CASE REPORTS

Meningococcal meningitis in a patient with urticarial vasculitis: is there a link?

A 53-year-old woman was referred to the immunology clinic for further assessment after an episode of serotype Y meningococcal meningitis. She had no history of exposure to meningococcal infection or of foreign travel. Otherwise, she had no history of infections. Six months before the admission with the meningitis, she had an episode of pleurisy, which did not respond to antibiotics but responded to a 5 day course of prednisolone. Apart from this short course of steroids 6 months before the meningitis she had not received any immunosuppressive drugs.

She had had persistent non-productive cough with breathlessness since the age of 47 years. A chest CT scan and spirometry, at this stage, were normal.

From the age of 48, she had been experiencing urticaria, mainly on her arms and legs, almost every day. The wheals took about 12 hours to develop and lasted for at least 24 hours, leaving bruise-like marks. In addition, she had episodes of angioedema affecting the face, cheeks, lips and eyelids. Because of the atypical features of her chronic urticaria, which were suggestive of urticarial vasculitis, a skin biopsy was done. This showed non-specific changes of dermal oedema and little perivascular inflammatory cell infiltration. Treatment with antihistamines had little benefit.

She had had recurrent episodes of aches and painful swelling of her knees, ankles, wrists and fingers, lasting for more than a week from the age of 50, but no morning stiffness or deformity. Most recently, she had been diagnosed with anterior uveitis.

On physical examination, she had non-scarring urticaria on legs and arms, angioedema of the upper lip and red left eye. Both knees and both ankles were tender and swollen with synovitis. There was no organomegaly. Her blood pressure was 159/87 mm Hg. Urinalysis showed +3 blood and +3 protein.

Investigations

Laboratory parameters were as follows (reference ranges in parentheses): erythrocyte sedimentation rate 25 mm/h, C reactive protein 66 mg/dl (0.3–5), haemoglobin 105 g/l (115–165), lymphocyte count $1.03 \times 10^9/l$ (1.5–4.0), with normal neutrophil, eosinophil and platelet counts; urea 9.6 mmol/l (3.5–7.4), creatinine 129 $\mu\text{mol/l}$ (44–80), estimated glomerular filtration rate 40 ml/min/1.73 m² (>60) and proteinuria 2.5 g/24 h (<0.15 g/24 h urine), with normal electrolytes, liver enzymes, albumin and total proteins.

Complement assessment revealed low C3 (0.40 g/l (0.62–1.6)), C4 (<0.02 g/l (0.14–0.39)) and total haemolytic activity CH₅₀ <7 U/ml (25–45 U/ml), and normal alternative pathway activity (AP₁₀₀ 82% (70–130%)). These results were suggestive of persistent classical pathway activation. She had normal C1 inhibitor level (30 mg/dl (19–60)) and function (105% normal (50–200)). Auto-antibodies including anti-nuclear antibody, anti-extractable nuclear antigens, anti-double stranded-DNA, rheumatoid factor, anti-neutrophilic cytoplasmic and cardiolipin antibodies were all negative. Cryoglobulin was

negative. Hepatitis B and C serology was negative. C1q was undetectable (<11 mg/l (50–250)), whereas anti-C1q antibody was strongly positive (>400 U/ml (0–15)). Mannose-binding lectin (MBL) was 76.6 ng/ml (MBL <75 ng/ml is associated with homozygous deficiency and very high risk of infection), and 75–400 ng/ml with increased risk of infection).

Immunoglobulins, including IgG subclasses were normal. She made a good response to the tetravalent ACWY meningococcal and 23 valent pneumococcal polysaccharide vaccines.

Abdominal ultrasound was normal. Renal biopsy histology was consistent with type I mesangiocapillary glomerulonephritis.

Lung function tests were consistent with mild airflow obstruction. Chest CT scan showed distributed ill-defined nodules, the largest being 18 mm in diameter, possibly inflammatory lesions. There were no features of emphysema or bronchiectasis.

Bronchoscopy was normal, and broncho-alveolar lavage cultures were negative for fungi, mycobacteria and other bacteria.

Management

A diagnosis of hypocomplementaemic urticarial vasculitis syndrome (HUVS) was made on clinical and serological grounds. The patient made a clear improvement after three doses of methylprednisolone 500 mg on alternative days; her rash largely disappeared, her cough and breathlessness improved and she felt generally better, in addition to the improvement in renal function and inflammatory markers. She was then started on oral prednisolone 40 mg/day, tapered gradually after 2 weeks. As she reduced the prednisolone to 20 mg/day, she experienced a flare in her symptoms.

