

Kawasaki Syndrome

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HISTORICAL ASPECTS

Kawasaki syndrome (KS) was first described by Tomisaku Kawasaki in the Japanese-language medical literature in 1967. At that time, he reported his experience with 50 children who presented from 1961 to 1967 with symptoms distinct from other known childhood illnesses (34). He termed the condition “mucocutaneous lymph node syndrome” and originally thought that the syndrome represented a benign childhood illness. However, by late 1970, it was clear that as many as 10 deaths had occurred in children younger than 2 years with KS in Japan, usually at a time when their clinical condition appeared to have improved. Kawasaki's original report was followed in 1976 by that of Melish et al., who described the same illness in 16 children in Hawaii (55). Melish and Kawasaki had independently developed the same diagnostic criteria for the disorder, which are still used today to make the diagnosis of classic KS.

Is KS a new illness which began in the 1960s to 1970s? Recently, the preserved heart of a 7-year-old boy who died in 1870 following “scarlatinal dropsy” was found at St. Bartholomew's Hospital in London (23). This heart showed three aneurysms of the coronary arteries with clots, as well as pathologic changes consistent with KS. It appears that prior to Kawasaki's report of the distinctive clinical features of the illness, KS was identified only postmortem by pathologists, who termed the illness “infantile periarteritis nodosa.” It is now recognized that fatal KS and infantile periarteritis nodosa are pathologically indistinguishable (43). Thus, only fatal KS was recognized, while milder forms of illness went undiagnosed.

KS is now recognized worldwide. In the United States and other developed nations, it appears to have replaced acute rheumatic fever as the most common cause of acquired heart disease in children (98). Asians are most commonly affected;

some 135,000 cases have now been diagnosed in Japan since Kawasaki's original report.

CLINICAL FEATURES

Classic Diagnostic Criteria

No diagnostic test exists for KS, since its cause remains unknown. Its diagnosis is based upon recognition of the clinical features of the illness, which include fever plus four of five other principal criteria without other explanations for the illness (Table 1). Patients with fever and fewer than four of the other principal criteria can be given a diagnosis of KS if coronary artery abnormalities develop.

In KS, fever is generally high-spiking (usually to 104°F [40°C] or higher) and remittent. The first day of fever is considered the first day of illness, although patients may have developed one or more other clinical features the day before the onset of fever. The duration of fever is generally 1 to 2 weeks in the absence of treatment but may extend for 3 to 4 weeks. In patients treated with high-dose aspirin at 80 to 100 mg/kg/day and a single 2-g/kg dose of intravenous gamma globulin (IVGG), fever generally resolves within 1 to 2 days after therapy is instituted (62).

Conjunctival injection in KS is distinctive; the bulbar conjunctivae are much more affected than the palpebral conjunctivae, and exudate is generally not present. It usually begins shortly after the onset of fever. Most treated patients have prompt resolution of conjunctival injection, although mild injection persists for 1 to 2 weeks in a subset of patients. Anterior uveitis may be present on slit-lamp examination (91).

Changes in the mouth and lips are characterized by erythema, dryness, fissuring, peeling, and bleeding of the lips; erythema of the oral and pharyngeal mucosa; and strawberry tongue with prominent papillae and erythema. Oral ulcerations, exudates, and Koplik spots are not observed in KS patients.

The findings in the hands and feet are very distinctive and

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TABLE 1. Diagnostic criteria for KS

Fever for at least 5 days ^a
Four of the following five signs:
Bilateral conjunctival injection
Changes of the oral mucosa (erythematous, dry fissured lips; erythema of the pharynx; strawberry tongue)
Changes of the hands and feet (redness and swelling in the acute phase, periungual desquamation in the subacute phase)
Rash, primarily on the trunk (maculopapular, erythema multiforme, or scarlatiniform; not vesicular)
Cervical lymphadenopathy (node diameter, >1.5 cm)
Illness not explained by other known disease process

^a In the presence of fever and the other diagnostic criteria for KS, experienced physicians may make the diagnosis before the 5th day of fever.

include erythema confined to the palms and soles. The erythema is often striking, with an abrupt change to normal-appearing skin at the wrists and ankles. Since the hands and feet may also be markedly swollen, infants and children frequently refuse to hold objects in their hands or to bear weight on their feet. In the subacute stage of illness, periungual desquamation of the fingers and toes is common; however, this is not a finding in acute KS. About 1 to 2 months after the onset of illness, deep transverse grooves across the nails may develop (Beau's lines). These grooves grow out with the nail, although occasionally a nail is shed.

The rash in KS may take many forms. Most common is a diffuse maculopapular erythematous rash, which appears quite nonspecific. A scarlatiniform rash and an erythema multiforme-like rash with target lesions are also seen. Vesicles and bullae are not seen, although fine pustules have occasionally been described, particularly over the extensor surfaces of the extremities. Erythema and desquamation in the groin area, frequently mistakenly diagnosed as a candidal diaper dermatitis, is quite common and is seen in both diapered and toilet-trained children. Desquamation in the groin is generally seen earlier than periungual desquamation and may in fact be present in the acute phase of illness.

