
Case report

Prevention of pneumococcal infection in a patient with normal immunoglobulin levels but impaired polysaccharide antibody production

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Background: Patients with normal immunoglobulin levels may have an impaired response to immunization with pneumococcal vaccine and increased susceptibility to infection with encapsulated organisms. In children, but not adults, immunoglobulin replacement has been shown to be effective in reducing the infection rate.

Objective: To reduce the incidence of infection in an adult with impaired response to pneumococcal vaccine but normal serum IgG levels.

Methods: Intravenous IgG, 350 mg/kg, was given every 4 weeks.

Results: The patient, who was hospitalized 3 times in 3 years with respiratory tract infections and who had documented infection with *Streptococcus pneumoniae* and *Haemophilus influenzae*, did not require antibiotic therapy for more than 15 months while undergoing intravenous immunoglobulin replacement therapy.

Conclusion: Adults with impaired response to vaccination with polyvalent pneumococcal vaccine and normal IgG levels may benefit from replacement therapy.

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INTRODUCTION

Impaired immunoglobulin production, reflected in low total class-specific levels, has been associated with increased susceptibility to infections, particularly those involving the respiratory tract. Patients have been identified who have normal total immunoglobulin levels but an impaired response to immunization with specific polysaccharide antigens. It has been shown in children that the increased frequency of infections seen in such patients can be prevented by intravenous replacement with therapeutic doses of IgG, even in the presence of normal total IgG levels. We describe an elderly patient with a history of recurrent respiratory tract infections (RTIs) and failure to demonstrate an adequate immunologic response to 23-valent pneumococcal vaccine who was successfully treated with IgG replacement therapy.

CASE REPORT

A 71-year-old woman was first seen in April 2002 for evaluation of shortness of breath of 3 years' duration, with a

40-pack-year smoking history, having stopped 20 years previously. She reported no respiratory issues as a child or adolescent, but while employed as a pediatric nurse she encountered frequent upper RTIs that "always went to her chest." She developed a chronic cough in her fourth decade of life that subsided when she quit smoking. At the time of initial evaluation, the patient's lungs were clear to auscultation, and her forced expiratory volume in 1 second was 1.17 L (56% of predicted). She provided no history of upper respiratory difficulty and had only a little nasal crusting on initial examination, with a small amount of mucus in her posterior pharynx. Baseline chest radiograph revealed hyperinflation only. She returned in May 2002 with an exacerbation of chronic obstructive pulmonary disease, and her sputum culture was positive for *Streptococcus pneumoniae*. Despite outpatient therapy with antibiotics and oral corticosteroids, she was subsequently admitted to the hospital with a white blood cell count of 51,000/ μ L and a left lower lobe infiltrate on a chest radiograph. She reported that she had been given pneumococcal vaccine in the early 1990s, but those details were not available. She was given a dose of 23-valent pneumococcal polysaccharide vaccine in June 2002, after her treatment for acute pneumonia was completed. At that time she was receiving a prednisone taper, dating to her hospital stay. Her dose was reduced from 10 mg/d on the day of vaccination to 5 mg/d for 1 week and then 5 mg every other day for a week. Three additional episodes of bronchitis occurred between July 2002 and March 2003, each of which

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was treated with oral antibiotics. She was hospitalized in June 2003 with multifocal pneumonia, again with an *S pneumoniae*-positive sputum culture. Immunoglobulin evaluation in July 2003 showed normal serum immunoglobulin levels (IgG, 1,470 mg/dL; IgA, 187 mg/dL; and IgM, 88 mg/dL), but specific antipneumococcal antibody levels, although greater than 1.0 $\mu\text{g/mL}$ in all 12 serotypes tested, showed little increase between prevaccination and postvaccination titers obtained 1 month after administration of her second 23-valent pneumococcal polysaccharide vaccine (Table 1). An RTI in December 2003, diagnosed as influenza A, slowly resolved in 1 month despite the use of oseltamivir. In November 2004 she developed pneumonia again, confirmed by a chest radiograph, and was hospitalized. Sputum Gram stain and culture showed many white blood cells and small gram-negative bacilli identified as *Haemophilus influenzae*. In February 2005, the patient started monthly intravenous IgG replacement therapy, 25 g or 350 mg/kg per dose. She was without infection and did not require antibiotic therapy for any reason until May 2006, 15 months after starting replacement therapy. At that time she was given a single outpatient antibiotic course for a mild increase in symptoms and yellow sputum. She completed that course with a prompt response to therapy and remains free of infection as of July 2006.

