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CHAPTER 11

Kawasaki Disease

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1. Introduction

Kawasaki disease (KD) is an acute febrile systemic vasculitis usually occurring in children younger than 5 years, and rarely reported in neonates and adults (Kawasaki, 1967). The etiology still remains unknown, although epidemiological and clinical features strongly suggest an infectious cause. Immunological abnormalities in the acute phase of the disease reflect activation of immune system and marked production of cytokines by activated cells (Burns et al., 2004; Sundel et al., 2005).

The disease is self-limited but when coronary arteries are involved, sudden death in the acute phase and myocardial ischemia are life-threatening complications. Timely administration of intravenous immunoglobulins (IVIG) and aspirin (ASA) has significantly reduced the risk of cardiac damage up to 5% conversely to 20–35% of untreated patients, and the mortality rate is reduced to approximately 0.1% in the United States and Japan. Since coronary damage also develops in about 5% of the children who have received timely IVIG treatment, KD is reported as the leading cause of acquired heart disease in children in North America, Europe, and in Japan (Newburger et al., 2004). There is evidence that KD is a potential risk factor for adult ischemic heart disease and sudden death in early adulthood (Kato et al., 1992; Nakamura et al., 1998; Silva et al., 2001). Given that KD is a systemic vasculitis, all blood vessels may eventually be involved, and aneurysms and thrombotic occlusion may develop in axillary, brachial, celiac, mesenteric, iliac, femoral, and renal arteries (Tomita et al., 1992; Foster et al., 2000; Cura et al., 2004). Lacking specific laboratory tests the diagnosis is based only upon clinical criteria. In the acute phase, high-dose IVIG (2 g/kg) and ASA (50–80 mg/kg) have been proven to prevent coronary artery aneurysms (CAA) when given within 10 days from the onset of fever. However, 10–20% of KD patients do not respond to IVIG and require additional treatment. In refractory cases, following 1–3 IVIG infusions, corticosteroids either pulsed or orally may be given (Newburger et al., 2004; Burns et al., 2004). Recently, patients with persistent fever and severe CAA had successfully responded to anti-Tumor necrosis factor (anti-TNF-α) therapy (Weiss et al., 2004). The current main concerns are represented by infants younger than 6 months often displaying an atypical or incomplete disease and misdiagnosed with other infantile febrile illnesses with rash (Chang et al., 2006a, b).

2. Epidemiology

KD mainly affects children aged 1–5 years (85%) with an average age of approximately 2 years. It is more common in boys than in girls with a

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male/female ratio of 1.3–1.8:1. The peak incidence age is lower in Japanese (9–11 months) than in North American children (2 years) with a few cases at the extreme ages of childhood, and in adulthood. Infants younger than 6 months are rarely encountered but they possibly are at high risk of CAA (Chang et al., 2006a, b). Although KD has been reported all over the world, it is most highly expressed among Asian populations. In Japan, the annual incidence is reported as 90–130 cases per 100,000 children per year, significantly greater than in Europe (3.6–6.9 cases per 100,000), and in the United States (6–9 per 100,000 children under age 5) (Taubert, 1997; Harnden et al., 2002; Gardner-Medwin et al., 2002; Nakamura et al., 2004). In Hawaii, where most people are of Asian ancestry, the incidence, though higher than in US, is lower than in Japan supporting the assumption that both genetic predisposition and environmental factors are critical in KD.

The recurrence rate in Japanese children is reported as 1–2% while in Caucasians it is less than 1%. The second episode of KD carries a higher risk of coronary damage, thus requiring appropriate treatment as at the first attack (Nakamura et al., 1998). Siblings of patients with KD have a significantly greater chance of acquiring the disease than do children in the general population (Fujita et al., 1989). Furthermore, patients with parental KD are prone to develop a more aggressive disease with higher incidence of CAA (Uehara et al., 2005). Therefore, a family history of KD may be a risk for increased severity and recurrence of the disease. The seasonal incidence varies in the different countries with most cases in winter and spring months, even though KD may spread at any time over the year.

3. Etiology

The etiology of KD remains uncertain despite roughly four decades have passed since its first report (Kawasaki, 1967), and more than 200,000 patients have been recorded in Japan. Although an infectious origin is deeply suspected and previous studies have proposed several viral or bacterial candidates, no one has been settled as the proper cause of the disease (Rowley, 2004). Besides, no correlation has been found among the presence or absence of any specific agent at disease onset and either the response to treatment or the outcome of coronary disease. (Benseler et al., 2005). The peak incidence in early childhood and the virtual absence in adulthood suggest that a microbe causing an asymptomatic infection in most individuals could be a possible trigger, with acquired immunity by adulthood. The rarity of illness in infants in the first months of life supports passive protection by maternal antibodies. The clinical pattern of KD (fever, exanthema, conjunctivitis, lymph node enlargement, and mucositis) closely resembles a bacterial or viral infection of childhood such as scarlet fever. Among other common infantile febrile diseases, adenoviral infection is characterized by prolonged fever, conjunctivitis, lymphoadenopathy, and mucous membrane changes, high erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) and may closely mimic KD, especially in infants (Rocholl et al., 2004; Shike et al., 2005). Recently, an association between KD and a novel coronavirus has been reported (Esper et al., 2005), even though the results have not been confirmed by a further study (Chang et al., 2006a, b). Mycoplasma infection (fever, rash, conjunctivitis, and lymphoadenopathy) has also been proposed as one of the potential triggers of KD (Wang et al., 2001; Leen and Ling, 1996; Merlin et al., 2004).

