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Case Report

Inevitable Lethal Outcome of Severe Meningococcal Sepsis

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Introduction

Meningococcal infections caused by the gram-negative bacteria Neisseria meningitidis are still a serious problem especially where pediatrics pathology is concerned, both for developed and developing countries [1,2]. Clinical presentations vary from a local asymptomatic nasopharyngeal inflammation to acute pyogenic meningitis and a severe septic condition which could be fatal [3,4]. The most grievous form of meningococcal infection, is the Fulminant meningococcal sepsis (FMS) which presents with Waterhouse-Friderichsensyndrome (WFS) which can develop into multiple organ failure [2-4]. Nowadays, despite great progress within medical sciences and all the knowledge we have acquired within the realm of infectious diseases, such conditions remain a huge issue because of its rapid development and 100% mortality [3,5,6].

Meningococcal disease frequency varies from <1 (less than 1) to 5 in 100 000 people in high income countries[1,2]. In low income countries, the frequency can be up to 1000 in 100 000 people [1,7,8]. There were 3221 registered cases in 2017, 282 of which were fatal, that were presented by ECDC [9]. In recent years, there has been a significant reduction in meningococcal diseases in Bulgaria; there were 10 cases presented in 2015 countrywide, with a reduction to 4 cases in 2018 [10].

A patient's age is a leading risk factor for developing meningococcal infection. Many records clearly indicate the prevalence of such conditions in children and young age. Another important risk factor could be residence or traveling to endemic areas of the world. However, even more significant and determinative could be the existence of immunodeficiency disorders [8]. According to medical references, cases of FMS and Waterhouse-Friderichsen syndrome become more and more frequent in patients of different ages, suffering from asplenia, oncologic diseases or HIV/AIDS [1,11]. There are records for higher frequency of these conditions in MSM as well [11,12].

Clinical Presentation

Case 1

A 16 years old male patient was presented to the ER in an extremely severe general condition after a collapse. He had no history of previous medical suffering. The parents reported that the boy fell ill all of a sudden with complaints of a headache, nausea and vomiting, high temperature over 39°C. At admission, there

were no signs of skin exanthema, however within a post 2-hour period, purpuric lesions appeared. The rash was noticed firstly on the forehead, and in short time enlarged in size and spread to other parts of the body (Figure 1 and 2). Instantly, a diagnosis of meningococcal sepsis was suspected and the patient was admitted to the Infectious Diseases clinic.

The severe general condition, accompanied by a fever and a serious intoxication was continually worsening. During the physical examination, increasing number of multiple hemorrhagic lesions were reported, as well as cyanosis of the skin and mucosa, tachycardia and tachypnea. The Kernig's sign was positive, whereas the other symptoms of meningism were negative. Laboratory analysis of the blood samples arepresented in Table1.Low levels of the WBC and platelet count were revealed from the complete blood count (CBC) as well as elevated liver enzymes, and variation of the clotting factors. The blood gas analysis showed a metabolic acidosis. The chest X-ray revealed an area of inflammation in the left lung which likely represents pneumonia. Lumbar puncture was performed, and the results proved infection of central neural system (CNS): high protein content (1.7g/L), glycorrachia (1.70mmol/L); CSF pleiocytosis (1088x10^9 leukocytes with 90% of polymorphonuclear (PMNs).

An immediate intravenous therapy was started with administration of high dose of Dexamethasone (4x8mg), Mannitol 10% 750 ml/24h, a broad-spectrum antibiotic (Ceftriaxone 100mg/kg/24h), Human albumin 10% solution, Immunoglobulin G solution, and correction of the metabolic acidosis. Unfortunately, 3 hours after the hospitalization, the patient died from multiple organ failure. 24 hours later Neisseria meningitidis was found in CSF culture. Blood cultures were negative.

Case 2

One month after the afore-presented case, a 7-year old child presented to the ER in the same severe general condition, accompanied by psychomotor agitation. He was not known to be suffering from any diseases in the past. The parents reported, that the previous day, the boy was hit in the abdomen by a ball. The same night a fever was registered up to 38°C, as well as 2-3 vomits. A seizure ensued in the early hours of the following morning (day of admission). During the physical examination, hemorrhagic lesions of various size and location on the body were reported. With regards to neurological status, there was no evidence for meningeal signs. As shown in Table 2, the laboratory data revealed leukopenia, thrombocytopenia,hypoglycemia, liver and renal dysfunction. The abdominal echography, chest x-ray and CT scan of the head were absolutely normal. The results of lumbar puncture and CSF analysis was disturbing because of the lack of any signs for inflammation: WBC - 3x10^9, protein content - 0.25g/L, glucose levels – 4.42 mmol/l.

