

Recurrent septic shock in a 34-year-old woman

Shenil Shah, M.D.,¹ Thomas Mertz, D.O., PharmD.,² and Timothy Craig, D.O.²

ABSTRACT

A 34-year-old woman presented to the Emergency Room (ER) with an acute presentation of septic shock that required fluid and pressor support in the Intensive Care Unit. History revealed this was her third episode of such a presentation with asymptomatic periods in between. She responded well to medical interventions but reported persistent joint pain. Immunologic workup revealed her diagnosis.

(Allergy Asthma Proc 33:437–440, 2012; doi: 10.2500/aap.2012.33.3591)

CASE PRESENTATION

Chief Complaint

A 34-year-old woman presents to the Emergency Room with a 4-day history of joint pains and vaginal bleeding before becoming hypotensive, tachycardic, lethargic, and pale in what is her third lifetime episode of septic shock.

History of Present Illness

Initial laboratory evaluation revealed an elevated white blood cell count and thrombocytopenia. Her clinical status deteriorated requiring Intensive Care Unit management of septic shock. She was intubated for airway protection and required fluids and pressors. Broad-spectrum antibiotics were initiated and were later switched to ceftriaxone based on culture and sensitivity.

Based on the Aforementioned Clinical Presentation, What Initial Laboratory Evaluation Should Be Performed?

1. CH50
2. Full complement panel
3. IgG
4. IgM
5. IgA

Answer: CH50, Quantitative Immunoglobulin Levels (IgG, IgM, and IgA). Based on her severe recurrent infections initial laboratory evaluation included a complement screen as well as immunoglobulin levels. Results revealed a low CH50, total IgG, IgG1, and IgG2. (Table 1) The CH50 encompasses the entire complement pathway and helps determine the functionality of the innate immune system.¹ CH50 serves as the best screening test for patients who manifest with recurrent infections suspicious for a complement deficiency. A reduction in any of the complements shows an abnormally low CH50. This necessitates a full complement panel, which ultimately helped confirm this patient's diagnosis of complement C2 deficiency. After initiating appropriate antibiotics she responded well to medical interventions; however, she reported persistent joint pain and fatigue.

Based on Her Deficiency of C2, What Organism Would Most Likely Be Isolated from Her Blood?

1. *Streptococcus pneumoniae*
2. *Pseudomonas aeruginosa*
3. *Aspergillus*
4. *Pneumocystis jiroveci*
5. Group B *Streptococcus*
6. *Candida*

Answer: *S. pneumoniae* Would Be Expected because It Is the Most Commonly Isolated Organism in Patients with C2 Deficiency.² Group B *Streptococcus*, an unlikely organism in C2 deficiency, was isolated from this patient's serum. Immunoglobulin deficiency is more likely to predispose a patient to encapsulated organisms such as *S. pneumoniae*. Our literature search revealed only one other case report of a patient with C2 deficiency who grew group B *Streptococcus*-positive blood cultures.³ *S. pneumoniae* was isolated from our patient's serum during her previous episode of sepsis (Table 2).

From the Departments of ¹Medicine and ²Section of Allergy, Asthma and Immunology, Pennsylvania State University College of Medicine, Hershey, Pennsylvania
The authors have no conflicts of interest to declare pertaining to this article
Address correspondence and reprint requests to Timothy Craig, D.O., Section of Allergy, Asthma and Immunology, Penn State University, 500 University Drive, Hershey, PA 17033
E-mail address: tcraig@hmc.psu.edu

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Table 1 Laboratory results

Laboratory	Result	Normal Range
IgG	470 L	700–1600
IgM	89	40–230
IgA	125	70–400
IgG1	257 L	382–929
IgG2	164 L	241–700
IgG3	72	22–178
IgG4	7.2	4.0–86.0
CH50	<10 L	31–60
C2	Undetectable	1.6–3.5
C3	173 H	88–165
C4	22	14–44
ANA	<1:40	<1:40
RF	37 H	<12
Anti-CCP	<16	<20
CRP	11.66 H	<1.0
ESR	59 H	0–20

Table 2 Complement deficiency manifestations

Deficiency	Clinical Findings
C1q	SLE or SLE-like conditions most common, as well as bacterial infections
C1r	
C1s	
C4	Bacterial infections most common, with some patients presenting with SLE or SLE-like conditions
C2	
C3	
C5	Recurrent <i>Neisseria</i> infections, with the most common being meningococcal
C6	
C7	
C8	Hereditary angioedema; some patients found to have secondary C2 deficiencies
C9	
C1 inhibitor	

SLE = systemic lupus erythematosus.