KD has some similarities to toxin-mediated diseases, both from a clinical and an immunological point of view. The role of one or more superantigens competent of stimulating large numbers of T cells produced by certain strains of *Staphylococcus* or *Streptococcus* has been discussed in the etiology of KD, but no general agreement has been achieved (Leung et al., 2002). After the first reports (Abe et al., 1992, 1993; Pietra et al., 1994) describing selective expansion of Vβ2+ and Vβ8.1+ T cells in patients with acute KD, but not in the convalescent phase, a plethora of other similar studies have been published, both with positive and with negative evidence for a

superantigen-mediated process (Choi et al., 1997; Leung et al., 2002).

4. Pathogenesis

A complex immune response followed by a significant overproduction of different cytokines and activation of endothelial cells has a pivotal role in the pathogenesis of KD. Pro-inflammatory cytokines have been shown to be critical in the disease pathogenesis (Matsuhara et al., 1990), and a recent study has provided preliminary evidence for an increased frequency of alleles associated with elevated TNF-α levels (Quasney et al., 2001).

Despite a polyclonal B-cell activation, autoantibodies in KD have not been found consistently. An exception is represented by anti-endothelial cell antibodies (AECA) that have also been implicated in the disease pathogenesis, as reported in a study showing endothelial dysfunction in mice immunized with AECA from a KD patient (Grunebaum et al., 2002). Other markers of immune and endothelial activation that have been described in KD patients include Von Willebrandt factor and angiotensin converting enzyme (Falcini et al., 1999), circulating intercellular adhesion molecules, CD30, and soluble CD23.

Systemic inflammation in many organs including myocardium, central nervous system, liver, lungs, kidneys, and lymph nodes in addition to artery involvement has been well documented in KD. The pattern of vessel inflammation is characterized by edema and infiltration of neutrophils, CD8+ T cells, and macrophages. The role of IgA immune response in KD has also been investigated, suggesting that a viral agent entering the respiratory tract provokes an oligoclonal IgA response; indeed, IgA-secreting plasma cells have been found in the inflammatory infiltrate of tissues and vascular walls of KD patients (Rowley et al., 2001; Shulman et al., 2004). In addition, vascular endothelial cell growth factor may play part in vessel wall edema, leading to subendothelial accumulation of monocytes and macrophages; the inflammatory infiltrate then migrates to the media, causing its destruction and the development of aneurysms (Kariyazono et al., 2004).

5. Clinical manifestations

The typical clinical manifestations of KD are high fever lasting more than 5 days without reasonable explanation and unresponsive to antibiotics *plus* (a) bilateral nonexudative conjunctivitis; (b) polymorphous exanthemata, (c) bilateral nonsuppurative cervical lymphoadenopathy (at least one lymph node larger than 1.5 cm), (d) mucous membrane changes (i.e. injected or fissured lips, redness of pharynx, strawberry-like tongue) and (e) extremity changes (e.g. erythema of palms and soles, edema of the hands and feet, periungueal digital peeling). Figs. 1–5 are representative examples of such manifestations. All symptoms are not present at onset and evolve over the first 10 days, then gradually resolving in most children even in absence of the specific treatment. Besides the characteristic clinical manifestations other less common symptoms include uretritis, aseptic meningitis, pneumonia, otitis, and gastroenteritis (Newburger et al., 2004; Royle et al., 2005). Arthritis is included in the clinical spectrum of KD, usually developing both in the acute and in convalescent phase, and involving one or more large joints (Gong et al., 2006). Fever of 5 days duration plus four of the five remaining criteria or the presence of fever and CAA detected on two-dimensional (2D)-echocardiogram with three additional criteria are needed for the diagnosis of complete KD (Table 1) (Japan Kawasaki Disease Research Committee, 2002; Ayusawa et al., 2005). In the recent proposal of new classification criteria for KD fever is mandatory, in addition to four of the five remaining typical clinical manifestations. It has been suggested that the presence of desquamation in the perineal area should be added in the diagnostic criteria to changes in peripheral extremities (Ozen et al., 2006). Recurrence of skin peeling after the disease recovery does not mean recurrence of the disease and does not require IVIG re-treatment, as it may be also observed in a number of other conditions

