Published in final edited form as:

Pediatr Blood Cancer. 2008 April ; 50(4): 861–864. doi:10.1002/pbc.21426.

Transient Parvovirus-Associated Hypoplasia of Multiple Peripheral Blood Cell Lines in Children With Chronic Hemolytic Anemia

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Abstract

Human parvovirus infection typically causes transient red blood cell aplasia. However, contrary to common perceptions, the hematopathologic effects of parvovirus infection are not always limited to the erythroid lineage. We describe here a consecutive series of 17 patients with chronic hemolytic anemia hospitalized for aplastic crisis, of whom 13 had transient hypoplasia of multiple peripheral blood cell lines.

Keywords

aplastic crisis; hereditary spherocytosis; neutropenia; pancytopenia; parvovirus; thalassemia; thrombocytopenia

INTRODUCTION

Infection with human parvovirus causes transient erythroblastopenia and reticulocytopenia in the healthy host, but not anemia because of the long lifespan of mature red blood cells [1,2]. However, in patients who have a chronic hemolytic anemia, which shortens red blood cell survival, the erythroblastopenia and reticulocytopenia may result in a dramatic decrease in hemoglobin concentration [3–5]. This episode of transient and often severe anemia is called the aplastic crisis. Spontaneous recovery begins about 1 week after the onset of reticulocytopenia due to antibody-mediated clearance of the virus. The need for red blood cell transfusion depends on the severity of anemia.

Parvovirus infection of immunocompetent subjects classically produces an isolated, or pure, red blood cell aplasia. In the immunocompromised, parvovirus can also affect other hematopoietic lineages and cause multiple peripheral blood cytopenias. Parvovirus infection in patients who have primary immunodeficiencies may be chronic and suppress more than one hematopoietic lineage [6–8]. Similarly, parvovirus-associated pancytopenia has been

reported in HIV-infected individuals and patients receiving intensive anti-neoplastic chemotherapy [9,10]. Parvovirus infection has also been reported to cause pancytopenia in otherwise healthy, immunocompetent individuals [11–13]. However, there is a disconnect between this evidence and many hematologists' perceptions of the hematologic effects of parvovirus. To help correct the misconception that parvovirus causes only a pure red blood cell aplasia in patients with hemolytic anemia, we report a consecutive series of patients with hereditary spherocytosis or thalassemia who had multiple transient parvovirus-related cytopenias.

CASE REPORTS

Between 2001 and 2005, nine children known to have congenital hemolytic anemia presented to our tertiary care center in Dallas, Texas with a febrile illness, signs and symptoms of increasingly severe anemia, and hypoplasia of multiple peripheral blood cell lines. These nine patients were identified for inclusion in this manuscript by recall of treating physicians who were intrigued by their clinical observations. Eight of these children were known to have hereditary spherocytosis (HS), and one child had hemoglobin E- β^0 -thalassemia. Upon presentation, all had marked anemia well below their baseline hemoglobin (Hgb) concentrations and absolute reticulocytopenia. Each also had leukopenia, thrombocytopenia, or both. Because these children had both splenomegaly and hypoplasia of multiple peripheral blood cell lines, some of their treating physicians initially considered the possibility of acute leukemia. The final diagnosis in all cases was a parvovirus-related aplastic crisis.

The clinical and laboratory features of these nine children at baseline and during their aplastic crisis are shown in Table I. Parvovirus infection was documented by polymerase chain reaction (PCR) testing of peripheral blood at the time of the acute anemic episode, except in one child (patient G) whose sibling with HS (patient D) had a parvovirus-related aplastic crisis 1 week previously. The spleen sizes, determined by physicians' examinations, were acutely smaller than baseline in three patients (E, H, and I) and larger in the remaining six. Patient A had anemia and thrombocytopenia, while the others had differing degrees of pancytopenia. No patient had neutropenia or thrombocytopenia before the aplastic crisis. All but one received one or more transfusions of packed red blood cells (10–40 ml/kg). None had a bone marrow examination performed. Complete blood counts of all patients returned to baseline within 2–4 weeks of presentation.

