Clinical Case Report

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Persistent cholestasis resulting from duodenal papillary carcinoma in an adolescent male

A case report

Haiyan Fu, MS[a], Yingchao Li, MD[b], Gelan Bai, BS[a], Runkai Yin, MS[a], Chunlan Yin, MS[a], Weina Shi, MS[a], Lili Zhang, MS[c], Rongpin Li, MS[d], Ruiqin Zhao, MS[a,*]

Abstract

Rationale: Cholestasis in pediatric patients has diverse etiologies and can be broadly classified as intrahepatic or extrahepatic. The common causes of extrahepatic cholestasis are bile duct calculus, inflammation, or pancreatitis. Malignant tumor is a rare cause of bile ducts obstruction in adolescent. Here we report a 14-year-old male patient with cholestasis due to poorly differentiated adenocarcinoma.

Patient concerns: A 14-year-old male patient with cholestasis was admitted because of jaundice, weakness, weight loss, and stomach pain for 2 months. The patient had been diagnosed with epilepsy 4 years previously and was being treated with sodium valproate and oxcarbazepine. On admission, laboratory studies showed elevated levels of aspartate aminotransferase (271 IU/L), alanine aminotransferase (224 IU/l), γ-glutamyltransferase (1668.9 IU/L), total bilirubin (66.4 μmol/L), and direct bilirubin (52.6 μmol/L). Additional laboratory tests eliminated common causes of cholestasis such as bacterial/viral infection, autoimmune liver disease, Wilson disease, Alagille syndrome, or progressive familial intrahepatic cholestasis type 3. The results of laboratory investigations showed no improvement after 10 days of treatment with ursodeoxycholic acid and vitamins A, D, and K1. Enhanced magnetic resonance imaging demonstrated a tumor of 22 mm diameter in the duodenal lumen and dilatation of the common bile duct. Endoscopic retrograde cholangiopancreatography detected a tumor in the duodenal lumen.

Diagnosis: Considering the clinical features, imaging manifestation, endoscopic findings, and pathologic characteristic, the patient was diagnosed with poorly differentiated adenocarcinoma.

Interventions: The patient underwent pancreaticoduodenectomy and chemotherapy.

Outcome: The patient recovered well. Elevated levels of tumor biomarkers or abnormal liver function tests have not occurred during the 2-year follow-up.

Conclusion: Cholestasis resulting from primary duodenal papillary carcinoma is rare in pediatric patients but should be considered in the differential diagnosis.

Abbreviations: ARC = arthrogryposis-renal dysfunction-cholestasis, CT = computed tomography, DILI = drug-induced liver injury, ERCP = endoscopic retrograde cholangiopancreatography, MRI = magnetic resonance imaging, PFIC = progressive familial intrahepatic cholestasis.

Keywords: cholestasis, differential diagnosis, duodenal papillary carcinoma, pediatric patient

Editor: N/A.

Informed written consent was obtained from the patient for publication of this case report and accompanying images.

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[a] Department of Infectious and Digestive Diseases, Children' Hospital of Hebei Province, [b] Department of Pediatric Surgery, The Second Hospital of Hebei Medical University, [c] Department of Pathology, Children' Hospital of Hebei Province, [d] Department of Medical Imagine, Children' Hospital of Hebei Province, Hebei Shijiazhuang, China.

[*] Correspondence: Ruiqin Zhao, Department of Infectious and Digestive Diseases, Children' Hospital of Hebei Province, Shijiazhuang, No 133 Jianhua South Street, Hebei 050030, China (e-mail: etyyxhk@outlook.com).

