

Case Report

Cerebral and coronary vasculitis following meningococcal meningitis: an incomplete form of Kawasaki disease. A case report

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Abstract

Kawasaki disease is the most common cause of acquired heart disease in developed countries. An exaggerated degree of immune activation caused by bacterial or viral protein toxins is considered the basis of this pathology. Early diagnosis can be challenging as 20 % of Kawasaki disease are incomplete forms, but imperative as early treatment reduces the development of coronary aneurysms.

We present the case of a 7-month-old-child with confirmed meningococcal B meningitis. Despite adequate antibiotherapy fever persisted for more than 5 days. Echocardiographic examination and laboratory findings were suggestive of incomplete Kawasaki disease. Moreover, magnetic resonance imaging of the brain showed cerebral vasculitis. The fever subsided after 2 doses of immunoglobulins and a course of glucocorticosteroids.

Our case demonstrates that, even with a confirmed bacterial diagnosis, Kawasaki disease should be considered in the differential diagnosis when fever persists. Our case also demonstrates that procalcitonin may be helpful to differentiate an uncontrolled infection from inflammation.

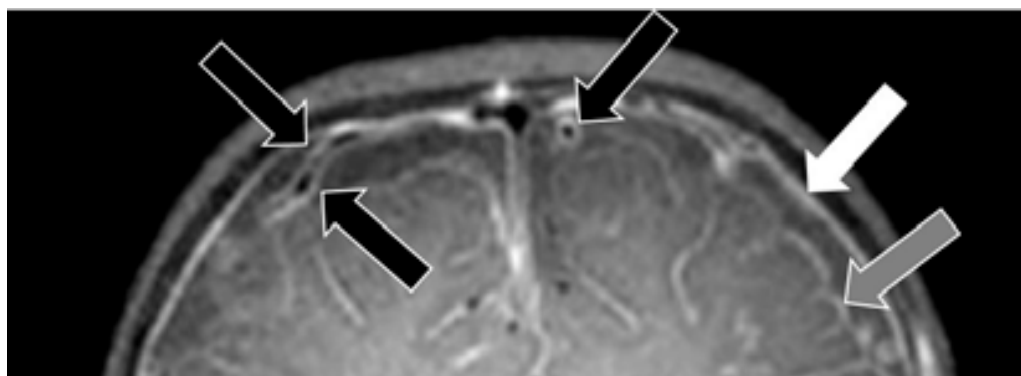
Case Report

A previously healthy 7-month-old Caucasian girl was admitted to the hospital with fever (temperature maximum of 40.7 °C), with onset on the preceding day, lethargy and vomiting. Blood analysis showed high c-reactive protein (3162 nmol/L, [< 47.62 nmol/L]) and procalcitonin (53.23 µg/L, [< 0.1 µg/L]). The white blood cells count ($3.68 \times 10^9/L$, [$< 0.005 \times 10^9/L$]) and protein (267 g/L, [< 40 g/L]) in her cerebrospinal fluid were elevated. Her chest x-ray was normal and urine sample clear. Intravenous antibiotic treatment (ceftriaxone 100 mg/kg/day) was started immediately. A broad qualitative multiplexed nucleic acid-based *in vitro* diagnostic test performed on cerebrospinal fluid identified the presence of *Neisseria meningitidis*. A positive cerebrospinal fluid culture confirmed the diagnosis of meningococcal meningitis. The serogroup B was known a few days later. Antibiotic susceptibility testing showed sensitivity to Ceftriaxone. Blood cultures remained negative and hemodynamically she remained stable.

Her temperature remained above 38.5 °C after 96 hours of antibiotic therapy, despite a declining c-reactive protein (1905 nmol/L). Brain magnetic resonance imaging (MRI) was performed to exclude purulent complications, which were absent. There were signs of meningeal enhancement and vasculitis (Figure 1).

On day seven, persistent fever, anaemia (haemoglobin 90 g/L, [111-141 g/L]), leucocytosis ($17.5 \times 10^9/L$, [$8-12 \times 10^9/L$]), and hypoalbuminemia (316 µmol/L, [571.8-812.5 µmol/L]) were noted with a rising c-reactive protein (2762 nmol/L). Her procalcitonin had however decreased to 4.07 µg/L ($< 10\%$ of initial value), indicating that the initial bacterial infection was well controlled and suggesting that the persisting fever and increasing c-reactive protein were likely of inflammatory origin. She showed no clinical feature of classic Kawasaki disease (KD).

