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Waterhouse Friderichsen Syndrome: Medico-legal issues

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ABSTRACT

The Waterhouse-Friderichsen Syndrome (WFS) is a pediatric emergency characterized by high mortality due to the combination of bilateral adrenal haemorrhage, meningococcal infection and cutaneous purpura. WFS often raises medico-legal problems related to missed or delayed diagnosis mainly related to the short clinical course, the sudden onset of symptoms and unexpected death. We report the death of a 2-year-old child who had no other pathologies. Death occurred quickly about 20 h after the first care visit. The forensic autopsy was ordered following the parental complaint for diagnostic delay in primary care. Clinical data, autopsy and histological findings were consistent for WFS by Neisseria meningitidis (NM) serotype B. Medical malpractice was excluded. WFS has a rapid clinical course. By the time fever and purpura are reported, it may be too late as thrombotic and bleeding complications may already be present.

1. Introduction

Waterhouse–Friderichsen syndrome (WFS) also known as *purpura fulminans* is a sepsis with poor prognosis to death [1] that occurs usually in pediatric population at infancy or childhood. WFS is an acute and massive haemorrhagic necrosis of adrenal gland from meningococcal infections. More than 80% of WFS cases are caused by the meningococcus *Neisseria meningitidis* [2,3], but various other micro-organisms like gonococci, streptococci, and pneumococci, are also well-recognized. They may lead to fulminant septic shock like the WFS by triggering the release of cytokines [4,5].

Sepsis with patchy purpura and associated bilateral haemorrhagic necrosis of the adrenals are key findings for the diagnosis of WFS [6]. However, cases with only one adrenal haemorrhage have also been reported [7]. In fact, when only adrenal haemorrhagic necrosis is present, other causes must be considered, (for example trauma, coagulopathies, anticoagulation therapy, hypotensive events, complicated pregnancies, etc.) [8]. The adrenal necrosis as well as the generalized rash of the skin have been attributed to coagulation abnormalities and intravascular changes consistent with disseminated intravascular coagulation (DIC) and consumption of clotting factors caused by endotoxins, hypotension and clinical adrenal insufficiency [4].

Unfortunately, WFS is characterized by high mortality (95% approximately), sudden onset of symptoms, rapid clinical development, and unexpected death [9,10]. These factors raise several medico-legal issues related to the assessment of the cause of death but also in terms of medical malpractice. Delayed diagnosis can be fatal and avoid a prompt prophylaxis to contacts. Victims' relatives often blame the general practitioner or pediatrician who first take care of the patient. Therefore, emergency services and physicians are at risk for professional liability due to a missed or delayed diagnosis/treatment that may have prevented lethal outcomes. These are the most common questions of interest in similar death investigations under civil or penal law [9,11]. However, clinical diagnosis of WFS may be extremely challenging.

A case of WFS with a fulminant clinical course of about 20 h in a previously healthy 2-year old child has presented.

2. Case report

A two-year-old boy was admitted, late in the evening, to the hospital with fever up to 38,7 °C and cutaneous rash. The laboratory tests showed a mild thrombocytopenia and leukopenia. An immune thrombocytopenic purpura was suspected. Physicians requested the hospitalization of the child that the relatives refused taking back home the child.

During the night, the child woke up several times because of intense thirst and developed a more pronounced and diffuse purpura with fever

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up to 39 °C. During the second access in Emergency Unit a diagnosis of meningococcal sepsis was made. Antibiotic therapy (ceftriaxone) along with cortisone was administered. However, the clinical conditions worsened quickly and the patient died 1 h after the second arrival in the Hospital but 12 h after the first access to the same Hospital. The relatives alleged the physicians of the first Emergency Service to have underestimated the symptoms showed by the infant at the arrival. They raised the question whether or not a prompt diagnosis/treatment could prevent the lethal outcome. The case became of medico legal interest for the evaluation of the alleged medical malpractice.

3. Results

The autopsy was performed within 72 h after death, according to Tsokos [12].

