Unique Angiopathy After Herpes Virus Infection

JUN SHIMIZU, AKIHITO INATSU, SATOSHI OSHIMA, and TAKAO KUBOTA

ABSTRACT. ***Objective.*** We describe 3 Japanese patients with peculiar renal and/or coronary arterial stenosis and/or multiple aneurysms after herpes virus infection, following ischemic symptoms. We investigated for viral antigens and viral DNA *in situ*, and for shared abnormalities of cellular immunity.

Methods. Panarteriography was performed diagnostically, and patients were grouped as follows: 3 patients with peculiar renal and/or coronary artery narrowing and/or multiple aneurysms; another 3 patients with renal fibromuscular dysplasia; and other young adults with effort angina, with no history of herpes virus infection, as controls. Detection of viral antigens and viral DNA *in situ* was done by polymerase chain reaction method and immunohistochemical staining. Cellular immunity was examined at the time of ischemic symptoms.

Results. Viral antigens and DNA were scarcely detected, except in herpes zoster skin lesion with leukocytoclastic vasculitis. However, shared abnormalities of cellular immunity, such as a decreased CD4+ T cell number and reduced natural killer cell activity, were more prominent in the 3 patients with unique vasculopathy after herpes virus infection.

Conclusion. Unique vasculopathy following herpes virus infection might be a more severe and extensive disease. We speculate that sustained viral infection, repetitive activation of virus related antigens, and suppressed immune state might contribute to formation of peculiar vascular alterations. (J Rheumatol 2004;31:925–30)

Key Indexing Terms:
HERPES VIRUS INFECTION VASCULOPATHY ALTERED CELLULAR IMMUNITY

Recently, various causative agents have been shown to promote atherosclerosis, including homocysteine and lipoprotein (a), in addition to well known risk factors like high blood pressure, hyperlipidemia, and smoking. The immune system may also be involved in the atherosclerotic process, and some investigators have suggested that chronic inflammation could promote coronary atherosclerosis. Chlamydia, cytomegalovirus (CMV), and herpes simplex virus have been speculated to be among the factors contributing to such chronic inflammation[1]. It is reported that influenza vaccination would reduce the risk of death and ischemic events in patients with coronary heart disease[2].

We encountered 3 Japanese patients with unique angiopathy of the coronary and/or renal arteries after episodes of probable herpes virus infection of about one year. They had had recurrent or chronic herpes viral infections. We were scarcely able to detect the virus antigens or DNA in tissue specimens; however, in all patients we observed chronic abnormalities of cell-mediated immunity, such as decreased CD4+ T cell numbers and reduced natural killer (NK) cell activity, which were more prominent in the 3 patients with unique vasculopathy after herpes virus infection.

Unique vasculopathy after herpes virus infection differs to some extent from the syndrome involving large or medium-size vessels, such as polyarteritis nodosa, Takayasu's arteritis, Kawasaki disease, and fibromuscular dysplasia (FMD). In some vasculitides, organ damage may result because the antigen in question has a particular affinity for a specific tissue. We investigate whether herpes virus antigens or acquired abnormalities of cellular immunity may have a potential role in the specific vascular alterations.