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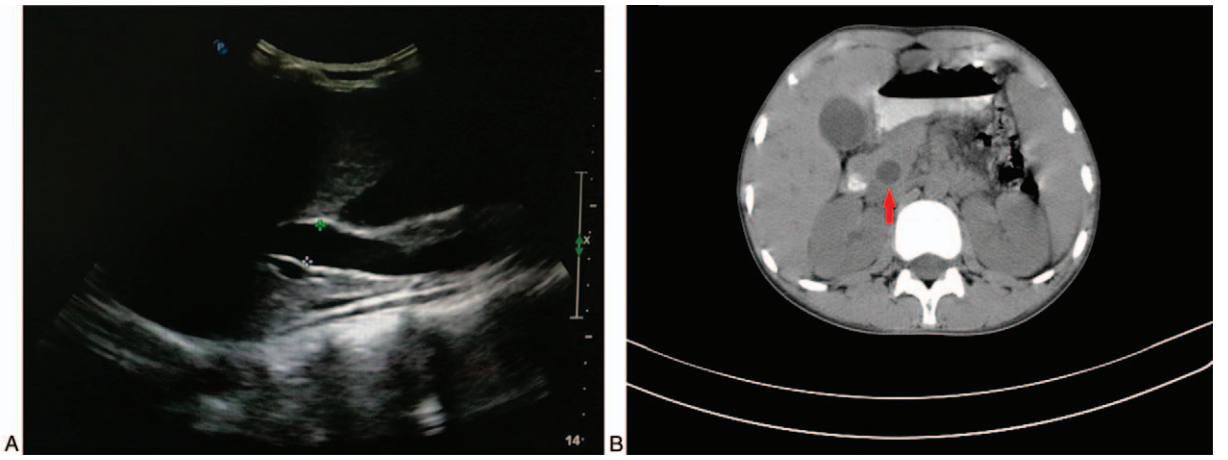

Figure 1. Abdominal imaging performed 2 days after admission of the 14-year-old male patient. (A) Ultrasonography revealed dilatation of the extrahepatic bile duct (inner diameter: approximately 14 mm at the widest segment). Dilatation of the extrahepatic bile duct and splenomegaly were also detected (not shown). (B) Computed tomography demonstrated similar findings to those of ultrasonography.

1. Introduction

Cholestasis in children has various causes depending on the age of the child and the type of jaundice.[1] Frequent causes of cholestasis in infancy are infection, α1-antitrypsin deficiency, biliary atresia, progressive familial intrahepatic cholestasis types 1 and 2 (PFIC1 and PFIC2), citrin deficiency, bile acid synthesis defects, arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome, and cystic fibrosis.[2] In contrast, the common causes in adolescents include drug-induced liver injury (DILI), Alagille syndrome, Wilson disease (hepatolenticular degeneration), autoimmune hepatitis, PFIC3, primary sclerosing cholangitis, bile duct stones, and other rare causes. In this study, we describe a case with cholestasis caused by duodenal papillary carcinoma.

2. Case report

The patient and his parents provided informed consent for the patient's inclusion in this study, and the Ethics Committee of our Hospital approved this case report (No: 2016034). A 14-year-old male patient was referred to our hospital on September 11, 2016 with a 2-month history of jaundice, weakness, intermittent pain in the middle, and upper abdomen and weight loss (2 kg from symptom onset to admission). The patient had been diagnosed with epilepsy (clonic seizures) 4 years previously and since then had received continuous drug therapy with sodium valproate (300 mg BID) and oxcarbazepine (300 mg BID). No episodes of epilepsy had occurred since the initiation of drug therapy. There was no history of perinatal complications (full-term vaginal delivery; birth weight of 3600 g), or family history of note.

Physical examination indicated a body temperature of 36.6°C, a respiratory rate of 20 breaths/min, a heart rate of 80 beats/min, and blood pressure of 90/60 mm Hg. The child was conscious and had normal reflexes. The skin all over the body and sclera were slightly yellow, while no hemorrhagic spots or ecchymoses were found. The superficial lymph nodes were not palpable or enlarged, and cyanosis of the lips or pharyngeal hyperemia was not detected. The oral mucosa was smooth, and the breath sounds in the bilateral lungs were clear on auscultation with no dry or moist rales. The heart rhythm was regular, and the heart sounds were normal. The abdomen was soft, borborygmus was present, and the liver and spleen were not palpable below the ribs. No abnormalities were detected in the limbs or nervous system.

