Early Cardiac Iron Overload in a Child on Treatment of Acute Lymphoblastic Leukemia

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An 11-year-old boy with Down syndrome and acute lymphoblastic leukemia developed hepatic dysfunction after only 10 months of treatment. MRI revealed severe iron deposition in the liver, pancreas, and heart. In stark contrast to what is seen in hemoglobinopathies, pancreatic and cardiac iron overload occurred with relatively low transfusion exposure and in a very short time period in this patient. Although extensive experience managing iron overload in hemoglobinopathies informs our approach in other diseases, it is clear that factors not present in hemoglobinopathies may be operative in patients with malignancy undergoing intense chemotherapy that lead to high levels of free iron and rapid loading of the heart and endocrine organs.

Children diagnosed with acute lymphoblastic leukemia (ALL) undergo intensive myelosuppressive chemotherapy and often require packed red blood cell (PRBC) transfusions. Each unit of PRBC contains ~200 mg of iron1 and, because humans cannot excrete iron, as little as 10 to 20 transfusions can result in significant accumulation of iron.2 Liver iron accumulates in direct proportion to the amount of iron transfused. However, iron is loaded into endocrine organs and the heart only when the highly reactive, free Fe2+ iron or labile plasma iron and labile cellular iron fractions of nontransferrin-bound-iron (NTBI) are high. This occurs when the transferrin saturation exceeds ~50%. Reactive labile plasma iron and labile cellular iron enters the heart, pancreas, pituitary gland, and other cells via unregulated ion channels and causes clinically significant cellular damage and organ dysfunction.3,4 After treatment of ALL, which results in long-term survival for the majority of patients, several complications may occur including subsequent malignant neoplasms, cardiomyopathy, endocrinopathies, and neurocognitive deficits.5 The extent to which iron overload contributes to these problems is not currently known.

The purpose of this report is to describe the early onset of clinically significant multisystem iron overload in a child undergoing treatment of ALL. This case illustrates the potential for cardiac iron loading at a remarkably early time and suggests there are modulating factors during the course of treatment of malignancy causing transport of iron into the heart and endocrine organs to be different than that seen in hemoglobinopathies.

CASE REPORT

This 11-year-old boy with Down syndrome presented with cough and petechiae. A complete blood count revealed white blood cell count 16 000 per µL with 67% lymphoblasts, hemoglobin level 6.6 g per dL, and platelet count 17 000 per µL. Pertinent serum biochemistry results included alanine aminotransferase (ALT) 50 U/L (normal range, 3–35 U/L) and...
aspartate aminotransferase (AST) 31 U/L (normal range, 15–46 U/L). Bone marrow examination confirmed the diagnosis of precursor-B cell ALL. Cytogenetic analysis demonstrated a karyotype of 47, XY (+21), as well as the absence of TEL/AML1 translocation, BCR/ABL fusion, or MLL gene rearrangement.

The patient was treated according to the Children’s Oncology Group CCG-1961 protocol for high-risk ALL. During his 10th month of treatment, the patient’s clinical course was complicated by increasing AST, ALT, and abdominal girth. Abdominal computerized tomographic scan revealed a large amount of ascites and an abnormal liver with surface nodularity and multiple, ill-defined, hypodense lesions. Liver biopsy demonstrated severe iron deposition.

The patient received a total of 31 PRBC transfusions, which equated to ∼200 mL/kg PRBCs and 140 mg/kg elemental iron. At the time of liver biopsy, his iron saturation and serum ferritin level were 98% (normal range, 20%–50%) and 1100 ng/mL (normal range, 10–140 ng/mL), respectively. Mutation analysis for hereditary hemochromatosis genes C282Y, H63D, and S65C was normal. Visceral iron burden was determined by MRI and revealed the following: (1) elevated liver iron concentration (LIC) of 14.6 mg/g dry weight liver (normal <1.1 mg/g), indicating marked hepatic iron overload; (2) elevated pancreatic R2* at 200 Hz (normal <27 Hz), indicating significant pancreatic iron deposition; and (3) decreased cardiac T2* of 15.6 milliseconds (normal >20 milliseconds), indicating moderate myocardial iron deposition. Left ventricular ejection fraction measured by MRI was 61%. At the time of the diagnosis of iron overload, the patient had received a cumulative anthracycline dose of 175 mg/m².

With clear evidence of iron overload causing organ dysfunction, iron chelation was started by using deferasirox because the patient was unlikely to tolerate phlebotomy in the context of ongoing cytotoxic chemotherapy. However, because the patient was not chronically transfused and to reduce likelihood of toxicity with concurrent chemotherapy, oral deferasirox was started at a lower than standard dose of 15 mg/kg per day given once daily for convenience. Thirteen months after initiating deferasirox, the LIC had dropped from 14.6 to 2.1 mg/g dry weight liver. After 20 months, the serum ferritin, iron saturation, AST, and ALT values had returned to values within normal limits, at which time the deferasirox dose was decreased to 5 mg/kg per day. The current plan is to continue oral deferasirox until the LIC is between 0.8 and 1.5 mg/g dry weight liver and the cardiac T2* is normal.