What Additional Testing Would You Order to Determine the Cause of Her Arthralgias?

1. Rheumatoid factor
2. Anti-CCP
3. ANA
4. Anti-ds DNA

Answer: All of the Above. Joint culture was negative for a septic joint and a rheumatologic panel that included ANA, Anti-ds DNA, and Anti-CCP were all within normal limits. Rheumatoid factor was positive but not thought to be of clinical significance to the case.

Most Common Organisms Isolated

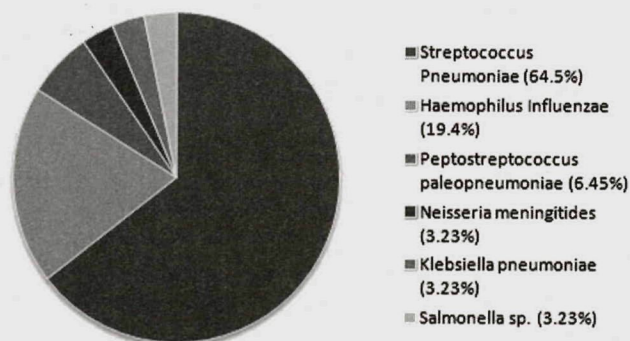


Figure 1. The percentages for the different organisms that cause infections in patients with complement deficiencies.

The frequency of rheumatic diseases associated with complement deficiency is believed to be secondary to complement's removal of immune complexes from the blood.^{4–6} For this reason, patients with complement deficiency are predisposed to systemic lupus erythematosus (SLE)-like disease.⁷ It is quite possible that her joint pains could be attributed to a rheumatologic manifestation of her complement deficiency.

On Follow-Up after Discharge, What Further Steps Would You Take?

1. *S. pneumoniae* vaccination
2. Amoxicillin prophylaxis
3. *Neisseria meningitidis* vaccination
4. *Haemophilus influenzae* vaccination
5. Ceftriaxone prophylaxis
6. Moxifloxacin prophylaxis
7. Complement testing of family members

Answer: S. pneumoniae, N. meningitidis, and H. influenzae vaccinations and amoxicillin prophylaxis, as well as complement testing of family members. One month later she was back to her baseline health and energy level. Vaccinations for encapsulated organisms were administered based on current recommendations for *S. pneumoniae*, *N. meningitidis*, and *H. influenzae*.^{8,9} She was started on amoxicillin prophylaxis because of her frequent severe infections and instructed to begin taking Augmentin at the first sign of a fever or illness.

The majority of complement disorders are inherited in an autosomal recessive pattern.^{10,11} After her diagnosis was made we recommended the patient's children be screened with a CH50.

DISCUSSION AND LITERATURE REVIEW

It is well known that a defect in the complement system inhibits the ability of antibodies to destroy pathogens *via* inducing inflammation, opsonization, and cell lysis.¹² Different components of the complement system are responsi-

Table 3 Associated diseases with complement level laboratory abnormalities

Disease	C3	C4	Other Labs
Cryoglobulinemia	↓ or Normal	↓	
Hereditary angioedema	Normal	↓	Decreased or poorly functioning C1-INH; C2 during attack
Hypocomplementemia vasculitis	↓ or Normal	↓	Decreased C1q
Inflammation	↑	↑↑	
Poststreptococcal glomerulonephritis	Normal	↓	
SLE	↓	↓ or Normal	Associated with primary complement defects

C1-INH = C1-inhibitor; SLE = systemic lupus erythematosus.

ble for aiding the recognition and clearing of specific organisms. C2 deficiency is the most common homozygous complement deficiency, especially among white subjects, at a frequency of ~1:20,000.¹³ Manifestations of C2 deficiency are diverse, and not all patients may present with recurrent infections and septic shock. When infections are seen in patients with C2 deficiency, they often involve the upper respiratory tract and are caused by encapsulated bacteria such as *S. pneumoniae*.¹⁴ Fasano *et al.* showed that *S. Pneumoniae* was the most common organism isolated among 31 C2 complement-deficient individuals² (Fig. 1).