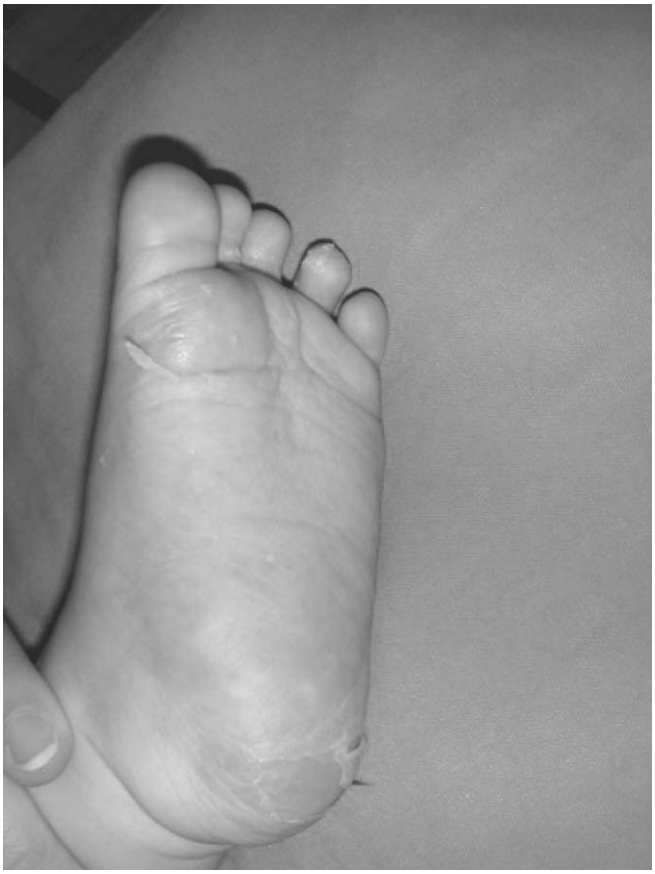

Figure 1. Esfoliative desquamation of foot.

caused by infectious agents and their toxins (Michie et al., 2000).

6. Laboratory findings

Laboratory findings are not specific for KD, as they are shared by other acute inflammatory febrile diseases. Early in the course of illness all parameters of inflammation are increased, namely ESR, CRP, white blood cell (WBC), and neutrophil counts. Platelet count is normal in the acute phase and markedly increases at the end of the second week, reaching 1,000,000 mmc^{-1} in the most severe cases. A low platelet count may be detected in approximately 10% of patients in the acute phase and may correlate with a poor prognosis. Approximately 50% of patients develop anemia with hemoglobin concentrations <2 SD below the mean for age. Urinalysis may show leukocytes and erythrocytes but no bacteria. Cerebral fluid contains increased numbers of WBC, mainly lymphocytes, as expression of aseptic meningitis. Hyponatremia frequently occurs in patients displaying a more aggressive disease; however its pathogenesis remains uncertain (Muta et al., 2005; Watanabe et al., 2006). In several patients liver enzymes and bilirubinemia are significantly elevated; jaundice and hydrops of gallbladder are relatively uncommon, and abdominal ultrasound may be helpful in detecting this complication that may support in the acute phase the diagnosis of atypical or incomplete KD (Falcini et al., 2000). An interesting finding, possibly related to a cross-reactivity between T cells and epitopes of mycobacterial and human heat

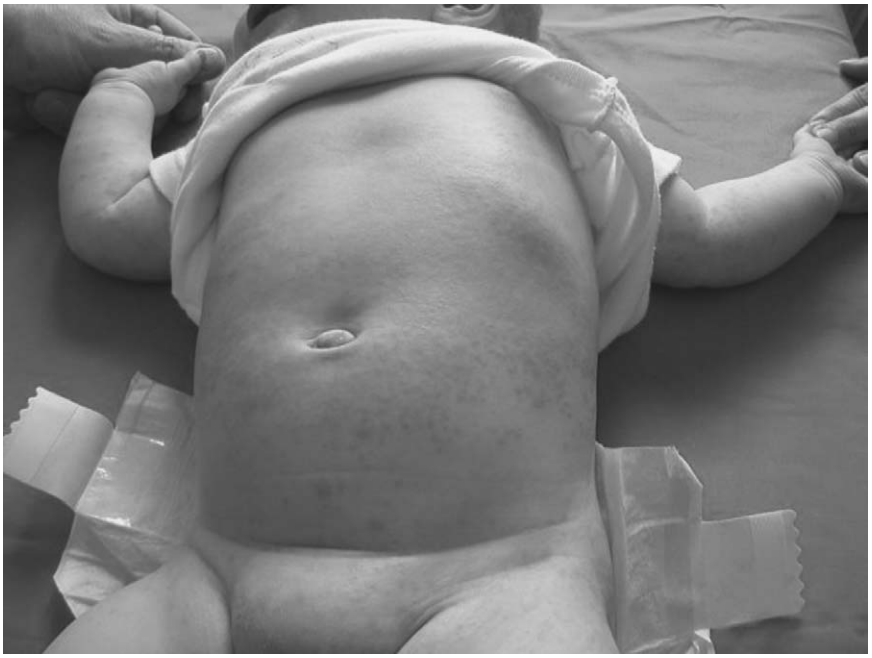

Figure 2. Macular morbilliform rash of trunk in an infant. (See Colour Plate Section.)

shock proteins, is the development of erythema and induration at sites of BCG immunization (Hsu et al., 1987; Wenstein, 2006**).** In the subacute phase changes of serum lipid profiles are detected, with increased levels of triglycerides and low-density lipoproteins, and reduced high-density lipoproteins that usually normalize within a few weeks after IVIG therapy. A correlation among abnormal serum lipid profile and intima-media thickness and arterial stiffness after KD has been reported (Cheung et al., 2004).

