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# Recurrent invasive meningococcal disease in a patient with complement deficiency: a case report

## Rekurirajuća invazivna meningokokna bolest u bolesnika s deficijencijom komplementa: prikaz bolesnika

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Case report

Most cases of invasive meningococcal disease occur in immunocompetent children and young adults. Serogroup B accounts for most cases in Europe followed by serogroup C, while serogroups W and Y are uncommon. We describe a case of recurrent invasive meningococcal disease (IMD) caused by two different serogroups in a 16-year-old boy with complement deficiency. All tested cultures were negative, but PCR from blood was positive in both episodes. Our patient gradually recovered without sequelae. This case report emphasizes also the need to provide appropriate chemoprophylaxis and/or immunoprophylaxis to certain individuals.

Prikaz bolesnika

Većina slučajeva invazivne meningokokne bolesti pojavljuje se u imunokompetentne djece i mladih odraslih. Serogrupa B najčešća je u Europi, potom slijedi serogrupa C dok su serogrupe W i Y rijetke. Ovdje opisujemo rekurirajuću invazivnu meningokoknu bolest uzrokovanu s dvije različite serogrupe u šesnaestogodišnjeg dječaka s deficijencijom komplementa. Sve testirane hemokulture bile su negativne, ali je PCR metodom iz krvi dokazan uzročnik u obje epizode. Naš bolesnik se postupno oporavio bez posljedica. Ovim prikazom bolesnika ističemo značaj primjene odgovarajuće kemoprofilakse i/ili imunoprofilakse u određenih osoba.

## Introduction

*Neisseria meningitidis* (*N. menigitidis*) is a Gram-negative, strictly human respiratory transmitted bacterium causing invasive meningococcal disease (IMD), with most cases occurring in the winter. Serogroup B dominates in Croatia as elsewhere in Europe, followed by serogroup C, while serogroups W and Y are uncommon. In some European countries, there is a decline in IMD cases caused by serogroup C in adolescents due to implementation of routine vaccination against meningococci of this serogroup, leading to a reduction in the number of healthy carriers as well as the incidence of IMD, with consequent emergence of collective immunity[1, 2, 3].

Most cases of IMD occur in immunocompetent children and young adults. Underlying immune defects that confer a predisposition to IMD include functional or anatomical asplenia, a deficiency of properdin, and a deficiency of terminal complement components [4].

Culture is the gold standard in confirmation and characterization of *N. meningitidis*. However, the diminished sensitivity of the cerebrospinal fluid (CSF) culture in patients who received antibiotics before the lumbar puncture (LP) hinder clinicians from reaching a prompt diagnosis and starting the treatment in the ideal period. Non-culture molecular standardized methods, such as the real-time polymerase chain reaction (PCR) or multiplex PCR, are now essential tools and almost "new gold standard" in microbiological diagnostics of IMD for detecting microorganisms in the CSF with high sensitivity and specificity [5, 6]. In the European Union, 25 % of cases are confirmed by PCR alone. In the United Kingdom and Ireland, this rises to around 50 %. In the United States, the Center for Disease Control and Prevention (CDC) only recently included PCR as confirmatory in its case definition. There is yet no international consensus on their use, although PCR methods incorporating a number of targets have been developed [7].

Cefotaxime, ceftriaxone, and penicillin during a 7 to 10 day course, are preferred as initial intravenous therapy in patients with a clinical diagnosis of IMD.

The efficacy of conjugated anti-meningococcal vaccines is greater than 95 % and indicates a protective effect on the unvaccinated when high vaccine coverage is reached in the population (collective immunity) [1]. Early in 2013, the European Commission approved the four-component protein meningococcal serogroup B (4CMenB) vaccine, "Bexsero". This and the bivalent recombinant lipoprotein vaccine, "Trumenba", have subsequently been used prior to licensure in the United States as a respond to outbreaks of serogroup B disease among university students [1].

We describe a case of recurrent IMD caused by two different serogroups in a 16-year-old boy with complement deficiency. This case report emphasizes the need to provide appropriate chemoprohylaxis and/or immunoprophylaxis to certain individuals.

