SciMedCentral

Journal of Dermatology and Clinical Research

Case Report

Acute Lymphoblastic Leukemia Masquerading as Hepatotoxicity in an Isotretinoin Patient

Emily E. Boes[1], Brandon G. Shutty[2]*, Kristin J. Witfill[2], and Richard A. Miller[2]

[1]*Des Moines University College of Osteopathic Medicine, Des Moines, Iowa, USA*
[2]*Department of Dermatology, Nova Southeastern University, Largo Medical Center, Largo, Florida, USA*

***Corresponding author**

Brandon Shutty, Largo Medical Center, 201 14th Street SW, Largo, FL, USA, 33770, Tel: 727-588-5200; Email: brandon.shutty@med.lecom.edu

Submitted: 15 November 2016

Accepted: 23 January 2017

Published: 23 January 2017

Keywords

- Acute lymphoblastic leukemia (ALL)
- Hepatitis
- Hepatotoxicity
- Isotretinoin

Abstract

Isotretinoin (13-cis-retinoic acid) has well-documented adverse effects, including hepatitis, elevated serum lipids, depression, anxiety, and teratogenicity; monthly lab draws during therapy are commonly utilized to ensure safe administration. We describe the case of a 16-year-old boy who underwent isotretinoin therapy with monthly lab evaluations, subsequently presenting with acute hepatitis while being treated. He was thereafter diagnosed with acute lymphoblastic leukemia (ALL) confirmed with bone marrow biopsy, and isotretinoin was discontinued; the patient achieved remission after proper treatment with induction chemotherapy. Even though recent literature suggests routine monthly lab monitoring during isotretinoin therapy is unnecessary, it may still be prudent in select cases.

ABBREVIATIONS

ALL: Acute Lymphoblastic Leukemia; CMP: Complete Metabolic Panel; CBC: Complete Blood Count; LDH: Lacate Dehydrogenase; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; HDL: High-density Lipoprotein; LDL: Low-density Lipoprotein; FDA: Federal Drug Administration; HIV: Human Immunodeficiency Virus

INTRODUCTION

In rare circumstances, acute lymphoblastic leukemia (ALL) presents as acute hepatitis. Isotretinoin (13-cis-retinoic acid) is another well-known cause. Knowledge of ALL's differential and diagnostic protocol is paramount, and appropriate subspecialty referral must occur promptly when indicated. With early diagnosis ALL is responsive to chemotherapy, with possible remission and regeneration of liver function.

CASE PRESENTATION

A 16-year-old healthy Caucasian male with a BMI of 27.4 (height 176 cm and weight 89.0 kg) was treated with isotretinoin for cystic acne. Upon registration with the iPLEDGE program (https://www.ipledgeprogram.com), initial labs were drawn, including a complete blood count (CBC) with differential, lipid panel, and complete metabolic panel (CMP). Labs were within normal limits; total bilirubin was 0.8mg/dL, alkaline phosphatase was 119U/L, AST was 17U/L, and ALT was 15U/L. CBC showed white cell count was 6.2 thousand/uL, absolute neutrophils were 2856 cells/uL, and absolute lymphocytes were 1519 cells/uL.

The patient was prescribed oral isotretinoin, at an initial dose of 40 mg daily. During therapy, the patient presented for monthly follow-up appointments and lab draws. Due to persistent cystic lesions, after 8 weeks of therapy, the dose was increased to 80mg daily, and after 16 weeks it was increased to 100mg daily. Soon after the dose change at 16 weeks, the patient began having presyncopal episodes, generalized malaise, nausea, and vomiting. He denied symptoms of headache, vision change, arthralgias, or myalgias. His subsequent lab evaluation showed total cholesterol of 230 mg/dL, HDL cholesterol of 29 mg/dL, triglycerides of 157 mg/dL, and LDL cholesterol of 170 mg/dL. CMP showed elevated total bilirubin of 5.3 mg/dL, alkaline phosphatase of 820 U/L, AST of 256 U/L, ALT of 393 U/L. CBC showed white cell count of 13.9 thousand/uL, absolute neutrophils of 8173 cells/uL, and absolute lymphocytes of 5216 cells/uL. When these laboratory results were received, the patient was asked to return to clinic for evaluation.

Physical examination at this visit revealed right upper quadrant abdominal tenderness, hepatomegaly and scleral icterus. Patient was directed to discontinue the medication, and referred to pediatric gastroenterology. After evaluation by gastroenterology, the patient was referred to oncology, and diagnosed with ALL by bone marrow biopsy. Remission of his malignancy was achieved with induction chemotherapy, and his hepatitis resolved.