The final diagnostic criterion, cervical lymphadenopathy, is seen in approximately 50 to 75% of patients, whereas the other features are estimated to occur in 90% of patients. Although the least commonly seen feature of the illness, cervical lymphadenopathy paradoxically is the most prominent feature in some patients (92). Lymphadenopathy in KS patients is usually not subtle; diagnostic criteria state that the node must be at least 1.5 cm in diameter, but in most patients cervical node swelling is easily visible. The node may be erythematous, but it is nonfluctuant and does not yield pus if aspirated. We have cared for many patients referred for cervical adenitis unresponsive to antibiotic therapy who have KS. In these patients, other features of the illness are often present but are overlooked or attributed to an antibiotic reaction. Therefore, the diagnosis of KS should be considered in any febrile child with cervical adenitis who does not respond to antibiotic therapy and does not have an obvious alternative diagnosis.

Associated Features

A variety of other features are characteristic of KS, although they are not included in the diagnostic criteria. One of these is extreme irritability, which occurs to a greater extent than that generally seen in other childhood febrile illnesses. It is particularly common in young infants and may lead the physician to perform a spinal tap. About one-fourth of patients with KS have aseptic meningitis, with 25 to 100 leukocytes/mm³ in the spinal fluid, predominantly lymphocytes, and normal glucose

levels and normal to mildly elevated protein levels in cerebrospinal fluid. Arthralgia and arthritis may also be seen, and were probably more common before the use of intravenous gamma globulin (IVGG) in the treatment of KS than at present. Arthritis of the hands, knees, ankles, and occasionally the hips may be seen in the first week of the illness or may occur during the second to third weeks. Early-onset arthritis in the first week of illness is generally associated with leukocyte counts of 100,000 to 300,000/mm³ in synovial fluid, with a polymorphonuclear cell predominance, while late-onset arthritis is associated with a lower leukocyte count, of approximately 50,000/mm³, in synovial fluid with 50% polymorphonuclear cells.

Hepatic dysfunction, as manifested by mild elevations in the transaminase levels, is seen in many patients with acute KS; jaundice is less common. Acute distension of the gallbladder (hydrops) is common in patients with KS and presents with a right upper quadrant mass and/or guarding in the acute stage of illness. Ultrasonography is useful for diagnosis, and the condition resolves without surgical intervention. Other associated features of KS include diarrhea, which is commonly seen early in the illness; pneumonitis, which is radiographically but not clinically apparent; and otitis media.

An interesting feature of KS in some patients is erythema and induration at the site of a recent vaccination with Calmette-Guérin bacillus (BCG) for tuberculosis (95). Since BCG vaccine is rarely administered in the United States, U.S. patients rarely present with this finding. In contrast, this feature is commonly seen in Japan, where the vaccine is routinely administered to children, and generally occurs when KS develops within 6 months to 1 year after vaccination. Takayama et al. reported erythema at the BCG inoculation site in 36% of 295 KS patients (95); this finding has been incorporated into diagnostic guidelines for KS outlined by the Japan Research Committee on Kawasaki Disease. The cause of this reaction is unknown.

Cardiac involvement is the most important associated feature of KS; it is discussed separately below.

Clinical Phases of Illness

The course of KS can be divided into three clinical phases (Table 2). The acute febrile phase, which usually lasts for 1 to 2 weeks, is characterized by fever, conjunctival injection, erythema of the oral mucosa, erythema and swelling of the hands and feet, rash, cervical adenopathy, aseptic meningitis, diarrhea, and hepatic dysfunction. Myocarditis is common during this time, and a pericardial effusion may be present. Coronary arteritis may be present, but aneurysms are generally not yet visible by echocardiography. The subacute phase begins when fever, rash, and lymphadenopathy resolve at about 1 to 2 weeks after the onset of fever, but irritability, anorexia, and conjunc-

TABLE 2. Clinical phases of KS

Phase	Characteristics	Duration
Acute febrile	Fever plus other acute features; myocarditis; pericardial effusion	1-2 wk
Subacute	Fever resolution, possible persistence of conjunctival injection and irritability, desquamation of fingers and toes, thrombocytosis, coronary arteritis; risk of sudden death greatest	Until day 30 of illness
Convalescent	All clinical signs of illness resolved; lasts until sedimentation rate normalizes	6-8 wk after onset of illness

tival injection persist. Desquamation of the fingers and toes and thrombocytosis are seen during this stage, which generally lasts until about 4 weeks after the onset of fever. Coronary artery aneurysms usually develop during this time, and the risk for sudden death is highest during this stage. The convalescent stage begins when all clinical signs of illness have disappeared and continues until the sedimentation rate returns to normal, usually at 6 to 8 weeks after the onset of illness.

Unusual Manifestations

A rare but serious complication of KS is the development of severe peripheral ischemia with resultant gangrene (103). Patients with this complication are generally young, non-Asian infants younger than 7 months at the onset of KS. Most affected patients have giant coronary artery aneurysms (coronary artery lumen of ≥ 8 mm in internal diameter), the most serious coronary abnormality following KS, and some have peripheral arterial aneurysms, particularly axillary aneurysms. Possible pathogenic mechanisms of peripheral gangrene include severe arteritis of digital or other peripheral small arteries; arteriospasm of peripheral small to medium-sized arteries, perhaps in association with severe vasculitis; thrombosis of inflamed or spastic small to medium-sized arteries as a result of stagnant blood flow and damaged endothelium; thrombosis of a more proximal arterial aneurysm (particularly axillary) with embolism distally; rarely, cardiogenic shock with decreased peripheral perfusion; and, most likely, a combination of some or all of these factors (103). Unfortunately, most of these patients experience autoamputation of fingers or require amputation of extremities. Optimal therapy for this condition is unknown. Anti-inflammatory agents, such as salicylates and IVGG, vasodilators (prostaglandin E_1 and/or sympathetic nerve block), and thrombolytic/anticoagulant therapy have all been used (103).

