Presentation of Case

Dr. Nicole de Paz (Pediatrics): A 20-month-old boy was admitted to the pediatric intensive care unit of this hospital because of severe anemia.

The patient was well until 5 days before admission, when his aunt noted that he had begun tugging his ear and suspected that he might be having pain. He did not have fever, nasal congestion, rhinorrhea, or cough. His aunt took him to the emergency department at another hospital, where acute otitis media was diagnosed and a course of oral amoxicillin was prescribed.

The next day, the patient began vomiting. During the next 3 days, multiple episodes of nonbloody, nonbilious emesis occurred. His aunt fed him an oral electrolyte solution. During this time, the patient did not have a bowel movement. He also appeared pale, was less active than usual, and had a decreased volume of urine output. The day before admission, he drank milk and ate pizza without vomiting, but he seemed tired and increasingly pale. On the morning of admission, the patient’s aunt took him to a primary care pediatric clinic for evaluation.

In the clinic, the patient appeared ill; pallor, tachycardia, and tachypnea were present. The hemoglobin level, obtained by fingerstick testing, was reportedly 2.9 g per deciliter, the hematocrit 9.0%, and the white-cell count 33,000 per microliter. The patient was referred to the emergency department of a community hospital affiliated with this hospital for further evaluation.

In the emergency department, the patient’s aunt reported that the child seemed to be short of breath. On examination, he appeared listless and pale and had occasional grunting. The temperature was 36.8°C, the pulse 150 beats per minute, the blood pressure 84/59 mm Hg, the respiratory rate 44 breaths per minute, and the oxygen saturation 100% while he was breathing ambient air. The weight was 11.7 kg (61st percentile for age). The mucous membranes were pale. On auscultation of the heart, tachycardia and a gallop rhythm were present. The radial and dorsalis pedis pulses were normal, and the capillary refill time was less than 2 seconds. The lungs were clear. The abdomen was distended, and hepatosplenomegaly was present,
with no tenderness or masses and with normal bowel sounds. There was firm stool in the rectal vault; a fecal occult blood test was negative. Multiple café au lait macules were present. The remainder of the examination was normal. A peripheral intravenous catheter was inserted, and supplemental oxygen was administered through a nasal cannula at a rate of 3 liters per minute. A blood sample was obtained for culture and laboratory testing; the hematocrit was 6.7%, the white-cell count 36,450 per microliter, and the platelet count 995,000 per microliter. Other laboratory test results are shown in Table 1.

Dr. Randheer Shailam: Frontal and lateral chest radiographs showed hyperinflated lungs, cardiomegaly, and enlargement of the central pulmonary vessels (Fig. 1A and 1B). There was no evidence of pleural effusion. These findings are nonspecific and can be present in patients with congenital heart diseases, including those with a left-to-right shunt, cardiomyopathy, or heart failure.

Dr. Ana M. Rosales: An electrocardiogram (Fig. 2A) showed sinus tachycardia at a rate of 155 beats per minute with left ventricular hypertrophy and nonspecific T-wave abnormalities. The QRS axis of depolarization was 54 degrees. The QRS duration and the remainder of the intervals were normal for the patient’s age. The estimated corrected QT (QTc) interval was 404 msec.

Dr. de Paz: After consultation with a pediatric hematologist–oncologist was obtained, the patient was transferred to the pediatric intensive care unit at this hospital.

On admission of the patient to this hospital, the aunt reported that the child had not been seen by a pediatrician as frequently as is typically recommended for infants and toddlers because of a complex social situation; she did not think that he had ever undergone any blood testing. He had not received all the recommended routine immunizations; a detailed vaccination history was not immediately available. The patient had been born after 36 weeks 5 days of gestation and had been treated with oral morphine after birth because of neonatal abstinence syndrome. He was receiving amoxicillin and had no known allergies. He lived with his aunt and cousins in an urban area of New England and had not traveled. His diet included a variety of foods, including meats and vegetables, and he typically drank 0.6 liters of cow’s milk each day. His father had multiple café au lait macules, and his mother and father had substance-use disorders.

