

Postmortem detection of *Neisseria Meningitidis* in a case of Waterhouse-Friderichsen syndrome from fulminant meningococcal disease in an adult patient

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Abstract: Waterhouse-Friderichsen syndrome (WFS) from meningococcal sepsis is a rare life-threatening condition which generally occurs during infancy and childhood with a high mortality rate (from 10-30% up to 95%). It is very rare in the adult population, usually with pathological risk factors of invasive meningococcal infection. In such fatalities, the condition may rapidly progress into septic shock and disseminated intravascular coagulation with skin lesions (known as “purpura fulminans”) and early recognition and therapy is often difficult owing to the unspecific findings at onset. The purpose of this case report is to present an unusual case of WFS from fulminant meningococcal disease with no meningeal involvement in a previously healthy adult patient, unexpectedly associated with dysmegakaryocytopoiesis findings in bone marrow. The conclusive diagnosis was due to the detection of *Neisseria Meningitidis* in cerebrospinal fluid despite a postmortem interval of four days and the long cadaver refrigeration.

Key Words: meningococcal infection, purpura, malpractice, septic shock, autopsy.

Neisseria meningitidis is a gram-negative diplococcus representing the leading cause worldwide of fatal sepsis and cases of meningitis [1, 2] (Guarner). NM is detected in the naso-oropharyngeal mucosa in 5% - 10% of asymptomatic carriers in the general population, most of all in adolescents and young adults, and rarely causes an invasive disease by invading the respiratory epithelium and entering the blood stream [3-5].

NM can ultimately originate a meningococcal sepsis with Waterhouse-Friderichsen syndrome (WFS), a rare and life-threatening condition which may occur during infancy and childhood [6] but is even more

uncommon in adults [5].

An expression of WFS is the so called purpura fulminans (PF), presenting with dermal and epidermal tissue necrosis described as a “Shwartzman-like” reaction caused by endotoxin from NM, reaching the peripheral tissues through white blood cells and inducing oedema formation and capillary thrombosis [7]. Five to 25% of patients with meningococcal disease develop the most severe PF, which may rapidly progress manifesting as septic shock, disseminated intravascular coagulation, multiorgan dysfunction syndrome until death [8]. Meningococcal disease can have a nonspecific prodrome with acute onset of high fever, myalgia, headache, rash,

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Figure 1. Purpuric lesions covering the face, limbs, anterior chest, abdomen and upper limbs (A) and posterior trunk (B).

and other symptoms which can be confused with many diseases like flu or gastrointestinal diseases [2]. It is not rare a late diagnosis of the disease at postmortem examination, which can reveals the findings of WFS (hemorrhagic adrenal glands) or meningitis.

We report a rare case of fatal WFS in a previously healthy 43-year-old man without meningitis symptoms, leading to a rapid death caused by meningococcal infection which could be explained by a bone marrow failure.

CASE REPORT

A 43-year-old man with a few hours' history of fever, vomiting and asthenia was admitted to Emergency Room (ER). His wife reported that he worked as a prison guard, and had always been in good health and disease-free except for an unremarkable thrombocytopenia of unknown origin.

The neurological examination was normal and he was discharged home with a diagnosis of influenza, in course of resolution (at 8 p.m.). Due to worsening clinical condition, at 6:00 a.m. his wife called the Emergency Service physician who found no fever but hypotension and a rash, supposed to be due to an allergic reaction. He was brought back to the local hospital with stupor, hypotension, fever (38°C), and petechiae covering the face, trunk and arms. A shock of unknown origin was established and the man was transferred to Intensive Care Unit (at 7.40 a.m.) where the hemorrhagic skin lesions rapidly increased over the body into patchy purpura. Laboratory investigations revealed thrombocytopenia, disseminated intravascular coagulation (DIC) and anaemia requiring blood and platelet transfusions. The head CT scans and abdominal US did not revealed any pathological changes. He was treated empirically with Clarithromycin but died a few hours later; the diagnosis was "severe respiratory failure and septic shock". Liability for medical malpractice was evaluated because the prosecutor alleged that the ER physicians had

underestimated or misinterpreting the man's symptoms, discharging him home the first time.

Therefore a medico-legal autopsy was performed after four days of refrigeration of the cadaver at - 4°C. External examination of the body revealed purpuric lesions (Fig. 1 A, B) covering the face, limbs, anterior and posterior chest, abdomen and thighs, with haemorrhages of the conjunctiva.

A sample of intracranial cerebrospinal fluid (CSF) was collected by puncture of the cisterna magna after sterilization of the skin [9]. Internal examination revealed numerous petechiae in the scalp and galea as well as in the subepicardic and subendocardic tissue. Also a massive hemorrhagic infiltration of the periaortic and retroperitoneal soft tissue was observed. The brain showed edema and massive bilateral hemispheric subarachnoid hemorrhages with no macroscopic evidence of meningitis. Lungs were congested and hemorrhagic, with foamy material coming out during sections. Both adrenal glands showed diffuse parenchymal hemorrhage (Fig. 2).

