

Ellis-van Creveld Syndrome and Dyserythropoiesis

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● **Ellis-van Creveld (EVC) syndrome or chondroectodermal dysplasia is a rare autosomal recessive disorder characterized by a variable spectrum of clinical findings. Classical EVC syndrome comprises a tetrad of clinical manifestations of chondrodysplasia, polydactyly, ectodermal dysplasia, and cardiac defects. In several case reports, dysplasia involving other organs has also been identified. Hematologic abnormalities have been rarely reported in patients with EVC syndrome. Here, we report a case of a 3-year-old Hispanic boy with EVC syndrome and marked dyserythropoiesis. The dyserythropoiesis may be part of an isolated myelodysplastic change or a primary myelodysplastic syndrome and likely represents an unusual EVC syndrome association. To our knowledge, this association has not been previously reported.**

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Ellis-van Creveld (EVC) syndrome or chondroectodermal dysplasia is a rare autosomal recessive disorder that was initially described in 1940 by Drs Richard Ellis and Simon van Creveld as a tetrad of chondrodysplasia, ectodermal dysplasia, polydactyly, and congenital heart disease.¹ Although this tetrad constitutes the classical syndrome description, a variable spectrum of clinical manifestations is frequently present.²

Other organs of endodermal origin are sometimes affected in EVC syndrome. Pulmonary, renal, hepatic, pancreatic, and central nervous system abnormalities have been reported previously but constitute some of the rarer syndrome associations.^{3–5}

Reported instances of hematologic abnormalities in EVC syndrome are extremely rare. A single case report from 1969 includes the description of a neonate with a possible variant of EVC syndrome with acute myeloblastic leukemia.⁶ Overall, the hematopoietic system, including peripheral blood characteristics and morphology, is seldom discussed in patients with EVC syndrome.

We present the case of a 3-year-old boy with EVC syndrome and marked dyserythropoiesis. To our knowledge,

this is the first such case report noting the association between these 2 conditions.

REPORT OF A CASE

The patient was a Hispanic boy delivered at 39 weeks' gestation and was the product of nonconsanguineous parents. The patient's physical findings at birth included short-limb dwarfism, bilateral postaxial polydactyly, and hypoplastic spoon-shaped nails. His facial and dental anomalies included multiple frenula with gum abnormalities and supernumerary upper teeth including one conical in shape. His length during the last 3 years has remained at less than the 5th percentile, although his weight has been between the 25th and 50th percentile. Cardiac defects consisted of cor triatriatum, ostium primum, and secundum atrial septal defects.

A clinical diagnosis of EVC syndrome was made based on the physical and radiographic findings strongly characteristic of chondroectodermal dysplasia (short-limb dwarfism, dysplastic nails, dental anomalies, abnormal frenuli, polydactyly, and cardiac defects). A sister 13 months older than the patient also had similar physical features and underwent successful repair of a similar complex cardiac defect at 2.5 years of age.

Because of worsening symptoms, the patient presented at 3 years of age for repair of his cardiac defects. Following successful repair of the cardiac defect, hematologic consultation was requested for evaluation of persistent leukocytosis. A bone marrow aspiration and biopsy were performed.

Despite surgical repair of his cardiac defect, the patient developed congestive heart failure and eventually sustained multiorgan failure. The patient died on postoperative day 58.

PATHOLOGIC FINDINGS

Peripheral blood examination revealed normochromic microcytic red blood cells (hemoglobin, 13.9 g/dL; hematocrit, 40.8%) with anisopoikilocytosis, polychromasia, and many nucleated red blood cells. Leukocytosis with a left shift was present (47900/ μ L) with a differential of 54% neutrophils, 14% band forms, 10% lymphocytes, 1% monocytes, 18% metamyelocytes, and 3% myelocytes. Review of the blood smear confirmed the presence of many reactive neutrophils; however, no myeloblasts were identified. Granulocytes were without evidence of dysplastic changes, and no hypersegmented neutrophils were identified. Platelet numbers were low ($73 \times 10^3/\mu$ L), and a few large forms were identified.

