Corticosteroid-Induced Meningococcal Meningitis in a Patient With Chronic Meningococcemia

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Although chronic meningococcemia is an uncommon disorder, it is of great importance to clinicians across multiple disciplines because it presents similarly to reactive, neoplastic, or rheumatic disorders. Ruling out chronic meningococcemia, however, represents a diagnostic challenge because routine microbiological investigations frequently fail to identify *Neisseria meningitidis*. Although treatment with corticosteroids might be helpful in various conditions, corticosteroid treatment may lead to severe complications in underlying chronic meningococcemia.

Report of a Case

A male patient in his early 30s presented to the Ludwig-Maximilians-University Clinic of Dermatology with a history of recurrent fever, arthralgia, and disseminated skin lesions. The patient was assumed to have Sweet syndrome and was treated with corticosteroids. Subsequently the patient developed meningococcal meningitis and was admitted to the neurointensive care unit. Chronic meningococcemia was confirmed retrospectively by nonroutine polymerase chain reaction and silver staining of skin biopsy specimens. Immunologic workup revealed decreased IgG subclass 3.

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matosis, the patient was administered prednisolone, 80 mg orally per day. After 7 days without clinical improvement and further elevation of inflammatory blood parameters, the patient experienced headaches and developed neck stiffness. A lumbar puncture disclosed a white blood cell count of 8000/μL (85% neutrophils), cerebrospinal fluid (CSF) total protein level of 2.81 g/L, CSF to serum albumin ratio of 49.4 × 10⁻³, and a CSF to serum glucose quotient of 0.36 (49.6/138.0 mg/dL), indicating acute bacterial meningitis. Corticosteroid therapy was immediately discontinued, and therapy with ceftriaxone and acyclovir was started. The patient was treated in accordance with droplet precautions and was transferred to the neurointensive care unit of the Ludwig-Maximilians-University Department of Neurology. The results of rapid latex agglutination testing for the most common types of meningococcal capsid antigens (A, B, C, Y, and W135) and testing for pneumococcal antigen, Haemophilus influenzae type B antigen, and Escherichia coli K1 antigen were negative. Microscopy of CSF Gram and methylene blue staining failed to reveal bacteria. Because the patient reportedly had had contact with raw milk products in Turkey, the therapy was expanded to include ampicillin for Listeria and rifampicin for Brucella species. The next day, N meningitidis tested positive in the CSF; polymerase chain reaction (PCR) detected the neisserial genes ctrA and porA. The results of CSF PCR testing for several herpesvirus strains were negative. Acyclovir and ampicillin therapies were discontinued. Rifampicin therapy was continued until serologic test results for specific antibodies against Brucella species were negative. In the meantime, the patient’s symptoms had rapidly improved. Two days later the patient’s clinical symptoms had completely resolved, and he was discharged from the hospital 7 days after initial admission to the neurointensive care unit. Retrospectively, N meningitidis was confirmed in the patient’s skin biopsy specimens with PCR and silver staining (Figure 3). We performed an immunologic workup because host immune deficiencies have been suggested to play a role in the pathogenesis of chronic meningococcemia. Lymphocyte subpopulation analysis revealed normal results. No functional deficiencies 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, SC5b-9, C3d, mannose-binding lectin, and properdin) could be identified. Interestingly, although the total IgG level was normal (1360 mg/dL; to convert to grams per liter, multiply by 0.01), IgG subclass examination revealed reduced levels of IgG3 (16 g/dL).
were simultaneously negative. Because PCR had proven negative; however, it was unusual in our patient that all of them were simultaneously negative. Because PCR had proven meningoococcal disease that the results of cultures or microscopy after Gram and methylene blue staining were negative. Panbacterial PCR was nonrevealing because of a low bacterial load in the sample material. None of the blood or CSF cultures yielded any bacteria. It is not uncommon in meningococcal disease that the results of cultures or microscopy and rarely rapid antigen testing remain negative; however, it was unusual in our patient that all of them were simultaneously negative. Because PCR had proven meningococcal disease in the CSF of the patient, we considered chronic meningococcemia to be the origin of the meningitis and applied PCR to the paraffin block of the patient’s skin biopsy specimen. The proof of neisserial DNA in the skin specimen retrospectively confirmed the diagnosis of chronic meningococcemia complicated by meningitis as a consequence of steroid therapy. Thereafter, we also successfully confirmed diplococci in the patient’s skin biopsy specimens by nonroutine silver staining.

