Twenty-year-old woman presenting with typical Kawasaki disease

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Abstract

We describe adult-onset Kawasaki disease (KD) and review clinical manifestations and treatment guidelines. Our patient is a 20-year-old female who initially presented to an outside hospital for fever, cervical lymphadenopathy, malaise, exudative tonsillitis, and skin eruption. She received antibiotics for suspected exudative pharyngitis, but experienced continued fevers and presented to the UCLA emergency room one week later. She had diffuse petechial macules coalescing into reticulated patches, fingertip peeling, conjunctival injection, oral erosions, and tongue swelling. Despite her age, given her constellation of symptoms, a diagnosis of typical KD was favored. She was started on high dose aspirin and IVIG, with improvement of rash and conjunctivitis. She was discharged on 325mg of aspirin daily with close follow-up. This case highlights the challenge of diagnosing KD in adults. Although this patient had classic symptoms, she was likely misdiagnosed because KD is rare in adults and without validated criteria. Our patient met the pediatric criteria, suggesting these should be considered when clinical suspicion for adult-onset KD is high. Adult-onset KD is most commonly misdiagnosed as toxic shock syndrome or drug-induced hypersensitivity syndrome and these are important to rule-out. Treatment with high-dose aspirin and IVIG is well established and should be initiated promptly.

Keywords: Kawasaki disease, adult-onset, polymorphous exanthem, medical dermatology

Introduction

Kawasaki disease (KD) was first described in 1967 by Tomikasu Kawasaki in Japan and termed mucocutaneous lymph node syndrome after he observed 50 Japanese children with a similar constellation of symptoms, most notably a desquamating rash [1]. In developed countries, KD has replaced rheumatic fever as the leading cause of acquired heart disease in children [2]. The disease is classified as a systemic vasculitis, most commonly affecting infants and children under 5 years of age [3]. In the United States, 10-to-15 out of 100,000 children are affected each year [2]. The incidence is 10-to-20 times higher in Japan and Korea than in western countries [3]. In KD, inflammatory cells cause degradation of structural proteins in the arterial wall as these cells infiltrate the medium sized arteries. Most significantly, this can lead to coronary artery involvement if KD remains untreated [3]. Approximately 15-to-25 percent of untreated patients will develop a coronary artery aneurysm (CAA), [2]. Development of a CAA predisposes patients to long-term coronary artery disease and the potential for ischemic heart disease and myocardial infarction [4].

The etiology of KD remains unknown although a variety of theories have been proposed. Many believe that there is a component of genetic susceptibility given the higher incidence in children of East Asian descent; additionally, there is a higher relative risk within families [3, 5]. Family linkage and genome-wide studies have implicated single nucleotide polymorphisms in 6 gene regions that are correlated with developing KD [6]. Exposure to environmental triggers is also thought to be contributory and is supported by seasonal and temporal clustering of cases and predominance of IgA plasma cells at mucosal surfaces and vascular walls during the acute phase of KD [5]. The IgA response may represent response to an antigen entering a mucosal site [4]. Additionally, during the acute phase of KD, inclusion bodies that appear to contain RNA can be found within the bronchial epithelium, consistent with a viral etiology for KD [7]. Review of adult onset KD has shown some potential association with HIV infection, which would suggest an immune-compromised state may additionally play a role in pathogenesis [8].

Whether presenting typically or atypically, a diagnosis of KD relies heavily on a clinical diagnosis as definitive laboratory testing does not exist. It is worth noting that some authors refer to typical and atypical KD as complete and incomplete KD [9]. Diagnosis of typical KD requires the presence of fever for greater than 5 days and the presence of four out of five major clinical features. These clinical features include: changes in extremities (culminating in desquamation of the fingertips 1-2 weeks after presentation), polymorphous exanthem, bilateral conjunctival injection, changes in the lips and oral cavity, and cervical lymphadenopathy [9]. Typical KD may also be diagnosed with three clinical features if coronary artery abnormalities are visible on echocardiography [2]. Patients with atypical or incomplete KD do not fulfill the four out of five classic clinical findings and paradoxically have a higher rate of CAA if not treated [2].

