Case Reports in Oncology

Case Rep Oncol 2010;3:505–509
DOI: 10.1159/000323487

Published online:
December 24, 2010

ISSN 1662–6575
www.karger.com/cro

Acute Hepatitis A Induction of Precursor B-Cell Acute Lymphoblastic Leukemia: A Causal Relationship?

V. Senadhi[a] D. Emuron[b] R. Gupta[a]

[a] Department of Internal Medicine, Sinai Hospital, Johns Hopkins University/Sinai Hospital Program in Internal Medicine, Baltimore, Md., [b] Mbarara University of Science and Technology, Mbarara, Uganda

Key Words
Acute hepatitis A · Precursor B-cell acute lymphoblastic leukemia · Epstein-Barr virus · Adult-onset ALL · Hepatitis A-induced aplastic anemia

Abstract
Background: Precursor B-cell acute lymphoblastic leukemia accounts for 2% of all lymphoid neoplasms in the United States and occurs most frequently in childhood, but can also occur in adults with a median age of 39 years. It is more commonly seen in males and in Caucasians.
Case Report: We present a case of a 51-year-old Caucasian female with the development of precursor B-cell acute lymphoblastic leukemia after suffering acute hepatitis A 4 weeks prior to her diagnosis. She presented with malaise for a month without spontaneous bruising/bleeding, infections, or B-symptoms, such as fevers, night sweats, or unintentional weight loss.
Conclusion: Nonspecific viral transformation of bone marrow has been discussed in the literature, but we specifically describe hepatitis A-induced adult-onset precursor B-cell acute lymphoblastic leukemia, which is the first reported case in the literature.

Introduction

Classically, precursor acute lymphoblastic leukemia (ALL) is most commonly a childhood disease that is extremely responsive to chemotherapy (88%) and has an excellent prognosis in most cases. ALL has known associations with radiation exposure, benzene, hair dyes, and Down syndrome. In addition to these risk factors, adult-onset or atypical ALL may also be a complication of previous chemotherapy regimens. Unlike its childhood counterpart, adult-onset ALL has an unfavorable response to chemotherapy (20–40%) and has a poor prognosis. In the literature, there have been numerous

Viplove Senadhi

Johns Hopkins University/Sinai Hospital, Program in Internal Medicine
Sinai Hospital, 2401 W. Belvedere Ave
Baltimore, MD 21215 (USA)
Tel. +1 410 601 8135, E-Mail vsenadhi@hotmail.com

references to a viral etiology involved in the pathophysiology and transformation of the bone marrow in children predisposing them to the development of ALL. However, there have not been any cases reported in the literature that were able to establish a causal relationship between ALL and a viral infection in a temporal manner.

We report a case of acute hepatitis A-induced adult-onset precursor B-cell ALL, which is, to our knowledge, the first reported case in the literature. This paper reports a case where acute viral transformation of the bone marrow took place in a rather short time period.

Case Presentation

A 51-year-old Caucasian female with a history of migraine headaches managed with Topamax for the last year presented with increased malaise and fatigue when walking up a flight of stairs. These symptoms had been occurring for the previous month. Several months prior, she had had normal laboratory studies and had been in great health. A day prior to her admission, she had been found to have severe anemia by her outpatient physician and was hospitalized for further evaluation. Her physical assessment showed pallor and splenomegaly without any lymphadenopathy or bruises. Computed tomography of the head, thorax, abdomen, and pelvis, checking for malignancy, was unremarkable except for splenomegaly. Complete blood count at the time of admission showed pancytopenia with a hematocrit (Hct) of 15%, a platelet count of 17,000, a white blood cell count of 1.58 K/mm^3, with no indication of hemolysis or reticulocytosis. She was transfused with 5 units of blood during her hospital course, which increased her Hct up to 24.7%, but was not an appropriate response. The patient also had an alanine transaminase level of 2,840 IU/l and an aspartate transferase level of 1,600 IU/l in the absence of hypotension, which warranted acute hepatitis serologies. Hepatitis serologies were negative for hepatitis B and C antibody, but positive for hepatitis A IgM antibody. Further questioning after the identification of the positive hepatitis IgM antibody revealed that the patient had experienced a bout of extreme diarrhea, nausea, vomiting, extreme malaise, and yellow-colored skin approximately a month prior to her admission. According to the laboratory findings and history, the patient had suffered acute hepatitis A approximately 1 month prior to her admission, from which she had recovered spontaneously without medical treatment. Evaluation of her pancytopenia revealed a negative Monospot test, but she was found to have high titers of Epstein-Barr virus (EBV), antibody IgG and EBV nuclear antigen antibody IgG, which was consistent with an old or a convalescent phase of EBV infection and ruled out EBV as a cause of her pancytopenia.

