Acute Kawasaki Disease: Not Just for Kids

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Kawasaki Disease is a small-to-medium-vessel vasculitis that preferentially affects children. Kawasaki Disease can occur in adults, but the presentation may differ from that observed in children. Typical findings in both adults and children include fever, conjunctivitis, pharyngitis, and skin erythema progressing to a desquamating rash on the palms and soles. Adults more frequently present with cervical adenopathy (93% of adults vs. 15% of children), hepatitis (65% vs. 10%), and arthralgia (61% vs. 24–38%). In contrast, adults are less frequently affected by meningitis (10% vs. 34%), thrombocytosis (55% vs. 100%), and coronary artery aneurysms (5% vs. 18–25%). We report a case of acute Kawasaki Disease in a 24-year-old man who presented with rash, fever, and arthritis. He was successfully treated with high-dose aspirin and intravenous immunoglobulin (IVIG). Our case highlights the importance of considering Kawasaki Disease in adults presenting with symptoms commonly encountered in a general medical practice.

KEY WORDS: Kawasaki Disease; adult; coronary artery aneurysms; vasculitis; adenopathy; arthritis; mucocutaneous lymph node syndrome.
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INTRODUCTION

Kawasaki Disease is a small-to-medium-vessel vasculitis that preferentially affects infants and young children. The first cases were identified among Japanese children in the 1960s.[1] Acute Kawasaki Disease is rare in adults, and therefore the diagnosis can easily be missed in a patient presenting to a primary care clinic. We describe an adult with Kawasaki Disease and review the literature regarding this rare adult illness.

CASE DESCRIPTION

A 24-year-old White man presented to our hospital with a 3-week illness that began in early February with fever, headache, nausea, sore throat, and cough, followed 5 days later by arthralgia. Two weeks later the patient noted an erythematous, diffuse skin rash beginning on his torso and spreading to his extremities. At a local hospital, he was diagnosed with scarlet fever and placed on penicillin, although a throat culture was negative for Streptococcal species. His skin desquamated from his fingernails, progressing centrally. He was placed on cephalexin and referred to our institution.

The patient was previously healthy and reported no drug allergies. He worked as a dairy farmer in Wisconsin. He recently married and traveled to Las Vegas on his honeymoon. He denied intravenous drug use, new sexual partners, or tattoos. Animal exposure included contact with domestic cats, cattle, and deer. The patient did not use tobacco products but consumed alcohol socially. His father was recently ill with an upper respiratory infection; no other ill contacts were identified. The family history was otherwise noncontributory and the patient identified no Asian antecedents or family members with rheumatic disease. Review of systems was positive for a self-reported 20-pound weight loss over the course of the illness, although the patient's clothes fit normally. He denied cardiac, pulmonary, or gastrointestinal symptoms.

On physical examination, the patient's temperature was 38.3°C, his pulse was 96 beats per minute and regular, and his blood pressure was 119/65 mmHg. We observed a desquamating rash involving his fingers, palms, and soles. Radial pulses were easily palpable and symmetric. Head and neck examination revealed injected conjunctivae with sparing of the limbi, dry mucus membranes with an erythematous pharynx, fissured tongue, and 2 labial ulcers. An 8-cm firm, nontender, matted mass was visible over the right anterior neck with scattered adjacent palpable anterior cervical lymph nodes. A I/VI systolic heart murmur was audible at the right upper sternal border. Musculoskeletal examination revealed a small right knee effusion without warmth or erythema and pain with active motion of the wrists, hips, knees, and ankles. Examination of the lungs, abdomen, and neurologic systems were normal.

Initial laboratory tests were notable for an anemia (hematocrit, 29 mL/dL), a mildly elevated platelet count (363,000 L/uL), and an elevated erythrocyte sedimentation rate and C-reactive protein (89 mm/hr and 30 mg/dL, respectively). Hepatitis was evident with an elevated AST (276U/L), ALT (375U/L), alkaline phosphatase (149U/L), and GGT (112U/L). The ASO titer was normal and the sodium was low at 131 mmol/L. A positive antinuclear antibody (ANA) was noted (1:160 titer, nucleolar pattern).

Diagnostic considerations at the time of admission were diverse. Infectious illnesses were suggested based on recent fever, headache, sore throat, cough, heart murmur, and monoarthritis. We suspected streptococcal or staphylococcal bacteremia leading to bacterial endocarditis and/or septic arthritis. Vector-born illnesses were also entertained including Brucellosis and Lyme disease. Marked cervical adenopathy raised concern for cervical abscess, acute HIV, or Epstein-Barr virus infection.