Atypical or Incomplete Kawasaki Syndrome

Not all patients with KS have illnesses which fulfill classic diagnostic criteria. Children with illnesses manifested by fever and fewer than four of the other features of the illness, so-called atypical or incomplete KS, may develop coronary artery aneurysms (74). Such cases have been reported worldwide. Atypical KS is apparently most common in young infants, who are unfortunately at greatest risk of developing coronary disease (8, 10, 74). Recognition of such cases can be quite difficult, and fatal outcomes have occurred. KS should be considered in the differential diagnosis of prolonged fever in infants; many physicians experienced in the diagnosis and treatment of KS at large pediatric centers have encountered patients in whom prolonged fever was virtually the sole manifestation of KS. Diagnosis in these cases has usually been based upon the finding of coronary artery aneurysms by echocardiography. The existence of such cases emphasizes the need to identify the etiologic agent of KS so that a diagnostic test can be developed. In general, the laboratory profile of atypical cases seems to be similar to that of classic cases (see below). Whenever possible, patients with illnesses suggesting atypical KS should be referred to physicians with considerable experience in making the diagnosis.

Differential Diagnosis

The differential diagnosis of KS should include scarlet fever, staphylococcal scalded-skin syndrome, Stevens-Johnson syndrome and other drug reactions, Rocky Mountain spotted fever, toxic shock syndrome, leptospirosis, juvenile rheumatoid arthritis (JRA), and measles. Clinical and laboratory data should help in excluding these possibilities. Of note, measles

demonstrates striking clinical similarities to KS. Outbreaks of measles in 1989 in Chicago and Los Angeles allowed for close comparison of the clinical features of the two illnesses; findings emphasized the difficulty in identifying cases of KS in countries where measles remains epidemic. Important differences between measles and KS include the presence of exudative conjunctivitis, Koplik spots, and severe cough in patients with measles. The rash in measles generally starts on the face, behind the ears, whereas the rash in KS is generally most prominent on the trunk and extremities. The rash in measles generally becomes confluent as it fades and leaves a distinctive brownish hue to the skin, whereas the rash in KS generally fades abruptly without residua. Perineal accentuation of the rash is typical of KS but not of measles. Swelling of the hands and feet occurs in both illnesses and is not a helpful distinguishing feature. The leukocyte count and sedimentation rate in uncomplicated measles are both low, whereas they are generally high in KS. In cases where it is difficult to distinguish the two diseases, a measles immunoglobulin M (IgM) test is invaluable.

KS also demonstrates clinical similarities to staphylococcal and streptococcal diseases. Toxic shock syndrome can be differentiated from KS on the basis of a number of clinical features. First is the presence of hypotension in toxic shock syndrome, which is not seen in KS in the absence of overwhelming cardiogenic shock. In addition, renal involvement, elevation of the creatinine phosphokinase level in serum, and a focus of staphylococcal infection are all characteristic of toxic shock syndrome but not of KS. Scarlet fever should be easily diagnosed by the presence of exudative pharyngitis with group A streptococci isolated by throat culture. Elevations in the leukocyte count and sedimentation rate may be seen both in KS and in staphylococcal or streptococcal infections. Therefore, these tests are unlikely to help distinguish the conditions. A common clinical problem is the differentiation of scarlet fever from KS in a child who is a group A streptococcal carrier. Since 20 to 25% of children may carry group A streptococci in their throats, many children with KS will have positive throat cultures for the organism. Because patients with scarlet fever have a rapid clinical response to penicillin therapy, treatment with penicillin for 24 to 48 h, with clinical reassessment at that time, generally clarifies the diagnosis.

Experienced clinicians can often distinguish drug reactions from KS based upon the nature of the rash and other features of illness such as periorbital edema, which is often present in drug allergy but not in KS, and oral lesions, which are characteristic of Stevens-Johnson syndrome but not of KS. In difficult cases, obtaining a sedimentation rate may be useful, since it is generally less elevated in patients with drug reactions and very high in those with KS.

Systemic-onset JRA may resemble KS. The presence of lymphadenopathy and hepatosplenomegaly suggests JRA as the diagnosis, as does the presence of an evanescent, salmon-colored rash. Rarely, a patient with systemic-onset JRA may be treated for KS, with the diagnosis becoming apparent over time as symptoms persist or relapse.

LABORATORY FEATURES AND IMMUNOLOGIC FEATURES

There are certain characteristic laboratory features of KS. An elevated leukocyte count with a predominance of neutrophils or a normal leukocyte count with a left shift is typical in the acute phase of illness. An elevated sedimentation rate and elevations in the levels of other acute-phase reactants are almost universally present in the first week of illness and may

persist for 4 to 6 weeks. Low leukocyte counts are almost never seen in KS; if present, they should prompt consideration of another diagnosis. A normocytic anemia is a common feature of acute KS and may be more severe in patients with a prolonged acute stage of illness and in those who develop coronary disease. A low platelet count at presentation has been associated with the development of severe coronary disease and myocardial infarction (65). The platelet count is generally normal in the first week of illness. Thrombocytosis during the second to third week of illness is classically associated with KS; platelet counts in excess of $1,000,000/\text{mm}^3$ may be seen. Antinuclear antibody and rheumatoid factor are not detectable. Sterile pyuria of urethral origin occurs in about one-third of patients in the first week of illness and may be intermittent. The development of a specific diagnostic test for KS awaits the discovery of the etiologic agent(s) of the illness.