Patient 1

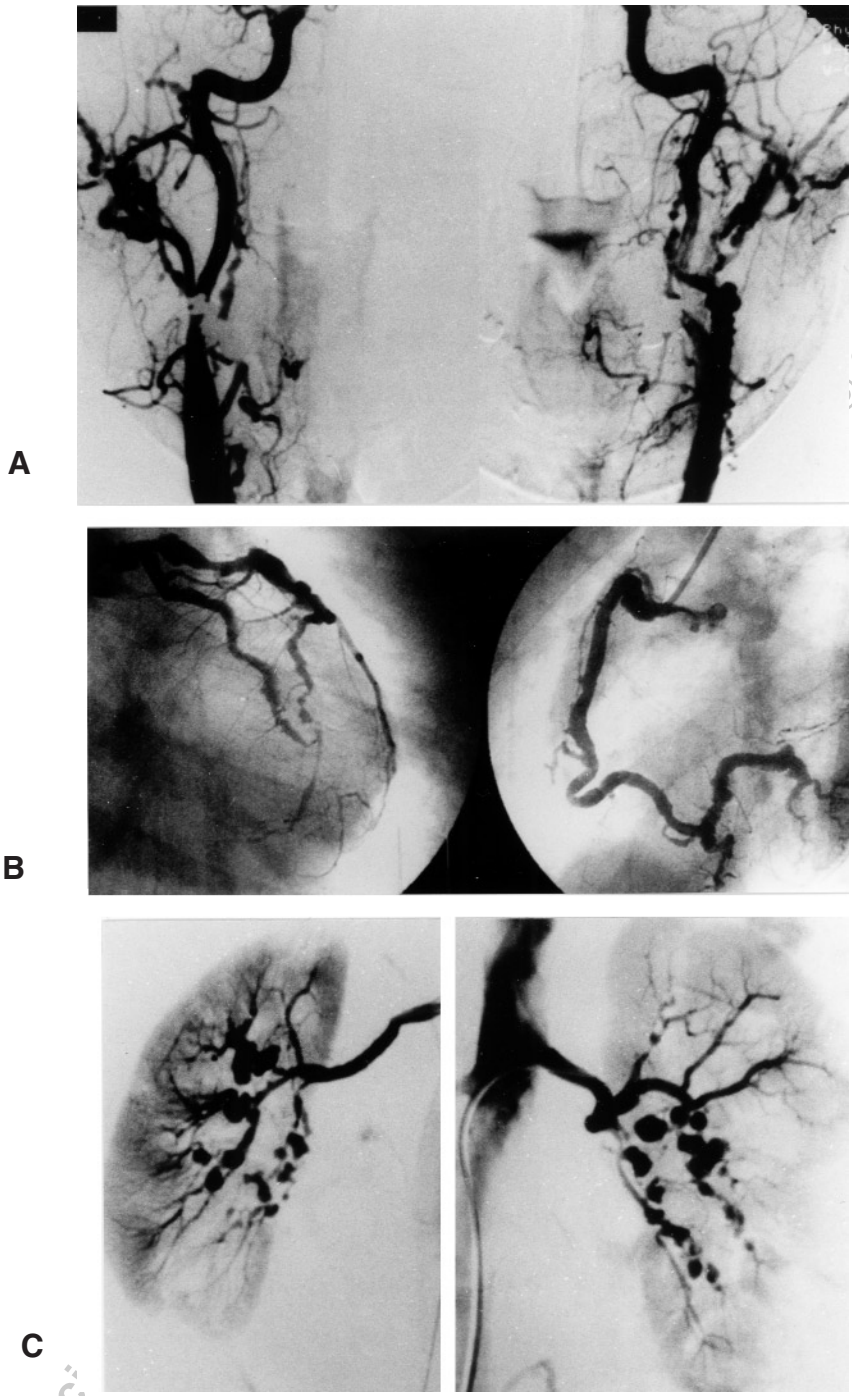
The patient was a 25-year-old woman. Her history was unremarkable, except for recurrent episodes of herpes zoster viral infection. She had been diagnosed based on her skin lesion and treated. She developed left facial nerve palsy with pancytopenia and hypertension for the first time at the age of 26 years, and responded well to corticosteroid for one month. Her fourth episode of herpes zoster viral infection with left facial nerve palsy occurred in the following year. At the age of 28, right facial nerve palsy occurred; subsequently she also had proteinuria with mild renal dysfunction, and was found to be positive for antinuclear antibodies (ANA). Her facial palsy responded again to corticosteroid therapy for several weeks. Thereafter she showed a weight loss of 10 kg over 3 years. Visceral angiography was performed diagnostically and showed peculiar multiple aneurysms of medium-size renal arteries. Similar changes were observed systemically, in the coronary arteries, both the internal and external carotid arteries, and in other vessels (Figure 1A, 1B, 1C). At that time a left renal biopsy revealed a severe ischemic lesion with no deposition of immune complex on the injured glomeruli and interstitium. We diag-

From the Department of Medicine, the Japan Self Defense Forces Central Hospital, Tokyo, Japan.