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Autoimmune diseases were also entertained. In particular, arthritis, throat pain, elevated platelets and liver enzymes suggested Adult Still's disease, although the normal white count and desquamating rash were atypical. Systemic vasculitis might explain the patient's constitutional symptoms, ocular, joint, and liver inflammation, although he did not have nephritis or palpable purpura. Systemic lupus erythematosus was entertained on the basis of arthritis, anemia, and positive ANA, although male gender made this diagnosis less likely. Finally, Kawasaki Disease was a possibility, although the rarity of this disease in adults demanded exclusion of other conditions.

We considered other diseases as well. Malignancy was considered because of significant weight loss, anemia, and striking cervical adenopathy, although physical examination revealed a well-nourished male without muscle wasting, suggesting that self-reported weight loss was inaccurate. A hypersensitivity drug reaction could cause arthritis and rash, but would not explain presenting symptoms or be expected to cause hepatitis.

Subsequent diagnostic tests were directed at excluding infections and confirming a working diagnosis of Kawasaki Disease. Synovial fluid from the right knee contained 6,600 nucleated cells with a predominance of polymorphonucleocytes (78%); bacterial cultures were negative. Six blood cultures were also negative. A chest x-ray and electrocardiogram were normal as was a transthoracic echocardiogram. A computerized tomographic scan of the neck showed right cervical lymphadenopathy and multiple hypoattenuating lymph nodes. A brucellosis titer was negative. A Lyme test was not requested because of the winter-time presentation.

Kawasaki Disease was diagnosed based on the absence of infection, failure to improve with antibiotic therapy, and the presence of all diagnostic criteria for childhood Kawasaki Disease (Table 1). More specifically, the patient had fever, desquamating rash of the palms and soles, bilateral nonsuppurative conjunctivitis, significant cervical lymphadenopathy, oral changes including pharyngitis, a fissured tongue and labial ulcers, and extremity edema (Table 1). Additionally, hepatitis and joint complaints were explained by this diagnosis, as these features are common in adults with Kawasaki Disease (Table 2).

Chest computerized tomography with coronary artery protocol subsequently revealed no aneurysms or stenotic lesions. The patient was subsequently treated with 1,000 mg of aspirin daily and IVIG at 400 mg/kg/day for 4 days, with clinical improvement illustrated by rapid resolution of arthritis, oral findings, conjunctivitis, and rash. IVIG was administered over 4 days to minimize exacerbation of preexisting hyponatremia and to lessen the risk of osmotic nephropathy and hyperviscosity. He was discharged on 325 mg (4.6 mg/kg) of aspirin daily. Repeat chest computerized tomographic imaging with coronary artery protocol completed 2 months later confirmed the absence of coronary artery aneurysms.

Table 1. Diagnostic Criteria for Kawasaki Disease[1]

Fever >5 Days or Coronary Artery Aneurysms and at Least 4 Additional Criteria:
1. Polymorphous rash
2. Conjunctivitis
3. Cervical lymphadenopathy with lymph nodes >1.5 cm in size
4. Oral changes including injected pharynx or lips, cracked or fissured lips, strawberry tongue
5. Extremity changes starting with edema or erythema then progressing to desquamation of the feet or hands starting periungually

Table 2. A Comparison of Clinical Findings in Adults and Children with Kawasaki Disease[2]

Clinical Finding	Adults (%)	Children (%)
Desquamation	96	94
Conjunctivitis	93	95
Cervical Adenopathy	93	15
Injected pharynx	80	90
Strawberry tongue	80	77
Erythema of the palms and soles	80	88
Liver function test abnormalities	65	10
Arthralgia	61	24–38
Thrombocytosis	55	100
Meningitis	10	34
Coronary aneurysms	5	20

DISCUSSION

Kawasaki Disease is a childhood vasculitis involving small and medium-sized arteries.[1,2] Over 90% of cases occur in young children and infants. Japan reports an annual incidence of 112 cases per 100,000 children under age 5 years; new cases preferentially affect male infants.[3] In contrast, American cases appear more commonly in toddlers and number about 10 per 100,000 children.[4] Less than 60 patients with acute adult Kawasaki Disease have been reported, most of whom present between the ages of 18 and 30 years and represent patients from North America (n=23), South America (n=2), Asia (n=5), Africa (n=2), and Europe (n=25).[2] To date, there are no reported deaths from acute adult Kawasaki Disease.