Figure 1. MRI axial contrast enhanced T1-weighted black-blood image. The enhancement of the dura mater (white arrow) and the leptomeninges (grey arrow) on the surface of the brain and deep in the sulci can be depicted. The enhancing walls of the vessels are best seen in the frontal region where the vessels are surrounded by CSF (black arrows). This can be visualised because the flowing blood remains black on these images even after contrast administration, hence the name black-blood.



An echocardiography performed on day eight showed perivascular inflammation and vascular wall thickening of the coronary arteries and aortic root without aneurysm formation (Z-score for the right coronary artery +1.71 standard deviation and for the left anterior descending coronary +1.67 standard deviation) (Figure 2). Even without any clinical sign of KD, as these ultrasound findings resembled the perivascular inflammation seen in KD and our patient fitted the criteria for incomplete KD with persistent fever, high c-reactive protein, anaemia, leucocytosis and hypoalbuminemia, she was treated with a single dose of intravenous immunoglobulins (2 g/kg) (1). From day nine, a thrombocytosis $> 450 \times 10^9/L$ was also noted which fulfils another diagnostic criterion (1).

On day ten her c-reactive protein and procalcitonin had declined but her fever persisted. Echocardiographic re-evaluation was similar to day eight, the suspicion of immunoglobulin resistance was raised. A second dose of intravenous immunoglobulins (2 g/kg) together with a regimen of intravenous glucocorticosteroids according to the RAISE-study protocol was given (2). On day eleven, her fever subsided and c-reactive protein diminished to 1533 nmol/L (the evolution of fever and blood parameters is shown in figure 3). Despite the strong suspicion of KD raised up from day eight, we have not interrupted the antibiotic treatment before day fourteen. Cardiac follow-up showed normalization of the echocardiography over the next months.

Discussion

KD is a necrotizing multisystemic vasculitis which primarily affects children under 5 years of age. The aetiology is still unknown. In developed countries, it is the most common cause of acquired heart disease. An exaggerated immune activation caused by bacterial or viral protein toxins acting as superantigens is currently considered the pathogenetic basis of KD (3). Meningococcal toxins may act in this way. To our knowledge, only three other similar cases have been reported in the literature (4-6).

Early diagnosis of KD is of utmost importance, given the benefit of early administration of intravenous immunoglobulins in preventing coronary artery aneurysm formation. The incidence can be reduced to 4 % (compared to 25 %) by timely treatment (1). Twenty percent of KD are however "atypical" or "incomplete" forms, which compromises early diagnosis. This should be suspected in any child with an unexplained prolonged fever of more than five days with less than four of the principal clinical findings of typical KD. Biochemical markers and echocardiographic abnormalities help in establishing this diagnosis. McCrindle et al., in their article for the American Heart Association, published an algorithm as an aid for early diagnosis (1).

Laboratory parameters are unfortunately non-specific for this diagnosis. In our patient, due to persistent fever, we were primarily concerned about an insufficiently targeted anti-infective treatment, although 4 laboratory findings

suggestive of incomplete KD were present. In differentiating between infection and another origin of inflammation, procalcitonin was helpful. This protein is synthesized in response to a bacterial, fungal or certain parasitic infection : the measured blood levels are significantly higher in bacterial infections than during viral infections or inflammatory diseases (7). In adult studies, it has been shown that this measure can support the clinical decision to initiate, prolong or discontinue antibiotherapy (8). In our patient, procalcitonin was 53.23 µg/L at admission and had dropped to 4.07 µg/L after six days of Ceftriaxone, suggesting an excellent response to antibiotic therapy and decreasing the likelihood of resistance to antibiotherapy. Indeed, a study carried out in a paediatric population showed significant higher values of procalcitonin among patients with confirmed bacterial infection compared to patients with low suspicion of bacterial infection (9). However, there was high variability in procalcitonin values, making it difficult to interpret (9). What's more, neither single nor serial procalcitonin measurements were able to predict the presence or absence of confirmed bacterial infection with enough certainty to recommend initiating or withholding antibiotics (9). So, this laboratory finding must be carefully interpreted within the particular clinical context and taking into account other available analyses and images.