Although KD is well recognized in the pediatric population, adult-onset KD is exceedingly rare, with approximately 100 cases reported in the literature [10]. One of the earliest descriptions of KD in adults stems from Butler and Friedman's review of a group of adult patients fulfilling criteria for KD [11]. Prior to their assertion that KD can affect adults, many practitioners believed that reports of adult-onset KD simply represented early cases of toxic shock syndrome [11]. In adults, toxic shock syndrome (TSS) is the most likely clinical mimic as it also presents with cutaneous erythema, high fevers, and acral changes that can culminate in desquamation of the palms or soles.

Adults and children can present with very similar clinical symptoms, although adults more commonly present with arthralgias, adenopathy, and elevated liver enzymes, whereas children more frequently have cheilitis, aseptic meningitis, and thrombocytosis [8]. Perhaps the largest discrepancy between adults and children with KD is the rarity, leading to frequent misdiagnosis of KD in adults [10]. We present a case of an adult female with persistent fever and multiple visits to healthcare providers prior to a diagnosis of typical KD.

Case Synopsis

A previously healthy 20-year-old woman with a past medical history of herpes labialis originally presented to another hospital for fever, lymphadenopathy, malaise, exudative tonsillitis, and rash. She reported a diffuse morbilliform eruption on the arms, legs, palms, and soles with sparing of the trunk as well as right-sided neck swelling and tenderness. Computed tomography scan revealed cervical lymphadenopathy measuring 1.5cm without abscess and routine blood work was unremarkable. *Borrelia* serologies and PCR, RPR, influenza A and B antigen, monospot, and rapid streptococcal testing were negative. She received empiric treatment for suspected exudative pharyngitis with one gram of ceftriaxone and 600mg of clindamycin as well as a single dose of dexamethasone. She was discharged on clindamycin and doxycycline, which she took for two or three days. However, she experienced worsening skin eruption, increased malaise, formation of oral ulcers, and continued fevers; she subsequently self-discontinued the antibiotics. She reported taking ibuprofen and acetaminophen since the onset of