A bone marrow aspirate and biopsy revealed erythroid hyperplasia (myeloid-erythroid ratio of 0.9:1) with numerous dysplastic forms (Figure 1), including nuclear irregularities and budding (Figure 2). Megaloblastoid changes were absent. Both granulopoiesis and megakaryopoiesis had normal maturation sequences. Giant bands and metamyelocytes were not evident. Iron stores were decreased, and no ringed sideroblasts were noted.

Ellis-van Creveld syndrome is a rare autosomal recessive

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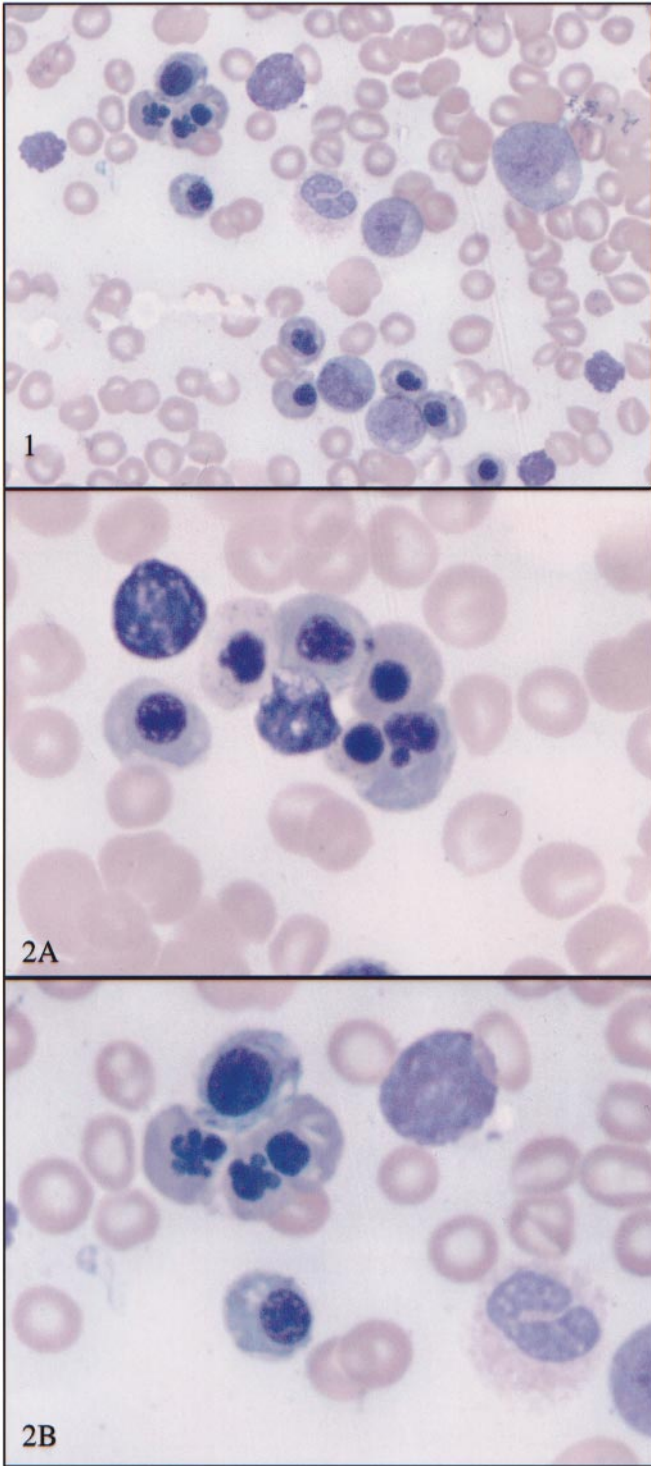


Figure 1. Erythroid dysplasia and normal maturation of granulocytes (Giemsa stain, original magnification $\times 50$).

