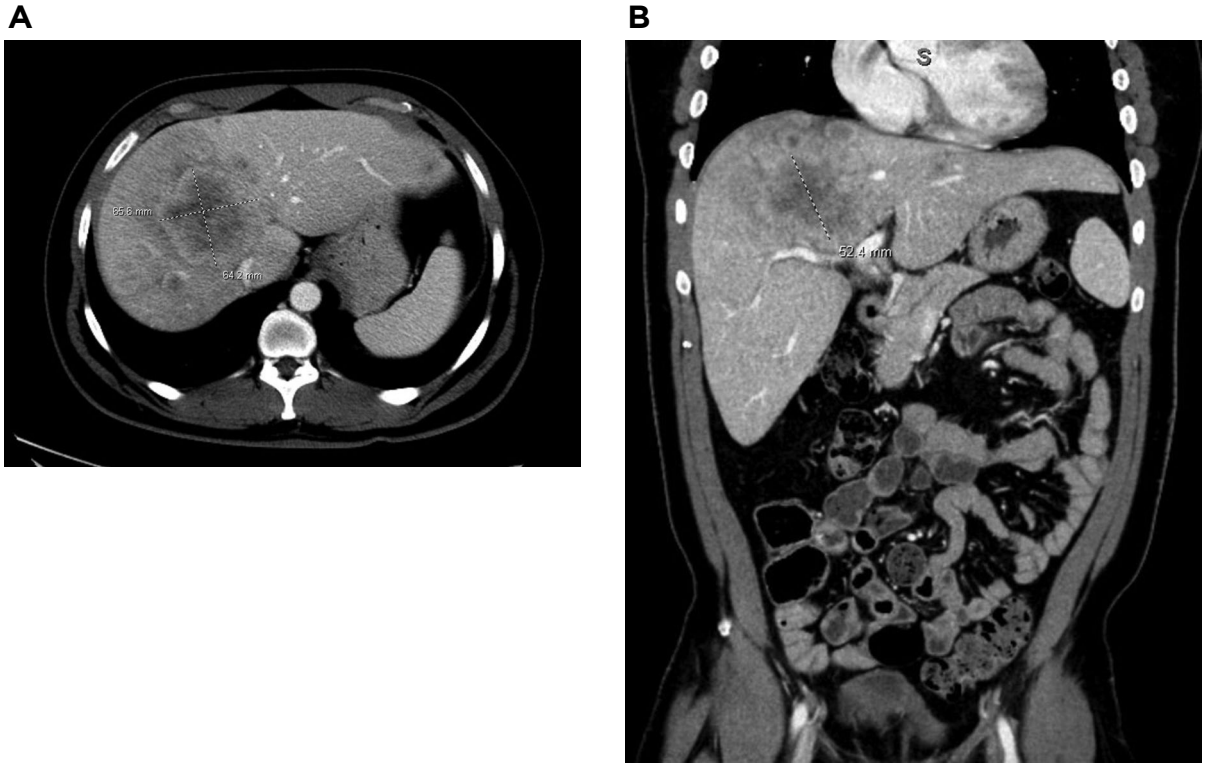

Figure 2. (A) Axial view of CT abdomen for Mr. ER. (B) Anterior view of CT abdomen for Mr. ER.

of EMH occurs to meet the demands of the body not met by the bone marrow and is not necessarily shown as malignant growth outside of the bone marrow (MS). Extramedullary hematopoiesis is microscopic and may manifest as hepatosplenomegaly; however, it may form tumefactive masses (which appear as neoplasms on imaging studies), making distinction from other pathologies difficult (Malla et al., 2020).

While the incidence of extranodal manifestations of hematologic malignancies is increasing, the combination of imaging features with clinical manifestations and laboratory values helps to facilitate correct diagnosis (Tomasian et al., 2015).

In the case of Mr. ER, the bone marrow did indicate hypocellularity, which is found in hypocellular MDS; however, pathology still revealed trilineage hematopoiesis, which is not characteristic of MDS. An overlap syndrome of AA with hypoplastic MDS can occur; however, Mr. ER did not meet the criteria. Hypoplastic MDS is also characterized by the presence of dysplasia and cytogenetic and molecular alterations (Fattizzo et al., 2021). In addition, imaging findings were not consistent with leukemic infiltration of the liver (MS) and must be used in association with clinical context of known hematologic disease.