7. Atypical and incomplete KD

In children with the characteristic clinical findings, KD should be diagnosed within the first 5 days from the onset of fever and IVIG timely given to reduce the risk of coronary disease. Conversely, the diagnosis is a challenge in atypical and incomplete cases, as other common febrile infantile illnesses with rash closely resemble KD. Lacking specific and sensitive diagnostic test, an increasing number of children, particularly infants, are undiagnosed and develop CAA, raising concerns about the suitability of diagnosis based upon clinical criteria (Witt et al., 1999).

In atypical forms, along with fever lasting 5 or more days, acute surgical symptoms (e.g. appendicitis, acute pancreatitis) or neurological manifestations (e.g. seizures, facial palsy) can be the presenting signs, while the characteristic clinical findings may neither develop or develop over time (Fukushige et al., 1994; Zulian et al., 2003). The term ''incomplete'' should be reserved for patients with fever for at least 5 days, at least two of the clinical criteria for KD, in absence of other reasonable explanation of the disease, and laboratory data consistent with systemic inflammation. The presence of coronary alterations detected by 2D-echocardiogram helps to confirm the diagnosis. Recently, there have been proposals to add laboratory tests and minor clinical signs in diagnosing children with KD (Burns et al., 2004; Simonini et al., 2005).

An algorithm recently published by American Hearth Association (Newburger et al., 2004) suggests measuring CRP and ESR on day 5 of fever in

Figure 3. Edema and erythema of the palm in an infant.

children with 2 or 3 of the clinical criteria. Children with CRP $\geqslant$ 3 mg/dL and/or an ESR $\geqslant$ 40 mm/h should be also evaluated for additional tests. Albumin $\leqslant$ 3.0 g/dL, anemia, increased amino transferase levels, platelet count after 7 days $\geqslant$ 450,000 mmc^{-1}, WBC $\geqslant$ 15,000 mmc^{-1}, and sterile pyuria can all contribute to the correct diagnosis, which can be confirmed by the presence of echocardiographic alterations. The presence of uveitis can provide additional support to the diagnosis in patients with incomplete KD, and ocular evaluation with slit-lamp examination should be included as a part of the work-up of any suspected patient (Burns et al., 1985; Blatt et al., 1996). Another sign not included in the diagnostic criteria, but helpful in recognizing KD, is the disproportionate irritability of most children with KD that can be related to aseptic meningitis.

8. Infants and adolescents

Currently, there are few reports of patients with KD aged less than 6 months. Unfortunately, this small group seems to be at higher risk for CAA as

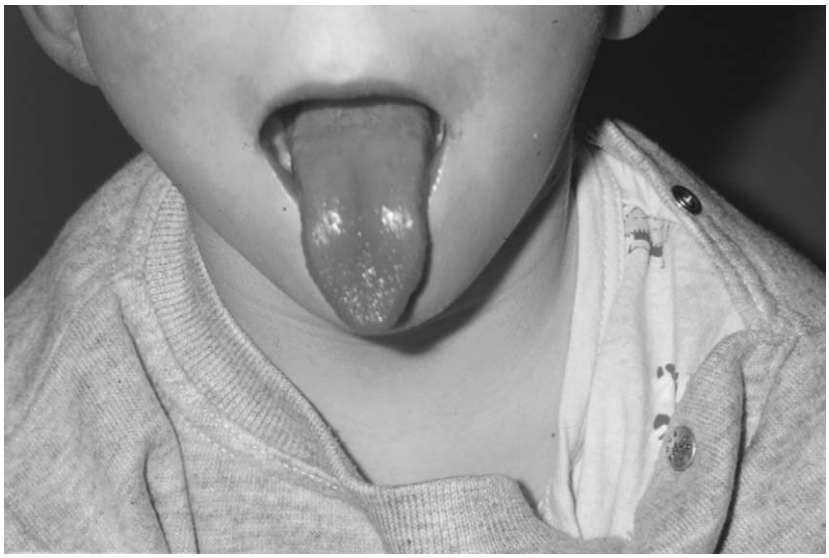

Figure 4. Strawberry-like tongue in an infant. (See Colour Plate Section.)

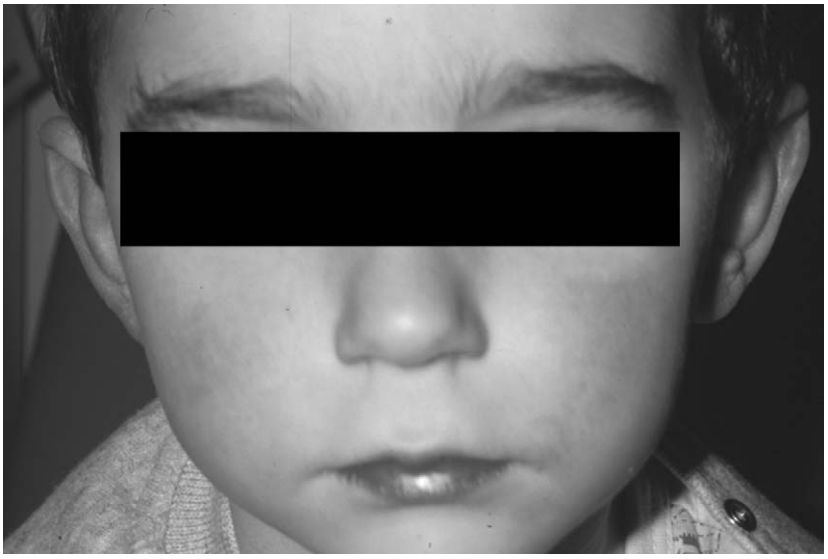

Figure 5. Reddening and cracking of the lips in an infant. (See Colour Plate Section.)

