CASE REPORT

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Human Parvovirus B19 in Children with Sickle Cell Disease; Poking the Spleen

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ABSTRACT

Parvovirus is a known culprit of transient red cell aplasia (TRCA) in children with sickle cell disease (SCD). Few reports have previously described the association between the virus and acute splenic sequestration crisis (ASSC) in the same patient. Here, we are shedding light on such a potentially serious combination by reporting two cases of siblings with SCD complicated with concurrent ASSC and TRCA and presenting a review of the relevant literature.

Parvovirus B19 (HPV B19) is a small non-enveloped single stranded DNA virus. It is highly infectious and spreads mainly through respiratory droplets.[1] Between 30–67% of patients with sickle cell disease (SCD) get infected causing transient red cell aplasia (TRCA), otherwise called aplastic crisis.[2] Moreover, HPV B19 is implicated as an etiological factor for complications escorting TRCA in patients with SCD. These complications include acute chest syndrome (ACS), hepatic sequestration, stroke, acute painful crisis, nephrotic syndrome, and acute splenic sequestration crisis (ASSC).[2] Concomitant TRCA and ASSC usually manifest in profound anemia necessitating hospital admission and blood transfusion.[3–5]

CASE REPORTS

Both patients presented to the pediatric hematology department, Sultan Qaboos University Hospital in 2014. ASSC and TRCA were diagnosed according to the Cooperative Study of Sickle Cell Disease (CSSCD) definitions:

ASSC is defined as: 1) decrease in the hemoglobin or hematocrit of ≥ 20% from baseline; 2) evidence of increased erythropoiesis such as a markedly elevated reticulocyte count; 3) an acutely enlarging spleen (≥ 2 cm).[6]

TRCA is defined as: 1) decrease in hemoglobin ≥ 20% from baseline; 2) reticulocytopenia (absolute reticulocyte count < 50 000/uL) or reticulocyte count, which is disproportionately low with respect to the hemoglobin level.[6]

Case one

A two-year-old male with homozygous sickle cell disease (Hb SS) presented with severe pallor and lethargy preceded by a one-week history of low-grade fever, cough, and coryza. His investigations showed anemia with reticulocytopenia. He received multiple packed red blood cell (PRBC) transfusions but had a poor increment in his hemoglobin level. On day three of admission, he suddenly became pale and developed enlargement of the spleen. He was given a PRBC transfusion. His general condition gradually improved with resolution of fever.

Case two

A three-year-old male (the brother of case one) with homozygous Hb SS presented with history of fever, cough, and coryza for three days, which started one day after his younger sibling became symptomatic. On presentation, the child was pale with marked splenomegaly. His investigations revealed anemia with reticulocytopenia. He received a PRBC transfusion and was discharged.

After two days, the child became febrile with increasing pallor and severe pain in his back and limbs. Over the span of a few hours, he deteriorated with worsening of fever and pain and developed an ACS as evidenced by oxygen desaturation and new

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Table 1: Clinical parameters of 11 patients with SCD with concomitant ASSC and TRCA.

Clincal parameters	Case no.										
	1	2	3	4	5	6	7	8	9	10	11
Genotype	Hb SS	Hb SS	Hb SS	Hb SS	Hb SS	Hb SC	Hb SC	Hb SC	Hb SC	Hb SS	Hb SS
Age	22m	8y	10y	4m	3y	8y	15y	11y	6y	22m	3y
Gender	M	F	F	M	F	F	F	M	M	M	M
On prsentation											
Spleen size, cm#	5	10	7	7	6	4	7	10	10	6	11
Hb, g/dL	1.6	2.0	4.5	1.1	3.7	4.3	3.9	3.9	4.2	2.7	7.1
Reticulocytes	0.1	0.6	0.3	NA	0.1	0.2	0.1	0.4	0.4	0.8	0.2
Platelets, $\times 10^9$/L	72	97	125	72	48	108	40	85	100	104	64
Baseline											
Spleen size, cm	1	2	3	2	NA	NA	NA	NA	NA	2	4
Hb, g/dL	10.0	10.7	10.0	NA	9.2	NA	11.4	10.3	10.4	8.0	10.0
Parvovirus IgM	+ve	+ve	+ve	-ve*	+ve	+ve	+ve	+ve	+ve	+ve	+ve
Complications	Coma, shock	None	-	Coma, shock death	None	Painful crisis	MODS	-	None	None	None
References	3	-	-	4	5	-	-	-	-	Case 1	Case 2

*SCD: sickle cell disease; ASSC: acute splenic sequestration crisis; TRCA: transient red cell aplasia; M: male; F: female; NA: not available; Hb: hemoglobin; IgM: immunoglobulin M; MODS: multiple organ dysfunction syndrome. *Evidence of infection was demonstrated by parvovirus B19 inclusion bodies found in the spleen at autopsy. #Clinical palpable spleen below the left costal margin along the midclavicular line.*

infiltrate in the chest X-ray. He was managed with PRBC transfusion. His clinical condition slowly improved over the period of two weeks.