Despite rapid preventative action, the general condition of the patient continued to worsen. The purpuric lesions were spreading extremely fast, covering larger and larger parts of the skin, all

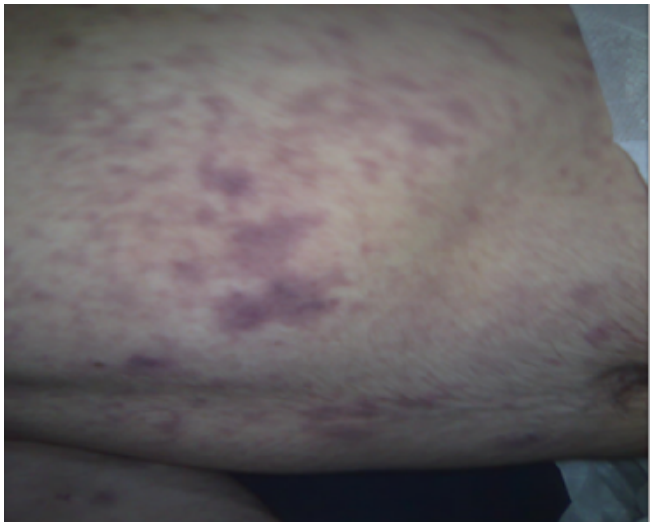

Figure 1: Purpuric lesions covering the abdomen (Case 1).

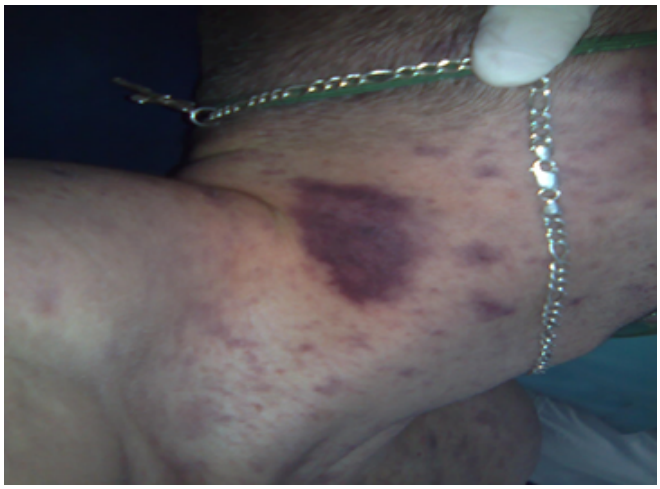

Figure 2: Purpuric lesions covering the neck (Case 1).

Table 1: Laboratory data on admission (Case 1).

Complete blood count (CBC)			
White blood cells (WBC)	2,6x10^9/l	Aspartate transaminase (AST)	76 U/L
Neutrophilis	70%	Alanine transaminase (ALT)	56 U/L
Lymphocytes	28%	Blood urea nitrogen (BUN)	7.9 mmol/L
Monocytes	2%	Creatinine	231 µmol/L
Red blood cells (RBC)	4.82x10^{12}/l	Amylase	256 U/l
Hemoglobin (Hb)	138 g/l	Blood glucose	5.8 mmol/l
Hematocrit (Ht)	42%	Total protein	51.4 g/l
Platelet count (Plt)	65x10^9/l	Prothrombin time (PT)	27 %

Table 2: Laboratory data on admission (Case 2).

Complete blood count (CBC)			
White blood cells (WBC)	3,3x10^9/l	Aspartate transaminase (AST)	85 U/L
Neutrophilis	67%	Alanine transaminase (ALT)	23 U/L
Lymphocytes	29%	Blood urea nitrogen (BUN)	13.3 mmol/L
Monocytes	4%	Creatinine	163,4 µmol/L
Red blood cells (RBC)	5.2x10^{12}/l	Amylase	432 U/l
Hemoglobin (Hb)	108 g/l	Blood glucose	1.18 mmol/l
Hematocrit (Ht)	34%	Total protein	44.5 g/l
Platelet count (Plt)	79x10^9/l	Prothrombin time (PT)	14 %

over the body. After conducting an urgent concilium of various specialists, the diagnose 'Sepsis by vague etiologic agent' was accepted, and thepatient wastransferred toICU. A complex therapy was initiated with a combination of antibiotics (Meronem 2x300 mg/24h and Amikacin 2x250 mg/24h), high dose of Dexamethasone (2x4mg/24h) and Mannitol injection 10% (2x150 ml/24h), supplemented by endotracheal intubation. Unfortunately, two hours post, the patient passed away.

