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Case study

Chronic meningococcemia presenting with recurrent painful rash and poly-arthralgia without fever

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ABSTRACT

Chronic meningococcemia is an uncommon disorder, representing a diagnostic challenge. Classically, this pathology would be considered in young adults with a history of episodes of fever, disseminated cutaneous vasculitis and arthralgia. Exact and rapid diagnosis is often further challenged by the fact that routine microbiological investigations frequently failed to identify incriminated micro-organism, *Neisseria meningitidis*. Here we present the case of a young man not presenting with the classical triad.

Case report

A 21 year old patient was admitted to our emergency department with recurrent (one or two days) generalized and pruritic skin lesions, during one or two days, with polymyalgia and polyarthralgia without fever in the third time for four weeks. Standard biological analyses performed after the second episode showed significant inflammatory syndrome (CRP: 100 mg/L), hyperleukocytosis (WBC: 13800/mm^3), negativity of rheumatoid factor and negative viral serology (*Treponema pallidum*, *Chlamydia* and *Mycoplasma pneumoniae*, Coxsackie and Echovirus, Adenovirus, Parvovirus, *Borrelia* spp., *Bartonella henselae and* HIV). In our emergency department, clinical examination revealed a neurologically conscious and well-oriented patient with generalized papular cutaneous lesions and an erythematous pharynx without fever (36.8 °C), without headache, photophobia and neck stiffness. The vital signs showed a cardiac frequency at 92/min, a blood pressure at 10.5/80 mm Hg and the saturation at 100%. Pulmonary and cardiac examinations were normal. The abdomen was soft and painless. Chest radiography showed no systematic focus or pleural effusion. Blood analysis revealed leukocytosis at 18.36 10^3/mm^3 (Reference Values – RV 4.00–11.0) with relative polyneutrophilia of 88% (RV 45.0–70.0) and a CRP at 243 mg/L (RV 0–5). No abnormalities of renal and hepatic functions and coagulation were found. All requested serologies (*Treponema pallidum*, *Chlamydia* and *Mycoplasma pneumoniae*, Coxsackie and Echovirus, Adenovirus, Parvovirus, *Borrelia* spp., *Bartonella henselae*) were negative. A dermatological opinion was requested and a skin biopsy was performed. Blood cultures were performed even in the absence of fever.

The patient was hospitalized in the internal medicine department. 24 h after his admission, three pairs of blood cultures, taken without fever, became positive for Gram negative diplococci. A PCR was immediately carried out using the E-Plex® technique (Genmark, California), identifying the organism as *N. meningitidis*. An intravenous treatment was initiated with Ceftriaxone 2 g twice daily. The patient was transferred to the intensive care unit for observation. As it is well known that chronic meningococcemia can progress to acute meningitis, a lumbar puncture was performed showing a slightly turbid cerebrospinal fluid (CSF). Analysis revealed numerous leucocytes (284 leukocytes/mm^3, 88% of neutrophils, 8% of lymphocytes and 4% of mono-macrophages), a protein of 0.56 mg/dL and a glucose of 68 mg/dL (serum glucose: 110 mg/dL).The Gram staining examination did not show any bacteria. After 72 h, CSF culture was still negative but PCR was positive for *N. meningitidis* serotype B. A regression of skin lesions was observed over the next two days. From the neurological point of view, the patient was always well conscious and well oriented, from the biological point of view, leukocytosis and CRP were decreasing. The patient was transferred to a medical unit. Transesophageal ultrasound and otolaryngology examination concluded normal. Histologic examination of two admission skin biopsy specimen revealed dermal ectatic lymph vessels and

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capillaries with perivascular lymphocytic infiltration and some neutrophil granulocytes. Given the histological appearance largely compatible with a septic vasculitis, PAS and Gram staining were performed. No mycelial and bacterial elements were highlighted. PCR performed on patient's skin biopsy paraffin block confirmed the presence of *N. meningitidis* and the chronic meningococcemia diagnosis. Our patient didn't present any deficiency of the classic and alternative pathway of hemolytic complement activity and lectin pathways (classical pathway of hemolytic complement activity, alternate pathway of hemolytic complement activity, mannose-binding lectin and properdin). Although the total IgG level was slightly lower than normal (6.5 g/L), IgG subclasses were normal. The ceftriaxone treatment was continued for a total of 7 days with a favorable evolution. In the absence of consensus regarding the chronic form, a per oral quinolone (ciprofloxacin 500 mg twice daily) relay was continued for 7 more days.

