International Journal of General Medicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

CASE REPORT

Disseminated Gonococcal Infection Associated with Eculizumab Therapy for Paroxysmal Nocturnal Hemoglobinuria: A Case Report and Literature Review

This article was published in the following Dove Press journal:
International Journal of General Medicine

Makoto Saito
Shinpei Harada
Reiki Ogasawara
Koh Izumiyama
Akio Mori
Masanobu Morioka
Takeshi Kondo

Department of Internal Medicine and Hematology, Blood Disorders Center, Aiiku Hospital, Sapporo, Japan

Abstract: Eculizumab has been developed as a breakthrough treatment for paroxysmal nocturnal hemoglobinuria (PNH). Not only for breakthroughs, eculizumab therapy is also known to increase the risk of invasive meningococcal infection. It has also been recently reported that, although rarely, administration of eculizumab may result in disseminated gonococcal infection (DGI). We report here a case in which a young patient who had used eculizumab for PNH developed DGI. A 22-year-old Japanese male with PNH who had been treated with eculizumab complained of high fever, mild nausea, headache and right knee joint pain. The patient was admitted and suspected to have sepsis due to meningococcal infection and began to receive ceftriaxone (CTRX). Gonococci were detected in a venous blood culture a few days later, and this case was diagnosed as DGI. CTRX was effective, and the patient was discharged. However, four weeks later, he complained of the same subjective symptoms as at the beginning and was hospitalized again. The presence of gonococcus was proven by venous blood culture, CTRX was re-administered and the patient responded. After discharge, he was counseled on safer sexual activity, including accurate and consistent use of condoms, by urologists. He has not relapsed with DGI for more than one year. When serious signs of infection occur in patients receiving eculizumab, it is recommended to consider DGI as well as invasive meningococcal infection, and CTRX should be given.

Keywords: disseminated gonococcal infection, DGI, eculizumab, paroxysmal nocturnal hemoglobinuria, PNH, ceftriaxone

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease that exhibits intravascular hemolysis, thrombosis, and renal dysfunction due to the clonal expansion of hematopoietic stem cells that have acquired mutations in the *phosphatidylinositol glycan class A* gene and increased erythrocyte complement sensitivity.[1] Eculizumab (Soliris®; Alexion Pharmaceuticals, New Haven, CT, USA); complement component 5-targeted agents, has been developed as a breakthrough treatment for PNH. This drug has been shown not only to reduce hemolysis and prevent thrombosis, but also to improve anemia, renal function, quality of life and patient survival.[2] However, it has been reported that its use increases the risk of developing invasive meningococcal infection 1000–2000 times,[3] and recently, it was reported that disseminated gonococcal infection (DGI) could occur.[4] This condition is rare, but

Correspondence: Makoto Saito
Email ikyoku@aiiku-hp.or.jp

submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/IJGM.S255298

considered an important disease concept. We report here a young patient with PNH using eculizumab who developed DGI.

Case Report

A 22-year-old Japanese male patient with PNH was treated with eculizumab in our department six months prior to this presentation, and eculizumab was given every two weeks thereafter. The patient was injected with Menactra®, a quadrivalent meningococcal vaccine against serogroups A, C, Y, and W-135, at the beginning of eculizumab treatment, while prophylactically receiving fluoroquinolones antibacterial agent, levofloxacin, for 6 weeks. Then, he had not taken antibiotics for more than four months and had never been injected with a serogroup B meningococcal vaccine. The patient complained of a high fever of 39.5 °C, mild nausea and headache, and was sent to our department by ambulance. The patient was aware of pain with urination and pyuria the night before. The patient had been given eculizumab one week prior, and at that time, there was no remarkable change in his physical condition; no new drugs, including antibiotics, were prescribed. On admission, laboratory data were as follows: hemoglobin (Hb) 11.5 g/dL (decreased to 8.3 g/dL after 3 days; presumed to be hemolysis after infection), white blood cell count (WBC) 8600/μL (neutrophils 90%), C-reactive protein (CRP) 2.24 (normal range: 0–0.3) mg/dL and LDH 334 (120–245) U/L. Urinalysis showed a WBC of 10–19/high power field in the sediment, but urine culture was negative. Neither cerebrospinal fluid nor synovial fluid collection tests were performed. No abnormalities were found on a CT image (brain - pelvis). Venous blood culture was collected from the bilateral upper limbs, and 2 g of ceftriaxone (CTRX) was administered twice per day (total: 4 g). Thereafter, *Neisseria gonorrhoeae* was detected in cultures, and our case was diagnosed as DGI. CTRX was administered for 8 days beginning from the day of hospitalization. His subjective symptoms and physical condition immediately improved, and laboratory data other than anemia were generally normalized. The patient was discharged.