## Case report

At the end of May, a 16-year-old boy from Zagreb was transferred to the University Hospital for Infectious Diseases from another hospital in Zagreb as suspected bacterial meningitis. Upon suspicion for IMD, the patient received one dose of ceftriaxone intravenously before admission to our hospital.

He had fever lasting for two days, occipital headache and sore throat with cough. He vomited in 3 occasions and in the last 24 hours he had had at least 3 liquid stools. He complained of intense pain in his legs. He had been previously healthy except from asthma for which he was taking daily therapy (fluticasone and salbutamol inhalations). His father had diabetes mellitus, his mother had asthma and his three siblings were all healthy. They lived in a flat in Zagreb where he attended the second grade of an industrial trade school. He negated animal contact, tick bites and international travels.

At admission, his blood pressure was 110/60 mmHg, heart rate 70/min, temperature 37.3 °C, respiratory rate 15/min, Glasgow coma scale 13 and oxygen saturation 100 %. He was somnolent, but well oriented, afebrile after antipyretic medications, with diminished appearance and difficulty walking. Meningeal sings were positive. His skin was without rash or signs of bleeding except for one painless necrotic-haemorrhagic skin lesion 3 × 3 cm with red outer layer, above skin surface, located in his parietal scalp area left (Figure 1.). Petechial haemorrhages were noted on the soft palate. Further physical examination was unremarkable.

Laboratory data on admission included: C-reactive protein of 285.8 mg/L, serum procalcitonin of 19.7µg/L, white blood cell (WBC) count of $26.4 \times 10^9$/L with 85 % neutrophils and blood platelet count of $123.0 \times 10^9$/L. Glucose in blood was 4.6 mmol/L and serum creatinine was 133.0 umol/L. Coagulation tests included: prothrombin time of 0.6, fibrinogen levels of 5.8 g/L and D-dimers of more than 4.4 mg/L. Emergency CT of the head showed an arachnoid cyst of the left middle cranial fossa with dimensions 42 × 20mm (Galassi 1) that compressed left temporal parenchyma along with oedema of the right maxillary sinus mucosa – acute sinusitis. The rest of the CT exam was unremarkable. CSF findings included WBC count of 17920 cells/$mm^3$ (78 % polymorphonuclears, 22 % mononuclears) – 76 % neutrophils, 7 % lymphocytes, 8 % monocytes; protein levels of 2.7 g/L, glucose of 1.4 mmol/L, lactate was 10.9 mmol/L and chloride ions were 120.0 mmol/L.

*N. meningitidis* was not found in blood cultures, nasopharyngeal and pharyngeal swab culture or in CSF culture. However, PCR for *N. meningitides* in blood came back positive for serogroup Y. Chest X-ray, thoracic and abdominal ultrasound showed normal findings. Electroencephalography (EEG) showed diffuse irregularity.

The patient received intravenous ceftriaxone 2 × 2 g for 10 days and mannitol 10 % solution during 5 days. His close contacts (family members) prophylactically received one tablet of ciprofloxacin 500 mg.

Nine months later, in the middle of February, he was readmitted with a similar, but slightly milder clinical pre-

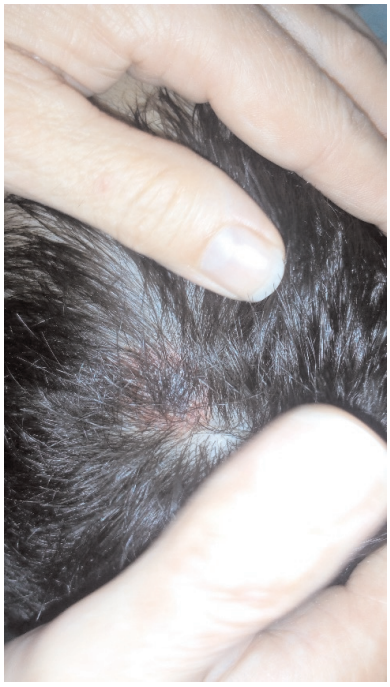

**Figure 1.** Localised necrotic-haemorrhagic skin lesion in the patient's left parietal scalp area (3 × 3cm)
**Slika 1.** Lokalizirana nekrotična-hemoragična kožna lezija u lijevom parietalnom području skalpa (3 × 3cm)

sentation of fever, headache and leg pain. At admission his vital signs were normal, he was conscient and well oriented. Meningeal signs were negative. He had skin erythema of the abdomen and lower legs without signs of haemorrhagic rash. Herpes labialis of the upper lip was noted as well as trismus (mostly because of the neck pain upon opening the mouth). Further physical examination was unremarkable.