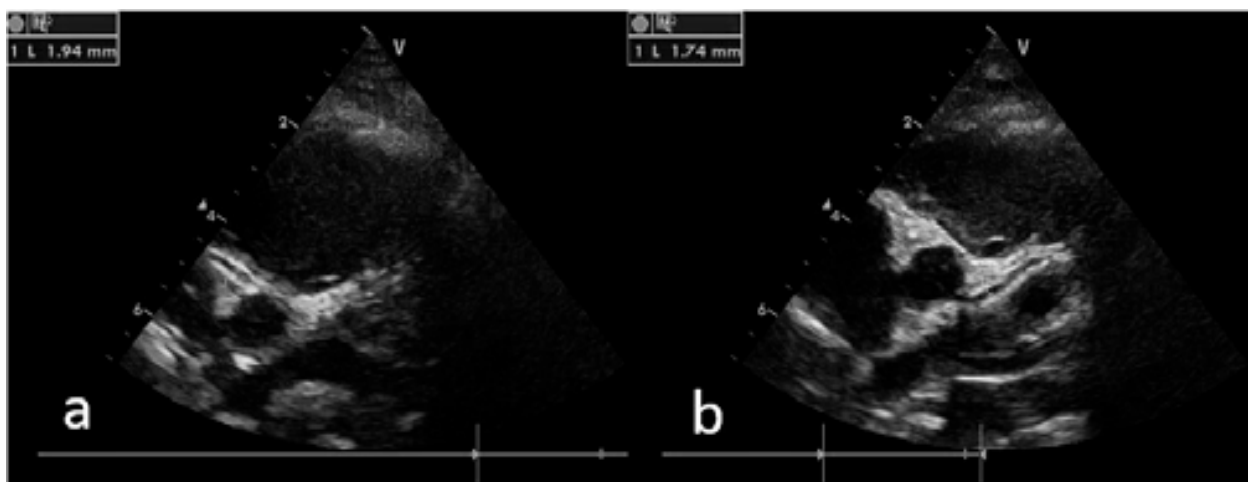
Imaging is helpful in establishing the diagnosis of (incomplete) KD. Echocardiography showing vasculitis with coronary dilation is considered diagnostic – diagnosis of KD can be established when this coronary artery anomaly is detected on echocardiography even without any clinical classic feature (1). In our patient, echocardiography showed perivascular inflammation and vascular wall thickening without enlargement. This does not fulfil echocardiographic incomplete KD criteria (1). However, this measure lacks sensitivity and dilation is generally not identifiable at the beginning of the disease. The hyperechogenicity of the aortic root and coronary walls was suggestive of vasculitis as the coronary abnormalities during KD are known to follow a progressive pathophysiological process (1).

In addition to these echocardiographic signs, brain MRI showed also vasculitis. KD is a systemic disease that involves many organs, including the brain. Central nervous system involvement resulting from KD is found in up to 30 % of cases (10).

Conclusion

KD is the most common cause of acquired heart disease in developed countries. An exaggerated degree of immune activation caused by bacterial or viral protein toxins is considered the basis of this pathology. Meningococcal toxins may also act in this way. Early diagnosis can be a challenge, as 20 % of KD are incomplete forms, but imperative as early treatment reduces the development of coronary aneurysms. Unfortunately, laboratory parameters are non-specific. In a child with persistent fever and high c-reactive protein,

Figure 2. echocardiography showing perivascular inflammation and vascular wall thickening of the coronary arteries. View "a" shows the right coronary artery and view "b" the left anterior descending coronary artery.



we support that measuring procalcitonin may be helpful to differentiate an uncontrolled infection (procalcitonin will remain high) from an inflammatory origin such as KD (procalcitonin will decrease). Even if its clinical relevance among children is still debate, we think that this finding could be useful in some specific situation like this one. In combination with cardiac imaging – echocardiography showing vasculitis with coronary dilation is diagnostic – cerebral MRI can also help diagnose KD as the central nervous system is involved in up to 30% of cases.

The core message is that, even with a confirmed bacterial diagnosis, Kawasaki disease should be considered in the differential diagnosis when fever persists.

Conflicts of interest statement

The authors of this case report declare that they have no conflict of interest. They do not have any affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this case report.

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Figure 3. evolution of maximal temperature (Max T, °C), PCT (procalcitonin) (µg/L), CRP (C-reactive protein) (nmol/L) and PLT (platelets) (·10⁹/L).

