

SHORT REPORT

Fatal Kawasaki disease caused by early occlusive coronary artery disease

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In Kawasaki disease severe coronary artery narrowing may develop at an early stage despite treatment with gammaglobulin and in the absence of prominent aneurysm formation or thrombosis. Vaso-occlusive disease may not be clinically or echocardiographically apparent until very severe.

Two children with Kawasaki disease (KD) died from severe fibrocellular proliferation of the coronary arteries causing fatal myocardial infarction within four months of presentation. They received intravenous gammaglobulin (IVIG) on days 8 and 10 from the onset of illness and in neither was prominent aneurysmal dilatation or intramural thrombus present.

CASE 1

A previously well 6 month old white boy developed fever, abdominal distension, vomiting, rash, irritability, redness of lips, and cervical lymphadenopathy. KD was diagnosed and treated with 2 g/kg of IVIG and aspirin 80 mg/kg/day on day 8. Echocardiograms on admission and day 10 showed no coronary artery dilatation.

On day 20 further IVIG 2 g/kg was given because of continued irritability. Hb remained approximately 80 g/l; platelets peaked at $2316 \times 10^9/l$ (day 16) falling only to $964 \times 10^9/l$ (day 46) when aspirin was reduced to 5 mg/kg/day. C reactive protein (CRP) peak was 84 mg/l (day 12) declining to 28 mg/l (day 46). Echocardiogram on day 50 showed mild left coronary artery dilatation to 3 mm diameter and normal right coronary artery.

On day 95 he was readmitted with cardiac failure and shock. Biochemical, ECG, and echocardiographic features indicated myocardial infarction. He deteriorated rapidly and arrangements were made for transport to the national paediatric cardiac centre, but he died before transfer.

Postmortem findings showed pallor of the endocardium of the left ventricular free wall and interventricular septum. There was prominent segmental mural thickening and luminal stenosis affecting all three main coronary arteries and branches, with a mild degree of aneurysmal dilatation of proximal left anterior descending (LAD) and right coronary arteries. Further small local aneurysmal dilatations, 2-3 mm luminal diameter, were found in the right coronary artery 10 and 20 mm from the ostium and on a side branch at 15 mm.

Histological examination revealed extensive patchy acute subendocardial myocardial infarction. Multiple epicardial coronary artery branches showed circumferential mural fibrosis replacing both intima and media, often with notable luminal stenosis. The mural fibrous tissue contained patchy, generally mild, chronic inflammatory cell infiltrate, and the latter was also present in surrounding congested epicardial tissue (fig 1). No luminal thrombi were seen.

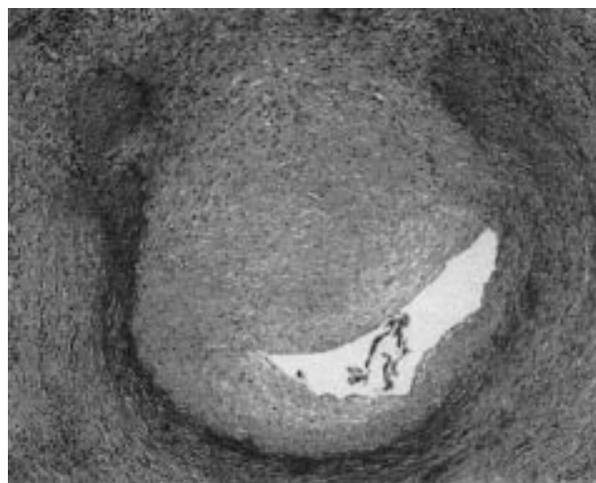


Figure 1 Case 1: epicardial and intramural infiltrate.

CASE 2

A previously healthy 4 year old white boy presented with three days of fever, lethargy, and irritability. He had bright red cheeks and lips, truncal rash, bilateral conjunctivitis, and periungual desquamation. Hb was 105 g/l, WBC $24.4 \times 10^9/l$, and erythrocyte sedimentation rate 42 mm/h. On day 10 of his current illness KD was diagnosed and treated with 2 g/kg IVIG and high dose aspirin. Echocardiography showed diffuse dilatation of the left and right coronary arteries to 4 mm and 5 mm diameter respectively and a possible left ventricular regional wall abnormality. Two days later he received another 2 g/kg dose of IVIG for persistent fever and was discharged the next day, afebrile.

Over the next 10 weeks he remained unwell with haemolytic anaemia, arthritis, abdominal pain, and intermittent fever. Repeated echocardiography showed 4-5.5 mm diameter coronary arteries. He developed unstable angina with ST elevation on ECG and was admitted to the national paediatric cardiology centre.

