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Cholangiocarcinoma, Primary Sclerosing Cholangitis, or IgG4-Sclerosing Cholangitis: Similar Presentations with Different Managements

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Abstract

In our case, we present a case of an 80-year-old male who was referred to the gastroenterologist for evaluation of a suspicious mass. CT imaging at the time had shown intrahepatic and extrahepatic biliary dilations, and the patient was thought to have a pancreatic or a common bile duct mass. A mass biopsy showed no malignancy, and further evaluation was warranted. The patient was found to have elevated IgG4 levels and was diagnosed with IgG4-sclerosing cholangitis (IgG4-SC). IgG4 has been found to create a wide array of pathologies, including autoimmune pancreatitis, dacryoadenitis, and sialadenitis. These pathologies have been grouped under an IgG4-Related Disease (IgG4-RD) category. In some cases, this IgG4-RD can present as a subclass of primary sclerosing cholangitis due to immune depositions and swelling of the CBD. Due to the strictures caused by the sclerosing cholangitis, intrahepatic and extrahepatic dilations might be found on endoscopic ultrasound (EUS). It is imperative to differentiate this from a malignant mass as the early recognition and treatment of IgG4-SC can lead to complete resolution. In this case report, we present a case of a patient who was found to have IgG4-SC and responded well to steroid treatment.

Keywords

Cholangiocarcinoma, Sclerosing Cholangitis, IgG4 Related Disease, IgG4, IgGSclerosing Cholangitis, ERCP, CBD Dilation

1. Introduction

Sclerosing cholangitis is a diffuse inflammation and fibrosis that progressively

leads to stenosis and destruction of the bile ducts [1]. Further subclassification includes three types: primary sclerosing cholangitis (PSC), secondary cholangitis, and IgG4 sclerosing cholangitis (IgG4-SC) [2]. IgG4-SC is one of the forms in which IgG4-RD can present. IgG4-RD became recognized as a systemic disease in 2003 after patients with autoimmune pancreatitis were also found to have other manifestations [3]. IgG4 has been contrasted to IgG1, 2 and 3 due to the unstable disulfide bond between the heavy chains. This unstable bond leads to the dissociation of the heavy chains and the bonding of other heavy chains with different antigen-combining sites. This became known as the fragment antigen-binding (Fab)-arm exchange [3]. This altered immune complex can lead to dense lymphoplasmacytic infiltrates. In glandular organs, this can lead to a pathological aggregation and obstruction of the ductal structures leading to the destruction of the involved organs. Specifically, in the case of IgG4-SC, the presentation is similar to the other types of sclerosing cholangitis. They usually present with cholestatic symptoms like pruritus, abdominal pain, elevated ALP and GGT, and bilirubin. The obstruction and demolition of the CBD can lead to hepatic damage and subsequent failure. In contrast to the other types of sclerosing cholangitis, IgG4-SC has been shown to have better outcomes, treatment response to steroids, and less recurrence [4]. We hereby present a case of IgG4-SC presenting as cholangiocarcinoma.

2. Case Presentation

An 80-year-old male with a previous medical history of hypertension, diabetes, coronary artery disease, and bladder cancer was referred to the gastroenterology service for further workup after CT abdomen with IV contrast revealed intrahepatic and extrahepatic biliary dilations with an abrupt cutoff in the common bile duct (**Figure 1**). Mild streaky densities were also seen around the pancreatic head. Initial bloodwork was completed, which showed an ALT of 320 IU/L (Normal: 10 - 60 IU/L), AST of 297 IU/L (Normal: 1 - 40 IU/L), Bilirubin 1.4 mg/dL (Normal: <1 mg/dL), and GGT of 2032 IU/L (Normal: 5 - 40 IU/L), all steering the patient's differential diagnosis to a pancreatic or CBD mass. Endoscopic Ultrasound (EUS) was done, which showed an irregular mass in the CBD wall highly suspicious of cholangiocarcinoma. At that time, an endoscopic retrograde cholangiopancreatography (ERCP) was done, and malignant strictures were seen, consistent with the cholangiocarcinoma differential seen on EUS. These findings were suggestive of Bismuth-Corlette 2 and possibly 3A classification. The surgical service was then consulted, and the patient underwent an exploratory laparotomy with portal node biopsy. The biopsy results failed to show any signs of malignancy with completely benign margins leading to the reassessment by the gastroenterology service. A repeat ERCP with direct visualization cholangioscopy showed a diffusely dilated main bile duct with sludge and pus, a single diffuse stenosis in the right duct with nodularity and dilated vessels similarly seen in malignant mucosa (**Figure 1**), but the biopsy and cytology showed atypical glandular proliferation but no signs of dysplasia or neoplasia.