J. Shimizu, MD; A. Inatsu, MD; S. Oshima, MD; T. Kubota, MD.

Address reprint requests to Dr. J. Shimizu, Department of Medicine, The Japan Self Defense Forces Central Hospital, Ikejiri 1-2-24, Setagaya-ku, Tokyo, Japan 154-8532. E-mail: hemijun@nyc.odn.ne.jp

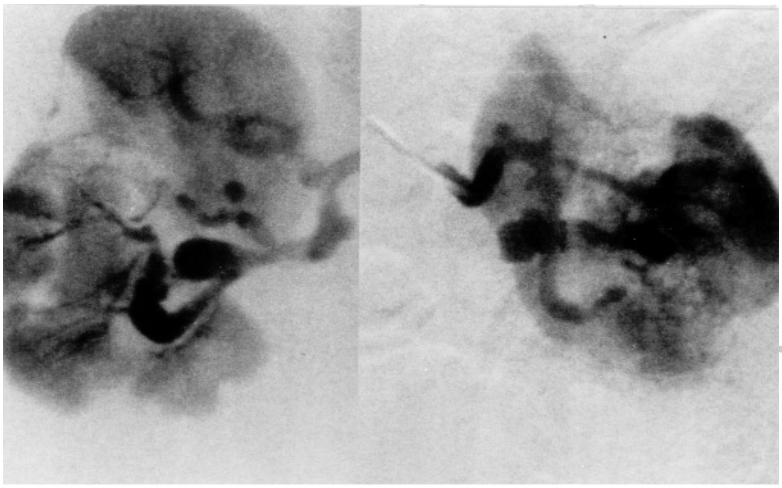
Submitted March 4, 2003; revision accepted October 7, 2003.



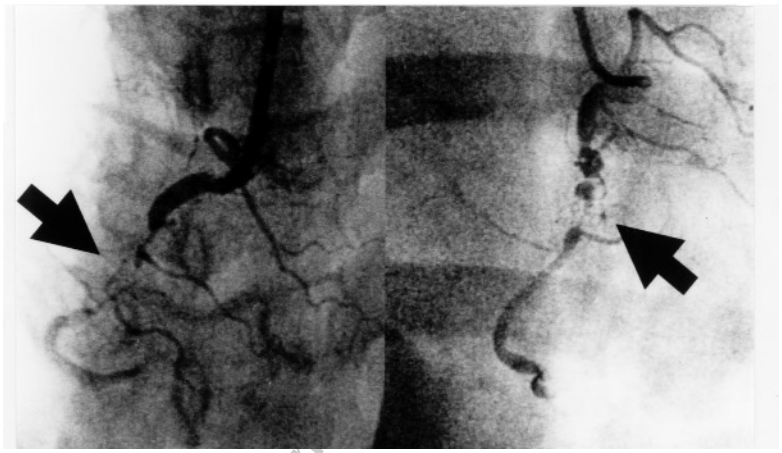
nosed polyarteritis and started a combination treatment with antihypertensive agents, antiplatelet agents, and anticoagulants. Six months later, she developed erythema multiforme on the elbows and heels with leukocytoclastic vasculitis (Figure 2), with no deposition of immune complex. Laboratory investigations at this time showed hypocomplementemia, LE cells, and anti-single-stranded DNA antibodies, but no anti-Sm antibody. A combination therapy of corticosteroid, cyclophosphamide, and plasmapheresis was added to her treatment regimen. Clinical and laboratory findings subsequently improved, and she has remained well since then, but she had 2 more episodes of herpes zoster.

