Transient Erythroblastopenia of Childhood
A Review for the Pediatric Emergency Medicine Physician

Rebekah A. Burns, MD and George A. Woodward, MD, MBA

Abstract: Transient erythroblastopenia of childhood is a form of pure red cell aplasia that is self-limited and occurs in children 4 years old and younger. It is characterized by an absence or a significantly reduced quantity of erythroblasts in the bone marrow without underlying congenital red cell abnormalities. Transient erythroblastopenia of childhood should be considered in previously healthy children who present with normocytic anemia and lack of reticulocytosis without evidence of blood loss, hemolysis, or other causes of bone marrow suppression. Evaluation should be targeted at ruling out other causes of anemia. Management is mainly supportive, although some children may require blood transfusions for symptomatic anemia. Most patients demonstrate a return of hematopoiesis within two weeks of diagnosis and normalization of blood counts within two months.

Key Words: transient erythroblastopenia of childhood, anemia, pure red cell aplasia

(Pediatr Emer Care 2019;35: 237–242)

TARGET AUDIENCE

This CME article is intended for medical personnel involved in the care of children presenting with findings concerning for anemia including pediatric emergency medicine physicians, emergency medicine physicians, pediatricians, nurse practitioners, and physician assistants.

LEARNING OBJECTIVES

After completion of this CME article, readers should be better able to:

1. Describe the physical examination findings and laboratory evaluation consistent with transient erythroblastopenia of childhood.
2. Differentiate transient erythroblastopenia from other potential causes of anemia in young children.
3. Formulate an evaluation and treatment plan for a patient with isolated normocytic anemia.

Transient erythroblastopenia of childhood (TEC) is a self-limited disorder characterized by normocytic anemia secondary to the absence of erythrocyte progenitor cells. It falls under the larger umbrella of pure red cell aplasia (PRCA) and is generally defined as anemia with a hemoglobin level at least 2 SDs below normal and a low reticulocyte count in relationship to the anemia in the absence of evidence of alternative causes of anemia. Bone marrow aspiration, if obtained, will be normal with the exception of absent or reduced levels of erythroid precursors. The cause of TEC is not well understood and has yet to be linked to any one infection or other stimulating cause. It is rarely recurrent, and no treatments other than supportive measures are required.

CASE

A 22-month-old girl is referred to the emergency department for anemia identified on laboratory evaluation in the primary care clinic. The parents report that the child has been fussy for the past three days with decreased oral intake. The child's grandmother came for a visit yesterday and commented that she appeared quite pale. She does not currently have fever, cough, or congestion, although the parents report that she was sick last month with these symptoms. She has not been vomiting or having diarrhea. They have not noted any easy bleeding or bruising, and the child has not lost weight recently.

The girl was born at 39 weeks gestation and has not had any medical problems. She has two older siblings who are healthy. The parents do not know of any blood disorders in the family. Her family reports that she eats a wide variety of foods and drinks 18 oz of cow's milk a day.

On examination, she is fussy but alert. She is significantly more pale compared to her other family members. Her heart rate is 160 beats/min. She is breathing 35 times a minute and has an oxygen saturation of 100% on room air. Her blood pressure is normal, and her temperature is 37.4°C. Her examination is notable for a grade III/VI systolic ejection murmur. Her lungs are clear. Hepatosplenomegaly and lymphadenopathy are not noted. She does not have bruising or petechiae. The remainder of her examination is unremarkable.

Her clinic laboratory report shows a complete blood count (CBC) with a hemoglobin level of 6.1 g/dL, hematocrit level of 18.1%, white blood cell count of 8200/mm³, and platelet count of 450,000/mm³. The differential is normal, and there are no blasts seen. The mean corpuscular volume (MCV) is 82 fl. Her reticulocyte count is 0.1%. Her iron studies are within normal limits.

