Clinics in Oncology

Case Report
Published: 29 May, 2019

Beta Thalassaemia Trait as a Likely Link between Hyper-Reactive Malarial Splenomegaly and Myeloproliferative Disorders

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Abstract

The various Myeloproliferative Disorders (MPDs) have been reported in patients with beta thalassaemia, a disorder characterized by ineffective erythropoiesis and marrow stress. Hyperreactive Malarial Splenomegaly (HMS) associated with massive splenomegaly is a diagnosis of exclusion in malaria endemic region. Here, we describe a patient who was treated as HMS without response, but two decades later developed primary proliferative polycythaemia. Beta Thalassaemia Trait (BTT) is believed to be the link between HMS and MPD in the patient because of the low red cell indices and high red cell distribution width in the presence of normal iron store. The possibility of BTT should therefore be considered in cases with HMS, it could also be possible that a cohort of patients with BTT have the Janus Kinase 2 mutations which predispose them to developing MDS.

Keywords: Red cell indices; Red cell distribution width; Ineffective erythropoiesis; Janus Kinase; Stressed marrow

Introduction

Myeloproliferative Disorders (MPDs) is a term for describing a group of related disorders with the ability to transform to one another. This concept assumes that these disorders are an expression of excessive proliferation of any one of the cell lines, all of which are derived from a common haemopoietic cell. Primary Proliferative Polycythaemia (PPP) is an MPD with clinical stages which include the spent phase and postpolycythemic myeloid metaplasia; it could also terminate in acute leukemia or Chronic Myeloid Leukemia (CML). Hyperreactive Malarial Splenomegaly (HMS) is associated with massive splenomegaly as a result of exaggerated immune response to persistent exposure to malaria parasites. Though HMS is mostly a diagnosis of exclusion, it is thought to be a pre-malignant state with propensity to lymphoid malignancies [1,2]. It is therefore believed that HMS and lymphoproliferative disorders are indistinguishable [3]. There is also a genetic predisposition to HMS because of its association with HLA-DR2 haplotype and HLA heterozygosity [4,5]. Also, relatives of patients tend to have splenomegaly than is expected in the general population [6] Beta thalassaemia is a genetic disorder of hemoglobin synthesis which has ineffective erythropoiesis and marrow stress as an underlying pathology. Though there is no previous link between HMS and the MPDs nor BTT, the MPDs that have been reported in patients with beta thalassaemia include polycythaemia, [7-9] myelofibrosis, [10,11] and CML [12,13]. We describe here a patient with BTT who, over a period of about twenty years, after unsuccessful treatment for HMS developed features of polycythaemia, CML and myelofibrosis sequentially.

Case Summary

A 72-year-old woman was referred to Hematology for persistently high haematocrit (48% to 55%) and massive splenomegaly (22 cm below the coastal margin). Full blood count at presentation showed high haematocrit with low red cell indices (Table 1), a diagnosis of primary polycythaemia with background Beta Thalassaemia Trait (BTT) was made. The diagnosis of BTT was based on the low red cell indices and increased red cell distribution width (Table 1) and normal serum ferritin of 21 µg/ml. Twenty–two years before this, she had been seen in internal medicine on account of mild splenomegaly (4 cm) and massive ascites. The ascitic fluid was drained and the cytology showed

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Received Date: *11 May 2019*
Accepted Date: *24 May 2019*
Published Date: *29 May 2019*

Citation:
Kotila T, Odebiyi H, Lawal T, Adeoye O, Shonde-Adebola K. Beta Thalassaemia Trait as a Likely Link between Hyper-Reactive Malarial Splenomegaly and Myeloproliferative Disorders. Clin Oncol. 2019; 4: 1621.

Table 1: Hematological Parameters in the course of the illness.

Date	PCV	WBC (× 10^9/L)	Platelet (× 10^9/L)	MCH (pg)	MCV (fl)	RDW	Serum Ferritin (µg/L)
11/10/1995 First presentation in the hospital	37	5.4	ND	ND	ND	ND	ND
11/4/2013 First Presentation (Hematology)	52	7.7	84	21.9	72.3		21
28/09/2016 Pre-splenectomy assessment	44	10	89	17.6	57.2	24.3	
8/11/2016 Post-splenectomy	32	19.6	205	19.8	70.7	24.1	ND
2/3/2017 Commencement of Hydroxyurea	38	46.6	1056	17.8	62	27.3	ND
29/1/2018 At the diagnosis of CML/Myelofibrosis	46	106	108	16.5	57.3		37

