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CASE REPORT

Selective IgM deficiency in an adult presenting with *Streptococcus pneumoniae* septic arthritis

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Septic arthritis caused by *Streptococcus pneumoniae* is uncommon. Most of the patients who have invasive pneumococcal infection have underlying diseases associated with impaired immune function. We report a case of polyarticular pneumococcal septic arthritis in a previously healthy adult as the first manifestation of selective immunoglobulin (Ig)M deficiency. The patient had no evidence of autoimmune disease or malignancy. Serum IgG, IgA, and complement levels were normal. Numbers of lymphocyte subsets were in normal range except that of CD4+ cells, which was slightly low. Invasive pneumococcal disease in a healthy adult should lead to further investigation for underlying diseases including primary immunodeficiencies.

Introduction

Streptococcus pneumoniae is an extracellular pathogen, in which host defenses against infection have been well studied. Both innate and adaptive immunity play an important role in protection against this pathogen. Specific antibody, complement, and polymorphonuclear cells (PMN) are known to play a major role. Many primary immunodeficiency diseases have been shown to be associated with invasive pneumococcal disease at various risks.[1]

Selective immunoglobulin (Ig)M deficiency is a rare disease that might be associated with higher risk of certain infections.[2] The disease is an isolated absence or deficiency of serum IgM associated with infection, with normal levels of other immunoglobulin and normal T cell immunity.

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Patients with IgM deficiency may be asymptomatic, have repeated infections, and/or present with associated conditions (e.g., autoimmune disorder and malignancy). We report a case of selective IgM deficiency in an adult who primarily presented with pneumococcal septic arthritis.

Case report

A 59-year-old female with unremarkable clinical history other than hyperlipidemia presented with pain in the right leg for 1 week. The clinical course began with pain on the left foot after falling on that foot. She sought medical attention in which physical examination revealed mild tenderness at the base of the fifth metatarsal bone, swelling at dorsum of the foot, and limited range of motion due to pain. She was diagnosed with ankle sprain for which a short leg slab was applied. Etoricoxib and acetaminophen/orphenadrine were prescribed. The symptoms then subsided. Later, however, she had pain in the right leg and knee, which were not the affected part of the recent injury. She went to a hospital and a slab was applied to her right leg but the symptom did not improve. She also noticed redness and swelling on her right leg, but did not have fever. Physical examination revealed bilaterally warm and swollen knee joints with associated effusion. Erythematous and swelling of the right leg was also noted. Physical examination of other organs was unremarkable. Her initial laboratory result was significant for a white blood cell (WBC) count of 22.1×10^9/L, hematocrit of 29%, with hemoglobin of 106 g/L. Her baseline hematocrit and hemoglobin were 38% and 125 g/L, respectively, in the previous 2 weeks.

Arthrocenthesis was performed on both knee joints. The joint effusion showed numerous PMN without visible microorganism by Gram stain. Joint fluid analysis showed 18.0×10^9 WBC/L with 94% PMN on the left knee, and 61.9×10^9 WBC/L with 95% PMN on the right knee. The joint fluid from the right knee and blood culture grew *S. pneumoniae*. The minimum inhibitory concentration of penicillin against the bacterium was 0.094 mg/L. Intravenous penicillin G sodium was given for a course of 10 days, and then switched to high dose oral amoxicillin because the patient could not tolerate the phlebitis associated with antibiotic infusion. Arthroscopic debridement was performed. Her symptoms gradually improved and subsequent culture was negative.

Anemia in patients with invasive pneumococcal infection has been shown to be associated with multiple myeloma.[3] Evidence of this disease in this patient was not found. However, serum IgM level, as a part of the investigation, was shown to be low (0.30 g/L; normal range for adult, 0.40–2.30 g/L). Immunologic evaluation was pursued and results are shown in Table 1. Other immunoglobulin and complement levels were normal. Lymphocyte subsets were

Table 1 Immunologic studies.

	Patient results	Reference range
White blood cell count, $\times 10^9$/L	9.89	4–10
Hemoglobin, g/L	102.4	120–160
Platelet, $\times 10^9$/L	753	140–450
Neutrophils, %	76	40–74
Monocytes, %	5	19–48
Eosinophils, %	0	0–7
HIV antibody (ELISA)	Negative	Negative
Adaptive immunity		
Lymphocyte subsets, %, $\times 10^9$/L		
CD3	68.90%, 1.27	67–76%, 1.1–1.7
CD4	26.9%, 0.50	38–46%, 0.7–1.1
CD8	32.5%, 0.6	31–40%, 0.5–0.9
CD19	15.4%, 0.28	11–18%, 0.2–0.4
CD16+56	11.7%, 0.22	10–19%, 0.2–0.4
Serum immunoglobulin		
IgM, g/L	0.26	0.4–2.3
IgA, g/L	3.18	0.7–4.0
IgG, g/L	16.2	7.00–16.00
IgG1, g/L	12.5	4.05–10.11
IgG2, g/L	4.32	1.69–7.86
IgG3, g/L	0.558	0.11–0.85
IgG4, g/L	1.360	0.03–2.01
Specific antibodies		
Clostridium tetani antibody IgG, IU/mL	0.50	>0.1
Rubella virus antibody IgG, IU/mL	<5	>12
Innate immunity		
C3, mg/L	1910	(900–1800)
C4, mg/L	500	(100–400)
CH50, %	100	100
CRP, mg/L	154.54	<5

ELISA = enzyme-linked immunosorbent assay; HIV = human immunodeficiency virus.

in normal range except for CD4 cell count, which was slightly low. She already harbored an antibody response to tetanus toxoid, but not rubella. Repeated determination still showed low levels of IgM after 1 month from the initial diagnosis. Her delayed type hypersensitivity skin test revealed normal response. She denied previous history of repeated infection or allergic disease. The patient was given a diagnosis of selective IgM deficiency. She was given conjugated 13-valent pneumococcal vaccine and an extended course of amoxicillin was given due to the defect in her immune status.

