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Interferon alpha and pancytopenia in a thalassemic patient who treating for HCV; Cause of death

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ABSTRACT

Thalassemic patients are at high risk for developing hepatitis C virus (HCV) infection. Interferons (alpha, peg) are the treatment of choice for treating HCV infection. Pancytopenia though is an uncommon side effect of interferon therapy, may occur in thalassemics for the nature of the disease. Herein, we report an HCV-infected 23-year-old man with thalassemia intermedia referred to our clinic with pancytopenia following interferon therapy (alpha interferon ,3 injection / wk ; no Ribaverin). The drug was discontinued, but his condition got worse over time and he did not response to any supportive treatment such as Oxymethalone and GSCF and he died 17 months after his first presentation with the picture of pancytopenia and septicemia. Although pancytopenia is a rare side effect in non-thalassemic patients treated with interferon, in thalassemics, it is more frequent.

Implication for Health policy/practice/research/medical education:
Pancytopenia as one of the rare side effects in non-thalassemic patients treated with interferon should be considered by internists, infectious diseases specialists who want to treat this population.

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Introduction

Hepatitis C virus (HCV) infection is a major, worldwide health problem. It is estimated that from over 170-200 million people who are infected worldwide, Iran in located in a low endemic area of HCV infection (1). Thalassemia is a severe hereditary anemia which required to be treated as lifelong transfusion (2, 3). Up to 80% of the adult thalassemia patients are infected with HCV infection in the world (4). The prevalence rate in Iranian thalassemia patients varies between 2 and 32% while the pooled estimate of positive anti-HCV serostatus in Iran is 18% (5, 6). Prevalence of HCV in thalassemia patients varies among different places and depends on the patient's age: adults or pediatrics. In our center, the prevalence of HCV infection is about 27% (6, 7) .

Currently, interferon alpha (IFNα) is widely used as the first line of medications for treatment of chronic HCV infection in transfusion-dependent thalassaemic patients (8, 9). This therapy has many side effects especially in thalassemia patients due to the nature of their hemolytic diseases. The usual side effect of Interferon is flu-like symptoms such as headache, fever, chills, vomiting, nausea, muscle aches, pains, and fatigue which may relief by analgesic medications. Cytopenia is discussed as an uncommon or a rare side effect in normal population whether is more common in thalassemia patients (8). Although in our clinic which is an adult clinic center, we had eight patients with transient cytopenia who resolved with discontinuation the medication or adding the granulocyte-colony stimulating factor (G-CSF) for more complicated cases, here we want to report a case of thalassemia developed severe pancytopenia after starting the treatment regimen with alpha-interferon 2b (PDferon B, Pooyesh Darou, Tehran, Iran) for 3 MIU three times a week subcutaneously. Unfortunately, this case did not improve after discontinuation of the medication and supportive treatments and leads to patient's death.

Case Presentation

A 23-year-old man with thalassemia intermedia came to our clinic with thrombocytopenia. He was diagnosed since he was five months old; he had received regular blood transfusion until he reached five years when a hematologist had started hydroxy urea (HU) as an alternative treatment. He was relatively well with lower limit of hemoglobin and had infrequent transfusion till seven years before (2003). He went under regular transfusion