Table 1
Kawasaki disease: diagnostic criteria

Fever	Duration of 5 days or more plus 4 of the following
1. Conjunctivitis	Bulbar, non-suppurative, bilateral
2. Lymphadenopathy	Cervical >1.5 cm
3. Rash	Polymorphous, non vesicles or crusts
4. Changes of lips or oral mucosa	Red cracked lips; "strawberry tongue"; diffuse erythema of oropharynx
5. Changes of extremities	Initial stage: erythema and edema of palms and soles. Convalescent stage: peeling of skin from fingertips

Notes: Kawasaki disease may be diagnosed with fewer than 4 of these features if coronary artery aneurysms are detected by 2D-Echocardiography; fever is mandatory.

the disease displays an atypical course (45% vs. 12% in children >1 year) with persistence of inflammation leading to rapid and severe coronary damage, and treatment delay (Joffe et al., 1995; Mason and Takahashi, 1985; Chang et al., 2006a,b). The incidence of CAA is reported as high as 45% in this age group. Fatal outcome has been reported despite aggressive treatment with IVIG, aspirin, corticosteroids, and antithrombotics (Heaton et al., 2002).

On the other end of the age ranges, older children with KD are also at higher risk to develop cardiac complications (Muta et al., 2004). A recent study carried out in children aged 6 or more years showed that age resulted an independent risk factor for coronary sequelae (Pannaraj et al., 2004). This seems to be due to the delayed diagnosis and treatment in the older group when compared to the younger one. A survey involving general pediatricians and pediatric infectious disease specialists faced with children with a high fever reports that KD is rarely suspected at the extremes of pediatric age (Muta et al., 2004; Pannaraj et al., 2004). In adults, KD is seldom observed and usually has an atypical onset (Rozo et al., 2004; Seve et al., 2005).

9. Therapy

The current treatment regimen in any patient with definite or suspected KD includes IVIG (2 g/Kg) as a single infusion over 8–12 h and ASA (50–100 mg/Kg in four divided doses); the prevalence of coronary artery abnormalities is dependent on IVIG dose but independent from that of ASA (Durongpisitkul et al., 1995; Terai, 1997; Yanagawa et al., 1999).

Only for infants with cardiac compromise who may not tolerate the fluid challenge associated with a single infusion, divided doses over several days may be appropriate. IVIG should be administered as soon as the disease is suspected, and possibly within the first 10 days from the onset of fever. However, in presence of persistent signs of inflammation IVIG have to be given even in patients who are diagnosed later than 10 days from onset. Possible mechanisms of action of IVIG include the effect of specific antibodies to infectious agents or toxins, anti-idiotypic antibodies, or nonspecific effects such as blockage of Fc receptors and accelerated clearance of complement fragments. After the acute phase has resolved and platelet count rises, the dose of ASA is reduced to 3–5 mg/Kg/day as inhibitor of platelet function. In the absence of cardiac complications, low-dose aspirin is maintained for at least 6–8 wk. Long-term treatment is required in children with coronary alterations up to normalization of aneurysms, and long-life therapy is needed if they persist (Newburger et al., 2004). In children with aspirin intolerance another antiplatelet agent is suggested (dypiridamole 2–3mg/Kg) to prevent thrombi formation. In patients with giant aneurysms (GA) the addition of warfarin to aspirin is suggested, but there is no general agreement on this subject.

No specific guidelines are available for the management of patients refractory to this treatment (10–20%) in whom parameters of inflammation do not subside and fever persists or recurs, resulting in the risk of coronary artery sequelae. While a second infusion of IVIG (2 g/Kg) in addition to high dose ASA is strongly recommended in all children with persistent or recurrent fever, no consistent proposals have been made about how to treat the small group (3–4%) still remaining febrile (Hashino et al., 2001; Freeman et al., 2004; Nachiappan et al., 2004).

Since previous studies reported a high rate of coronary alterations in patients treated with corticosteroids, there has been some reluctance to use this therapy either as first-line treatment or as additional therapy in children who do not respond to IVIG (Wooditch et al., 2005). However, no association between corticosteroids and an zincreased incidence of CAA has been observed in recent reports, the use of corticosteroids as rescue therapy, either oral or pulsed (methylprednisolone 30 mg/Kg, 1–3 courses), in children refractory to IVIG has been suggested as an alternative and safe treatment (Newburger, 1999; Raman et al., 2001; Hung et al., 2004; Al-Mayouf, 2004; Jibiki et al., 2004; Takeshita et al., 2005; Lang et al., 2006).