A full understanding of the immunology of KS also awaits information about the etiology and pathogenesis of the illness. Several observations regarding immunologic perturbations in the peripheral blood of patients with KS have been made. In the acute phase of illness, IgG levels in serum are lower than normal for age (62). In the subacute phase of illness, elevations in the levels of IgG, IgM, IgA, and IgE in serum have been reported (41, 50). Circulating immune complexes can be detected in the subacute to convalescent phases of illness but do not appear to correlate with the development of coronary disease in KS (53, 79). Some investigators have detected IgG antibody in these complexes (48, 79), while others have detected IgA antibody in the complexes (47, 67). Studies of the distribution of T cells in the acute and subacute stages of KS have yielded conflicting results ranging from no significant changes in the distribution of CD4, CD8, CD19, and CD3 cells during any stage of illness (13) to significant decreases in CD8 (46, 100) or CD4 (100) cell numbers in the acute phase of illness. Results of studies testing for the presence of activated T cells in peripheral blood in samples from patients with acute KS have also been conflicting (17). Recently, expansion of V β 2 and V β 8 T-cell receptor family members in acute KS has been reported (1, 14), prompting a search for a superantigen as a cause of the illness (45). However, this finding is also controversial and has not been reproduced by other investigators (2, 52, 57, 64, 69, 101). A recent paper demonstrating a clonal expansion of CD8 T cells in acute KS provides support for the hypothesis that a conventional antigen is involved in the pathogenesis of the illness (13). A variety of cytokines have elevated levels in sera of patients with acute KS, including gamma interferon, tumor necrosis factor alpha, interleukin-6 (IL-6), IL-4, IL-10, and IL-8 (26, 51, 54, 75), attesting to the marked immunologic activation seen in acute KS.

EPIDEMIOLOGY

KS occurs almost exclusively in young children; 80% of patients are younger than 4 years. Although the illness is rare in infants younger than 3 months, KS has been observed in infants as young as 20 days (104). However, older children may develop KS; we have cared for several teenagers with the disorder. Reports of KS in adults exist, but many such cases in retrospect represented toxic shock syndrome. Young adults may present with ischemic heart disease as a sequela of unrecognized KS in childhood (9). KS occurs worldwide and affects children of all races, although Asians are at highest risk (16).

In Japan, the reported annual incidence has been about 5,500 cases/year since 1987. Two large-scale epidemics of illness occurred in Japan. In 1982, more than 15,000 cases were diagnosed, and in 1986, more than 12,500 cases occurred (108),

as well as a smaller-scale epidemic in 1979. The male-to-female ratio of Japanese cases is 1.35:1, dropping to 1.23:1 during epidemics. The peak age of onset of illness is 6 to 11 months (107). During nonepidemic years, no strong seasonal distribution is seen, although cases are somewhat more common during the winter months. During epidemic years, a definite trend toward an increased number of cases from winter to early spring has been noted (108). A wavelike spread of illness has been noted during epidemics, resembling that observed with known viral illnesses such as measles and influenza (106). KS is unusual in very young infants, suggesting the possibility that passive maternal antibody is protective against the disorder. For the 25-year period from 1970 to 1995, only six cases of KS occurred in infants 30 days of age or younger in Japan, and infants 90 days of age or younger accounted for only 1.67% of all KS cases (104). The recurrence rate of KS in Japan is 3% (108); it appears to be about 1% in North America.

A study of KS in Japanese families revealed that the overall rate of a second case in a household within 1 year after onset of the first case was significantly higher than the rate for the general population of aged-matched children. In addition, more than half of the second cases occurred within 10 days after the first case occurred, and in three of four sets of twins who both developed KS, the illness began on the same date (20). These findings suggest common exposure to an infectious agent in genetically predisposed individuals.

Studies in the United States and other countries reveal similar epidemiologic findings, although the peak age of onset of illness is approximately 18 to 24 months, higher than the peak age of 6 to 11 months in Japan (78, 84, 87, 96). Multiple epidemics of illness have been reported in the United States: Hawaii in 1978 (16), Rochester, N.Y., and eastern and central Massachusetts in 1979 to 1980 (7); Maryland in 1983 (49); and 10 areas of the United States in 1984 to 1985 (11). Outbreaks have also been reported in Finland in 1981 to 1982 (80) and in Korea in 1979 and 1983 (44). For unknown reasons, epidemics have not been observed in Japan or other countries in the past 10 years. The mean annual incidence of KS in non-Asians is about 10 cases/100,000 children younger than 5 years (97), whereas the annual incidence of KS in Japanese children in Chicago was 44 cases/100,000 children younger than 5 years in 1979 to 1983 (87). The annual incidence of KS in children in Japan is approximately 10-fold higher than that seen in non-Asians in the United States and other non-Asian countries, with a rate of 95 cases/100,000 children younger than 5 years in the Japanese 1993 to 1994 nationwide survey (108). In the United States, KS occurs more commonly in children of middle or upper socioeconomic status (16, 87).