**DISCUSSION**

Iron is loaded into the liver via both transferrin receptor-1/transferrin receptor-2 mediated routes and ion channels, whereas the pancreas and heart have only transferrin receptor-1 and ion channels. When cellular iron is increased, transferrin receptor-1 is down-regulated such that the ion channels, which are not significantly modulated by iron levels, remain and transport NTBI into cells even though iron is elevated. Thus, the fact that this patient had measurable pancreatic and cardiac iron means there were significant elevations of toxic NTBI for a long time, because this is the only iron species that can enter the nonregulated ion channels. Cardiac iron loading is thought to occur primarily through L- and T-type calcium channels that involve transport of NTBI into the heart. NTBI levels are highest in disorders with absent or ineffective erythropoiesis. Red cell production utilizes ∼25 mg of iron per day, and when erythropoiesis is suppressed and utilization of iron decreases, transferrin becomes saturated and NTBI rises. Elevated NTBI levels without iron overload have been documented after administration of myelosuppressive cytotoxic chemotherapy. As observed in this patient, the sequence of visceral iron loading (liver, pancreas followed by heart), the elevation of hepatic transaminase levels with transferrin saturation >80%, and correction of the abnormalities with iron chelation are consistent with what has been described in other settings. A striking feature of this case is the early onset of iron loading in the pancreas and heart. In general, patients with ineffective rather than normal or accelerated hematopoiesis appear to load cardiac iron more readily. For example, patients with thalassemia major transfused every 3 weeks require nearly 10 years to demonstrate cardiac iron loading. Patients with sickle cell disease compared with thalassemia major patients with equal duration and magnitude of iron loading exhibit much less iron-related cardiotoxicity and only ∼2.5% ultimately develop cardiac iron. In contrast, patients with Diamond-Blackfan anemia or congenital dyserythropoietic anemia receiving transfusions demonstrate cardiac iron deposition much earlier, within ∼2 years, a difference attributable to their relatively higher NTBI levels. Why this patient loaded his pancreas and heart so quickly is not clear. Our patient’s cardiac T2* of 15.6 milliseconds indicated moderate cardiac iron load. Lutz et al reported 2 other children with ALL who developed cardiac iron overload, where the cardiac T2* values were 19 and 20 milliseconds, respectively. However, those patients were exposed to blood transfusions over 5 to 6 years and subsequently underwent regular phlebotomy because their iron overload was diagnosed after the completion of
chemotherapy. Although the cardiac iron levels in their patients and ours are not usually associated with cardiac dysfunction, they do indicate substantial exposure to toxic free iron. The identification of accelerated iron overload should prompt evaluation for underlying etiology. In addition to quantifying cumulative volume of previous PRBC transfusions, a comprehensive workup should consider determining mutation status of genes associated with hereditary hemochromatosis and other, rarer conditions that could predispose to iron overload. Baseline iron status would be helpful to detect preexisting disorders of iron metabolism, although this is not routinely determined in initial evaluation of newly diagnosed leukemia patients.

In addition to neoplastic infiltration of the marrow, intensive chemotherapy used to treat ALL and other malignancies causes sustained suppression of erythropoiesis. Iron overload itself may contribute to the need for blood product support. Leitch et al17 suggest that elevated serum iron levels suppress marrow function and result in PRBC transfusions and/or delay the start of subsequent cycles of chemotherapy. Although it is not known whether chemotherapy itself facilitates loading through iron channels, certain classes of these agents may be relevant to developing iron-related toxicity. Our patient received the anthracyclines daunorubicin and doxorubicin, which are associated with the development of cardiomyopathy in dose-dependent fashion, at a combined cumulative dose of 175 mg/m².18 Cascales et al19 reported increased cardiac iron concentration in adults treated with a cumulative doxorubicin dose >200 mg/m², independent of liver iron load or transfusion history. Furthermore, Panjrab et al20 demonstrated the potentiation of doxorubicin cardiotoxicity by iron loading in a rodent model. Although the left ventricular ejection fraction of our patient was not below normal, it is conceivable that the anthracycline exposure might have facilitated his cardiac iron loading.

Although there are no long-term studies documenting the benefit of correcting iron overload in pediatric oncology patients, substantial information from other diseases suggests this would be beneficial. In patients with chronic anemias, transfusion-related iron overload is an indication for intervention with chelation therapy and/or phlebotomy to remove iron.21 Reduction of LIC to near-normal levels in patients with thalassemia is associated with significant improvement in cardiac and endocrine function.4,22 In a recent meta-analysis of 8 studies of myelodysplastic syndrome, an acquired condition involving ineffective hematopoiesis, higher median survival, and improved marrow function were noted for subjects who received iron chelation therapy.23 This case clearly indicates that the physiology of iron loading, particularly through ion channels, may be different in patients with cancer rather than hemoglobinopathies. Conceivably, this difference might increase the toxicity of the loading. Although we have published 1 cross-sectional study characterizing the anatomic distribution and severity of iron deposition in childhood cancer survivors,24 much remains to be learned about the kinetics of iron loading in this population. Such information will be critical for understanding and guiding management of iron overload in both patients undergoing cancer treatment as well as long-term survivors, where the possibility exists that long-term iron exposure could influence the development of late effects.4

REFERENCES

ABBREVIATIONS
ALL: acute lymphoblastic leukemia
ALT: alanine aminotransferase
AST: aspartate aminotransferase
LIC: liver iron concentration
NTBI: nontransferrin-bound-iron
PRBC: packed red blood cell


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