Initial evaluation of laboratory parameters showed elevated levels of aspartate aminotransferase (271 IU/L; normal range 5–40 IU/L), alanine aminotransferase (224 IU/L; normal range 5–40 IU/L), γ-glutamyltransferase (1668.9 IU/L; normal range 11–50 IU/L), total bilirubin (66.4 μmol/L; normal range 3.4–17 μmol/L), and direct bilirubin (52.6 μmol/L; normal range 1.7–6.8 μmol/L) and normal values for blood glucose (4.2 mmol/L), serum albumin (35.7 mg/L), serum ammonia (53 μmol/L), serum lactate (0.99 mmol/L), and international normalized ratio (0.98). The concentrations of the antiepileptic medications in the blood were normal. Abdominal ultrasonography performed 2 days after admission showed dilatation of the intrahepatic bile duct (inner diameter of approximately 5.6 mm at the widest segment) and extrahepatic bile duct (inner diameter of approximately 14 mm at the widest segment) as well as splenomegaly (Fig. 1A). Computed tomography (CT) of the abdomen demonstrated similar findings to those of abdominal ultrasonography (Fig. 1B). Treatment was initiated with ursodeoxycholic acid (150 mg BID) and lipid-soluble vitamins A (5000 IU PO QD), D (800 IU PO QD) and K1 (10 mg IV drip QD). Further examinations were performed after withdrawal of the antiepileptic drugs. Tests for hepatotropic viruses, Epstein–Barr virus, cytomegalovirus virus, parvovirus B19, and herpes simplex virus were negative, as were bacterial cultures of blood, urine, and stool. Antibodies associated with autoimmune hepatitis were absent, and normal results were obtained for serum levels of immunoglobulin G, ceruloplasmin, and copper and for 24-hour urinary excretion of copper. Kayser–Fleischer rings and posterior embryotoxon were not detected on ophthalmologic examination. Furthermore, next-generation sequencing ruled out hereditary metabolic diseases (Wilson disease, Alagille syndrome, PFIC3, or benign recurrent intrahepatic cholestasis) as a cause of the cholestasis.

Laboratory investigations on day 10 of admission showed persistent elevation of aspartate aminotransferase (143 IU/L), alanine aminotransferase (174 IU/L), γ-glutamyltransferase (1074 IU/L), total bilirubin (113.9 μmol/L), direct bilirubin (109.3 μmol/L), total bile acids (69.4 μmol/L; normal range 0–