ETIOLOGY

The etiology of KS remains unknown. However, clinical and epidemiologic aspects of the illness strongly suggest an infectious etiology. A self-limited, generally nonrecurring illness manifested by fever, rash, enanthem, conjunctival injection, and cervical adenitis fits well with an infectious cause. The epidemiologic features described above, including the occurrence of well-defined epidemics with periodicity, winter-spring predominance in temperate climates, and a geographic wavelike spread of illness during epidemics are features of an infectious process. However, conventional bacterial and viral cultures and serologic investigations have failed to yield an infectious cause (7, 16); early etiologic studies of KS were reviewed previously (76).

In two outbreaks of KS in the United States, a history of an antecedent respiratory illness was obtained from significantly

more patients than controls (7). More frequent exposure of KS patients than controls to rug shampoo has been reported in some outbreaks (68) but not in others (38, 49). A variety of other environmental exposures have been sought in KS patients without yielding any risk factors for the development of disease, including the use of medications, exposure to pets, and immunizations (7, 16).

One hypothesis is that KS is caused by a ubiquitous infectious agent that leads to clinically apparent disease in certain genetically predisposed individuals, particularly Asians. The rarity of the illness in the first few months of life and in older children and adults is consistent with the hypothesis that KS is caused by an agent to which virtually all adults are immune and from which very young infants are protected by passive maternal antibody. The paucity of evidence of person-to-person spread of KS may fit this hypothesis, since most individuals would experience asymptomatic infection and only a restricted number would develop clinical features of KS.

The genetic factors responsible for an increased susceptibility to KS are unknown. No consistent human leukocyte antigen association appears to exist. A study of Ig allotypic markers in KS patients of different ethnicities has revealed that certain markers which are common in Japanese populations are more prevalent in non-Asian KS patients than in non-Asian controls, suggesting a possible link between susceptibility to KS and the Ig genes (88).

Studies of KS etiology have included a search for a retrovirus as a causative agent; extensive research did not confirm this hypothesis (56, 72). More recently, expression of the V β T-cell receptor family in peripheral blood T cells in patients with acute KS has been examined by many investigators; in these studies, the results about whether increased usage of V β 2 T-cell receptor occurs in acute KS were conflicting (1, 2, 14, 57, 64, 69). The finding of such a skewed T-cell receptor response by some investigators has led to a search for a superantigen related to KS, with one group reporting such an association (45). However, other investigators have been unable to reproduce these findings (2, 52, 57, 64, 101); therefore, this hypothesis remains unproven.

Clearly, conventional methods have failed to yield the causative agent of KS. Diagnosis continues to be difficult, particularly in young infants, who are also at greatest risk of developing coronary artery sequelae (70), and in patients with incomplete or atypical presentations (8, 10, 74). Without the etiologic agent, a diagnostic test cannot be developed. In addition, more specific treatment for KS and prevention both await discovery of the etiology of the illness. With the use of newer molecular biology techniques (73, 77), it is hoped that significant progress in finding the etiology of the illness will be made in the near future.

CARDIOVASCULAR MANIFESTATIONS

KS was initially thought to be a benign self-limited childhood illness. However, soon after Kawasaki's original report, it became apparent that a few children diagnosed with KS died suddenly and unexpectedly, usually during the third or fourth week of illness and at a time when their clinical condition appeared to have improved. Death was usually due to massive myocardial infarction secondary to coronary thrombosis in areas of coronary artery aneurysm formation (35).

About 20% of untreated KS patients develop coronary artery abnormalities, including diffuse dilatation and aneurysm formation. Hirose et al. demonstrated that coronary dilatation in patients with KS is first detected at a mean of 10 days of

illness and that the peak frequency of coronary dilatation or aneurysms occurs within 4 weeks of onset (27). Thus, KS is an acute vasculitis; there is no evidence of chronic, ongoing vasculitic changes in the arterial wall of the KS patient whose acute illness has resolved. Saccular and fusiform aneurysms usually develop between 18 and 25 days after the onset of illness. The fatality rate in KS is dependent upon prompt recognition of cases and institution of appropriate therapy. Initial reports from Japan in the 1970s indicated a 1 to 2% fatality rate; this has dropped to 0.08% (108) due to improved recognition and therapy of the disorder. Recently, fatality rates of 6% from Auckland (24), 2% from Sweden (84), and 3.7% from the British Isles (19) were reported. Death in these series was due either to myocardial infarction secondary to thrombosis of a coronary artery aneurysm or to rupture of a large coronary artery aneurysm. Death is most common 2 to 12 weeks after the onset of illness.

The fate of coronary aneurysms over time was well described by Kato et al. (29). At 1 to 3 months after the onset of KS, 15% of KS patients in this study had angiographic evidence of coronary artery aneurysms. Repeat angiography 5 to 18 months later in those with abnormalities showed that the aneurysms had resolved in about 50% of the patients. Of those with persistent aneurysms, one-half had smaller aneurysms than previously, with or without stenosis, one-third had resolution of the aneurysms but had developed obstruction or stenosis of the coronary arteries, and the remainder had fine irregularities of the vessel walls without stenosis. Stenosis, which occurs as a result of the healing process of the vessel wall, often leads to significant coronary obstruction and myocardial ischemia. A recent longer-term follow-up study by Kato et al. indicated that 10 to 21 years after acute KS, additional patients with persistent aneurysms had developed stenosis of the vessel (33). Myocardial infarction occurred in 39% of patients with persistent aneurysms with stenosis, or 1.9% of all the KS patients in this series. Bypass surgery was performed in 1.2% of all KS patients, or 25% of patients with persistent aneurysms with stenosis. The overall mortality in this group of 594 patients was 0.8% (33).

