Periorbital Vasculitis Complicating Kawasaki Syndrome in an Infant

ABSTRACT. Periorbital vasculitis is a previously unreported complication of Kawasaki syndrome (KS). We describe an infant with severe KS refractory to initial management with salicylate and intravenous immunoglobulin (IVIG). Retreatment with IVIG and high-dose pulsed steroids was required for persistent fever and inflammatory manifestations. Despite aggressive medical therapy, a large left coronary artery aneurysm developed. After apparent complete KS remission, acute periorbital vasculitis developed in the left upper eyelid and orbit, requiring operative intervention for diagnosis and high-dose pulsed steroids for therapy. The significance of this previously unreported ophthalmic complication of KS is reviewed, along with a discussion of the role of steroids in KS manifestations refractory to IVIG.

Kawasaki syndrome (KS) is a systemic vasculitis of uncertain etiology. Manifestations in infants, particularly males, can be atypical and unusually severe. We report an infant with KS and a large coronary aneurysm who responded to aggressive initial management including intravenous immunoglobulin (IVIG) and corticosteroids but who subsequently developed periorbital vasculitis, a complication previously unreported in KS.

CASE PRESENTATION

In September 1996, a previously healthy breastfed 8-month-old white boy was diagnosed with KS, based on the presence of five of six published criteria: 1) fever for 7 days to 40.4°C, refractory to antibiotics; 2) conjunctival injection, transient and bilateral; 3) edema of all four extremities; 4) adenopathy, with a single posterior cervical node 2 cm in diameter; and 5) truncal rash, erythematous, macular, and pleomorphic. Manifestations were severe and also included anorexia and irritability despite oral acetaminophen, hydrocortisone formation, ascites, bilateral pleural effusions, and extreme hypoproteinemia. The sixth criterion for KS diagnosis, enanthem, was not observed. All bacterial and viral blood, urine, and cerebrospinal fluid culture results were negative, as were serologies for several infectious agents. Echocardiography revealed no aneurysm. Initial laboratory data are summarized in the Table 1.

Treatment was initiated on day 7 of illness with rectal salicylate (100 mg/kg/day) and IVIG (2 g/kg) (Polygam, American Red Cross), resulting in partial improvement in KS manifestations (fever, malaise, rash, edema) and reduction in effusions on chest film. Recurrent fever (40°C) with irritability prompted retreatment on day 11 with IVIG 1 g/kg, resulting in a reduction in fever and malaise but in the development of anaphylaxis (stridor, wheeze, lip swelling) at the terminus of infusion, requiring subcutaneous epinephrine. Echocardiography on day 14 revealed 4.3 mm of ectasia in the proximal trunk of the left anterior descending (LAD) coronary artery. Rectal salicylate was discontinued after 5 days, when resumption of adequate oral intake allowed high dose oral salicylate (100 mg/kg/day) from day 12 to day 17.

Recurrent fever to 39°C on day 15, with persistent anemia (hemoglobin 5.9 g/dL) and evidence of ongoing inflammation (erythrocyte sedimentation rate [ESR] > 150 mm/hour; C-reactive protein [CRP] = 14 mg/dL), led to high-dose pulsed steroid therapy for KS refractory to IVIG. The infant received 30 mg/kg of methylprednisolone as a single dose over a 4-hour period on day 17, with no complications. Resolution of fever and systemic symptoms was prompt and lasting.

Echocardiography on day 18 demonstrated a single 6.3-mm aneurysm in the proximal LAD, larger and more fusiform than on study 4 days previously. No myocarditis or effusion was seen. The electrocardiogram was normal. The platelet count peaked at 750 000/mm. Despite enlargement of the coronary aneurysm, the child was playful, ate well, and had a normal physical examination. Desquamation of hands and feet was never documented. No hypertension, hematuria, or hepatitis developed. He was discharged on low-dose salicylate (4 mg/kg/day) as recommended for the subacute phase of KS.

The child remained in clinical remission, gained weight, and began to walk at age 9 months. Hemoglobin increased to 10 g/dL. Total protein, albumin, ESR, and CRP normalized within 2 weeks after steroid therapy. Follow-up echocardiography over a 3-week period demonstrated progressive reduction in aneurysm size from 6.3 to 5.8 mm. He remained on salicylate (4 mg/kg/day).

On day 35 after onset of illness, and 18 days after pulsed IV steroids and apparent KS remission, the infant developed sudden progressive erythema and distension of the left upper eyelid (Fig 1). No trauma, fever, exanthem, pain, or irritability was noted, and the child remained playful. General physical examination was otherwise normal. Ophthalmic examina-
tion revealed marked edema of the left upper eyelid, with 2 mm of downward displacement of the globe. Injection of the left bulbar conjunctiva was more prominent laterally than medially. Ocular motility was impaired, with a severe deficit of upward gaze in the left eye only. The pupils were equal in size and normally reactive. No afferent pupillary defect was detected. Visual fixation appeared to be intact bilaterally. Dilated ophthalmoscopic examination showed a normal optic nerve, retina, and retinal vessels. Computed tomography revealed an inflammatory reaction or neoplastic infiltration involving the soft tissues of the left upper eyelid, anterior temporal fossa, and superior orbit; the sinuses were normal. White blood cell count was 11 900/mm³ with 19 bands, 24 PMNs, and 39 lymphocytes; hemoglobin was 8.3 g/dL. ESR and CRP were again elevated at 114 mm/hour and 6.2 mg/dL, respectively. Echocardiography revealed no new or enlarging coronary aneurysms. Diagnostic considerations included orbital/periorbital cellulitis, rhabdomyosarcoma, lymphoma or leukemic infiltrate, and atypical vasculitis.