On examination, the patient was whimpering and reaching out to be held by his aunt; he appeared ill and pale. The temperature was 36.2°C, the pulse 155 beats per minute, the blood pressure 98/49 mm Hg, the respiratory rate 66 breaths per minute, and the oxygen saturation 100% while he was breathing oxygen through a nasal cannula at a rate of 3 liters per minute. On auscultation of the heart, tachycardia, a gallop rhythm, and a systolic murmur (grade 4/6) were present; the precordium was hyperdynamic. Tachypnea, nasal flaring, abdominal breathing, and mild subcostal retractions were present, and soft crackles could be heard occasionally on examination of the lungs. The abdomen was distended, the spleen extended 6 cm below the left costal margin, and the liver extended 5 cm below the right costal margin. The hands and feet were cool, and the capillary refill time was less than 2 seconds. On examination of the skin, multiple café au lait macules were noted, as were inguinal freckling and a hemangioma on the right buttock that measured 1 cm in diameter. The remainder of the examination was normal.

Dr. Shailam: An anteroposterior radiograph of the chest showed severe cardiomegaly with mild interstitial pulmonary edema (Fig. 1C).

Dr. Rosales: Echocardiography (Fig. 2B through 2E) revealed normal segmental anatomy, with a patent foramen ovale and left-to-right blood flow. No septal defects were identified. The valvular anatomy was normal, and there was mild mitral regurgitation with mild enlargement of both atria. The origin and proximal course of the coronary arteries appeared normal. The pulmonary and systemic venous return appeared normal. The aortic arch had normal branching and was not obstructed. There was no evidence of a ductus arteriosus. The left ventricle was moderately to severely dilated, with preserved systolic function.

Dr. de Paz: A diagnostic test result was received, and additional diagnostic tests were performed.

Differential Diagnosis

Dr. Brian M. Cummings: This child presents with multiple clinical signs that are suggestive of biventricular heart failure, including gastrointestinal symptoms, tachycardia, tachypnea, crackles,
Variable | Reference Range, Other Hospital | Emergency Department, Other Hospital†
--- | --- | ---
Hemoglobin (g/dl) | 10.5–13.0 | 2.2
Hematocrit (%) | 33–39 | 6.7
White-cell count (per μl) | 6000–17,500 | 36,450
Platelet count (per μl) | 135,000–400,000 | 995,000
Red-cell count (per μl) | 3,700,000–5,300,000 | 72,000
Mean corpuscular volume (fl) | 70–86 | 93.1
Mean corpuscular hemoglobin (pg) | 27–34 | 30.6
Mean corpuscular hemoglobin concentration (g/dl) | 31.5–36.5 | 32.8
Red-cell distribution width (%) | 11.9–14.8 | 17.2
Mean platelet volume (fl) | 9.7–11.9 | 12.8
Reticulocyte count (%) | 0.5–1.5 | 1.2
Prothrombin time (sec) | 9.4–12.5 | 20.5
Prothrombin-time international normalized ratio | 0.9–1.1 | 1.9
Activated partial-thromboplastin time (sec) | 25.1–36.5 | 19.0
Sodium (mmol/liter) | 136–145 | 140
Potassium (mmol/liter) | 3.5–5.2 | 5.1
Chloride (mmol/liter) | 95–106 | 102
Carbon dioxide (mmol/liter) | 20–31 | 14
Anion gap (mmol/liter) | 3–17 | 24
Calcium (mg/dl) | 8.7–10.4 | 8.5
Phosphorus (mg/dl) | 2.7–4.5 | 3.6
Magnesium (mg/dl) | 1.3–2.7 | 3.4
Urea nitrogen (mg/dl) | 9–23 | 29
Creatinine (mg/dl) | 0.5–1.30 | 0.41
Glucose (mg/dl) | 74–106 | 119
Alanine aminotransferase (U/liter) | 10–49 | 17
Aspartate aminotransferase (U/liter) | 6–40 | 28
Alkaline phosphatase (U/liter) | 70–250 | 103
Bilirubin (mg/dl) | | |
| Total | 0.0–1.0 | 0.7
| Direct | 0.0–0.4 | 0.2
Protein (mg/dl) | | |
| Total | 5.9–7.0 | 6.5
| Albumin | 3.5–4.8 | 4.0
| Globulin | 1.9–4.1 | 2.5
| Amylase (U/liter) | 30–118 | 3
| Lipase (U/liter) | 6–51 | 5
| Lactate dehydrogenase (U/liter) | 160–370 | 808
| Uric acid (mg/dl) | 3.4–7.0 | 13.8
| C-reactive protein (mg/liter) | 0.0–8.0 | 7.3
| Procalcitonin (ng/ml) | 0.00–0.08 | 0.33

* To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for magnesium to millimoles per liter, multiply by 0.4114. To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to millimoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for uric acid to micromoles per liter, multiply by 59.48.

