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CASE REPORT

Shin-ichi Ban · Yoshiya Goto · Kouichi Kamada
Motohide Takahama · Hiroshi Watanabe
Taiki Iwahori · Hiroaki Takeuchi

Systemic granulomatous arteritis associated with Epstein-Barr virus infection

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Abstract A 61-year-old woman initially presented with symptoms and findings reminiscent of infectious mononucleosis, and her illness then took a rapidly fatal course. Autopsy revealed widespread granulomatous arteritis, with multinucleated giant cells but without eosinophils and fibrinoid necrosis, affecting small arteries and arterioles and infiltration of haemophagocytic histiocytes into many organs. In situ hybridization with Epstein-Barr virus (EBV)-specific oligonucleotide probes showed positive signals in the infiltrating immune cells and epithelial and endothelial cells of the affected organs. EBV-associated haemophagocytic syndrome (EBV-AHS) with systemic granulomatous arteritis was diagnosed. From the immunophenotypes of the infiltrating immune cells, a possible role of CD4+ T-cells in the pathogenesis of this haemophagocytic syndrome and granulomatous vasculitis was suggested.

Key words Systemic granulomatous arteritis · Epstein-Barr virus · Virus-associated haemophagocytic syndrome · In situ hybridization · Immunohistochemistry

S. Ban (✉) · Y. Goto · K. Kamada · M. Takahama
Department of Pathology, Saitama Medical School,
38 Morohongo, Moroyama, Iruma, Saitama 350-0495, Japan
e-mail: shinba@saitama-med. ac. jp,
Tel.: +81-492-76-1164; Fax: +81-492-76-1583

H. Watanabe
Department of Medical Technology,
Saitama Medical School Junior College, Saitama, Japan

T. Iwahori
Third department of Internal Medicine,
Saitama Medical School, Saitama, Japan

H. Takeuchi
Department of Microbiology,
Yamaguchi University School of Medicine, Ube, Japan

Introduction

Epstein-Barr virus (EBV) is a human herpesvirus that infects most individuals by adulthood, with persistent latent infection. Primary EBV infection is usually silent or causes a self-limiting lymphoproliferative disorder (LPD), infectious mononucleosis (IM) [11]. However, EBV infection can be associated with more severe disease and is implicated in the pathogenesis of human malignancies, including X-linked lymphoproliferative syndrome (XLP) and non-XLP fulminant/fatal IM, chronic active EBV infection, virus-associated haemophagocytic syndrome (VAHS), T (NK) cell lymphoma, Burkitt's lymphoma, Hodgkin disease, LPDs associated with immunodeficient and posttransplant states, pyothorax-associated pleural lymphoma, nasopharyngeal carcinoma and gastric carcinoma [11, 24]. The association of EBV infection and such autoimmune diseases as Sjögren's syndrome and rheumatoid arthritis has also been suggested [31, 32].

We experienced a case in which a previously healthy adult initially showed IM-like symptoms and findings, followed by a rapidly fatal course. Autopsy revealed granulomatous arteritis and infiltration of haemophagocytic histiocytes into multiple organs. We detected EBV genomes in the autopsied tissues by in situ hybridization (ISH) with oligonucleotide probes. This case was regarded as one of EBV-associated haemophagocytic syndrome (EBV-AHS) associated with systemic granulomatous arteritis.

Various viruses can be responsible for vasculitis [3, 18]. Several cases of EBV-associated vasculitis have been reported [4, 7, 22, 23], but to our knowledge, no case of systemic granulomatous vasculitis associated with EBV-related diseases, including EBV-AHS, has previously been described. We here report a case with immunophenotypic identification of the infiltrating immune cells and discuss its pathogenesis.

