Case report

Fulminant *Neisseria meningitidis* septicaemia with purpura fulminans requiring limb amputation

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ABSTRACT

Despite the isolation of *Neisseria meningitidis* over 200 years ago, meningococcal disease remains a feared cause of bacterial sepsis, with significant morbidity and mortality, despite prompt antibiotic use and modern critical care support. *Neisseria meningitides* is a Gram-negative encapsulated diplococcus, which exists only in the human host (Kvalsvig and Unsworth, 2003). The bacterium can cause life-threatening septic shock and coagulopathy, which may rapidly manifest within a matter of hours from preceding mild symptoms (Kvalsvig and Unsworth, 2003). Whilst *N. meningitidis* is recognised as a common commensal organism in the nasopharynx, associated with asymptomatic carriage in up to 10 %, manifestation of life-threatening disease is rare (Rappuoli and Pizza, 2015). We report the case of 31-year-old male presenting with devastating meningococcal septicaemia with disseminated intravascular coagulopathy (DIC) and purpura fulminans, requiring surgical debridement and a right above-knee amputation for sepsis-driven skin necrosis. The patient suffered extensive tissue loss secondary to a type 3 immune hypersensitivity reaction involving immune-complex mediated inflammation and tissue necrosis. Due to a strong immune component driving the patient's failure to convalesce pulsed intravenous methylprednisolone was used alongside antimicrobial therapy. The use of steroids was associated with fever subsidence and significant clinical improvement, highlighting the benefit of corticosteroid use in immune-complex mediated pathology.

Introduction

Despite the isolation of *Neisseria Meningitidis* over 200 years ago, meningococcal disease remains a feared cause of bacterial sepsis, with significant morbidity and mortality, despite prompt antibiotic use and modern critical care support. *Neisseria meningitidis* is a Gram-negative encapsulated diplococcus, which exists only in the human host [1]. The bacterium can cause life-threatening septic shock and coagulopathy, which may rapidly manifest within a matter of hours from preceding mild symptoms [1]. Whilst *N. meningitidis* is recognised as a common commensal organism in the nasopharynx, associated with asymptomatic carriage in up to 10 %, manifestation of life-threatening disease is rare [2].

We report the case of 31-year-old male presenting with devastating meningococcal septicaemia with disseminated intra-vascular coagulopathy (DIC) and purpura fulminans, requiring surgical debridement and a right above-knee amputation for sepsis-driven skin necrosis. The patient suffered extensive tissue loss secondary to a type 3 immune hypersensitivity reaction involving immune-complex mediated inflammation and tissue necrosis. Due to a strong immune component driving the patient's failure to convalesce pulsed intravenous methylprednisolone was used alongside antimicrobial therapy. The use of steroids was associated with fever subsidence and significant clinical improvement, highlighting the benefit of corticosteroid use in immune-complex mediated pathology.

Case report

A 31-year-old man presented to his general practitioner with a one day history of bilateral joint pains and swelling, with the ankle and wrist joints most severely affected (*see* Fig. 1). Polyarthralgia was preceded by coryzal symptoms, sore throat, and fever. The patient did not have any symptoms suggestive of meningism including headache, photophobia and neck stiffness. The patient was born in the U.K. and received the U.K. childhood vaccination scheme. He worked as a full-time bus driver and had been in a heterosexual relationship for the last 16 years. The patient had no significant medical or family history. No foreign travel was reported.

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Fig. 1. Medical photographs taken on admission to hospital reflecting the patient's swollen joints. Left to right: right ankle, left hand, left hand.

