IgG4-Related Gallbladder Disease Mimicking Mirizzi Syndrome

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ABSTRACT
A woman in her sixth decade was transferred to our tertiary hospital for management of obstructive jaundice and concern for a polypoid gallbladder mass. Magnetic resonance cholangiopancreatography demonstrated a 3.7 cm gallstone in the gallbladder neck, thickened gallbladder wall and common hepatic duct stricture adjacent to the stone with resultant intrahepatic biliary ductal dilation suggesting a diagnosis of Mirizzi syndrome versus neoplasia. Endoscopic retrograde cholangiopancreatography showed a severe biliary stricture and a stent was placed to span the stricture. Cytology brushings of the stricture were negative for malignant cells. Surgical pathology from a diagnostic laparoscopy converted to an open partial cholecystectomy revealed a histological diagnosis of IgG4 related cholecystitis. Following hospital discharge, the patient was referred to our gastroenterology clinic for evaluation of IgG4 cholangiopathy with magnetic resonance cholangiopancreatography evidence of persistent biliary stricture post-operatively. The patient was successfully treated with steroid therapy, as follow-up imaging demonstrated resolution of biliary dilation and improvement in the common hepatic duct stenosis and normalization of serum bilirubin and alkaline phosphatase.

INTRODUCTION
IgG4 related disease (IgG4-RD) is an uncommon diagnosis that may involve multiple organ systems and now unifies many previously isolated diagnoses [1]. There is a growing body of literature describing the clinical presentation, diagnostic criteria, and demographic affected by this immune mediated condition. The most commonly recognized gastrointestinal manifestation of IgG4-RD is autoimmune pancreatitis. However, two additional gastrointestinal manifestations include cholangiopathy [2] and cholecystitis [3]. This case report describes a novel presentation of IgG4-RD involving the biliary tract and gallbladder appearing as a pseudo-Mirizzi type syndrome.

CASE REPORT
A woman in her sixth decade was referred to our gastroenterology clinic following a hospital admission for obstructive jaundice. Her symptoms began two months prior, when she presented to a community hospital emergency department (ED) reporting a three-day history of jaundice, right upper quadrant abdominal pain, and nausea. She was previously healthy, except for psoriasis and ongoing tobacco use.

In the outside hospital ED the patient was hemodynamically stable and afebrile. The physical exam was significant for jaundice, dry mucus membranes and right upper quadrant abdominal tenderness. Laboratory studies demonstrated elevated alkaline phosphatase 801 U/L (reference 40-150 U/L), elevated total bilirubin 17.7 mg/dL (reference 0.0-1.5 mg/dL) and elevated aspartate transaminase 150 U/L (reference 7-40 U/L) and alanine transaminase 159 U/L (reference 0-45 U/L). The white blood cell count was 12.62 k/uL (3.70-11.00 k/uL). The lipase and amylase were within normal limits. A right upper quadrant ultrasound demonstrated a polypoid gallbladder mass, cholelithiasis, and a dilated common bile duct (8 millimeters). Additionally, the ED records indicate the patient underwent computed tomography imaging prior to presentation at an outside hospital, which demonstrated elevated alkaline phosphatase 801 U/L, elevated total bilirubin 17.7 mg/dL, elevated aspartate transaminase 150 U/L and alanine transaminase 159 U/L. The white blood cell count was 12.62 k/uL (3.70-11.00 k/uL). The lipase and amylase were within normal limits. A right upper quadrant ultrasound demonstrated a polypoid gallbladder mass, cholelithiasis, and a dilated common bile duct (8 millimeters). Additionally, the ED records indicate the patient underwent computed tomography imaging prior to presentation at an outside hospital, which demonstrated a distended gallbladder with wall thickening and evidence of a single stone. The patient was transferred to our tertiary hospital for evaluation by a hepatobiliary surgeon given concern for an underlying malignancy.

Following transfer, MRCP revealed a 3.7 cm gallstone in the gallbladder neck and an asymmetric thickened gallbladder wall, the pancreas was normal in appearance and the extrahepatic bile duct was normal in caliber. The gallstone appeared to cause extrinsic mass effect on the common hepatic bile duct resulting in stricture with proximal intrahepatic dilation of the left and right biliary ducts (Figures 1a, 1b). The findings suggested Mirizzi...
syndrome, with a lesser likelihood of biliary malignancy. ERCP revealed a severe stricture of the common hepatic duct, and a biliary stent was placed to cross the biliary stricture. Brush cytology of the biliary stricture was negative for malignant cells.