The pathogenesis of Kawasaki Disease is unknown, although seasonal outbreaks suggest a possible infectious source, with cases presenting more commonly in winter and summer.[5] Leung and colleagues suggested a bacterial superantigen as the trigger for Kawasaki Disease.[12] Such a reaction might occur in subsets of patients with susceptibility to a specific microbial infection. An outbreak of Kawasaki Disease occurred after exposure to carpet cleaner, supporting arguments for an environmental trigger.[13]

The diagnostic criteria for Kawasaki Disease were developed for children and have not been validated in adults. Kawasaki Disease is marked by 5 or more days of fever or coronary artery aneurysms, plus at least 4 other diagnostic criteria (Table 1). In a recent analysis of 57 adult cases, Seve summarized the difference in presentation between children and adults with Kawasaki Disease (Table 2)[2]. Adults more frequently present with cervical adenopathy (93% of adults vs. 15% of children), hepatitis (65% vs. 10%), and arthralgia (61% vs. 24–38%). In contrast, adults are less frequently affected by meningitis (10% vs. 34%), thrombocytosis (55% vs. 100%), and coronary artery aneurysms (5% vs. 18–25%).

Kawasaki Disease can be divided into 3 phases: acute, subacute, and chronic. The acute phase lasts approximately 3 weeks and is marked by fever, carditis, mucocutaneous changes, and a polymorphous rash.[6] Coronary artery aneurysms typically develop in the acute phase.[2] Symmetric, polyarticular arthralgias may occur and favor larger joints.[2]

During the subacute phase lasting 2 or 3 weeks, periungual and perineal desquamation, arthralgia and myocardial disease may develop.[6] In the convalescent or chronic phase lasting weeks to months, the sedimentation rate normalizes, but cardiac disease may persist.[6]

In adult patients with acute Kawasaki Disease, diagnostic considerations include viral and vector-born infections, scarlet fever with lymphadenitis, toxic shock syndrome, adult onset Still's disease, systemic lupus erythematosus, vasculitis, and hypersensitivity drug reaction. Laryngitis, cough, and rhinorrhea suggest a viral infection and are uncommon in Kawasaki Disease. By contrast, patients with Kawasaki Disease often develop skin changes atypical for viral infections, including a desquamating rash of the palms and soles, painful erythema, and peripheral edema.[7] Desquamation may occur in toxic shock syndrome and scarlet fever, but is more extensive. The lips are red and cracked in both Kawasaki Disease and toxic shock syndrome. Conjunctivitis is nonspecific and may occur during viral or bacterial infections, but anterior uveitis, if present, would support Kawasaki Disease.

Laboratory abnormalities commonly found in Kawasaki Disease include an elevated erythrocyte sedimentation rate and/or C-reactive protein, elevated alanine aminotransferase, thrombocytosis (platelets>450,000 K/μL), leukocytosis (white cells>15,000 K/uL), anemia, sterile pyuria, and a positive antineutrophilic cytoplasmic antibody. Mild hyponatremia, as seen in this case, may also occur.[2]

A positive ANA is uncommon in Kawasaki Disease. Among 84 Italian children with Kawasaki Disease, none had a positive ANA.[8] In another series, less than one third of fourteen children with Kawasaki Disease had a positive ANA.[9] A single adult woman with Kawasaki Disease had an ANA of 1:160 (pattern not reported).[10] In summary, the positive ANA in our patient is unusual; there was no evidence of an underlying connective tissue disease in the patient or his relatives. If an infectious trigger precipitated the illness, this might explain the positive ANA, as viral infections are known to induce autoantibodies.[11]

COMPLICATIONS

In the acute stage of the illness lasting approximately 10 days, perivascular inflammation leads to panvasculitis. The vascular inflammation may progress to complete vascular obstruction, thrombosis, aneurysm, or fibrosis. It is believed that when IVIG is initiated within 10 days of illness, extension of the perivasculitis to panvasculitis is interrupted.[14]

Coronary artery aneurysms form in 18–25% of pediatric cases, but only 5% of adult cases.[2,15] Aneurysms most commonly form at the arterial bifurcations of proximal segments, and are associated with premature atherosclerosis and subsequent myocardial infarction.[15] Interestingly, 50–75% of aneurysms resolve without intervention, although microscopic fibrosis may alter vessel mechanics over the long term.[14]

Electrocardiograms, stress tests, and echocardiograms are used to screen and follow patients with coronary artery involvement. Cardiac catheterization is recommended if the patient develops ischemic symptoms or if stress testing reveals reversible ischemia.[1] Further study is needed to establish evidence supporting a preferred screening modality for adults.