Chronic meningococcemia is characterized by a prolonged clinical course with intermittent fever, migratory arthralgia, and disseminated skin lesions. On the basis of negative blood culture results, an unrevealing Gram stain of 2 skin biopsy specimens, and histopathologic examination findings considered reconcilable with an acute febrile neutrophilic dermatosis, the diagnosis of Sweet syndrome was suspected. Sweet syndrome is a diagnosis of exclusion and belongs to a set of differential diagnoses with similar clinical characteristics, including rheumatic disorders, neoplastic conditions, reactive erythemas, and infectious diseases, such as Neisseria infection or brucellosis. Whereas immunosuppression might be helpful in rheumatic, neoplastic, or reactive disorders, it may have counterproductive effects in systemic infectious diseases.

The diagnosis of acute bacterial meningitis was initially based on clinical symptoms (fever, headache, and neck stiffness) and CSF parameters (massive neutrophil leukocytosis, total protein content elevation, and glucose consumption). The only diagnostic test confirming meningococcal disease at that time was a positive PCR result from the CSF against the meningococcal capsule synthesis genes ctrA and porA the day after admission. We were unable to identify the serotype of the specific neisserial strain by DNA amplification, probably because the neisserial DNA was strongly fragmented. The results of rapid testing for the most common types of meningococcal (A, B, C, Y, and W135) capsid antigens and microscopy after Gram and methylene blue staining were negative. Panbacterial PCR was nonrevealing because of a low bacterial load in the sample material. None of the blood or CSF cultures yielded any bacteria. It is not uncommon in meningococcal disease that the results of cultures or microscopy and rarely rapid antigen testing remain negative; however, it was unusual in our patient that all of them were simultaneously negative. Because PCR had proven meningococcal disease in the CSF of the patient, we considered chronic meningococcemia to be the origin of the meningitis and applied PCR to the paraffin block of the patient’s skin biopsy specimen. The proof of neisserial DNA in the skin specimen retrospectively confirmed the diagnosis of chronic meningococcemia complicated by meningitis as a consequence of steroid therapy. Thereafter, we also successfully confirmed diplococci in the patient’s skin biopsy specimens by nonroutine silver staining.

Chronic meningococcemia is characterized by a prolonged clinical course with intermittent fever, migratory arthralgia, and erythematous macules or nodules. It is noteworthy that meningococcal and gonococcal infection may present clinically indistinguishable at the stage of disseminated infection. This is why an attempt to prove the pathogen directly is crucial. The medical history of our patient did not point toward a gonococcal infection. Only a few cases of chronic meningococcemia have been reported so far. To our knowledge, ours is only the second case of chronic meningococcemia complicated by acute meningitis triggered by steroid therapy. Molly-Søholm and Nielsen described a patient with recurrent fever, arthralgia, and maculopapular skin lesions. After repeatedly negative blood and skin biopsy culture results, a vasculitis was assumed and treatment was started with prednisolone, 50 mg/d for 12 days, followed by prednisolone, 1000 mg/d for another 3 days. On the third day of pulse therapy, the patient developed neck stiffness. A lumbar puncture revealed bacterial meningitis, and N meningitidis was proven by CSF microscopy and CSF PCR for neisserial 16S ribosomal DNA. The administration of penicillin G led to the patient’s recovery. However, N meningitidis was never proven directly outside the central nervous system.

The underlying mechanism of chronic meningococcemia is still unclear, although host immune deficiencies have been suggested to play a role in its pathogenesis. In our patient, the levels of classic and alternative complement, as well as lectin pathways and the complement-regulating protein properdin, were normal. A quantitative cellular immune defect could be ruled out by normal lymphocyte subpopulation counts. Interestingly, despite normal total IgG levels (1360 mg/dL), an assay of IgG subclasses revealed low IgG3 levels (16 mg/dL). IgG subclass deficiencies have been indicated to predispose patients to various infectious diseases, and hypogammaglobulinemia and low IgG2 and IgG4 levels have been reported in patients with chronic meningococcemia. However, diminished IgG3 levels have not been associated with chronic meningococcemia so far. Its definitive role in this context awaits further investigation.

The case presented illustrates the importance of considering chronic meningococcemia if a patient presents with a history of prolonged fever, arthralgia, and disseminated skin lesions. Even if meningococcemia is considered, it is important to keep in mind that the diagnosis can be a challenge because the results of blood and skin cultures, as well as microscopy, often remain negative. Parmentier and colleagues suggested that PCR testing of skin biopsy specimens should be used more systematically in patients for whom routine microbiological investigations failed to prove neisserial infection. In addition, immunohistochemical approaches have been dis-
cussed as a more sensitive method for the detection of Neis-
seria species in skin biopsy specimens.15 We found that, in ad-
dition to the methodologic approaches listed above, silver
staining of skin lesions can help establish a definitive diagno-
sis. If the diagnosis remains persistently obscure, clinicians
should consider antibiotic treatment before administering high
doses of steroids5 to avoid severe complications in the case of
an underlying infectious disease.

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