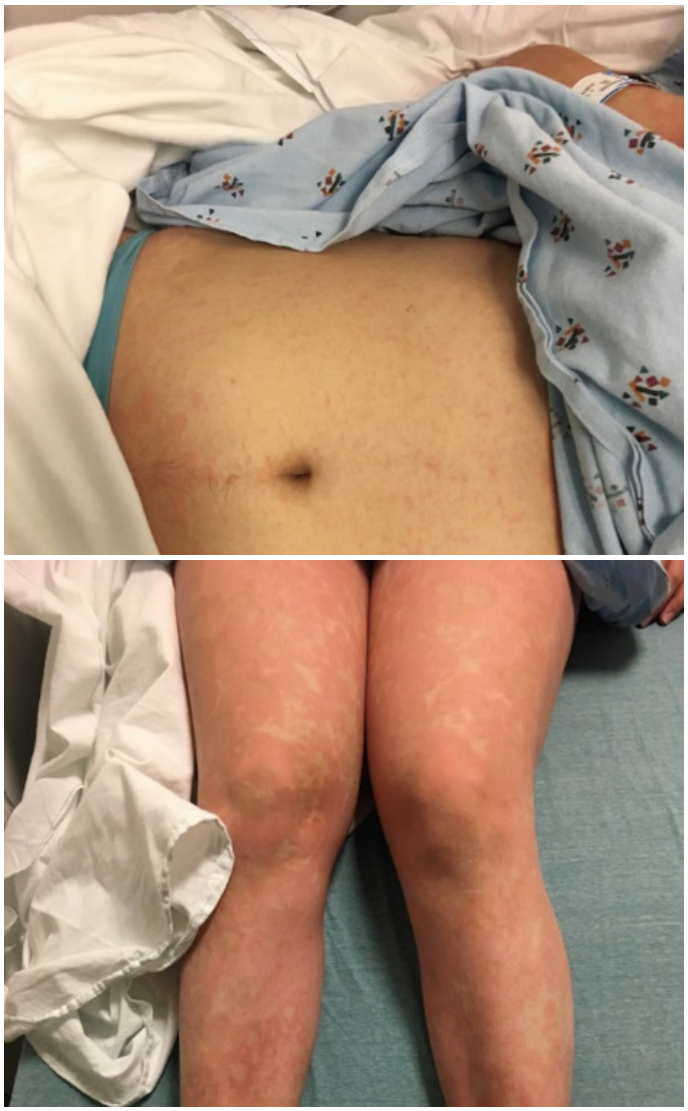

Figure 1. *Physical examination findings on the patient's trunk and bilateral legs, notable for petechial macules coalescing into reticulated patches.*

symptoms. She was not taking medications previously.

She later presented to the UCLA emergency room 10 days after the onset of symptoms and on the seventh day of fevers. She continued to experience daily fevers up to 40˚C and her painless non-pruritic rash had progressed. A dermatology consult was requested at this time for evaluation. On examination, she had multiple red, petechial macules coalescing into reticulated patches involving the trunk and bilateral upper and lower extremities (**Figure 1**). She had periungual peeling on the fingertips and scleral conjunctival injection. There was a 2mm shallow erosion on the left lateral tongue with generalized swelling of the tongue and a small patch of petechiae on the right buccal mucosa. Additional laboratory work showed an elevated erythrocyte sedimentation rate of 54, elevated C-reactive protein test of 7.2, decreased C4 of 11, and decreased total complement of 37. Infectious work-up, including blood cultures, HIV, rapid plasma reagin test, rickettsial antibodies, acute hepatitis panel, QuantiFERON-TB Gold, mycoplasma IgM, Epstein-Barr virus IgM, parvovirus IgM, and HSV 1&2 IgM, was negative. The patient did test positively for HSV 1 IgG, EBV IgG, and mycoplasma IgG.

A punch biopsy of the left thigh (**Figure 2**) showed a spongiotic dermatitis with superficial perivascular inflammation including lymphocytes, plasma cells, and rare eosinophils. Gram stain, periodic acid-Schiff stain, and Grocott methenamine silver stain were negative for infectious organisms. There was no evidence of vasculitis or malignancy.

At this time, the patient was started on prednisone empirically for possible autoimmune disorder. After a multidisciplinary discussion, the patient was diagnosed with KD given the persistence of fever for more than 5 days, cervical lymphadenopathy, conjunctival injection, polymorphous exanthem, desquamation of finger tips, and changes in her oral cavity. Additionally, KD was favored based on the negative infectious work-up. The patient was started on high dose aspirin at 650mg four times daily for one day and had one dose of IVIG prior to discharge with improvement of her eruption and conjunctivitis within one day. A transthoracic echocardiogram during the admission did not reveal any evidence of coronary artery aneurysm. Of note, controversy currently exists over which imaging modality has the highest sensitivity for diagnosing coronary artery involvement in adult-onset KD (i.e. cardiac MRI versus transthoracic echocardiogram). The patient was discharged on 325mg of aspirin daily with close cardiology follow up.

Case Discussion

Diagnosis of adult onset KD is a challenge, as illustrated by our patient who visited multiple centers prior to receiving a definitive diagnosis.