TREATMENT

Information regarding the utility of IVIG and aspirin therapy is based on research performed in children, as cases of acute adult Kawasaki Disease are extremely rare. In children, IVIG reduces the incidence of coronary artery aneurysms if given within the first 10 days of disease onset.[16] IVIG may help shorten disease duration even if started after the acute phase. The standard of care for children with acute Kawasaki Disease is a single 2-gm/kg infusion of IVIG along with 80–100 mg/kg/day of aspirin in 4 divided doses.[1,16,17] Once the fever resolves, the aspirin may be decreased to 3–5 mg/kg/day.[1,17] In patients with coronary artery aneurysms, aspirin should be continued until 2 years after the aneurysms resolve. If aneurysms do not resolve, then aspirin therapy is recommended indefinitely to prevent coronary artery thrombosis.[1] Unlike IVIG, aspirin does not decrease the formation rate of coronary aneurysms.[17]

Initial trials of IVIG therapy used a low dose administered over 4 days. In a pivotal trial, aspirin monotherapy was compared to 400 mg/kg/day of IVIG plus aspirin in 85 children with Kawasaki Disease.[18] Children receiving IVIG enjoyed a significant reduction in the incidence of coronary artery aneurysms (15% vs. 42%, $p<.01$). Similarly, another trial randomized 75 children to aspirin and IVIG (400 mg/kg/day for 4 days) and 78 children to aspirin monotherapy.[16] Two weeks into the trial, 23% of the aspirin monotherapy group and 8% of the IVIG group had coronary artery aneurysms. At 7 weeks, 18% of the aspirin monotherapy group and 4% of the IVIG group had coronary artery aneurysms, suggesting a significant decrease in incidence of coronary artery aneurysms with IVIG therapy.[16]

A more recent trial suggested that a single infusion of IVIG (2 g/kg) may accelerate resolution of inflammation compared to the 4-day regimen.[18] Patients receiving 400 mg/kg/day for 4 days were almost twice as likely to have coronary artery aneurysms than those receiving a single 2-gm/kg dose (14 of 252 patients vs. 6 of 254 patients, $p=.067$).[18] As a result, the higher single dose has become the current standard of care for children with acute Kawasaki Disease.[1,19,20] Although case reports describe benefit when adults with Kawasaki Disease receive IVIG, there are no controlled studies regarding the optimal dose, timing, or clinical benefit of IVIG therapy in adults.[2,14,15,21,22] Potential risks of IVIG therapy include infusion reactions, volume overload, and osmotic nephropathy.

Surprisingly, corticosteroid therapy is not recommended for initial management of Kawasaki Disease, although a recent metaanalysis reports a reduction in the rate of coronary artery aneurysms with its use.[24,25] In 92 patients with Kawasaki Disease, aneurysms developed in 64.7% of the patients treated with steroids, 20% of those treated with antibiotics, and 11% of those treated with aspirin[23], raising concern that corticosteroids enhance the formation of coronary artery aneurysms. In a prospective randomized trial comparing aspirin and IVIG with or without corticosteroid therapy, patients receiving steroids enjoyed more rapid resolution of fever and shorter hospitalization, but no significant decrease in the rate of coronary aneurysms.[24] A recent metaanalysis of 862 children reported fewer coronary artery aneurysms in patients treated with corticosteroids [OR 0.546, 95% CI: 0.371–0.803].[25]

SUMMARY

In summary, we present an adult male with acute Kawasaki Disease who improved after aspirin and IVIG therapy. Clinicians should consider Kawasaki Disease in a patient presenting with unusual features such as oral, ocular, cutaneous, or joint inflammation. Delays in diagnosis may increase the risk for complications, but fortunately coronary artery aneurysms are uncommon in adults with Kawasaki Disease.

Because acute Kawasaki Disease is rare in adults, it is important to publish data on patient presentations and outcome, which may permit development of diagnostic criteria and treatment guidelines for adults with Kawasaki Disease. Additional data on adult patients is needed to establish an evidence-based standard of care for adults, although such a trial must involve multiple centers to recruit sufficient patients. We suggest a worldwide registry for adults with Kawasaki Disease, to address questions on how to test and treat adults with the condition.

Potential Financial Conflicts of Interest: *None disclosed.*

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