Patient 2

The patient was a 42-year-old male soldier. His history was unremarkable. He had had herpes zoster about one year before hospitalization, and received treatment with an antiviral agent. One year later, he complained of intermittent



D



E

Figure 1. Panarteriographic findings in Patients 1–3. Panels A, B, C: arteriograms from Patient 1, showing multiple aneurysms and segmental narrowing in both common carotid arteries (A), coronary arteries (B), and main branches of both renal arteries (C), but scarcely in supratentorial arteries. D. Patient 2, arteriogram showing aneurysms in main branches of both renal arteries, nonfilling of interlobular arteries, and indistinct nephrograms. E. Patient 3, arteriogram showing severe stenosis in the right coronary artery (left side, arrow); restenosis occurred several months after stenting (right side, arrow).

headache and weight loss (decrease of 4 kg over one year). The headache gradually worsened; he was referred to our hospital and was admitted with the diagnosis of malignant hypertension syndrome. His blood pressure became stable after several days of rest and low dose of angiotensin-converting enzyme (ACE) inhibitor. Because plasma renin activity was high, we performed angiography, which revealed multiple aneurysms of the renal arteries (Figure 1D). However, renal biopsy revealed almost normal kidney architecture. Presently, he remains well on treatment with only ACE inhibitor, but has had discontinuous mild skin pain with small eruptions; the pathological finding was discoid lupus erythematosus. We barely detected any deposition of immune complexes or viral antigens.

Patient 3

The patient was a 37-year-old woman with unremarkable history. Multiple small ulcers had developed in her oral cavity from 2 months before hospitalization and her weight decreased by 7 kg over 3 months. She was admitted to hospital because eating had become difficult. We diagnosed probable herpes virus infection from the typical endoscopic findings of her esophagus, showing scattered vesicles and multiple small ulcers on mucosa. She responded well to acyclovir and became stable for a time, but the illness recurred intermittently. On therapy of low dose corticosteroid for 2 weeks, her esophagitis improved drastically. Ten months later, she developed symptoms of angina, and coronary angiography revealed multiple stenoses (Figure 1E), following transluminal angioplasty. Angina recurred about 2

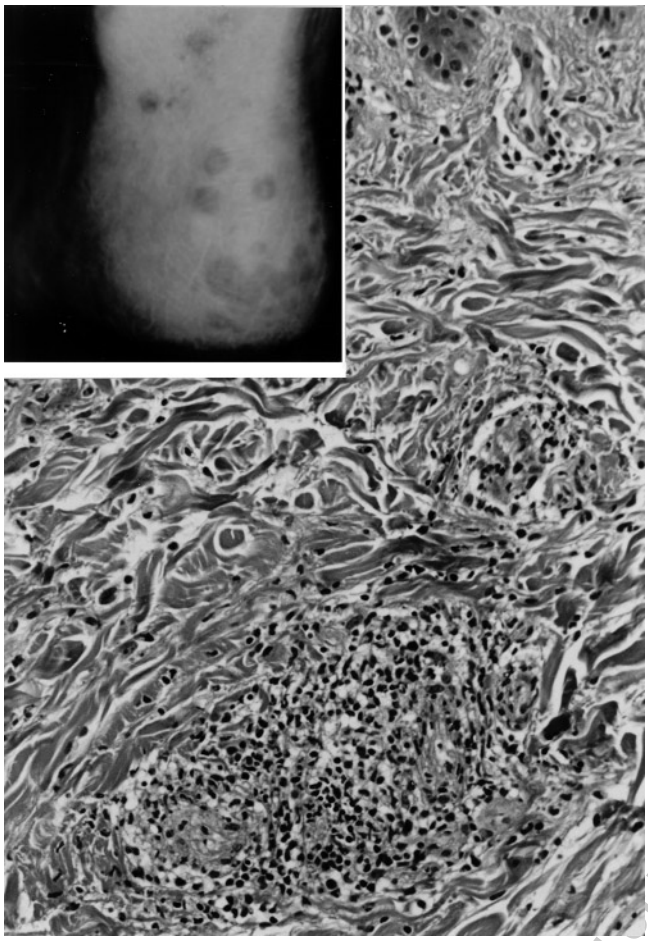


Figure 2. Varicella-zoster virus infected skin lesion in Patient 1. Erythema multiforme on her heel (insert) revealed leukocytoclastic vasculitis (H&E, ×10).

months later, and angiography revealed restenosis of the lesion; a stent was inserted. She has been well with no ischemic symptoms, but followup coronary angiography has revealed total occlusion of her stent.

