Chronic Human Parvovirus B19 Infection Associated with Interstitial Lung Disease

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Human parvovirus B19 is the cause of several clinical syndromes, including fifth disease, influenza-like disease and intrauterine infection. In patients with chronic hemolytic anemia, B19 infection may cause aplastic crisis [1]. Moreover, chronic pure red cell aplasia during parvovirus B19 infection has been observed in patients with various immunodeficiency syndromes. Respiratory manifestations of parvovirus B19 infection are very rare and include: acute respiratory disease, pneumonia, productive cough, laryngitis, recurrent bronchitis, prolonged obstructive bronchitis and acute exacerbation of asthma [2].

We report the detection of human parvovirus B19 genome by polymerase chain reaction [3] in the blood, bone marrow, bronchoalveolar lavage and lung tissue samples of a 6 year old girl with mucocutaneous candidiasis, pure red cell aplasia, and chronic interstitial lung disease.

Patient Description

A 6 year old girl known to suffer from undefined immune deficiency presented at the age of 4 with recent-onset anemia following (recurrent) pneumonia and prolonged cough. She is the youngest of four girls whose parents are first cousins of Jewish-Persian origin.

During the first 2 years of life she suffered from recurrent diarrhea, cutaneous and oral candidiasis, and one episode of urinary tract infection. Failure to thrive was noted at age 1 year. Routine vaccination was completed. At age 2 she was hospitalized in our department due to *Salmonella* sepsis, which manifested as prolonged fever and diarrhea. Physical examination revealed weight under the fifth percentile, alopecia areata, skin and oral candidiasis, splenomegaly and absence of palpable lymph nodes. Laboratory investigations revealed hemoglobin 11.5 g/dl, white blood cells 10,300 mm^3 with normal differential, and thrombocytes 250,000 mm^3. Routine blood biochemistry and urinalysis were normal. Evaluation for human immunodeficiency virus, the sweat test for cystic fibrosis, and serum zinc levels were all normal. Immunologic investigation at various ages is summarized in Table 1.

During the fourth year of life, following recurrent episodes of pneumonia, she developed progressive lung disease and pure red cell aplasia. Hemoglobin was 4.9 g/dl with 0.1% reticulocytes, white blood cells 10,500 mm^3 and thrombocytes 220,000 mm^3. Positive immunoglobulin M and negative IgG anti-parvovirus antibodies (detected by enzyme-linked immunosorbent assay; Parvoscan B19, Ferring Diagnostica, Sweden) suggested an acute infection with B19 as the cause of the anemia. Parvovirus B19 infection was further confirmed by PCR detection of the B19 genome in serum and bone marrow samples.

The anemia resolved completely following administration of four once-monthly courses of intravenous gammaglobulin (2 g/kg). However, B19 virus was not eliminated and the genome was still detected by PCR in her serum 18 months later. Anti-B19 IgM (but *not* IgG) was still detected 2 years following the acute infection, indicating a defect in IgG production. The lung disease progressed to a chronic productive cough with mild to moderate hypoxemia (oxygen saturation of 89–92% in room air). Auscultation revealed diffuse rales and decreased breath sounds over different lung segments during each exacerbation. Digital clubbing was noted. Chest X-ray and high resolution computerized tomography demonstrated diffuse interstitial infiltrates, mild bronchiectasis and segmental opacifications. Fiberoptic bronchoscopy demonstrated purulent secretions. Microscopic examination of the bronchoalveolar lavage revealed an abundance of neutrophils (95%). Nontypable *Haemophilus influenzae* was recovered from the culture.

A lung biopsy was performed. Histologic examination showed interstitial infiltration

Ig = immunoglobulin

PCR = polymerase chain reaction

Table 1. Immunologic study

Immunoglobulins (g/L)	**2 wk**	**2 yr**	**3 yr**
IgG	5.6	17.0 (high)	24.3 (high) (N < 12)
IgM	0.5	4.2 (high)	8.2 (high)* (N > 2)
IgA	0	0.1	2.0 (N < 1.6)
IgE		15 units	N
IgG subclasses (g/L)			
IgG1	10.6	7.4	
IgG2	–	2.1	
IgG3	1.3	2.3	
IgG4	0.2	0.7	
Specific antibody response (IgG)**			
Tetanus		1.2 IU/L (normal)	
Diphtheria		0.048 IU/L (low)	
Lymphocyte subsets***		CD19 = 26, CD3 = 42, CD4 = 32, CD8 = 10, CD3+DR = 26, CD16+CD57 = 30. All within normal limits	
Mytogenic stimulation			
Phytohemagglutinin		Normal	
Pokeweed		Normal	
Concanavalin A		Low	
Skin tests for:			
Candida		Non-reactive	
Tetanus toxoid		Non-reactive	
Trichophyton		Non-reactive	
Purified protein derivative		Non-reactive	
Specific enzymes			
Adenosine deaminase		Normal activity	
Phosphoribosine nucleoside		Normal activity	

* CD40 ligand was not deficient.

** Levels according to Ministry of Health laboratories.

*** Lymphocyte subpopulations were measured by flow cytometry and are presented as a percentage of the total lymphocyte population.

N = normal.

of lymphocytes and plasma cells, mild fibrosis and a small number of hemosiderin-laden macrophages. Bacterial cultures including specific cultures for pertussis and tuberculosis, and viral cultures for adenovirus, respiratory syncytial virus, influenza and rhinovirus were all negative. PCR analysis for Epstein-Barr virus, cytomegalovirus, herpes virus and tuberculosis genomes were all negative, as were *Pneumocystis carinii, Candida* and other fungi by silver stain.

PCR analysis for parvovirus B19 genome was positive in both BAL fluid and lung biopsy specimen [3]. Treatment of the chronic interstitial lung disease with steroids and hydroxychloroquin did not improve her condition. After 2 years of follow-up, the patient continues to suffer from productive cough and hypoxemia requiring oxygen 2 L/min by nasal prongs at night.

Comment

The patient described here suffers from an undefined immune deficiency characterized by mucocutaneous candidiasis and the inability to produce IgG immunoglobulins against parvovirus. During the fourth year of life she developed pure red cell aplasia that persisted for 4 months and responded to repeated courses of intravenous immunoglobulin. Concomitantly she developed chronic interstitial lung disease. B19 genome was detected by PCR in both BAL and lung tissue.

We suggest that the human parvovirus B19 is associated with the patient's lung disease, either by a direct effect through the P antigen receptor for B19 on endothelial cells, or indirectly by an immune mediated process, supported by the presence of plasma cells in our patient's lung (observed on lung biopsy) and by the successful treatment using cyclophosphamide and prednisone in another patient with interstitial lung disease associated with parvovirus [4].

The finding of the B19 genome in the lung biopsy specimen could be due to the presence of blood in the sample. However, contamination of the BAL fluid is highly unlikely since no red blood cells were found in the lavage fluid.

Pneumonitis and pneumonia associated with parvovirus B19 have been reported, however only in one report was the diagnosis supported by detection of B19 by PCR in lung biopsy [4]. Our patient's lung disease did not respond to treatment with IVIG or prednisone, possibly due to irreversible changes (fibrosis) in the lung.

Interstitial lung disease in childhood is rare, and in some cases viral etiologies such as Epstein-Barr virus, cytomegalovirus and adenovirus have been reported [5]. Most cases are termed "idiopathic." Only one previous report has described the association of B19 with interstitial lung disease [4].

Based on this knowledge we recommend that evaluation for B19 become a part of the routine work-up of interstitial lung disease in children.

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