

Clinical Communications

Functional antipolysaccharide immunoglobulin deficiency, recurrent pneumococcal sepsis, and hypergammaglobulinemic purpura

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Clinical Implication

- Immune deficiencies, particularly defects in antibody production or function, should be suspected in patients who present with recurrent pneumococcal infections. Immunologic workup must include a critical interpretation of antibody titers in response to vaccine administration, while carefully considering the clinical presentation.

TO THE EDITOR:

We report a 26-year-old white woman who was referred for an immunologic workup after hospitalization for the second episode of pneumococcal sepsis. She had presented with 2 days of fever, malaise, and vomiting. She was admitted with

pneumonia, septic shock, and disseminated intravascular coagulation and subsequently received aggressive resuscitation, mechanical ventilation, and pressor support. Blood cultures were positive for *Streptococcus pneumoniae* serotype 22F. She was treated with antibiotic therapy and 3 doses of intravenous immunoglobulin (IVIG) for suspected immunoglobulin deficiency, which led to interval recovery. Prophylactic antibiotics were continued after hospitalization.

Two years earlier, she had her first episode of severe pneumococcal sepsis with disseminated intravascular coagulation and multiorgan failure, which required ventilation and prolonged pressor support and which resulted in bilateral toe necrosis and transmetatarsal amputations. She recovered with appropriate antibiotics and had reportedly been given 1 dose of IVIG during sepsis empirically. After hospital discharge, she did not start prophylactic antibiotics. She had intermittent episodes of sinopulmonary infections until the presentation discussed here. Her medical history included sacroiliitis, xerostomia, keratoconjunctivitis sicca, and Raynaud's phenomenon, with serologies that suggested Sjögren's syndrome, to include positive antinuclear antibodies, anti-Sjögren's syndrome SSA/Ro and SSB/La antibodies, and positive rheumatoid factor. She was never treated with corticosteroids, although hydroxychloroquine was used for arthralgias.



Immunoglobulin class/subclass	Four months post-hospitalization	Six months post-hospitalization	Twenty months of SCIG	Reference ranges (mg/dL)
Total IgG	3,910	3,656	3,109	694-1,618
IgG1	3,140	2,910	2,816	382-929
IgG2	122	136	215	241-700
IgG3	60	61	60	22-178
IgG4	2.9	3.0	4.2	4-86
IgA	3,636	1,061	1,144	81-463
IgM	114	136	--	48-271

FIGURE 1. Manifestations of autoimmune hypergammaglobulinemia. **A**, Hypergammaglobulinemic purpura of Waldenström and noted transmetatarsal amputations. **B**, Immunoglobulins 4 and 6 months after hospitalization, and after 20 months of SCIG therapy; note elevations of total IgG, IgG1, and IgA, with deficiency of IgG2 (and possibly IgG4). Laboratory studies by Quest Diagnostics, Tempe, Ariz.

TABLE I. Antipolysaccharide vaccine responses to pneumococcal polysaccharide vaccine PPV23 and meningococcal polysaccharide vaccine MPSV4

	Prevaccine*	After vaccine*	2-Fold increase in titers	Postvaccine pneumococcal titer ≥ 1.3 $\mu\text{g/mL}$
<i>Streptococcus pneumoniae</i> antibody serotype				
1	1.5	1.6	—	Protective
2	0.3	1.0	Responsive	—
3	0.4	1.1	Responsive	—
4	0.3	1.4	Responsive	Protective
5	6.0	5.0	—	Protective
6B	1.8	1.4	—	Protective
7F	1.8	7.4	Responsive	Protective
8	0.7	1.7	Responsive	Protective
9N	0.6	2.7	Responsive	Protective
9V	0.4	0.5	—	—
10A	2.8	>20.0	Responsive	Protective
11A	1.0	2.7	Responsive	Protective
12F	1.0	1.6	—	Protective
14	2.7	15.8	Responsive	Protective
15B	0.5	1.1	Responsive	—
17F	1.2	1.7	—	Protective
18C	1.1	3.8	Responsive	Protective
19A	1.4	2.2	—	Protective
19F	1.9	7.7	Responsive	Protective
20	0.6	0.7	—	—
22F	0.2	<0.2	—	—
23F	2.1	4.2	Responsive	Protective
33F	0.2	0.6	Responsive	—
<i>Neisseria meningitidis</i> serogroup antibody				
A	1.8	12.0	Responsive	
C	<0.5	<0.5	—	
Y	0.6	<0.5	—	
W-135	<0.5	<0.5	—	

Pneumococcal serotype antibodies post-PPV23 vaccine: 16/23 (70%) ≥ 1.3 $\mu\text{g/mL}$, however, 14/23 (60%) with 2-fold response; 10/23 (43%) ≥ 1.3 $\mu\text{g/mL}$ and 2-fold response. Meningococcal serogroup antibodies post-MPSV4 vaccine: 1/4 (25%) responsive.

*Antibody titers ($\mu\text{g/mL}$).