3.1. Autopsy

External examination revealed a normal development of the child related to his age and no signs of external injuries. Irregular purplish-red petechiae, distributed all over the body, but mainly on the face, trunk and limbs were present (Fig. 1). At autopsy, brain was oedematous and congestion of the leptomeninges was also found. However, leptomeninges looked clear and congested but mostly inconspicuous with no macroscopic signs of meningitis. The cut surface of the brain did not show any focal lesions but cerebrospinal fluid was cloudy. Both adrenals showed haemorrhagic necrosis. No relevant pathological signs of the other internal organs were observed. They were unremarkable on macroscopic examination except for a multi-organ vascular congestion and lung oedema with some foamy material coming out from the airways.

3.2. Histology

Microscopic observation showed diffuse microvascular thrombosis in the lungs, brain, and heart as commonly described in DIC (Figs. 2 and 3). The generalized early microthrombi contained thrombocyte aggregates, fibrin, and embedded erythrocytes in homogeneous distribution. In addition, interstitial and focal intra-alveolar inflammatory cells with diffuse congestive aspects and extravasation were observed especially in the lungs (Fig. 2A and B). Macrophages and neutrophils were also noted in the small vessels consistent with a neutrophilic response to infection. The pattern of pulmonary changes was represented by interstitial and alveolar oedema, erythrocytes extravasation in the alveolus along with necrosis of alveolar epithelium and endothelial injury. The brain findings were characterized by areas of intraparenchymal haemorrhage and intravascular meningeal inflammatory infiltrate (Fig. 2C and D). A mild degree of meningitis was represented by clusters of granulocytic

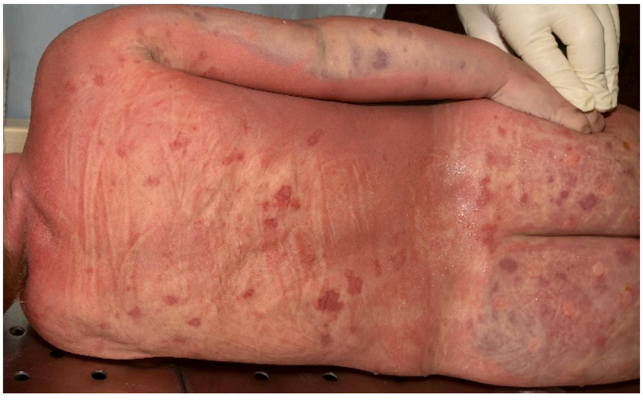

Fig. 1. External examination. Macroscopic appearance of purpura localized mainly to the trunk.

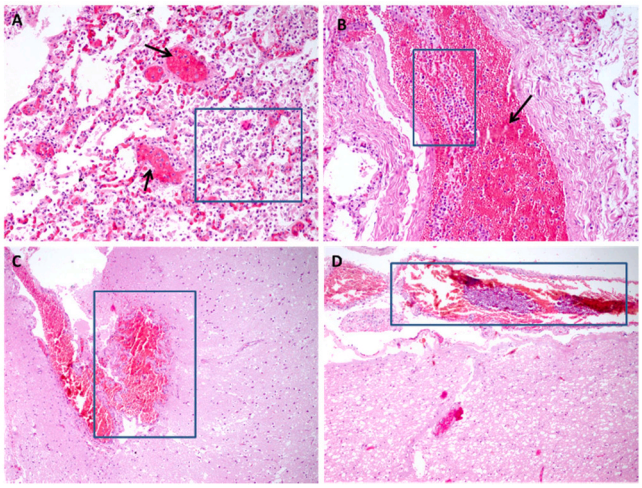

Fig. 2. A–D. A: Black arrows indicate thrombi in small pulmonary vessels; the inset indicates intra-alveolar inflammatory cells in a context of congestion (H&E ×10); B: larger pulmonary vessel containing inflammatory elements (inset), and fibrin (black arrow) (H&E ×20); C: intra-parenchymal brain haemorrhage (inset) (H&E ×10); D: meningeal vessel with inflammatory elements and fibrin (inset) (H&E ×20).

inflammatory infiltrate in the meninges. Erythrocyte extravasation and intravascular inflammatory infiltrate has also been observed in the heart, liver and kidney as aspects of haemorrhage and sepsis (Fig. 3A–D). Finally, a diffuse haemorrhagic necrosis was observed in the adrenal glands (Fig. 4A–D). Adrenal glands presented diffuse haemorrhagic necrosis associated to the destruction of the medulla.

