# Diagnostic Challenges and Novel Insights in Kawasaki Disease, a Case Report

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## Abstract

This report highlights the case of a 3-year-old girl with Kawasaki disease and concurrent *Mycoplasma pneumoniae* infection. Treatment with intravenous immunoglobulin, high-dose aspirin and corticosteroids led to clinical remission and resolution of cardiac abnormalities. This case highlights the need for timely recognition of KD and co-infection, and stresses the role of early, tailored management in preventing serious complications. Co-infection, pathophysiological hypotheses and pharmacogenetics are briefly explored.

## Background

Kawasaki disease (KD) is a leading cause of acquired heart disease in children, characterised by acute vasculitis (1, 2). Classic symptoms include prolonged fever, conjunctivitis, changes in oral mucosa, oedema of the hands and feet, cervical lymphadenopathy, and polymorphous rashes. Atypical KD may lack these hallmark features, making diagnosis more challenging and often reliant on laboratory findings. A resurgence in KD has been reported following the relaxation of SARS-CoV-2 pandemic restrictions, highlighting the need for clinical vigilance (3). This case report aims to raise awareness of KD.

## Case description

We present the case of a 3-year-old girl who developed a severe rash, refusal to bear weight, and systemic symptoms following an acute infection with parotitis epidemica. She initially presented to the emergency department with fever and a neck swelling accompanied by torticollis, but was otherwise well. Initial investigations showed a normal complete blood count and mildly elevated CRP (41 mg/L [<5 mg/L]), along with locoregional inflammation on echography. Antibiotics were administered for presumed lymphadenitis colli and discontinued once serology confirmed parotitis epidemica. She was discharged with an expected recovery. However, 11 days after fever onset, she re-presented with persistent fever, irritability, a severe desquamating rash with superinfection in the groin and sacral region, eyelids and perioral area, bilateral foot swelling with refusal to bear weight, anorexia, and mild conjunctivitis (Figure 1). She had no relevant medical history.

Upon closer clinical examination, the patient had bilateral submandibular lymphadenopathy and cracked lips. Nikolsky's sign was negative. Laboratory investigations showed elevated CRP (92 mg/L), thrombocytosis (546,000/µL [150,000-400,000/µL]), neutrophil-predominant leucocytosis (18,770/µL [6,000-17,000/µL]), hyperferritinaemia (1,100 ng/mL [4.6-200 ng/mL]), normocytic normochromic anaemia and hypoalbuminaemia (25.5 g/L [38.0-54.0 g/L]). Liver enzymes, synthetic functions (other than albumin), high-sensitivity troponin, and electrolytes were within normal limits. Lactate dehydrogenase was only mildly elevated. The clinical and laboratory findings were most consistent with KD. Differential diagnosis included Lyell syndrome, Stevens-Johnson syndrome, toxic shock syndrome (TSS), TSS-like syndrome, staphylococcal scalded skin syndrome, and hyperinflammatory conditions. Given the severity of her presentation and potential alternative diagnoses, high-dose flucloxacillin was initiated and she was admitted for further evaluation.

Transthoracic echocardiography (TTE) on the first day revealed coronary artery dilation with increased echogenicity, measuring 4.5 mm in the left and 3.4 mm in the right coronary artery, along with mild pericardial effusion (Figure 2). Chest X-ray showed mild bronchitis, and abdominal echography revealed mesenteric lymphadenopathy. Nasal swab PCR was positive for *Mycoplasma pneumoniae*, while serology ruled out acute viral infections. These findings made alternative diagnoses unlikely. Treatment was adjusted for KD, with a Kobayashi score of 1 indicating a low risk of resistance to intravenous immunoglobulin (IVIG).

IVIG at 2g/kg body weight was administered, and the patient was started on high-dose aspirin and a course of azithromycin. Other antibiotics were discontinued. Despite clinical and biochemical improvement, the fever persisted. On day 3, intravenous methylprednisolone was initiated at 1mg/kg body weight twice daily. She became afebrile by day 5, after which the aspirin dose was reduced. TTE on day 7 showed normalisation of coronary artery diameter (<3 mm bilaterally), with persistently increased echogenicity and no pericardial effusion. Intravenous treatment was switched to oral therapy with a tapering corticosteroid schedule, and the patient was discharged. At six-week follow-up, cardiac abnormalities had fully resolved and the patient remained symptom-free.

