THROMBOTIC THROMBOCYTOPAENIC PURPURA IN A PATIENT PRESENTING WITH SICKLE CELL –HEMOGLOBIN S DISEASE VASO-OCCLUSIVE CRISES AND ACUTE CHEST SYNDROME

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ABSTRACT
The association of sickle cell disease (SCA) vaso-occlusive crises and Thrombotic thrombocytopaenic purpura (TTP) has been rarely described. Here we report a case of sickle cell – haemoglobin S disease (HbSS) in which a patient presented with painful vaso-occlusive crises and acute chest syndrome and TTP which was a diagnostic challenge. We also conducted a Medline search to review reported cases previously.

Key Words: Sickle cell disease, Thrombotic thrombocytopenic purpura, vaso-occlusive crises, Acute chest syndrome.

INTRODUCTION

Thrombotic thrombocytopaenic purpura (TTP) is a rare multi – systemic disorder of small vessels that is associated with deficiency of the von Willebrand factor – cleaving protease ADAMTS,[13] which promote platelet adhesion and aggregation, leading to multiple platelet thrombi in the microcirculation.[1,2] It is classically characterised by a pentad of fever, neurological abnormalities, renal abnormalities, microangiopathic haemolytic anaemia, and thrombocytopaenia.[3]

Sickle cell disease (SCD) is an autosomal recessive genetic disorder characterised by the Hb S variant of the β-globin gene.[4] The most common clinical problem is the painful vaso-occlusive crisis (VOC) resulting as a consequence of intravascular sickling in capillaries and small vessels. Morbidity in SCD arises primarily from acute chest syndrome, cerebrovascular accidents, and splenic and renal dysfunction.[5]

There are several causes of thrombocytopaenia in SCA including platelet consumption and sequestration in multiple organ infarcted sites accompanying sever vaso-occlusive crisis, disseminated intravascular coagulation due to infections or fat embolism.[6,7]

Here we present a case of SCD presenting with painful vaso-occlusive crises, acute chest syndrome and thrombocytopaenia secondary to TTP as supported by peripheral blood film and low ADAMTS[13] activity and response to plasma exchange therapy.

CASE REPORT

Thirty year old male Saudi patient with history of mild sickle cell disease (SCD) since childhood, presented for the first time with history of fever, body aches (chest, back and lower limbs, headache) for one week and respiratory distress and confusion for one day prior to admission. There was no previous history of vaso-occlusive crises, hospital admissions or blood transfusion. He denied any history of medications intake except acetaminophen tablets at onset of his illness. Family History revealed that his father and mother are first degree relative with 11 siblings and one of his brothers had SCD with frequent hospital admission. On initial examination, he was confused, pale and appeared to be in respiratory distress. His Pulse rate was 140 / minute, regular in rhythm, and blood pressure was 180 / 90 mmHg. His respiratory rate was 28 per minute and Oxygen saturation (SPO2) was 84% on room air. He was febrile with an oral temperature 39°C. There was no jaundice, lymphadenopathy, skin rash or lower limb oedema and jugular venous pressure was normal.

Chest examination revealed bilateral coarse inspiratory and expiratory crepitation all over lung fields with bilateral rhonchi. Neurological examination showed that he was confused with a Glasgow coma scale of 13 / 15. There were no focal neurological signs, papillodema or signs of meningeal irritation. Abdominal examination revealed: hepatosplenomegaly. Rest of the systemic examination was unremarkable.

His initial laboratory results showed WBC of 6.9 K/ul, haemoglobin of 7.2 g/dl, platelet count of 72,000 k/ul and reticulocyte count was 2.4%. Partial thromboplastin time (PTT) was 46.9 seconds against control 34.9 seconds, prothrombin time (PT) was 14.8 seconds, and international normalised ratio (INR) was 1.6. Serum lactate dehydrogenase (LDH) was 3750 μ/l. Total bilirubin was 19 μmol/ and alanine trans-aminase (ALT) was 155 μ/l, Sickling test was positive. Erythrocyte sedimentation rate (ESR)

Table 1: *Laboratory Results and Vital Data in ICU.*

	Day 1	*Day 3*	*Day 7*	*Day 10*	*Day 13*	*Day 16*	*Day 19*	*Day 22*	*Day 25*
Haemoglobin (g/L)	7.2	8.6	5.3	8.4	7.4	8	7.6	6.5	7.7
Platelets ($\times 10^9$/L)	71.9	42	65.5	36	37.3	56	94	139	184
LDH (U/L)	3935	6996	3344	2495	1617	1418	1176	902	846
CPK (U/L)	1089	894	7942	849	110	49	100	94	29
Urea (mmol/L)	9.2	5.2	6.9	11.8	8	9.9	8.2	8.4	5.3
Creatinine (µmol/L)	84	69	80	90	92	86	80	74	80
Fibrinogen (µmol/L)	490	499	692	589	613	565	463	475	421
PTT (seconds)	46.9/34.9	37.8/39.2	41.3/36.3	44.1/36.3	41.4/36.4	37.9/32.3	36.6/30.0	39.0/30.0	32.6/35.7
INR	1.6	1.1	1.2	1.2	1.2	1.2	1.1	1.2	1.0
BP (mmHg)	178/103	201/160	133/78	129/70	137/70	136/66	123/63	126/71	129/71
Temp (C)	37.1	39.1	39.2	38.4	38.2	39	38.9	38	37.6
Pulse Rate (/ minute)	140	152	129	109	111	107	114	112	102