3.3. Microbiology

The microbiology from blood samples were negative. Real-time PCR assays were performed on blood and Cerebrospinal Fluid (CSF) samples and the genetic material of Group B Neisseria meningitidis (NM) was detected in CSF samples. WFS was assessed as cause of death due to meningococcal sepsis leading to haemorrhagic necrotic phenomena of the adrenal glands and purpura of the skin.

4. Discussion

Adrenal apoplexy was first described by Waterhouse in 1911 [13] and Friderichsen in 1918 [14]. Actually, the diagnosis of WFS can be established based on clinical history that is commonly represented by fulminant sepsis, bilateral haemorrhagic necrosis of the adrenals and patchy skin purpura as a result of impaired coagulability. However, due to the rapid fatal course, the WFS diagnosis is mostly made post-mortem, based on autopsy and histological results, measurement of serum procalcitonin concentration (as well-established diagnostic marker of bacteremia and sepsis) and microbiological cultures from central or peripheral blood samples [15]. However, a negative post-mortem microbiological analysis can occur due to antibiotic therapy given before death or due to a post-mortem interval of two days or more [12, 15]. These two conditions occurred both in the present case where antibiotic therapy was just administered few hours before death and the autopsy was performed 3 days after death due to its judicial interest raised by victim's relatives. In cases with PMI higher of 72 h it is recommended to carry out molecular method [9]. In our case blood microbiology was negative but NM serogroup B, a micro-organism responsible of most of WFS cases, was detected by Real-time PCR in CSF samples.

In WFS, bacteremia/meningococcemia may present without signs of meningitis in 20–50% of patients [4]. It seems that meningitis does not play a leading role in the clinical course of the disease neither the cause

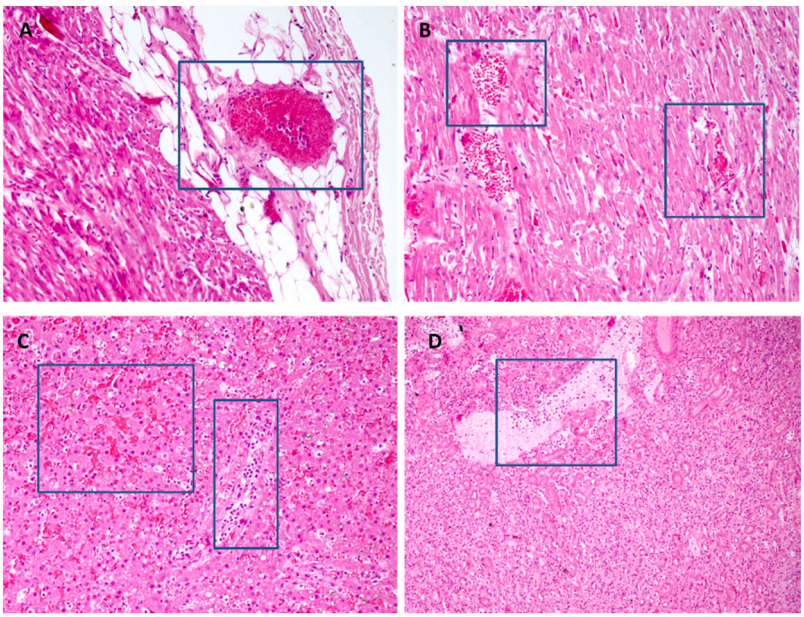

Fig. 3. A–D. A: epicardial vessel containing fibrin and inflammatory elements (inset) (H&E ×20); B: multiple myocardial interstitial red cell extravasations (inset) (H&E ×20); C: congestion of hepatic sinusoids and inflammation in the portal vascular structures (insets respectively) (H&E ×20); D: medullary kidney with areas of intra- and extravascular inflammation (inset) (H&E ×10).