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again due to poor response to HU. He had no history of splenectomy and his spleen was intact. He was well without monthly blood transfusion and his laboratory data did not show leucopenia or thrombocytopenia but there was a minimal to moderate anemia which was related to transfusion treatment. Through a regular checkup (in 2005), he found to have HCV infection for which he received α-interferon 2b (PDferon B, Pooyesh Darou, Tehran, Iran) 3MIU, three times a week subcutaneously without ribavirin. After two months of the treatment (injection of 24 vial of interferon), he developed pancytopenia, especially thrombocytopenia and his gastroenterologist discontinued the treatment and to concult about hematologic disorders referred him to our clinic. His first hemoglobin electrophoresis (without transfusion) on May 2006 revealed HbA of 47.2%, HbF 50.4%, and HbA2 of 2.4%. His other laboratory findings included a WBC of 3700/mm3, Hgb 8.8 g/dL, platelet count of 116,000/mm3, SGOT of 29 IU/L, SGPT 61 IU/L, total billirubin of 0.6 mg/dL, alkaline phosphatase of 395 IU/L, and serum ferritin of 1152 ng/mL. He had a positive PCR test for HCV with a viral load of 1,480,000 copies/mL (genotype 1a). In the first visit, he was looking well, had no petechia, purpura, splenomegaly nor other physical abnormalities. So we decided to discontinue the medication. Blood transfusion had continued for five months when his CBC revealed a WBC of 3200/mm3, Hgb 6.8 g/dL, a platelet count 31,000/mm3. The patient was admitted to hospital. Bone marrow (BM) aspiration revealed a hyper cellular marrow, erythroid hyperplasia (M/E =1/1), mild increase in megakaryocytes, and mild dyshematopoietic changes. Other investigations were negative. He discharged home with broad-spectrum antibiotics, but his condition got worse. We started oxymethalone 50 mg/day. He was also received regular blood transfusion. His condition got even worse; he developed mucosal bleeding and herpes keratitis. His CBC then revealed a WBC of 1900/mm3, Hgb 7.6 g/dL, and platelet of 22,000/mm3. Therefore, he was also received platelet transfusion now and then. A daily injection of G-CSF was started for the patient. He got better—while his bleeding stopped his thrombocytopenia remained. After few weeks, his condition got worse again. Then, his CBC revealed a WBC of 1400/mm3, Hgb 5.9 g/dL, and a platelet count of 16,000/mm3. Another BM aspiration (four months after the first one) was similar to the first BM results except for the mild decrease in megakaryocyte counts. G-CSF and oxymethalone were continued. We started consultation for BM transplantation and finding a matched donor among his siblings. He took G-CSF for 90 days but his condition got worse. His CBC then revealed WBC of 3400/mm3, Hgb 7.9 g/dL, and a platelet count of 8000/ mm3. He developed sever episodes of mucosal bleeding and infections. Finally, he died 17 months after the first visit on September 2007, with the picture of pancytopenia and septicemia.

Discussion

In course of his treatment, we searched literatures to find the best treatment regimen for this patient. There were some reports about autoimmune hemolytic anemia in non-thalassemic patients with positive coombs test which had positive response to corticosteroids (10) but in our patient we had negative coombs test. Also there were some reports about complications such aplstic anemia (11) or pure red cell aplasia (12) after treatment for their HCV infection while in our patient we had hypercellular BM. One of the main treatment regimens for treating HCV infection in thalassemia patients is using interferon (with or without ribavirin) (13-16). However, some side effects such cytopenia and hemolysis are more frequent in thalassemia patients as a result of the nature of their hemolytic disease (17). First, owing to the matter of active bone marrow especially in intermediate thalassemia cases that do not perform regular transfusion, BM suppression may develop seriously. On the other hand thalassemia, as a disease, has some consequences like chronic anemia and iron overload related to repeated transfusion. Thus the second cause of cytopenia may be related to the usage of other treatment regimens which used meanwhile such as hydroxy urea or some medications for iron chelators, osteoporosis, cardiac disease, diabetes, or other endocrinopathies. Repeated transfusion and splenectomy which may occur in the course of the disease is responsible for almost 60% of all causes of spelenectomies among thalassemia patients(6) and are able to prone patients to other infectious. Consequently, concomitant infections are considered to be the third cause of cytopenia. There are more than 2700 adult thalassemic patients who refer for their general treatment to our clinic as the only referral center in Tehran. From those, 500 patients are considered ad fixed patients for all treatments aspects while the other come for hematological consultations and take their routine treatment including blood transfusion and iron chelation in the other centers. We already reported that HCV infection rate in our clinic was 27.8% (66% of them with PCR positive) (6, 7). We had eight other cases with pancytopenia who resolved with discontinuation the medications or using G-CSF for more complicated cases. One of the possible reasons of mortality in this case was related to the side effect of interferon and it may be the extreme domain of HCV treatment's consequence. As a conclusion of our experience in thalassemia patients, cytopenia should be considered as one of the most important side effects and regular CBC control should be performed and close observation, early supportive treatment or decision making for stop treatment must be done. Finally, treatment of thalassemic patients with HCV infection needs a team work; especially a close team work between hematologists and gastroenterologists.

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