Hepatitis A-induced aplastic anemia along with the ingestion of Topamax were considered as possible causes of the bone marrow depression, although Topamax is not classically associated with blood dyscrasias. A peripheral blood smear revealed 54% immature cells, true thrombocytopenia and the absence of hemolysis. Because her pancytopenia did not resolve, a bone marrow biopsy was warranted, which revealed a B-cell lymphoproliferative disorder (fig. 1, fig. 2). Immunostain markers for CD3 and CD5 were negative. However, markers were diffusely positive for CD10 and CD20 and a subsequent flow cytometry confirmed precursor B-cell ALL. Molecular genetic analysis was positive for the Philadelphia chromosome, which occurs in 25% of the adult ALL cases. The incidence increases with age, approaching 50% in patients older than 50 years of age. ALL cases with a positive Philadelphia chromosome have a worse prognosis and therefore our patient immediately received induction chemotherapy.

Discussion

ALL typically affects patients between 2 and 5 years of age with symptoms of fever, bleeding, bone pain and lymphadenopathy. Our patient was diagnosed with precursor B-cell ALL at the age of 51 with no risk factors (including family history) in the setting of recent Topamax use, acute hepatitis A, and high Epstein-Barr viral titers. Unlike other anti-epileptic drugs, there are no reports of Topamax causing bone marrow dysplasia at

Case Rep Oncol 2010;3:505–509
DOI: 10.1159/000323487
Published online: December 24, 2010

ISSN 1662–6575
www.karger.com/cro

either therapeutic dosages for seizures or migraine headaches. On the other hand, EBV-associated hepatitis could occur with aplastic anemia [1]. EBV-induced aplastic anemia presents in the setting of Burkitt's lymphoma, acute infection or reactivation in the immunodeficient. However, our patient's laboratory evaluation revealed an EBV IgG antibody and EBNA IgG antibody consistent with an old or convalescent EBV infection. Thus, the possibility of an acute EBV hepatitis or Topamax-induced bone marrow suppression in the aforementioned setting would be nullified even in the absence of the peripheral smear or bone marrow results.

Acute hepatitis A manifests as fever, nausea, vomiting, abdominal pain, and jaundice. Fecal-oral transmission is predominant, which explains the increased prevalence of acute hepatitis A in developing countries. Although major hematologic manifestations of acute hepatitis A are rare, transient granulocytopenia and thrombocytopenia are often seen with extremes of aplastic anemia [2–4]. The hematological mechanisms of hepatitis A are variable. Hepatitis A virus can induce an autoimmune reaction [5] and chromosomal damage in the hematopoietic system with subsequent stem-cell failure [6]. In some cases, liver cell damage impairs the detoxifying metabolism of drugs with subsequent bone marrow toxicity [7, 8]. Viral hepatitis A has numerous mechanisms of action, which allows it to impact the bone marrow in a complex way [5, 6]. The major differential in our case was related to hepatitis A-induced aplastic anemia, which was ruled out with the peripheral smear as well as the bone marrow biopsy.