Given these clinical observations in nine selected cases, and to determine the relative frequency of isolated anemia versus hypoplasia of multiple peripheral blood cell lines during aplastic crisis, we reviewed all hospitalizations in our center during the same interval (2001–2005) for aplastic crisis in HS patients. We identified eight additional patients whose clinical and laboratory features are also shown in Table I. No patient had neutropenia or thrombocytopenia before the aplastic crisis. All were known to have HS upon presentation, except patient O, whose diagnosis was elucidated by a thorough history, physical examination, and inspection of the peripheral smear. Only patients K, P, and Q had laboratory evidence of parvovirus infection; the others (J, L, M, N, and O) had no laboratory testing for parvovirus, and parvovirus infection was inferred from the clinical scenario.

Among these eight patients, four had isolated severe anemia, two had anemia and either leukopenia or thrombocytopenia, and two had pancytopenia. Considering only the patients without parvovirus testing (J, L, M, N, and O), four had isolated anemia and one had pancytopenia. None of the three patients with laboratory documentation of parvovirus infection (K, P, and Q) had isolated anemia.

DISCUSSION

Patients who have chronic hemolytic anemia, such as HS, classically develop transient red cell aplasia during parvovirus infection (1–5). In this series of hospitalized patients with aplastic crisis, however, only 23% (4 of 17) had isolated anemia. The majority had either hypoplasia of two peripheral blood cell lines (3 of 17) or pancytopenia (10 of 17). Considering only the patients in this series who had definitive evidence of parvovirus infections, none had isolated severe anemia. Our findings partly reflect the analysis of a biased population of severely affected patients who were hospitalized for aplastic crisis and a testing or confirmation bias where evidence of parvovirus infection was sought only for atypical presentations. Nevertheless, our report highlights the effects of human parvovirus that many hematologists may not fully appreciate.

Parvovirus infection is known to cause pancytopenia in the immunocompetent host. For example, Anderson et al. [11] demonstrated that intranasal inoculation of healthy subjects with parvovirus led to mild anemia with reticulocytopenia, neutropenia, and thrombocytopenia. Pancytopenia from community-acquired parvovirus infection in a child with no known underlying disease has also been reported [14]. In search of a mechanism of parvovirus-associated pancytopenia in a patient with HS, Hanada et al. [15] showed that the incubation of bone marrow with parvovirus-containing serum significantly inhibits erythroid (CFU-E), myeloid (CFU-GM), and megakaryocytic (CFU-Mgk) growth. The inhibition of the erythroid precursors was most pronounced [15], and the erythroid P antigen (globoside), the site of viral entry into erythroid precursors, certainly mediates this preferential toxicity [16].

The exact mechanisms of parvovirus-associated pancytopenia are not known in the patients reported here, but possible explanations include viral inhibition of megakaryopoiesis [17] and myelopoiesis [15], hypersplenism, and hemophagocytosis. Why viral inhibition of non-erythroid lineages would differ dramatically among patients is unclear. Increased splenomegaly during an aplastic crisis could produce concomitant thrombocytopenia and neutropenia because of hypersplenism. However, there was no clear association here between the degree of splenomegaly and the severity of the cytopenias. Indeed, some of the patients who had the most severe pancytopenia did not have an acute increase in spleen size. Given the patients' baseline blood counts, we also infer that chronic hypersplenism did not cause the multiple cytopenias. Finally, parvovirus is a reported trigger of infection-associated hemophagocytic syndrome [18]. Perhaps some of these children had a self-limited hemophagocytic process.

Patients with sickle cell disease (SCD) are also susceptible to parvovirus-related transient aplastic crisis, but we did not make our initial clinical observations in this patient

population. Smith-Whitley et al. [19] reported that 18% and 27% of SCD patients with parvovirus-related aplastic crisis had neutropenia or thrombocytopenia, respectively. We found, in contrast, that 65% of patients with HS or thalassemia had leukopenia or neutropenia and 71% had thrombocytopenia. We speculate that the steady-state leukocytosis and thrombocytosis of patients with SCD might decrease the effect of parvovirus on non-erythroid cell lines in peripheral blood.

