Persistent pancytopenia and a hypocellular bone marrow after induction chemotherapy in a young adult with acute myelogenous leukemia; What is missing here?

LAYLA VAN DOREN1,3, JOSHUA SAPKIN1,3, MOJTABA AKHTARI2,3

1 LAC+USC Medical Center, Internal Medicine Residency Program, 2 Division of Hematology, 3 Department of Medicine, University of Southern California, Los Angeles, CA.

ABSTRACT

Congenital bone marrow failure syndromes (CBMFS) are generally diagnosed in infancy and early childhood, but may go unrecognized until adulthood. These syndromes are increasingly being diagnosed into adulthood, possibly due to the availability of genetic testing.

We describe a young gentleman diagnosed with acute myelogenous leukemia (AML) who underwent induction chemotherapy with resulting persistent pancytopenia and hypocellular bone marrow without any signs of recovery which is usually seen about 4 weeks after induction. He was incidentally found to have near complete fatty replacement of the pancreas on imaging. The constellation of findings was consistent with a CBMFS. The patient was subsequently diagnosed with Shwachman Diamond syndrome.

Key words: Shwachman diamond syndrome, congenital bone marrow failure syndrome, acute myelogenous leukemia

INTRODUCTION

Congenital bone marrow failure syndromes are a group of genetic disorders with decreased production of one or more cell lineage and are characterized by a predisposition for malignancy, particularly hematologic malignancies.1 Shwachman Diamond syndrome most often presents in infancy with bone marrow failure and exocrine pancreatic dysfunction. The management of these syndromes was once thought to be a field limited solely to pediatric subspecialties; however, there is increasing recognition of these syndromes being diagnosed in adulthood. It is imperative to recognize these syndromes when they do present in adulthood for appropriate management, as treatment related toxicities can be life threatening. This case highlights a patient with Shwachman Diamond syndrome initially presenting with acute myelogenous leukemia and subsequent bone marrow failure after induction chemotherapy.

CASE REPORT

A 39-year-old male with a past medical history of acute myelogenous leukemia (AML) status post induction chemotherapy presented to our institution to establish care for further management and surveillance of his AML. 18 months prior to presentation, the patient was diagnosed with AML (Fig. 1) and received induction chemotherapy with cytarabine and daunorubicin. Following induction chemotherapy, he was deemed not a candidate for post-induction consolidation due to complications of pulmonary aspergillosis, acalculous cholecystitis requiring laparoscopic cholecystectomy, chemotherapy related hepatic failure, and persistent pancytopenia and hypocellular bone marrow on subsequent bone marrow biopsies.

On the initial clinic visit, the patient was noted to be febrile to F°102.7; thus, he was admitted for further management. Upon admission, the patient was noted to have non-productive cough, fevers, and chills with associated pleuritic chest pain several days prior to admission. Clinical exam was revealing for faint left lung crackles, short stature, and temperature was F°102.4. Initial set of laboratory investigations was

Correspondence:
Layla Van Doren
LAC+USC Medical Center, Department of Medicine 3,
University of Southern California, Los Angeles, CA
E-mail: Layla.VanDoren@med.usc.edu

Figure 1, February 2013, bone marrow aspirate with >20% myeloblasts (arrows).
notable for an Absolute neutrophil count (ANC) 0.6 K/cumm, platelet (Plt) 34 K/cumm, and hemoglobin (Hgb) 12 g/dL. Therefore, he was started on cefepime for neutropenic fever treatment.

A Chest CT was obtained to assess for pulmonary infection and the patient was incidentally found to have near complete fatty replacement of the pancreas (Fig. 2). This finding prompted further testing of pancreatic function. Pancreatic enzyme concentrations were all decreased; elastase 37 mcg/g (normal >200 mcg/g), amylase 14U/L (21 -101 U/L), isoenzyme 4 U/L (16 -46 U/L), and serum trypsinogen <5ng/mL (19 -68 ng/mL). The results of the fat soluble vitamins were vitamin A 27 mcg/dL (38 -98 mcg/dL), vitamin D 24 ng/mL (30 -96 ng/mL), and vitamin E 8.4mg/L (5.7-19.9mg/L). Bone marrow biopsy the day after admission was significant for a hypo-cellular bone marrow with 5-15% blasts and bone thinning (Fig. 3). Based on fatty replacement of the pancreas, hypoplastic marrow, and short stature, he had clinical features suggestive of Shwachman Diamond syndrome.

