

# Comorbidity of Kawasaki disease and group A streptococcal pleural effusion in a healthy child: a case report

Ahmed H Alhammadi  
Mohamed A Hendaus

General Pediatrics Section,  
Department of Pediatrics, Hamad  
Medical Corporation, Doha, Qatar

**Background:** Kawasaki disease is an acute self-limiting vasculitis that affects children. The most dreaded complication of Kawasaki disease reported in the literature over the years is coronary artery disease, which is considered as the main cause of acquired heart disease. However, pulmonary associations with Kawasaki disease have been overlooked. We present a rare, if not unique, case of Kawasaki disease associated with group A streptococcus pleural effusion in the English language literature. A search of the PubMed database was carried out, using a combination of the terms “Kawasaki disease”, “pneumonia”, and “group A streptococcus”. The majority of studies conducted in children with Kawasaki disease have concentrated on the coronary artery implications. Kawasaki disease is considered a self-limiting illness, but can have detrimental consequences if not diagnosed early. When there is a prolonged inflammatory reaction, with no infectious agent identified or remittent fever unresponsive to antibiotics, Kawasaki disease should be taken into consideration. Elevated Vβ2+ T cells compared with healthy controls suggest possible involvement of a superantigen in the etiology of Kawasaki disease, so it is wise that the health care provider concentrates not only on the cardiac consequences, but also on pulmonary associations.

**Keywords:** Kawasaki disease, pneumonia, group A streptococcus

## Introduction

Kawasaki disease, also known as mucocutaneous lymph node syndrome, is an acute self-limiting vasculitis of childhood.<sup>1</sup> Kawasaki disease surpassed rheumatic fever as the most common cause of acquired heart disease. If left untreated, 15%–20% of patients may develop coronary artery lesions and coronary artery dilatation.<sup>2</sup> The majority of the literature focuses on the cardiac implications of Kawasaki disease, but little is known about its pulmonary complications or associations. Here we report a rare, if not unique, case of Kawasaki disease associated with group A streptococcus (GAS) pleural effusion and a review of the English language literature.

## Case presentation

A 3-year-old female patient presented with a 5-day history of fever, sore throat, and cough, but no rash. Past medical history was unremarkable, as was family history. Immunizations were up to date for age. On admission to the ward, her vital signs were: temperature 39.5°C; pulse 130 beats per minute; blood pressure 100/70 mmHg, respiratory rate 50 per minute; oxygen saturation 90% on oxygen 2/L per minute via nasal cannula; weight 13.8 kg (50th percentile); and length 94 cm (48th percentile). Her skin had normal texture, with no rashes, hypopigmentation, or hyperpigmentation,

Correspondence: Ahmed H Alhammadi  
General Pediatrics Section, Department  
of Pediatrics, Hamad Medical  
Corporation, PO Box 3050, Doha, Qatar  
Tel +974 4439 2239  
Fax +974 4443 9571  
Email aalhammadi@hmc.org.qa

her capillary refill was around 3 seconds, and the oral mucosa was mildly dry. The patient had decreased air entry and coarse crackles in the right lower and middle zones of the lung. The throat was erythematous and there was no cervical lymphadenopathy. The rest of the physical examination was unremarkable.

Initial laboratory results were: white blood cells 24,000/ $\mu$ L (neutrophils 60.2%, lymphocytes 35.4%, monocytes 4.3%, basophils 0.1%), hemoglobin 10.3 g/dL, and platelets 206,000/ $\mu$ L. C-reactive protein was 100 mg/L, erythrocyte sedimentation rate was 65 mm/hour, albumin was 18 g/L, creatinine was 66  $\mu$ mol/L, aspartate aminotransferase was 100 U/L, and alanine aminotransferase was 60 U/L. Serum glucose, blood urea nitrogen, calcium, sodium, chloride, and potassium were normal. Venous blood gas was pH 7.2, pCO<sub>2</sub> 44 mmHg, pO<sub>2</sub> 29 mmHg, and HCO<sub>3</sub> 17 meq/L, with a base excess of 11. Anteroposterior chest radiographs showed a right middle and lower lobar consolidation with moderate pleural effusion.