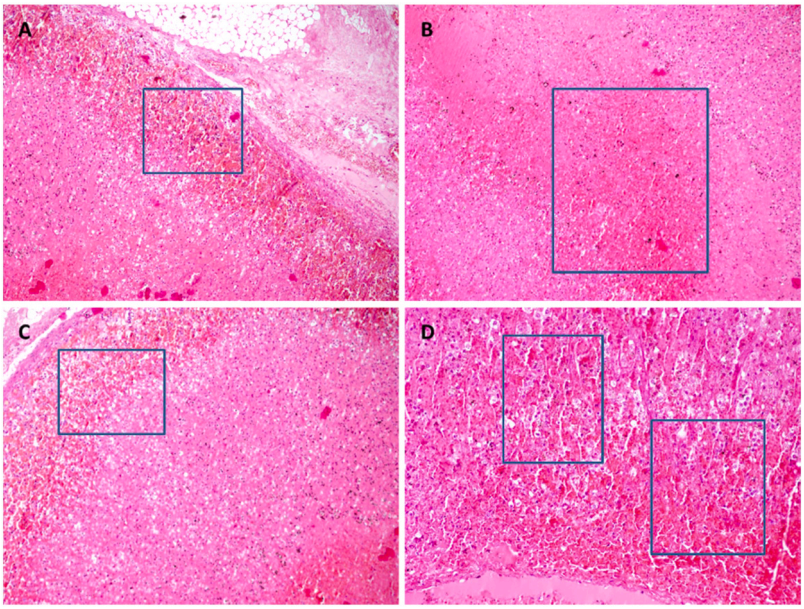

Fig. 4. A–D. Adrenal cortical (inset in A and C) (H&E ×10), and medullary (inset in B) (H&E ×10) haemorrhagic necrosis; detail of the haemorrhagic necrosis at higher magnification (inset in D) (H&E ×20).

of death. Histologically, a mild to moderate degree of WFS-associated meningitis as occurred in our two-year-old boy has been reported in the literature in several other WFS deaths [11,12].

In previous case studies interstitial myocarditis has often been reported and considered to be of importance for the clinical course and a leading cause of death [2,12,16], no myocardial infiltrates neither clusters of diplococci were found in the myocardium of the child.

In the present case the medical malpractice was excluded for two main reasons: the first one is related to the rapid clinical course of WFS that worsen quickly resulting in an unexpected death within few hours. Secondly, the parents of the child refused hospitalization suggested by the physicians at the first access. There is wide agreement around the world that parents have the legal right to decide what medical care their child could receive. However, their refusal of medical care can be sometimes not in the child's best interest, especially in case of a non-life-threatening illness at initial stage but with devastating consequences such as in the WFS.

In fact, patients in the initial stage of WFS without skin lesions or toxic appearance may be difficult to distinguish from a more common and benign viral illness such as a common flu or enteritis [9,12]. In most of WFS cases, the symptoms can be usually represented by cough, dizziness, headache, sore throat, weakness, myalgias, arthralgias, and fever. These are nonspecific symptoms and do not allow a diagnosis to be made in the very early stages [4]. In more than 75% of patients a generalized rash can occur as maculopapular eruption of the extremities becoming soon after ecchymotic and haemorrhagic [4,17]. The purpura

was not observed at the first arrival of the child as it was just in the beginning. The causes of a rash can be numerous including food allergy, medication side effects, reaction to vaccination, irritation by abrasives impregnated in clothing, etc. so that its evaluation can be extremely difficult, especially at the beginning. In approximately 50–60% of patients, petechiae can be spread to any part of the body including the conjunctiva but sparing the palms, soles and head [4,18].

In cases of WFS, clinical conditions worsen rapidly due to sepsis, dysregulation of coagulation and fibrinolysis with purpura in the haemorrhagic phase of DIC, until shock to death [4,19,20]. The generalized purpura as well as the adrenal necrosis have been attributed to coagulation abnormalities and intravascular changes consistent with DIC by sepsis [4].