Upon presentation to the emergency department the patient was alert and orientated in time, place and person. The following observations were recorded on admission: temperature 36.9 °C, heart rate 101 bpm, blood pressure 125/85 mmHg, respiratory rate 16 breaths per minute, and oxygen saturations were 99 % in room air. In line with the bedside clinical screening tool, qSOFA (quick Sepsis-related Organ Failure Assessment), introduced in 2016, this patient would have had a qSOFA score of zero. A score of zero, outside of intensive care, is associated with a low risk of poor clinical outcome [3]. Physical examination identified bilateral swelling and pain in the small joints of the hands and wrist joints, associated with a reduced range of movement. The same findings were demonstrated in the knee joints. A mild purpuric rash was noted on the limbs. Systemic examination was unremarkable. Importantly, no cardiac murmurs were identified. An arterial blood gas demonstrated metabolic acidosis with a raised lactate of 9.29 mmol/L. This is in keeping with a diagnosis of "cryptic shock", defined as a hyperlactataemia in the absence of hypotension, indicative of cellular and metabolic stress [3]. Radiographs of the chest, abdomen, wrist, knee, and ankle joints were all normal. Routine laboratory blood tests demonstrated a significant inflammatory response (C reactive protein 223 mg/L, erythrocyte sedimentation rate 45 mm/h, white cell count 4.9×10^9/L), coagulopathy (international normalised ratio 2, prothrombin time 24.9 s, D-dimer 42,011 ng/mL), and mild liver dysfunction (alanine aminotransferase 58 U/L, alkaline phosphatase 81 U/L). A urine sample demonstrated haematuria and proteinuria with negative leucocytes and nitrites. A provisional diagnosis of 'sepsis of unknown source with associated DIC' was made. Blood cultures were taken followed by commencement of broad-spectrum intravenous antibiotics (piperacillin/tazobactam) and intravenous fluids. Ten milligrams of intravenous vitamin K was administered to address the coagulopathy. Both ankle joints were aspirated to exclude multi-focal septic arthritis. The joint fluid was negative for both organisms and crystals.

Further blood tests were sent including anti-neutrophil cytoplasmic antibodies (ANCA), anti-nuclear antibodies (ANA), anti-Streptolysin O titre (ASOT), rheumatoid factor and lupus anticoagulant to exclude a possible undiagnosed connective tissue disease. Human Immunodeficiency Virus (HIV), hepatitis B and C tests were sent. All aforementioned tests were negative except for a mildly raised rheumatoid factor and lupus anticoagulant which, in the context of sepsis, was of no clinical significance. Urine total protein: creatinine ratio was markedly raised (164.2 mg/mmol). After 48 h, blood cultures grew gram-negative diplococcus, *N. meningitidis* group W135 (type 2A), sensitive to penicillin. The antibiotic regime was appropriately tailored to the identified pathogen and switched to benzylpenicillin (2.4 g 4 hourly). *Neisseria meningitidis* is a notifiable disease, therefore Public Health England was informed and household contacts were given prophylactic ciprofloxacin.

After nine days of intravenous antibiotics and supportive therapy, the patient remained febrile and inflammatory markers continued to rise (CRP 354 mg/L). Over this period the patient developed extensive ecchymosis with purpuric macules, large bullous lesions and soft tissue induration. The cutaneous lesions were predominantly on the limbs. Both ankle and wrist joints remained significantly swollen (*see* Fig. 2). The progressive skin lesions largely reflected a significant vasculitic element to the patient's initial presentation, consistent with a diagnosis of purpura fulminans. This is well recognised in the context of meningococcal disease. It is also known, albeit rarely, that meningococcus can seed to other anatomical sites including the pericardium, myocardium, spleen, chest and joints [4]. Therefore, to exclude suppurative sequelae of meningococcal infection, a computed tomography (CT) scan of the chest, abdomen and pelvis and a transthoracic echocardiogram were performed. Both investigations were normal, and no secondary foci of infection was identified.

Fig. 2. Medical photographs of the lower limb, foot, forearm and hand demonstrating evolving purpuric and bullous lesion with areas of skin necrosis consistent with a diagnosis of purpura fulminans.

Fig. 3. Medical photographs of the right lower limb and foot demonstrating extensive, well demarcated, necrotic skin lesions.

The cutaneous lesions evolved into well-demarcated areas of skin necrosis (see Fig. 3). A magnetic resonance imaging (MRI) scan of all four limbs was performed to exclude a deeper-seated infection in the soft tissues such as necrotising fasciitis. After ten days of intravenous therapy, the failure to defervesce (daily fevers recorded up to 39.5 °C, together with a marked non-resolving inflammatory response) combined with the development of new skins lesions suggested that the patient was displaying post-infectious, immune-driven complications. Such complications are largely driven by the formation of immune-complexes by antibody and antigen [4]. Historically, non-steroidal anti-inflammatories have been used been used to good effect [4,5]. However, the use of ibuprofen 400 mg three times per day did not ameliorate the patient's symptoms and pulsed intravenous methylprednisolone was required. The first dose of methylprednisolone (500 mg) was associated with fever lysis and continued clinical and biochemical improvement was observed throughout the duration of pulsed steroid therapy. Antibiotics were stopped after two weeks of treatment.

