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Lesson of the Week

Delayed diagnosis of Kawasaki disease presenting with massive lymphadenopathy and airway obstruction

David Burgner, Marino Festa, David Isaacs

Kawasaki disease should be considered in any child with persistent fever as early treatment improves outcome

Kawasaki disease is an acute, self limiting febrile illness of infants and young children. In children under 5 years of age the incidence varies from about 3-6 per 100 000 in Europe[1] to 90 per 100 000 in Japan.[2] It causes coronary artery lesions in about 20% of untreated patients, up to 2% of whom die.[3] Diagnosis is based on the presence of a prolonged fever (of more than five days duration) plus four of the following five signs: conjunctival injection, changes in the mucous membranes, changes in the peripheries (erythema of the palms and soles and swelling of the hands and feet), rash, and lymphadenopathy. The clinical features may be supplemented by non-specific laboratory investigations—for example, thrombocytosis and an increased erythrocyte sedimentation rate—but there is no specific diagnostic test. Prompt diagnosis permits early treatment with intravenous immunoglobulin, which reduces the incidence of coronary artery lesions by up to two thirds.[4,5]

Lymphadenopathy is the least constant of the diagnostic features of Kawasaki disease, occurring in 50-75% of patients; the other clinical criteria occur in about 90%.[3] We describe a case of Kawasaki disease in which massive lymphadenopathy was the overriding clinical feature, resulting in upper airway obstruction and delayed diagnosis.

Case report

A previously well and fully immunised 4 year old white boy presented with a 10 day history of sore throat and fever that was unresponsive to oral antibiotics. Two days earlier he had developed a painful swelling in the right side of his neck which continued to enlarge. Initial examination showed that he was feverish, with a painful torticollis. He had large red tonsils, and the right tonsil was displaced medially. There was a large (5 × 3 cm), tender, and erythematous swelling in the posterior triangle of the right side of the neck. His respiratory function was not compromised, and none of the other features of Kawasaki disease was evident.

An initial full blood count showed moderate leucocytosis (16.4×10^9/l) and normal numbers of platelets. Cervical lymphadenitis was diagnosed and he was treated with intravenous ampicillin and flucloxacillin. Over the next 24 hours he remained unwell and feverish, and the cervical mass increased, with erythema and oedema spreading caudally to the chest wall. The antibiotic regimen was changed to cefotaxime, metronidazole, and penicillin to cover a possible polymicrobial fasciitis.

Respiratory embarrassment and increasing dysphagia necessitated intubation and ventilation. A fine needle aspiration of the neck mass gave only scanty return, which was sterile on bacterial culture. A cervical computed tomogram showed no focal collection but pronounced lymphadenopathy (fig 1). On the third day of admission rash, palmar erythema, non-purulent conjunctivitis, palmar erythema, a scalded skin appearance of his buttocks, together with pronounced thrombocytosis (537×10^9/l) and leucocytosis (26.1×10^9/l) developed. Kawasaki disease was diagnosed clinically and he was given intravenous immunoglobulin (2 g/kg) and low dose aspirin (2 mg/kg). His fever immediately subsided. His initial echocardiogram was normal and he was extubated uneventfully. Three days later his palmar and groin rash desquamated. A repeat echocardiogram at six weeks was normal. An antistreptolysin O titre taken two weeks into his illness was negative (< 150 IU/ml: normal range < 200 IU/ml).

Comment

This child eventually fulfilled the diagnostic criteria for Kawasaki disease; the negative culture and antistreptolysin O titre made a diagnosis of streptococcal or staphylococcal lymphadenitis less likely. The presentation of Kawasaki disease with predominantly upper airway symptoms is rare but well recognised.

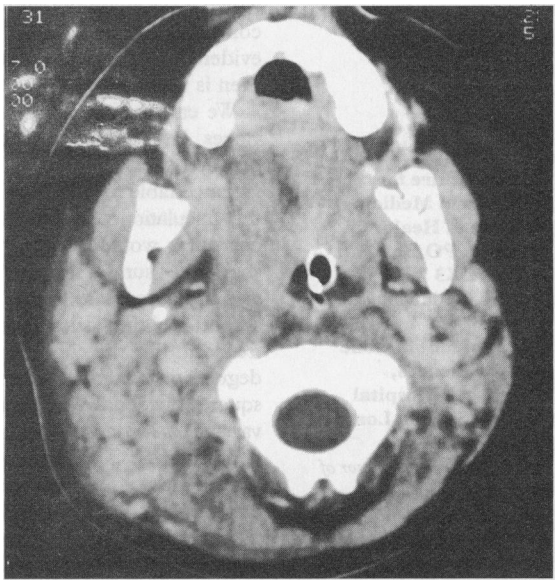

Fig 1—*Transverse cervical computed tomogram showing pronounced lymphadenopathy and oedema.*