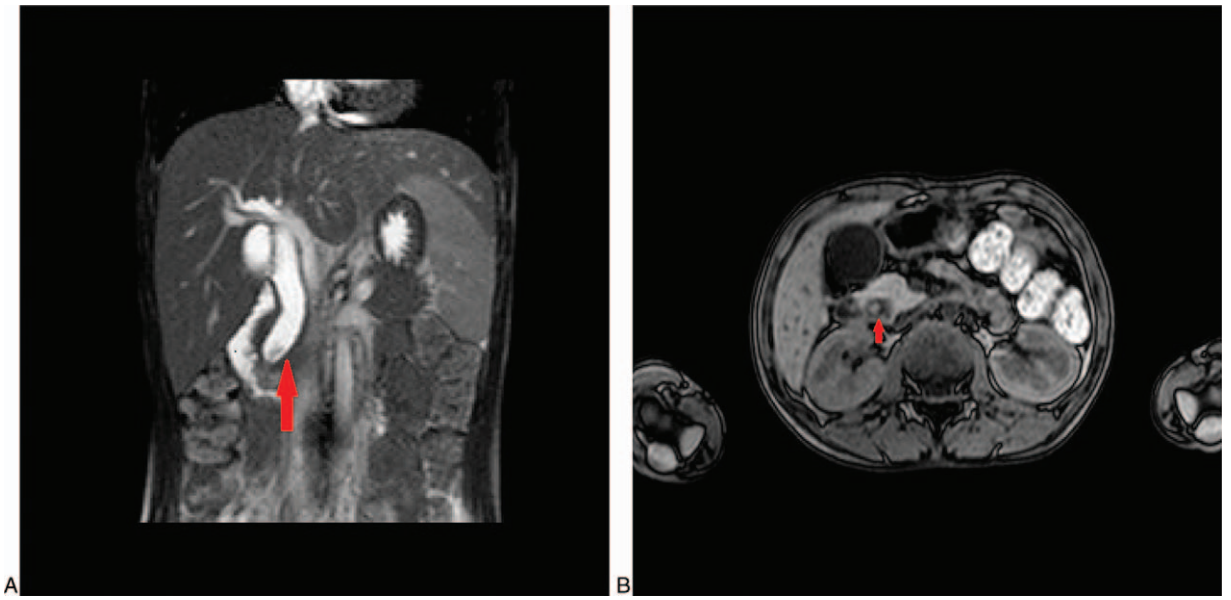

Figure 2. Magnetic resonance imaging performed 10 days after admission of the 14-year-old male patient. (A) Dilatation of the extrahepatic bile duct (arrow). (B) Soft-tissue mass protruding into the lumen of the duodenum.

20 μmol/L), and alkaline phosphatase (670 IU/L; normal range 50–500 IU/L). Abdominal ultrasonography showed a medially echoic mass of 2.2 × 1.2 cm in the extrahepatic bile duct. Magnetic resonance imaging (MRI) revealed dilatation of the extrahepatic bile ducts and a soft-tissue mass (approximately 2.2 × 1.1 cm in size) protruding into the duodenal lumen (Fig. 2). The common bile duct had a width of about 18 mm and was attenuated at its distal end. The signals in the segment of the common bile duct below the dilated segment were uneven, with mass-like T1 signals and slight T2 signals.

The patient was immediately referred to the surgery department for endoscopic retrograde cholangiopancreatography (ERCP), and a duodenal papillary tumor with a diameter of 2.2 cm was detected (Fig. 3). The patient was transferred to cancer hospital for surgical resection of the tumor and oral chemotherapy. Histopathology indicated a poorly differentiated adenocarcinoma (Fig. 4).

At the last follow-up in July 2018 (nearly 2 years after the initial admission and diagnosis), the patient had no jaundice, and liver function was normal. Tumor biomarker examinations, MRI, and enteroscopy provided no evidence of tumor recurrence. In the period between the initial admission and last follow-up, the patient's height had increased from 174 to 177 cm, and the patient's body weight had increased from 35 to 38 kg.

3. Discussion

Cholestasis generally needs early diagnosis and intervention. The differential diagnosis of cholestasis in pediatric patients includes various causes and depends on the age of the patient and the type of cholestasis. In the present case, the initial differential diagnosis included bacterial or viral infection, DILI, hereditary metabolic disease, and autoimmune liver disease.

Blood cultures demonstrated no bacterial growth, and tests for various viral infections, including hepatotropic viruses, Epstein–Barr virus, cytomegalovirus virus, parvovirus B19, and herpes simplex virus, were negative. Therefore, infection was excluded as a likely cause of cholestasis in the present case.

The DILI presents with acute or chronic cholestasis and abnormally high levels of transaminases. Specific diagnostic markers for DILI are lacking, and the disorder may mimic other intrahepatic and extrahepatic cholestatic diseases. The most common causes of DILI are antimicrobial agents and drugs used to treat disorders of the central nervous system.[3,4] The patient described in this case report had been taking 2 antiepileptic medications for approximately 4 years and was therefore at risk

