Case Report

Chronic meningococcaemia and immunoglobulin A deficiency

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Chronic meningococcaemia is an unusual clinical presentation of *Neisseria meningitidis* infection. We describe the case of a patient, who presented with total IgA deficiency and partial IgM deficiency with a low switched memory B cells count, suggestive of a borderline form of common variable immunodeficiency (CVID). The role of IgA in the protection against *Neisseria meningitidis*, and the link between IgA deficiency and CVID are discussed.

Case report

A 20-year-old woman was referred to the Department of Internal Medicine (Hôpitaux Universitaires de Strasbourg) with a 3 week history of fever, rash and arthralgia. She had a history of mild asthma, and frequent ear, nose and throat infections. Three weeks previously, she had experienced fever up to 40 °C and polyarthralgia of knees and ankles, followed 2 days later by a maculopapular eruption of her arms and legs, rapidly improving in a few days.

A second episode occurred the following week, with fever up to 40.3 °C. Laboratory studies revealed a high neutrophil count (25 000 neutrophils mm⁻³) and a high C-reactive protein (CRP) level (210 mg l⁻¹). Infectious (especially blood culture) and auto-immune investigations were negative. A chest radiograph was normal. Clinical symptoms spontaneously improved in 4 days: neutrophil counts normalized and her CRP level clearly decreased (32 mg l⁻¹).

Ten days later, the patient was admitted to the Department of Internal Medicine (Hôpitaux Universitaires de Strasbourg) with recurrence of the same symptoms. The patient was complaining of pain in her shoulders, wrists, hands, knees and ankles, associated with cutaneous eruption and fever. Examination revealed a maculopapular rash affecting her trunk and limbs, including the palms and the soles of her feet (Fig. 1), and petechial purpura with some necrosis (Fig. 2). There was no synovitis, signs of meningitis or other focal symptoms. Her temperature was 39.2 °C at admission, and remained normal during the whole hospitalization, except for a 39.5 °C temperature spike on the fourth day. The rash suggested first a *Neisseria gonorrhoeae* sepsis.

At admission, the patient's CRP rose to 213 mg l⁻¹ and her neutrophil count reached 13 000 neutrophils mm⁻³. Cutaneous biopsy showed a thrombotic vasculopathy with neutrophils, consistent with cutaneously localized bacteraemia. Real-time PCRs (Applied Biosystems 7000), using primers for the meningococcal capsular transport gene (*ctrA*) and sialyltransferase gene (*siaD*) (Corless *et al.*, 2001), were positive for the skin biopsy sample. Blood cultures drawn during the fourth day fever spike were positive for *Neisseria meningitidis* serogroup B, phenotype B:4:P1.4. The patient's condition improved significantly within 7 days of ceftriaxone treatment (1 g once daily for 7 days).

After recovery, immunological investigations (Table 1) revealed a total IgA deficiency and a decreased IgM level, as well as a slightly decreased IgG3 level, while total IgG was normal. Anti-tetanus antibodies were within the normal range. There were no signs of nephrotic syndrome or protein-losing enteropathy. The absolute lymphocyte count was 2472 lymphocytes mm⁻³ with significantly decreased switched memory B cells (CD27⁺/IgM⁺/IgD⁺). The patient's family history was not evocative of familial immunodeficiency.

Discussion

Clinical and biological similarities between the three episodes of fever, cutaneous eruption and arthralgia suggest a persistent infection with *N. meningitidis*, although blood cultures were negative in the first two episodes. This case is strongly suggestive of chronic meningococcaemia, a rare clinical form of invasive *N. meningitidis* infection, defined as a meningococcaemia with a persistence of fever lasting at least one week, but without symptom of meningitis (Benoit, 1963).

Abbreviations: CRP, C-reactive protein; CVID, common variable immunodeficiency.

Fig. 1. Third episode of eruption, with maculopapular lesions affecting the palms.