In view of the temporary response to steroids and the results of the renal biopsy, cyclophosphamide was given, 500 mg every 2 weeks for 9 months, then monthly for another 6 months. There was a noticeable improvement in clinical manifestations and laboratory parameters, including inflammatory markers and kidney function. The nodules on the lung CT scan decreased. Immunologically, she showed sustained improvement in C4 and C1q levels, with some dissociation between symptoms and test results (see table 1).

Discussion

Our patient fulfilled the diagnostic criteria of HUVS established by Schwartz *et al.*¹ The diagnostic criteria for this rare autoimmune disease are chronic urticaria and hypocomplementaemia, with at least two of the following: vasculitis features from skin biopsies; arthralgia or arthritis; glomerulonephritis, uveitis or episcleritis; abdominal pain; or the presence of anti-C1q antibody in the plasma.^{1–2}

Urticarial vasculitis can be associated with normal or low complement levels (hypocomplementaemic vasculitis, HUV). The latter is more frequently associated with systemic involvement³ and has been linked to systemic lupus erythematosus (SLE), Sjögren syndrome, cryoglobulinaemia/hepatitis C virus infection and monoclonal gammopathy.^{4–5} In some HUV cases, there is no evident underlying disease, and HUVS is then defined serologically by the presence of autoantibodies to C1q only.⁶ These antibodies may play a pathogenic role, forming immune complexes with C1q and activating the complement classical pathway, leading to depletion of the complement components with very low serum levels of C1q, C4 and C2, and moderately reduced levels of C3.

Various immunosuppressive agents have been used depending on the clinical presentation. HUVS patients should be monitored for manifestations of renal, pulmonary and ocular disease.

Although our patient had troublesome urticaria, angioedema, painful arthritis and respiratory symptoms for years, the diagnosis of HUVS was not made until she presented with *Neisseria meningitidis* serogroup Y meningitis. As serogroup Y is considered to be an organism of relatively low virulence,⁷ the possibility of underlying complement deficiency was raised.⁸

Both inherited and acquired disorders of the complement system are associated with increased susceptibility to infections with encapsulated bacteria, particularly meningococcus.^{9–10} Complement deficiency is present in about 5–18% of patients who have experienced a meningococcal infection.^{9–11} The highest prevalence was found in patients who developed infections due to serogroups X, Y, W135, or non-groupable strains (45%).^{9–12} Of the complement deficiencies, 42% involved a component of the alternative pathway, 12% a deficiency of C3, and 46% a component of the terminal route.^{10–13} About a third of patients with C1q deficiency have recurrent bacterial infections, including meningitis and pneumonia.¹⁴

MBL deficiency is associated with increased susceptibility to meningococcal disease in children, particularly under 12 months of age, and those who are homozygous for the defective allele.¹⁵ The high frequency of MBL deficiency¹⁶ suggests that the defective MBL-mediated innate immunity can be compensated by alternative defence strategies, including antibody-mediated classical pathway activation in most adults.¹⁷ Thus the impact of MBL deficiency is very modest and its phenotypic expression is modified by concomitant inherited or acquired defects in the immune response.¹⁶

Meningococcal infections have been reported in patients with acquired complement deficiencies particularly patients with membranoproliferative glomerulonephritis^{18–19} and

Table 1 Results of immunological investigations

Immunological investigations	At diagnosis	4 months after treatment	1 year after treatment	Reference range
C3	0.36	0.57	0.60	0.62–1.6 g/l
C4	<0.02	0.06	0.07	0.14–0.39 mg/dl
Anti-C1q antibody	400	114	44	0–15 U/ml
C1q	<11	28	32	50–250 mg/l

SLE.^{7, 18–20} These patients develop acquired hypocomplementaemia due to immune complex activation of the classical pathway leading to consumption of C3 and C4, resulting in defective opsonisation and chemotaxis,²¹ or the terminal membrane attack complex formation²² and increased risk of infection. The persistent consumption of C3 may also affect the ability to activate the alternative pathway; the very low C2 and C4 levels prevent the complement activation via the MBL pathway.