MATERIALS AND METHODS

Polymerase chain reaction (PCR). PCR was done with the aim of detecting varicella-zoster virus (VZV) DNA *in situ*. Tissue from kidney, muscle, bone marrow, and skin was obtained from Patient 1, kidney and skin from Patient 2, and esophageal mucosa from Patient 3. Two specimens of skin lesion from other patients with herpes zoster, 2 renal specimens from patients with FMD, and 25 abdominal aneurysm specimens were used as the controls. Whole DNA was extracted from paraffin-embedded vasculitis sections, and PCR was done with the Light-Cycler PCR amplification system. Specific primers were generated for VZV (open reading frames 38 and 29 and unique sequence) herpes simplex virus, CMV, and Epstein-Barr herpes virus, respectively.

Immunohistochemical staining. Monoclonal antibody to VZV and polyclonal antibody to herpes simplex virus were used as the primary antibody for immunohistochemical staining by the streptavidin-biotin method. Samples of kidney, muscle, bone marrow, and skin from Patient 1, kidney and skin from Patient 2, and esophageal mucosa from Patient 3 were examined. Skin specimens from 2 patients with herpes zoster were used as control.

Assessment of humoral and cellular immunity. Immune function was examined to determine whether our patients were immunocompromised. Blood samples were taken at the time that ischemic symptoms appeared in all 3 patients. Two patients with FMD and 3 patients with young-onset effort angina were used as controls. We assessed 3 or 4 times at intervals over one month. No patient had antibodies for hepatitis B or C or human immunodeficiency virus I. The number of T cells, especially CD4+ T cells, and NK cell activity was examined. Additional autoantibodies to NK cell-surface antigen were detected by Western blot analysis, as described[3].

RESULTS

PCR findings and immunohistochemical staining. Viral DNA and antigens were scarcely detected in any of the specimens tested, except for varicella-zoster DNA in the skin specimens from 2 patients with herpes zoster (Figure 3). Viral antigen signals were localized in the vesicles and hair follicules, but were not observed at the site of leukocytoclastic vasculitis.

Humoral and cellular immunity. In Patient 1, many abnormal immunologic findings similar to those seen in patients with systemic lupus erythematosus (SLE) were detected, but anti-Sm antibody was negative, or anti-single-stranded DNA antibody was detected. In Patient 2, low titers of ANA and hypocomplementemia were observed; there were no lupus-like findings in Patient 3. In all 3 patients with herpes virus infection, anti-varicella-zoster virus IgG antibody was positive, but IgM antibody was negative (Table 1). A mild decrease in the number of CD4+ T lymphocytes and reduction of NK cell activities at the time of ischemic symptoms were found (Figure 4).

Patients 1, 2, and 3 were negative for autoantibody to NK cell-surface antigen (data not shown). One patient with young-onset effort angina (Patient 7, Table 1) had the autoantibody, and he also had low titers of IgM antibody for herpes simplex virus. His autoantibody and virus antibody may indicate latent infection of herpes simplex virus.

DISCUSSION

We describe 3 relatively young adults with visceral ischemia of the heart and/or kidneys following herpes virus infection; we postulated a role of sustained herpes virus infection *in situ*, following progression of their vascular lesions. There have recently been reports on virally mediated inflammatory vasculitis[4]. VZV infection has been shown to cause various types of vasculitis[5,6]. The participation of a virus in cases of

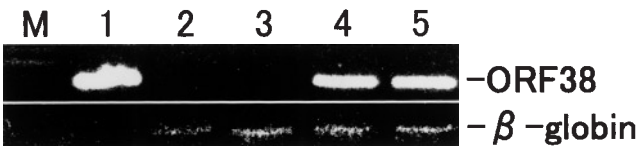


Figure 3. Varicella-zoster virus DNA detection by PCR method. VZV DNA (ORF 38: 216 bp) was detected from zoster skin lesion in lanes 4 and 5, while not detected from Patient 1 in lanes 2 and 3. Beta-globin was used as the housekeeping gene. M: marker. Lane 1: VZV DNA. Lane 2: Skin of Patient 1. Lane 3: Bone marrow of Patient 1. Lane 4: Skin from herpes zoster Case 1. Lane 5: Skin from herpes zoster Case 2.