EPIDEMIOLOGY OF TEC

Transient erythroblastopenia of childhood is an illness of the young child with a median age at diagnosis of 19 months. Most cases occur in children between 1 and 4 years old, but some may present before their first birthday or after the age of 4 years. In one case series, 20% of patients diagnosed with TEC were younger than 6 months. The incidence in children younger than 4 years has been reported as 4.3 to 20 per 100,000 children, although the true incidence may be higher given that cases may go undiagnosed and resolution is spontaneous.
**ETIOLOGY**

The cause of erythroblastopenia in TEC is not well understood. Transient erythroblastopenia of childhood has been reported to occur in siblings pairs both concurrently and many years apart. In approximately 50% of children with TEC, a history of viral infection in the preceding 2 to 3 months can be elicited. A common environmental trigger could be the explanation for family members presenting with acute findings concomitantly, but cases that are separated by years suggest a potential underlying inherited factor. Seasonal clustering of cases suggests a possible infectious stimulus, although the patterns vary by geographic region. Case reports have identified viral infections such as human parvovirus B19, echovirus, and human herpesvirus 6 as potential causes. However, further investigation into common infections including these as well as Epstein-Barr virus and cytomegalovirus has failed to find supporting evidence. Given that a singular infectious agent has not been reliably implicated, it is likely that suppression of hematopoiesis is secondary to an immune-mediated process. IgG, IgM antibodies, and T cells may all potentially mediate/suppress/inhibit development of erythroid progenitor cells, but there does not seem to be a singular pathogenic etiology. Diagnosis is often delayed from the onset of symptoms, likely due to the insidious nature of the illness. Given that the life-span of a red blood cell is 100 to 120 days, arrest of erythropoiesis will not manifest itself clinically for some time. In fact, it will take approximately 60 days for the hemoglobin level to decrease by one-half if there is a complete stop in red blood cell production. Ultimately, approximately 67% of patients are referred for evaluation because of symptoms of anemia such as fatigue, poor appetite, or pallor. However, it may be identified incidentally during routine laboratory evaluation or evaluation for an unrelated medical concern.

**PHYSICAL EXAMINATION**

Children with TEC often have examination findings suggestive of marked anemia. New pallor may be noted by families or medical providers. Children may have a systolic ejection murmur consistent with increased flow. Tachycardia and tachypnea may also be present secondary to the decreased oxygen-carrying capacity of the blood. Generalized lymphadenopathy and hepatosplenomegaly are rare and should prompt further evaluation. Children with TEC do not have any increased bleeding risk or abnormal examination findings such as bruising or petechiae, which would be consistent with coagulopathies or platelet dysfunction.

Rare but potentially serious concomitant findings have been reported in children with TEC. Ectopic atrial tachycardia described in a 7-month-old was considered to be secondary to increased catecholamine release in the setting of acute anemia and decreased oxygen delivery to tissues. Pericarditis has been described in a patient presenting with TEC and evidence of human parvovirus B19 infection. Neurologic changes including altered mental status, gait disturbances, abnormalities of extraocular eye movements, and transient hemiparesis may occur. Although the etiology of these findings is not well understood, it has been postulated that cerebral hypoxia secondary to significant anemia may be causal. Some patients with neurologic changes, however, have hemoglobin levels unlikely to be associated with hypoxia, suggesting that another factor may be at play such as an immune response to the underlying inciting factor that led to the erythroblastopenia.

**DIFFERENTIAL DIAGNOSIS**

As with any case of anemia, the differential diagnosis includes blood loss, increased red blood cell destruction, or decreased red blood cell production. See Table 1 for a review of the causes of anemia in children. A careful history and examination should eliminate bleeding as the etiology of normocytic anemia. In patients with TEC, laboratory evaluation will not be consistent with hemolysis, nor will the patient be jaundiced or have an enlarged spleen. Given that TEC is caused by an arrest in red blood cell production, other causes of PRCA must be considered during the evaluation. Often TEC is a diagnosis of exclusion after other causes have been considered.

Diamond-Blackfan anemia (DBA) is a congenital condition that must be distinguished from TEC. It most often presents in the first year of life. Nearly half of patients will have associated congenital anomalies and nearly half of cases are familial. However, some patients with DBA will have a normal appearance and/or a sporadic mutation, making their diagnosis more difficult. Laboratory evaluation before transfusion may be helpful in making the distinction if clinical factors such as patient age do not help exclude a congenital etiology. Mean corpuscular volume of red blood cells and fetal hemoglobin are elevated in children with DBA after the first few months of life, and erythrocyte adenosine deaminase activity is elevated in most patients. Genetic testing may be used to evaluate for DBA when the diagnosis is uncertain, although only approximately 65% of patients with the disorder have an identified mutation.