Abbreviations: CV: Packed Cell Volume; WBC: White Blood Cell Count; MCH: Mean Corpuscular Hemoglobin; MCV: Mean Corpuscular Volume; RDW: Red Cell Distribution Width; ND: Not Done

mainly lymphocytes and reactive mesothelial cells, she was treated empirically for tuberculosis for six months with little improvement, after which a diagnosis of HMS was entertained. The splenic size continued to increase in size despite the use of malaria prophylaxis (Proguanil). Whilst receiving care in Hematology, she had several sessions of phlebotomy, and later had splenectomy on account of hypersplenism. The histology of the spleen was reported as 'spent phase of polycythaemia'. A bone marrow biopsy was done at the same time; this showed a normocellular marrow with focal areas of fibrosis. Post splenectomy, though the haematocrit was well controlled, the white cell and platelet counts continued to rise (Table 1). Seven months after splenectomy, she was diagnosed with type 2 diabetes mellitus and seven months after the diagnosis of diabetes, a provincial diagnosis of chronic myeloid leukemia was made based on hemogram but BCR-ABL was not detected. At the same time, a bone marrow biopsy showed myelofibrosis and JAK2V617F mutation was positive. She was commenced on hydroxyurea five months after splenectomy because of a rising platelet count. Two years after commencing hydroxyurea, her hemoglobin analysis by HPLC showed HbA 81.5%, HbA2 2.4% and HbF 16.1%.

Discussion

The likely diagnosis in this patient is an underlying beta thalassaemia trait with superimposed primary proliferative polycythaemia with gradual progression to post-polycythaemia myeloid metaplasia. The presence of JAK2 V617F mutation and the absence of BCR-ABL gene support the diagnosis of PPP. The low red cell indices in the presence of normal iron levels favors the diagnosis of alpha or beta thalassaemia, but a high red cell distribution width is in keeping with beta thalassaemia trait rather than alpha thalassaemia. The diagnosis of HMS when the patient was first seen is equivocal especially with the non-response to treatment with antimalarial. However, the diagnosis of HMS is not uncommonly difficult and especially so in malaria endemic areas due to chronic malaria and the high likelihood of reinfection [3,14]. Life-long or intermittent therapy is therefore recommended in endemic areas [3].

Acquired alpha and beta thalassaemia have been reported in the setting of myelodysplastic syndrome, with the former more commonly associated with the syndrome than the later [15]. An acquired thalassaemia could not be ruled out in this patient because the initial investigations before presentation to hematology did not include red cell indices. However, the progressive splenomegaly and normal haematocrit which predates the polycythaemia would not support an acquired thalassaemia but rather that the polycythaemia was a consequence of the thalassaemia. Also, there is no report in the literature of acquired thalassaemia in the setting of MPD; rather MPDs arise as a result of beta thalassaemia as suggested in this patient [7-13]. It is interesting to note that polycythaemia (haematocrit >52%), thrombocytosis (platelet of >1000 × 109/L), marrow fibrosis and leukocytosis and hemogram in keeping with CML were seen in this patient at different times in the course of the illness. This is in support of the interrelatedness of the MPDs. It could therefore be inferred that the ineffective erythropoiesis and associated marrow stress seen in beta thalassaemia predisposes patients with BTT to the MPDs.

The diagnosis of hyper-reactive malarial splenomegaly and the suspected background beta thalassaemia trait raises the possibility of BTT in cases of HMS. This is not just because HMS is mostly a diagnosis of exclusion but also because both disorders are mostly prevalent in the same geographical location. It would be worthwhile therefore to also consider BTT in patients suspected to have HMS. This case report also brings to the fore the difficulty in making the diagnosis of BTT, especially in regions where both alpha and beta thalassaemias coexist and BTT has not been proven previously at the molecular level. Though the low red cell indices are suggestive of alpha or beta thalassaemia (in the presence of normal iron stores), the normal HbA2 makes the diagnosis of BTT difficult. However, there are known BTT cases with normal HbA2 and red cell indices, more so, in our environment where alpha thalassaemia is equally common. The elevated RDW is in favor of BTT and makes the diagnosis more likely. Mild elevation of HbF is the norm in BTT, the moderate elevation of HbF seen in this patient could possibly be as a result of hydroxyurea therapy. The development of type 2 diabetes mellitus in the course of the disease also makes the diagnosis of BTT more likely. A draw back in the investigation of this patient is the inability to confirm the BTT at the molecular level and failure to document the premorbid hematological parameters of the patients.

Conclusion

This case report has brought up the need to include BTT in disorders to be considered before a diagnosis of HMS is made. There is also the need to consider the likelihood of MPDs arising from a bone marrow that is already distressed by BTT. Furthermore, it could be possible that a cohort of patients with BTT have the Janus Kinase 2 mutations which predispose them to developing MDS.

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