The immunopathological mechanisms responsible for chronic evolution of a meningococcaemia have not yet been elucidated. Complement system protein deficiency, especially for the complement membrane attack complex (C5, C6, C7 and properdin), are most often described (Nielsen *et al.*, 1990), but were not found in our case. A complete IgA deficiency has already been described in a patient with a history of chronic meningococcaemia (Farron *et al.*, 1996). Because of the high incidence of IgA deficiency in the population, this could be a fortuitous association, but a review of the literature argues in favour of a prominent role of IgA in the protection against *N. meningitidis*.

Fig. 2. Maculopapular rash and purpura with some necrotic elements from the third episode.

A total of 5 to 10 % of the general population and as many as 35 % of the older teenagers are asymptomatic carriers of *N. meningitidis* in the nasopharynx. Nevertheless, the bacteria will exceptionally be able to invade the nasopharyngeal mucosal epithelium and the submucosal layer, to enter into the bloodstream, and to cause infection. Most of the time, invasive infections occur in children and young adults. This low incidence of invasive meningococcal infection may partly be explained by the low virulence of some strains, but isolated phenotype B:4:P1.4, one of the most representative phenotypes of B serotype in France (Parent du Châtelet *et al.*, 2009), is not particularly associated with a low virulence. It may also be explained as a consequence of naturally acquired protective immunity (Horton *et al.*, 2005). As secretory IgAs are considered to be important for limiting colonization by *N. meningitidis* and preventing early invasion (Horton *et al.*, 2005), an IgA deficiency could facilitate mucosal invasion. Secretion by *N. meningitidis* of proteases that specifically cleave secretory IgAs supports this hypothesis (Vidarsson *et al.*, 2005).

Exploring the reasons for the low incidence of invasive meningococcal infections, Horton and colleagues studied a group of 258 students, in which 37 carried *N. meningitidis* serogroup B. These carriers had higher levels of specific IgA than the 221 others. They also showed that salivary levels of IgA specific for a range of meningococcal antigens increased with age (whereas the incidence of meningococcal infection decreased with age) (Horton *et al.*, 2005). These data argue for a key role of IgA in the host defence against meningococcal invasion.

The prevalence of IgA deficiency is high, reaching 1 in 500 in white populations (Latiff & Kerr, 2007). Primary IgA deficiency results from an underproduction of serum and mucosal IgAs, and the genetic mechanisms are multiple, although the IgA-encoding genes are normal. The disease may evolve into common variable immunodeficiency (CVID) in a single patient, or coincide with CVID in the same family (Blanco-Quirós *et al.*, 2006). This suggests that IgA deficiency and CVID may be different phenotypic manifestations of a similar genetic background (Litzman *et al.*, 2007). CVID includes a marked decrease of IgG (at least 2 SD below the mean for age) and in at least one of the isotypes IgM or IgA, the onset of clinically significant immunodeficiency after 2 years of age and the exclusion of defined causes of hypogammaglobulinaemia. In most CVID patients, there is a decrease in non-secretory CD27⁺ memory B cells, which include IgD⁺ cells (non-switched memory B cells) that produce only IgM antibodies, and IgD⁻ cells [switched memory B cells (smB)] that may produce IgG, IgM or IgA.

Recently, the EUROclass trial suggested a new classification based on total B cell counts, switched B memory cell counts and expansion of transitional cells or IgM⁺ CD21^{low} B cells (Wehr *et al.*, 2008). Our patient did not have CVID, but her lymphocyte counts would classify her in the B⁺ smB-21^{low} group, since she had no expansion of transitional B cells. The low count of CD27⁺ IgD⁻ B cells is probably