The most severe form of coronary artery aneurysm is the giant aneurysm (internal luminal diameter of the coronary artery lumen, ≥ 8 mm). These lesions are less likely to resolve and more likely to thrombose, rupture, or eventually develop stenosis than other, smaller aneurysms (58). In the long-term follow-up study by Kato et al. 26 of 594 patients (4.4%) developed giant coronary aneurysms (33); in 12 of the 26 patients (46%), stenosis or complete obstruction occurred over time, and 8 of the 12 (67%) experienced a myocardial infarction, with a 50% mortality rate. The other 14 patients showed persistent coronary aneurysms without stenosis over the 10- to 21-year follow-up period.

Myocardial infarction in children presents with different symptoms from that in adults. A review of 195 cases of myocardial infarction due to KS in children in 74 hospitals in Japan indicated that the main symptoms were shock, unrest, vomiting, and abdominal pain; chest pain was most common in older children (28). In 63% of children, the attack occurred during sleep or at rest, and 37% of attacks were asymptomatic. These findings emphasize the need for a very high index of suspicion to make the diagnosis. KS patients with myocardial infarction have typical electrocardiographic and cardiac enzyme changes.

Although coronary artery aneurysms are the most significant cardiovascular complication in KS, noncoronary complications also occur. Myocarditis is the most common noncoronary complication and is present in at least 50% of patients with acute KS. Myocarditis is often clinically manifested by tachycardia

that is excessive for the degree of temperature elevation. Electrocardiographic changes such as a prolonged PR interval, ST-T segment changes, and decreased voltage of R waves may indicate the presence of myocarditis. Rarely, myocarditis is severe enough to cause congestive heart failure and cardiogenic shock. Pericarditis with pericardial effusion occurs in about 25% of patients in the acute phase (30). Valvular disease, predominantly mitral regurgitation, has been seen in about 1% of patients and occasionally has required valve replacement (3, 25, 30, 37).

KS results in vasculitis of the large to medium-sized arteries; weakening of the arterial wall leads to dilatation and aneurysm formation. Some patients experience mild vasculitis, which is insufficient to cause weakening of the wall of the coronary artery; the long-term consequences of this less severe vasculitis is unknown. The vasculitis of KS also may affect other non-coronary medium-sized arteries throughout the body. Systemic artery aneurysms occur in about 2% of patients, generally in those who also have coronary artery aneurysms (30). The most commonly affected arteries are the renal, paraovarian or paratesticular, mesenteric, pancreatic, iliac, hepatic, splenic, and axillary arteries (43, 59). Since arteritis in these vessels is less likely to be the cause of death in KS than is coronary arteritis, this complication has received less attention. It is likely that vasculitis without aneurysm formation occurs in many vessels in KS patients with coronary disease; the true extent of the vasculitis is probably apparent only at autopsy (43, 59).

The long-term implications of resolution of coronary artery aneurysms are unknown. Such vessels have been shown to have lower distensibility (40) and reduced vasodilatory response to isosorbide dinitrate (90) than normal vessels do. Intravascular ultrasonography has revealed that areas of coronary artery with resolved aneurysms are not normal blood vessels but have a remarkably thickened intima-media complex (89, 94). One group has reported a generalized decrease in systemic endothelial cell function following KS (18). Whether childhood KS results in an increased risk of atherosclerosis when the patient reaches adulthood is unknown, but this is of potential concern. There are reports of young adults with ischemic coronary disease most consistent with sequelae of KS (9, 31).

Studies of lipid profiles following KS have yielded conflicting results. Although these profiles are clearly abnormal during acute KS, they may be altered during many acute infectious and inflammatory processes as part of the acute-phase response. Further study is required to determine whether any consistent lipid abnormalities are present in the long term in individuals following KS (60, 81).

Although certain clinical factors appear to be predictive of increased risk for the development of coronary disease, no scoring system to date has been shown to be sufficiently sensitive in the acute phase of illness to allow for selective treatment of patients based on risk. However, it is useful for the clinician to be aware of some of the features that suggest a poorer prognosis: duration of fever for more than 16 days, recurrence of fever following an afebrile period of at least 48 h, arrhythmias other than first-degree heart block, male gender, age younger than 1 year, cardiomegaly, and low platelet count, hematocrit, and albumin level in serum at presentation (6, 58a, 83, 87).

PATHOLOGY

KS causes a vasculitis which is most severe in the medium-sized arteries; however, careful pathologic examination at autopsy reveals that small arterioles, larger arteries, capillaries, and veins are also affected to a lesser extent (5, 21). Fatal KS is pathologically indistinguishable from infantile periarteritis

nodosa; therefore, these two diseases are now accepted as representing the same entity (43). In the acute stage of KS, systemic inflammatory changes are evident in many organs. Myocarditis, pericarditis, valvulitis, aseptic meningitis, pneumonitis, lymphadenitis, and hepatitis may be present and are manifested by the presence of inflammatory cells in the affected tissues (21).