Our patient's C4 level has not returned to normal, raising the question of abnormal C4 alleles. C4B deficiency has been linked to meningococcal disease, but as for MBL deficiency, this typically presents in childhood.²³

Our patient had acquired classical complement pathway deficiency as seen in active SLE; simultaneously she had MBL deficiency, which acted as a contributing factor to her increased susceptibility to meningococcal infection.

Management of complement deficiency consists primarily of preventive measures including immunisation with polysaccharide and available conjugated meningococcal, pneumococcal and *Haemophilus influenzae* b vaccines. In addition, the patient should be educated to early recognise signs and symptoms of meningitis.

Conclusion

A high index of suspicion for an underlying complement deficiency should arise when a patient presents with recurrent meningococcal disease or a disease caused by uncommon serogroups, particularly Y, W135, and X.

Although urticaria is a common condition, atypical features should alert the doctor to the possibility of urticarial vasculitis and an underlying autoimmune systemic disease.

Hana Alachkar

Immunology Department, Hope Hospital, Manchester, UK

Faieza Qasim, Yasmeen Ahmad, Matthew Helbert

Central Manchester and Manchester University Children's Hospitals, Manchester, UK

Correspondence to: Dr Hana Alachkar, Immunology Department, Hope Hospital, Manchester M6 8HD, UK; hana.alachkar@srht.nhs.uk

doi: 10.1136/jcp.2007.047522

Accepted 4 July 2007

Competing interests: None declared.

References

- Schwartz HR, McDuffie FC, Black LF, et al. Hypocomplementemic urticarial vasculitis. Association with chronic obstructive pulmonary disease. *Mayo Clin Proc* 1982;**57**:231–8.
- Wisniewski JJ, Baer AN, Christensen J, et al. Hypocomplementemic urticarial vasculitis syndrome. Clinical and serologic findings in 18 patients. *Medicine (Baltimore)* 1995;**74**:24–41.
- Mehregan DR, Hall MJ, Gibson LE. Urticarial vasculitis: a histopathologic and clinical review of 72 cases. *J Am Acad Dermatol* 1992;**26**:441–8.
- Davis MD, Daoud MS, Kirby B, et al. Clinicopathologic correlation of hypocomplementemic and normocomplementemic urticarial vasculitis. *J Am Acad Dermatol* 1998;**38**:899–905.
- Wisniewski JJ. Urticarial vasculitis. *Curr Opin Rheumatol* 2000;**12**:24–31.
- Wisniewski JJ, Naff GB. Serum IgG antibodies to C1q in hypocomplementemic urticarial vasculitis syndrome. *Arthritis Rheum* 1989;**32**:1119–27.
- Feliciano R, Swedler W, Varga J. Infection with uncommon subgroup Y *Neisseria meningitidis* in patients with systemic lupus erythematosus. *Clin Exp Rheumatol* 1999;**17**:737–40.
- Fijen CA, Kuijper EJ, Hannema AJ, et al. Complement deficiencies in patients over ten years old with meningococcal disease due to uncommon serogroups. *Lancet* 1989;**2**:585–8.
- D'Amelio R, Agostoni A, Biselli R, et al. Complement deficiency and antibody profile in survivors of meningococcal meningitis due to common serogroups in Italy. *Scand J Immunol* 1992;**35**:589–95.
- Swart AG, Fijen CA, Te Bulte MT, et al. Complement deficiencies and meningococcal disease in The Netherlands. *Ned Tijdschr Geneesk* 1993;**137**:1147–52.
- Tedesco F, Nurnberger W, Perisutti S. Inherited deficiencies of the terminal complement components. *Int Rev Immunol* 1993;**10**:57–64.
- Figuerola JE, Densen P. Infectious diseases associated with complement deficiencies. *Clin Microbiol Rev* 1991;**4**:359–95.
- Ross SC, Densen P. Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency. *Medicine (Baltimore)* 1984;**63**:243–73.
- Bowness P, Davies KA, Norsworthy PJ, et al. Hereditary C1q deficiency and systemic lupus erythematosus. *Q J Med* 1994;**87**:455–64.
- Hibberd ML, Sumiya M, Summerfield JA, et al. Association of variants of the gene for mannose-binding lectin with susceptibility to meningococcal disease. *Lancet* 1999;**353**:1049–53.
- Casanova JL, Abel L. Human mannose-binding lectin in immunity: friend, foe, or both? *J Exp Med* 2004;**199**:1295–9.
- Roos A, Garred P, Wildenberg ME, et al. Antibody-mediated activation of the classical pathway of complement may compensate for mannose-binding lectin deficiency. *Eur J Immunol* 2004;**34**:2589–98.
- Garty BZ, Nitzan M, Danon YL. Systemic meningococcal infections in patients with acquired complement deficiency. *Pediatr Allergy Immunol* 1993;**4**:6–9.
- Hulton S, Risdon RA, Dillon MJ. Mesangiocapillary glomerulonephritis associated with meningococcal meningitis, C3 nephritis factor and persistently low complement C3 and C5. *Pediatr Nephrol* 1992;**6**:239–43.
- Mitchell SR, Nguyen PQ, Katz P. Increased risk of neisserial infections in systemic lupus erythematosus. *Semin Arthritis Rheum* 1994;**20**:174–84.
- Hepburn AL, Davies KA. Infection and SLE. *Ann Rheum Dis* 2002;**61**:668–9.
- Ellison RT 3rd, Kohler PF, Curd JG, et al. Prevalence of congenital or acquired complement deficiency in patients with sporadic meningococcal disease. *N Engl J Med* 1983;**308**:913–16.
- Rowe PC, McLean RH, Wood RA, et al. Association of homozygous C4B deficiency with bacterial meningitis. *J Infect Dis* 1989;**160**:448–51.

