Jaundice, elevated carbohydrate antigen 19-9, pancreaticobiliary duct stenosis, post-pancreatic swelling imprint

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Date: 2019-02-25T00:00:00+00:00

Abstract

An 80-year-old male patient with a chief complaint of "darkened urine for 1 month, and incidentally discovered bile duct wall thickening and hypoechoic pancreatic body for 1 week" was admitted to the Department of General Surgery at Peking Union Medical College Hospital on March 5, 2016.

Full Text

Preamble

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1. Case Summary

1.1 Present Illness

The patient was a 65-year-old male who presented with darkened urine for one month without obvious precipitating factors. Laboratory tests at a local hospital revealed: hemoglobin (Hb) 110 g/L, white blood cell count (WBC) 7.91×10 /L, total bilirubin (TBil) 42.4 mol/L, direct bilirubin (DBil) 29.5 mol/L, gamma-glutamyl transpeptidase (GGT) 695 U/L, alkaline phosphatase (ALP) 313 U/L,

alanine aminotransferase (ALT) 113 U/L, and aspartate aminotransferase (AST) 82 U/L. Erythrocyte sedimentation rate (ESR) was 37 mm/h. Tumor markers showed carbohydrate antigen 19-9 (CA19-9) at 121.1 U/mL (negative for CA72-4). Abdominal Doppler ultrasound demonstrated heterogeneous liver echotexture, a 42 mm×27 mm hyperechoic lesion in the right liver lobe with indistinct margins (considered hemangioma), irregular pancreatic morphology with diffuse swelling, inhomogeneous internal echoes, and no dilatation of the main pancreatic duct. The gallbladder wall was rough, and no enlarged lymph nodes were visualized. Contrast-enhanced CT suggested diffuse thickening of the common bile duct wall with accompanying abdominal lymph node enlargement, irregular pancreatic head morphology, and swelling of the pancreatic body and tail, raising suspicion for malignancy. The patient was treated with cefoperazone-sulbactam without significant improvement. Surgical consultation recommended pancreaticoduodenectomy, which the patient and family declined.

Two weeks later, the patient developed skin and scleral icterus. Repeat laboratory tests showed: TBil 155.2 mol/L, DBil 121.7 mol/L, GGT 545 U/L, ALP 403 U/L, ALT 78 U/L, AST 86 U/L, high-sensitivity C-reactive protein (hsCRP) 9.24 mg/L, and CA19-9 98.2 U/mL. The patient reported no significant weight loss and maintained good mental status.

1.2 Past Medical History

The patient had a history of allergic rhinitis and lumbar spinal stenosis. He had a prior cerebral hemorrhage in the right basal ganglia. He had newly diagnosed hyperglycemia two weeks before presentation, with fasting blood glucose (FBG) of 5.5 mmol/L and 2-hour postprandial blood glucose (2hPBG) of 13.8 mmol/L; HbA1c was 6.80%. He had no history of hepatitis or tuberculosis. He reported allergy to sulfonamide drugs.

1.3 Personal and Family History

The patient previously worked as an orthopedic surgeon with frequent radiation exposure. He had a history of alcohol consumption but had quit. His mother died of rectal cancer.

1.4 Physical Examination

Vital signs were stable. Cardiopulmonary examination was unremarkable. The abdomen was flat and soft, with no tenderness in the hepatic region. Liver and spleen were not palpable below the costal margins. Shifting dullness was negative.

1.5 Laboratory Investigations

Repeat liver function tests after admission showed: TBil 155.2 mol/L, DBil 121.7 mol/L, GGT 284 U/L, ALP 299 U/L. Serum amylase and lipase were

normal. ESR was 84 mm/h, hsCRP 7.82 mg/L. IgG4 subclass measurement revealed 32.5 g/L. WBC count was 7.9×10 /L with neutrophil proportion of 84%, absolute neutrophil count 0.11×10 /L.