Discussion

S. pneumoniae is a rare cause of septic arthritis at the present time due to the advancement in antibiotic treatment. In the previous decade, *S. pneumoniae* septic arthritis was not uncommon: Ross et al reported that *S. pneumoniae* contributed 3% of total septic arthritis cases during 1979–1994.[4] The classic clinical presentation is concomitant pulmonary and/or meningeal and joint infections in the presence of predisposing local and systemic factors. Middle-aged and elderly adults seem to be more likely to have *S. pneumoniae* septic arthritis. Major risk factors in adults include rheumatoid arthritis, alcoholism, osteoarthritis, prosthetic joint, corticosteroid use and multiple myeloma, or monoclonal gammopathy. From one study of adults with pneumococcal septic arthritis, only 15% of patients had no obvious risk factors for the infection.[4]

As *S. pneumoniae* is an encapsulated bacterium, antibody- and complement-mediated opsonization and phagocytosis play an important role in protection against pneumococcal infection. Selective IgM deficiency is a rare immune disorder with a reported prevalence of 0.03–0.1%.[5] There have been fewer than 300 cases reported in literature. Because of its rarity, understanding of this disorder is preliminary. A level of IgM $<$ 2 standard deviations from the mean is generally accepted as a cutoff value for defining IgM deficiency ($<$0.3 g/L in adults). The patients with this condition may be asymptomatic, have repeated infections, and/or present with related conditions, such as atopic diseases, autoimmune disorders, or malignant and hematologic disorders. Several case reports of infectious conditions including *Brucella* infection,[6] meningococcal septicemia,[7] and recurrent staphylococcal skin infection[8] have been shown to be associated with this immunodeficiency disease.

Adult-onset IgM deficiency is usually associated with autoimmune disease or malignancy and CD4 lymphocyte count may be lower than normal.[9] Although this patient had a relatively low CD4 lymphocyte count, T cell functions were normal. No evidence of either autoimmune diseases or malignancy was identified. Other secondary causes of immunodeficiency were not found in this patient, including human immunodeficiency virus (HIV) infection. Causes of IgM deficiency could be either from low production or loss of the protein. The laboratory investigations that may suggest loss of protein, (e.g., serum albumin), other immunoglobulin subclasses, and/or urine protein, were all within normal limits in this patient. These suggested low production as a primary cause of IgM deficiency in this patient.

Many primary immunodeficiencies predispose affected individuals to pneumococcal disease.[1] Most B and T cell defects, deficiencies of the early component of the classical complement pathway, and defective Toll-like receptor signaling have been reported to confer individuals to high risk of invasive pneumococcal disease. In this patient, selective polysaccharide antibody deficiency could not be excluded since she was immunized with the conjugated vaccine, not the polysaccharide vaccine. An enzyme-linked immunosorbent assay of anti-*S. pneumoniae* capsular polysaccharide IgG in this patient did not show adequate antibody response. However, this condition is usually associated with low IgG2 level, as IgG2 is the major responsible immunoglobulin to polysaccharide antigen. Strictly, the patient with this condition should have other classes of immunoglobulin in normal ranges. The normal IgG2 level and low IgM level in this patient suggest selective polysaccharide antibody deficiency to be less possible. For interleukin-1 receptor associated kinase-4 (IRAK-4) deficiency and myeloid differentiation primary response 88 (MyD88) mutation, most people with these conditions have their first bacterial infection before age 2 years, and all before age 8 years. The infections can be life threatening in infancy and childhood, and become less frequent with age. This patient was previously healthy. This clinical setting would suggest that IRAK-4 deficiency and MyD88 mutation might not be the primary cause of immunodeficiency in this patient.

To date, there has been only one report that showed a case of selective IgM deficiency who presented with life-threatening invasive pneumococcal infection.[10] IgM is a circulating immunoglobulin. Its deficiency is often associated with systemic infections and blood-borne pathogens. Serum IgM usually exists as a pentamer and readily forms antigen–antibody complexes with high avidity, and is an exceptionally potent activator of the classical complement pathway, which is well known as a major host defense to *S. pneumoniae* infection. This may explain the increased susceptibility to pneumococcal infection in patients with selective IgM deficiency.

In conclusion, we have presented a case of pneumococcal septic arthritis in a previously healthy individual. Invasive pneumococcal disease in a previously healthy adult should lead to further investigation for underlying diseases including immunodeficiency, autoimmunity, and malignancy. While rare, selective IgM deficiency should be added to a list of primary immunodeficiency diseases associated with increase susceptibility to pneumococcal infection.

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