However, convalescence was complicated by recrudescence of fever and re-introduction of intravenous antibiotics (Meropenem 1 g three times per day) and oral steroids (prednisolone 40 mg once daily). Whilst the majority of cutaneous lesions regressed, a significant amount of tissue loss persisted over the dorsum of the right foot. A CT angiogram was performed which excluded macrovascular ischaemia. A repeat MRI scan of the right foot demonstrated an extensive, deep-seated soft tissue collection likely of inflammatory aetiology or related to associated soft tissue fat necrosis, given the overall clinical improvement in the patient including continued defervescence. At this point, the patient was referred to plastic surgeons for consideration of a skin graft. Unfortunately, surgical debridement and attempted flap cover was unsuccessful, and the patient underwent a life-saving right above-knee amputation.

Discussion

Neisseria meningitidis is an obligate, gram-negative diplococcus, which is a common commensal organism in the nasopharyngeal mucosal epithelium [2]. The bacterium lives innocuously in up to 10 % of the population in non-epidemic settings, with asymptomatic carriage rates increasing up to 35 % during epidemics. Contrastingly, in other colonised individuals the bacterium can lead to life-threatening fulminant sepsis. The clinical spectrum of disease associated with the pathogen is vast but includes three main categories: isolated meningitis, meningococcaemia, or both. Meningitis is the most common presentation as a result of meningeal tropism [4]. This is associated with the most favourable outcome with a uniformly good prognosis if diagnosed and treated promptly [1,6]. Mortality rates are highest when meningococcal sepsis presents in the absence of localised meningitis with reported mortality rates of up to 80 % [1]. Our case reports meningococcal infection presenting as an inflammatory arthritis, which is a rare manifestation previously documented in only 2%–12.5% of cases [5].

One prerequisite for the development of invasive meningococcal disease is the ability to bypass the host's mucosal immunity [1]. It is well recognised that invasive meningococcal disease is often preceded by viral upper respiratory tract infections. It is deduced that this preceding infection damages the integrity of epithelial cells, thereby promoting passage of the bacterium across the mucosa and into the bloodstream, leading to invasive disease [6]. Our patient similarly reported preceding coryzal symptoms and a sore throat, consistent with this theory. However, the susceptibility of the host is predominantly driven by a maladaptive immune response [1].

Our case illustrates fulminant meningococcal sepsis (meningococcaemia), as defined by the presence of both shock and DIC. These two pathological processes are largely driven by meningococcal endotoxin production. Microvascular injury occurs alongside consumption coagulopathy, which results in cutaneous haemorrhagic lesions. In this way, meningococcaemia can lead to the rare life-threatening condition, purpura fulminans [7]. The bacterium-produced endotoxin stimulates a 'Shwartzman-like' reaction [8]. This is a necrotising inflammatory response induced by the endotoxin resulting in local thrombohaemorrhagic lesions, and systemic coagulopathy and microthrombi [9]. The culminating event is full-thickness skin necrosis, as seen in our case. The disturbance between procoagulant and anticoagulant activities of endothelial cells results in depletion of protein C and protein S. Therefore, the use of recombinant Protein C in the management of purpura fulminans in the setting of septic shock remains a field for research [10]. Activated protein C was previously considered however, it was later withdrawn due to concerns over excess haemorrhage. At present, the use of recombinant protein C is only approved for congenital protein C deficiency [11].

In the context of sepsis-driven necrosis, the mainstay of treatment is skin grafting. Whilst small areas of necrosis can be managed conservatively, this is associated with significant scarring [12]. Skin grafting was attempted in our case however, it was unsuccessful. This is not uncommon given the procedure is performed on a less than ideal patient with necrosis extending into deep fascia and underlying muscle providing an inadequate graft bed [12]. Consequently, limb amputation is necessitated, as in our case. The literature reports less than 1 % of patients having a leg amputation as a consequence of *N. meningitidis* infection [13]. It has been demonstrated that the presence of metabolic acidosis on admission is predictive of the need for surgical intervention for tissue necrosis [13].