## Course of hospitalization

The patient was started on intravenous normal saline 20 mL/kg due to dehydration. She was then transferred to the pediatric intensive care unit due to increased oxygen requirement. A chest tube was inserted and 200 mL of pus was drained. The pleural fluid culture yielded GAS. The patient was started on intravenous cefuroxime and clindamycin. Nasopharyngeal and throat swabs, blood culture, and a Mantoux skin test were all negative.

On the eighth hospital day, there was no clinical response to antibiotics, and fever persisted, with new onset of abdominal pain, diarrhea, and slight tachycardia at a heart rate of 150 beats per minute.

A repeat blood count showed a significant white cell count of 30,000/ $\mu$ L, hemoglobin 7.7 g/dL, platelets 600,000/ $\mu$ L, aspartate aminotransferase 180 U/L, alanine aminotransferase 120 U/L, and albumin 18 g/L, with a rise in erythrocyte sedimentation rate and C-reactive protein.

The differential diagnosis included bacterial resistance to antibiotics, nonbacterial etiologies such as a virus or aspiration of a foreign body, bronchiolitis obliterans, hypersensitivity pneumonitis, atypical Kawasaki disease, eosinophilic pneumonia, Wegener's granulomatosis, pulmonary sequestration, and cystic adenomatoid malformation.

Since atypical Kawasaki disease was in the differential diagnosis, an echocardiogram was ordered which showed a prominent of left anterior descending artery (0.26 cm, z-score 3.2) and left main coronary artery

(0.35 cm, z-score 3.2), with no vegetations or pericardial effusion. Our team decided to give one dose of intravenous immunoglobulin 2 g/kg, and high-dose aspirin (80 mg/kg/day) was started. The fever resolved in 24 hours and the patient's general condition improved, but desquamation developed on the hands and feet. The diagnosis of atypical Kawasaki disease was confirmed.

The patient was discharged home in a stable condition on oral antibiotics for 2 weeks and on an antiplatelet dose of aspirin. She was seen in the outpatient clinic in good condition, and a repeat echocardiogram at 6 weeks was normal.

## Discussion

Kawasaki disease is common in Japan, with an incidence of approximately 112 cases per 100,000 children under the age of 5 years, and there were 4248 cases of Kawasaki disease reported in the United States in 2000.<sup>3</sup> The culprit in Kawasaki disease is not as yet known, so diagnosis might be a challenge for the physician, given that there are no specific tests. However, superantigens might have a role.<sup>2</sup> In a recent study, Natividad et al concluded that a superantigen could be the possible cause or trigger for Kawasaki disease. The authors based their decision on the elevated levels of V $\beta$ 2+ T cells found in patients with Kawasaki disease compared with healthy controls.<sup>4</sup> Another study showed that the inflammation in Kawasaki disease could be due to several infectious agents in genetically susceptible persons. Staphylococcal and streptococcal superantigens have also been reported as possible culprits.<sup>5</sup>

The diagnostic criteria for diagnosis of classic Kawasaki disease include high fever for at least 5 days, in addition to four or more of the following symptoms: polymorphous rash, cervical lymphadenopathy (more than 1.5 cm), bilateral nonpurulent conjunctivitis, "strawberry" tongue, swollen hands and feet, erythema of the soles of feet and palms, and red, swollen cracked lips.<sup>1</sup>

Atypical Kawasaki disease is the term used to describe patients with incomplete presentation of the disease and usually constitutes up to 36.2% of all cases of the disease. Cervical lymphadenopathy and extremity changes are the two most common symptoms not seen in a patient with atypical Kawasaki disease.<sup>6</sup> Since Kawasaki disease is considered to be a vasculitis, symptoms like cough, abdominal pain, diarrhea, and vomiting might appear around ten days prior to the diagnosis of the disease.<sup>7</sup>