Given the suspicion for Mirizzi syndrome, the patient underwent a diagnostic laparoscopy converted to open partial cholecystectomy based on the intraoperative findings. Intraoperative frozen section of the gallbladder wall showed fibrosis and chronic inflammation but no evidence of malignancy. On surgical pathology, there were reactive epithelial changes, hemorrhage, and storiform mural fibrosis. Obliterative phlebitis and prominent lymphoplasmacytic aggregates were noted. Up to 29 IgG4 positive plasma cells were seen per high power field (hpf). The final histological diagnosis was IgG4-related cholecystitis.

The patient was discharged to home and referred to our gastroenterology clinic for follow-up regarding a new diagnosis of gastrointestinal IgG4-RD. The patient was seen 8 weeks post-operatively and reported doing well until ten days prior to the clinic visit when she noted weight loss, daily nausea and loose stool. At this time, laboratory studies demonstrated improvement in the bilirubin from prior to surgery (1.5 mg/dL, reference 0.0-1.5 mg/dL) but persistently elevated alkaline phosphatase (852 U/L reference 40-150 U/L). The serum IgG Subclass 4 level was within normal limits (85.9 reference 5.0-131.0). MRCP showed a 2.7 cm area of signal abnormality near the confluence of the right and left hepatic ducts with associated intrahepatic biliary dilation (Figures 2a, 2b). ERCP demonstrated a dominant stricture of the common hepatic duct and diffuse intrahepatic biliary strictures. Endoscopic ultrasound (EUS) revealed an isoechoic mass in the region of the porta hepatis corresponding to the above MRCP abnormality. Fine needle aspiration (FNA) of this region was negative for malignant cells but demonstrated fibrosis and chronic inflammation.

Given the latter imaging findings, the surgical pathology results, and persistent cholestasis the patient was treated for IgG4 cholangiopathy with prednisone 40 mg daily. One month later, MRCP demonstrated resolution of the intrahepatic biliary dilation with stability in the stenosis of the proximal common hepatic duct (Figure 3). Laboratory studies demonstrated complete resolution of cholestasis. Given the dramatic response to therapy the patient was transitioned to a steroid taper until discontinuation approximately 6 weeks later, with plans to monitor hepatic function every two to three weeks.

Subsequent laboratory studies remained within normal limits at 10 months of follow-up while the patient remained off steroid therapy. However, at this time the patient was readmitted to the hospital for evaluation of acute kidney injury secondary to bilateral ureteral obstruction. Magnetic resonance imaging demonstrated a likely recurrence of biliary IgG4-RD and a new finding of retroperitoneal fibrosis (Figure 4). On admission, liver function studies remained within normal limits. The levels peaked on the last day of the patient's 10-day admission, alanine transaminase was 129 U/L (reference 0-45 U/L) and aspartate transaminase was 71 U/L (reference 7-40 U/L). It was suspected the retroperitoneal fibrosis was also secondary to IgG4-RD and the etiology for the bilateral ureteral obstruction. Of note, the Rheumatology consultant described the magnetic resonance imaging as strongly suggestive of IgG-4 related fibrosis and therefore biopsy confirmation was not pursued.

The patient received a three-day course of intravenous soludmedrol and then was transitioned to an oral prednisone regimen. Bilateral ureteral stents were placed for obstructive uropathy. Following discharge, the patient began azathioprine, as a steroid-sparing agent, while prednisone was tapered. The patient continues to be followed by Rheumatology and Urology.

![Figure 1a](http://pancreas.imedpub.com/ - Vol. 18 No. 1 – Jan 2017. [ISSN 1590-8577])

**Figure 1a.** Coronal 3-D MIP image from MRCP demonstrates focal stricture of the proximal common hepatic duct (arrow) with upstream common hepatic bile duct and also diffuse intrahepatic biliary dilatation.