Microscopic examination performed by using formalin-fixed paraffin embedded tissue sectioned at 4 mm and stained with hematoxylin-eosin (H&E), confirmed the macroscopic findings. In the brain, subarachnoid hemorrhages with congested



Figure 2. Cut sections of adrenal gland showing intraparenchymal hemorrhage.

leptomeningeal and intraparenchymal vessels were detected, with no histological evidence of meningitis. The lungs were markedly congested with areas of hemorrhagic extravasation; the heart and the spleen was quite normal. Adrenal glands showed diffuse intraparenchymal hemorrhage. No other abnormalities were found in the histological examination of other organs. A bone marrow biopsy from the sternum [10] showed dysmegakaryocytopoiesis with abnormal size and picnotic and dysmorphic nuclei. Apart from diffuse congestion, no other remarkable pathological findings were noted. Toxicological analysis was negative.

Polymerase Chain Reaction (PCR) assay were performed on the CSF for *Neisseria meningitidis* (NM) detection using a commercial multiplex PCR kit (Seeplex Meningitis ACE Detection kit – Seegene Inc., Korea) [11] and resulted positive for NM. Death was attributed to Waterhouse-Friderichsen syndrome (WFS) with meningococcal sepsis.

DISCUSSION

The diagnosis of WFS is based on the following criteria: fulminant sepsis, skin patchy purpura, and bilateral hemorrhagic necroses of the adrenals [6, 12]. The skin lesions, also known as “purpura fulminans” (PF) have an acute onset with cutaneous haemorrhage and necrosis [13, 14].

The infectious type is mainly caused by Gram-negative organisms, and NM is the commonest haematogenous infection [14] even if other infectious agents, such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, Group A streptococci, *Legionella pneumophila* and viral infections can cause a similar clinical and pathologic patterns [8].

The incidence is influenced strongly by age because infants have the highest risk, while typically it is low among adolescents and young adults, such as the case-fatality rate [5]. Among the most important host risk factors there is a low levels of serum bactericidal antibodies. Low socioeconomic status and minority ethnicity have also been found to be related with increased risk [5]. In adults, pathological risk factors for invasive meningococcal infection include functional or anatomic asplenia, deficiencies or genetic anomalies of the innate immune system, human immunodeficiency virus infection, congestive heart failure, malignancy, diabetes mellitus, organ transplantation, and corticosteroid use [5]. Even environmental and behavioral factors have been known to play a role in the risk of both invasive meningococcal disease and carriage, including concurrent or recent upper respiratory infection, population crowding, passive and active smoking, pub

and bar patronage, close contact, and living in a university dormitory [15].

The mortality rate of meningococcal disease rises dramatically with WFS (from 10-30% up to 95%) [5, 16], that needs early recognition and prompt therapy, which is often difficult owing to the frequently rapid clinical course and unspecific findings at onset. In such cases a delayed diagnosis or medical malpractice could be supposed, especially if there is meningococcal disease mimicking a common viral infection (cold, influenza or enteritis) [5].

Sepsis may precede the meningitis manifestations and can be fulminant with no signs and symptoms of meningeal involvement [17], as in our case, despite CFS contamination.

The mechanism by which NM crosses the blood-brain barrier and cause meningitis is not completely understood. An immunohistochemical study by Guarner *et al.* [2] demonstrated a high concentration of NM in blood vessels of the choroid plexus, probably representing the place where meningococci cross the blood-brain barrier. The reason why NM invades meninges in some patients rather than in others is not well understood but factors like host or bacterial virulence factors, the time course of the disease and the amount of meningococci in the bloodstream may play a role [2].

In the presented case, an explanation of such an unusual outcome in a previously healthy man could be the chronic dysmegakaryocytopoiesis findings in bone marrow, as a possible expression of bone marrow failure [18] that could foster the infection and correlate to the asymptomatic thrombocytopenia reported by the patient.

The source of NM infection remained undefined even if a variety of environmental and behavioral risk factors need to be considered in view of the deceased's job (prison guard).

The detection of NM in postmortem CSF led to the conclusive diagnosis despite a postmortem interval of four days and, above all, the long cadaver refrigeration. NM detection in cadavers after a prolonged postmortem interval has been reported only few times in literature [19-21] and no valid data about its survival are available. Indeed, NM is a fragile bacteria susceptible to temperature variations, desiccation, and pH variations [20-21] and frequently undergoes autolysis. Therefore the postmortem identification of NM from CFS in a corpse after three days of refrigeration (PMI of four days) has great value from a medico-legal standpoint, considering that the disease has, as in the case presented, such a rapid course that WFS fatalities are most often investigated by forensic pathologists because of the sudden, rapid nature of such deaths.

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