In terms of laboratory studies, inflammatory markers that might aid in the diagnosis of Kawasaki disease include: elevated platelet count, erythrocyte sedimentation rate, C-reactive protein, leukocyte count, aspartate aminotransferase, alanine

aminotransferase, and a high white cell count in urine. However, albumin, sodium, potassium, total cholesterol, lymphocytes, and hemoglobin might be low.<sup>8</sup> Patients with atypical Kawasaki disease have been reported to have a low frequency of pyuria, low frequency of hyponatremia, low levels of gamma glutamyl transferase, and low levels of serum alanine aminotransferase compared with patients with classical Kawasaki disease.<sup>6</sup> Kentsis et al found that high concentrations of two urine proteomes (filamin C and meprin A) are specific for the diagnosis of Kawasaki disease.<sup>9</sup>

There are few cases of Kawasaki disease associated with pulmonary changes, but they were not associated with GAS. De Maddi et al<sup>10</sup> and Uziel et al<sup>11</sup> described five patients diagnosed as having atypical Kawasaki disease with unspecified pneumonia. Other authors also describe pulmonary changes not related to GAS.<sup>2,12–15</sup> In addition, Huang et al reported a case of atypical Kawasaki disease associated with *Mycoplasma pneumoniae* and Epstein-Barr virus infection.<sup>16</sup>

Prompt initiation of therapy in Kawasaki disease can decrease the risk of coronary artery lesions and dilatation from 20% to 5%. The initial treatment is a single dose of intravenous immunoglobulin (2 g/kg) and high-dose aspirin (80–100 mg/kg/day, divided into four doses). Treatment is more effective if started within ten days of onset of fever, but it is also advisable to initiate it even after ten days. The aspirin dose is usually switched from an anti-inflammatory dose to an antiplatelet dose (3–5 mg/kg/day, given as a single dose) after 48–72 hours of defervescence. The antiplatelet dose of aspirin is usually continued for 6–8 weeks after the child is afebrile and if there are no coronary artery abnormalities.<sup>17</sup>

Retreatment with a second dose of intravenous immunoglobulin (2 g/kg) is recommended if there is persistent fever for  $\geq 36$  hours after completion of the initial intravenous immunoglobulin infusion.<sup>18</sup>

Steroids have been used for refractory cases of Kawasaki disease, especially the combination of intravenous methylprednisolone and oral corticosteroids; however, their use is controversial because of some reports indicating that steroids might cause coronary artery aneurysm and rupture.<sup>19</sup>

Tumor necrosis factor-alpha might play a role in the inflammatory process in acute Kawasaki disease, so studies were conducted on the efficacy and safety of anti-tumor necrosis factor-alpha (infliximab) for the treatment of refractory cases of Kawasaki disease. Hirono et al reported success using infliximab in eight of 11 patients with refractory Kawasaki disease, with success measured by resolution of fever and a decrease in levels of serum interleukin-6, soluble tumor necrosis factor-alpha receptor 1, and C-reactive protein.<sup>20</sup>

Burns et al reported a complete response to infliximab therapy, with cessation of fever and decrease in C-reactive protein in 14 of 16 patients.<sup>21</sup> Song et al also reported a complete response of 80% in patients with refractory Kawasaki disease after use of infliximab. The response was measured by defervescence and decreased levels of C-reactive protein.<sup>19</sup>

## Conclusion

Kawasaki disease is considered a self-limiting disease, but it can have detrimental consequences if not diagnosed early. When there is a prolonged inflammatory reaction and no infectious agent is identified or there is remittent fever unresponsive to antibiotics, Kawasaki disease should be taken into consideration. The finding of elevated V $\beta$ 2+ T cells suggests possible involvement of a superantigen in the etiology of Kawasaki disease, so it is wise for the health care provider to concentrate not only on the cardiac consequences, but also on pulmonary associations.

## Disclosure

The authors report no conflicts of interest in this work.

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