Kawasaki disease manifesting with acute cholangitis

A case report

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Summary

A 3-year-old boy, who developed the signs and symptoms characteristic of Kawasaki disease, is described. The child also had an 8 cm tender hepatomegaly. Hydrops of the gallbladder could not be shown. Liver biopsy showed marked infiltration of inflammatory cells, including neutrophil and eosinophil leukocytes in the portal tracts involving the periphery of the portal arteries and veins, and acute inflammation of the bile ducts with neutrophil and eosinophil infiltration of the walls. Overt cholangitis has been described only once before in Kawasaki disease, when a viral agent was suggested as being important in the pathogenesis.

Although the clinical and laboratory findings in cases of Kawasaki disease clearly suggest an acute infection — as they did in this case — no aetiological agent has yet been incriminated. The possibility of a drug-induced auto-allergic or hypersensitivity state is considered. Evidence for such a state includes a history of drug administration, pathological findings similar to peri-arteritis nodosa — a condition often associated with a hypersensitivity state — the presence of eosinophils in the lesions and a response to treatment with aspirin, a drug known to ameliorate hypersensitivity states.

Since 1967, when Kawasaki of the Japan Red Cross Hospital in Tokyo described a condition he called mucocutaneous lymph node syndrome, now generally known as Kawasaki disease, many cases have been identified in Japan. In 1976 Melish and associates described cases occurring in Hawaii and soon afterwards Goldsmith and his associates described a case in New York. Since then several thousand cases have been reported to the Centers for Disease Control in the USA and the disease has been recognised world-wide. The clinical features, diagnostic criteria and pathology have been clearly defined.1,2

Case report

A 3-year-old boy first became ill on 4 September 1987 complaining of severe abdominal cramps; however, he did not vomit or have diarrhoea. The mother administered paracetamol. Two days later the patient was diagnosed as having pharyngitis and penicillin was prescribed. He became lethargic and complained of pain in the flanks. Subsequently he developed conjunctivitis, gingivitis and complained of pain in the flanks. Subsequently he developed conjunctivitis, gingivitis and complained of pain in the flanks. Subsequently he developed conjunctivitis, gingivitis and complained of pain in the flanks. Subsequently he developed conjunctivitis, gingivitis and complained of pain in the flanks. Subsequently he developed conjunctivitis, gingivitis and complained of pain in the flanks. Subsequently he developed conjunctivitis, gingivitis and complained of pain in the flanks. Subsequently he developed conjunctivitis, gingivitis and complained of pain in the flanks.

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diuretics. The cervical, occipital and axillary glands were enlarged and slightly tender, there was a maculopapular rash, the hands and feet were swollen and oedematous, the liver was enlarged to 8 cm below the costal margin and was slightly tender, the tip of the spleen was palpable and ascites was present. He had a stiff neck and was obtunded. Thereafter the skin of the hands and feet began peeling.

Laboratory investigations showed marked anaemia (haemoglobin 7.6 g/dl), leucocytosis of 18 400/µl with 83% neutrophil leucocytes and the presence of an occasional metamyelocyte. Serological tests for Toxoplasma, Toxocara and schistosomiasis, mycoplasma, Leptospira, arboviruses, rubella, hepatitis B surface antigen, human immunodeficiency virus, antinuclear factor and rheumatoid factor gave negative results. Tests showed high-titre antibody against Coxsackie B2 virus but virus was not isolated from the faeces, suggesting that the antibody was the result of a recent not a present infection. On repeat lumbar puncture the CSF showed a pleocytosis and a raised protein count. Initial liver function tests showed a total serum bilirubin value of 25 µmol/l (direct 5 µmol/l) and the alkaline phosphatase level increased to 448 UI. The serum alanine aminotransferase and aspartate aminotransferase levels remained normal. The serum alkaline phosphatase and bilirubin levels returned to normal after definitive therapy.

On 23 September an open liver biopsy was performed. An enlarged pale smooth liver was found. The gallbladder was not noted to be hydropic on ultrasonography or by direct inspection; no calculi were present. The section of the liver stained with haematoxylin and eosin revealed an acute cholangitis with marked inflammatory infiltration of the portal tracts, which showed peri-arteritis and perihepatitis and a considerable eosinophilia, and an acute cholangitis with neutrophil and eosinophil leucocyte infiltration of the bile ducts (Figs 1 and 2). This patient had all the signs of Kawasaki disease, in addition to biopsy-proven acute cholangitis.