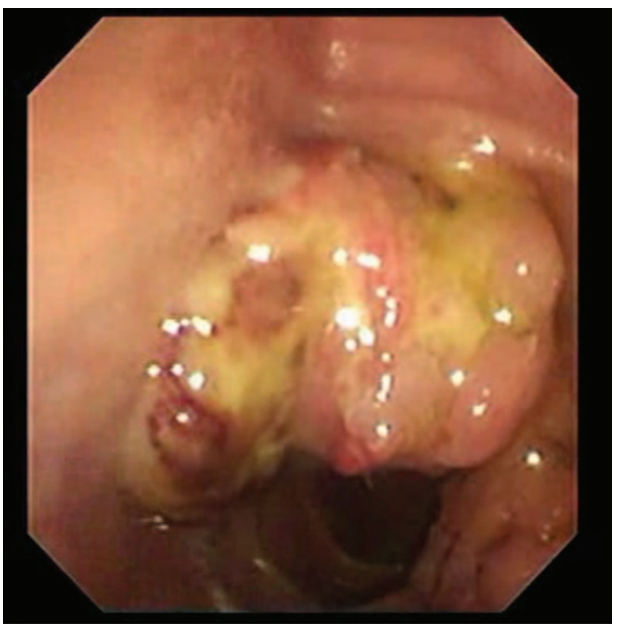

Figure 3. Endoscopic retrograde cholangiopancreatography demonstrated a duodenal papillary tumor with a diameter of 2.2 cm.

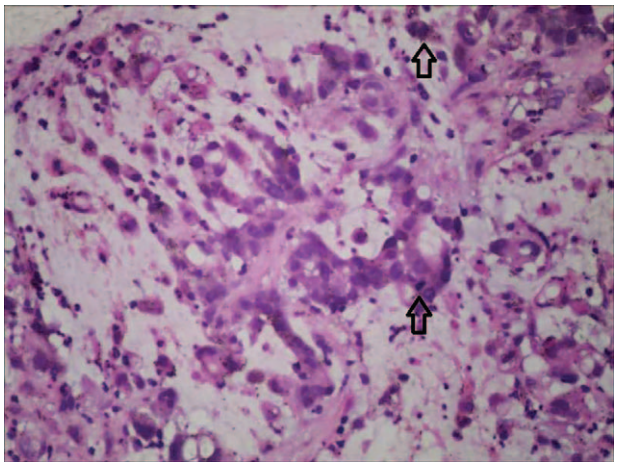

Figure 4. Histopathology after surgical resection of the tumor indicated a poorly differentiated adenocarcinoma. Microscopy demonstrated the destruction of glandular structures and cellular disarrangement. The polarity of the cells had disappeared. The tumor cells formed small nests. The malignant cells contained enlarged nuclei that stained deeply and had abnormal shapes (arrows). Mitotic figures and cellular necrosis was evident.

of DILI. Although we suggested percutaneous liver biopsy to facilitate diagnosis, the patient's parents declined this procedure. However, the concentrations of the antiepileptic drugs in the blood were within the normal ranges, and liver function tests did not improve after withdrawal of the medication. These observations reduced the likelihood of DILI being the cause of cholestasis in our patient.

Autoimmune liver diseases are progressive disorders characterized by elevated serum levels of immunoglobulin G and transaminases, the presence of autoantibodies, and the detection of interface hepatitis by histologic analysis of the liver.[5,6] Autoimmune liver disease can affect both intrahepatic and extrahepatic bile ducts, and cholestasis may be the major presentation. Autoimmune liver disease should always be considered in the differential diagnosis of liver disorders in children because it will culminate in end-stage liver disease if not treated in a timely manner.[7] In the present case, the levels of immunoglobulins A, M, and G were normal at admission, and tests for a variety of autoantibodies (including smooth muscle actin antibody, antinuclear antibodies, antimitochondrial antibodies, and liver-kidney microsomal antibodies) were negative. Thus, the results of these investigations did not support the diagnosis of autoimmune liver disease.