**FIGURE 1**: Patient presented with a severe desquamation of the urogenital region. A small patch suspicious of superinfection is visible in the right groin.

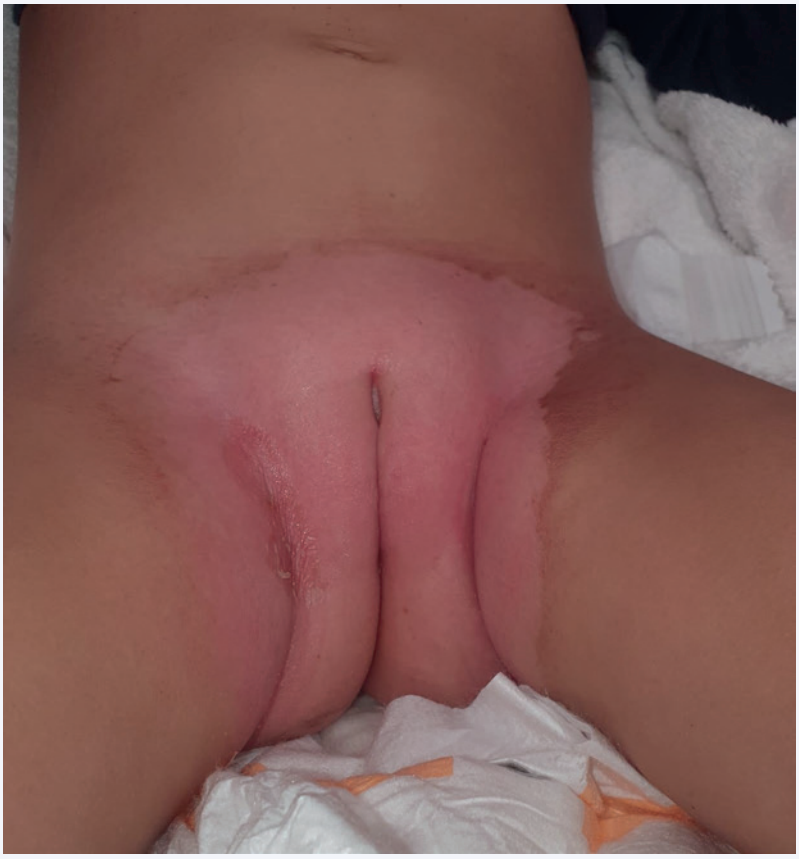
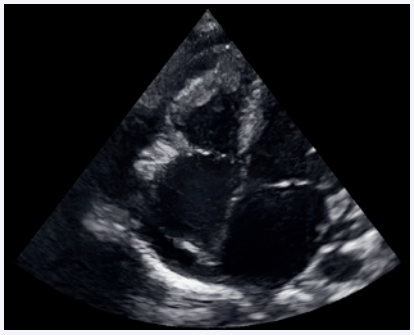


**FIGURE 2**: Transthoracic echocardiography, apical four chamber view. Mild pericardial effusion is visible.



## Discussion

In this case, a high suspicion of KD was maintained while treating for several less likely but potentially serious differential diagnoses. The case illustrates the diagnostic complexity of KD, even when key features are present, particularly in the context of co-infections with uncertain relevance. Treatment was adjusted based on TTE findings, which strengthened the suspicion of KD and allowed for the discontinuation of antibiotics. It is important to note that TTE findings may be normal in the early stages of KD. This diagnosis should still be considered in patients who do not respond to initial treatment for alternative conditions.

Further investigations identified a co-infection with *Mycoplasma pneumoniae*. While co-infections, particularly pulmonary infections, have been associated with KD, the significance of *Mycoplasma pneumoniae* has only recently been recognised. One study reported that such an infection may aggravate the risk of coronary aneurysm formation (4). Clinicians should therefore consider PCR testing for co-infections and initiate appropriate treatment when identified.