DISCUSSION

It is well established that IgG deficiency is associated with recurrent infection and that replacement therapy can be valuable in treating chronic lung disease associated with this condition.¹ In patients with normal immunoglobulin levels, however, there may still be a specific IgG antibody production defect involving polysaccharide-encapsulated organisms, such as *S pneumoniae* and *H influenzae* type b. A variety of

terms have been used for this condition, including *impaired polysaccharide responsiveness* and *specific antibody deficiency*. The latter is the preferred designation in the Practice Parameter for the Diagnosis and Management of Primary Immunodeficiency,² and it has been identified in adults³ and children.⁴ It is characterized by recurrent sinopulmonary infections, an absent or subnormal response to a polysaccharide vaccine, normal or elevated IgG levels, and an intact immunologic response to protein antigens.⁵ Its origin is likely multifactorial, with etiologies ranging from immunologic immaturity and genetic predisposition to nutritional deficiencies and a defective B-cell repertoire.^{6,7} The use of intravenous IgG replacement therapy in children with specific antibody deficiency-associated recurrent RTIs is of demonstrated benefit.⁸ The efficacy of IgG replacement therapy in adults with specific antibody deficiency has not yet been established, however, despite reports that it may be an underlying cause in 8% of all cases of recurrent community-acquired pneumonia⁹ and in 15% of all cases of bronchiectasis of unknown etiology.¹⁰ Recently, Vendrell et al¹¹ hypothesized that intravenous IgG replacement therapy may be useful in this patient population. One barrier to the recognition of this condition has likely been the lack of consensus regarding what constitutes a normal protective level of specific pneumococcal antibody. Several studies have published data on mean levels in healthy adults, but a meta-analysis by Go and Ballas¹² showed that a variety of responses exist in healthy individuals, and there is no apparent minimum absolute antibody level of diagnostic value, before or after immunization. They also concluded that not only did healthy individuals not respond to all serotypes, but not all positive responders exhibited a 2-fold rise after vaccination. It is also suspected that at least some elderly persons will produce pneumococcal antibody with diminished opsonic or functional activity, rendering quantitation of antibody levels even more difficult to interpret.^{13,14}

The patient described herein had several serious RTIs in the 3 years before starting immunoglobulin replacement therapy, although there was no history of sinusitis and chest computed tomography showed emphysema, consistent with her smoking history, but not bronchiectasis. Three of her RTIs had proven associations with organisms that have polysaccharide capsules. She required 3 hospitalizations during that time. During the first 15 months after the initiation of immunoglobulin replacement therapy, however, she did not have an RTI requiring antibiotic therapy or hospitalization. Although her prevaccination and postvaccination specific pneumococcal IgG levels would have been considered adequate by some standards, her history of recurrent bacterial RTIs supports the notion that the antibody present may have been functionally deficient. She received prednisone at the time of her June 2002 immunization, which theoretically may have impaired her response, but she was not taking prednisone at the time of her second immunization in August 2003. Although serotypes of the actual organisms she was infected with were not available, it seems apparent that she

Table 1. Patient Specific IgG Concentrations Before and After Her Second Vaccination With 23-Valent Polysaccharide Pneumococcal Vaccine

Pneumococcal serotype	Specific IgG concentration, $\mu\text{g/mL}$	
	Before second vaccination (July 2003)	After second vaccination (September 2003)
1	1.4	2.0
3	0.9	1.2
4	2.6	3.0
26 (6B)	1.7	1.3
8	3.6	5.2
9 (9N)	1.6	2.1
12 (12F)	1.8	1.9
14	10.1	>12.5
19 (19F)	1.9	2.1
23 (23F)	9.7	>12.5
51 (7F)	4.4	3.6
56 (18C)	5.0	5.8

could not respond to novel antigens in a sufficiently timely manner to prevent infection.