† These data are from the emergency department of another hospital on the morning of admission to this hospital.
hepatosplenomegaly, cool hands and feet, a gallop rhythm, and a systolic murmur (grade 4/6). In addition, his chest radiograph shows cardiomegaly, laboratory testing reveals a low serum bicarbonate level suggestive of acidosis, and an echocardiogram shows left ventricular dilatation with preserved ejection fraction and no evidence of structural congenital heart disease. The patient’s cardiac output has increased to compensate for low oxygen content in the blood resulting from anemia, and I am concerned that cardiogenic shock will occur if the patient does not receive immediate intervention. Given his degree of anemia, there are three interventions that we should quickly consider to stabilize the patient’s clinical condition.

**FLUID EXPANSION**

Would a fluid bolus enhance this patient’s cardiac output? On the basis of our understanding of cardiac physiology and the Starling curve, at first glance, a fluid bolus of 5 to 10 ml per kilogram would expand ventricular preload, resulting in enhanced ventricular stroke volume. However, in this patient, I am concerned that this intervention may actually worsen cardiac function, cause further hemodilution of the red cells, and worsen oxygen delivery. The Fluid Expansion as Supportive Therapy (FEAST) trial involving children with compensated shock showed higher mortality among children who received a fluid bolus than among those who received no bolus, particularly among the children who were anemic or were in states of sympathetic compensation. Thus, fluid should be given with extreme caution.1-3

**TRANSFUSION**

Transfusion of red cells should be considered early in this patient. The basic underlying physiological problem is low oxygen content in the blood and impaired oxygen delivery, resulting in a compensatory increase in the patient’s cardiac output. Although an immediate transfusion of packed red cells seems intuitive, it is important to first rule out hemolysis as the cause of this patient’s anemia. Recent guidelines emphasize a more restrictive transfusion strategy in pediatric critical care,4 but in this case, transfusion would be lifesaving and should be performed immediately.

**SUPPLEMENTAL OXYGEN**

Perhaps the most critical intervention for this patient is the administration of supplemental oxygen to increase the partial pressure of oxygen. An increase in the oxygen saturation will increase the amount of bound hemoglobin, and an increase in the partial pressure of oxygen as a dissolved component can also play an important role in critical states of anemia. A healthy child should have an arterial oxygen content between 15 ml and 20 ml per deciliter, depending on age. In a child with severe anemia, such as this patient,
Figure 2. Electrocardiogram and Echocardiogram.

A 12-lead electrocardiogram (Panel A) shows sinus tachycardia with left ventricular hypertrophy and nonspecific ST-segment and T-wave changes. On echocardiography, an apical four-chamber view (Panel B) suggests mild enlargement of both atria and left ventricular dilatation. Color Doppler images in an apical four-chamber view (Panel C) confirm the presence of mitral regurgitation (arrow). A side-by-side color comparison of parasternal long-axis views (Panel D) reveals left ventricular and atrial dilatation as well as mitral regurgitation (arrow). A parasternal short-axis view (Panel E) shows left ventricular dilatation and trivial pericardial effusion (arrow). LA denotes left atrium, LV left ventricle, MV mitral valve, RA right atrium, and RV right ventricle.
the oxygen content is reduced to 20% of the normal level. The administration of 3 liters of supplemental oxygen through a nasal cannula, as this patient initially received, will increase the oxygen content slightly — by approximately 15% — but the administration of high-flow oxygen through a nonrebreather face mask can potentially increase the oxygen content by 65% (although this increase would result in a level that is still only one third of the normal oxygen-content level). Studies in adults have shown that increasing the partial pressure of oxygen can decrease the heart rate to a rate similar to that achieved after transfusion. Thus, the most important lifesaving intervention in this patient is administration of supplemental oxygen through a nonrebreather face mask. Once these interventions are in place, we can take a step back and construct a differential diagnosis to explain why this patient is profoundly anemic and critically ill.

SEVERE ANEMIA

To establish the underlying cause of this patient’s anemia, we need to determine whether red cells are being lost, being destroyed, or not being produced. Or, is his anemia the result of a combination of these three processes?

