Chronic meningococccemia in a vertically HIV-infected adolescent

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\section*{Introduction}

Meningococcal disease may present as meningococcal meningitis, meningococcal meningitis with meningococccemia, and isolated meningococcemia. It is a disease caused by the bacterium \textit{Neisseria meningitidis}. Even though there are 12 bacterial serotypes, invasive meningococcal disease is associated with six, classified based on the polysaccharide capsule (A, B, C, W-135, X, Y) [1]. The bacterium colonizes the nasopharynx of asymptomatic carriers up to about 5–10\% of the population, being transmitted from person to person by respiratory secretions [2].

In Brazil, meningococcal disease is endemic with periodic outbreaks of epidemics in several municipalities. The incidence coefficients have remained stable in recent years, with approximately 1.8 cases per 100,000 inhabitants [3]. In São Paulo city, in 2018, 204 cases were confirmed, with 36 deaths, with incidence coefficient being 1.74 and mortality 0.31 [4]. The lethality of the disease in our country has been around 18–20\% in recent years, and it may achieve coefficients of almost 50\% in septic presentations [3]. Serotypes B and C cause disease predominantly in Europe and the Americas, being the most common in Brazil [3].

Although the most common clinical manifestations are fever and acute and rapidly progressive petechial and/or purpuric rash, progressing to septic shock within a few hours, there are some chronic, initially more benign presentations, such as chronic meningococcemia [5]. This form represents less than 5\% of all cases of meningococcemia, with incidence <0.05 cases per 100,000 inhabitants per year in developed countries [6]. It is a rare manifestation of meningococcal disease without meningitis, of prolonged course of more than one week, with intermittent or continuous fever, arthralgia and cutaneous vasculitis [1]. Few cases of this presentation have been reported, both in previously healthy and immunocompromised patients [5,7].

A case of chronic meningoccocemia diagnosed in a vertically infected adolescent with human immunodeficiency virus (HIV) infection will be described, providing a review of the literature on the topic. Its importance lies in the description of a rare disease with atypical manifestation, which is difficult to suspect, and which may be life-threatening if not diagnosed and treated promptly and adequately. This case report was approved by local ethics committee; the patient signed the consent form, with permission to disclose images.

\section*{Clinical case}

Adolescent, 19 years old, male, vertically HIV-infected, followed up since 3 months of age at our Pediatric Infectious Disease Clinical Care Center. Not adherent to the antiretroviral treatment, he has presented several clinical intercurrences during his life. At the time of this event, there was significant viral replication (HIV viral load...
87,802 copies/µL and severe immunosuppression (CD4+ count 17 cells/µL).

He came to our medical center with 5 days of prostration, epigastric pain, sparse petechiae, joint pain, ocular pain and conjunctival hyperemia. Fever at the beginning for three days. Initially, he sought another service and the laboratory tests performed detected leukocytosis 19,600/µl (81 % neutrophils), and thrombocytopenia 77,000/µl. He received intravenous hydration and was discharged with symptomatic medication. In our service, he was in good general condition, pale, presenting conjunctival hyperemia, some petechiae on the trunk and limbs, without other signs (see Pictures 1–3). Laboratory tests were performed: leukocytes 4330/µl (53 % neutrophils, 33 % lymphocytes) and improved thrombocytopenia 124,000/µl. As there is epidemiological conditions for arboviruses in our country, serology and blood viral research by polymerase chain reaction (PCR) were done for dengue, zika and chikungunya – all tested negative; serology tested non-reactive for toxoplasmosis and syphilis; for cytomegalovirus serology tested IgG reagent IgM non-reactive. He received symptomatic treatment with partial clinical improvement, keeping skin lesions unchanged. At this time, he was afebrile.

Sixteen days after the onset of symptoms, he presented a return of prostration, fever and disseminated hemorrhagic suffusions (see Pictures 4 and 5). He was hospitalized in septic shock, and during the diagnostic investigation, two blood cultures were positive for Neisseria meningitidis C, eighteen days since disease onset.

He presented normal cerebrospinal fluid examination with negative bacterioscopy and culture. The patient evolved with acute respiratory distress syndrome and acute renal failure, requiring endotracheal intubation and hemodialysis. He was hospitalized for 46 days, received 10 days of ceftriaxone 2 g 12/12 h. During hospitalization, HIV viral load 382,863 copies/µL and CD4+ count 13 cells/µL. He progressively evolved with improvement, being discharged in good clinical conditions, receiving combined antiretroviral therapy.