Parvovirus infection in individuals who have a shortened red blood cell lifespan causes either the classical aplastic crisis or transient hypoplasia of multiple peripheral blood cell lines. Neutropenia and thrombocytopenia seem to be more common features of a parvovirus infection in patients with HS compared to those with SCD. Because parvovirus-related pancytopenia may arouse a clinical suspicion of aplastic anemia or acute leukemia, physicians' increased awareness of the atypical, yet transient, hematologic effects of human parvovirus may prevent unnecessary and invasive diagnostic procedures. This is especially important, because an aplastic crisis may be the presenting feature of an unrecognized congenital hemolytic anemia.

ACKNOWLEDGMENT

We thank Dr. George R. Buchanan for assistance in reviewing this manuscript and James W. Sargent for review of selected medical records. This Research was supported by NRSA Training Grant 5 T32-CA09640 from the National Cancer Institute (B.E.C.).

Abbreviations

ANC	absolute neutrophil count
Eβ⁰	hemoglobin E- β ⁰ -thalassemia
Hgb	hemoglobin
HIV	human immunodeficiency virus
HS	hereditary spherocytosis
PCR	polymerase chain reaction
Retic	reticulocyte count
WBC	total white blood cell count

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TABLE I

Patient Characteristics and Laboratory Findings

Patient	Age (years)	Diagnosis	Baseline characteristics ^a					Characteristics during aplastic crisis ^b						
			Hgb (g/dl)	Retic (%)	Platelets ^c (mm ⁻³)	WBC (mm ⁻³)	ANC ^c (mm ⁻³)	Spleen size (cm)	Hgb (g/dl)	Retic (%)	Platelets ^c (mm ⁻³)	WBC (mm ⁻³)	ANC ^c (mm ⁻³)	Spleen size (cm)
Patients identified by clinical observation and recollection														
A	3	HS	8.1	13	560,000	16,900	3,200	3	2.9	0.8	81,000	9,300	3,160	5
B	4	HS	8.4	12	305,000	6,900	1,900	4	2.6	0.9	56,000	1,100	264	9
C	6	HS	9.5	10	350,000	5,500	3,500	4	5.2	5.6	136,000	2,400	1,272	10
D	6	HS	12.4	6	460,000	8,800	2,700	1	6.9	0.7	130,000	5,500	1,210	5
E	6	HS	8.8	14	240,000	6,800	3,800	3	2.0	1.0	69,000	2,000	1,060	2
F	7	HS	9.5	16	250,000	8,100	4,200	6	3.9	1.3	109,000	1,900	1,390	10
G	8	HS	10.8	7	340,000	9,400	4,700	1	6	2.2	127,000	2,400	1,310	6
H	10	HS	8.3	19	330,000	6,900	3,100	8	3.3	5.7	129,000	800	470	7
I	12	E β^0	6.5	4	270,000	6,300	3,000	9	3.3	0.1	65,000	800	136	6
Patients identified by review of hospitalization records														
J	4	HS	11.5	5	300,000	3,700	1,200	0	3.5	0.8	370,000	7,500	4,200	0
K	6	HS	10.4	2	320,000	10,700	6,700	ND	6	0	120,000	5,700	1,710	2
L	10	HS	11.5	6	340,000	8,900	3,900	1	3.8	1.4	162,000	7,600	3,952	2
M	10	HS	11.6	10	300,000	4,500	2,500	6	1.4	1.4	52,000	900	351	4
N	10	HS	12	9	390,000	11,300	7,100	1.5	4.2	4.7	295,000	7,100	7,326	2
O	11	HS	11.1	6	360,000	5,600	2,700	1	6.5	3.2	596,000	13,300	6,650	0
P	11	HS	11.3	10	280,000	12,300	9,100	1	5.8	1.4	89,000	3,200	ND	0
Q	11	HS	8.2	18	260,000	6,900	3,600	ND	4.4	0.4	230,000	2,900	ND	4

ANC, absolute neutrophil count; cm, centimeters below the left costal margin; E β^0 , Hgb E- β^0 -thalassemia; Hgb, hemoglobin; HS, hereditary spherocytosis; ND, not documented or performed; PCR, polymerase chain reaction; Retic, reticulocyte count; WBC, total white blood cell (leukocyte) count.

^a Average baseline blood counts and spleen size;

^b Maximum spleen size or nadir blood count values;

^c Normal values: platelets 150,000 mm⁻³; ANC 1,500 mm⁻³.