Other therapies that have been tried in cases of aggressive disease recalcitrant to IVIG and corticosteroids, mainly published as single case reports or small series, include cyclophosphamide, cyclosporine, ulinastatin, and plasma exchange (Imagawa et al., 2004; Freeman et al., 2004).

Infliximab, a monoclonal antibody against TNF-α, has also been successfully given to IVIG- and corticosteroid-refractory children with severe coronary involvement, but results of different reports have been conflicting (Weiss et al., 2004; Stenboeg et al., 2005).

Although diagnostic criteria suggest that KD cannot be diagnosed before day 5 from fever onset, the presence of all typical symptoms may argue for earlier diagnosis and brings up the question of when to start IVIG therapy. It is still controversial whether IVIG have greater efficacy in preventing cardiac sequelae when given before or after day 4 from fever onset (Wanitkun, 2005). In addition, it is likely that early administration of IVIG may require additional infusions. Children treated before day 5 could have a different viral disease that did not respond to IVIG, thus requiring a supplementary infusion (Fong et al., 2004). Yet, the duration of fever in patients treated early is shorter than in the usual group, and since fever duration correlates with higher risk of CAA a timely treatment should prevent cardiac complications. The prevention of thrombosis and stenosis following myointimal proliferation is a great concern in children with KD. Up to now, low-dose aspirin (3–5 mg/Kg/day)

has proven to be effective in children with small to medium sized aneurysms, and there are only anecdotal reports of the association between aspirin and other antiplatelet agents (e.g. clopidrogel) (Newburger et al., 2004). Notwithstanding, long-term oral anticoagulation with warfarin is recommended in children with GA secondary to KD, although its efficacy and safety are not yet well defined. A recent study did not confirm a protective role of warfarin neither in the prevention against ischemia nor in the regression of aneurysms (Levy et al., 2005). The potential benefit, the risk of bleeding, and the difficulty in monitoring INR in children given long-term warfarin therapy require further large studies before inclusion of oral anticoagulation in the guidelines for GA treatment.

In children with severe cardiac sequelae surgical options (e.g. percutaneous transluminal coronary angioplasty, coronary bypass grafting, and cardiac transplantation) need also to be considered.

10. Cardiac follow-up

All patients with typical or suspected KD have to be closely monitored with electrocardiogram (ECG) and 2D-echocardiography. ECG can reveal arrhythmia, myocardial dysfunction, and ischemia. 2D-echocardiography is useful in detecting pericardial effusion, valvular inflammation and regurgitation, and coronary artery dilatation and aneurysms, which may be revealed by ultrasound also in peripheral arteries (Cura et al., 2004). Assessment by 2D-echocardiography is recommended at 10 days, and at 6–8 wk from the onset of fever as new aneurysms rarely occur later; in absence of CAA no further follow-up is suggested (Newburger et al., 2004). In children with transient coronary artery alterations that eventually restore, echographic control up to normalization is recommended. However, following the recent reports that marked thickening of the intima at the site of regressed aneurysms develop over time associated to endothelial dysfunction, stress testing to define myocardial function should be performed before starting sports. In all patients with GA at the risk of developing stenosis a close monitoring by a pediatric cardiologist over adolescence and early adulthood is warranted.

10.1. Coronary artery lesions

The long-term prognosis in KD has significantly improved in recent years due to a better knowledge of the disease and earlier appropriate treatment; however, coronary damage including dilatation, aneurysms, and GA remain a concern in approximately 5% of timely treated patients (Kato et al., 1996). Even after IVIG introduction KD is a disease at high morbidity, and in Japan the mortality among persons with a history of KD and cardiac sequelae is reported higher than in normal population (Oki et al., 2000; Nakamura et al., 2000). Risk factors for cardiac sequelae are male sex, age younger than 1 year or older than 5 years, high CRP, WBC $>30.000\,\mathrm{mmc}^{-1}$, and low serum albumin (Honkanen et al., 2003, Newburger et al., 2004) in addition to IVIG treatment after 6 days from the onset of fever (Zhang et al., 2002; Onouchi et al., 2005).

Although most of cardiac complications repair without further abnormalities, the coronary damage as firstly revealed by the wall brightness may progress to either ectasia or aneurysms (Tulloh et al., 2004). In contrast to aneurysms (diameter of coronary lumen $\geqslant 4$ mm) that may regress in size and restore over time, GA (diameter of coronary lumen $\geqslant 8$ mm) rarely improve, becoming stenotic in up one-third of patients. In these cases myocardial ischemia may develop, leading to myocardial infarction and sudden death even in early adulthood (Kato et al., 1992; Newburger et al., 2004). Therefore GA, a potential risk for rupture in the acute phase or subsequent thrombosis due to the stasis of blood flow and the procoagulant endothelial surface of inflamed vessels, are major concerns in KD and raise the dilemma of long-term anticoagulation in children, especially in infants (Levy et al., 2005).

