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Hereditary hemochromatosis and its complications in a girl with severe aplastic anemia

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Hemochromatosis is a disorder associated with deposits of excess iron that causes multiple organ dysfunction. Normally, iron absorption is tightly regulated because the body is incapable of excreting excess iron. Hemochromatosis occurs when there are high pathological levels of iron accumulation in the body [1]. Secondary hemochromatosis occurs as a result of erythropoiesis disorders and blood transfusions. In hereditary hemochromatosis (HH), retained iron is mainly deposited in parenchymal cells, whereas in transfusional hemochromatosis, it is mainly deposited in reticuloendothelial cells. The excess iron is deposited in the cells as hemosiderin. This eventually leads to cell death and the replacement of these cells by a fibrous deposit that destroys or impairs organ function [2]. HH is the most common autosomal recessive disorder in Caucasians, and occurs in homozygotes with a mutation in the hemochromatosis gene (*HFE*) protein. This mutation causes increased absorption of iron despite normal dietary iron intake. C282Y and H63D are the most common mutations in the *HFE* gene. Because of the variable penetrance of clinical HH, end-organ damage is seen in less than 10% of patients who are homozygous for the C282Y mutation. The clinical phenotype is expressed in 24–43% of males and 1–19% of females [3]. Severe aplastic anemia (SAA) is an extremely rare disease [4]. It can be caused by many factors, both congenital and acquired (e.g. viruses, toxins, radiation, drugs) [5]. However, the most common etiology is idiopathic. The symptoms of SAA result from pancytopenia due to bone marrow aplasia or hypoplasia, and are varied [6].

A 12.5-year-old girl was admitted to the department for further diagnosis of thrombocytopenia. She had had symptoms of thrombocytopenia in the skin resolving spontaneously and nosebleeds for the preceding c.2–3 years. Blood count test showed decreased platelet (PLT) count (50.0–99.0 × 10^9/L) and mild leukopenia [white blood cells (WBC) 3.3–3.6 × 10^9/L]. Several bone marrow aspirations and trephine biopsies revealed bone marrow with suppressed granulocytes and megakaryocytes formation. The SAA criteria [7, 8] were confirmed three years after the first blood count test. Human leukocyte antigen (HLA) tests were performed in the family to find a sibling donor. The mother was a matched donor, but she had been suffering from breast cancer. For this reason, the first-choice treatment was immunosuppressive therapy (IST): rabbit anti-thymocyte globulin (ATG) and cyclosporin A [9]. Because of heavy menstrual and intermenstrual bleeding during IST, the girl underwent hormone therapy, which stopped the bleeding. Due to a partial response to treatment on day +90 and dependence on platelet transfusions, eltrombopag (a thrombopoetin agonist) was added to the therapy. Unfortunately, the patient became ill with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which clearly influenced the deterioration of the treatment response. An urgent search for an unrelated donor was initiated. Chelation therapy was used due to frequent red cell transfusions. In the 7th month of therapy, a hyperpigmentation of the skin was observed. A blood examination showed significantly increased iron concentration, ferritin, and transferrin saturation (Table I). A very dark, almost black, serum drew attention. Hemolysis was excluded. Abdominal magnetic resonance imaging (MRI) was performed (disseminated foci of iron overload in the liver and spleen). Genetic testing for HH confirmed mutation of the *HFE* gene

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Table I. Laboratory test results of ferritin, iron concentration and transferrin saturation at different timepoints of patient's treatment

Element (reference range)	Start of SAA treatment	Diagnosis of hemochromatosis	After 6 days of chelation therapy	After 30 days of chelation therapy
Ferritin [ng/mL] (reference: 4.4–207)	564.9	3,813.6	1,908	1,377.1
Iron concentration [µg/mL] (reference: 33–102)	625	1,060	841	384
Transferrin saturation [%] (reference: 15–50)	–	93	92	45

SAA — severe aplastic anemia

protein (homozygosity H63D). Intensive chelation consisting of daily subcutaneous infusions of deferoxamine was started. Clinical and laboratory improvement was achieved after a few days (Table I). Almost two months later, the girl underwent transplantation from an HLA 10/10 unrelated donor. She is currently in remission from SAA, but continues to receive chelating therapy (weekly subcutaneous deferoxamine infusions).

Hereditary/primary hemochromatosis affects one in every 150–220 people, but up to 19% of women have clinical manifestations. Typically, the symptoms of hemochromatosis occur in the 4th decade of life, but in women they can appear later, due to the 'protective' influence of menstruation, pregnancy and lactation, which compensate for excessive iron absorption [1–3]. Severe symptoms of congenital hemochromatosis at a young age, as in our patient, is extremely rare [10]. Frequent red cell transfusions, cessation of menstruation, and a genetic mutation cause earlier symptoms of hemochromatosis. The first line treatment for hemochromatosis is phlebotomy, but this is contraindicated in SAA. The second line treatment is chelation therapy, which our patient received with improvement and without complications. Genetic testing for HH in children with SAA appears to be indicated, especially in cases of massive iron overload. Further studies are required to make an informed recommendation.

Authors' contributions

All authors have made a substantial, direct and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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