1.6 Imaging Studies

Abdominal and pelvic contrast-enhanced CT with thin-section pancreatic scanning revealed diffuse pancreatic swelling with homogeneous capsule-like enhancement. The common bile duct showed circumferential wall thickening throughout its entire course, with severe narrowing at the pancreatic segment. Marked dilatation of intra- and extrahepatic bile ducts was noted proximal to the stricture. The splenic vein was closely related to the pancreas, with increased density of peripancreatic fat. [Figure 1: see original paper]

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2. First Multidisciplinary Discussion

2.1 Radiology

Imaging demonstrated diffuse pancreatic swelling with capsule-like enhancement and disappearance of lobular architecture. The pancreatic parenchyma showed delayed hepatic venous phase enhancement. The pancreatic duct was not dilated, and the pancreatic tail was surrounded by a long, low-signal capsule. Diffusion-weighted imaging (DWI) showed markedly high signal intensity, with corresponding decreased apparent diffusion coefficient (ADC) values. The common bile duct exhibited circumferential wall thickening throughout its length, with severe narrowing at the middle segment and multiple segmental strictures and dilatations in the proximal intrahepatic ducts. The left and right hepatic duct bifurcation and intrapancreatic segment showed luminal narrowing, though the wall remained intact. The lesions appeared skip-pattern. Combined CT and MRI findings suggested diffuse pancreatic parenchymal and signal abnormalities, with proximal bile duct involvement being prominent, consistent with immune-related disease.

2.2 Nuclear Medicine

[1] F-FDG PET/CT showed diffuse increased metabolic activity in the pancreas with slight enlargement. The maximum standardized uptake value (SUVmax) ranged from 6.1 to 6.4. The common bile duct was thickened (1.5 cm × 1.8 cm × 2.3 cm) with heterogeneous radioactive uptake and SUVmax of 6.1. The left and right hepatic ducts also showed abnormal increased metabolism. Several small nodules were visible around the hepatic hilum and peripancreatic region with SUVmax of 1.2-1.9, considered metabolically active lymph nodes. The findings suggested pancreatic and biliary system involvement by IgG4-related disease.

2.3 Gastroenterology

Endoscopic ultrasound (EUS) revealed diffusely enlarged pancreatic body and tail with hypoechoic parenchyma and inhomogeneous internal echoes. The pancreatic duct was not dilated. A capsule-like change was vaguely visible. The common bile duct showed symmetric marked wall thickening with internal flocculent material. No definite mass was identified. A peripancreatic lymph node measured 1.0 cm. These findings were consistent with autoimmune pancreatitis (AIP) and IgG4-related sclerosing cholangitis.

According to the 2011 International Consensus Diagnostic Criteria for IgG4-related disease (IgG4-RD), diagnosis requires: (1) typical diffuse or localized organ enlargement/mass on imaging; (2) elevated serum IgG4 1350 mg/L; and (3) histopathology showing lymphoplasmacytic infiltration, storiform fibrosis, and IgG4-positive plasma cell infiltration (>10/HPF with IgG4/IgG ratio >40%). Definitive diagnosis requires (1)+(2)+(3) or (2)+(3). Our patient met the imaging and serological criteria. However, obtaining histology from the bile duct is difficult and risky. Therefore, we recommended evaluating for peripheral lymph node or salivary gland involvement that could be biopsied for histological confirmation.

2.4 Rheumatology and Immunology

IgG4-RD is a chronic inflammatory fibrosing condition characterized by typical diffuse or localized swelling in one or more organs, lymphoplasmacytic infiltration with abundant IgG4-positive plasma cells, and elevated serum IgG4. The disease must be distinguished from other immune-related conditions like primary sclerosing cholangitis (PSC) and secondary sclerosing cholangitis.

International consensus classifies sclerosing cholangitis into: (1) primary sclerosing cholangitis (PSC), (2) IgG4-related sclerosing cholangitis (IgG4-SC), and (3) secondary sclerosing cholangitis (SSC). PSC predominantly affects the middle and upper bile ducts with band-like strictures and diverticulum-like protrusions, often associated with inflammatory bowel disease. IgG4-SC mainly involves the lower bile duct with long segmental strictures or distal common bile duct narrowing, frequently associated with AIP. Differentiation from pancreatic head cancer and distal cholangiocarcinoma is crucial.