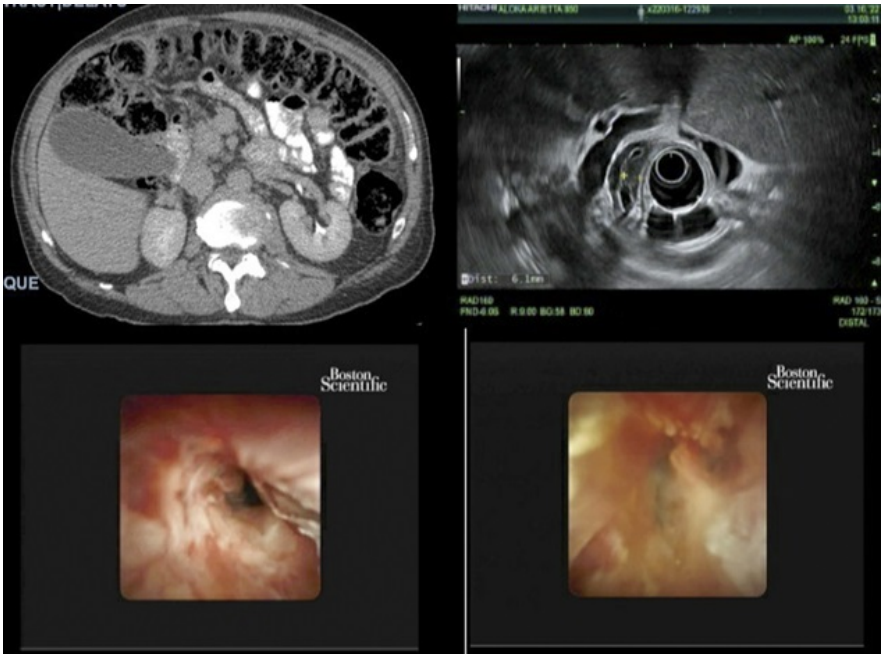

Figure 1. Top: CT of abdomen and ERCP. Bottom: Exploratory laparotomy.

Further evaluation later revealed that the patient had an IgG4 of 931 mg/dL. The combined picture of the dilated hepatic ducts, the nodularity seen on ERCP, and the IgG4 level led to the diagnosis of IgG4-SC. At this time, the patient was begun on a 20 mg prednisone daily regimen for one month, but his IgG4 levels continued to be elevated at 547 mg/dL, so the patient was asked to increase his dose of prednisone to 40 mg daily. At a follow-up two weeks later, the patient's IgG4 continued to trend down to 335 mg/dL.

3. Discussion

Sclerosing cholangitis (SC) can be categorized as primary sclerosing cholangitis (PSC), secondary cholangitis, and IgG4 sclerosing cholangitis. IgG4 related-diseases classification was proposed after autoimmune pancreatitis was found to haveextrapancreatic manifestations [3]. IgG4 immune complexes led to CD4+ and CD8+ depositions in various organs [1]. IgG4 related-diseases are subsequently the deposition of these IgG4 plasma cells and lymphocytes, leading to storiform fibrosis presenting as tumefactive lesions [3]. More specifically, the depositions of these IgG4 immune complexes in the bile duct wall have led to sclerosing of the CBD and hence the IgG4 sclerosing cholangitis subcategory of SC. IgG4 has been contrasted with IgG1, IgG2, and IgG3 as having weaker and unstable disulfide bonds between the heavy chains of the antibody [3]. This unstable bond led to the bonding of different heavy chains with different antigen-combining sites, known today as the fragment antigen-binding (Fab)-arm exchange. It is because of this immune antibody cross-matching that has led to the pathogenesis of IgG4-RD. The deposition of IgG4 plasma cells in ductal structures has led to the narrowing and strictures of these organs. IgG4-RD and, more specifically,

IgG4-SC can not be diagnosed simply by the elevation of IgG4 levels as the IgG4 concentrations can vary by a factor of more than 100 in different healthy people [3] [5] [6]. Because of that, it is the elevation of IgG4 from a known baseline of a specific patient with physical findings that one can be diagnosed with IgG4-SC.