Table 1. Results of immunological investigations

Immunological feature	Value in the patient [$\uparrow$ or $\downarrow$ normal range]	Normal range
Total immunoglobulin	14.1 g l ⁻¹	7.0–15.0 g l ⁻¹
IgA	<0.24 g l ⁻¹ [$\downarrow$]	1.10–3.60 g l ⁻¹
IgM	0.26 g l ⁻¹ [$\downarrow$]	0.48–3.10 g l ⁻¹
Total IgG	15.5 g l ⁻¹	7.20–14.7 g l ⁻¹
IgG1	8.09 g l ⁻¹	3.41–10.3 g l ⁻¹
IgG2	4.30 g l ⁻¹	2.07–6.59 g l ⁻¹
IgG3	0.20 g l ⁻¹ [$\downarrow$]	0.21–1.45 g l ⁻¹
IgG4	0.218 g l ⁻¹	0.013–1.03 g l ⁻¹
Total complement protein activity	70 U ml ⁻¹	35–59 U ml ⁻¹
Complement C3	1.44 g l ⁻¹	0.79–1.53 g l ⁻¹
Complement C4	0.30 g l ⁻¹	0.15–0.40 g l ⁻¹
Lymphocytes	2472 mm ⁻³	1600–2400 mm ⁻³
B lymphocytes		
CD19 ⁺	279 mm ⁻³	200–400 mm ⁻³
B lymphocytes subpopulations		
Memory B cells (CD27 ⁺)	15.7 %	
Switched memory B cells (CD27 ⁺ IgM ⁻ IgD ⁻)	0.11 % [$\downarrow$]	2.60–13 %
Non-switched memory B cells (CD27 ⁺ IgM ⁺ IgD ⁺ or mantle zone B cells)	5.75 % [$\uparrow$]	0.80–2.20 %
Naive B cells (CD27 ⁻ IgM ⁺ IgD ⁺)	73.56 % [$\uparrow$]	9–20 %
Transitional B cells (CD38 ^{high} /IgM ^{high})	0.50 % [$\downarrow$]	1.00–3.00 %
Plasma cells (CD38 ^{high} /IgM ⁻)	0.6 % [$\downarrow$]	1.50–6.50 %
Plasmablasts (CD19 ⁺ CD21 ^{low} CD38 ^{low})	13.7 %	
T lymphocytes		
CD3 ⁺	1781 mm ⁻³	1100–1700 mm ⁻³
CD3 ⁺ /CD4 ⁺	1087 mm ⁻³	700–1100 mm ⁻³
CD3 ⁺ /CD8 ⁺	555 mm ⁻³	500–900 mm ⁻³
Memory/naive T lymphocytes		
Naive T cells (CD3 ⁺ /CD45RA ⁺)	49.1 %	
Memory T cells (CD3 ⁺ /CD45RO ⁺)	36.9 %	
Natural killer cells		
CD56 ⁺ /CD3 ⁻	329 mm ⁻³	200–400 mm ⁻³
Complement		
Component C3	50 U ml ⁻¹	35–59 U ml ⁻¹
Component C4	1.32 U ml ⁻¹	0.79–1.53 U ml ⁻¹
Total haemolytic complement (CH50)	0.25 U ml ⁻¹	0.15–0.40 U ml ⁻¹
HLA antigens	A3, A29(19), B44(12), B62(15)	

$\uparrow$, Above; $\downarrow$, below.

related to the IgA deficiency. There was no decrease in CD4⁺ T cell counts, frequent in CVID and IgA deficiency (Litzman *et al.*, 2007).

In IgA-deficient patients, Litzman *et al.* (2007) found no significant abnormalities in B cell development when compared with healthy controls. Since IgA deficiency and CVID are genetically closely related diseases, this suggests that B cell abnormalities in CVID are probably acquired and non-congenital, and are a part, or the consequence of, immunodeficiency in CVID.

Our hypothesis is that our patient could be in an intermediate stage between IgA deficiency and CVID (another hypothesis for the Litzman observation is that different types of IgA deficiency could exist, some of them

similar to CVID). Those immunological abnormalities (IgA deficiency and low switched memory B cell counts) could have led to a *N. meningitidis* bacteraemia, resulting in a chronic infection.

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