Our case illustrates the concept of an immune-mediated persistent inflammatory response, demonstrated here by the patient's failure to defervesce and development of new cutaneous lesions, which has been previously described in meningococcal disease. During the sub-acute phase of meningococcal infection, immune-complex hypersensitivity reactions occur, defined by Gell and Coombs as type three immune reactions [14]. The antigen-antibody complex, also known as an immune-complex, causes inflammation and activation of the complement pathway. This results in recruitment of leukocytes leading to extensive tissue

damage and, in severe cases, skin necrosis. In meningococcal disease, these immune-complex reactions can manifest in several ways including cutaneous vasculitis, pericarditis, iritis, and arthritis [4]. Immune-complex reactions are frequently associated with re-emergence of fever and an acute phase response. Therefore, we postulate that this gentleman's initial persistent fever (and subsequent fever recrudescence), together with a persistently and significantly elevated CRP, reflected not only the initial meningococcal insult but secondary immune-complex driven inflammation. Serological studies have previously shown the circulating titre of meningococcal antigen to dramatically deplete within the first 48 h of illness [7]. Bacterial lysis of meningococcal organisms occurs very quickly owing to its sensitivity to penicillin and cephalosporin antibiotics [15]. Therefore, fever lysis would be expected to occur quickly in uncomplicated cases, with antibiotic treatment. This supports the idea that our patient's continued fever and evolving cutaneous lesions were not driven by a persistent infectious insult but on overstimulated host immune response [16]. The most commonly documented manifestation of immune-mediated complications in meningococcal disease is aseptic mono-articular arthritis, which has been reported in 1.6–16 % of cases [4]. Polyarthritis is a less recognised manifestation.

The first randomised-controlled trial (RCT) on the use of corticosteroids in sepsis was performed fifty-five years ago, however their therapeutic use in sepsis remains a contentious issue [17]. Cortisol deficiency in sepsis is a well-defined concept. It is multi-factorial, involving cortisol metabolism, alterations in glucocorticoid receptors, and delivery to tissues. Moreover, in the context of DIC, the adrenal glands are particularly susceptible to haemorrhage resulting in Waterhouse-Friderichsen syndrome and adrenal insufficiency. The therapeutic application of steroids in the management of sepsis is based on these physiological foundations. The recently published APROCCHSS trial provided evidence that the use of steroids in septic shock is associated with a reduction in all-cause mortality [18]. This was a multi-centre, double-blinded, randomised-control trial, which included only intensive care patients with septic shock requiring vasopressor therapy [18]. The use of adjuvant corticosteroids in our case was considered on a different pathophysiological rationale. The patient exhibited a profound and persistent immune-complex mediated inflammatory response, unresponsive to non-steroidal medications, which have previously been reported to be an effective treatment in immune-driven arthritis secondary to meningococcal infection [5]. In our case, corticosteroids were used for their anti-inflammatory properties in effort to downregulate the host's immune response. A clinical improvement was seen within 24 h of administration, in terms of defervescence, joint pain and the patient's overall constitution, highlighting the benefit of steroid use in the setting of immune-complex driven complications in meningococcal infection.

Conclusion

The manifestation of meningococcal disease is extensive varying from a mild febrile illness to fulminant, life-threatening bacteraemia with or without the presence of meningitis. Due to the bacterium's ability to hyperstimulate the host's immune system, a proportion of patients will develop type III hypersensitivity reactions as a result of immune complex formation. Such reactions may manifest for example, as arthritis and cutaneous lesions, as discussed in this case. Failure to convalesce in a patient with meningococcal disease should alert the treating physician to consider immune-complex pathology. Antimicrobial therapy is unlikely to completely attenuate immune-mediated disease. The role of corticosteroids should be considered for patients with meningococcal sepsis where refractory fever and persistent inflammation is seen, despite appropriate antibiotic treatment and in the absence of any suppurative complications.

Declaration of Competing Interest

None.

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