Sepsis is almost invariably associated with haemostatic abnormalities [19,20] ranging from subclinical activation of blood coagulation (hypercoagulability) to acute DIC [21–23], partly responsible of the multiple organ dysfunction syndrome (MODS). In fact, sepsis in WFS is characterized by an unusual and destructive endothelial response of the host, leading to endotheliopathy [18] and it represents the very leading cause for so high mortality in WFS cases [19]. The consumption of platelets and coagulation proteins related to microvascular thrombosis can result in localized and/or widespread thrombotic manifestations along with simultaneous bleeding such as the extensive purpura of the skin but also the adrenal haemorrhages [23,24]. The alterations of the blood cells and of the coagulation and any therapies presupposes knowledge of the transfusion medicine risk management so to have high quality and safety standards and to minimize the risks of allogeneic blood transfusion [25,26].

Therefore, haemostatic changes are responsible for the subclinical activation of blood coagulation (hypercoagulability), but also for the acute DIC, and the (MODS) [18,19]. Although, the precise mechanism of adrenal haemorrhage is probably multifactorial [8]. Several factors can contribute to the intrinsic vulnerability of adrenal haemorrhage such as an extremely high rate of blood flow, an arterial network that abruptly transitions to a capillary plexus, and drainage by a single, central adrenal vein [23,24]. Bilateral adrenal haemorrhage is also very difficult to recognize in vivo because of its nonspecific presentation and in most cases the definite diagnosis is made at autopsy [24,27]. Even if diagnosis is timely in an early stage of the disease, it is impossible to predict the outcome in an individual case [17,28].

Although potentially life-threatening event [8], the adrenal haemorrhage is considered along with the DIC as the most fearsome complication [9,20].

There is a general agreement that the key event underlying the life-threatening sepsis complications is the overwhelming inflammatory host response to the infectious agent leading to the overexpression of pro-inflammatory mediators and cytokines [20,27]. Sepsis-induced endotheliopathy promotes inflammation and disseminated intravascular micro thrombosis [19–22] which can contribute to the high mortality of WFS cases. Systemic endothelial injury activates two independent pathways: inflammatory and microthrombotic. In fact, the inflammatory cascade together with the endothelial damage are at the basis of the pathophysiology of DIC [29,30] that occurs in the WFS [19,20,27].

Due to WFS devastating consequences it has been recommended that when a child presents with fever and petechiae, WFS must be considered and therapy should be started as soon as possible [4,11,17]. In our case, at first access of the child, the physicians had at their disposal only a couple of clinical signs such as fever and early rush. They recommended further medical care refused by the parents. At the second access, once the diagnosis was made, antibiotic therapy was administered according to international guidelines [4,31]. Such guidelines recommend to start a broad antibiotic coverage consisting of a third-generation cephalosporin (e.g. ceftriaxone) combined with ampicillin and corticosteroids in infants [4,18,32] as soon as the diagnosis is suspected. Therefore, medical negligence was excluded as symptoms and signs were vague and nonspecific to diagnose WFS. Moreover, it was not possible to state beyond any reasonable doubt that an antibiotic therapy administered few hours before, at an early stage, could have changed the rapidly lethal course of the syndrome. Patient monitoring in the hospital was recommended but it was not authorised by the parents. When the diagnosis of WFS was clear, a purpura and fever were already present but it was too late. No supportive therapy would have saved the child No supportive and effective therapy could be adopted to save the child's life [4,9,12,33].

5. Conclusion

Currently, WFS is characterized by high mortality from fulminant sepsis, diffuse microvascular thrombosis and haemorrhagic syndrome. A prompt diagnosis of WFS can improve chances of survival of patients. However, it is not always easy to assess the diagnosis of WFS at initial stage. Because of the short clinical course and sudden onset of symptoms, WFS is often a medico-legal issue [33]. From the viewpoint of forensic pathology, questions concerning malpractice can be of interest in subsequent investigations under civil or penal law [1,33]. However, at the time when fever and haemorrhagic rash of the skin are reported, it can be too late to save the child's life [16] because of coagulation abnormalities and widespread thrombosis in the microcirculation causing MODS along with adrenal haemorrhages already occurred due to sepsis-associated DIC [4,19,20].

The knowledge of this rare but fatal pathology can provide useful indications both for the early diagnosis and for the management of professional misconduct in forensic medicine.

Declaration of conflicting of interests

The authors declare that there is no conflict of interest.

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