Both patients had positive parvovirus polymerase chain reaction (PCR) with a viral load of 6.4 × 10^5 copies/mL and 5.9 ×10^5 copies/mL for cases one and two, respectively. There was no history of ASSC, and they did not suffer another attack in a follow-up period of six months. Both children were running a mild course of the disease with infrequent admissions due to acute painful crises. Therefore, hydroxyurea treatment was not deemed indicated.

Including our two patients with SCD with concomitant TRCA and ASSC, a total of 11 patients with thoroughly described clinical parameters have been reported in the literature.

DISCUSSION

We report two cases of parvovirus infection in children with SCD presenting with concomitant TRCA and ASSC. Among the 11 cases illustrated in Table 1, two were Hb SB-thal and the rest were equally divided among Hb SS and Hb SC genotypes. Considering the overall higher incidence of Hb SS compared to Hb SC, the latter seems to be the commonest affected phenotype.[7] This finding is attributed to the relative preservation of splenic function into adulthood in patients with the Hb SC genotype and the predilection of HPV B19 infection for older children.[8,9] Such questionable hyposplenic status in patients with Hb SC genotype casts doubts regarding the need for prophylactic penicillin in early childhood.[10]

There was no age preference among the reported cases. This could be explained by the different prevalence of TRCA and ASSC during childhood. While ASSC commonly affects preschool children, TRCA is more common in older children.[11] Amongst the 11 cases reported, only one case was on hydroxyurea, which could have contributed to both their susceptibility to parvovirus infection and the ensuing reticulocytopenia.[12] It is also noteworthy that all the 11 cases had high baseline hemoglobin ≥ 8.0 g/dL levels denoting that they had no underlying chronic hyperhemolysis.

Previous reports suggested that infection could induce ASSC.[13] The autopsy of the single mortality reported demonstrated parvovirus inclusion bodies in the spleen, which might indicate that ASSC is a direct effect of the virus on the spleen rather than an immune-mediated process.[8] Moreover, nine out of the 11 patients had no history of previous ASSC, underscoring parvovirus as a

powerful stimulus for ASSC bearing in mind that a history of ASSC makes the spleen vulnerable for such a complication.[13]

In our two cases, the chronology of events described suggests that TRCA might have ensued before the ASSC. Additionally, one of these two cases developed ACS. Such a case when summed with three other reported cases in the literature, two with multiorgan dysfunction syndrome and one death, demonstrate the possible gravity of prognosis of such a combined pathology.[4,5]

A large epidemiological study was carried out between November 1996 and December 2001, which screened 633 SCD patients for HPV B19 infection. Among the 68 patients who developed TRCA episodes during the study period, 13 had evidence of concomitant TRCA and ASSC. Of these, four had the Hb SS genotype, seven were Hb SC, and two were Hb SB-thal. The study showed that children acutely infected with HPV B19 were more likely to develop fever, painful crises, and ASSC than uninfected children.[2] Consistent with other reports, the study also revealed that patients with SCD SC had more ASSC events compared with the SCD SS group.[3–5] Unfortunately, clinical and laboratory data specific to the group of concurrent ASSC and TRCA were not segregated from the rest of the study group. The clinical parameters of the remaining nine patients along with our two reported cases are given in Table 1.

How parvovirus causes TRCA in children with SCD has been the subject of intensive studies. The virus targets erythroid progenitor cells with the blood group P antigen serving as the receptor for the virus. Poor P antigen expression by megakaryocytes and white blood cells explains the rare incidence of thrombocytopenia or leucopenia in HPV B19 infection.[14] The infected erythroid precursors suffer arrest of maturation beyond the normoblast stage leading to the formation of giant pronormoblasts in the bone marrow and peripheral reticulocytopenia.[15,16] Such reticulocytopenia tend to be transient and clinically silent in healthy persons.[17] On the other hand, this transient reticulocytopenia augments the existing anemia in patients with a shortened erythrocyte life span, such as SCD, resulting in a further drop in hemoglobin and symptomatic anemia.[18] The concurrence of ASSC further complicates the picture. While hemoglobin in patients affected solely by TRCA is dependent upon surviving mature red blood cells, these get pooled inside the spleen and escalate the ongoing hemoglobin drop in patients with combined pathologies. The development of ASSC turns the clinical picture into an emergency situation. In contrast to TRCA, where anemia develops over days, the drop of hemoglobin in ASSC happens in a matter of hours.[19] The coexistent peripheral destruction along with central aplasia of the erythroid cell line might result in serious anemia. It is readily conceivable that ASSC and TRCA can form a deadly combination bearing in mind that ASSC alone can induce circulatory collapse.[20] The exact pathophysiology of ASSC is unknown. Fever or infection may trigger or augment red cell trapping in the splenic red pulp.[21] None of the previous reports of concomitant ASSC and TRCA have postulated a clear mechanism.

CONCLUSION

Parvovirus infection presenting with concomitant TRCA and ASSC is an uncommon but potentially serious complication in children with SCD. Therefore, we strongly recommend that patients who present with TRCA to be closely observed for evolving ASSC. Any child with SCD who presents with a sudden drop in hemoglobin, reticulocytopenia, and an acute enlargement of spleen should be managed as a potentially life-threatening emergency.

Disclosure
The authors declared no conflicts of interest.

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