**Discussion**

This patient presented the typical picture of Kawasaki disease and all the salient features characteristic of this condition were noted.1,2,5 namely fever lasting more than 5 days and not responding to antibiotics; swelling of the eyes and congestion of the conjunctivae; red, dry and fissuring lips; prominent tongue papillae and red and inflamed mucous membranes of the mouth and pharynx; oedema of the extremities with red palms and soles, followed in convalescence by desquamation of the skin of the fingertips and toes; a polymorphous nonvesicular maculopapular rash on the trunk and acute lymphadenopathy of the cervical glands. Other features in keeping with this diagnosis were the onset of severe abdominal cramps and meningo-encephalitis. A full blood count showed a leucocytosis of over 18 000 white cells/µl with a marked neutrophilia and the CSF a pleocytosis with a raised protein level, but no bacterial antigens. The blood cultures gave a negative result. Late in the course of the illness, the patient developed a marked thrombocytosis of over 800 000 platelets/µl.

Of special interest were the findings on examination of the liver biopsy, which was taken during the acute phase of the condition. This showed acute inflammation of the bile ducts within the liver with moderate infiltration of the portal tracts with acute inflammatory cells including round cells and neutrophil and eosinophil leucocytes. The mucous membrane of the bile ducts showed infiltration of neutrophil and eosinophil leucocytes, clearly indicating that the patient had acute cholangitis. This cholangitis presumably was part of the acute inflammation of the mucous membranes characteristic of this condition, the notable manifestation clinically visible is the acute inflammation of the mucous membrane of the mouth and lips followed later by desquamation.

Cholecystitis with gallbladder hydrops occurs in 5 - 11% of patients3 and was first described in 1976.4 Acute cholangitis has been described only once previously in association with gallbladder hydrops. Thus, although raised liver enzymes occur fairly frequently,2 overt cholangitis has been an unusual finding.

The aetiology of this acute inflammation remains undetermined although this patient had a marked leucocytosis with neutrophilia suggestive of an acute bacterial infection; however, blood cultures remained negative and no aetiological agent was isolated. It is of interest, however, that this patient showed a positive result in the Weil-Felix test with agglutination Proteus OX2 in a relatively low titre of 1:100, possibly suggestive of a rickettsial infection.7 Suspicion has also been cast on Propionibacterium acnes, which has been cultured from
lymph nodes and occasionally recovered from the blood, and on a possible retrovirus infection. The antibodies to Coxsackie B viruses were in high titre — in the case of Coxsackie B2 in a titre of 1:640 and Coxsackie B4 in a titre of 1:320, suggestive of a recent infection with this virus, but it was not isolated from the faeces at the time of the acute illness, suggesting that the infection had taken place some time in the recent past.

The failure to find or identify an aetiological agent, of course, does not exclude the possibility of an infection; however, it suggests that other causations should be, and indeed have been, considered. Prominent among these is a hypersensitivity or an auto-allergic state, possibly related to drugs used in treatment of acute febrile episodes in infants and children or induced by the administration of a vaccine such as BCG.

A hypersensitivity state resulting from tuberculosis is now strongly suspected as the cause of Takayasu disease, which involves the arteries, as does Kawasaki disease in many cases, although the pathology of the two conditions differs considerably. Of great interest in this regard has been the finding in Japan by a number of workers, including Tornisaku Kawasaki himself as long ago as 1967, that patients with Kawasaki disease during the course of their illness often present with erythema and induration at the sites of inoculation of BCG and PPD, and even in some cases vesicle formation at the site. Such a reaction clearly suggests a hypersensitivity state and that this may manifest as peri-arteritis nodosa, which the arterial lesions of Kawasaki disease closely resemble. In this patient histological study of the liver biopsy showed that, in addition to the infiltration of neutrophil leucocytes in the portal tracts, there was a significant number of eosinophil leucocytes, suggestive of a hypersensitivity state.

The beneficial effect of the administration of aspirin, a drug known to ameliorate hypersensitivity or auto-allergic states, is also in keeping with this possible pathogenesis. It has been noted that patients with Kawasaki disease are usually infants of well-to-do parents and this patient's mother was typical of the mothers of Kawasaki patients who are conscientious, often even over-conscientious, and tend to call in their medical practitioners at the slightest sign of illness of their children. The medical practitioner usually prescribes some drug or antibiotic for treatment. Thus, these patients frequently receive drugs or antibiotics in early childhood, increasing their liability to develop a drug-induced hypersensitivity state. Such mothers would also ensure that their children received a full course of vaccination, including the administration of BCG, as did this patient.

Clearly, the role of an auto-allergic or hypersensitivity state, possibly induced by the administration of a commonly prescribed analgesic or antipyretic drug to possibly genetically predisposed infants, should be further investigated for the pathogenesis of Kawasaki disease.

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REFERENCES