DISCUSSION

Isotretinoin, a vitamin A derivative, was approved by the

FDA for use in the treatment of severe, refractory cystic acne in 1982. Due to widespread use of the medication, the side effects of isotretinoin are well documented. These include lipid abnormalities, hepatitis, depression, anxiety, and teratogenic effects during pregnancy. Because of this, labs and clinical status are commonly monitored monthly during therapy. Isotretinoin comes with a package insert suggesting baseline fasting lipid and liver function testing with repeated evaluations weekly or biweekly until "the response has been established" [1]. Recent literature suggests minimizing lab monitoring for those on isotretinoin in an effort to be cost-effective; however, gathering baseline labs and instituting follow-up when clinical changes and comorbidities exist remains advisable [2]. Per standard of care, isotretinoin is discontinued in cases of severe hypertriglyceridemia (greater than 800 mL/dL or 9 mmol/L) or elevated liver transaminases (greater than 3 times normal values). Long-term effects of the medication remain unclear; controversial evidence indicates a greater risk of development of metabolic syndrome and inflammatory bowel disease later in life in patients who have used the medication [3]. While isotretinoin has been shown to cause and compound liver dysfunction acutely, likely due systemic oxidative stress in patients treated at therapeutic doses, it has not been linked specifically to induction of leukemia but rather has been used as a treatment modality [4]. Isotretinoin has been used in advanced refractory lymphomas due to its anticarcinogenic activity since it modifies differentiation and apoptotic pathways [5]. Isotretinoin also may induce long-term responses in some patients with juvenile chronic myelogenous leukemia [6]. Moreover, all-trans retinoic acid, another vitamin A derivative, is used as induction chemotherapy to treat acute promyelocytic leukemia [7].

Hypertriglyceridemia most commonly presents after 4 weeks of therapy in males, and after 12 weeks in females [8]. Minimal changes in cholesterol levels are commonly noted after 8 to 16 weeks of isotretinoin therapy. Elevated triglycerides usually return to baseline by 4 weeks post-treatment, and elevated cholesterol levels return by 8 weeks [8,9]. Mechanisms for the elevation of cholesterol and triglyceride levels observed with isotretinoin therapy are speculative, and may involve increased synthesis of cholesterol and triglycerides by the liver [9].

The mechanism for isotretinoin-induced hepatitis is also poorly understood. Some believe that because isotretinoin is a vitamin A derivative, it may act as a direct hepatotoxin due to systemic oxidative stress induced by the medication [4]. Liver transaminases are elevated in approximately 15% of patients who are taking isotretinoin; elevations necessitating cessation of the medication are rare, occurring in less than 1% of patients. Hepatitis secondary to isotretinoin use is typically transient and asymptomatic, without apparent injury to the liver [10].

Aside from adverse drug reactions, there are many causes of acute elevation of transaminases with or without changes in lipid lab values. Hepatic involvement is a common finding in pediatric diseases and malignancies, and attention may be diverted from these and other possible diagnoses due to the fact the patient is being treated with isotretinoin; this is especially true in young patients without any past medical history. The differential diagnosis of acute hepatitis in a child includes hematologic malignancies, infections such as hepatitis A, hepatitis B, hepatitis C, human immunodeficiency virus, Epstein-Barr virus, adenovirus, bacterial infection, sepsis, Wilson's disease, autoimmune hepatitis, other adverse drug reactions, and many others [11].

The patient in our report was diagnosed with ALL, the most common childhood malignancy, representing nearly one-third of all pediatric malignancies. Patients are typically diagnosed between the ages of 2 and 5 years, and rarely diagnosed after age 15. ALL in pediatric patients presents with hepatomegaly and liver involvement in 68% of cases and is one of the most common presentations. ALL may present with elevated transaminases [12]. The pathogenesis of liver disease in ALL is not well documented. Ischemia of hepatocytes may occur secondary to blast cell infiltrate of the portal and sinusoidal tracts. Risk factors for the presence of acute hepatitis at disease onset included female sex, older age at disease onset (> 10 years of age), elevated uric acid, elevated LDH, mediastinal mass (associated with greater tumor load), T-cell mediated disease, and higher white cell count at diagnosis (> 50,000 x 10^6/L) [13]. Fulminant hepatic failure is a rare presentation of ALL; these patients were more likely to have comorbid viral infections or sepsis [12].

Isotretinoin therapy in the pediatric population has a wide range of well-documented adverse effects, and regular clinical follow-up with pertinent laboratory monitoring are warranted. Although hepatitis is among the most common of these effects, isotretinoin does not appear to be carcinogenic and in fact exhibits chemotherapeutic potential.

