

## CONTINUING MEDICAL EDUCATION ΣΥΝΕΧΙΖΟΜΕΝΗ ΙΑΤΡΙΚΗ ΕΚΠΑΙΔΕΥΣΗ

### Hematology Quiz - Case 3

A 19-year-old female patient who came to Greece from Syria was admitted to Outpatient Clinic of our Department because of anemia. The family history was unremarkable and the patient was unaware of any case of blood disease among his family members. She had one child (boy) who was healthy with no anemia documented in his medical record.

Physical examination revealed no characteristic abnormalities except of pallor. Neurology and ophthalmoscopic examination was normal. Her hematology profile was as follows: Hb 9.9 g/dL, Ht 31.5%, MCV 105 fL, reticulocytes counts 1.5%, white blood cell counts  $6.7 \times 10^9/L$  with normal differentiation counts and platelet counts  $188 \times 10^9/L$ . The peripheral blood film revealed marked anisopoikilocytosis, macrocytosis, hypochromia, and basophilic stippling of red blood cells.

The serum basic biochemistry including bilirubin, total protein, liver enzymes and renal function tests were normal. However, lactate dehydrogenase was slightly increased (320 U/L; upper normal limit 240 U/L), serum erythropoietin was elevated (66.8 mIU/mL; upper normal limit 20 mIU/mL), and serum haptoglobin level was low (1.2 mg/dL). Serum levels of iron, ferritin, transferrin, folic acid, and  $B_{12}$  were within normal range. Hemoglobin electrophoresis, Coombs' test, Ham and sucrose lysis tests, G6PD levels and osmotic fragility of the red cells were also normal. Serum soluble transferrin receptor level was increased (34.5 nM; upper normal limit in our laboratory was 18 nM). Furthermore, the red cells were not agglutinated by anti-i serum.

No abnormalities were observed in the electrocardiogram and the thorax X-rays. The abdominal ultrasound revealed only cholelithiasis.

The bone marrow aspiration revealed a severe erythroid hyperplasia with the presence of giant multinucleated erythroblasts with up to 8 nuclei/cell and a low number (~3%) of ringed sideroblasts (figures 1–3). Some erythroblasts showed also megaloblastoid changes, basophilic

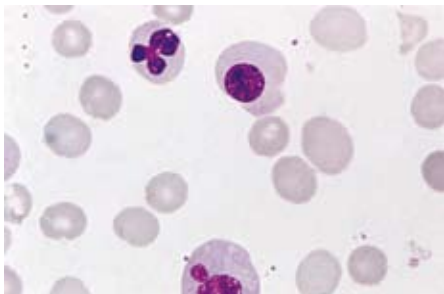


Figure 1.

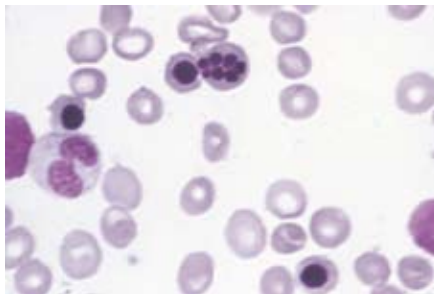


Figure 2.

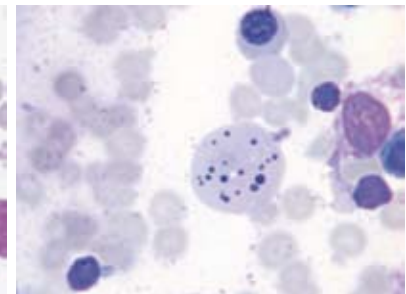


Figure 3.

stippling of the cytoplasm, nuclear lobulation, and karyorrhexis. A small number of erythroblasts had also large autophagic vacuoles. The other blood series had no significant abnormalities.

The diagnosis was established and during the next 2-year follow-up period the patient required blood transfusions every 3–4 months, while oral chelation therapy was started due to increased ferritin levels.

#### Comment

*Congenital dyserythropoietic anemia (CDA) type III is the rarest of the three classical types of CDA and both familial and sporadic cases have been reported. The type of inheritance and the clinical features are different among patients. Splenomegaly and hepatomegaly is present in some patients but not in others. Visual disturbances with macular degeneration and angioid streaks have been described in six Swedish patients but it is not characteristic finding in others. In the few reported sporadic cases (our patient may belong to such cases) the parents and relatives that were examined were hematologically normal and the disorder may have been caused by a spontaneous dominant mutation or may have been inherited as an autosomal recessive character. The sporadic cases are clinically heterogeneous. The characteristic of the disease is that the bone marrow contains giant multinucleate erythroblasts with up to 12 nuclei/cell and total DNA contents up to 48c (1c=haploid DNA content) and giant mononucleate*

*cells with total DNA contents up to 28c. Bi- and multinuclearity are seen at all stages of erythropoiesis including the basophilic erythroblasts. Some erythroblasts show vitamin  $B_{12}$ - and folate-independent megaloblastic changes. Erythroblasts show a variety of non-specific ultrastructural abnormalities, most commonly long intranuclear clefts, karyorrhexis, abnormalities in the nuclear membrane and large autophagic vacuoles. Other abnormalities include iron-laden mitochondria, intracytoplasmic myelin figures and differences in the ultrastructural appearance of the individual nuclei within the same multinucleate cell. Giant multinucleate and mononucleate erythroblasts are not specific for CDA type III but may also be seen in some myelodysplastic syndromes and erythroleukemia. In a Swedish family, linkage analysis and recombination studies have shown that the disease gene (CDAN3) is located on chromosome 15 within a 4-5-cM interval in the region 15q22, some distance telomeric to the CDAN1 gene. However this has not been found in other cases.*

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**Diagnosis:** *Dyserythropoietic anemia type III*

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2007, 24(6):636

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