Clinical history

On 26 November 1994, a previously well, 61-year-old Japanese woman visited a physician because of fever (up to 38°C), sore throat, and erythematous eruptions on the chest. Appendectomy and uterine myomectomy had been performed in 1959 and 1961, respectively. There was no history of blood transfusion. She had not smoked or used illicit drugs, and she consumed little alcohol. There was no remarkable family history. Antibiotics and antipyretics were administered without bringing about any improvement, and appetite loss, cough, peripheral oedema, and systemic erythema with desquamation developed. This patient was hospitalized on 16 December 1994. On admission, haematological values were as follows: white blood cell count 10,800/μl with 25% lymphocytes (10% atypical lymphocytes), red blood cell count 3.2×10^6/μl, haemoglobin 9.2 g/dl, haematocrit 28.3%, and platelet count 19.9×10^4/μl. Blood chemical values were: total bilirubin 1.4 mg/dl, glutamic oxaloacetic transaminase 66 U/l, glutamic pyruvic transaminase 107 U/l, lactate dehydrogenase 555 U/l, alkaline phosphatase 2,979 U/l, γ-glutamyltranspeptidase 374 U/l, urea nitrogen 61.8 mg/dl, and creatinine 2.9 mg/dl. Serum C-reactive protein was 17.2 mg/dl. Antibiotics were administered. However, the patient's condition did not improve and jaundice was noted.

The patient was transferred to the Saitama Medical School Hospital on 26 December 1994. At that time, her height was noted to be 151 cm and weight 56 kg. Her temperature was 37.6°C, pulse 92, and blood pressure 140/82 mmHg. On examination, the patient was jaundiced and showed systemic erythema with desquamation, peripheral oedema, and bilateral tonsillar swelling. A soybean-sized lymph node was palpable in the cervical and in the inguinal regions. An abdominal examination revealed the liver edge 4 cm below the right costal margin. Radiographs of the chest showed bilateral pleural effusion, and an ultrasound examination of the abdomen revealed liver swelling and ascites. Haematological values were: white blood cell count 16,200/μl with 23% lymphocytes (no atypical lymphocytes), red blood cell count 2.6×10^6/μl, haemoglobin 8.5 g/dl, haematocrit 27.4%, and platelet count 19.1×10^4/μl. Blood chemical values were as follows: total protein 5.6 g/dl with albumin 2.0 g/dl, total bilirubin 10.8 mg/dl with conjugated bilirubin 7.4 mg/dl, glutamic oxaloacetic transaminase 90 U/l, glutamic pyruvic transaminase 58 U/l, lactate dehydrogenase 553 U/l, alkaline phosphatase 809 U/l and γ-glutamyltranspeptidase 130 U/l, urea nitrogen 52 mg/dl, and creatinine 3.1 mg/dl. Serum C-reactive protein was 9.8 mg/dl. The blood glucose level was 743 mg/dl, and the urine was strongly positive for glucose. Serum IgG and IgM levels were 2,801 mg/dl and 1,048 mg/dl, respectively. The Paul-Bunnel test was positive (1:224). The test for EBV anti-VCA-IgG antibody was positive (1:320); however, the results of tests for EBV anti-VCA-IgM, anti-EA-IgG, and anti-EBNA antibodies were all negative (<1:10). Tests for antibodies to measles and rubella were negative (1:8 and 1:32, respectively). Tests for HBs antigen and antibody, HCV antibody, syphilis, and *Streptococcus* were negative. Tests for antinuclear and antimitochondrial antibodies, C-ANCA, and P-ANCA were negative.

The patient was treated conservatively. However, the high blood glucose level persisted in spite of insulin administration, and convulsions and coma developed. She died on 5 January 1995. The autopsy was performed 9.5 h after death.

Materials and methods

Tissues from all autopsied organs were fixed in formaldehyde, processed routinely and stained with haematoxylin-eosin. Elastica van Gieson and Masson trichrome stains were added if necessary.

To clarify the phenotypes of the infiltrating cells and to detect cytotoxic protein expression of them, immunohistochemistry using the labelled streptavidin-biotin method (Dako, Glostrup, Denmark) was performed on the formaldehyde-fixed paraffin-embedded sections of the submandibular gland, pancreas, and kidney. The following antibodies (monoclonal antibodies except for CD3) were used (source; clone; dilution in parenthesis): CD20 (Dako; L26; 1:100), CD79α (Dako; JCB117; 1:50), CD45RO (Dako; OPD4; 1:100), CD3 (Dako; polyclonal; 1:100), CD4 (Novocastra Laboratories, Newcastle, UK; 1F6; 1:40), CD8 (Dako; C8/144B; 1:50), CD16 (Novocastra Laboratories; 2H7; 1:40), CD57 (Novocastra Laboratories; NK-1; 1:50), CD68 (Dako; KP1; 1:100), antigranzyme B (CHEMICON, Temecula, Calif.; GrB-7; 1:20), and TIA-1 (Coulter Immunology, Hialeah, Fla.; TIA-1; 1:20). Antigen retrieval treatments by autoclaving for CD79α, CD4 and antigranzyme B, by microwaving for CD8, CD16, CD68 and TIA-1, and by trypsin digestion for CD3 and CD57, were carried out before immunostaining.