Dermatologists must consider a broad differential diagnosis when elevated liver transaminases are encountered during isotretinoin therapy. Other conditions can present coincidentally, and isotretinoin therapy can distract the dermatologist from other causes of hepatitis, and due to oxidative stress placed on the liver could exacerbate transaminitis. If hepatitis presents during isotretinoin therapy, it is reasonable to consider additional testing. Although recent literature recommends against monthly lab draws for patients on isotretinoin in an effort to be cost-conscious, follow-up labs are prudent at presentation of new signs and symptoms, with certain comorbidities, and after 2-4 months of treatment [2,14,15]. Any abnormal findings should be followed promptly with appropriate sub-specialty referral, as outcomes of hematologic malignancies such as ALL are time sensitive, and success of therapy depends on early diagnosis and treatment.

REFERENCES

1. Roche Laboratories. Accutane (isotretinoin capsules) [package insert]. Nutley, NJ: Roche Laboraties; 2014.
2. Shinkai K, McMichael A, Linos E. Isotretinoin Laboratory Test Monitoring-A Call to Decrease Testing in an Era of High-Value, Cost-Conscious Care. JAMA Dermatol. 2016; 152: 17-19.
3. Peck GL, Olsen TG, Yoder FW, Strauss JS, Downing DT, Pandya M, et al. Prolonged remissions of cystic and conglobate acne with 13-cis-retinoic acid. N Engl J Med. 1979; 300: 329-333.
4. Erturan I, Naziroglu M, Akkaya VB. Isotretinoin treatment induces oxidative toxicity in blood of patients with acne vulgaris: a clinical pilot study. Cell Biochem Funct. 2012; 30: 522-527.

5. Cheng AL, Su IJ, Chen CC, Tien HF, Lay JD, Chen BR, et al. Use of retinoic acids in the treatment of peripheral T-cell lymphoma: a pilot study. J Clin Oncol. 1994; 12: 1185-1192.

6. Castleberry RP, Emanuel PD, Zuckerman KS, Cohn S, Strauss L, Byrd RL, et al. A pilot study of isotretinoin in the treatment of juvenile chronic myelogenous leukemia. N Engl J Med. 1994; 331: 1680-1684.

7. Visani G, Gugliotta L, Tosi P, Catani L, Vianelli N, Martinelli G, et al. All-*trans* retinoic acid significantly reduces the incidence of early hemorrhagic death during induction therapy of acute promyelocytic leukemia. Eur J Haematol. 2000; 64: 139-144.

8. Baxter KF, Ling TC, Barth JH, Cunliffe WJ. Retrospective survey of serum lipids in patients receiving more than three courses of isotretinoin. J Dermatolog Treat. 2003; 14: 216-218.

9. Marsden J. Hyperlipidemia due to isotretinoin and etretinate: possible mechanisms and consequences. Br J Dermatol. 1986; 114: 401-407.

10. Thune P, Mork NJ. A case of centrolobular toxic necrosis of the liver due to aromatic retinoid - Tigason(Ro-10-9359). Dermatologica. 1980; 160: 405-408.

11. Clemente MG, Schwarz K. Hepatitis: general principles. Pediatr Rev. 2011; 32: 333-340.

12. Rivet C, Leverger G, Jacquemin E, Bernard O. Acute Leukemia Presenting as Acute Hepatitis Without Liver Failure. J Pediatr Gastroenterol Nutr. 2014; 59: 640-641.

13. Segal I, Rassekh SR, Bond MC, Bond MC, Senger C, Schreiber RA. Abnormal Liver Transaminases and Conjugated Hyperbilirubinemia at Presentation of Acute Lymphoblastic Leukemia. Pediatr Blood Cancer. 2010; 55: 434-439.

14. Kelleher JF, Monteleone PM, Steele DA, Gang DL, Angelides AG. Hepatic Dysfunction as the Presenting Feature of Acute Lymphoblastic Leukemia**.** J Pediatr Hematol Oncol. 2001; 23: 117-121.

15. Lee YH, Scharnitz TP, Muscat J, Chen A, Gupta-Elera G, Kirby JS. Laboratory Monitoring During Isotretinoin Therapy for Acne. A Systematic Review and Meta-analysis. JAMA Dermatol. 2016; 152: 35-44.

Cite this article

Boes EE, Shutty BG, Witfill KJ, Miller RA (2017) Acute Lymphoblastic Leukemia Masquerading as Hepatotoxicity in an Isotretinoin Patient. J Dermatolog Clin Res 5(1): 1091.