

Case Report

Evolution of IgG Subclass Deficiency into Common Variable Immunodeficiency in a Child with Pulmonary Interstitial Glycogenosis

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We present a 5-year-old boy who initially presented during infancy with pulmonary interstitial glycogenosis (PIG) and recurrent sinopulmonary infections. At 3.5 years old, IgG-2 subclass deficiency associated with low IgA level and selective antibody deficiency was diagnosed. Subsequently, the immune deficiency evolved into common variable immunodeficiency (CVID). This is the first case reported of the association of PIG and CVID. In children with PIG who have recurrent infections, associated immunodeficiency should be suspected.

Introduction

ANTIBODY DEFICIENCIES OF IgG subclass deficiency, selective antibody deficiency (SAD), selective IgA deficiency (SIgAD) and common variable immunodeficiency (CVID) form a spectrum of B-cell immunodeficiencies.^{1–4} IgG-2 subclass deficiency is defined as a subnormal IgG-2 level that may be an isolated finding or present in combination with IgG-4 and/or IgA deficiency.^{2–10} Because IgG-2 is responsible for the antibody responses against polysaccharide capsular antigens, IgG-2 deficient patients are at increased risk for infections with *Streptococcus pneumoniae*, *Hemophilus influenzae* type B (HiB), and *Neisseria meningitidis*. IgG-2 subclass deficiency is one of the most frequently identified disorders in patients with recurrent infections. IgG-2 deficiency may resolve with age, or in a minority of patients, may progress to CVID. Sinopulmonary infections, including sinusitis, otitis, and bronchitis predominate; however, more severe infections, such as pneumonia and meningococemia have been described. In this report, we describe a boy who initially presented in infancy with pulmonary interstitial glycogenosis (PIG) and then developed IgG-2 deficiency, low IgA level, and impaired antibody responses to polysaccharide antigens, which later evolved into CVID.

Pulmonary interstitial glycogenosis is a recently described variant of neonatal interstitial lung disease (ILD) that was first described in 2002.^{11–14} Similar to other forms of neonatal ILD, PIG typically presents in the first month of life with

tachypnea and hypoxia associated with diffuse interstitial pulmonary infiltrates on chest radiograph. In PIG, lung biopsy reveals enlarged interstitial cells containing excessive cytoplasmic glycogen with little or no inflammation. The etiology of PIG is unknown, although a developmental abnormality of pulmonary mesenchymal cells may be present.^{11–14} The prognosis for PIG is generally favorable.¹¹ Canakis et al.¹² reported that six of seven infants showed clinical resolution and radiographic improvement. Onland et al.¹⁴ reported that with two infants with PIG who were treated with corticosteroids had a favorable outcome. Pulmonary interstitial glycogenosis has been described in monozygotic identical twins, suggesting the possibility of an underlying genetic defect.¹² To our knowledge, immunodeficiency has not been previously reported in children with PIG.

Case Report

The patient is a 5-year-old boy who developed tachypnea, hypoxia, and respiratory distress shortly after his term birth. Lung biopsy performed at 5 weeks of age revealed interstitial lung disease (ILD) with a predominately mononuclear and lymphocytic infiltrate. A repeat pathology examination of biopsy specimens with periodic acid Schiff staining revealed findings consistent with PIG (Fig. 1). He was treated with oral corticosteroids and his respiratory status improved. After a few weeks he was weaned off oxygen. He