Because of the atypical, progressive nature of the eyelid distension and ophthalmoplegia, and the lack of significant improvement after 24 hours of intravenous cefotaxime, surgical exploration and diagnostic biopsy were performed. Incision in the upper eyelid crease laterally exposed orbicularis muscle, which appeared edematous and pale on gross inspection. The orbital fat appeared slightly edematous but otherwise normal, as did the lacrimal gland. The superior rectus muscle was inspected via a conjunctival peritomy and appeared somewhat pale with attenuation of the anterior ciliary vessels. Biopsy specimens (Fig 2) of the orbicularis muscle showed areas of panarteritis with leukocytoclasis and a single focus of myositis. Orbital fat showed no significant pathology, and the temporalis muscle showed only mild edema and fibrosis. Special stain studies for bacteria, mycobacteria, and fungi were negative, as were culture results of biopsy specimens. Granulomatosis was not noted. The histopathologic findings were consistent with small- and large-vessel vasculitis accompanying KS.

After discussion with local consultants in ophthalmology, rheumatology, and infectious disease, and with two nationally recognized KS investigators, the child was treated with pulsed intravenous methylprednisolone (30 mg/kg) for 3 days, with dramatic improvement. The left upper eyelid edema decreased rapidly, and ocular motility steadily improved. Ultrasonography and computed tomography imaging of the chest and abdomen revealed no evidence of vasculitic involvement of the aortic arch, subclavian, pulmonary, renal, or mesenteric arteries. Antinuclear antibodies, antineutrophil cytoplasmic antibodies, and complement were normal. The patient was discharged after 1 week on a slowly tapering regimen of oral steroids and long-term aspirin (4 mg/kg/day). ESR and CRP normalized within 1 week. On serial follow-up evaluations over a 12-month period, visual acuity was normal bilaterally, and ocular motility was full without any evidence of strabismus. The eyelid incision was well healed and levator muscle function was normal, without ptosis. At age 20 months, and off steroid therapy for 4 months, the child was meeting all growth and development milestones and had a normal physical examination. Serial echocardiography over 12 months documented progressive normalization of the proximal LAD lesion and no new aneurysm formation.

**TABLE 1. Initial Laboratory Values and Ancillary Studies**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC/mm³</td>
<td>7600</td>
</tr>
<tr>
<td>Differential (bands; PMNs; lymphs) (%)</td>
<td>34; 23; 43</td>
</tr>
<tr>
<td>Peripheral smear</td>
<td>Toxic granulations; Dohle bodies</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.0</td>
</tr>
<tr>
<td>Platelet count/mm³</td>
<td>345 000</td>
</tr>
<tr>
<td>ESR (mm/hour)</td>
<td>70</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>12 (normal, &lt;1)</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>4.9</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.1</td>
</tr>
<tr>
<td>Antineutrophil cytoplasmic antibody</td>
<td>1+ (by IFA)</td>
</tr>
<tr>
<td>CSF protein (mg/dL)</td>
<td>36</td>
</tr>
<tr>
<td>CSF cell count/differential</td>
<td>6/100% lymphs</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>Normal</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**Fig 1.** Distended, erythematous left upper eyelid when the patient was age 9 months.

**Fig 2.** Biopsy of left orbicularis; acute panarteritis (400× magnification).
DISCUSSION

Review of the literature revealed reports of orbital vasculitis complicating Wegener’s granulomatosis and Churg-Strauss vasculitis, but not KS. Our case did not meet diagnostic or pathologic criteria for either of the first two syndromes, which are exceedingly rare in infancy. Our patient did, however, fulfill diagnostic criteria for KS during the initial febrile phase of illness and had histologic evidence compatible with KS on subsequent orbital biopsy. Nonophthalmic focal vasculitis associated with KS has been reported involving subclavian, renal, iliac, mesenteric, and digital arteries. In contrast, the most common ophthalmologic manifestations of KS are bilateral conjunctival injection and nongranulomatous iridocyclitis. Uveitis and papilledema with transient vitreous opacities also have been reported. Even less common manifestations are dacryocystitis, conjunctival scarring, and retinal artery occlusion secondary to ophthalmic artery vasculitis. To our knowledge, extraocular muscle palsy and peri-orbital vasculitis, as observed in our patient, have not been reported in KS. Not uncommonly, KS patients achieve temporary remission of all inflammatory manifestations, only to experience rebound symptomatology such as fever and rash several weeks after resolution of initial illness. Such patients are known to be at increased risk for coronary artery disease. Our patient is distinctive in that clinical rebound occurred but in an unusual site (the eyelid and orbit), without fever or new aneurysm formation. Our case, then, adds to the spectrum of atypical manifestations of this multisystem vasculitic syndrome.

Although the aggressive use of steroids in KS remains controversial, especially in patients with coronary artery aneurysms, our patient demonstrated dramatic improvement with high-dose pulsed methylprednisolone during two serious clinical episodes, one life-threatening and one vision-threatening. No adverse effects were observed in our case. In retrospect, the stormy course of the initial febrile phase of illness, coupled with refractory KS manifestations and coronary aneurysm development despite timely and repeated IVIG infusions, may have foreshadowed a subsequent relapse of some sort, although the eye was certainly an unanticipated site. Until the precise role of steroids in KS is clarified in controlled studies, we suggest that high-dose methylprednisolone may have a valuable role in managing selected vasculitic complications of KS in infants.

ACKNOWLEDGMENTS

We are grateful to Dr. Rita S. Jerath, Pediatric Rheumatology; Dr. Kenneth A. Murdison, Pediatric Cardiology; and Dr. Christopher B. White, Pediatric Infectious Disease, for helpful insights into the manuscript.

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Pediatrics 1998;101;e9
DOI: 10.1542/peds.101.6.e9

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