There are several models reviewed by the National Institute of Health that support an infectious etiology to ALL induction [9]. One of the models specifically views ALL as a rare response to a childhood infection and assumes that the leukemia-inducing effect is related to the timing of the infection, with a greater leukemic effect with later infections as opposed to those which occurred in infancy [9]. In fact, this suspicion was so strong that various viruses from the Polyomaviridae family, such as JC virus and BK virus, have been sequenced and compared to childhood ALL sequences; however, there was no causal relationship with these viruses [10]. In a review regarding the etiology of acute childhood leukemias, it was concluded that delayed dysregulated responses to common infectious agents played a major part in the conversion of preleukemic clones that were present genetically into overt precursor B-cell ALL [11]. If common infectious agents can induce such a transformation, one can only speculate the impact of a severe viral infection, such as acute hepatitis A. This concept supports the classic 'two-hit hypothesis' in many 'nature combined with nurture' models of disease, which describe a genetically predisposed individual (nature), who is environmentally exposed to a severe insult (nurture). Similar models have been referenced in the pathogenesis of inflammatory bowel disease in relation to gut microbial flora. Additionally, in the pediatric population, it is difficult to assess the degree of delay and transformation into overt ALL as there are numerous variables which influence the outcome in patients at risk [12]. However, this issue is not significant in our patient due to the timing and course of her acute hepatitis A infection. Lastly, there is the rare possibility that precursor B-cell ALL developed independently of her acute hepatitis A, but there are no reported cases in the literature where acute hepatitis A independently occurred in a chronological fashion with precursor B-cell ALL.

Our patient had been serially followed by her primary care physician throughout her life and had never had any evidence of blood dyscrasias. Immediately prior to her hepatitis A infection, she had been in good health and had a normal laboratory

Case Rep Oncol 2010;3:505–509
DOI: 10.1159/000323487
Published online: December 24, 2010

ISSN 1662–6575
www.karger.com/cro

evaluation. Approximately 2 weeks after her acute hepatitis infection, she had a low Hct at another hospital; then she developed pancytopenia 2 weeks later, at the time she was admitted to our facility. In a thorough review of the literature, no reported cases with this type of temporal and causal relationship of a proven viral infection subsequently inducing acute lymphoblastic transformation were found. We propose that this viral transformation was induced through one of the previously mentioned mechanisms, such as chromosomal damage to the hematopoietic system.

In conclusion, this case illustrates a temporal, chronological, and causal relationship in which bone marrow transformation was induced by an acute hepatitis A infection leading to precursor B-cell ALL in the absence of any other known risk factors. To our knowledge, this is the first such case reported in the literature.

Acknowledgements

I would like to greatly thank Dr. Alan Lefkowitz in the Internal Medicine Department for his dedication to advocating for our patient and ensuring the highest standard of care. Additionally, I greatly appreciated all of Dr. Lefkowitz's support and guidance.

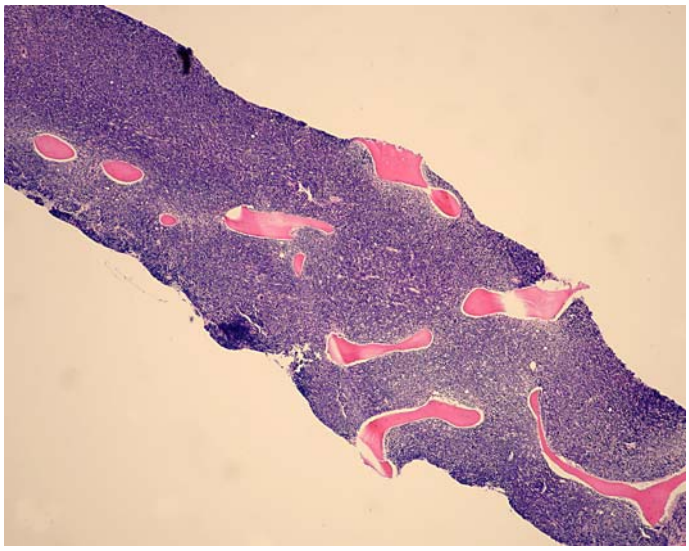

Fig. 1. Photomicrograph of bone marrow biopsy showing 100% cellularity.