In the early stages of KS vasculitis, edema of endothelial cells with nuclear degeneration is seen, along with edema and mild inflammatory changes in the adventitial layer (4). Inflammatory cells are at first polymorphonuclear cells but rapidly change to mononuclear cells (59). In the larger arteries with vasa vasorum, inflammatory infiltration is typically seen around and in these vessels (4). In more severely affected vessels such as the coronary artery, the media develops inflammatory changes with edema and necrosis of smooth muscle cells; thus, the process involves the entire vascular wall. Splitting and fragmentation of the internal and external elastic laminae may be observed in severely affected vessels (4). These changes eventually make the layers of the wall indistinguishable. The wall loses its structural integrity, forming an aneurysm. At 1 to 2 months following the onset of illness, inflammatory cells begin to disappear and fibrous connective tissue, consisting of collagen and elastic fibers, begins to form within the structure of the vessel wall. The intima proliferates and becomes thickened. Fibrinoid necrosis, if it is present, is generally confined to the area between the thickened intima and adventitia and probably represents necrotic smooth muscle cells. Over time, the wall may become stenotic or occluded, either by the stenosis itself or by superimposed thrombus. In some cases, calcification occurs, and thrombus within the vessel lumen may become organized and recanalized (4, 59, 82).

It has been suggested that the extent of inflammation in various arteries in acute KS is influenced by hemodynamics, since vessels which contain features of elastic and muscular arteries are most often affected and areas of arterial branching are particular targets (59).

Few studies of the nature of the inflammatory infiltrate in the vessel wall or myocardium have been performed. Terai et al. demonstrated the presence of helper T cells and monocytes/macrophages in the arterial wall of one patient with fatal KS (99). We have recently demonstrated the presence of many plasma cells in the vascular walls of seven patients with fatal cases; incubation of the vascular tissues with antibodies to Ig isotypes revealed that most of these plasma cells were producing IgA (73). We speculate that the presence of IgA-producing cells within the vascular wall indicates an antigen-driven immune response to an etiologic agent with a respiratory or gastrointestinal portal of entry. Examination of the clonality of the IgA genes produced in the vascular wall in patients with KS may provide further information about the etiology of the illness.

THERAPY IN THE ACUTE STAGE

Treatment of acute KS in the first 10 days of illness with a single 2-g/kg dose of IVGG and with aspirin at 80 to 100 mg/kg/day reduces the prevalence of coronary artery abnormalities from approximately 20% in patients treated with aspirin alone to 4% (62). This nonspecific but highly effective therapy for KS was first used in Japan (22), and was subsequently studied for its efficacy in KS patients in the United States (62, 63). The second U.S. multicenter IVGG study provided evidence for the efficacy of a large, single dose of IVGG rather than the multiple daily doses used previously (62, 63). IVGG not only reduced the prevalence of coronary disease in

KS patients but also resulted in rapid defervescence and more rapid normalization of acute-phase reactants than is seen in patients treated with aspirin alone (62, 63). In addition, IVGG improves myocardial function in patients with acute KS (61). More specific therapy awaits the discovery of the etiologic agent of KS.

Aspirin has been used to treat KS patients for many years and is administered for both its anti-inflammatory and antithrombotic effects. During the acute phase of illness, aspirin is administered at 80 to 100 mg/kg/day every 6 h, in addition to IVGG. On day 14 of illness, when the fever has resolved, the dose of aspirin is reduced to antithrombotic doses of 3 to 5 mg/kg/day as a single daily dose. The pharmacokinetics of aspirin in children with acute KS is altered, with decreased absorption and increased clearance of the drug (39); therefore, some children with acute KS do not achieve a therapeutic salicylate level despite the administration of high doses of aspirin. Because this does not appear to be a clinically significant problem in most cases, it is generally not necessary to monitor aspirin levels. Somewhat lower aspirin doses (30 to 50 mg/kg/day) are used in the treatment of acute KS in Japan.

In the United States, a single dose of 2 g of IVGG per kg given over 10 to 12 h is recommended for the treatment of KS, but in Japan, lower doses are sometimes used because of cost issues. The optimal dose of IVGG for the treatment of KS is unknown, but there is a strong inverse relationship between the IVGG dose and the prevalence of coronary artery abnormalities at follow-up (102). The mechanism of action of IVGG in KS is unknown, but it may be due to an immunologic blockade of Fc receptors by IVGG, due to the presence of antibody against the specific etiologic agent, or due to some other mechanism (86). The comparative efficacy of various IVGG products is largely unknown, although side effects have been reported to differ (71). The effect of IVGG has been studied only in the first 10 days of illness in KS. However, consideration should be given to treatment of patients after the 10th day if they are persistently febrile, since fever is a risk factor for the development of coronary artery disease in KS. In general, patients who present with desquamation and a history consistent with KS who have been afebrile for many days are not treated with IVGG; there are no data to suggest efficacy in this situation, and IVGG is unlikely to prevent coronary disease after the acute phase of illness when the inflammatory response has subsided.