Figure 2. Red cell precursors with marked dysplasia (Giemsa stain, original magnification $\times 100$).

sive disorder that has recently been mapped to human chromosome 4p16.⁷ Classical EVC syndrome comprises a tetrad of clinical manifestations consisting of chondrodystrophy, polydactyly, ectodermal dysplasia, and cardiac defects. However, clinical presentation is variable, and the full spectrum may be lacking in any particular patient.

Chondrodystrophy, the most consistent clinical feature, is due to a defect in ossification that results in short stature and limb shortening, which is more striking in the distal rather than proximal extremities.² Polydactyly is typically seen as postaxial hexadactyly of the hands or in a few cases the feet.⁸ Ectodermal defects frequently manifest as nail hypoplasia, malformed teeth, and thin scanty hair.⁹ Cardiac defects are present in 50% to 60% of patients. A common atrium and persistent atrioventricular canal are the most common cardiac defects.^{2,3} Additional endocardial cushion defects have also been described, including patent ductus arteriosus, ventricular septal defects, and atrial septal defects.^{2,3}

The patient in this case exhibited the full tetrad of clinical findings of EVC syndrome. This patient also had significant dyserythropoiesis. To our knowledge, this association has not been previously described.

Reported instances of documented hematologic abnormalities in EVC syndrome are rare. In a single case report from 1969, Miller et al⁶ noted that a neonate with some features of EVC syndrome developed acute myeloblastic leukemia defects. The neonate reportedly had features of chondrodystrophy and ectodermal dysplasia but lacked polydactyly or cardiac defect. In the present case, examination of peripheral blood revealed leukopenia with 8% myeloblasts. Bone marrow examination revealed marked myeloid proliferation with 41% myeloblasts, consistent with acute myeloblastic leukemia. Chromosomal analysis revealed a normal male karyotype. The infant died at 34 days of age from progressive disease. Aside from the case report in 1969, the hematopoietic system has been infrequently discussed in patients with EVC syndrome.

The hematologic findings in this case include myelodysplastic changes confined to the erythroid series, with dyserythropoiesis manifested primarily by nuclear irregularities. The presence of significant dyserythropoiesis without anemia is unusual. The patient had not been recently transfused and had no past history of anemia.

Possible etiologies for dyserythropoiesis in this patient include nutritional and toxic factors and myelodysplastic syndromes (MDS). There are several nutritional factors associated with dyserythropoiesis, most notably deficiencies of vitamin B12 and folate. During the patient's hospital course, vitamin B12 and folate concentrations were not monitored. However, the other characteristic changes seen in patients with vitamin B12 and folate deficiencies (eg, macrocytosis, hypersegmented neutrophils, and megaloblastoid bone marrow changes) were absent. Clinical evidence of toxic exposure to known myelodysplastic agents such as benzene and pesticides was not present.

Myelodysplastic syndromes are clonal hematopoietic disorders associated with dysplasia in one or more myeloid cell lines and may develop as primary disorders with no known etiology or as therapy-related secondary disorders. Secondary MDS has been associated with chemotherapeutic agents and radiotherapy. The patient in this case had no known exposure to such agents. Primary and secondary MDS are often associated with evidence of clonality and cytogenetic abnormalities, although these abnormalities are not required for diagnosis.¹⁰ Unfortunately, cytogenetic studies were not available for this patient.

Myelodysplastic syndromes typically affect older adults (median age, 70 years) and are uncommonly encountered in children.¹⁰ However, the association of MDS in pediatric

patients with predisposing genetic abnormalities such as Down syndrome is well recognized.¹¹

The dyserythropoiesis identified in this child with EVC syndrome may signify a unilineage myelodysplastic change or a primary myelodysplastic syndrome. The dyserythropoiesis may be a coincidental occurrence or may represent an unusual EVC syndrome association. Patients with EVC syndrome that present with unexplained hematologic findings may warrant evaluation for possible myelodysplasia or MDS.

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