Coronary arterial lesions are known to develop progressive intimal hyperplasia even many years after acute KD (Wilson et al., 2004). An immunohistochemical study performed on a child with history of KD without evidence of CAA who died of sudden infant death syndrome, showed a slightly thick intima, disruption of the lamina interna, and signs of persistent inflammation suggesting that even coronary arteries that appear normal on ultrasound may be damaged (Suzuki et al., 2004).

Furthermore, KD seems to predispose to premature atherosclerosis in adulthood (Cheung et al., 2004). An adverse cardiovascular risk profile (low HDL and apo-A1 but high apo-B1 levels, and increased peripheral arterial stiffness) after resolution of acute inflammation has been detected in KD children with CAA when compared to those without CAA, and controls. There is evidence of increased arterial stiffness related to the severity of inflammation in acute KD (Cheung et al., 2004). Ensuing regressed aneurismal lesions both myocardial flow reserve and endothelial function are impaired even in absence of artery stenosis (Dhillon et al., 1996).

10.2. Cardiac imaging

Even though 2D-echocardiography still remains the gold standard in the early cardiac assessment of KD children and in detecting CAA of proximal right and left coronary arteries, more invasive methods are needed in order to better visualize in detail the entire coronary artery system. To define the degree of cardiac damage, assessment of ventricular ischemia and myocardial blood flow is recommended. Dobutamine stress echocardiography has shown to be a safe and sensible tool in evaluating the outcome of CAA, comparable to cardiac catheterization (Zilberman et al., 2003).

Coronary magnetic resonance angiography (MRA) has proven to be equivalent to X-ray coronary angiography (XCA) and successful in the identification of CAA and in their follow-up (Mavrogeni et al., 2004). Electron beam computed tomography (EBT) is a noninvasive tool that enables the early detection of myocardial ischemia progressing from endocardial to central and epicardial region, thus allowing a prompt therapeutic approach (Endoh et al., 2004). Positron emission tomography (PET) has been reported useful in revealing flow reserve in children with normal epicardial coronary arteries, addressing the risk of residual coronary damage in absence of evident coronary involvement (Ohmocki et al., 1995; Furujama et al., 2002; Furujama et al., 2003; Hauser et al., 2004). Recently, multislice spiral computed tomography (MSCT) has proved to be a noninvasive sensitive tool comparable to coronary angiography in visualizing coronary artery stenosis in KD children. In the future MSCT could become the standard diagnostic tool and possibly replace angiography in patients with CAA (Sato et al., 2004).

11. Vaccinations

Live viral vaccines are an additional concern for children with KD, since IVIG therapy blocks an active immune response. Whereas an interval of 6–11 months is recommended in Japan and USA, there is not yet agreement about the nonresponders who had received a second IVIG pulse. A recent study (Miura et al., 2004) points to 9 months as the optimal time interval for measles vaccination and possibly for mumps, rubella, and varicella viruses in re-treated children.

Key points

- Kawasaki disease still remains a challenge for pediatric rheumatologists.
- Atypical cases are those with fever, acute surgical symptoms or neurological manifestations as presenting signs (the remaining typical clinical manifestations may or may not develop over time), while the term ''incomplete'' is reserved for patients who lack the classical diagnostic criteria but who present fever, at least two of the clinical criteria, and coronary alterations by echocardiography.
- Medical history, physical examination, and laboratory tests including elevated WBC count, ESR, CRP, and low hemoglobin, sodium and albumin levels may help to rule out illnesses mimicking KD.
- Treatment of refractory KD is still a dilemma. Oral or pulsed corticosteroids in children refractory to IVIG are an alternative and safe treatment. Infliximab, a monoclonal antibody against TNF-α, has been given to children with coronary aneurysms, refractory to IVIG and corticosteroids, but still with conflicting results.

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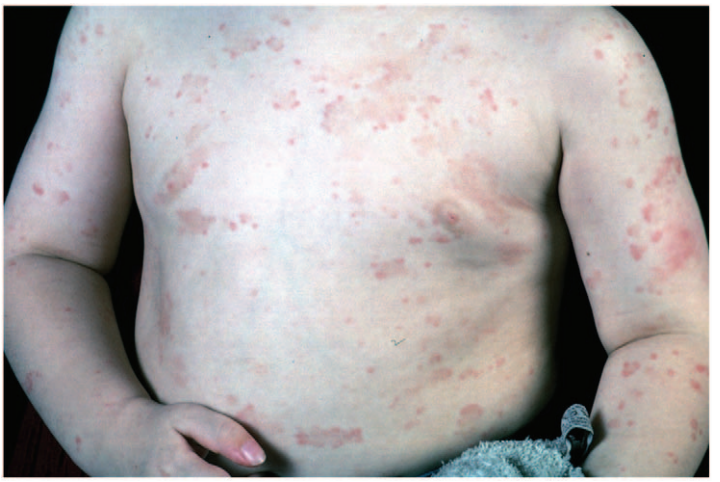

Plate 12. Urticaria-like rash in NOMID patient. (For Black and White version, see page 126.)