C Metastatic cholangiocarcinoma (correct answer). Cholangiocarcinoma is an epithelial cell malignancy arising from locations of the biliary tree, 90% adenocarcinoma, with markers of cholangiocyte differentiation (Razumilava & Gores, 2014). The most characteristic and common symptom is jaundice. Intrahepatic cholangiocarcinoma typically presents as a malignant mass lesion in a noncirrhotic liver with heterogeneous uptake due to a highly vascularized interface from peritumoral inflammation with arterial enhancement at the tumor parenchymal margins (Razumilava & Gores, 2014). Markers of cholestasis, such as bilirubin, alkaline phosphatase, and gamma-glutamyltransferase, are often elevated, while a high serum level of carbohydrate antigen 19-9 (CA 19-9)

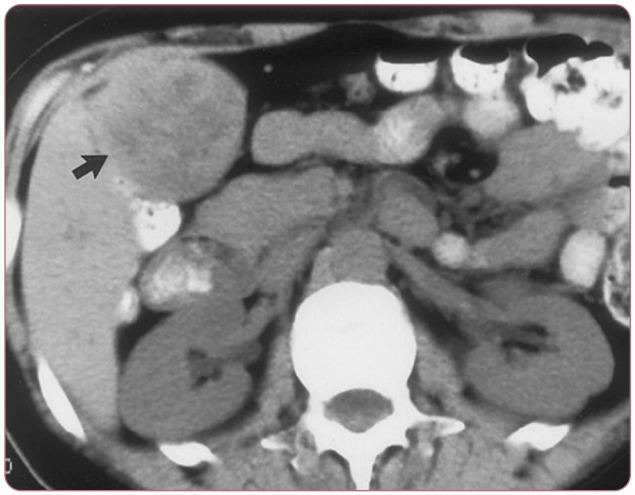

Figure 3. Example of hepatocellular adenoma. Reproduced from Grazioli et al. (2001).

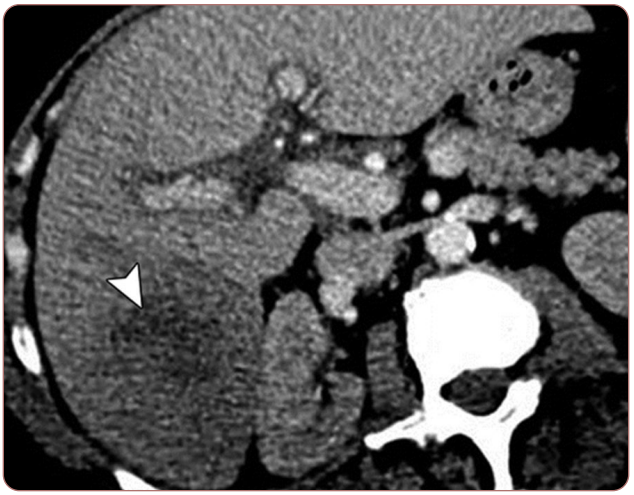

Figure 4. Example of myeloid sarcoma of the liver. Reproduced from Tomasian et al. (2015).

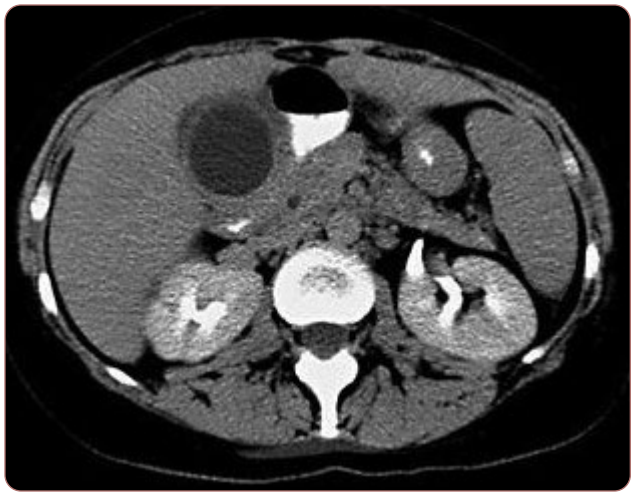

Figure 5. Example of myeloid sarcoma. Thick gallbladder with bile duct dilation. Reproduced from Norsworthy et al. (2016).

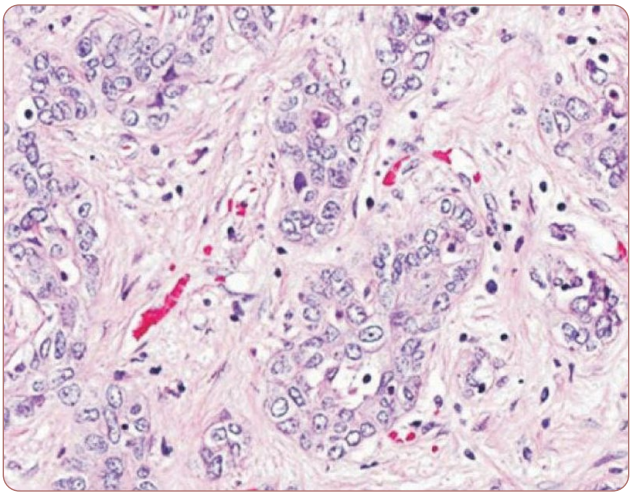

Figure 6. Histopathology of cholangiocarcinoma (Courtesy of Dr. Wai Chin Foo, MD Anderson Cancer Center, Houston, Texas, USA).

has a sensitivity of 89% and specificity of 86%, and carcinoembryonic antigen (CEA) alone has a low predictive value (Squadroni et al., 2017). Initial diagnostic exams include an abdominal ultrasound or CT scan, which can demonstrate biliary obstruction or dilatation in the absence of calculi (Squadroni et al., 2017). Tissue diagnosis of cholangiocarcinoma can be difficult due to the location, size, and desmoplastic characteristics; however, it is necessary for histological confirmation of proper diagnosis.