Our patient presented with jaundice, imaging showing multiple segmental pancreaticobiliary strictures and dilatations, elevated IgG4, and diffuse pancreatic swelling, strongly suggesting IgG4-RD with AIP and IgG4-SC. Possible parotid gland involvement was also noted. We recommended screening for tuberculosis infection (TB-SPOT.TB) and EBV/CMV to exclude infectious causes before initiating steroid therapy.

2.5 General Surgery

The diagnosis of obstructive jaundice was clear in this elderly male patient. The differential diagnosis primarily included pancreatic cancer and extrahepatic cholangiocarcinoma. The patient had newly diagnosed hyperglycemia and markedly elevated CA19-9, which can assist in diagnosis, monitoring recurrence, and metastasis for gastrointestinal malignancies. However, the imaging features and the dramatic response to diagnostic steroid therapy favored IgG4-RD. PET/CT showed high metabolic activity, but the pattern was consistent with inflammatory disease. We recommended evaluating resectability while pursuing tissue diagnosis to avoid unnecessary surgery.

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3. Management After First Discussion

The patient was transferred to the Gastroenterology Department for further evaluation. Thyroid ultrasound showed multiple small cysts in the right lobe and a solid nodule in the left lobe, considered benign. Salivary gland ultrasound revealed bilateral submandibular gland enlargement with inhomogeneous echotexture, suggesting possible salivary gland involvement. Infectious workup including hepatitis viruses, EBV DNA, CMV, and TB-SPOT.TB was negative, with no evidence of active infection.

The patient was started on prednisone 40 mg/d. After two weeks, repeat labs showed: TBil decreased from 155.2 to 74.5 mol/L, IgG4 from 32,500 to 19,700 mg/L, ESR from 83 to 33 mm/h, and hsCRP from 9.7 to 1.06 mg/L. The treatment response was excellent. However, the patient developed hyperglycemia (2hPBG up to 15.5 mmol/L) and leukocytosis (WBC 20.03×10 /L, neutrophils 15.56×10 /L). Blood smear showed no abnormalities, and there were no signs of infection. A second multidisciplinary discussion was convened to address these steroid-related side effects.

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4. Second Multidisciplinary Discussion

4.1 Gastroenterology

The patient showed excellent response to steroids with declining TBil, IgG4, ESR, and hsCRP. We recommended maintaining current dose. The hyperglycemia was likely multifactorial: (1) IgG4-RD can cause pancreatic interstitial fibrosis and destruction of islet tissue by plasma cell infiltration, leading to endocrine dysfunction; and (2) glucocorticoids affect glucose metabolism. We suggested continued glucose monitoring. If blood glucose improves with disease remission and steroid taper, this would support the diagnosis. If not, Type 2 diabetes mellitus should be considered.

4.2 Rheumatology and Immunology

The patient responded well to glucocorticoids, confirming the diagnosis of IgG4-RD. After 2 weeks of initial dose (40 mg/d), gradual tapering should begin. Recommended regimens include: (1) reduce by 5 mg every 1-2 weeks to maintenance of 5-10 mg/d; or (2) reduce by 5 mg weekly to 20 mg/d, then by 2.5 mg weekly to 5 mg/d. Total induction course should not be shorter than 3 months.

Regarding immunosuppressive agents, international consensus shows 分歧. Japanese experts do not recommend initial combination therapy, while some Western experts suggest adding immunosuppressants (azathioprine 50-100 mg/d or mycophenolate mofetil 0.75-1.5 g/d) for high-risk patients or those with relapse. Given our patient' s good response and pre-existing obstructive jaundice with infection risk, we recommended holding off immunosuppressants for now.

4.3 Hematology

Steroid-induced leukocytosis is common, with WBC increases primarily due to neutrophilia. The mechanism involves glucocorticoid-induced demargination of neutrophils from the vessel wall into the circulation. The marginating pool contains about half the total neutrophil count. Our patient' s WBC pattern was consistent with this phenomenon. With declining infection markers (ESR, hsCRP) and no clinical infection signs, no treatment adjustment was needed. Close monitoring was recommended.

