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Acute lymphoblastic leukemia presenting as cholestatic jaundice in a 7-year-old boy

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Abstract

This is a case of a 7-year-old boy with acute lymphoblastic leukemia presenting with cholestasis and elevated transaminase levels. Acute lymphoblastic leukemia is the most common malignancy in children and can have variable presenting clinical manifestations. However, cholestasis is less commonly encountered in the pediatric population and can be a diagnostic challenge. We present a case of a 7-year-old boy discovered to have elevated transaminase levels while undergoing an evaluation for motor tics, which subsequently progressed to cholestasis and acute liver failure secondary to acute lymphoblastic leukemia. He demonstrated marked improvement after induction therapy and is in clinical remission. Clinicians should be ever mindful of the potentially unique presentations of childhood leukemia.

Keywords

Cholestasis, gastroenterology, leukemia, oncology

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children and accounts for almost 25% of all pediatric cancers.[1] It is usually classified by cell lineages and often presents with fatigue, pallor, lymphadenopathy, hepatosplenomegaly, and bone pain. However, it can also present with atypical findings and extranodal involvement, including the liver, spleen, testes, and skin. Leukostasis, or symptomatic hyperleukocytosis, can occur when white cell plugs affect the microvasculature, leading to decreased tissue perfusion, but is a rare finding in the lymphoid leukemias. This is a case of a 7-year-old boy who was found to have cholestasis and subsequent acute liver failure secondary to ALL-related leukostasis.

Case presentation

A 7-year-old boy with a history of recent-onset motor tics presented to his pediatrician with 4 days of scleral icterus, decreased appetite, and vomiting. He denied fevers, trauma, diarrhea, easy bleeding and bruising, changes in bowel habits, and recent travel. Other than being treated for streptococcal pharyngitis the week prior, the patient was in his usual state of health and had no other recent illness. During evaluation of tics 2 months before presentation, he had been found to have moderately elevated transaminases, with alanine aminotransferase (ALT) of 322 U/L and aspartate aminotransferase (AST) of 224 U/L. Total bilirubin; a hepatitis panel for hepatitis A, B, and C titers; and head imaging were normal at that time. He was not on any medications, and there was no family history of liver disease or other malignancy. He was evaluated by his pediatrician in clinic for the above symptoms and directly admitted to the hospital for further evaluation.

Physical examination on the day of admission revealed a tired-appearing child with scleral icterus, cervical and inguinal lymphadenopathy, hepatomegaly to 8 cm below the right costal margin, and palpable splenomegaly to 3 cm below the left costal margin. Laboratory evaluation on admission yielded significantly elevated transaminase levels with ALT of 1295 U/L, AST of 1693 U/L, gamma glutamyl transferase

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Table 1. Liver function testing during admission and after chemotherapy.

	Admit	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Post-induction chemotherapy
AST (U/L)	1693	1284	1309	1227	1385	1375	1240	1266	1020	1188	1298	37
ALT (U/L)	1295	1116	1052	1016	992	1086	939	1004	887	917	954	80
Total bilirubin (mg/dL)	9.3	10.0	11.1	12.4	10.7	11.5	12.5	16.2	18.4	19.1	20.5	1.6
Direct bilirubin (mg/dL)	6.8	7.4	8.0	9.2	8.3	8.8	9.2	11.8	13.1	13.8	14.2	0.9
GGT (U/L)	212	212	213	218	220	220	287	311	282	243	209	–
Albumin (g/dL)	3.8	3.4	3.3	3.2	3.0	3.3	3.0	3.1	3.0	2.8	2.5	4.6
PT (s)	14.4	14.9	14.6	14.9	15.0	15.1	15.3	16.0	16.7	17.7	18.0	15.0
PTT (s)	28	28	28	28	27	27	28	28	30	32	28	22
INR	1.1	1.2	1.1	1.2	1.2	1.2	1.2	1.3	1.3	1.5	1.5	1.2

AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyl transferase; PT: prothrombin time; PTT: partial thromboplastin time; INR: international normalized ratio.

