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Iron Overload in Two Children after Allogeneic Hematopoietic SCT with Concomitant HFE p.s65cgene Mutation

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Abstract

Acute Myelomonoblastic Leukaemia (ANLL M4) and Aplastic Anemia (AA) are rare childhood diseases. Treatment of ANLL involves chemotherapy and radiotherapy, while immunosuppressive therapy is used in the treatment of AA. In selected cases, both disorders can be treated by performing a Hematopoietic Stem Cell Transplantation (HSCT). In addition, supportive medical care which includes antibiotics, antifungal drugs, packed red cells and platelets, is usually essential due to adverse effects caused by the therapy. Herein, we present a 15- year- old boy with ANLL M4 and a 17- year- old girl suffering from Severe Aplastic Anemia (SAA) for 3 and 4 years respectively, in whom iron overload was noted after they had undergone allogeneic HSCT (allo HSCT). On further diagnosis, co-existence of S65C HFE gene carriage was identified in both of them.

Keywords: Children; HFE mutation; Allogeneic hematopoietic

Case Presentation

ANLL M4 was diagnosed in the boy at the age of 12 by bone marrow examination after he presented with malaise, pyrexia, anemia and thrombocytopenia. He was treated in accordance to the Interim 2002 protocol, which was then followed by an allo HSCT from a matched sibling donor. Three years after the procedure, which had been further supplemented with multiple transfusions, a high ferritin concentration of 1050 ng/ml was noted. The remaining laboratory findings were within the normal range with iron concentration at 82 μg/dl, transferrin saturation 26% and Alanine Aminotransferase (ALAT) 29 U/l and Aspartate Aminotransferase (ASPAT) 27 U/l.

The girl was diagnosed with SAA at the age of 13 by bone marrow examination of samples obtained through trephine biopsy after she presented with pyrexia, pancytopenia and malaise. After undergoing two ineffective courses of immunoablative therapy (Bacigalupo protocol), she underwent allo HSCT from a matched unrelated donor. Prior to the allo HSCT, due to multiple transfusions, the patient received three months therapy of deferasirox (20 mg per kg) for the management of possible iron overload. We have no record of an elevated iron status during the period prior to and after the allo HSCT until 4 years after the procedure. Noted laboratory findings were as follows: iron concentration 219 μg/dl, ferritin concentration 5290 ng/ml, transferrin saturation 84%, and elevated aminotransferases: ALAT 111 U/l, AST 52 U/l. Concomitant infection was excluded in both patients using routine biochemical, bacteriological and viral tests. Genetic testing for HFE mutations (H63D S65C C282Y) were performed using Real-Time PCR and melting curve analyses which revealed heterozygotic S65C gene (the substitution of cysteine for serine at amino acid position 65) mutation in both cases. The patients are presently in complete remission and remain under clinical observation. The girl received 30 mg/kg of deferasirox, while the boy did not receive any treatment.

Hereditary hemochromatosis is an autosomal recessive disease which causes a defect in iron metabolism. It is characterized by enhanced intestinal absorption of dietary iron. The excessive accumulation of iron in organs generates reactive oxygen-mediated damage resulting in serious complications, which include liver cirrhosis, joint, and cardiac diseases in the fourth to fifth decades of life [1]. The most common form of this medical condition is autosomal recessive hemochromatosis type 1, arising due to missense mutations (C282Y, H63D, S65C) in the HFE gene localized on the short arm of chromosome 6 [2]. Homozygous C282Y mutations, which account for more than 80% of the cases, affect predominantly the Caucasian population in North Europe while H63D mutations have a higher prevalence in Southern Europe. Serine to cysteine mutations - S65C have been found only in 1.6-5.5% Caucasians [3,4]. The impact of C282Y carriage, homozygosity or heterozygosity of H63D and S65C mutations, and mixed heterozygotes (C282Y/H63D, C282Y/S65C) on iron overload still remains unknown [5-8].

Despite hemochromatosis type 1 being the most common type of congenital iron overload, other types of hemochromatosis (e.g. juvenile hemochromatosis type 2A, 2B, type 3, and type 4) should be considered in the differential diagnosis [8,9]. Juvenile hemochromatosis is a rare disorder of iron overload leading to cardiomyopathy, liver damage and endocrine dysfunctions before the age of 30. The above described patients do not demonstrate any such symptoms.Phlebotomy is a well-known procedure used in the treatment of iron overload in congenital hemochromatosis, while deferasirox which is well tolerated, is effective in reducing ferritin levels in transfusional iron overload patients with AA [10,11]. To date, it has been proven that children with HFE mutation present only with biochemical abnormalities, but precise population studies have not been done. The above mentioned patients received multiple transfusions which resulted in secondary hemochromatosis. Furthermore, the co-existence of hemochromatosis gene carriage might have resulted in a prolonged high iron status.

The above presented patients highlight the need for broad spectrum clinical thinking, adequate management, and the necessity of additional

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and precise studies on the cause of an increased iron profile in patients suffering from bone marrow diseases.

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