There were two disease-causing mutations identified in the Swachman-Bodian-Diamond (SBDS) gene in the patient. The first was c.258+2 T>C mutation, which is a common mutation in Swachman-Diamond syndrome because it is present in a nearby SBDS pseudogene which is an inactive gene with many mutations. Sections of the pseudogene are transferred to the SBDS gene, causing Swachman-Diamond syndrome. The other mutation found was c.693delA, a frameshift mutation, causing loss of normal protein function. The presence of these two mutations was consistent with the diagnosis of Swachman-Diamond syndrome.

Pancreatic enzyme replacement was not warranted, as he was pancreatic sufficient. Upon discharge, he continued to be followed in Hematology clinic every two to three weeks. He continued to receive granulocyte colony-stimulating factor (G-CSF) for neutropenia and remained on prophylactic anti-microbials (levofloxacin, fluconazole, and acyclovir) until two months after his initial presentation, at which time repeat bone marrow biopsy revealed recurrence of AML with 60% blasts. He was then initiated on dose reduced chemotherapy with fludarabine and cytarabine as bridging to an allogeneic hematopoietic stem cell transplant. The patient’s brother was a match for transplant and found to be heterozygous for Shwachman Bodian-Diamond gene; thus, the patient is currently undergoing hematopoietic stem cell transplant.

**DISCUSSION**

Shwachman Diamond syndrome is a rare congenital bone marrow failure syndrome. It is an autosomal recessive disorder implicated in ribosome biogenesis and expressed in all human cells. It was first described in 1964 and thought to affect 1/76,000. The syndrome is a multi-system disease characterized by bone marrow failure, exocrine pancreatic dysfunction, and skeletal abnormalities. It most often presents in infancy with malabsorption and recurrent infections. Pancreatic insufficiency and bone marrow failure are the hallmarks of the syndrome. Exocrine pancreatic dysfunction is characterized by nutrient maldigestion, quantified by an elevated 72 hr fecal fat content. Low serum trypsinogen, pancreatic iso-amylase, and fat soluble vitamins A, D, and E are seen on laboratory. Histologically there is extensive fatty replacement of the acini with preserved ductal architecture and islets of Langerhans. Extensive fatty replacement can be appreciated on radiologic imaging with CT or MRI. For uncertain reasons, there is often spontaneous improvement in pancreatic function during childhood with >50% no longer require pancreatic supplementation. Other causes of exocrine pancreatic insufficiency, such as cystic fibrosis must be ruled out. Bone marrow failure is characterized by persistent neutropenia and is the most common hematologic abnormality occurring in nearly all patients. It can be persistent or intermittent, but must be present on three different occasions over a period of three months. Anemia is also present with a low reticulocyte count,
Persistent pancytopenia and a hypocellular bone marrow after induction chemotherapy along with thrombocytopenia. Bone marrow biopsy often reveals a hypoplastic marrow with increased fat deposition.\(^5\)

Skeletal abnormalities consistent of skeletal dysplasia, most often with metaphyseal dysostosis in the long bones, rib cage dysplasia, and low turnover osteopenia. Short stature may be attributed to growth failure with malnutrition and recurrent infections as a child.\(^2\)

Given the lack of large studies, rarity of the disease, and few database, there are no guidelines for management and surveillance, making it difficult and complex to manage these patients. In a patient with exocrine pancreatic dysfunction, treatment guidelines for cystic fibrosis can be of use. For bone marrow failure, chronic transfusions with packed red blood cells and platelets may be warranted (leukoreduced and irradiated blood products). Careful consideration should be given for the use of G-CSF because there is a theoretical concern of progression to AML, as occurred in our patient. Attempts should be made to provide hematopoietic stem cell transplant on an urgent basis to the patient presenting with MDS. If the patient progresses to AML, chemotherapy will only help control the disease, but will be unsuccessful in obtaining a prolonged remission in the patient with SDS. Survival rates with hematopoietic stem cell transplant is around 50%, irrespective of the donor being a matched sibling.\(^6\)

This case report demonstrated the adverse effect of administering high dose induction chemotherapy in a patient with a CBMFS.

It is necessary for adult physicians to recognize a CBMFS for appropriate management, minimization of treatment related toxicity, and to facilitate genetic counseling.

**CONCLUSION**

This case report demonstrated the adverse effect of administering high dose induction chemotherapy in a patient with Shwachman Diamond syndrome. Furthermore, recognizing a CBMFS allowed for appropriate management with a dose reduced chemotherapy regiment to minimize treatment related toxicity, and facilitate genetic counseling. It is necessary for physicians to recognize CBMFS can go undiagnosed until adulthood and malignancy may be the initial presentation.

**REFERENCES**