An autopsy of the body was performed a day after, with the following findings: hemorrhagic lesions all over the skin, massive bilateral hemorrhage in the adrenal glands, signs of aseptic meningitis with brain edema (Figure 3-5). The conclusion was 'Fulminant meningococcal sepsis with Waterhouse-Friderichsen syndrome, which could explain the rapid development into multiple organ failure. CSF culture was later reported as testing positive for Neisseria meningitidis.

Discussion

WFS is a critical condition which is defined as an acute adrenal failure related to massive hemorrhagic necrosis of the adrenal glands. The progressive fulminant meningococcal sepsis induced thrombocytopenia, microvascular thrombosis and disseminated intravascular coagulopathy (DIC). As a result of these changes typical symptoms of WFS appear, most frequent of which arefever, purpurafulminans, cyanosis of the extremities, and shock [13-15]. The mortality rate of WFS varies from 20% to more than 50% depending on if the patient is in a shock condition. Unfortunately, the fulminant meningococcal sepsis could not be treated even with the correct therapy, and that is confirmed by many reported cases in worldwide [13,16]. The severe condition is characterized with very rapid evolution. Many reported analysis and cases demonstrate lethal outcome within 12 to 24 hours after the appearance of first symptoms [17,18].

Both of the presented cases show a fulminant meningococcal infection with Waterhouse-Friderichsen syndrome which has led to a severe multiple organ failure that developed within hours. Several important conclusions could be drawn: Although there appear

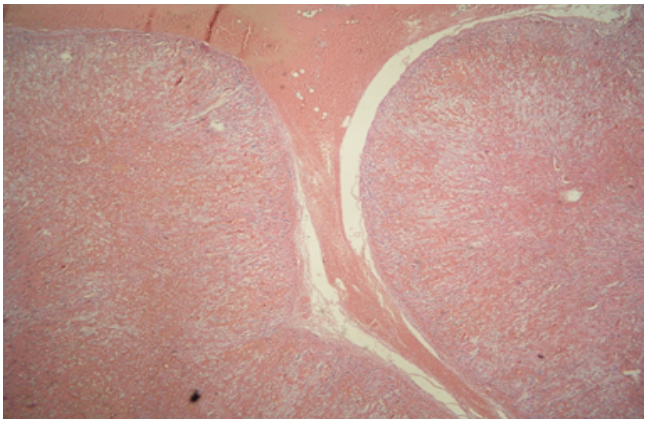

Figure 3:Intraparenchymal hemorrhagein adrenal glands stained with hematoxylineosin(H&E) x40 (Case 2).

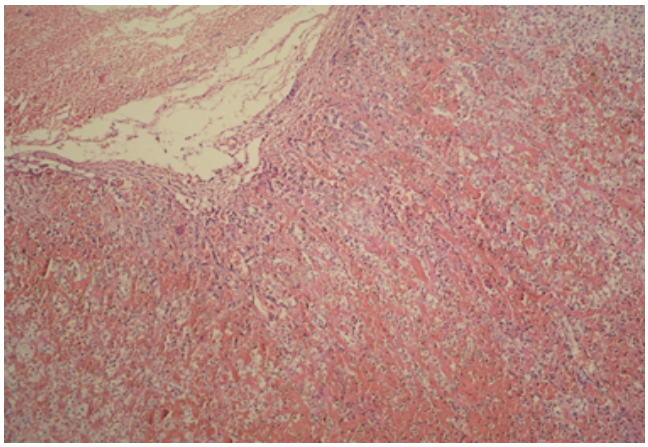

Figure 4:Diffuse intraparenchymal hemorrhage and necrosis in adrenal glands stained with hematoxylineosin (H&E) x100 (Case 2).