BLOOD LOSS

In children, severe anemia that is due to blood loss typically results from trauma; the most common type, seen in neonates, is birth trauma. In children and teenagers, bleeding from the gastrointestinal tract or menses are also common sources of severe anemia from blood loss. Finally, one might consider a bleeding disorder. This child has no family history of bleeding disorders, although a new mutation resulting in a coagulation disorder is possible. There is no history of blood in the stool or of changes in the consistency of the stool that would lead to suspicion of a gastrointestinal tract disorder, and there is no known history of trauma. A guaiac stool test, which was negative in this case, should always be performed to rule out occult blood loss from the gastrointestinal tract.

RED-CELL DESTRUCTION

Increased red-cell destruction is another common functional cause of anemia. This process can be antibody-mediated and acquired during an acute infection, or it can be caused by exposure to a drug or toxin. Red-cell membranopathies, such as spherocytosis and elliptocytosis, can lead to rapid red-cell destruction. Hemoglobinopathies, such as sickle cell anemia and thalassemia, may also lead to a shortened red-cell life span. Defects in red-cell metabolism could also result in red-cell destruction. Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common red-cell enzyme deficiency in the world, affecting more than 400 million people, mainly those of Mediterranean descent. It results from a defect on the X chromosome that leads to accumulation of reactive oxidative species in the red cells and hemolysis. This male patient had a recent acute ear infection and exposure to amoxicillin, each of which could potentially cause hemolysis and could explain the findings of an elevated lactate dehydrogenase level and splenomegaly. However, the absence of icterus and of elevated bilirubin levels in this patient makes hemolysis unlikely. The patient has had no exposure to a food or medication that would suggest hemolysis resulting from G6PD deficiency, such as ingestion of fava beans or use of sulfa drugs. A Coombs’ test, a peripheral-blood smear, and blood typing and screening should be performed to further assess whether hemolysis is contributing to this patient’s clinical presentation.

DECREASED RED-CELL PRODUCTION

Could decreased production of red cells be causing this patient’s profound anemia? Parvovirus B19 infection can cause severe aplastic anemia, usually in the context of an underlying hematolytic process. Conditions that result in ineffective erythropoiesis, such as iron deficiency, vitamin B12 deficiency, folate deficiency, and toxic effects from exposure to lead, are possible. This patient has a slightly elevated mean corpuscular volume that is consistent with macrocytic anemia. The fact that the patient typically drank 0.6 liters of milk per day and has a high red-cell distribution width and an elevated platelet count suggests iron deficiency, but the fact that he does not have microcytosis is not consistent with iron deficiency. Diamond–Blackfan anemia should be considered in young persons, although patients typically have a normal white-cell count and platelet count and characteristic facial features. Testing for the levels of adenosine deaminase and hemoglobin F might be helpful to make a
Transient erythroblastopenia in children can lead to anemia and reticulocytopenia and can be seen in children younger than 6 years of age. Typically, there is a preceding viral illness and mild neutropenia, and it occurs more commonly in boys than in girls. Hemophagocytic lymphohistiocytosis is a consideration in this case, but I would expect elevated liver-function test results and cytopenia. The level of ferritin or soluble interleukin-2 can be measured to assist in the evaluation for hemophagocytic lymphohistiocytosis. Finally, one should consider leukemia as a potential cause of this patient’s anemia; leukemia could cause pancytopenia but could also be associated with an elevated white-cell count.

It is unclear whether this child is presenting with an acute or chronic disease. His condition appeared to be stable when he presented to the emergency department a few days before this admission, but a complete blood count had not been performed. There is no evidence of bleeding or hemolysis. The laboratory evaluation is not diagnostic for iron deficiency, and the severity of his presentation suggests a more serious disorder. It appears that anemia due to decreased red-cell production is the most likely cause of his illness. The elevated white-cell count, the presence of thrombocytosis, and the elevated prothrombin time, as well as the elevated uric acid and lactate dehydrogenase levels, suggest high cell turnover, pointing the differential diagnosis toward a potential cancer.

NEUROFIBROMATOSIS TYPE 1

The patient has multiple café au lait macules on his body. Although this is a common finding in children and is reported to occur in 10% of the general population, the presence of multiple lesions can suggest genetic disorders, such as the McCune–Albright syndrome or neurofibromatosis. Neurofibromatosis type 1 is the most common such disorder, and the presence of more than six café au lait lesions is highly predictive of this diagnosis. The patient also has inguinal freckling, which enhances suspicion. Neurofibromatosis type 1 is a clinical diagnosis, and there are clinical diagnostic criteria to help establish the diagnosis (Table 2).