IMMUNOLOGIC EVALUATION AND FOLLOW-UP

Laboratory studies performed 4 and 6 months after her second hospitalization demonstrated elevated polyclonal IgG1 and IgA, with deficiency of IgG2 (Figure 1). She had significantly impaired antibody responses to the unconjugated meningococcal (1/4 serogroups were responsive) and pneumococcal (16/23 serotypes were ≥ 1.3 $\mu\text{g/mL}$; however, only 14/23 serotypes with a 2-fold response) polysaccharide vaccines (Table I). It was notably observed that there was no response to *Streptococcus pneumoniae* serotype 22F, both after infection and after the vaccine was given. Complement and antiprotein (diphtheria and tetanus toxoids) vaccine studies were normal. T-cell mitogen studies showed mild hyperreactivity. Peripheral blood lymphocyte phenotyping was within normal limits. While on prophylactic antibiotics, she continued to develop sinopulmonary infections. Given the poor results of prophylaxis and the inadequate antipolysaccharide vaccine response, a decision was made to start immunoglobulin therapy.

She continued to have purpuric lesions on her lower extremities, consistent with hypergammaglobulinemic purpura of

Waldenström (Figure 1). Serum viscosity was mildly elevated given her hypergammaglobulinemic state (2.5 serum to water). We instituted treatment with subcutaneous immunoglobulin (SCIG) (7 g weekly) rather than IVIG, which may be of benefit when taking into account her risks of hyperviscosity because there is a lower reported incidence of thromboembolic events compared with IVIG. Her total IgG remains elevated while on SCIG therapy (Figure 1). Two years after starting SCIG, the patient had an episode of community-acquired pneumonia, with negative blood and sputum cultures, and was responsive to empiric antibiotics and fluids.

DISCUSSION

Patients who present with recurrent sinopulmonary infections require a quantitative and qualitative humoral immune system evaluation.¹ Immune deficiencies are often associated with autoimmune diseases.² Hypergammaglobulinemia has been widely observed in patients with Sjögren's syndrome.³ Less common are reports of patients with Sjögren's syndrome who

present with recurrent infections.^{3,4} Upon literature review, a strikingly similar case of Sjögren's syndrome with recurrent pneumococcal sepsis, hypergammaglobulinemic purpura, and IgG2 subclass deficiency had been reported.⁴ The investigators described antibody responses to the pneumococcal polysaccharide vaccine, with 13 of 14 IgG serotypes present.⁴ Our patient did not appropriately respond to the initial infection or to the polysaccharide vaccine antigens.

The clinical significance of IgG subclass deficiency has been debated, but it is relevant in the setting of recurrent sinopulmonary infections.⁵ Studies of healthy patients have demonstrated deficiencies of immunoglobulin subclasses, thus questioning the clinical significance of this isolated finding.⁶ More relevant is the diagnosis of specific antibody deficiency in which a complete evaluation of the immune system reveals an impaired response to vaccination. This qualitative assessment of immunoglobulin function is necessary before considering long-term immunoglobulin therapy.⁷

With regard to the pattern of hypergammaglobulinemia with functional antibody deficiency in Sjögren's syndrome, the underlying mechanism of dysfunction is poorly understood. The abnormal synthesis of antibodies may be influenced by the overproduction of anti-SSA/Ro autoantibodies by plasma cells.⁸ If the production of autoantibodies is the primary cause of immunoglobulin dysregulation, then it could be hypothesized that suppressing autoantibody production would allow more normalized plasma cell function. Some effects of immunoglobulin administration on the immune system include clearance of autoantibodies, enhancement of regulatory T cells, and cell receptor modulation.⁹ IVIG has been used for treating rheumatologic diseases with some proven benefit reported in clinical trials and case reports for rheumatoid arthritis and systemic lupus erythematosus.⁷ Immunoglobulin therapy may be an additional treatment approach for immune modulation in Sjögren's syndrome.

Our patient was unable to make antibodies to the etiologic *Streptococcus pneumoniae* serotype 22F both after sepsis and after vaccination. There is significant complexity and controversy regarding the interpretation of antipneumococcal antibody titers in probing the immune response.¹ We used the consensus protective antibody titer value of 1.3 µg/mL for pneumococcal serotypes, or 2-fold increase in preimmunization titers.¹ She had 70% of titers ≥1.3 µg/mL, but there were only 60% of titers with at least a 2-fold increase compared to prevaccine titers (Table I). However, a 2-fold or more rise in titer, together with achievement of ≥1.3 µg/mL, occurred to only 43% of serotypes, (10/23). Orange et al¹ describe memory, mild, moderate, and severe phenotypes of polysaccharide nonresponsiveness. Our patient would be classified as having a mild phenotype ("failure to generate protective titers to multiple serotypes or failure of a 2-fold increase in 70% of serotypes").¹ Memory phenotype (polysaccharide vaccine response initially protective but lost within 6 months) could be considered given the patient's recurrent infections, inadequate prevaccine titers, and marginal vaccine response. Lastly, only 25% of *Neisseria meningitidis* serogroups were vaccine responsive. It is mentioned that these are

expert opinion guidelines, and phenotype classification should include a careful clinical correlation.¹

The case presented demonstrates the near fatal consequences of immune deficiency, while emphasizing a thorough analysis of immunoglobulin function, in a young patient with recurrent pneumococcal sepsis. The investigation of the immune system from a quantitative and qualitative approach, while carefully considering clinical symptoms, is necessary when patients present with recurrent infections.

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