Infections are thought to play a primary role in the pathophysiology of KD by activating the immune system. However, the American Heart Association notes that a definitive causative agent has yet to be identified (1). The innate immune response involves the release of proinflammatory cytokines such as interleukin (IL)-1, IL-6 and tumour necrosis factor, which are nonspecific. Furthermore, the adaptive immune system modulates both proinflammatory and regulatory T cells, which may explain the effectiveness of IVIG therapy, as it promotes regulatory T cell upregulation. Notably, the recurrence rate of KD is very low, possibly due to the protective role of B cell memory.

Most children do not develop KD despite the presence of proinflammatory cytokines during infection, underscoring that the disease's pathophysiology remains poorly understood. This aligns with one report, which found that the incidence pattern in Japan does not support person-to-person transmission as the sole cause (2). An alternative hypothesis proposes that airborne transmission of an infectious agent may contribute to the disease's occurrence, perhaps explaining its geographical distribution. Indeed, several studies have linked KD incidence to tropospheric wind currents (1, 2). Additionally, the marked decline in KD cases during the COVID-19 pandemic further supports a connection with transmissible agents (2).

Recent studies suggest that a subset of KD patients may share a common disease trigger. In one study, Rowley et al. identified a protein epitope recognised by antibodies that develop during KD (5). Using plasmablasts isolated from confirmed KD cases, they generated monoclonal antibodies to detect a specific antigen, which was then cross-tested with sera from other patients. A subsequent study used amino acid substitution matrix analysis to identify a variant of the epitope that enhanced binding to KD monoclonal antibodies (6). This led to the discovery of a convergent antibody response, supporting the hypothesis of a predominant causative agent. Given that such responses are typically associated with infection, a respiratory pathogen is considered the most likely candidate. These findings further our understanding of KD pathophysiology and may contribute to the development of a disease-specific diagnostic test.

Host genetic factors may influence susceptibility to KD. This was first suggested when individuals of Japanese ancestry living in Hawaii, located along the same tropospheric wind path as Japan, were found to have a risk of KD similar to that of native Japanese individuals. In addition, siblings of a KD patient have a 10- to 30-fold higher risk of developing the disease compared to the general population (7). While a detailed discussion of implicated genes is beyond the scope of this report, insights into patients' genetic backgrounds may help explain differences in susceptibility. Notably, certain gene associations appear population-specific. For example, human leukocyte antigen determinants have been linked to KD susceptibility in individuals of Japanese or Taiwanese ancestry, but not in those of European descent (3). Identifying these differences may inform tailored treatment and prevention strategies. Expanding our knowledge of KD-related genes could also support the use of next-generation sequencing (NGS) to refine prognosis and guide therapy.

Some polymorphisms have already shown clinical relevance, informing current treatment approaches in KD. Variants in *ITPKC* and *CASP3* genes have been associated with IVIG-refractory KD, in which corticosteroids are sometimes used (7). While a randomised trial found no overall benefit of corticosteroids over IVIG, subgroup analysis showed reduced coronary artery abnormalities in refractory cases (8). This finding was supported by a trial targeting patients with a high Kobayashi score, which predicts IVIG resistance (9). Genetic insights have also guided the development of novel therapies. For instance, *ITPKC* and *CASP3* variants downregulate a calcineurin-mediated pathway, exacerbating inflammation. Cyclosporine, a calcineurin inhibitor, may restore immune regulation and has prompted trials for its use in IVIG-refractory KD (7). Additionally, pharmacogenomics has driven interest in statins. Their pleiotropic effects may help prevent complications, and they appear to be safe in children (10). Their efficacy is under investigation.

## Conclusion

KD remains a leading cause of acquired heart disease in children, making prompt recognition and treatment essential. With rising post-pandemic incidence, renewed clinical awareness is needed. Despite decades of research, our understanding of its aetiology and pathophysiology remain incomplete. Recent findings suggest that concurrent infections may influence outcomes, supporting the need to consider co-infection testing during diagnosis. Genetic factors likely contribute to both disease susceptibility and treatment response, and novel therapies are under investigation. Integrating clinical, genetic, and infectious insights may ultimately improve diagnosis, stratify risk, and personalise treatment for children with KD.

## Statements

Written informed consent was obtained from the parents to publish the case report and figures.

The authors have no conflicts of interest in relation to the subject matter of this manuscript.

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