(GGT) of 212 U/L, and direct bilirubin of 6.8 mg/dL. A complete blood count (CBC) showed mild leukocytosis with a white blood cell count of 15.7×10^3 cells/μL, a normal hemoglobin of 13.7 g/dL, and mild thrombocytopenia with platelets of 195×10^3 cells/μL. Differential was notable for 44% lymphocytes, 31% neutrophils, 14% eosinophils, 3% basophils, and 2% monocytes. Coagulation profile, lipase, antinuclear antibody, thyroid studies, Epstein–Barr virus titers, and a repeat hepatitis panel were within normal limits. An abdominal ultrasound demonstrated diffuse gallbladder wall thickening and surrounding lymphadenopathy with nonspecific hepatomegaly.

On the second day of admission, he developed a new fever for which he was started on antibiotics for presumed ascending cholangitis. Gastroenterology was consulted and recommended a hepatobiliary iminodiacetic acid scan, which showed increased uptake in the hepatic parenchyma with poor hepatic clearance and no filling of the gallbladder. Further evaluation, including comprehensive infectious testing, was negative. Labs were trended while undergoing evaluation (Table 1). CBC remained stable with continued mild leukocytosis and mild thrombocytopenia with no other significant abnormalities, and transaminases remained significantly elevated. On hospital day 11, the direct bilirubin peaked at 14.2 mg/dL and he developed acute liver failure with a prothrombin time (PT) of 18 s, an international normalized ratio (INR) of 1.5, and an albumin of 2.5 g/dL. Supportive treatments were given including glutathione supplementation, vitamin K, and ursodiol. He was then transferred to a quaternary center where a liver biopsy was performed and a presumptive diagnosis of autoimmune hepatitis was made. He was started on 60 mg of prednisone daily with improvement in his direct hyperbilirubinemia and coagulopathy. His hepatic pathology report returned with findings of atypical lymphocytes on microscopic examination, suggestive of malignancy. He then underwent a bone marrow biopsy which was consistent with pre-T-cell ALL.

He was transferred back to the local tertiary center and transitioned to dexamethasone; however, further chemotherapy was delayed due to continued high direct bilirubin. After 3 weeks of steroid treatment, his bilirubin level was low enough to begin induction chemotherapy with vincristine and daunorubicin in addition to dexamethasone. He was minimal residual disease–negative 1 month later at the end of induction and remains in remission after 15 months on maintenance therapy.

Discussion

Cholestasis is an infrequent presenting complaint in the pediatric population and usually manifests with conjugated hyperbilirubinemia. A conjugated bilirubin level greater than 2 mg/dL or greater than 20% of the total bilirubin level is diagnostic of conjugated hyperbilirubinemia.[2] This condition is never considered normal and always warrants further evaluation.

The differential diagnosis can be separated into obstructive and hepatocellular etiologies. Choledocolithiasis can cause obstruction of the common bile duct and resulting jaundice. Choledocal cysts and other obstructive lesions such as an annular pancreas can also obstruct bile flow and lead to jaundice, although these conditions more commonly present in the infantile period.[3] Rarely, parasitic infections, primary sclerosing cholangitis, and hematologic malignancy may present with obstructive jaundice. Hepatocellular causes commonly include viral hepatitis and medication-induced injury, as well as autoimmune hepatitis, Wilson's disease, alpha-1-antitrypsin deficiency, cystic fibrosis, Dubin–Johnson syndrome, and Rotor syndrome. Initial testing includes total and conjugated bilirubin, AST and ALT, alkaline phosphatase, GGT, and synthetic function markers such as PT and INR. Ultrasonography is useful to evaluate for gallstones, choledochal cysts, and other obstructive lesions. If the cause is not readily determined after thorough history, physical examination, and laboratory and radiographic evaluation, liver biopsy is necessary to establish the diagnosis. Management is directed toward the underlying pathology; however, ensuring adequate nutrition, optimizing levels of fat-soluble vitamins, and monitoring for long-term sequelae of chronic liver disease are necessary in all patients.