Hereditary metabolic diseases that can cause cholestasis include Wilson disease, Alagille syndrome, PFIC3, and benign recurrent intrahepatic cholestasis. Alagille syndrome is a multisystem disorder caused by defects in the *JAG1* and *NOTCH2* genes. The patients often present with chronic cholestasis and pruritus, with other clinical manifestations including a characteristic facial appearance, cardiovascular anomalies, posterior embryotoxon, abnormal vertebrae, vascular accidents, renal anomalies, growth failure, and learning difficulties.[8–12] Chronic cholestasis and elevated γ-glutamyltransferase occur in a very high proportion of patients with Alagille syndrome. Another hereditary disease considered in the differential diagnosis was PFIC3, a rare disorder due to *ABCB4* gene mutation. Children with PFIC3 develop cholestasis between late infancy and adolescence and can present with abnormal liver tests (including elevated γ-glutamyltransferase), drug-induced cholestasis, cholesterol gallstone disease, adult idiopathic cirrhosis, and transient cholestasis in infancy. Some patients with PFIC3 may progress to biliary cirrhosis and liver failure. Alagille syndrome and PFIC3 were considered as possible causes of cholestasis in the present case because of the increased γ-glutamyltransferase at admission and age of onset. However, these and other hereditary metabolic diseases were excluded by a combination of detailed physical examination and genetic testing for mutations in 244 genes, including *JAG1* and *NOTCH2* (Alagille syndrome), *ABCB4* (PFIC3), *ABCB11* (recurrent benign cholestasis), *ATP7B* (Wilson disease), and *ABCC2* (Dubin–Johnson syndrome).

Since the biochemical markers did not improve after 10 days of supportive therapy with ursodeoxycholic acid and lipid-soluble vitamins (A, D, and K1), we arranged for additional imaging examinations that subsequently identified a mass in the ampulla of Vater. Because we had no ERCP facilities, ERCP and surgical resection of the tumor were carried out in other hospitals. Postoperative pathology confirmed a diagnosis of poorly differentiated adenocarcinoma of the duodenal papilla. Duodenal papillary carcinoma represents 5% of all gastrointestinal tract malignancies, and although the average age of onset is in the seventh decade of life, rare cases of this malignancy occurring during adolescence have been reported.[13,14] Our patient presented with early onset of a highly aggressive carcinoma. Since no mass was identified at admission by abdominal ultrasound or CT, we initially focused on medical causes of cholestasis. However, after numerous examinations had excluded medical causes, we reevaluated the patient and detected the tumor. This highlights the importance of not definitively excluding malignancy as a cause of cholestasis in adolescents on the basis of initial imaging with abdominal ultrasonography or CT.

Although neoplastic disease is a rare underlying cause of cholestasis in pediatric patients, it should not be ignored even in the absence of positive findings in imaging examinations. Early and accurate diagnosis is important for patients with carcinoma as delayed diagnosis and treatment can lead to a poorer prognosis.

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Author contributions

Conceptualization: Haiyan Fu, Rongpin Li, Ruiqin Zhao.
Data curation: Haiyan Fu, Yingchao Li, Gelan Bai, Runkai Yin, Weina Shi, Lili Zhang.
Formal analysis: Haiyan Fu, Yingchao Li, Gelan Bai, Runkai Yin, Weina Shi, Lili Zhang.
Funding acquisition: Weina Shi.
Investigation: Yingchao Li, Runkai Yin, Rongpin Li.
Methodology: Haiyan Fu, Yingchao Li, Gelan Bai, Chunlan Yin.
Project administration: Chunlan Yin, Ruiqin Zhao.
Resources: Chunlan Yin, Lili Zhang, Rongpin Li.
Software: Haiyan Fu, Chunlan Yin, Lili Zhang, Rongpin Li.
Writing – original draft: Haiyan Fu.

Writing – review & editing: Haiyan Fu, Yingchao Li, Gelan Bai, Runkai Yin, Chunlan Yin, Weina Shi, Lili Zhang, Rongpin Li, Ruiqin Zhao.

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