Neurofibromatosis type 1 is associated with cancer, including malignant peripheral-nerve sheath tumors in 10% of affected patients and optic gliomas (which are often indolent) in 15% of affected patients. Associations with rhabdomyosarcoma and pheochromocytoma have also been described. A feature of neurofibromatosis type 1 that is especially pertinent to this patient is the risk of leukemia, particularly juvenile myelomonocytic leukemia, with the subsequent risk of progression to acute myeloid leukemia owing to a loss of the wild-type allele through mutation or recombination.

Given this patient’s multiple café au lait macules, which are suggestive of neurofibromatosis type 1, his severe anemia, and the lack of findings consistent with blood loss or hemolysis, I suspect that leukemia is the most likely diagnosis.

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<tr>
<th><strong>Clinical Diagnostic Criterion</strong></th>
<th><strong>Findings Present in This Patient</strong></th>
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<tr>
<td>Six or more café au lait macules (&gt;0.5 cm in diameter in children or &gt;1.5 cm in diameter in adults)</td>
<td>Yes</td>
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<tr>
<td>Two or more cutaneous or subcutaneous neurofibromas or one plexiform neurofibroma</td>
<td>No</td>
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<tr>
<td>Axillary freckling or freckling on the groin</td>
<td>Yes</td>
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<tr>
<td>Glioma of the optic pathway</td>
<td>No</td>
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<tr>
<td>Two or more Lisch nodules (iris hamartomas) seen on slit-lamp examination</td>
<td>No</td>
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<tr>
<td>Bony dysplasia (dysplasia of the sphenoid wing or bowing of a long bone with or without pseudarthrosis)</td>
<td>No</td>
</tr>
<tr>
<td>First-degree relative with neurofibromatosis type 1</td>
<td>Unknown, but his father had multiple café au lait macules</td>
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* Adapted from Ferner et al.

Table 2. Clinical Diagnostic Criteria for Neurofibromatosis Type 1.
in this case. A peripheral-blood smear and a bone marrow biopsy would be the most expeditious strategy to establish the diagnosis of acute leukemia.

**DR. BRIAN M. CUMMINGS’S DIAGNOSIS**

Neurofibromatosis type 1 and severe anemia, probably due to leukemia.

**PATHOLOGICAL DISCUSSION**

Dr. Valentina Nardi: Examination of the peripheral-blood smear revealed profound anemia, marked thrombocytosis, monocytosis, mature and occasional left-shifted myeloid elements, and immature cells with fine chromatin and prominent nucleoli consistent with blasts (Fig. 3A). No Auer rods were seen. Flow-cytometric analysis of the peripheral-blood specimen confirmed the presence of blasts (approximately 5% of the cells) and revealed that they were of myeloid origin on the basis of their immunophenotype (CD33+/−, CD13+/−, MPO−, CD117+, CD34+, HLA-DR+, and CD19−). The bone marrow biopsy specimen revealed 100% cellularity; numerous small, hypolobated, dysplastic megakaryocytes highlighted by an immunohistochemical stain for CD61; increased eosinophilic forms; increased myeloid blasts (approximately 5 to 10% of the marrow cells, highlighted by immunohistochemical staining for CD34); and reticulin fibrosis of grade 2 to 3 of 3 (Fig. 3B through 3H). These findings are diagnostic of a myeloid neoplasm and are strongly suggestive of a diagnosis of myelodysplastic–myeloproliferative neoplasm.

Conventional cytogenetic analysis revealed monosomy 7 in 17 of 17 metaphases and no evidence of a BCR-ABL1 rearrangement or of any other genetic abnormalities consistent with acute myeloid leukemia — for example, inv(16) or t(16;16)(p13.1;q22). Mutational analysis of 103 genes by means of a clinical anchored multiplex polymerase-chain-reaction–based next-generation sequencing assay performed on the bone marrow aspirate revealed four mutations: two pathogenic mutations in neurofibromin 1 (NF1) (NF1 splice donor variant [ENST00000358273.4: c.2850+1G→A] at a variant allele frequency of 52% and NF1 ENSP00000351015.4: p.Ile679AspfsTer21 [ENST00000358273.4: c.2033dupC] at a variant allele frequency of 34%) and two presumed pathogenic mutations in enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) (EZH2 ENSP00000320147.2: p.Cys528Arg [ENST00000320356.2: c.1582T→C] at a variant allele frequency of 26% and EZH2 ENSP00000320147: p.Asn152IlefsTer15 [ENST00000320356.2: c.455delA] at a variant allele frequency of 24%). The NF1 splice donor mutation c.2850+1G→A, detected at a variant allele frequency of approximately 50%, can occur as a germline pathogenic mutation and can lead to neurofibromatosis type 1 (ClinVar NM_000267.3[NF1]: c.2850+1G→A; SCV000581340.3 and SCV000808263.1).