IgG4-SC can present similarly to that of a cholangiocarcinoma or pancreatic mass; because of that, IgG4-SC can go unnoticed and undiagnosed. The strictures of these pathologies cause the narrowing of the intrahepatic and extrahepatic bile ducts may not be differentiated on imaging. In 2021, the Mendoza criteria were published to help differentiate malignant vs. benign causes of biliary strictures [7]. The criteria included visualization of the strictures and noted tortuous vessels, irregular nodulations, raised intraductal lesions, irregular surfaces, and tissue friability [7]. These signs have been associated with an increased likelihood of malignancy. The Mendoza criteria were found to have an overall diagnostic accuracy of 77% [7]. In our case, the patient did not meet any of the Mendoza criteria, which was in line with the benign nature of IgG4-SC.

IgG4-SC is distinctly different than that of primary sclerosing cholangitis. IgG4-SC is not associated with inflammatory bowel disease like PSC and is also found in older patients [1]. IgG4-SC is more commonly associated, but not always, with autoimmune pancreatitis, hence the reason that they were initially studied and understood to be of the same entity and pathology. The histological appearance of IgG4-SC is also different than that found in PSC. In PSC, mucosal erosion is seen, whereas, in IgG4-SC, dense lymphoplasmacytic infiltration of the bile duct wall and fibrosis of the periportal area of the liver is seen but with intact mucosa throughout [1]. Neutrophils, usually seen in PSC, are not a distinct feature of IgG4-SC. The distinction between these types of sclerosing cholangitis is essential due to the responsiveness to therapy. IgG4-SC is known to respond well to treatment with steroids such as prednisolone, whereas PSC has been managed supportively, and patients sometimes require liver transplants. In Japan, at the Teikyo University School of Medicine, a study was conducted to see the responsiveness of IgG4-SC to prednisolone [2]. It was noted that a total of 376 (90%) patients from a sample of 462 were found to have a reduction of ALP levels and alleviation of biliary strictures on imaging [2]. IgG4-RD can easily be mistaken for cholangiocarcinoma and can take a toll on the healthcare systems if initial testing is not initiated. Although it can be mistaken for a life-threatening pathology such as cholangiocarcinoma, this subtype of sclerosing cholangitis has significantly better outcomes and prognosis than the PSC subtype of sclerosing cholangitis.

4. Conclusion

Cholestatic symptoms such as jaundice, weight loss, and pruritis can be found in an array of gastrointestinal pathologies. When examining a patient and ordering investigative testing, a clinician should be aware of possible differentials. Pancreatic malignancies, cholangiocarcinoma, and sclerosing cholangitis should be

differentiated, and proper laboratory and procedural testing should be done. IgG4-sclerosing cholangitis can present very similarly to cholangiocarcinoma as it did with our patient, but further investigation will warrant a different prognosis and treatment. IgG4-SC is an IgG4-related disease presentation that may or may not present with autoimmune pancreatitis, dacryoadenitis, and sialadenitis. In all cases of suspected IgG4-SC, patients should be screened for the possibility of cholangiocarcinoma. If negative, IgG4-SC should be differentiated from other causes of sclerosing cholangitis, such as primary sclerosing cholangitis. IgG4-SC can be diagnosed with visualization of strictures, biopsy, and an elevation of IgG4 levels in a patient. In conclusion, although IgG4-SC can present similarly to cholangiocarcinoma or primary sclerosing cholangitis, it has significantly greater outcomes and can be managed with steroid therapy.

Consent

As this is a case report, consent was obtained for the purpose of this paper.

Conflicts of Interest

The authors report no conflict of interest. An ethical review is not necessary because this is a case report. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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