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SURFACE AND CYTOPLASMIC IMMUNOGLOBULIN EXPRESSION IN CIRCULATING B-LYMPHOCYTES IN ACUTE KAWASAKI DISEASE

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We have reported that IgA plasma cells infiltrate vascular and some nonvascular tissues in fatal acute Kawasaki Disease (KD). The presence of these cells in vascular tissue might reflect a large increase in circulating IgA B lymphocytes in acute KD, with non-specific entry of these cells into vascular tissue along with other inflammatory cells in the peripheral blood. To determine whether peripheral blood IgA B lymphocytes are increased in acute KD, we performed three-color flow cytometry to detect surface and cytoplasmic immunoglobulin expression (IgA, IgM, IgD, and IgG) of peripheral B lymphocytes in 15 KD patients during the acute, subacute, and convalescent stages of illness and in age-matched febrile (n=10) and afebrile (n=15) controls. Unexpectedly, absolute numbers of peripheral blood B lymphocytes expressing surface IgA were significantly lower in acute KD compared with febrile ($p=0.01$) and afebrile ($p<0.001$) age-matched controls. Absolute numbers of B lymphocytes expressing cytoplasmic IgA were also lower in acute KD compared with febrile ($p=0.003$) and afebrile ($p<0.001$) age-matched controls. Additionally, absolute numbers of B lymphocytes expressing cytoplasmic IgG was significantly lower in acute KD patients compared with febrile ($p=0.02$) and afebrile ($p<0.001$) age-matched controls. There were no differences among groups in absolute numbers of B lymphocytes expressing surface IgG, surface and cytoplasmic IgM, and surface and cytoplasmic IgD. These findings indicate that IgA plasma cells are not present in KD tissue as a result of excess numbers of IgA B lymphocytes in peripheral blood. We speculate that IgA B lymphocytes selectively move from the peripheral circulation into KD target tissues as a part of a specific IgA immune response.

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OXIDIZED LOW DENSITY LIPOPROTEIN IN PATIENTS WITH KAWASAKI DISEASE

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Background: Recently, more and more studies have demonstrated that oxidized low density lipoprotein (ox-LDL) played a key role in the pathogenesis of adult coronary artery disease. This study was to investigate the ox-LDL and general lipoprotein profiles in patients with Kawasaki disease.Methods: Forty consecutive patients with Kawasaki disease who underwent cardiac catheterization were studied prospectively. We classified the patients into two groups: Group A consisted of 12 patients with coronary artery disease, coronary stenosis or aneurysm. Group B consisted of 28 patients with normal coronary angiography. Blood sample was tested for the levels of ox-LDL autoantibody, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG).Results: There were no significant differences between two groups in gender, age of onset of disease, TG, cholesterol, HDL-C, LDL-C, and TC/HDL. There was significantly higher level of ox-LDL in group A than that in group B ($p=0.008$).Conclusions: There is significantly higher level of ox-LDL in patients of Kawasaki disease with coronary artery disease. The role of Ox-LDL needs further studies.

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THE HEART-TYPE FATTY ACID-BINDING PROTEIN (H-FABP) IS A BIOCHEMICAL MARKER OF MYOCARDIAL INJURY IN ACUTE PHASE KAWASAKI DISEASE

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Background: In acute phase Kawasaki Disease (KD), subclinical myocarditis is usually complicated. In recent studies, the heart-type fatty acid-binding protein (H-FABP) can be used as an early indicator of myocardial injury in adults. Objective: To investigate silent myocardial injury in patients with acute phase KD, we studied the serum levels of several biochemical markers for detecting evidence of myocardial injury. Patients &Methods: We sequentially measured the serum concentrations of H-FABP, myoglobin (MYO), cardiac troponin-T (cTnT), cardiac troponin-I (cTnI), and myosin light chain-I (MLC-I), before and after treatment with intravenous gammaglobulin (IVGG) in 26 acute KD patients (mean age, 2.6 +/-1.4 years; M/F=14/12). Results: The mean levels of H-FABP were 4.3 $\pm$1.9 ng/ml before IVGG and decreased to 3.7 $\pm$1.5 ng/ml ($p<0.05$) after 1 month. H-FABP was significantly elevated in 15.4%(4/26) before IVGG treatment. Despite improvement in clinical symptoms and signs after IVGG, the serum levels of H-FABP still elevated in 15.4%(4/26). The mean levels of MYO were 27.0 $\pm$9.5 ng/ml before IVGG and decreased to 19.4$\pm$ 7.2 ng/ml ($p<0.05$) after 1 month. However, MYO level elevated in only 3.8% (1/26) than normal range before IVGG. cTnT, cTnI, and MLC-I were within normal ranges. Conclusion: Subclinical myocarditis can be detected by serum H-FABP and MYO. cTnT, cTnI, and MLC-I were not sensitive markers for silent myocardial injury. H-FABP seems to be a more reliable biochemical marker for early detection of myocardial injury in acute phase KD. Furthermore IVGG may to exert cardioprotective effects in KD.

