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FATAL KAWASAKI DISEASE (KD) DUE TO EARLY FIBROUS OBLITERATIVE CORONARY ARTERY DISEASE

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The purpose of the study is to describe 2 fatal cases of KD due to nonthrombotic obstructive coronary artery disease. Patient 1. 4yr Caucasian male, URTI, low grade fever, eventually had 4 of 5 KD criteria. Given IVIG x 2 about day 15 with no response: persistent fevers and hemolytic anaemia 1 month, small joint arthritis & arthralgias 2nd month, abdominal pains 3rd month. Initial coronary artery (CA) dilatation progressed with the development of unstable angina and low cardiac output 4 months after presentation. Died after anaesthetic induction for cardiac catheterization. Post mortem histology showed thick walled obstructed triple vessel CA disease. Histology showed marked fibrocellular intimal proliferation. There was recent myocardial and duodenal infarction. Patient 2. 6 month Caucasian male developed fever and 4 criteria for KD but no peripheral oedema or redness. Given IVIG day 8 and day 20 due to irritability without fever. Echo day 8 and day 50 showed mild CA dilatation. He represented day 95 with congestive heart failure, cardiogenic shock, poor LV function and died. Post mortem showed minor CA aneurysmal changes only. There was marked luminal obstruction caused by replacement fibrosis of the intimal and media. There was patchy chronic inflammatory infiltration.In summary, these 2 patients showed atypical KD histology with early intimal fibrosis and luminal obstruction. Conclusions:1. KD may be fatal due to early (within 3-4 months from onset) fibrotic obliterative CA disease rather than due to giant CA aneurysms and complications.2. New treatment strategies for KD are required for late presenters or non-responders to IVIG when there is evidence of continued disease process.

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ARTERIAL ANGIOGENESIS IN KAWASAKI DISEASE. A HISTOLOGIC THREE-DIMENSIONAL RECONSTRUCTIVE STUDY OF A SMALL ARTERY WITH MANY BRANCHES

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PATHOLOGICALLY NORMAL CORONARY ARTERY AFTER KAWASAKI DISEASE: A CASE REPORT

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It is well known that the sequelae of the vasculitis are observed pathologically in the coronary arteries of the patients with Kawasaki disease. It has been reported that these abnormal findings are commonly detected even in patients with clinical diagnosis of normal coronary arteries. We experienced a case of Kawasaki disease without clinically and pathologically significant coronary artery lesions. A 1 year 0 month-old male infant had an episode of Kawasaki disease. The diagnosis was established from the 5 principal clinical findings except lymphadenopathy. He also had redness of the skin at the site of BCG inoculation. He was treated with intravenous gamma globurin(1g/kg) administered two times. Echocardiographic evaluation of the coronary artery was carried out several times during the acute phase of the illness until 2 months after the onset of the disease, and no abnormal findings were obtained. His clinical diagnosis was complete recovery from the Kawasaki disease. He died suddenly when he was 2 years 1 month old. He had a febrile episode at night, and in the next morning, he was found dead. From the macroscopic autopsy findings, the cause of the death was diagnosed as an acute bronchitis. Histologically, the coronary arteries had normal architecture, and no particular sequelae of arteritis were found. Scar formation was not detected. Mild intimal thickening was observed in the proximal portion of the bilateral coronary arteries, but it was not thought to be pathologically significant. Distal portion of the coronary arteries were normal. Myocarditis and myocardial ischemia were also excluded. From these findings, we concluded that there were patients with complete recovery from Kawasaki disease, not only clinically but also pathologically. This fact may influence the follow up methods of the patients with clinically complete recovery from Kawasaki disease.

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A SUPERANTIGEN IN *LACTOBACILLUS CASEI* CELL WALL EXTRACT INDUCES CORONARY ARTERITIS: AN ANIMAL MODEL FOR KAWASAKI DISEASEE