20 mm/ 1st hr. Serum urea was 9.2 µmol/L and serum creatinine was 84 µmol/L (table 1). Peripheral blood film showed thrombocytopaenia with many fragmented RBCs. Serum fibrinogen level was 490 µmol/L, (Normal value: 470 – 530 µmol/L). D dimmer was negative. Haemoglobin electrophoresis showed: Hb A 76.3%. Hb S 19.9% and Hb A2 3.3%.

Plain chest X Ray (CXR) showed bilateral non-homogenous infiltrates in the lower zones. Computed tomography of the brain (CT) was normal. Abdominal ultasonographic examination (U/S) revealed hepatosplenomegaly. Serology for human immunodeficiency viruses (HIV), Hepatits B and C and dengue fever viruses and Direct Comb's test was negative. Blood films for Malaria were also negative. Cerebrospinal fluid examination was within normal limits. Antinuclear antibody, anti-double strand DNA was negative.

The patient was admitted to intensive care unit (ICU) with Presumptive diagnosis of SCA complicated by vaso-occlusive crises and acute chest syndrome with possible septicaemia based on the presence of hypoxia, fever, CXR findings and prolonged PTT and PT. He was incubated and mechanical ventilated because of uncorrectable hypoxia and decreased mental status level. He was started on IV antibiotics and exchange transfusion of red blood cells. He did not improve and remained febrile. His platelets decreased to 42,000. Review of peripheral blood film showed fragmented RBCs and schistocytes with progressively increasing LDH level. ADAMTS[13] factor activity was reported as 62% of expected value, indicating a severe deficiency. Meanwhile blood, urine and tracheal swab culture were reported as negative.

He was diagnosed as having TTP & started on plasma pharesis. Five sessions of plasma exchanges were done in one week. The patient was initially difficult to be weaned off ventilator, but was eventually taken off ventilator after 20 days of ICU admission. Patient clinically improved with electrophoreses and became fully conscious. His bilirubin and LDH returned to normal range and platelet count was increased to 202,000 before being discharged.

DISCUSSION

TTP is characterised by a pentad of fever, neurological abnormalities, renal abnormalities, microangiopathic haemolytic anaemia, and thrombocytopaenia. Up to 40% of patients with TTP present with the classic disease and the clinical diagnosis may be made based on the presence of thrombocytopaenia, schistocytes, and an elevated serum lactate dehydrogenase (LDH) in the absence of obvious causes[1-3] TTP is associated with an acquired or an inherited

deficiency of the von Willebrand factor – cleaving protease ADAMTS 13.[8] Decreased von Willebrand factor cleaving protease activity (VWFCP, ADAMTS[13]) leads to persistence of unusually large multimers of von Willebrand factor (vWF) that bind to platelets, causing platelet aggregates, and multiple platelet thrombi in many organs. The presence of thrombi in the vasculature leads to red blood cell destruction and platelet consumption causing microangiopathic haemolysis, and thrombocytopaenia.[9]

The ULVWF – cleaving protease is inhibited by the production of auto-antibodies in acquired idiopathic TTP, and ADAMTS[13] gene multiple mutations in familial TTP, causing inactivity or decreased activity of ADAMTS – 13.[8,9] TTP may be idiopathic (primary TTP) or secondary to drugs, infections, malignancies, autoimmune disorders, pregnancy and bone marrow transplantation.[10]

SCD is a family of haemoglobin disorders in which the sickle β-globin gene (βS) is inherited. The most common type is homozygous sickle cell anaemia (heamoglobin SS); while other clinically significant conditions include compound heterozygote states haemoglobin SC or β-thalasemia. Although mortality in SCA has improved, it is still a major public health concern and associated with significant morbidity and mortality. The ethnic groups most commonly affected are African – Americans, Arabs, Greeks, Italians, and Indians.[4,11]