To detect EBV genomes in the tissues, DNA-RNA and DNA-DNA ISH were performed using sense and antisense oligonucleotide probes labelled with alkaline phosphatase on the formaldehyde-fixed paraffin-embedded sections of the submandibular gland, pancreas, and kidney. The probes were specific to EBER1 for DNA-RNA ISH and the EBV BamHI W fragment for DNA-DNA ISH, respectively. The sequences of the probes and the method of ISH have already been described [6, 29]. Briefly, after dewaxing, rehydration, and proteinase K digestion, the sections were hybridized with the probes overnight at 37°C. For DNA-DNA ISH, the sections were denatured with formamide before hybridization. Signals were visualized by development with nitroblue tetrazolium chloride (NBT) and 5-bromo-4-chloro-3-indolylphosphate (BCIP). A dark purple-to-black colour within the nucleus was regarded as a positive reaction when it was more intense than the background level.

Pathological findings

The cadaver showed jaundice and exfoliation of the generalized skin. The icteric liver and the spleen were grossly enlarged and weighed 1, 750 g and 245 g, respectively. The left and right kidneys weighed 185 g and 200 g, respectively. They were oedematous and icteric, and microabscess-like small whitish patches were found in the cut surfaces. The same kind of white patches were also seen in the cut surface of the thyroid. The pancreas was oedematous and weighed 85 g. The left and right adrenals weighed 5.0 g and 6.0 g, respectively, and showed cortical lipoid depletion. Small scars were revealed in the left ventricular wall of the heart (280 g in weight). The left and right lungs weighed 500 g and 450 g, respectively, and showed congestion and oedema. Bloody ascites (400 ml) and bilateral bloody pleural effusion (left: 200 ml, right: 500 ml) were revealed.

Histological examination of the organs revealed two major findings. The first was granulomatous vasculitis with multinucleated giant cells of the small arteries and arterioles in multiple organs, including the kidneys, pancreas, liver, spleen, heart, lymph nodes, submandibular gland, intestine, and vagina (Fig. 1). The vasculitis contained lymphocytes, plasma cells, histiocytes (both phagocytic and nonphagocytic), and a few neutrophils. Infiltration of eosinophils, fibrinoid necrosis, and capillaritis were absent. In the kidneys, pancreas, and spleen many small arteries and arterioles showed granulomatous vasculitis. In the pancreas immune cells also infiltrated into the acini and even into the islets destructively. Granulomatous vasculitis was revealed in a small number of vessels in the other organs. In the submandubular gland vas-