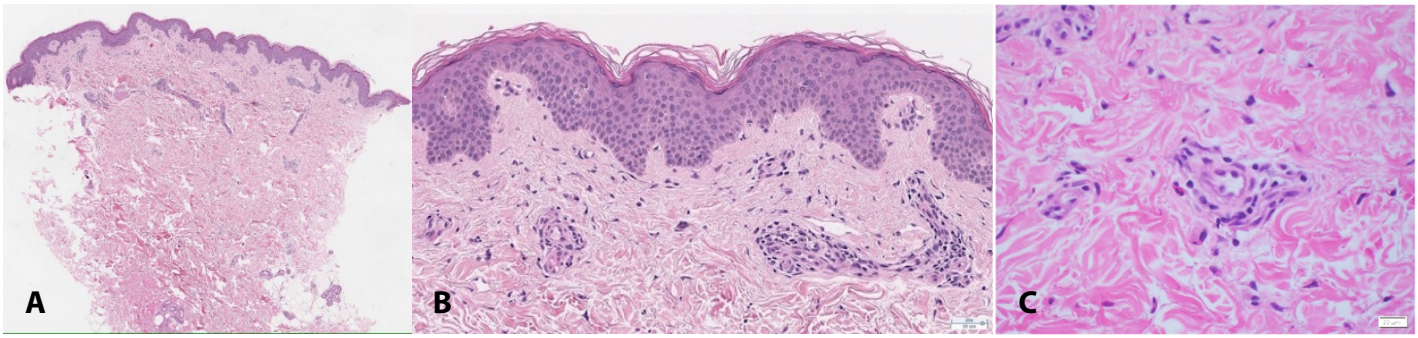

Figure 2. *Punch biopsy of the left inferior thigh showed superficial perivascular inflammation. H&E* ***A)*** *20×,* ***B)*** *Spongiosis and perivascular eosinophils and plasma cells, 200×.* ***C)*** *No evidence of vasculitis, 400×. There was no evidence of significant interface dermatitis. periodic acid-Schiff reaction, Grocott methenamine silver, and Gram stains appeared negative for infectious organisms.*

Although adult onset KD is rare, this case highlights that it should be considered in patients who present with prolonged fever with an unknown origin and negative infectious disease work-up. Even though the patient described in this case did present with the typical constellation of symptoms in KD, the prevalence of KD in the adult population is exceedingly rare and the diagnosis remains difficult as the criteria for diagnosis in the pediatric population is not validated for adults [8].

The differential diagnosis for KD in children mostly consists of infectious etiologies such as adenovirus, scarlet fever, rickettsial diseases, Epstein-Barr virus, and rheumatologic disorders (reactive arthritis, and juvenile rheumatoid arthritis), [8]. In contrast, in adults, the most crucial conditions to rule out are TSS and drug-induced hypersensitivity syndrome, [8]. In terms of making the diagnosis of KD in adults, it is important to exclude TSS and drug-induced hypersensitivity syndrome and to confirm the presence of typical symptoms of KD that one would expect in the pediatric population [8]. A review performed by Gomard-Mennesson et al. suggests screening adults with 7 days of fever with echocardiography and the following blood tests: albumin, liver function tests, and CBC [6, 12]. This approach may prove effective in capturing many atypical adult-onset KD, but will likely be cost prohibitive if not utilized sparingly unless clinical suspicion is high.

Regarding treatment for KD, the standard regimen consists of administration of IVIG and high-dose aspirin; our patient received this treatment with subsequent clinical improvement. The goal of treatment in the acute phase is to reduce inflammation and is achieved with high dose IVIG given concurrently with moderate-to-high dose aspirin [6]. High dose IVIG is well established for the prevention of CAA and should be administered as soon as a diagnosis is established [6, 13]. Low-to-moderate dose aspirin should be continued for four to six weeks after the acute phase of illness and may be continued chronically for patients who have ongoing coronary artery involvement [6].

Conclusion

This case adds to the literature regarding the rare presentation of adult-onset KD. Kawasaki disease should be considered in the differential diagnosis for all adults with persistent fevers and a negative infectious work-up as in our case. Although the diagnostic criteria is not validated in the adult population, our patient notably presented with all the classic findings of KD, demonstrating that pediatric criteria may be applicable to the adult population.

Potential conflicts of interest

The authors declare no conflicts of interests.

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