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TWO-GENERATION KAWASAKI DISEASE: MOTHER AND DAUGHER

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Evidence that the incidence of Kawasaki disease (KD) in siblings is much higher than general incidence, indicates that genetic factors may contribute to the susceptibility. We report a girl with KD whose mother also suffered from KD with the precise medical record when she was a child. **Case Reports**: Mother (27 years old); At 6 years of age, she was admitted to the reginal hospital because of persistent high fever for 4 days and cervical lymphadenitis. According to the medical record of 21 years ago, she fulfilled the revised criteria of KD. After admission, acetylsalicylate (ASA) was administered and became afebrile within 2 weeks, and then desquamation of fingertips was observed. Two months later, she was admitted for investigation of coronary artery lesion (CAL). The angiographic examination indicated normal coronary arteries, no aneurysms, and no abnormal dilatation of abdominal artery. ASA was ceased without any coagulation problems. Daughter (1 year old); A 1 year-old girl was admitted to the regional hospital with high fever for 3 days and cervical lymphadenitis. On admission, she fulfilled the revised criteria of KD. The BCG-injected site was reactivated and inflamed. And, the combination therapy of oral ASA and the high-dose intravenous gammaglobulin (1 g/kg for 2 days) was administered. However, high fever was still persisted, and she was estimated at the highest risk for CAL, and transferred to our hospital to be subjected to plasma exchange (PE) therapy on day 7 according to our inclusion criteria of PE. After the PE therapy both clinical manifestation and laboratory data were improved to normal ranges. The serial echocardiography revealed intact coronary arteries. **Discussion** : Two-generation KD may be an appropriate example to analyze the genetic predisposition of KD. It may be important to take a careful history of childhood diseases in the parents of children with KD.

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CORONARY ARTERITIS AND ARTERIAL REMODELING IN KAWASAKI DISEASE: IMMUNOHISTOCHEMICAL STUDY

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This study aimed to develop innovative therapy to prevent obstructive coronary arterial lesions in Kawasaki disease (KD). We studied fundamental mechanisms related to arteritis in acute phase and remodeling of the arteries in convalescent and late phase. We examined formalin-fixed specimens of coronary arteries from 18 patients with KD by immunohistochemical staining. We used antibodies against various vascular growth factors, including TGFβ1, PDGF-A, bFGF, VEGF and their receptors. We also used cell type-specific antibodies to CD68, CD34, factor VIII and α-actin. In acute phase (15th day of illness), severe edema and inflammatory cell infiltration were observed in the arteries, especially in the area from adventitia to intima. In convalescent phase (2.5-12.5 months after onset), we observed synthesis of loose gelatinous extra-cellular matrix (ECM) that leads to intimal thickening and occlusion of aneurysmal lumen. Inflammatory cells, such as *iNOS*$^+$ cells, VEGF$^+$ cells, and CD68$^+$ macrophages, infiltrated in the ECM of subendothelial layer and deep intima by one year after onset of KD. Among the infiltrating cells, a large number of CD34$^+$ cells, *Tie2*$^+$ cells and *KDR*$^+$ cells, known as endothelial progenitor cells (EPCs), were seen to migrate from adventitia to deep intima. In the later convalescent phase, the loose gelatinous ECM was replaced by smooth muscle cells (SMCs) and collagen fibers. In late phase (2.5-19 years after onset), the growth factors were strongly expressed in proliferating SMCs of progressively thickening intima. In conclusion, this study indicated that the remodeling of coronary arteries begins with synthesis of ECM in the intima and cellular infiltration. Thereafter, vascularization, remarkable proliferation of SMCs and fibrosis are occurred in order. In addition, it became obvious the remarkable vascularization in KD depends on not only angiogenesis but also postnatal vasculogenesis that was proved by infiltration of a large number of EPCs.

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PREDOMINANCE OF MONOCYTES AND MACROPHAGES IN THE INFLAMMATORY INFILTRATES OF ACUTE KAWASAKI DISEASE ARTERITIS

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BACKGROUND: Microscopic evaluation of arteritis in Kawasaki disease has demonstrated infiltration of the intima, muscularis and adventitia by predominantly mononuclear leukocytes; accompanied by edema, and, in severe lesions, by fibrinoid necrosis. There is limited published information on the phenotype of infiltrating leukocytes. The purpose of this study was to perform immunophenotyping of the leukocytes causing arteritis in kidneys from patients with Kawasaki disease. METHODS: Seven postmortem kidney specimens from children with Kawasaki disease were examined by light microscopy. Three of the seven specimens were selected for leukocyte immunophenotyping because they had a range of acute inflammation in arteries (mild, moderate, and severe arteritis). Only the specimen with severe arteritis had fibrinoid necrosis. Formalin-fixed sections were stained for immunoenzyme microscopy using antibodies specific for CD3 (T lymphocytes), CD4 (helper T lymphocytes), CD8 (cytotoxic T lymphocytes), CD20 (B lymphocytes), and CD68 (monocytes and macrophages). RESULTS: Arteritis was confined to the interlobar arteries. The arteritic infiltrates had an extremely high proportion of CD68 positive cells, most with the morphology of macrophages. Apparently early intimal lesions had almost exclusively CD68 positive cells beneath the endothelium. Most infiltrates in the intima, muscularis, and adventitia had approximately 90% CD68 positive cells. Most of the remaining cells were positive for CD3 (CD8CD4). CD20 positive cells were rare. Another interesting finding was increased numbers of CD68 positive cells in glomeruli. The severe arteritis specimen had 1.38 CD68 cells/glomerulus, moderate arteritis specimen 2.33 CD68 cells/glomerulus, and mild arteritis specimen 0.04 CD68 cells/ glomerulus. CONCLUSIONS: The mural and perivascular leukocytes in early as well as advanced acute Kawasaki disease arteritis are predominantly monocytes/macrophages. Although there is no overt glomerulonephritis, patients with moderate and severe renal arteritis have increased monocytes/macrophages in glomeruli. These data suggest that the pathogenesis of Kawasaki disease involves extensive monocyte activation.