The vaccine card was checked, he had received two doses of the meningococcal conjugate vaccine C before this clinical complication: 15 years before with HIV viral load 146,000 copies/µL and CD4+ count 762 cells/µL and 3 years before with HIV viral load 130,214 copies/µL and CD4+ count 75 cells/µL.

Currently, the patient presents good adherence to the antiretroviral medication, with an improvement in CD4+ cell count (445 cells/µL) and a decrease in viral load (155 copies/µL); he has cutaneous scars derived from meningococcal vasculitis (see Picture 6).

Discussion

We describe a case of a vertically HIV-infected adolescent with chronic meningococcal disease.

Chronic meningococemia is a disease caused by the bacterium Neisseria meningitidis, characterized by a period of more than one week of intermittent or continuous fever, arthralgia and skin lesions without meningitis [1]. Initial erythema develops to petechiae and purpura due to dermal microvascular thrombosis and perivascular hemorrhage [8]. Other clinical manifestations may occur, such as myalgia, abdominal pain, weight loss, iritis, retinitis [9]. It may be a self-limiting disease, but meningitis and death may occur as late complications [10]. These manifestations mimic several other infections, namely arboviruses, which was a confounding factor in our patient, delaying the diagnosis.

The gold standard diagnostic method is culture isolation of Neisseria meningitidis in sterile material [11].

Even if the course seems to be self-limited, the fact that the patient may remain as an asymptomatic carrier and thus develop an invasive disease or spread the agent has tended to favor antimicrobial treatment [12]. The suggested treatment is based on
the use of beta-lactams, namely 3rd generation cephalosporin, used in our patient [1,6].

The reason why these less severe forms of the disease occur is unknown; the susceptibility of the host and the virulence of the bacterium are possible explanations [1,13]. Although there seems to be a greater association with serotype B [1], serotype C was isolated in our patient. The disease can occur in previously healthy individuals or with some immunodeficiency [5,7,9].

After a literature review, we identified only four cases of chronic meningococcemia in horizontally HIV-infected adult patients since 1990, none with this serious evolution [6,9,14]. A recent study found a substantial increased risk of meningococcal disease among adults with HIV infection that met AIDS criteria; in this study they observed a similar clinical presentation and outcomes of meningococcal disease compared to those without HIV infection [15]. The increased relative risk observed for meningococcal disease was similar to those observed for HIV-infected individuals in New York City, South Africa and England, ranged from 3.4–6.6 per 100,000 (relative risk = 5–13 compared with HIV-uninfected persons) [15–18]. Among HIV-infected persons, a low CD4 count or high viral load were associated with an increased risk [17]. Considering this increased risk, in 2016 the US Advisory Committees on Immunization Practices approved a recommendation for routine vaccination of HIV-infected person [19]. In Brazil, meningococcal conjugate vaccine type C is routinely recommended for HIV-infected patients.

With this clinical case we intend to highlight the heterogeneity and low specificity of the symptoms that meningococcal disease may present, especially in immunocompromised hosts, leading to a possible diagnostic delay of a potentially fatal disease.

The association between Neisseria meningitidis infection and HIV infection is not yet well defined. Due to the potential for progression and the risk of N. meningitidis transmission, a better understanding of the association between HIV infection and meningococcal disease is important to prevention strategies.

Ethical approval

Written informed consent was obtained from the patient for publication of this case report and accompanying images. This case report was approved by local ethics committee.