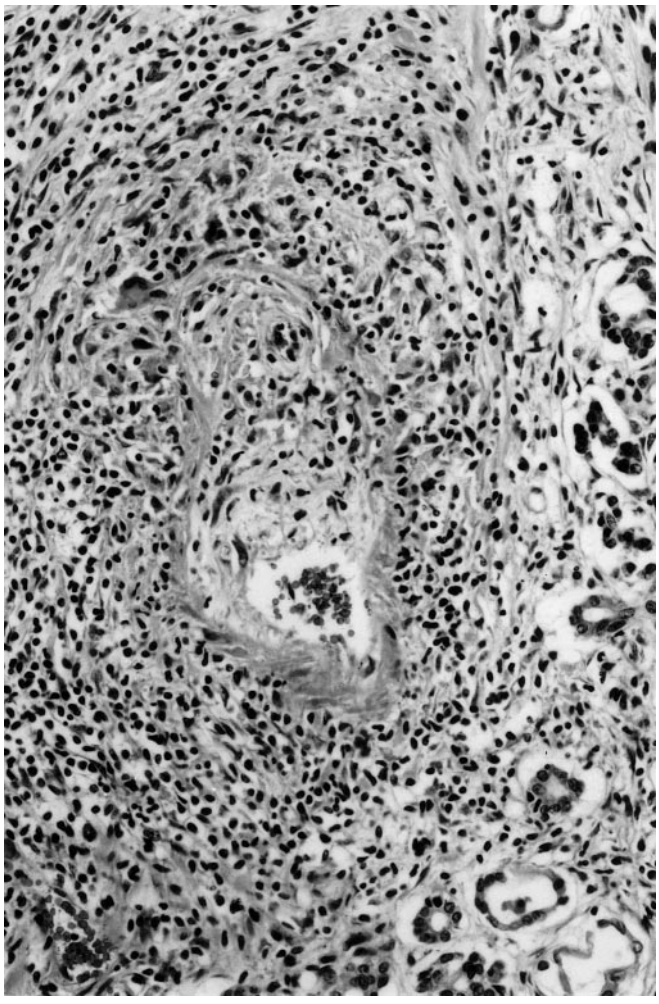

Fig. 1 Granulomatous arteritis with multinucleated giant cells affecting a small artery of the pancreas. Haematoxylin-eosin, original magnification ×250

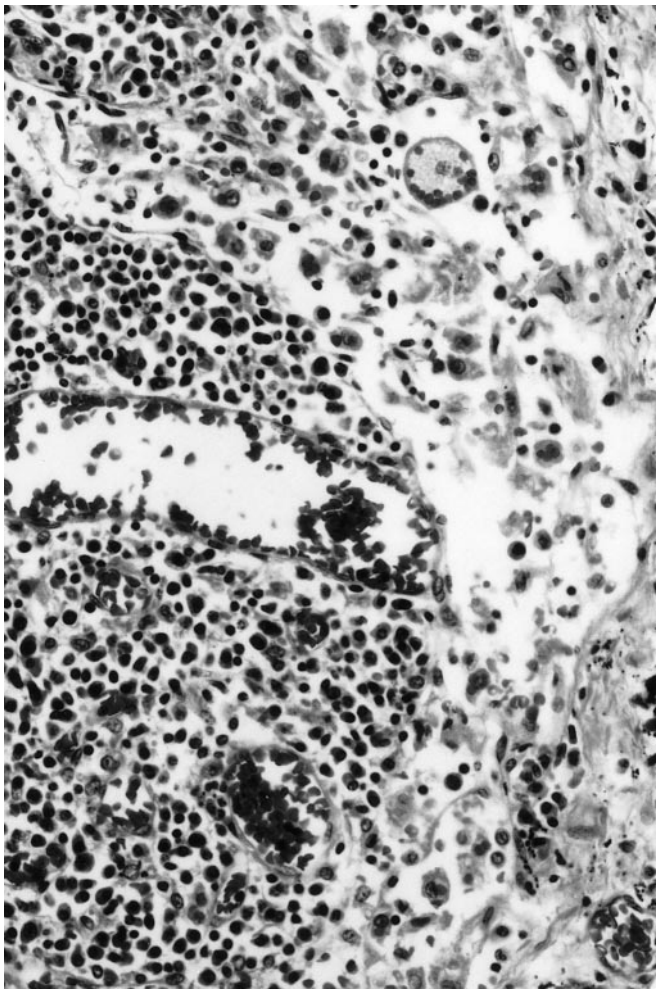

Fig. 2 Infiltration of haemophagocytic histiocytes in the marginal sinus of the lymph node. Haematoxylin-eosin, original magnification ×320

culitic lesions were few, but many foci of periductal infiltration of lymphocytes with atrophy of the acini were identified. In the thyroid several epithelioid cell granulomas with multinucleated giant cells were seen, but they were not associated with vessels.

The second finding was infiltration of many phagocytic histiocytes, some of which showed haemophagocytosis, into the bone marrow, sinuses of the lymph nodes, splenic sinuses, and hepatic sinuses (Fig. 2). The liver showed prominent proliferation of bile ductules in the portal areas and severe bile stasis.

Associated with the above, the following findings were seen. Interface dermatitis was noted on the skin with many cytoid bodies and parakeratosis. No granulomatous vasculitis or leucocytoclastic vasculitis was identified. The lungs were oedematous, and mild bronchopneumonia without vasculitis was evident. Atherosclerosis was present in the large arteries to a moderate to severe degree, but granulomatous vasculitis was not noted in these arteries. Neither vasculitis nor myositis was revealed in the iliopsoas muscle. Even with all the findings mentioned above, neither lymphocytes nor histiocytes showed atypia suggestive of malignant lymphoma or malignant histiocytosis. Autopsy of the central nervous system was not permitted.