Table 1. Clinical characteristics and laboratory findings.

Patient	Age/Sex	Probable Herpes Virus Infection	aHSV Ab IgG/IgM	aVZV Ab	Symptoms	ANF/aDNA	CH50, U/ml	Diagnosis
1	27f	Rash (4 times)	–/–	++/–	Bell's palsy/RVH	++/+*	16.1	PN-like
2	42m	Rash	++/–	++/–	RVH	+/–	35	PN-like
3	37f	Esophagitis	+/–	+/–	Angina	–/–	47	AP
4	20m	—	+/–	+/–	RVH	–/–	48	FMD
5	22m	—	++/–	+/–	RVH	–/–	48	FMD
6	27f	—	–/–	++/–	RVH/AHF	–/–	45	FMD
7	33m	—	++/+	++/–	Angina	+/–	41	AP
8	36m	—	–/–	+/–	Angina	–/–	44	AP
9	32m	—	++/–	+/–	Angina	–/–	39	AP

* Anti-SS-DNA IgG antibody, 80 U/ml, and anti-DS-DNA IgG antibody, 6 U/ml. HSV: herpes simplex virus, VZV: varicella-zoster virus, ANF: antinuclear factor, aDNA; anti-DNA antibody, Ab: antibody; RVH: renovascular hypertension, AHF: acute heart failure, PN: polyarteritis nodosa, AP: angina pectoris, FMD: fibromuscular dysplasia.

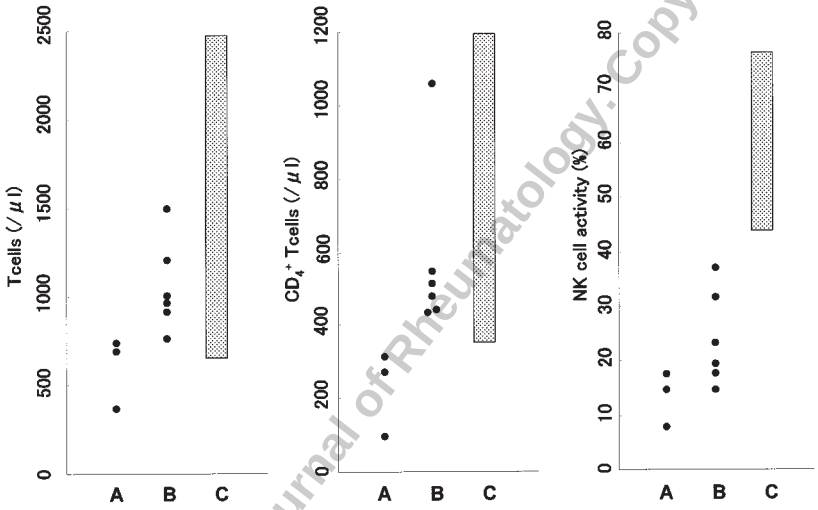


Figure 4. T cell count, CD4+ T cell count, and NK cell activity. The decrease of CD4+ T cells and suppression of NK cell activity were prominent in Patients 1–3. Column A: Patients 1–3. Column B: Patients 4–9. Column C: controls (n = 9).

vasculitis is identified by a positive PCR result, immunohistochemical staining, and *in situ* hybridization. However, VZV in the vessel walls was barely detected in our 3 patients. Viral antigens were found only in the vesicles and hair follicles in the skin of 2 patients with herpes zoster. Perivascular inflammatory cell infiltration is often observed in the dermis of patients with herpes zoster. It was difficult to detect VZV antigens within the vasculitic lesions, except for the endothelial linings of the capillaries in the vesicular stage[7]. Because we were unable to detect viral antigen in the perivascular infiltrating cells, we can only say that the macroscopic and microscopic findings of the skin in Patient 1 were similar to those of zoster rash.