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5. Final Diagnosis

IgG4-related disease (IgG4-RD) involving: (1) Type 1 autoimmune pancreatitis (AIP), (2) IgG4-related sclerosing cholangitis (IgG4-SC), and (3) possible salivary gland involvement.

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6. Follow-up

The patient continued oral prednisone with gradual tapering. All inflammatory markers (IgG4, TBil, ESR, hsCRP) decreased significantly. At 6 months after initial treatment, prednisone was reduced to 25 mg/d. The patient experienced a transient CA19-9 elevation without other parameter increases. At 1 year, prednisone was discontinued. No abdominal pain, jaundice, or other symptoms recurred. Two years post-treatment, IgG4, TBil, ESR, and hsCRP remained stable without significant elevation. Blood glucose control was similar to baseline. [Figure 4: see original paper][Figure 5: see original paper][Figure 6: see original paper]

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7. Discussion

IgG4-RD is a chronic inflammatory fibrosing condition involving multiple organ systems, characterized by lymphoplasmacytic infiltration with abundant IgG4-positive plasma cells. Diagnosis relies on comprehensive evaluation of imaging, serology, other organ involvement, and histopathology [1]. Our center reported the largest single-center Chinese cohort of IgG4-RD, with pancreatic involvement in 41.7% and biliary involvement in 38.4% of patients, similar to international reports [11].

IgG4-RD involving the pancreas and biliary system presents significant diagnostic challenges due to its mimicry of malignancy. Differentiating IgG4-SC from PSC and cholangiocarcinoma is critical. PSC typically shows band-like strictures of intrahepatic ducts, while IgG4-SC presents as long segmental narrowing of the distal common bile duct, often associated with AIP [5]. Our patient' s imaging showed characteristic diffuse pancreatic swelling with capsule-like enhancement and circumferential bile duct thickening, strongly suggesting IgG4-RD.

CA19-9 elevation can be misleading. Studies show CA19-9 correlates with bilirubin levels in benign biliary obstruction but not in malignancy [7,8]. Our patient' s CA19-9 normalized after biliary decompression and steroid therapy, supporting the benign diagnosis.

The management of IgG4-RD requires multidisciplinary collaboration. Glucocorticoids are first-line therapy, with most patients achieving excellent response [2]. However, 20-40% relapse during tapering. Immunosuppressants may be considered for refractory cases or high-risk patients. Surgical resection is reserved for severely fibrotic lesions unresponsive to medical therapy.

A critical consideration is avoiding unnecessary surgery. Meta-analyses show 30-43% of pancreaticoduodenectomies performed for presumed malignancy yield benign pathology, with IgG4-RD accounting for 9-26.1% of these cases [14,15]. Our case demonstrates the value of diagnostic steroid trials and comprehensive imaging (CT, MRCP, PET/CT, EUS) in distinguishing IgG4-RD from malignancy [16].

The IgG4-RD Responder Index, incorporating clinical, serological (IgG4, ESR, hsCRP), and radiological parameters, is valuable for monitoring treatment response [9]. Our patient showed excellent response across all domains.

MDT plays a crucial role in managing such complex cases, integrating expertise from surgery, gastroenterology, rheumatology, radiology, and nuclear medicine to achieve accurate diagnosis and optimal treatment while avoiding unnecessary morbidity.

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8. Expert Commentary

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IgG4-RD is a rare systemic disease that frequently involves multiple organs. This case of IgG4-RD (AIP/IgG4-SC) presented with obstructive jaundice, mimicking pancreatic or distal cholangiocarcinoma. The diagnostic dilemma was resolved through MDT discussion, comprehensive evaluation, and diagnostic steroid trial. This highlights the importance of recognizing IgG4-RD in the differential diagnosis of pancreaticobiliary malignancies. MDT is essential for accurate diagnosis, appropriate treatment selection, and avoidance of unnecessary major surgery. Enhanced awareness of IgG4-RD among hepatobiliary and pancreatic surgeons, combined with multidisciplinary collaboration, will improve patient outcomes.

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Note: Figure translations are in progress. See original paper for figures.