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Case Report

Incomplete Kawasaki Disease Following Meningococcal Serogroup B Meningitis

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Abstract

We report a case of incomplete Kawasaki disease following meningococcal serogroup B meningitis which we believe is a very rare and unique reported observation.

A five-month-old male infant presented with community-acquired meningitis. Gram stain and culture of the cerebrospinal fluid revealed *Neisseria meningitidis*. The patient received antibiotic treatment. However, his recovery was complicated by presenting spiking fever with elevated inflammatory markers. Repeated cerebrospinal fluid and blood cultures were negative. The fever persisted till day 12 of treatment. In the absence of the classic mucocutaneous features of Kawasaki disease, the patient was diagnosed with incomplete Kawasaki disease and treated with high-dose acetylsalicylic acid with good effect.

We suggest that our observation translates the potential pathogenicity of *N. meningitidis*, emphasizes the need for strong Kawasaki disease diagnosis criteria and suggests the superantigen-mediated process in Kawasaki disease.

Keywords: *Neisseria meningitidis*; Meningitis; Kawasaki disease

Background

Kawasaki Disease (KD) is an acute multisystem vasculitis. It is now the leading cause of acquired childhood heart disease in the developed world [1]. It was first reported in 1967 by Tomisaku Kawasaki [2]. Although, its diagnosis and etiology still remain unclear. Numerous researchers indicate the growing evidence supporting a role for superantigen in the KD process. Some have linked *N. meningitidis* invasive infection to KD. There is, to our knowledge, just only four associations of KD following meningococcal septicemia previously reported in literature [3-6]. We believe that our observation is a very rare and unique reported description of a KD following meningococcal serogroup B meningitis.

Case Presentation

A five-month-old male child was brought to our pediatric emergency department for evaluation of a two-day history of fever. He complained of diarrhea, sleep disturbance and being unwell. Six weeks ago, a diagnosis of bronchiolitis was established and the baby well treated and recovered.

On admission, he was whining and febrile (temperature, 39.7°C). His fontanelle was pounding with a head circumference of 43 cm. His heart rate was 178 beats/min and respiratory rate was 78 breaths/min. The other physical examinations were unremarkable. Cerebrospinal fluid (CSF) was collected from an urgent lumbar puncture. Intravenous fluids, antibiotics (300 mg/kg/day of cefotaxim and 60/kg/day of vancomycin). and dexamethasone (0.15 mg/kg/injection) were administered concurrently. Two hours later, his eyes appeared to roll backwards. A convulsion was considered and the baby was treated with phenobarbital.

Blood tests showed a white blood cell count of $12.3x10^9$ cells/L with 70% neutrophils, a hemoglobin level of 112 g/L and a platelet count of $407x10^9$ /L. C-reactive protein concentration (81 mg/L) was high. There were no serum electrolyte disturbances.

CSF findings were: Glucose <1 mmol/L (blood glucose: 1.67 mmol/L), protein 843 mg/dL, and leukocyte count 4100 per cubic millimeter with predominance of neutrophils (98%). The microscopic identification of Gram stained CSF revealed Gram negative diplococci. CSF culture on a chocolate agar plate showed smooth and non pigmented colonies giving positive results for oxidase activity. *N. meningitidis* was then identified by api NH testkit (bioMerieux, La Balme-les-Grottes, France). Serogrouping by latex agglutination test demonstrated serogroup B.

Despite an adequate anti-meningococcal treatment, our patient continued to spike high temperatures. Cranial computed tomography and transfontanellar ultrasound scans were normal. A lumbar puncture performed on day 6 revealed a clear improvement of CSF biochemistry. CSF and blood cultures have reported negative results. However, the fever continued. On day 8, our patient presented an axial hypotonia. CBC revealed leukocytosis (white blood cell $20.690x10^9$ /L), anemia (hemoglobin 97 g/L) and thrombocytosis (platelet $902x10^9$ /L). Serum inflammatory markers were elevated (C-reactive protein concentration 55.1 mg/L, erythrocyte sedimentation rate 93 mm/h). Other examinations, including a second cranial computed tomography scan and an abdominal ultrasound, all detected no abnormalities.