Approximately 10% of KS patients have persistent fever 48 h after IVGG infusion. These IVGG "nonresponders" represent a significant clinical dilemma, since prolonged fever is a recognized risk factor for the development of more severe coronary disease. Limited uncontrolled data suggests that these patients may benefit from an additional infusion of IVGG (93). Since the disease is self-limited and eventually resolves without specific therapy, it is unknown whether some patients retreated with IVGG might have defervesced on their own. A few patients remain febrile after a second infusion of IVGG. Currently, there are no data upon which to base a recommendation for appropriate therapy of these patients. One report has suggested a possible benefit of pulsed steroid therapy in such IVGG failures (105). This therapy requires cautious further study before it can be recommended, because Japanese data have suggested previously that steroids may aggravate coronary artery disease in patients with KS (32, 42).

MANAGEMENT AFTER THE ACUTE PHASE

Patients with acute KS should have a complete blood count with differential and platelet count and an erythrocyte sedi-

mentation rate performed as part of their initial laboratory evaluation. In addition, a baseline echocardiogram should be performed. This may reveal a pericardial effusion, and the coronary artery size is generally still normal, although occasionally abnormalities are seen as early as 7 to 10 days of illness. If the patient has a typical response to IVGG, the fever will abruptly resolve. We prefer that patients remain hospitalized, with frequent temperature measurements, until they have been afebrile for 24 h; prolonged fever in KS is a risk factor for coronary disease and must be viewed with great concern by the clinician. Patients should have weekly or every-other-week physical examinations during the subacute and convalescent phases of illness. Generally, a repeat echocardiogram is obtained at 2 to 3 weeks following the onset, and again at 6 to 8 weeks following the onset if the first study is normal. The blood count and sedimentation rate are monitored at approximately the same intervals. If the sedimentation rate has normalized at 6 to 8 weeks of illness and the echocardiograms obtained at that time and previously are also normal, we discontinue administration of aspirin. There are no significant data to indicate that long-term coronary artery abnormalities will develop in those with normal coronary arteries at 2 months after the onset of illness. Patients who develop coronary artery dilatation or aneurysm are kept on aspirin therapy indefinitely, even after apparent resolution of the abnormalities by echocardiogram, in view of data indicating that the vessel wall in an area of regressed aneurysm is not normal (89, 94).

Administration of live parenteral virus vaccines such as the measles-mumps-rubella vaccine and the varicella vaccine should be delayed for 6 to 11 months after administration of IVGG, since the presence of specific antiviral antibody in the product may interfere with the immune response to the vaccine. If a significant exposure to varicella virus occurs in an unvaccinated KS patient on chronic aspirin therapy, discontinuation of aspirin should be strongly considered to avoid the risk of Reye's syndrome should varicella develop. If there is a high risk of thrombosis, aspirin could be temporarily replaced by another antiplatelet agent such as dipyridamole (2 to 3 mg/kg two or three times a day). Influenza vaccine should similarly be considered in KS patients on chronic aspirin therapy to reduce the possible risk of Reye's syndrome.

It is important to emphasize that echocardiographic studies in patients with KS should be performed by a trained pediatric cardiologist. Cardiologists who specialize in treating adults do not have expertise in the measurement of coronary artery diameter in young children. Children who develop significant coronary artery disease should be managed in consultation with the pediatric cardiologist, who will assist in decisions about the timing of subsequent echocardiographic studies, the need for anticoagulation therapy such as coumadin in patients with large aneurysms, and the timing and need for other studies to assess cardiac function such as stress testing and coronary angiography.

Management of KS patients with aneurysms is dependent upon the severity of coronary disease. Patients with small to medium solitary aneurysms should be maintained on long-term aspirin therapy but should not be restricted in activities except for avoidance of competitive contact athletics with endurance training. Stress testing may be suggested by the pediatric cardiologist for older children, and coronary angiography may be indicated if stress testing suggests the possibility of coronary artery stenosis. Dobutamine stress echocardiography may be particularly useful in small children unable to cooperate with exercise stress testing (66).

Patients with multiple small to medium-sized aneurysms or one or more giant coronary artery aneurysms should be main-

tained on aspirin therapy with or without coumadin anticoagulation. Physical activity in the first decade of life is unrestricted, but after that time it should be determined by the pediatric cardiologist on the basis of the results of stress testing often with a myocardial perfusion scan. If coronary obstruction is suspected by these studies and confirmed by coronary angiography, consideration should be given to the therapeutic options of bypass grafting, balloon angioplasty, or other procedures to restore coronary blood flow. If myocardial infarction related to thrombosis occurs, acute thrombolytic therapy may be needed. Recommendations for the management of KS patients with coronary disease of various degrees of severity have been published by the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, of the American Heart Association (15).

Japanese experience indicates that the patency rate of arterial bypass grafts, which grow with the child, greatly exceeds that of venous grafts, which do not, in KS patients. In a study of 168 KS patients who underwent bypass grafting in Japan, the patency rate at 85 months after the operation was 77% for arterial grafts compared to 46% for venous grafts (36). A small group of KS patients worldwide have undergone heart transplantation (12); these patients were not candidates for revascularization because of distal coronary stenosis or aneurysms and/or severe irreversible myocardial dysfunction.

CONCLUSIONS

KS is a fascinating illness of very young children that is seen worldwide. It is an acute, self-limited vasculitis which has become the most common cause of acquired heart disease in children in the United States and Japan. KS causes significant coronary artery disease, which may lead to myocardial infarction and sudden death. Clinical and epidemiologic features support an infectious cause, but the etiology of the illness remains unknown. Clearly, additional research on the etiology and pathogenesis of KS is urgently needed to allow for improved diagnosis, more specific therapy, and, ultimately, prevention of the disorder.

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