His sexual partner (female) was also found to have gonococcal infection and was treated at another clinic. He had no history of sexually transmitted disease, and it was unknown when she became infected with gonorrhea. Both had no habit of having unusual sex, such as exchange sex, or sex with multiple partners. After discharge, they performed several sexual acts but did not strictly wear condoms. Four weeks after the previous discharge, the patient received eculizumab twice, complained of high fever (39.5°C), mild nausea, neck-occipital pain, and left femoral pain and was urgently admitted again. The patient was not aware of urethritis symptoms at this presentation. Laboratory data showed Hb 11.0 g/dL (decreased to 8.1 g/dL after 3 days), WBC 11,500/μL (neutrophils 85%), CRP 3.69 mg/dL, and LDH 285 U/L. Gonococcus presence was proven again in a venous blood culture. Similar to the last presentation, CTRX was administered at a daily total dose of 4 g divided into two doses for 8 days. Both his general condition and data improved early on, and he was discharged. The patient was counseled several times on safer sexual activity, including accurate and consistent use of condoms, by urologist. He was also prescribed by his urologist sultamicillin tosylate (750 mg/day), which was sensitive to this gonococcus, for one month. The patient eventually discontinued his relationship and was no longer a sexual partner. Since then, DGI has not recurred for more than 1 year, and his PNH has a stable clinical course.

Discussion

Eculizumab binds to the complement protein C5 and inhibits the release of C5a, as well as the production of the terminal membrane attack complex (MAC) C5b-C9 following C5b, thereby significantly limiting complement activity.[5] For this reason, eculizumab is a very useful drug for PNH with dysregulation of complement activation, but the drug inhibits MAC formation and prevents efficient serum bactericidal activity.[6] It has been confirmed that treatment with eculizumab is likely to result in serious infections with *Neisseria* species, including *N. meningitides*.[3,7,8] Patients with infections caused by *N. sicca/subflava* have also been observed; these organisms are considered nonpathogenic.[9]

Gonococci are a gram-negative bacilli belonging to the *Neisseria* species and have 70% DNA homology with meningococci. DGI is a rare condition that occurs in only 1 to 3% of all patients with gonococcal infection, and it occurs more frequently in women;[10] complement deficiency has long been reported to be a risk factor.[11] Recently, several cases of DGI associated with eculizumab were reported successively,[12–14] and in a recent review, 8 of 9 patients were women who were highly sexually active.[4] Nine of 11 patients with DGI reported from Japan before eculizumab use was launched were male.[15] The reason for this sex difference between Japan and other Western countries is unknown.

In our young male patients with PNH, bacteremia and arthritis-like signs developed rapidly within just 12 hours after he became aware of urethritis symptoms. In a recent review of DGI with eculizumab,[4] 3 out of 9 patients were

reported to develop dangerous and life-threatening general conditions, and one of those patients died. We used rapid and high-dose CTRX based on an invasive meningococcal infection in accordance with the guidelines of the Japanese Society for Neuroinfectious Diseases.[16] The general condition of the patient improved quickly, and he was able to return to his daily life. However, DGI redeveloped repeatedly within a short period of time. The source and route of the two gonococcal infections were truly unknown. According to their statements, with regard to the initial infection, his partner may have previously been affected without awareness. It was not clear whether the second DGI was a new infection or whether some of the bacteria survived after the first sepsis presentation. Our patient had meningitis-like symptoms when he developed DGI. The treatment of DGI recommended by the Japanese Society for Sexually Transmitted Infections guidelines is to administer 1.0 g of CTRX intravenously 1 time/day for 3–7 days.[17] In contrast, the recommended US Centers for Disease Control and Prevention regimen for DGI manifesting as gonococcal meningitis requires 1–2 g of CTRX intravenously every 12–24 hours for 10–14 days.[18] The first-line drug of severe infection, whether gonococcal or meningococcal, is currently considered to be CTRX. Regarding the optimal period of CTRX treatment (4 g/day), it recurred for 8 days of medication in this time, so it was thought that about 10 days would be suitable. In the future, it is necessary to establish the dosage and duration of intravenous CTRX for DGI in patients taking eculizumab.

In considering the preventive measures, we should explain to partner as well as the patient that young PNH patients using eculizumab are at risk of developing DGI, while checking whether both are infected with *N. gonorrhoeae*. In addition, we should educate them on regular use of condoms including during oral sex. Meanwhile, Petousis-Harris et al recently reported that it has been suggested that vaccination against group B Neisseria meningitidis may reduce the risk of gonococcal infection.[19] In Japan, Menactra® was finally approved in 2015, but until now (July 2020), the serogroup B meningococcal vaccine has not yet been approved and we did not administer to this patient. The group B meningococcal vaccine should be approved as soon as possible in Japan, as in Western countries.