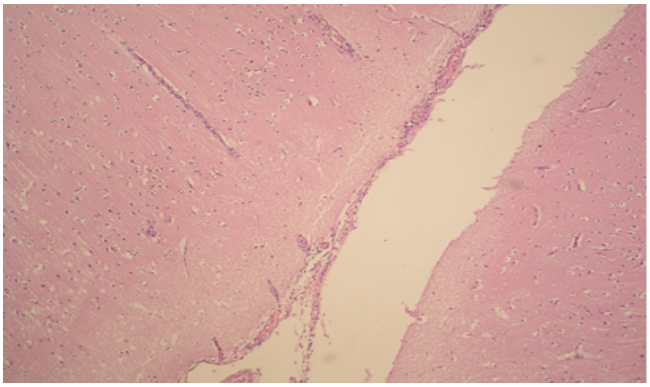

Figure 5: Aseptic meningitis with brain edema stained with hematoxylineosin (H&E) x40 (Case 2).

to be similarities between both the clinical presentation and the short period between the appearances of these two cases, there is no relationship or any contact found between them. Moreover, we did not find any signs of immunosuppression. Both of the patients had no history of traveling out of country or contact with potential contagious people. Interestingly there were no registered cases of Neisseria meningitidis in our country for this period of the year. What it is even more unexpected was that the CSF samples, examined with Real-time Polymerase chain reaction (PCR) turned out to be positive for NM group C – a type indistinctive for Bulgaria.

The rapid evolution of the condition as well as the absence of any prior symptoms and lack of any response to the aggressive etiological, pathogenic and resuscitative therapy for both of those clinical cases is a cause of worry. Consequently, the reaction time for applying antibiotics is extremely short, which leads to the conclusion that we need a detailed, precise and ultimately time-saving universal method for dealing with severe meningococcal conditions. Although there are already algorithms, for example the one drawn up by AJ Pollard[19], who's main diagnostic and resuscitative measures were followed in these cases too, it was hard to avoid a fatal ending.

Still controversial is the question if performing a lumber puncture is a necessary and safe diagnostic tool? Such decisions must be well assessed, taking in consideration the great danger of acute spinal cord trauma and coagulopathy. There were no pathological deviations described from the cerebrospinal fluid of the second case patient regardless of the early and immediate examination of the material. Despite the negative results, after cultivation on nutrient medium the bacterial agent had been isolated. There are other cases of severe meningococcal diseases described with no pathological findings in cerebrospinal fluid in the early hours of clinical presentation. The frequency of such cases is approximately 0.5 up to 12% by the official data, and the proposed reason why could be a premature lumber puncture [3,20-22].

Unfortunately, much of the knowledge we have about such conditions and how they affect the human body are acquired by examining deceased and autopsied patients. Consequently, it is thus required of us to acquire meticulous pathoanatomical expertise, as well as a careful observation of all organs and systems of human body, and use of all examination methods available.

The analysis made by GuendalinaGentilea, et al. [16] on 5 lethal

WFS cases shows a lot of similarities compared to our study. From the performed autopsies, they report severe signs of meningitis, adrenal bilateral hemorrhage, and involvement of other organs leading to multiple organs failure.

The hemorrhagic skin lesions are rare and more common in infants and young adults. The report of Biana Elena Tudosa, et al. [15] proves that purpurafulminans is sign of severe infection and it is mainly associated with protein C deficiency – rare congenital anomalies. The correlation of such low levels of protein C and poor prognosis is proven in some other analyses [17,23,24]. Quite promising results from protein C therapy has been reported worldwide. Treatment of WFS with plasmapheresis is associated with good results as well.

Conclusion

Taking into account everything written above, we can conclude that the meningococcal conditions although rare, still do exist. Moreover, they can be devastating to the patient, leading to long lasting consequences as well as fatalities.Despite all the attempts to resuscitate, all the antibiotic and pathogenic therapy, the fulminant sepsis could not be reversed [13]. However, some new studies reveal that plasma apheresis could turn out potentially successful in treating refractory WFS caused by Neisseria meningitidis[17]. Globally, the usage of Neisseria meningitidis vaccine has significantly reduced the incidence of these conditions including the severe forms, but unfortunately in Bulgaria it is still not that common and widespread. They are lots of questions remaining considering WFS treatment, and some of them are yet to be answered. The most important of them stays the one of the correct express therapy.

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