Immunohistochemically, infiltrating cells in the submandibular gland, pancreas and kidney included T-lymphocytes (CD45RO+ and/or CD3+), B-lymphocytes and plasma cells (CD20+ and/or CD79α+), CD68+ histiocytes and a few cells positive for CD16 or CD57 (markers for natural killer cells). Among the lymphocytes T-cells predominated, especially CD4+ T-cells rather than CD8+ T-cells in the vasculitic lesions (Fig. 3a, b). CD68+ histiocytes infiltrated diffusely into the pancreas and kidney, but were identified only in a few vasculitic lesions in the submandibular gland. Granzyme B was detected in a few lymphocytes, and TIA-1 was detected in neutrophils and a few lymphocytes.

By DNA-RNA (EBER1) and DNA-DNA (Bam HI W fragment) ISH, positive signals were identified in the ductal epithelial cells, acinar cells, and infiltrating cells of the submandibular gland and pancreas (Fig. 4a, b), in

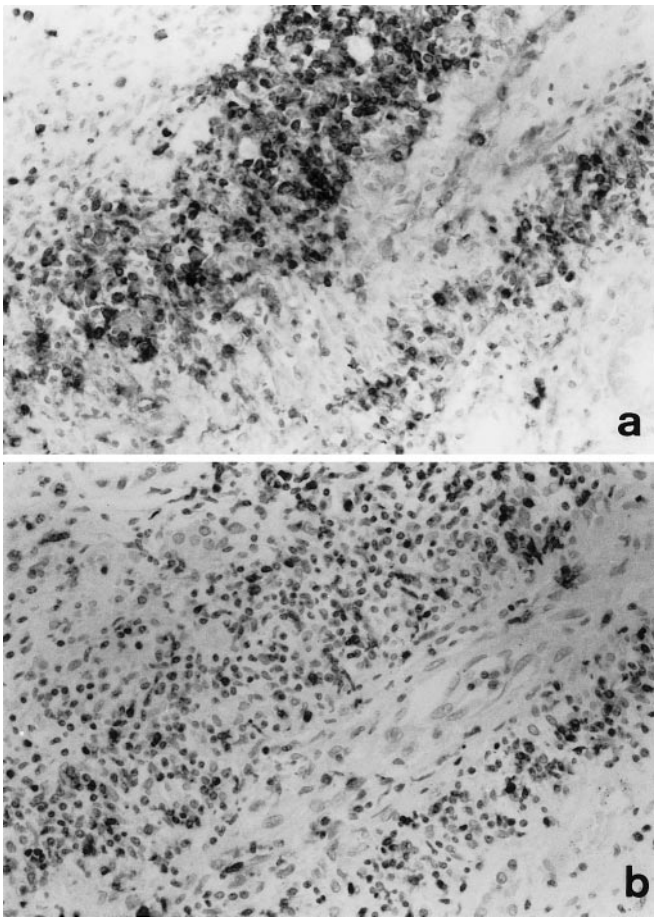

Fig. 3 Immunohistochemistry for phenotypic identification of the infiltrating cells of the kidney. **a** CD4. **b** CD8. Infiltrating cells of the vasculitis lesion are predominantly CD4+ T-cells. Labelled streptavidin-biotin method, original magnification ×320

a few endothelial cells of the pancreas and in the epithelial cells of the urinary tubules of the kidney. In the submandibular gland, positive infiltrating cells were lymphocytes. In the pancreas, positive infiltrating cells were mainly lymphocytes, but positivity of a few histiocytes was also probable, though it could not be confirmed, in the vasculitic lesions. No signals were detected with sense probes.