Neutropenia may be seen in the setting of TEC but, if present, should be only mild. Furthermore, blasts will not be present on the peripheral smear. However, many practitioners will be appropriately concerned about leukemia when faced with a CBC showing neutropenia and marked anemia. Clinical features can help distinguish many cases of TEC from malignancy, usually without requiring a bone marrow aspiration for diagnosis. Patients with TEC frequently have thrombocytosis rather than thrombocytopenia, which is often seen with leukemia. Fever, bone pain, lymphadenopathy, and hepatosplenomegaly should be absent. The presence of these abnormalities should lead to further workup for alternate causes.

Parvovirus B19 infection can cause lysis of proerythroblasts and result in PRCA in individuals with underlying conditions that shorten the life-span of red blood cells, such as G6PD deficiency, sickle cell anemia, and hereditary spherocytosis. A peripheral

**TABLE 1. Causes of Anemia in Pediatric Patients**

<table>
<thead>
<tr>
<th>Anemia Type</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcytic anemia (MCV &lt;80 fL/red cell)</td>
<td>Iron deficiency, Anemia of chronic disease, Thalassemia, Lead poisoning, Sideroblastic anemia</td>
</tr>
<tr>
<td>Normocytic anemia (MCV 80–100 fL/red cell)</td>
<td>Early iron deficiency anemia, Anemia of chronic disease, Blood loss, Hemolysis, Malignancy with bone marrow infiltration, Diamond-Blackfan anemia, TEC, Aplastic anemia, Myelodysplastic syndromes, Insufficient erythropoietin production</td>
</tr>
<tr>
<td>Macrocytic anemia (MCV &gt;100 fL/red cell)</td>
<td>Folic acid deficiency, B12 deficiency, Liver disease, Reticulocytosis, Hypothyroidism, Diamond-Blackfan anemia, Myelodysplastic syndromes</td>
</tr>
</tbody>
</table>
Laboratory Evaluation

Alternate causes of anemia must be excluded and initial laboratory evaluation should be directed at ruling out other causes. See Table 2 for a list of studies to consider when evaluating a child for anemia. In cases of TEC, the direct antiglobulin test results are negative. Iron studies including total iron, ferritin, total iron binding capacity, and percent saturation are normal or even slightly elevated because of decreased utilization as erythropoiesis decreases. Evaluations of vitamin B12 and red blood cell folic acid will be normal, if performed. Bone marrow aspiration reveals absent or decreased quantities of mature erythroid precursors with other cell lines preserved. Serum erythropoietin will be elevated, demonstrating that a nonrenal cause is underlying the disorder.12 During the acute phase, mean corpuscular volume will be normal, although it may be elevated in the recovery phase, reflecting reticulocytopenia. Neutropenia may be present, but the total white blood cell count is often normal.22 Many patients will demonstrate a mild thrombocytopenia, although mild thrombocytopenia has also been described.8,23 Although TEC may still be the ultimate diagnosis, any abnormalities in platelets or white blood cells may require further evaluation.

Management

Management of TEC is purely supportive. In the acute presentation, measures should be taken to ensure that the patient is hemodynamically stable. Some children, up to 72% in one study, will require blood transfusions for symptomatic anemia.1 In terms of long-term management, steroids do not seem to alter the clinical course. Most patients have complete spontaneous recovery within 1 to 2 months, with reticulocytosis occurring at a mean of 10 days from diagnosis.5

Case Resolution

Because of symptomatic anemia, our patient is admitted to the hospital for packed red blood cell transfusion and monitoring. While there, the hematology service consults and recommends the hospital for packed red blood cell transfusion and monitoring. A repeat CBC performed by her primary care physician one week after discharge demonstrates a hemoglobin level of 10.3 g/dL, hematocrit level 31.8%, blood cell count of 7900/mm³, and platelet count of 390,000/mm³. Her reticulocyte count is 5.2%. Follow-up two months after discharge reveals a normal CBC and reticulocyte count. No further evaluation or treatment is required.

Summary

Transient erythroblastopenia of childhood is a self-limited cause of anemia in young children. As a PRCA, laboratory features demonstrate an absent or low reticulocyte count in the setting of a normocytic anemia, potentially profound, without significant abnormalities in the other cell lines. The underlying cause of TEC is not well understood, although it is often found in conjunction with either a history of viral-like symptoms or laboratory evidence of recent viral infection. Initial evaluation should be directed at investigating other potential causes of anemia, and management should be supportive. The ultimate diagnosis of TEC is often not confirmed until follow-up when the hemoglobin level has normalized spontaneously.

References