The most common clinical problem in SCD is the painful vaso-occlusive crisis resulting from blockage of small vessels. Factors important in the pathophysiology of sickling include Polymerisation of sickle haemoglobin, abnormalities in vascular endothelium, coagulation, white cells, and damage to the membranes of red cells (1D). This results in the pathognomonic change in the shape of erythrocytes to the sickle shape which is stiff, deforms poorly, and can adhere to the vascular endothelium. The frequency of crisis, degree of anaemia, and the organ systems involved vary considerably from individual to individual.[12] Morbidity in sickle cell disease arises Primarily from acute chest syndrome, cerebrovascular accidents, and splenic and renal dysfunction.[13] Hb SS (sickle cell anaemia) or Hb S/β-0-thalassemia had higher frequency of acute chest syndrome or painful crises, than individuals and Hb S/β ± thalassemia or Hb SC.[14] However, individuals with Hb SC have increased risk for thromboembolic complications, retinopathy, and renal papillary necrosis when compared with individuals with Hb SS.[15] Additionally, the rate of cerebrovascular complications is highest among individuals with the Hb SS genotype compared with the other three genotypes.[16] Individuals with Hb SS have a lower survival rate than that of individuals with Hb SC.[17]

Acute chest syndrome is the most common form of organ failure affecting about 40 percent of all people with sickle cell anaemia. Its cardinal features are fever, pleuritic chest pain, referred abdominal pain, cough, lung infiltrates, and hypoxia. Its management should be aggressive, including adequate ventilation, multiple anti-bacterials and simple or exchange blood transfusion depending on its severity.[5]

The association of sickle cell S disease presenting with veno-occulusive disease and thrombotic thrombocytopaenic purpura is extremely rare and only a few patients have been reported previously. A Medline literature search revealed that only a few cases have been reported previously. However no case has been reported from the Middle East.

Venkata, et al, in 2010 reported a case of Thrombotic thrombocytopaenic purpura and multiorgan system failure in a child with sickle cell – haemoglobin C disease.[18] Shelat in April 2010 described a case of acute chest syndrome in a sickle – cell patient (hemoglobin SS) who also developed signs and symptoms of thrombotic thrombocytopaenic purpura, including thrombocytopaenia and haemolysis (anaemia, elevated lactate dehydrogenase, presence of schistocytes, dark – coloured plasma, and elevations in nucleated red blood cells).[19] In 2003, Lee, et al, reported a patient with life – threatening thrombotic thrombocytopaenic purpura (TTP) in a patient with sickle cell – hemoglobin C disease.[20] Chehal, in 2002 presented a case of severe multi-organ failure in a patient with sickle thalassemia, who had clinical and laboratory features consistent with thrombotic thrombocytopaenic purpura (TTP).[21] Meade and co-workers in 1999 also described a case of Thrombotic thrombocytopaenic purpura in a patient with sickle cell crisis.[22] Chinowsky MS. In 1994 described a case of thrombotic thrombocytopenic purpura (TTP) complicated a vaso-occlusive crisis in a patient with sickle cell – haemoglobin (HbSC) disease. Sustained, severe thrombocytopenia and the patient's failure to respond clinically to RBC exchange transfusion helped to identify the proper diagnosis that led to effective therapy.[23] Prichard, in 1988 also published first case report of thrombotic thrombocytopaenic purpura in a patient presenting with abdominal pain and was initially misdiagnosed as having sickle cell crisis.[24]

Our patient was known to have sickle cell – haemoglobin S disease (HbSS) who presented with painful vasoocclusive crises and acute chest syndrome and was initially diagnosed as having septicaemia. Subsequent examination of peripheral blood film led to the correct diagnosis. Patient responded well to plasma exchange treatment and was able to be discharged home in a stable condition.

A related disorder, haemolytic – uraemic syndrome (HUS), is clinically similar to TTP but is more common in children, who have more severe renal disease and less severe neurological symptoms. The

coagulation studies typically are normal or mildly abnormal in TTP / HUS in comparison to disseminated intravascular coagulation (DIC), in which most of these coagulation parameters are abnormal.

The mainstay of treatment in acute TTP is plasma exchange (PE) with fresh frozen plasma. In the seventies improved outcome was documented in patients treated with plasmapheresis.[25] Mortality rates have fallen from above 90% due to multi – organ failure to 10 – 20% since the institution of PE.[26] It works by removing ultra large von Willebrand factor (vWF) multimers and inhibitory antibody and by supplying normal protease. Plasma exchange can induce remissions in approximately 80% of patients with idiopathic TTP. A reduced level of consciousness has been identified as a poor prognostic factor in TTP with an overall survival of 54%.[27] Corticosteroids are commonly given to patients with TTP, although there is scanty evidence of their efficacy.[28] However, relapses are not uncommon, occurring in 13 – 36% of patients. The duration of treatment to achieve complete remission is highly variable. It is empirically recommended that daily plasma exchanges should continue for a minimum of two days after complete remission is obtained.[29] In patients who respond to plasma exchange, the mean time to resolution of neurologic changes is approximately 3 days, to a normal LDH is 5 days, to a normal platelet count is 10 days, and to normal renal function is 15 day.[25] Half of the patients in whom plasma exchange is ineffective usually respond to splenectomy or immunosuppression.[30] Refractory cases can be treated by cyclosporine or vincristine.[31] Recently many case reports have been published about the use of monoclenal antibodies, especially Rituximab for the successful treatment of TTP.[28,32]

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