Discussion

The systemic vasculitis in this case was characterized by granulomatous vasculitis with multinucleated giant cells affecting small arteries and arterioles and an absence of fibrinoid necrosis and eosinophils. Because of these characteristics, at first, we regarded this patient's condition as a case of disseminated visceral giant cell arteritis as described by Lie [17]. However, disseminated visceral giant cell arteritis may be a syndrome caused by various factors relating to autoimmunity, allergy, infection, and so on [17, 20]. In this case, clinical findings, such as positive results of tests for anti-EBV antibody and heterophil agglutinins and increased atypical lymphocytes in the peripheral blood, suggested EBV infection. Pathologically, haemophagocytic histiocytes were revealed in multiple organs. Although clinical findings in the present case did not fulfill the clinical criteria of the haemophagocytic syndrome (HPS) [5], pathological findings were consistent with HPS. Detection of EBV genomes by ISH in the affected tissues enabled us to confirm an association with EBV infection. Therefore, we regarded this case as one of EBV-AHS associated with systemic granulomatous arteritis.

VAHS, including EBV-AHS, usually occurs in childhood, and in adulthood HPS often occurs in association with lymphocytic malignancies [28]. However, VHAS or EBV-AHS in adults has also been reported [15, 27]. Shirono et al. reported cases of VAHS that occurred in previously healthy adults [27], as was the case for the present patient.

A problem was whether the condition in this case was a primary infection or a reactivation of EBV. The results of the serological tests: positive for anti-VCA-IgG antibody and negative for anti-EBNA antibody, suggest an acute primary infection. However, negative test results for anti-VCA-IgM and anti-EA-IgG antibodies are atypical. Nevertheless, in view of the patient's age, reactivation is a more likely cause than a primary infection. However, the titre of anti-EA-IgG antibody was low. This dilemma may be explained by the existence of an EBV-AHS case with unusual findings relating to EBV-related antibodies [14, 21] or an alteration of EBV-related antibody titres during the reactivation process [30], although the cause of the reactivation is unknown.

EBV is usually B-lymphotrophic. However, in EBV-AHS or chronic active EBV infection patients, T-cells are also infected by EBV [10, 13, 22]. The pathogenetic mechanism of EBV-AHS is currently explained with reference to findings showing that EBV-infected T-cells are activated and proliferate monoclonally or oligoclonally, producing excess cytokines, such as interferon-γ, tumour necrosis factor-α, interleukin-6 and macrophage-colony stimulating factor, followed by activation of monocytes/macrophages. Activated monocytes/macrophages in turn produce cytokines resulting in HPS [12, 16, 26, 28]. In this case, the infiltrating lymphocytes were mainly T-cells (CD4+ and CD8+), with a predominance of CD4+ T-cells. Therefore, EBV-infected lymphocytes identified by ISH were considered to be T-cells and to include CD4+ T-cells, suggesting that CD4+ T-cells are one target of EBV infection. Kikuta et al. also detected EBV genomes in CD4+ T-cells of a chronic active EBV infection patient [13]. Since CD4+ T-cells play an important part in cell-mediated immune responses to EBV infection through cytokine production [11, 26], it is believed that, in this case, EBV-infected activated CD4+ T-cells played a part in the activation of monocytes/macrophages through cytokine production, although we cannot confirm the clonality of T-cells or hypercytokinaemia. However, in this case, some of the cells with EBV genomes appeared morphologically to be histiocytes, although this was not confirmed. EBV-