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Adenopathy occurs more commonly in older children and may reflect greater immunological maturity.[6] In one large series 11 of 450 patients with Kawasaki disease presented with cervical lymphadenitis as the primary complaint.[6] The neck nodes were large and often erythematous and tender, although pronounced cellulitis, as seen in our patient, was not described. The diagnosis of Kawasaki disease was delayed in most of the children; three developed coronary artery lesions. None required intubation. The cervical lymphadenopathy and fever resolved promptly in those given intravenous immunoglobulin. Kawasaki disease may also present with upper airway inflammation[7] or mimic a retropharyngeal abscess.[8]

In the United States Kawasaki disease is the leading cause of acquired heart disease in childhood.[3] In most cases cardiac lesions can be prevented by prompt diagnosis and treatment. Not all of the diagnostic features of Kawasaki disease may be obvious on presentation, and one particular sign, such as lymphadenopathy, may predominate. The diagnosis of Kawasaki disease, however, should always be considered in a young child with unexplained and prolonged fever, and careful and repeated examination is needed as the classical features of Kawasaki disease may only become evident over time.

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Statistics Notes

Comparing several groups using analysis of variance

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This is the 20th in a series of occasional notes on medical statistics

Many studies, including most controlled clinical trials, contrast data from two different groups of subjects. Observations which are measurements are often analysed by the t test, a method which assumes that the data in the different groups come from populations where the observations have a normal distribution and the same variances (or standard deviations). While the t test is well known, many researchers seem unaware of the correct method for comparing three or more groups. For example, table 1 shows measurements of galactose binding for three groups of patients. A common error is to compare each pair of groups using separate two sample t tests[1] with the consequent problem of multiple testing.[2] The correct approach is to use one way analysis of variance (also called ANOVA), which is based on the same assumptions as the t test. We compare the groups to evaluate whether there is evidence that the means of the populations differ. Why then is the method called analysis of variance?

We can partition the variability of the individual data values into components corresponding to within and between group variation. Table 2 shows the analysis of variance table for the data in table 1. Fuller details about the calculations can be found in textbooks[3] (although a computer would generally be used). The first column shows the "sum of squares" associated with each source of variation; these add to give the total sum of squares. The second column shows the corresponding degrees of freedom. For the comparison of k groups there are k–1 degrees of freedom. The third column gives the sums of squares divided by the degrees of freedom, which are the variances associated with each component (perhaps confusingly called mean squares). When there are two groups the residual variance is the same as the pooled variance used in the two sample t test.

Analysis of variance assesses whether the variability of the group means—that is, the between group variance—is greater than would be expected by chance. Under the null hypothesis that all the population means are the same the between and within group variances will be the same, and so their expected ratio would be 1. The test statistic is thus the ratio of the between and within group variances, denoted F in table 2. The larger the value of F the more evidence there is that the means of the groups differ. The observed value of F is compared with a table of values of the F distribution using the degrees of freedom for both the numerator and denominator—this value is sometimes written as $F^{[2,39]}$. For the data in table 1 an F value greater than 3.24 would be significant with $P<0.05$. The observed value is far larger than this, giving strong evidence that the three populations of patients differ. With two groups one way analysis of variance is exactly equivalent to the usual two sample t test, and we have $F=t^2$.

When the groups are significantly different we will often wish to explore further to see where the differences lie. When we compare more than two groups

Table 1—*Measurements of galactose binding in three groups of patients (data from M Weldon)*

Crohn's disease	Ulcerative colitis	Controls	
1343	1264	1809	2850
1393	1314	1926	2964
1420	1399	2283	2973
1641	1605	2384	3171
1897	2385	2447	3257
2160	2511	2479	3271
2169	2514	2495	3288
2279	2767	2525	3358
2890	2827	2541	3643
	2895	2769	3657
	3011		
	3013		
	3355		
Mean 1910.2	2373.8	2804.5	
SD 515.7	727.1	526.8	

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