To our knowledge, this is the first article describing the successful use of IgG replacement therapy in an adult with documented recurrent RTIs with polysaccharide-encapsulated organisms and apparent insufficient response to 23-valent pneumococcal vaccine. Patients with recurrent purulent RTIs whose serum immunoglobulin levels are normal should be evaluated for specific antibody deficiency, and IgG replacement therapy should be considered for patients who do not respond to the pneumococcal vaccine appropriately.

REFERENCES

1. Roifman CM, Levinson H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinemia and chronic lung disease. *Lancet*. 1987;1:1075-1077.
2. Bonilla FA, Bernstein IL, Khan DA, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol*. 2005;94(suppl 1):S1-S63.
3. Ekdahl K, Branconier JH, Svanborg C. Impaired antibody response to pneumococcal capsular polysaccharides and phosphorylcholine in adult patients with a history of bacteremic pneumococcal infection. *Clin Infect Dis*. 1997;25:654-660.
4. Epstein M, Gruskay F. Selective deficiency in pneumococcal antibody response in children with recurrent infections. *Ann Allergy Asthma Immunol*. 1995;75:125-131.
5. Stiehm ER, Ochs HD, Winkelstein JA. Antibody deficiencies. In: *Immunologic Disorders in Infants & Children*. 5th ed. Philadelphia, PA: Elsevier Saunders; 2004:398-401.
6. Fata FT, Herslich BC, Schiffman G, Ast AL. Impaired antibody responses to pneumococcal polysaccharide in elderly patients with low serum vitamin B12 levels. *Ann Intern Med*. 1996;124:299-304.
7. Ambrosino DM, Siber GR, Chilmonczyk BA, Jernberg JB, Finberg RW. An immunodeficiency characterized by impaired antibody responses to polysaccharides. *N Engl J Med*. 1987;316:790-793.
8. Zora JA, Silk HJ, Tinkelman DG. Evaluation of postimmunization pneumococcal titers in children with recurrent infections and normal levels of immunoglobulin. *Ann Allergy*. 1993;70:283-288.
9. Ekdahl K, Braconier JH, Svanborg C. Immunoglobulin deficiencies and impaired immune response to polysaccharide antigens in adult patients with recurrent community-acquired pneumonia. *Scand J Infect Dis*. 1997;29:401-407.
10. Van Kessel DA, van Velzen-Blad H, van den Bosch JMM, Rijkers GT. Impaired pneumococcal antibody response in bronchiectasis of unknown etiology. *Eur Respir J*. 2005;25:482-489.
11. Vendrell M, de Gracia J, Rodrigo MJ, et al. Antibody production deficiency with normal IgG levels in bronchiectasis of unknown etiology. *Chest*. 2005;127:197-204.
12. Go ES, Ballas ZK. Anti-pneumococcal antibody response in normal subjects: a meta-analysis. *J Allergy Clin Immunol*. 1996;98:205-215.
13. Rubins JB, Prui AKG, Loch J, et al. Magnitude, duration, quality and function of pneumococcal vaccine responses in elderly adults. *J Infect Dis*. 1998;178:431-440.
14. Musher DM, Chapman AJ, Goree A, Jonsson S, Briles D, Baughn RE. Natural and vaccine-related immunity to *Streptococcus pneumoniae*. *J Infect Dis*. 1986;154:245-256.

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