Discussion

Although chronic meningococcemia is characterized by a classic clinical triad associating prolonged fever, rash and arthralgia [2], our patient did not present with fever preceding his admission. The age of our patient was in agreement with the description made by Benoit [2]. This disease can indeed be found at all ages, but especially among adolescents and young adults. The joint symptoms affecting our patient were also consistent with the classic pathology description. This can involve all joints except the spine and temporomandibular joint. Our patient classically presented intermittent symptomatology but his status remained good, as described by Benoit [2]. Cutaneous involvement is classically maculopapular, non-purpuric and not specific. These macular lesions are frequently described in chronic meningococcemia and may affect up to 86% of patients [2,7]. As described by Dupin [4], the lesions result either from septic embolizations (acute form) or from immune complexes and C3 deposit in vascular walls (chronic form).

Search for complement abnormality and immunoglobulin deficiency was performed although chronic meningococcemia occurred more frequently in immunocompetent patients [1,3,5]. In our patient, the levels of classic and alternative complement, as well as lectin pathways and the complement-regulating protein properdin, were normal. Despite a slightly low total IgG level, the IgG subclasses were normal, excluding a predisposition to chronic meningococcemia as described by Adams [1] and Nielsen [6]. We hypothesized that the *N. meningitidis* strain could have behaved with a low virulence profile, allowing to explain the chronic meningococcemia clinical form. Some strains notably show mutations in the gene *lpxL1* generating penta-acylated lipids A with decreased affinity for TLR4 [3], producing less pro-inflammatory cytokines favoring an easier escape to innate immune system. To exclude this hypothesis, a genomic and proteomic analysis of the strain has been considered.

The diagnosis was made on the basis of *N. meningitidis* positive blood cultures (group B). It is necessary to underscore here the importance to take and to repeat biological samples and especially to obtain blood cultures even if the patient does not present fever. Indeed *N. meningitidis* is a fragile bacterium whose culture can be rapidly falsely negative by earlier empirical antibacterial administration. The PCR technique has been therefore proved highly precious to confirm diagnosis and rapid treatment implementation. Microbiological research by PCR has the advantage of maintaining good sensitivity despite the introduction of antibacterial therapy and can be performed on different many samples [8,9]. In the case of our patient, bacteriological analyses involved several clinical samples including CSF, pharynx and skin biopsies [8,9]. As mentioned before, PCR confirmed secondary meningeal involvement. Nasopharyngeal carriage has been shown to be negative, although 10% of the population is colonized with 24–37 % carriers among 15–24 year old [1,11]. PCR testing of skin biopsy specimens should be used systematically in patients with negative microbiological investigation for chronic meningococcemia [10].

Early diagnosis of this type of meningococcemia is crucial to avoid complications that can be severe, mainly meningitis but also endocarditis, glomerulonephritis and ocular symptoms [1]. PCR carried out by E-plex (Genmark, California) on a positive blood culture allowed to rapidly initiate an adapted antibacterial therapy.

In conclusion, this case recalls that chronic meningococcemia must be considered even in the absence of the classic prolonged fever triad, absent here, with cutaneous and articular signs. This case highlights the importance of blood cultures even in the absence of fever as well as the important contribution of fast PCR techniques used on blood and skin samples. In general, treated rapidly by beta-lactate antimicrobials, prognosis is extremely favorable.

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