Laboratory findings on admission included: C-reactive protein of 37.7 mg/L, serum procalcitonin of 15.6 µg/L, WBC count of $8.2 \times 10^9$/L with 94 % neutrophils, blood platelet count of $178.0 \times 10^9$/L, prothrombin time of 0.7, fibrinogen levels of 3.4 g/L and D-dimers of 4.5 mg/L. PCR for *N. meningitidis* in blood was repeated and came back positive for serogroup W. Again, all taken cultures were negative although the patient did not receive prior treatment. Later immunological laboratory tests – IgA, IgM, IgG and flow cytometry – came back all within normal range. The investigation for complement parameters discovered deficient alternative pathway activity, decreased classical and lectin pathway activities. The level of antigenic factor I was decreased. The levels of C3, C1q, C4 and factor B antigen and factor H were within normal range. Complement activation product levels were in normal range. EEG showed normal finding.

The patient received intravenous ceftriaxone 2 × 2 g for 7 days, recovered fully and was discharged from the hospital. As chemoprohpylaxis he received phenoxymethylpenicillin 2 × 1 500 000 IU until he will be vaccinated with "Bexsero" and "Trumenba".

## Discussion

We report a case of a 16-year-old patient with complement deficiency who presented with meningococcal meningitis and sepsis caused by serogroup Y and nine months later with meningococcal septicaemia caused by serogroup W. Discovering arachnoid cyst by accident in our patient was not related to presenting symptoms in any of the two IMD episodes. In Europe, both serogroups Y and W are uncommon; however, serogroup W is increasing consistently from 2011, while serogroup Y remains stable [8]. In our patient, all tested cultures came back negative, but PCR from blood came back positive in both IMD episodes. The known limitations of culture, such as poor sensitivity, time dependence, and false-negative results under antibiotic therapy require the development of rapid reliable methods of pathogen identification such as PCR-based diagnostics. Under clinical conditions, PCR requires less time than culture-based methods for identification of causative pathogens from blood in patients with IMD [9]. PCR-based methods are not at risk from loss of viable organisms through early antibiotic treatment and sample processing. However, contamination is a problem of PCR-based diagnostic methods, since they detect the pathogens only if specific DNA segments are present, even from non-viable or already phagocytized pathogens [9]. The production of false positives due to contamination should be avoided by strict adherence to procedural guidelines. The general trend has been to include PCR as confirmatory in case definitions globally, although there is still some controversy on this point.

We confirmed complement deficiency in our patient. Testing for complement deficiencies in *Neisseria* infections is normally recommended in the case of a family history, a rare serotype, or when recurrent and systemic infections occur [3]. Our patient presented as recurrent systemic IMD caused by rare serogroups (for this part of the world) and therefore indicated further complement parameters investigation. Complement deficiencies (of both terminal and initial fractions) are associated with an increased susceptibility to the IMD. In such patients, the use of vaccinations (if possible conjugated) against pneumococcus, meningococcus and haemophilus could prevent further invasive diseases. Our patient gradually recovered without sequelae.

In conclusion, recurrent IMD is rare. In such case, one must consider complement deficiency or other immune defects as an underlying condition. PCR might have some advantages over culture in the identification of causal pathogens from blood samples. This might influence the impact of PCR-based methods in the identification of causal septic pathogens in clinical routine. There are widely available proper regimens for eradication of nasopharyngeal carriage and chemoprophylaxis of close contacts with a case of IMD; however, there are no clear objectives on how to prevent recurrent IMD. As a measure of secondary prevention our patient did not receive treatment after the first episode, but has received phenoxymethylpenicillin after the second episode of IMD. Several vaccines targeting different serogroups are available for the prevention of invasive meningococcal disease. Croatia does not have yet anti-meningococcal vaccines listed in routine national immunization programme and cases like this urge on considering it as an option. Continued strengthening of surveillance for IMD is essential to evaluate the impact of ongoing immunisation programmes and to support decision-makers in view of the availability of new vaccines.

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