![Figure 1b](http://pancreas.imedpub.com/ - Vol. 18 No. 1 – Jan 2017. [ISSN 1590-8577])

**Figure 1b.** Coronal T2 SPACE image from MR scan demonstrated a "dark" 3.7 cm gallstone in the neck (arrow) with mass effect on the common hepatic duct down stream to the biliary dilatation.
simultaneous presentation of two extra-pancreatic IgG4-RD manifestations in a patient who is an epidemiological outlier with respect to both age and gender. Additionally, this patient demonstrated the histological hallmarks of this diagnosis but without elevated serum IgG4 levels, a component in the diagnostic criteria of IgG4-RD. Interestingly, Ghazale et al. reported that serum IgG4 levels are only 74% sensitive for IgG4-associated cholangitis [5]. Finally, our case highlights a potentially new diagnostic presentation for IgG4-RD that of a pseudo-Mirizzi type syndrome. In a recent PubMed literature search using the terms “Mirizzi syndrome AND IgG4” there were no published reports that describe a concurrent presentation of IgG4-RD and Mirizzi syndrome. Mirizzi syndrome is an uncommon sequela of cholelithiasis in

**DISCUSSION**

IgG4-RD is a multiorgan fibroinflammatory process [1]. Numerous diagnoses once thought to be isolated conditions are now categorized into the spectrum of IgG4-RD [1]. One proposed method to diagnose IgG4-RD combines evidence of single or multiorgan growth and / or characteristic lesions on imaging, serum IgG4 concentration >135 mg/dl, and key histological findings on tissue biopsy [4]. The histological hallmarks outlined in this particular criteria include plasmacyte and lymphocyte infiltration, fibrosis, >10 IgG4 positive cells per hpf and a ratio of IgG4:IgG positive cells >40% [4]. The combination of these latter criteria provides one model for predicting IgG4-RD in suspected cases.

Previously described manifestations of IgG4-RD in the biliary tract are IgG4-associated cholangitis [2] and sclerosing cholecystitis [3]. Patients with IgG4-associated cholangitis are predominantly older men (85%), mean age 62, who present with obstructive jaundice (77%), weight loss (51%) and abdominal pain (26%) [5].

There are several unique features of this case that deserve attention. First, this case illustrates a

![Figure 2a](image1.png) Coronal 3D MIP image of the biliary tree demonstrating persistent stricture at confluence of the right and left intrahepatic biliary radicals (arrow).

![Figure 2b](image2.png) Axial HASTE image confirming moderate intrahepatic biliary dilatation in both lobes.

![Figure 3](image3.png) Coronal 3-D MIP image from an MRCP obtained 4 months post-cholecystectomy and 1 month after initiation of steroid therapy demonstrates resolution of the intrahepatic biliary dilation with near-resolution of the proximal common hepatic duct stricture (arrow).

![Figure 4](image4.png) Non-contrast CT scan at the level of the aortic bifurcation demonstrates new confluent retroperitoneal soft tissue (arrows) that is inseparable from the aortoiliac system. Findings are consistent with retroperitoneal fibrosis obstructing both ureters from progressed IgG4 systemic sclerosis.
which a gallstone causes extrinsic compression on the common hepatic duct [6].

This case highlights the possibility of IgG4-RD accounting for the hepatic bile duct stricture, either due to IgG4 related gallbladder wall inflammation causing extrinsic compression or due to intrinsic autoimmune cholangiopathy. The initial MRCP demonstrated a gallstone within the gallbladder fossa causing extrinsic compression on the hepatic duct resulting in stricture and proximal biliary dilation. The stricture and biliary dilation persisted after the cholecystectomy and removal of the stone (Figures 2a, 2b). This suggests IgG4-RD may present as a pseudo-Mirizzi type syndrome when involving the gallbladder and or biliary tract.

While this case provides insight into the spectrum of IgG4-RD, it has limitations. The gallbladder biopsy histology was consistent with IgG4-RD. However, no formal biopsy was taken of the biliary tract. It is presumed the patient’s biliary strictures were a separate manifestation of IgG4-RD, as opposed to an alternative diagnosis like primary sclerosing cholangitis or primary biliary cirrhosis. As previously described, bile duct brushings from ERCP and FNA of an isoechoic region seen on EUS were both negative for malignant cells. In our case, the diagnosis of IgG4-RD is predominantly based on the histological findings, imaging studies and the patient’s profound response to steroid therapy. Resolution of biliary strictures following steroid therapy is a hallmark of IgG4-RD and a feature that may differentiate this diagnosis from primary sclerosing cholangitis [5] (Figure 3).

IgG4-RD is a rapidly expanding field of study that warrants attention and research given the diversity in patients affected, the varied clinical presentations and numerous organ systems involved. This is supported by our case as it demonstrates a unique presentation of IgG4-RD manifesting as gallbladder and biliary tract disease in an uncommon patient demographic. Our case highlights previously described hallmark features of IgG4-RD while suggesting IgG4-RD may manifest as a pseudo-Mirizzi type syndrome when involving the gallbladder and or biliary tract.

Conflict of Interest

All authors declare having no conflict of interests or financial disclosures.

References