In the case of Mr. ER, ultrasound-guided core biopsy revealed moderately differentiated adenocarcinoma involving hepatic parenchyma with mild steatosis. Immunohistochemical (IHC) stains were positive for cytokeratin 7 (CK7), rare cytokeratin 20 (CK20), rare cytokeratin 19 (CK19), and negative for caudal-related homeobox gene 2 (CDX2), prostate-specific antigen (PSA), thyroid transcription factor 1 (TTF-1), synaptophysin, chromogranin A, and arginase 1. In situ hybridization of albumin was positive in neoplastic cells with weak focal positivity in anti-hepatocyte-specific antigen (Hep-par1), highly suggestive of cholangiocarcinoma. Unfortunately, the tumor did not harbor any targetable mutations.

MANAGEMENT

Mr. ER was evaluated by the gastrointestinal medical oncology team. The general recommendation following this diagnosis is surgical resection; however, this is not an option with advanced/metastatic disease. Mr. ER was recommended single-agent gemcitabine at a low dose of 300 mg/m^2 IV every other week given his concurrent diagnosis of AA, which prevented the option of combination chemotherapy. Immunotherapy with pembrolizumab (Keytruda) or durvalumab (Imfinzi) was not yet approved for cholangiocarcinoma at the time of this case. His performance status was 2 at this time. A BMBx was done prior to the start of systemic chemotherapy to assess his bone marrow reserve and revealed improvement in cellularity from 0% to 30%.

He was started on eltrombopag (Promacta) to assist with platelet production. The initial dosing was 50 mg daily for 2 weeks, 100 mg daily for 2 months, and a final dose increase to 150 mg daily. He displayed a partial response indicated by improvement in platelet transfusion requirements throughout treatment; however, he continued to require intermittent transfusions. He did not develop uncontrolled bleeding or thrombus formation while taking eltrombopag. He received four doses of gemcitabine; however, this was given at intermittent times due to dose limitations from thrombocytopenia.

Repeat CT of the chest, abdomen, and pelvis revealed progression with increased retrosternal lymph nodes, hepatic metastases, and abdominal ascites. Following insurance appeals, Mr. ER was approved for therapy with pembrolizumab; however, he continued to develop numerous episodes of abdominal ascites requiring paracentesis. He was not a candidate for an indwelling catheter due to pancytopenia. He qualified for two doses of pembrolizumab. He also received two doses of intravenous immunoglobulin and dexamethasone for potential immune-mediated cytopenias, but this proved unsuccessful. He developed a gastrointestinal bleed requiring intensive care unit admission. He was treated for potential acquired amegakaryocytic thrombocytopenia when his platelet count dropped to zero following a dose of pembrolizumab. He received rituximab (Rituxan), followed by cyclosporine for one course, and finally cyclophosphamide without response. He continued to have recurrent large ascites with signs of malnutrition and unfortunately expired a few days later.

DISCUSSION

Metastatic cholangiocarcinoma (CCA) is a primary hepatic malignancy originating from the bile duct epithelium and often develops without an identifiable etiology (Blechacz et al., 2011; Blechacz, 2017). Possible risk factors may include metabolic disease, diabetes mellitus, obesity, and a history of viral hepatitis. Patients with T2DM, for instance, are in a hyperinsulin state with insulin resistance; however, the anabolic effects of insulin remain present and support the proliferation of cholestatic cells (Ghidini et al., 2021). The histopathology of CCA (Figure 6) is 90% to 95% adenocarcinoma with mucin expression and highly desmoplastic stroma (Blechacz, 2017). CK7 and CK19 expression are characteristic of CCA but can also be expressed in hepatocellular and metastatic adenocarcinomas.

Surgical treatment options are limited as a majority are diagnosed with locally advanced or metastatic disease (Fostea et al., 2020). Systemic treatment with either a combination of gemcitabine/cisplatin or gemcitabine monotherapy is standard front-line therapy (Fostea et al., 2020). In patients with unresectable CCA with cholestasis, drainage of the liver parenchyma can improve survival while biliary metal stents have comparable survival rates, but the option is based on comorbidities and accessibility (Blechacz, 2017).

Growing evidence suggests an increased risk of hepatobiliary tumors in patients with autoimmune conditions. Immune and inflammatory responses are known to contribute to tumorigenesis and have been associated with increased cancer risk at various sites (McGee et al., 2019). According to a population based, case-control study from 1992 to 2013 by McGee and colleagues (2019), there is a 1.1- to 31.3-fold increased risk of developing hepatobiliary cancer in patients with autoimmune conditions and novel associations with aplastic anemia, in particular. Further research is needed to determine the biological mechanism; however, this information could assist with improved surveillance and early detection.

Disclosure

Ms. Geppner has served as a consultant for AbbVie, Bristol Myers Squibb, and Daiichi Sankyo.

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