The patient continued to have daily fever. His leukocyte ($22.13x10^9$ /L on day 11) and platelet ($1408x10^9$ /L on day 11) counts had increased gradually from his date of admission. Doppler echocardiography showed a little inter-auricular communication of 3 mm. Physical examination disclosed a painful mobilization of the

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right hip, but its ultrasound scan was normal. On day 13, the patient's erythrocyte sedimentation rate reached 105 mm/h. He presented none of the classical mucocutaneous symptoms of KD. Based on the persistent fever and the laboratory findings, the diagnosis of incomplete KD was considered which was not initially suspected during the first days of hospitalization. Consequently, intravenous immunoglobulin was not administered and the child was treated with a high-dose acetylsalicylic acid (80 mg/kg per day) with good clinical and biological effects. The fever resolved. On day 18, Doppler echocardiography demonstrated no obvious pathologic finding. In the improvement of the blood tests, he was discharged home and remained on acetylsalicylic acid with follow up arrangements.

Discussion

Worldwide, KD becomes a devastating disease occurring with approximately 75% of cases in children under 5 years of age [7]. 25% of untreated children develop coronary artery aneurysms [8].

Though approximately 50 years have passed since its first description, the KD remains with an eluding diagnosis for the researchers and clinicians. To date, there is no specific diagnostic test or pathognomonic clinical feature. Complete KD refers to patients with fever for at least 5 days in addition to four out of the five principal following criteria required by The American Heart Association [9]: bilateral conjunctival injection, polymorphous rash, oral mucosal changes, cervical lymphadenopathy and changes of the extremities as erythema, oedema or desquamation. Interestingly, approximately 25% of KD presentations are incomplete [10]. In our case, the diagnosis of incomplete KD was considered because of the persistent fever for 14 days, suggestive changes in laboratory markers and the lack of another known disease process to explain the severe systemic inflammation. Given our patient was younger than 6 months, he was more likely to have incomplete presentation so that we wouldn't miss the diagnosis considering that coronary artery abnormalities occur more often in young children with KD [11].

The quick diagnosis of KD is cause of concern, as is determining its etiology. Despite an extensive literature search, we could barely find two published studies describing KD following meningococcal serogroup B septicemia [3,4]. In view of the fact that the *N. meningitidis* is the leading agent of bacterial meningitis in young infants [12], there is much to be learned about its pathogenesis and unusual invasive infection manifestations such us KD.

In a world of increasing acute mortality in KD [13], our study highlights the need for creating a KD registry and making KD a reportable disease as suggested by Borzutzky [14]. Clinicians have to remain alert to the risk of unrecognized KD as well as a delayed diagnosis or a timely not given treatment. We hope that better epidemiological data can be then used to refine the clinical diagnostic features to increase their positive predictive value.

Although, clinicians should not only focus on those criteria but also pay close attention to the etiological infectious agents known to be associated with KD but not yet closely linked to a verified mechanism. The KD's etiology is challenging. The present epidemiological studies clearly propose various infectious triggers for KD [15]. Moreover, our case here reported of associated meningococcal serogroup B meningitis with KD is exceptional as no such case has ever been previously described. It contributes to prove the hypothetic role of *N. meningitidis* in stimulating a severe systemic inflammation and therefore a KD. To date, there have been only four previous reported cases of KD following meningococcal septicemia [3-6]: the two first ones with group B like our case, the third with group Y and the fourth with group A.

Based on the compelling theory in favor of superantigen-induced KD, we hypothesized that there is a meningococcal toxin capable of inducing an abnormal, uncontrolled and massive immune activation causing an acute inflammatory multisystem vasculitis with persistent fever, particularly in genetically susceptible hosts [4,6, 16-19].

In fact, as well as immune-mediated reactions, susceptibility genes have been suggested as possible etiologic factors for the KD [20]. In particular, a large-scale international combined genome-wide association study and replication analysis in individuals of European and Asian populations identified the FCGR2A locus (functional polymorphism in the IgG receptor gene) as a plausible biologically candidate for KD pathogenesis [21]. The involvement of this locus in increased susceptibility to KD may strongly prove the role of the IgG receptors in the immune activation in KD, clarify the mechanism of response to intravenous immunoglobulin and thereby validate a biological basis for the use of this KD treatment [21]. Thus, further studies on the meningococcus as a potential human pathogen would help elucidate the problem of KD etiology, pathogenesis, genetic susceptibility and also treatment.

As a result of the widespread of the mysterious KD, accurate studies are necessary especially regarding its diagnosis and etiology. In this document, we describe a case of KD with incomplete symptomatology following meningococcal meningitis which we believe deeply recommend a revision of the principal diagnosis criteria. Epidemiological data and further concluding investigations are needed to clarify the pathogenesis of KD and its noteworthy five-time-now-reported association with *N. meningitidis*. The meningococcal superantigen involvement in KD is still not incompletely understood. A direct evidence will depend on more detailed research.

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