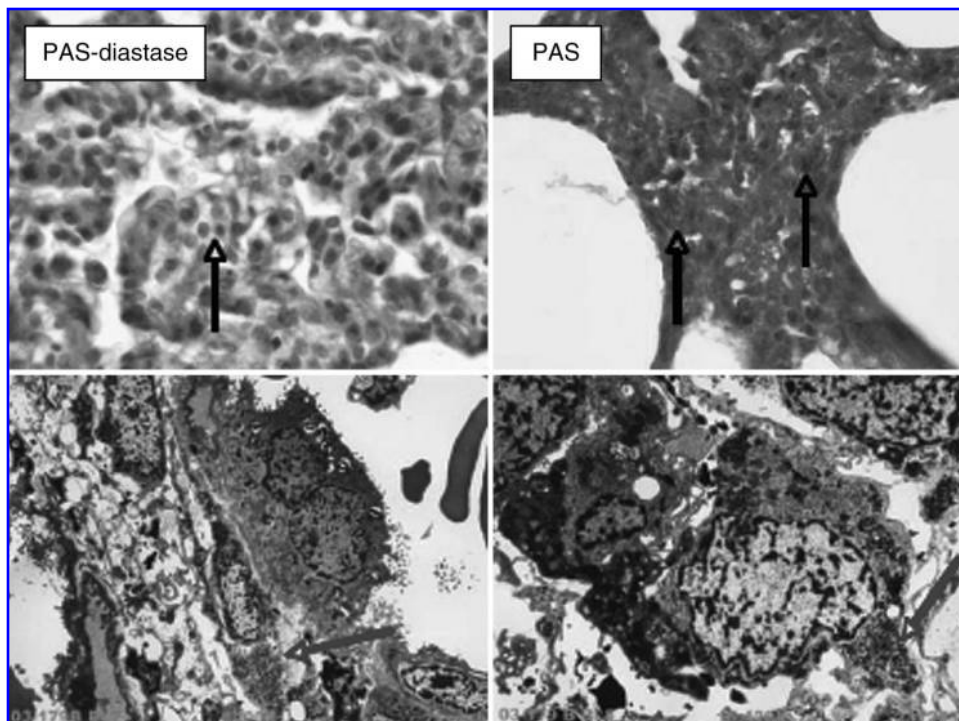


FIG. 1. Lung biopsies from patient were consistent with pulmonary interstitial glyco-genolysis. Light microscopy revealed alveolar septa that were thickened by a population of cells with oval nuclei and clear cytoplasm that contains PAS-positive, diastase digestible material (glycogen). Electron microscopy revealed that ultrastructurally these cells contained cytoplasmic pools of monoparticulate glycogen.

was subsequently maintained on inhaled budesonide and did fairly well from a respiratory standpoint. Beginning in the first year of life, he developed frequent recurrent infections that included otitis media, sinusitis, and pneumonia as well as poor weight gain. Immune evaluation at 3.5 years of age revealed normal serum IgG and IgM, but low IgA and IgG-2 levels and poor antibody responses to unconjugated pneumococcal and conjugated HiB consistent with IgG-2 subclass deficiency (Table 1). T-, B- and NK cells as well as naïve CD4+CD45RA+ T cell numbers and percentages were normal. IVIG therapy was initiated which resulted in a marked reduction in infections and improvement in weight gain. His respiratory status remained stable on inhaled budesonide. He was then changed to subcutaneous gammaglobulin (SCGG), which he received at home. The family subsequently stopped the SCGG, and the child was briefly lost to follow-up before representing at 5.5 years of age with a history of recurrent pneumonia. Computerized tomography scan of the chest during this admission revealed development of left lower lobe bronchiectasis. Re-evaluation of his immune system at 5.5 years demonstrated hypogammaglobulinemia (IgG 187 mg/dL, IgA < 6 mg/dL), poor antibody responses to tetanus toxoid, HiB, and unconjugated pneumococcal vaccines, decreased percentages and numbers of B cells, and absent (0%) CD27+ memory B cells and CD27+IgD-switched B cells, consistent with CVID. T cells numbers and function were normal. Intravenous gammaglobulin was reinitiated at high-dose, ~800 mg/kg/month, because of the bronchiectasis. This was subsequently changed to SCGG, ~240 mg/kg/weekly. The patient has received gammaglobulin therapy for 21 months and has remained free of infections. In addition, the patient improved globally with improved weight gain and increased activity. The bronchiectasis has been stable with no worsening but no improvement. Pulmonary function studies have been normal.