In conclusion, to our knowledge, this study is the first case report of DGI that developed in a Japanese patient with PNH receiving eculizumab. Although gonococcal infections rarely develop into DGI, hematologists and infectious disease specialists need to recognize that the risk is increased for patients with PNH receiving eculizumab. When serious signs of infection occur, it is recommended to consider DGI as well as invasive meningococcal infection as a differential diagnosis, and intravenous CTRX should be given early.

Consent for Publication and Ethics Approval

Written informed consent was obtained from the patient for his anonymized information to be published in this article. Our institution does not require ethical approval for reporting individual cases or case series (<10 patients).

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

Takeshi Kondo reports personal fees from Novartis Pharma, Bristol Squibb Meyers, Astellas Parma, and Otsuka Pharmaceuticals, outside the submitted work. The authors declare no other possible conflicts of interest in this work.

References

1. International PNH Interest Group, Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Blood*. 2005;106(12):3699–3709. doi:10.1182/blood-2005-04-1717.
2. Kelly RJ, Hill A, Arnold LM, et al. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. *Blood*. 2011;117(25):6786–6792. doi:10.1182/blood-2011-02-333997
3. McNamara LA, Topaz N, Wang X, et al. High risk for invasive meningococcal disease among patients receiving eculizumab (Soliris) despite receipt of meningococcal vaccine. *MMWR Morb Mortal Wkly Rep*. 2017;66(27):734–737. doi:10.15585/mmwr.mm6627e1
4. Crew PE, Abara WE, McCulley L, et al. Disseminated gonococcal infections in patients receiving eculizumab: a case series. *Clin Infect Dis*. 2019;69(4):596–600. doi:10.1093/cid/ciy958
5. Rother RP, Rollins SA, Mojcik CF, Brodsky RA, Bell L. Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria. *Nat Biotechnol*. 2007;25(11):1256–1264. doi:10.1038/nbt1344
6. Konar M, Granoff DM. Eculizumab treatment and impaired opsonophagocytic killing of meningococci by whole blood from immunized adults. *Blood*. 2017;130(7):891–899. doi:10.1182/blood-2017-05-781450
7. Winthrop KL, Mariette X, Silva JT, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors). *Clin Microbiol Infect*. 2018;24(Suppl 2):S21–S40. doi:10.1016/j.cmi.2018.02.002

8. Socié G, Caby-Tosi MP, Marantz JL, et al. Eculizumab in paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome: 10-year pharmacovigilance analysis. *Br J Haematol*. 2019;185(2):297–310. doi:10.1111/bjh.15790
9. Crew PE, McNamara L, Waldron PE, et al. Unusual Neisseria species as a cause of infection in patients taking eculizumab. *J Infect*. 2019;78(2):113–118. doi:10.1016/j.jinf.2018.10.015
10. Handsfield HH. Spading PF: Neisseria gonorrhoeae. In: Mandell GL, editor. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 6th. Philadelphia: Elsevier; 2005:2514–2529.
11. Petersen BH, Lee TJ, Snyderman R, Brooks GF. Neisseria meningitidis and Neisseria gonorrhoeae bacteremia associated with C6, C7, or C8 deficiency. *Ann Intern Med*. 1979;90(6):917–920. doi:10.7326/0003-4819-90-6-917
12. Gleesing J, Chiwane S, Rongkavilit C. Gonococcal septic shock associated with eculizumab treatment. *Pediatr Infect Dis J*. 2012;31(5):543. doi:10.1097/INF.0b013e3182503849
13. Hublikar S, Maher WE, Bazan JA. Disseminated gonococcal infection and eculizumab–a "high risk" connection? *Sex Transm Dis*. 2014;41(12):747–748. doi:10.1097/OLQ.0000000000000202
14. Khandelwal A, Wright JK, Pavenski K, Taggart LR. Risks of novel therapeutics: gonococcemia in an immune-suppressed patient receiving eculizumab. *CMAJ*. 2017;189(50):E1558–E1560. doi:10.1503/cmaj.170508
15. Suzaki A, Hayashi K, Kosuge K, Soma M, Hayakawa S. Disseminated gonococcal infection in Japan: a case report and literature review. *Intern Med*. 2011;50(18):2039–2043. doi:10.2169/internalmedicine.50.5586
16. Treatment of bacterial meningitis. In: Kamei S, editors. *Japanese Society for Neuroinfectious Diseases. Practical Guideline for Bacterial Meningitis 2014*. Tokyo: Nankodo Co., Ltd.; 2014:79–116.
17. Kiyota H. Sexually transmitted infections diagnosis and treatment guidelines 2016. Gonococcal infections. *Jpn J Sex Trans Infect*. 2016;27(Suppl 1):S53–S61.
18. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2015. Gonococcal infections. *MMWR Recomm Rep*. 2015;64(RR–03):60–68.
19. Petousis-Harris H, Paynter J, Morgan J, et al. Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study. *Lancet*. 2017;390(10102):1603–1610. doi:10.1016/S0140-6736(17)31449-6