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References

[1] Ferraz RV, Cofa F, Duro R, Carvalho AC, Andrade P, Silva S, et al. Chronic meningococcemia. Adv Infect Dis 2016;6:97–101, doi:http://dx.doi.org/10.4236/aid.2016.63012.
[2] Coureuil M, Join-Lambert O, Lécyeur H, Bouhours S, Marullo S, Nassif X. Pathogenesis of meningococcaemia. Cold Spring Harbor Perspect Med. 2013;5: a012393, doi:http://dx.doi.org/10.1101/cshperspect.a012393.
[3] Berezin E. Epidemiologia da infecção meningocócica. Doença Meningocócica 2015;1:3–7.
[4] São Paulo. Vigilância em Saúde da Prefeitura de São Paulo. Série histórica de casos e óbitos confirmados de doença meningocócica, coeficientes de incidência e mortalidade por 100.000 habitantes, residentes no Município de São Paulo. 2007 a 2019. https://www.prefeitura.sp.gov.br/cidade/secretarias/saude/vigilancia_em_saude/index.php?c=244832; 2019 [accessed 16 June 2019].
[5] Brouwer MC, Spanjaard L, Prins JM, van der Ley P, van de Beek D, van der Ende A. Association of chronic meningococcemia with infection by meningococci with underacetylated diplococcicxaride. J Infect 2011;62:479–83, doi:http://dx.doi.org/10.1016/j.jinf.2011.03.010.
[6] LeFebre B, Ponsignon Y, Pla C, Javagué EC, Talarmain JP, Lefebvre M, et al. Chronic meningococcemia: a report of 26 cases and literature review. Infection 2019;47(2):285–8, doi:http://dx.doi.org/10.1007/s15010-018-1238-x.
[7] Nielsen HE, Koch C, Mansa B, Magnussen P, Bergmann OJ. Complement and immunoglobulin studies in 15 cases of chronic meningococcal disease: profound deficiency and hypomonomucglobulinemia. Scand J Infect Dis 1990;22(1):31–6, doi:http://dx.doi.org/10.3109/03055909009023116.
[8] Hazelzet JA. Diagnosing meningococcemia as a cause of sepsis. Pediatr Crit Care Med 2005;6(3):S50–4, doi:http://dx.doi.org/10.1097/01.PCC.0000161947.57506.D6.
[9] Assier H, Chosidow O, Rekacewicz I, Lissone F, Pipau FG, Riosy JV, et al. Chronic meningococcemia in acquired immunodeficiency. J Am Acad Dermatol 1993;29(5):793–4, doi:http://dx.doi.org/10.1016/0190-9622(93)80709-4.
[10] Hardwood CA, Stevens JC, Orono D, Bull RC, Paige D, Lesing MP, et al. Chronic meningococcemia: a forgotten meningococcal disease. Br J Dermatol 2005;153(3):699–71. https://doi.org/10.1111/j.1365-2133.2005.06771.x.
[11] Centers for Disease Control. Meningococcal disease. Centers for disease control and prevention epidemiology and prevention of vaccine-preventable diseases. 13th edition .
[12] Prisata-Leão B, Almeida F, Carvalho AC, Silva S, Sarmento A. Chronic meningococcemia. IDCases 2019;15:1–3, doi:http://dx.doi.org/10.4236/aid.2019.150052.
[13] Dupin N, Lecuyer H, Carloiti A, Poyart C, Coureuil M, Chanal J, et al. Chronic meningococcemia cutaneous lesions involve meningococcal perversiva invasion through the remodeling of endothelial barriers. Clin Infect Dis 2012;54(8):1162–5, doi:http://dx.doi.org/10.1093/cid/cis120.
[14] Aguado JM, Vada J, Zufίga M. Meningococcemia, an undescribed cause of community-acquired bacteremia in patients with acquired immunodeficiency syndrome (AIDS) and AIDS-related complex. Am J Med 1990;88:314, doi:http://dx.doi.org/10.1016/0002-9343(90)90163-8.
[15] Harris CM, Wu HM, Li J, Hall HI, Lee A, Zell E, et al. Meningococcal disease in patients with human immunodeficiency virus infection: a review of cases reported through active surveillance in the United States, 2000-2008. Open Forum Infect Dis 2016;3(4):1–5, doi:http://dx.doi.org/10.1093/openfidofo226.
[16] Cohen C, Singh E, Wu HM, Martin S, de Gouveia L, Klugman KP, et al. Increased incidence of meningococcal disease in HIV-infected individuals associated with higher case-fatality ratios in South Africa. AIDS 2010;24(9):1351–60, doi:http://dx.doi.org/10.1097/QAD.0b013e32833a2520.
[17] Miller L, Arakaki L, Ramautar A, Bodach S, Braunstein SL, Kennedy J, et al. Elevated risk for invasive meningococcal disease among persons with HIV. Ann
[18] Simmons RD, Kirwan P, Beebejaun K, Riordan A, Borrow R, Ramsay ME, et al. Risk of invasive meningococcal disease in children and adults with HIV in England: a population-based cohort study. BMC Med 2015;13:297, doi:http://dx.doi.org/10.1186/s12916-015-0538-6.

[19] MacNeil JR, Rubin LG, Patton M, Ortega-Sanchez IR, Martin SW. Recommendations for use of meningococcal conjugate vaccines in HIV-infected persons—Advisory Committee on Immunization Practices, 2016. MMWR Morb Mortal Wkly Rep 2016;65(43):1189–94, doi:http://dx.doi.org/10.15585/mmwr.mm6543a3.