When complement deficiency is suspected, a hemolytic assay CH50 and AH50 is indicated as a screening test to determine the functionality of the classic and alternative pathways. A CH50 level below the lower limit of normal is suggestive of a complement deficiency.¹ In our case, the level was found to be <10. To confirm a specific deficiency, individual complement levels should be assayed. Because C2 deficiency is the most common homozygous deficiency, it may be cost-effective to obtain this assay first.¹⁵ Each complement component is inherited *via* two functioning production genes. It is worth noting that several medical conditions such as cryoglobulinemia, SLE, and other inflammatory states may lead to complement level abnormalities. Some of these conditions are included in Table 3.

Of note, our patient was also found to have low IgG1 and IgG2. IgG1 deficiency has been associated with a predisposition to pyogenic infections.¹⁶ In a study by Lacombe *et al.*, selective IgG1 deficiency was found in 119 patients of 3005 who sustained frequent infections.¹⁷ Because IgG2 is primarily responsible for an individual's antibody response to polysaccharide capsular antigens, deficiency states predispose the body to infections from *S. pneumoniae*, *H. influenzae* type b, and *N. meningitidis*.¹⁸ A deficiency of IgG1, IgG2, and complement C2 was unexpected in this patient; however, her response to pneumococcal and tetanus vaccines suggests that the main deficiency that predisposed her to infections was complement deficiency.

Because defects in the complement system inhibit the body's ability to remove immune complexes from cir-

culatation, it predisposes individuals to autoimmune manifestations such as SLE.¹³ Our patient had suffered from various joint pains through the years before her hospitalization. After her infection seemed to clear, her chief complaint became severe right shoulder pain, for which no clear etiology could be found despite multiple studies. We could not confirm lupus in our patient; however, we suspect a positive rheumatoid factor to be associated with her recent infection. Although patients with C2 deficiency may develop a lupus-like syndrome, there are many differences between the two conditions. Lupus-like syndromes associated with complement deficiency rarely have central nervous system or renal impairment.^{19,20} Cutaneous involvement is common in patients with C2 deficiency; however, this was not seen in our patient. Laboratory testing also has different results because they often do not have positive anti-dsDNA and ANA.¹⁹

One of the largest cohorts of C2-deficient patients was published by Jonsson *et al.* out of Sweden. Data from 40 years covering 40 patients with C2 deficiency were reviewed. Their data confirmed the well-known association between C2 deficiency and recurrent pneumonias, as well as SLE. Twenty-three of these 40 patients had a history of invasive infections, such as septicemia and meningitis, which was caused primarily by *S. pneumonia*. Twelve of these patients suffered from repeated infections of this type. Of the 40 patients, 29 patients were diagnosed with pneumonia and 10 of these cases were recurrent. SLE was found in 10 of the 40 patients. Seven additional patients were found to have undifferentiated connective tissue disease.¹⁵

FINAL DIAGNOSIS

Complement C2 deficiency.

CONCLUSION

Recurrent episodes of septic shock in otherwise young and healthy individuals should lead to a suspicion of an

underlying immunodeficiency. Despite having three episodes of septic shock, our patient did not have a formal immunologic workup until age 34 years. Although complement deficiencies are rare disorders, C2 deficiency is the most common of these. In patients with severe infections or recurrent meningitis, complement deficiency should be considered. Improved clinician awareness of immunodeficiencies will lead to an earlier consultation, appropriate assessment, treatment, and hopeful reduction in morbidity and mortality.

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