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Lactobacillus casei cell wall extract (LCWE)-induced coronary arteritis is currently the best animal model for Kawasaki disease. Kawasaki disease is a multisystem vasculitis and the leading cause of acquired heart disease in children of the developed world. In this study, we show that responses to LCWE possess all the hallmarks of a superantigen (SAg)-mediated response. LCWE induces massive activation of naive T lymphocytes, as measured by both in vitro proliferation and production of tumor necrosis factor-alpha. Interestingly, LCWE-mediated responses require antigen presentation but not processing by accessory cells. As in the case of other known SAgs, the response to LCWE is MHC non-classically restricted, and there exists a hierarchy of differing class II MHC in the ability to present LCWE. The most compelling evidence of superantigenic activity of LCWE is its ability to induce the characteristic activation and proliferation of T cells expressing specific T cell receptor variable beta families 2, 4, 6 and 14, followed by the deletion of these reactive cells. Most importantly, superantigenic activity of LCWE correlates with its ability to induce coronary vasculitis upon injection into mice. Only LCWE preparations possessing superantigenic properties mediate cellular infiltrations in the cardiac tissue leading to coronary arteritis in vivo.Taken together, these findings demonstrate that LCWE contains a novel superantigen, the activity of which may lead to disease pathogenesis. Since LCWE-mediated coronary arteritis in mice is currently the best animal model of Kawasaki disease, understanding of the mechanisms leading from immune activation to coronary artery lesions in this model will be of great benefit in designing new treatment strategies, reducing vascular damage, and, more importantly, the significant morbidity and mortality associated with Kawasaki disease.

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THE ROLE OF T LYMPHOCYTES IN THE PATHOGENESIS OF KAWASAKI DISEASE IN AN ANIMAL MODEL

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Kawasaki disease (KD) is the most common cause of multisystem vasculitis in children in the developed world. Although KD is widely believed to be the result of an infectious agent, its etiology is still unknown. Past research has reported the possible role for bacterial superantigens in the induction of KD. Our laboratory has characterized a novel superantigen found in Lactobacillus casei cell wall extract (LCWE) which is responsible for triggering the immune response leading to KD-like coronary vasculitis in injected mice. In this study, we investigated the T helper subsets responsible for disease induction by studying expression of signature cytokines. LCWE was injected into susceptible mouse strains and RT-PCR, flow cytometry, and immunohistochemistry were performed on peripheral lymphoid tissue at set time-points. Expression and production of T helper subset associated cytokines were determined. Cardiac tissue was also similarly analyzed to determine the relationship between the immune response in the periphery to that in the heart end organ. Semi-quantitation of cytokine mRNA expression demonstrated a Th1 predominated phenotype in the periphery at days 1 to 3 post LCWE injection (IFNγ). This was followed by Th2 cytokine upregulation after day 3 (IL-4). Flow cytometry confirmed this finding by the detection of intracytoplasmic IFNγ and IL-4 at similar relative timepoints. In the heart end organ, IFNγ expression was found to be abnormally upregulated 42 days after LCWE injection. Infiltrates identified as T lymphocytes were seen as early as 3 days post LCWE injection and observed in all latter time points (up to 6 months). Different T lymphocyte subsets, at different times, are able to mediate the immunologic responses leading to inflammation. Dissecting this immune response to LCWE in mice gives important clues to the etiology of Kawasaki disease in humans.

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A SWINE MODEL OF PROTEIN MEDIATED VASCULITIS: CLINICAL IMPLICATION FOR KAWASAKI CORONARY ARTERY DISEASE

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An attempt was made to produce immune complex vasculitis in piglets, hoping to produce as an experimental Coronary Artery Disease (CAD) animal model by administrating foreign protein, mimicking Kawasaki Disease (KD). Systemic type III hypersensitivity reaction by horse serum injection with clinical implication to CAD in KD was reported only in rabbits. Our study group consisted 22 pure bred male piglets of 1.5, 2 and 3 months of age. They were divided into control group (n=6) receiving 2 doses of intravenous normal saline, and test group A (n=8), receiving 2 doses at 10 days interval of virus and mycoplasma negative gamma globulin free horse serum (HS), 2.6gm (5ml) and 5.2gm (10ml) protein/Kg body weight, respectively, test group B (n=8) received 3 doses at 5 days interval of HS, 5.2gm protein/Kg body weight. Blood samples were collected for white blood cells, platelets, vascular endothelial growth factor, liver enzymes, cholesterol and haptoglobin. Both the test groups developed rashes, echocardiographic coronary artery dilatation and histopathological changes, whereas none of the control group developed immunopathological response. All the animals were sacrificed for the histopathological, and immuno histochemistry study at different dates after the second HS injection. There were asymmetric inflammatory coronary arteritis, such as intimal proliferation, necrosis, vacuolisation, smooth muscle cells proliferation and oedematous changes in arterial walls. The piglets, which received at 5 days interval of 3 doses of HS, manifested more skin rashes and histopathological changes in the coronary arteries than those received two doses at 10 days interval. Serum sickness is a prototype of immune complex vasculitis, it is concluded that swine may serve as an experimental model for CAD mimicking KD, for testing the efficacy of pharmacologic therapies.