Moreover, it is difficult to explain the relationship between vasculitis of skin arterioles and the vascular lesions observed in visceral arteries by angiography. Degeneration of the vasa vasorum that supplies blood to the media of arteries may be a possible cause of the angiopathy observed in our patients. Vasculitis of the vasa vasorum is involved in the pathology of FMD[8], and similar changes have been reported in patients with Takayasu's disease[9,10]. Murakami, *et al* have described a 10-year-old girl with chronic active Epstein-Barr virus infection who developed large-vessel arteritis. Histopathologic examination revealed mesoarteritis that featured moth-eaten-like destruction of the medial elastic lamina, as well as T lymphocyte infiltration around the vasa vasorum, and marked intimal thickening[11]. Cranial nerve involvement usually occurs some weeks after acute herpes zoster infection, suggesting that VZV spreads transaxonally along the trigeminal and other ganglionic afferent fibers from the carotid arteries to the vasa vasorum of small nerves[12]. We speculate that vasculitis or degeneration of the vasa vasorum may have an important role in the formation of small arterial aneurysms and stenoses like the vascular lesions seen in our patients. Several investigators report that VZV infection of the ganglions can become

systemic in herpes zoster due to early viremia[13] and infection of dendritic cells[14]. This peculiar or specific behavior of VZV might explain the widespread vascular lesions of our 3 patients.

We also observed a sustained alteration of cellular immunity in these patients. In transplant recipients or patients with acquired immune deficiency syndrome (AIDS), vascular changes are caused by immunological disorders. Angiitis of the vasa vasorum is recognized in the majority of coronary arteries after heart transplant surgery, and aneurysmal dilatation of the epicardial coronary arteries occurs with thinning and fibrosis of the media[15]. Similar lesions occur in the case of transplanted renal artery stenosis after kidney transplant, and a relationship with cellular immunity has been proposed[16]. CMV infection has been implicated in accelerated vasculopathy of cardiac allografts and in renal artery stenosis after kidney transplants[17,18]. With regard to cerebral aneurysm occurring in AIDS patients, the participation of VZV in vasculitis has been suggested[19]. Encephalitis associated with VZV is now recognized to be due to vasculopathy, which can affect either large or small vessels depending on the immune status of the patient, i.e., large vessel-associated encephalitis or granulomatous arteritis mainly occurs in immunocompetent patients, whereas small vessel-mediated encephalitis is found in immunodeficient patients[12]. Even in our controls with young-onset effort angina or FMD, a decrease of CD4+ T lymphocytes and reduced NK cell activity were observed. All patients in this study have been in an immunocompromised state, and the decline of cellular immunity may participate in the pathogenesis of vascular lesions and be accelerated by viral infection.

Matsui, *et al* reported that autoantibody for killer immunoglobulin-like receptors can be detected in patients with SLE or rheumatoid arthritis, and that patients who were positive also had elevated serum IgG concentrations[3]. The effect of this autoantibody is not clearly understood, but it did not seem to be related to the decline of cellular immunity in our patients.

We suggest that abnormalities of cellular immunity and repetitive activation of virus-related antigens may have had a crucial role in causing the systemic vascular lesions in our 3 patients. These 3 patients seemed to have a condition resembling Takayasu's arteritis, considering their silent clinical course, the sizes of injured vessels, and the decrease of cellular immunity. When vascular lesions occur in young adult patients, it may be important to take cellular immunity and viral infection into consideration.

ACKNOWLEDGMENT

We thank Prof. Tetsutaro Sata and Touru Katano, MD, PhD, National Institute of Infectious Disease, Tokyo, Japan, for performance of immunohistochemical staining for varicella-zoster virus; and Prof. Tomohiro Kato and Toshihiro Matsui, MD, PhD, St. Marianna Medical College, Kawasaki, Japan, for Western blotting to detect autoantibodies for killer immunoglobulin-like receptor.