Bickerstaff's brainstem encephalitis related to *Campylobacter jejuni* gastroenteritis

Campylobacter species are microaerophilic spiral-shaped Gram-negative bacilli which cause diarrhoeal and systemic illness in humans and animals. They are the most commonly identified cause of bacterial intestinal disease in the UK and elsewhere in the developed world. The bacterial cell wall of the organism contains an endotoxin which, when released, can result in acute enteritis and complications such as reactive arthritis, erythema nodosum, peripheral neuropathy, haemolytic uraemic syndrome and Bickerstaff's brain stem encephalitis (BBE). Here we report a case of BBE following a gastrointestinal infection with *Campylobacter*

jejuni. The patient presented with acute onset of confusion and ophthalmoplegia. The cerebrospinal fluid (CSF) showed lymphocytic pleocytosis and raised protein. This acute presentation was preceded by an episode of *Campylobacter*-related diarrhoea as confirmed by high titres of *Campylobacter*-specific IgM antibodies.

Over 50 000 laboratory confirmed cases of *Campylobacter* intestinal disease are reported annually in England and Wales.¹ *Campylobacter jejuni* is the most common species of the genus *Campylobacter* identified in clinical samples.¹ Transmission occurs throughout the year but rises in late spring and early summer, and requires only small inoculums.² Clinical features of *C. jejuni* infection range from an absence of symptoms to fulminant sepsis and death. In rare cases a potentially life threatening form of post-infectious encephalitis affecting the brainstem can arise.³ Initial colonisation occurs in the jejunum and ileum, which spreads distally to involve the colon and rectum. After a prodromal illness, the patient may develop abdominal pain and bloodstained diarrhoea. Other common complications include septic polyarthritides and peripheral polyneuropathy.

In 1957 Bickerstaff described eight patients with brainstem encephalitis presenting with ophthalmoplegia, ataxia and a reduced level of consciousness. Our extensive literature search has revealed only a few documented cases of BBE secondary to intestinal infection with *Campylobacter*.⁴

Case report

A 54-year-old man presented with a 1-week history of fever, anorexia and vomiting. On arrival at hospital he was febrile, confused and slightly dysarthric but there were no signs of meningism. Neurological examination showed a generalised weakness of all four limbs. He had absent lower limb reflexes and diminished reflexes in the upper limbs. The right plantar response was extensor while the left was equivocal. Owing to his confusion, adequate sensory testing could not be performed.

Initial investigations were unremarkable. In view of a working diagnosis of encephalitis, a lumbar puncture was performed following a

Table 1 Serological markers of *Campylobacter jejuni* infection

	Day 1	Day 6	Day 98
IgM	<80	1280	160
IgG	80	5120	320
IgA	<80	320	80

Table 2 Diagnostic criteria of Bickerstaff's brainstem encephalitis

Progressive symmetrical ophthalmoplegia
Ataxia
Decreased level of consciousness
Pyramidal signs
Bilateral limb weakness
Characteristic MRI findings
Absent or disappearing F-waves on electromyographic studies