ALL is the most common malignancy in children, of which T-cell ALL (T-ALL) accounts for approximately 15% of cases.[1,4,5] Common clinical manifestations include fatigue, pallor, hepatosplenomegaly, lymphadenopathy, and bone pain. Nearly 50% of patients with T-ALL present with a mediastinal mass and related sequelae such as superior vena cava syndrome or airway obstruction.[6] Extranodal involvement is less common but is usually found in the skin and testes. Direct abdominal involvement is rare but primarily involves the liver and spleen. Leukocytosis is another common presenting finding, as approximately 20% of children will present with a white blood cell count above 50,000/mm^3.[7] Other common laboratory findings include leukocytopenia, thrombocytopenia, transaminitis, and elevated levels of lactate dehydrogenase, uric acid, and other markers of tumor lysis.

Treatment with intensive chemotherapy is aimed at eliminating leukemic cells from the bone marrow and reestablishing normal hematopoiesis. Further therapy is selected based on presenting symptoms, including steroids to relieve venous congestion in the presence of a mediastinal mass. Overall survival rates for ALL have dramatically improved over the past few decades and now approach 90% at 5 years after diagnosis.[8,9]

Despite the frequent findings of hyperleukocytosis in acute leukemia, leukostasis is a relatively rare complication in ALL compared to both acute and chronic myeloid leukemia.[7] When present, it commonly affects the pulmonary and central nervous systems, manifested by hypoxemia, respiratory distress, headache, dizziness, confusion, and blurry vision. Coagulation abnormalities indicative of liver involvement are also observed in more than 20% of patients with ALL-related leukostasis.[10] However, some patients may present with leukostasis without hyperleukocytosis, making the clinical diagnosis significantly more difficult. In the present case, despite a relatively normal white blood cell count without blasts on his CBC, pathology showed atypical lymphocytes invading the liver sinusoids, suggestive of leukostasis-related hepatocellular damage and inflammation. While there are reports in the literature of pediatric B-cell ALL and adult T-ALL presenting with cholestasis, we found none describing cholestatic jaundice as the presenting symptom in pediatric T-ALL.[11–13]

Our case was challenging in several ways. First, the lack of obvious hematological findings obscured the diagnosis. Several case reports describing cholestatic jaundice as the presenting symptom of ALL had concomitant findings such as pancytopenia or a mediastinal mass as clues to the diagnosis, which were not identified in our case.[11–13] Second, the standard induction treatment of ALL involves many hepatotoxic agents, including vincristine and daunorubicin. Unfortunately, due to his hyperbilirubinemia, these drugs were unable to be used initially as part of his treatment. Therefore, he received induction therapy with dexamethasone for 3 weeks until his bilirubin trended down enough to begin additional chemotherapy agents. Vincristine and daunorubicin were then used at 50% and 25% of their standard dosages in an attempt to mitigate their hepatotoxicity in the setting of recent liver failure. Asparaginase was not used during his induction therapy due to the risk of severe hepatotoxicity. While other potentially less hepatotoxic induction regimens can be used in treating ALL in its initial stages, the most common induction regimen for T-ALL involves the above drugs.[14] Finally, our patient needed continued monitoring of his liver enzymes and synthetic function markers, necessitating multiple additional clinic and lab visits during his initial diagnosis and therapy. Continued supportive care was also required including ursodiol for cholestasis and gallstone prevention. There have also been reports of levocarnitine being useful in treating and preventing chemotherapy-related hepatic injury, although it was not used in our patient.[15]

Conclusion

We present a rare case of pediatric ALL presenting with cholestasis and acute liver failure. ALL is the most common malignancy in children and can present with atypical findings such as leukostasis affecting any organ, including the liver. Clinicians should keep ALL on their differential diagnosis of the child presenting with acute liver failure. Finally, although rare in the pediatric population, clinicians should be aware of the differential diagnosis, workup, and management of a child presenting with cholestatic jaundice, as seen in our patient.

Author Contributions

J.F., K.H., and H.K. contributed to conception and design. J.F. and S.R. drafted the manuscript. J.F., S.R., K.H., and H.K. reviewed and critically revised the manuscript for important intellectual content.

Declaration of conflicting interests

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Ethical approval

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