Echocardiography showed significantly impaired left ventricular function. The left main coronary artery and proximal LAD remained uniformly 4 mm and there appeared to be a giant aneurysm 8 mm in diameter just proximal to the first septal branch. The circumflex was possibly occluded but no thrombi were seen. A heparin infusion was started and 16 hours later, when considered to be more haemodynamically stable, he was taken for catheterisation. After induction of general anaesthesia he became pulseless with complete heart block, and died despite intensive resuscitation efforts.

Abbreviations: CRP, C reactive protein; IVIG, intravenous gammaglobulin; KD, Kawasaki disease; LAD, left anterior descending

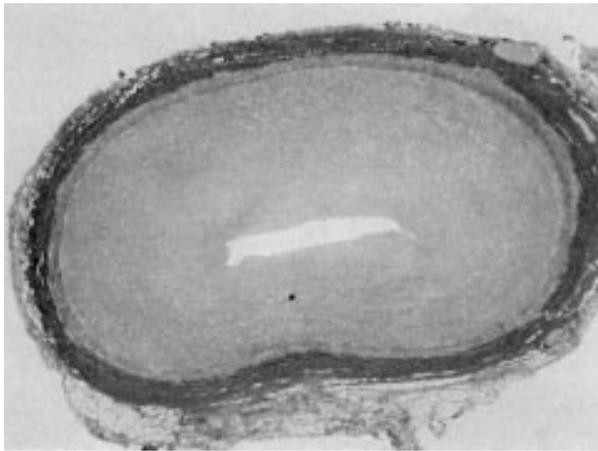


Figure 2 Proximal LAD luminal stenosis.

Postmortem examination revealed extremely thick walled stenotic and variably dilated coronary arteries but no giant aneurysms. At the level of the first septal branch the LAD was dilated externally, thus accounting for the echocardiographic appearance. Histology showed notable fibrocellular intimal proliferation causing severe luminal stenosis of all three coronary arteries (fig 2) and myocardial infarction. There were features of widespread systemic arteritis affecting other large and middle sized vessels with significant stenoses of the splenic, renal, superior, and distal mesenteric arteries. Duodenal infarction had occurred.

DISCUSSION

The two children died of severe obliterative coronary artery disease following KD within four months of the acute illness. Neither had echocardiographic or ECG evidence, immediately prior to the terminal phase of illness, indicating the severity of coronary artery stenosis. Case 1 had minimal coronary artery dilatation at any stage. Case 2 had dilated but not giant coronary artery aneurysms at diagnosis and six weeks later: in retrospect the arteries were extremely thick walled with an internal diameter of only 5 mm

There have been few reports of children with KD, treated or untreated, developing severe occlusive coronary artery disease without prominent aneurysm formation at any stage of their illness.¹⁻³

Most treatment guidelines advise treatment before day 10 of illness; however, in a comprehensive analysis of over 35 000 cases by Zhang *et al*, patients receiving treatment before the eighth day had significantly better cardiac outcomes than those treated later.⁴ Gammaglobulin was administered beyond the seventh day in both of our cases and was clearly ineffective in preventing the development of severe coronary artery disease. Unfortunately there can be difficulties in making a rapid diagnosis of KD; published data suggest that the median time of diagnosis is approximately nine days from onset of the illness.⁵

There is no reliable way of identifying children at risk of developing aggressive vaso-occlusive disease beyond speculating that they may share risk factors for more severe cardiac disease in general and aneurysm formation in particular. These are: young or relatively old age of onset, delayed diagnosis and treatment, and more laboratory evidence of increased inflammatory markers at diagnosis or after treatment.

Some authorities advocate that all children with KD receive coronary angiography at the eighth week following diagnosis; our cases support such an approach.⁶ However, the procedure is not without risk and there is no evidence that such an approach alters long term management or outcome.

KD remains a clinical diagnosis without specific markers predictive of coronary vascular outcome. In most instances early administration of IVIG will prevent serious cardiovascular sequelae. When abnormalities develop they can usually be adequately diagnosed and followed by echocardiography. Clearly there exists a small group of children with KD who, despite conventional therapy and normal or unremarkable echocardiographic appearances, have progressive coronary arteritis. This may cause very severe luminal stenosis which does not become clinically apparent until overt ischaemia or infarction results. The challenge remains to identify those children at risk, and to develop effective therapy to arrest or reverse coronary artery narrowing.

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