REFERENCES

1. Espinola-Klein C, Rupprecht HJ, Blankenberg S, et al. Impact of infectious burden on extent and long-term prognosis of atherosclerosis. Circulation 2002;105:15-21.
2. Gurfinkel EP, de la Fuente RL, Mendiz O, Mautner B. Influenza vaccine pilot study in acute coronary syndromes and planned percutaneous coronary interventions: the FLU Vaccination Acute Coronary Syndromes (FLUVACS) Study. Circulation 2002;105:2143-7.
3. Matsui T, Otsuka M, Maenaka K, et al. Detection of autoantibodies to killer immunoglobulin-like receptors using recombinant fusion proteins for two killer immunoglobulin-like receptors in patients with systemic autoimmune disease. Arthritis Rheum 2001;44:384-8.
4. Mandell BF, Calabrese LH. Infections and systemic vasculitis. Curr Opin Rheumatol 1998;10:51-7.
5. Gilden DH, Kleinschmit-DeMasters BK, Wellish M, Hedley-Whyte ET, Rentier B, Mahalingam R. Varicella-zoster virus, a cause of waxing and waning vasculitis: The New England Journal of Medicine case 5-1995 revisited. Neurology 1996;47:1441-6.
6. Gilden DH, Lipton HL, Wolf JS, et al. Two patients with unusual forms of varicella-zoster virus vasculopathy. N Engl J Med 2002;347:1500-3.
7. Muraki R, Baba T, Iwasaki T, Sata T, Kurata T. Immunohistochemical study of skin lesions in herpes zoster. Virchows Archiv A Pathol Anat 1992;420:71-6.
8. Luscher TF, Lie JT, Stanson AW, Houser OW, Hollier LH, Sheps SG. Arterial fibromuscular dysplasia. Mayo Clin Proc 1987;62:931-52.
9. Schoen FJ, Cotran RS. Blood vessels, Takayasu's arteritis. In: Cotran RS, Kumar V, Collins T, editors. Robbins pathologic bases of disease. Philadelphia: WB Saunders; 1999:519-20.
10. Seko Y. Takayasu's arteritis: Pathogenesis. In: Hoffman GS, Weyand CM, editors. Inflammatory disease of blood vessels. New York: Marcel Dekker Inc.; 2002:443-54.
11. Murakami K, Ohsawa M, Hu SX, Kanno H, Aozasa K, Nose M. Large-vessel arteritis associated with chronic active Epstein-Barr virus infection. Arthritis Rheum 1998;41:369-73.
12. Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. Neurologic complications of the reactivation of varicella-zoster virus. N Engl J Med 2000;342:635-45.
13. Straus SE. Clinical and biological differences between recurrent herpes simplex virus and varicella-zoster virus infections. JAMA 1989;262:3455-8.
14. Abendroth A, Morrow G, Cunningham AL, Slobedman B. Varicella-zoster virus infection of human dendritic cells and transmission to T cells: implications for virus dissemination in the host. J Virol 2001;75:6183-92.
15. Higuchi ML, Benvenuti LA, Macruz-Demarchi LM, Libby P. Histological evidence of concomitant intramyocardial and epicardial vasculitis in necropsied heart allograft. Transplantation 1999;67:1569-76.
16. Wong W, Fynn SP, Higgins RM, et al. Transplant renal artery stenosis in 77 patients — does it have an immunological cause? Transplantation 1996;61:215-9.
17. Koskinen PK, Nieminen MS, Krogerus LA, et al. Cytomegalovirus infection accelerates cardiac allograft vasculopathy: Correlation between angiographic and endomyocardial biopsy findings in heart transplant patients. Transplant Int 1993;6:341-7.
18. Pouria S, State OI, Wong W, Hendry BM. CMV infection is associated with transplanted renal artery stenosis. Q J Med 1998;91:185-9.
19. Dubrovsky T, Curless R, Scott G, et al. Cerebral aneurysmal arteriopathy in childhood AIDS. Neurology 1998;51:560-5.