Case Rep Oncol 2010;3:505–509
DOI: 10.1159/000323487
Published online: December 24, 2010

ISSN 1662–6575
www.karger.com/cro

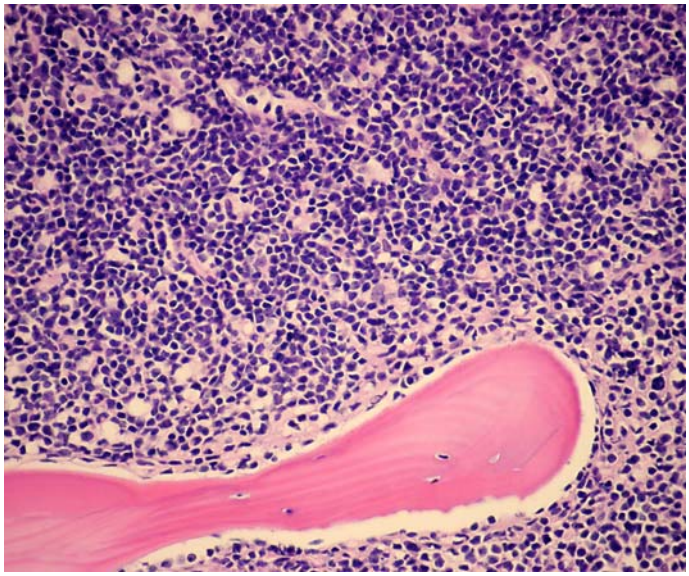

Fig. 2. Complete replacement of bone marrow by neoplastic lymphoid cells.

References

1 Nijhawan S, Joshi A, Shende A, Malhotra H, Mathur A, Rai RR: EBV-associated hepatitis with aplastic anemia: J Assoc Physicians India 2005;53:1079.

2 Conrad ME, Schwartz FD, Young AA: Infectious hepatitis – a generalized disease. Am J Med 1964;37:789–801.

3 Firkin FC, Nicholls K, Whelan G: Transient myeloid and erythroid aplasia associated with hepatitis. BR Med J 1978;2:1534.

4 Domenech P, Palomeque A, Martinez-Gutierrez A, Vinolas N, Vela E, Jimenez R: Severe aplastic anemia following hepatitis A. Acta Haematol 1986;76:227–229.

5 Deller JJ Jr, Cirksena WJ, Marcarelli J: Fatal pancytopenia associated with viral hepatitis. N Engl J Med 1962;266:297–299.

6 Rubin E, Gottlieb C, Vogel P: Syndrome of hepatitis and aplastic anemia. Am J Med 1968;45:88–97.

7 Hodgkinson R: Infectious hepatitis and aplastic anemia. Lancet 1971;1:1014.

8 Gonzalez-Casas R, Garcia-Buey L, Jones EA, Gisbert JP, Moreno-Otero R: Systematic review; hepatitis-associated aplastic anemia – a syndrome associated with abnormal immunological function. Aliment Pharmacol Thera 2009;30:436–443.

9 Smith M: Considerations on a possible viral etiology for B-precursor acute lymphoblastic leukemia of childhood. J Immunother 1999;22:90–91.

10 Smith MA, Strickler HD, Granovsky M, Reaman G, Linet M, Daniel R, Shah KV: Investigation of leukemia cells from children with common acute lymphoblastic leukemia for genomic sequences of the primate polyomaviruses JC virus, BK virus, and simian virus 40. Med Pediatr Oncol 1999;33:441–443.

11 Eden T: Aetiology of childhood leukaemia. Cancer Treat Rev 2010;36:286–297.

12 Ma X, Urayama K, Chang J, Wielmels J, Buffler P: Infection and pediatric acute lymphoblastic leukemia. Blood Cells Mol Dis 2009;42:117–120.