Discussion

In our patient at 3.5 years old, the IgA and IgG-2 levels were decreased and was associated with impaired antibody responses to polysaccharide antigens. SIgAD is characterized by decreased IgA <5 mg/dL with normal IgG and IgM levels and normal IgG antibodies to protein and polysaccharide antigens.³ Patients with SIgAD are susceptible to primarily recurrent upper respiratory tract infections with the lower airway spared. However, Bjorkander et al.¹⁵ reported that patients with SIgAD that had recurrent pulmonary infections and bronchiectasis also had impaired antibody responses to *S. pneumoniae*. Selective impairment to bacterial polysaccharide antigens with normal serum immunoglobulins and IgG subclasses is also seen in SAD.^{1,4,16} The natural history of SAD in younger children is that the majority "out-grow" their immunodeficiency,¹⁶ as may occur in IgG-2 subclass deficiency. However, in older children (>6 years old) and adults, SAD often persists. Furthermore, there is concern that SAD or IgG subclass deficiency may evolve into CVID.^{2,17} CVID is characterized by decreased IgG and IgA levels with normal or decreased IgM levels; IgG antibodies to both protein and polysaccharide antigens are decreased.¹ We also examined CD27+ memory B cells and IgM-IgD-CD27+ switched B cells in our patient. In CVID there is a defective terminal differentiation of IgG antibody secreting switched B cells,¹⁸⁻²⁵ which may also be seen in SAD.²⁶ In SIgAD, IgA+ B cells are present but there is defective terminal differentiation into IgA-secreting immunoblasts. In our patient, CD27+ memory B cells were absent when he was diagnosed with CVID; unfortunately, they were not measured earlier. Recently, Castigli and Geha²⁷ identified that a genetic mutation of transmembrane activator and calcium-modulator and cytophilin ligand interactor accounts for some patients with CVID and SIgAD.

TABLE 1. IMMUNOLOGIC STUDIES OF A CHILD WITH PULMONARY INTERSTITIAL GLYCOGENOSIS WHO DEVELOPED IgG-2 SUBCLASS DEFICIENCY THAT SUBSEQUENTLY EVOLVED INTO COMMON VARIABLE IMMUNODEFICIENCY

Patient	Patient		Normal for Age ^a
Age	3.5	5.5 yrs	5–10 years
IgG (mg/dL)	523	187	508–1359
IgA (mg/dL)	14	<6	21–129
IgM (mg/dL)	41	51	31–126
IgE (IU/mL)	<2	<2	9–69
IgG-1 (mg/dL)	344	86	300–850
IgG-2 (mg/dL)	17	<20	50–300
IgG-3 (mg/dL)	115	75	10–70
IgG-4 (mg/dL)	9	<0.2	3–80
Antidiphtheria (mcg/mL)	0.98	0.11	≥0.05
Antitetanus (mcg/mL)	0.17	<0.10	≥0.50
Anti-HiB (mcg/mL)	0.15	0.16	≥1.0
Antipneumococcal (mcg/mL)			
Serotype 1	0.2	0.2	≥1.3
3	0.3	0.1	≥1.3
4	0.2	0.7	≥1.3
6B	0.2	0.3	≥1.3
7F	0.0	0.2	≥1.3
8	0.3	0.1	≥1.3
9V	0.2	0.2	≥1.3
12	0.1	0.1	≥1.3
14	0.7	0.5	≥1.3
18C	0.2	0.6	≥1.3
19F	0.4	0.3	≥1.3
23F	0.5	0.5	≥1.3
ALC (cells/mm ³)	3216	2805	2300–5400
CD3 cells/mm ³	2347	62	900–4500
%	73	62	55–78
CD4 cells/mm ³	1608	1318	500–2400
%	50	47	23–48
CD8 cells/mm ³	611	364	300–1600
%	19	13	19–34
CD19 cells/mm ³	611	84	200–2100
%	19	3	10–31
CD19+CD27+ (%)	–	0	25–40 ^b
CD56 cells/mm ³	193	280	100–1000
%	6	10	4–26

ALC, absolute lymphocyte count; HiB, *Hemophilus influenzae* type B.

From

^aComans-Bitter WM et al.²⁸ for lymphocyte subpopulations.

^bBrouet JC et al.¹⁹ for CD27+ B cells.

The relationship of PIG and B-cell immunodeficiency is unknown. Pulmonary interstitial glycogenosis is thought to represent a developmental delay of pulmonary mesenchymal cells.^{11–14} We have also identified one other child with SAD and PIG. The association with CVID and SAD raises the theoretical possibility of a more widespread cellular developmental abnormality. Although there is no known physiologic link between pulmonary mesenchymal cells and humoral immune system development, these two separate cell lines may have a common feature of maturational delay.

In summary, we report a child who initially present with PIG and subsequently developed CVID. This report suggests that in children with PIG and signs and symptoms of recurrent infection, there may be a concomitant B-cell immunodeficiency such as SAD or CVID.

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