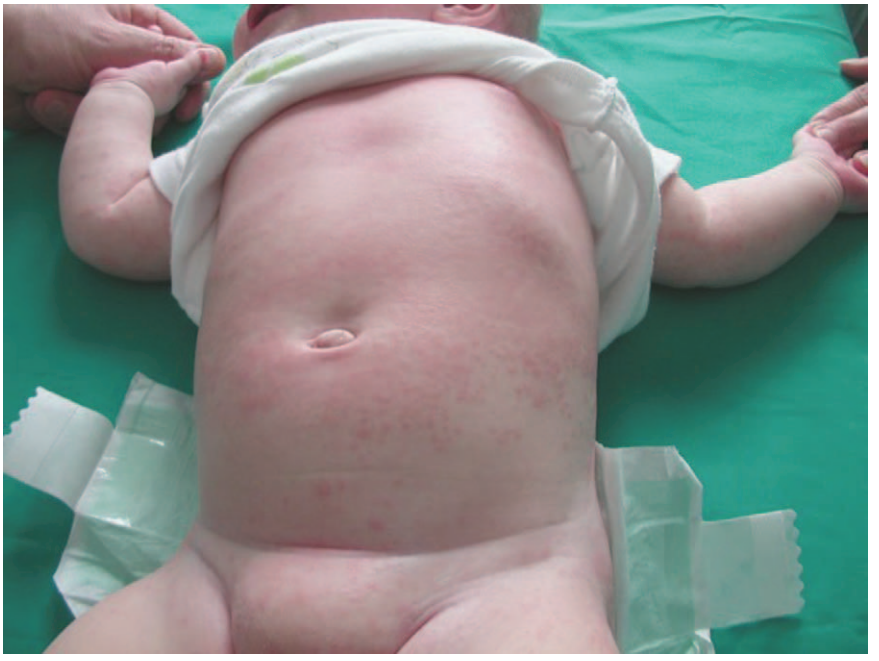

Plate 13. Macular morbilliform rash of trunk in an infant with Kawasaki disease. (For Black and White version, see page 141.)

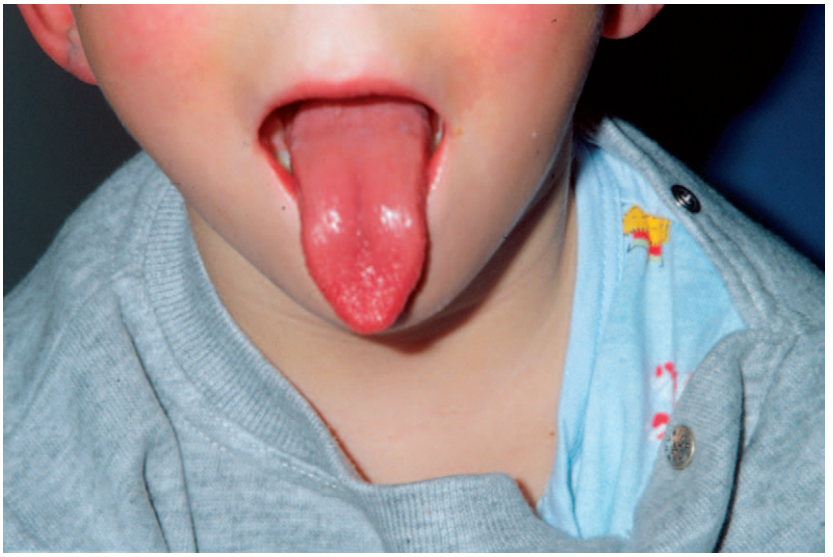

Plate 14. Strawberry-like tongue in an infant with Kawasaki disease. (For Black and White version, see page 142.)

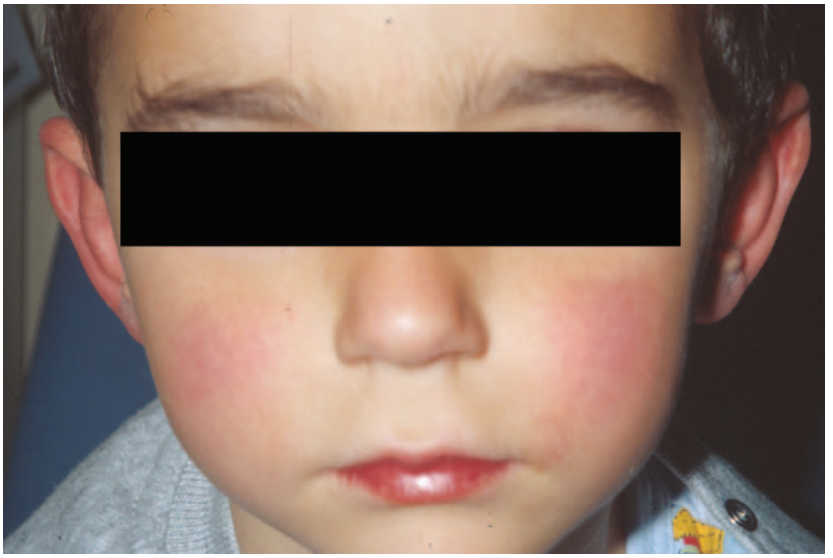

Plate 15. Reddening and cracking of the lips in an infant with Kawasaki disease. (For Black and White version, see page 143.)