Taken together, the clinical, morphologic, and genetic findings are consistent with a diagnosis of juvenile myelomonocytic leukemia, a rare myelodysplastic–myeloproliferative neoplasm that, in approximately 10% of cases, occurs in children with neurofibromatosis type 1. This case also included some unusual features (e.g., thrombocytosis, eosinophilia, and increased bone marrow fibrosis). Mutations in EZH2 have been described in patients with juvenile myelomonocytic leukemia who have NF1 mutations and monosomy 7.13

**DISCUSSION OF MANAGEMENT**

Dr. Mary S. Huang: The only curative treatment for juvenile myelomonocytic leukemia is allogeneic stem-cell transplantation. Until this treatment can be arranged, the standard of care is supportive management and disease control. Without transplantation, the median survival is less than 2 years. With transplantation, the percentage of patients who survive and are disease-free is estimated to be approximately 50%. In contrast to the use of intensive chemotherapy before transplantation in children with acute leukemias, there is no established role for intensive chemotherapy to eradicate juvenile myelomonocytic leukemia before transplantation is performed.
In addition, no specific chemotherapeutic regimen to control disease has been established as standard and beneficial before bone marrow transplantation. Nevertheless, on the basis of the results of recent trials, the disease burden and the intensity of the conditioning regimen for transplantation may be important to the clinical outcome.14,15

An inherent challenge to advancing therapy for this entity is the heterogeneity of disease that is characterized by various germline and somatic alterations that might predict the clinical course.

Figure 3 (facing page). Specimens of Peripheral Blood and Bone Marrow.

Wright’s staining of a peripheral-blood smear (Panel A) shows profound anemia, thrombocytosis, and occasional blasts (arrows). Hematoxylin and eosin staining of a biopsy specimen of the bone marrow (Panel B) shows that the marrow is 100% cellular, with increased eosinophilic forms and numerous dysplastic megakaryocytes. These findings are also shown at higher magnification (Panel C, arrows) as well as on Giemsa staining (Panel D, arrows). Wright–Giemsa staining of the aspirate smear at high magnification (Panel E) shows a blast (arrow) and a dysplastic megakaryocyte (arrowhead). Reticulin staining (Panel F) shows markedly increased reticulin fibers consistent with reticulin fibrosis of grade 2 to 3 of 3. Immunohistochemical staining for CD34 (Panel G) shows increased myeloid blasts (approximately 5 to 10% of the marrow cells). Immunohistochemical staining for CD61 (Panel H) confirms the increased number of megakaryocytes and highlights their small size and hypolobated appearance, findings consistent with a dysplastic morphologic abnormality.

In patients with underlying neurofibromatosis type 1, the recommendation to move forward with bone marrow transplantation seems clear. However, some research suggests that, in patients with other molecular subtypes, initial observation may be beneficial to see whether their disease stabilizes or resolves spontaneously. Some data also suggest that other features, such as the methylation profile, may be important and could predict response to targeted therapies, such as hypomethylating agents.

This patient received supportive care only, which included blood transfusion and splenectomy. The splenectomy, in this case, was performed to reduce the transfusion requirement, as well as to decrease disease burden and to facilitate engraftment after bone marrow transplantation. None of his three full siblings were an HLA match, but a search for an unrelated donor identified a suitable bone marrow donor. The patient underwent transplantation approximately 2.5 months after his initial presentation. Although he has had a complicated post-transplantation course, he has had full bone marrow engraftment and has no evidence of recurrent disease.

ANATOMICAL DIAGNOSIS

Juvenile myelomonocytic leukemia.

This case was presented at Pediatrics Grand Rounds.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available at NEJM.org.

REFERENCES


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