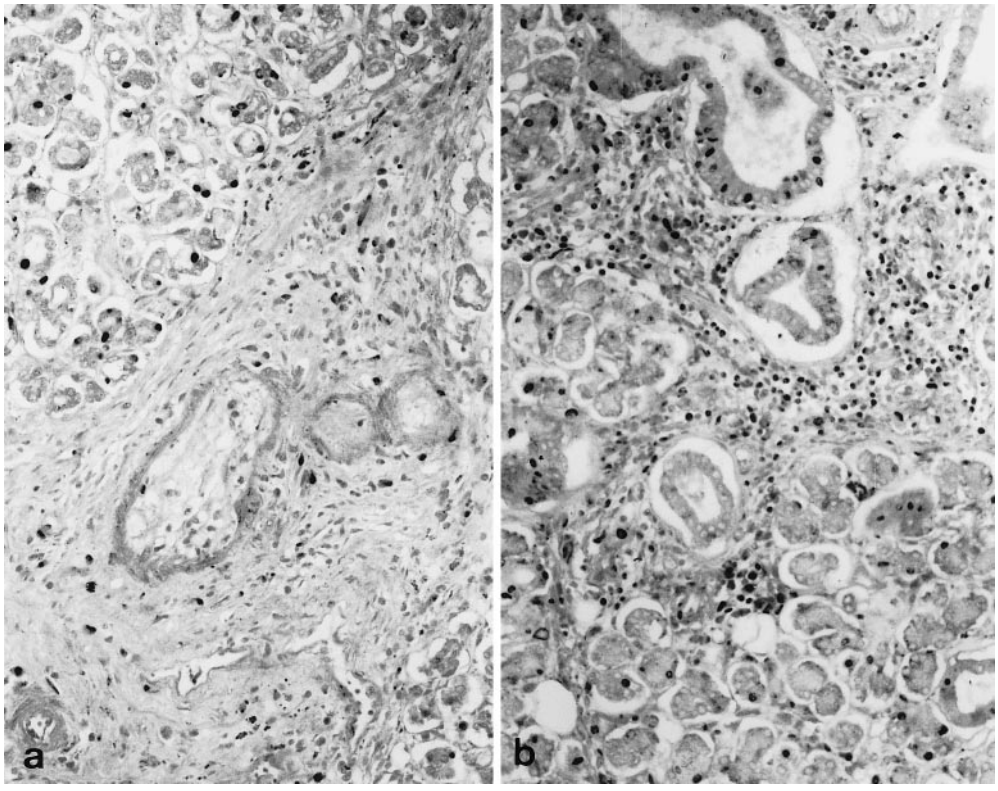

Fig. 4 In situ hybridization with EBV-specific oligonucleotide probes. **a** Pancreas showing positive signals in the vasculitis lesion and the acinar cells with the BamHI W fragment probe. Positive cells of the vasculitis lesion are lymphocytes and probably histiocytes. **b** Submandibular gland showing positive signals in the lymphocytes, acinar cells, and ductal epithelial cells with the EBER1 probe. original magnification ×200

infected histiocytes have been demonstrated in EBV-AHS patients [15, 25]. Therefore, direct activation of histiocytes by EBV infection is also assumed to have occurred instead of cytokine-mediated activation.

In this case, EBV genomes were detected not only in the immune cells but also in the epithelial and endothelial cells. Infection of nonneoplastic epithelial cells with EBV has been demonstrated in the stomach of patients with chronic atrophic gastritis or a carcinoma [35] and in the salivary glands of patients with T-cell lymphoma or Sjögren's syndrome [32, 33]. Infection of endothelial cells with EBV has also been reported [9]. Kikuta et al. reported a EBV-AHS patient in whom EBV genomes were detected in hepatocytes [14]. In chronic active EBV infection patient reported by Joh et al., EBV genomes were detected in the epithelial cells of the urinary tubules [8]. Therefore, various kinds of cells other than lymphocytes can become targets for EBV infection. However, one characteristic of this case was the generalization of EBV infection to the various kinds of tissues.

Cytotoxic T lymphocytes (CTLs) derived from both CD8+ and CD4+ T-cells emerge and are believed to play an important role in controlling EBV infection [11]. One of the main cytotoxic mechanisms of CTLs is exocytosis of granule-associated cytotoxic proteins, such as perforin, T-cell intracellular antigen-1 (TIA-1), and granzymes [1, 2]. However, in this case, only a few infiltrating lymphocytes expressed TIA-1 or granzyme B. The lack of this CTL activity might permit the widespread EBV infection.

This case, with destructive infiltration of EBV-infected T-lymphocytes (predominantly CD4+ T-cells) in both the pancreas and the submandibular gland, presents findings similar to those seen in Sjögren's syndrome, in which EBV infected CD4+ T-lymphocytes assault EBV-infected acinar and duct epithelial cells [31, 32]. Although the targets of the assault were not definitely identified [31], it is considered that in this case, EBV-infected epithelial cells generate immune responses and that CD4+ T-cells have a role in those immune responses.

The arteritis was granulomatous, and cell-mediated immune responses are believed to contribute to this form of vasculitis. We consider that the EBV-infected activated CD4+ T-cells and activated histiocytes infiltrating into the lesions are related to the pathogenesis of the arteritis in this case, although the targets of the immune response cannot be determined. In other diseases showing systemic granulomatous vasculitis, such as giant cell arteritis or Wegener's granulomatosis, the contribution of CD4+ T-cells to the pathogenesis has been reported [19, 34], supporting a major role for CD4+ T-cells in the pathogenesis of vasculitic lesions.

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