

Hypocomplementemic Urticarial Vasculitis Syndrome is Associated with High Levels of Serum IgG4: A Clinical Manifestation that Mimics IgG4-related Disease

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Abstract

A 58-year-old Japanese woman presented with recurrent abdominal pain, chronic urticaria, and petechiae on her extremities, and hypocomplementemia, findings that were consistent with hypocomplementemic urticarial vasculitis syndrome (HUVS). A laboratory examination revealed that she had markedly elevated IgG levels (4,448 mg/dL; normal range, 870-1,700 mg/dL) with particularly high IgG4 levels (1,050 mg/dL; normal range, 48-105 mg/dL) and a high IgG4/total IgG ratio (0.22; normal range, 0.02-0.05). A skin biopsy demonstrated leukocytoclastic vasculitis with IgG4 deposition in the vascular lumen and vascular walls. A lymph node biopsy revealed reactive lymphoid hyperplasia with numerous IgG4-positive cells in the perifollicular area, but no sclerotic findings. A chromosomal analysis of an enlarged lymph node, without phytohemagglutinin (PHA) stimulation, demonstrated that one in every three analyzed cells had abnormalities, such as 44, XX, -13, add(15)(p11), -17, -17, and mar.

Key words: IgG4-related disease, hypocomplementemic urticarial vasculitis syndrome (HUVS), vasculitis, lymphadenopathy

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Introduction

It is well established that hypocomplementemia can occur in patients with poststreptococcal acute glomerulonephritis, membranoproliferative glomerulonephritis, lupus nephritis, cryoglobulinemia, heavy chain deposition disease, and an acquired C1 esterase inhibitor deficiency. In the 1970s, a syndrome that was associated with recurrent abdominal pain, urticarial vasculitis, and hypocomplementemia was defined as hypocomplementemic urticarial vasculitis syndrome (HUVS) (1, 2). Because HUVS has been detected in patients with lupus nephritis and cryoglobulinemia, HUVS is now considered a clinical syndrome and not a disease entity (3, 4). Recently, it was determined that hypocomplementemia occurs in 30-40% of patients with IgG4-related disease, a condition that has received much attention since it

was identified as a new disease entity in the early 2000s (5-7). Here, we report a patient with HUVS who presented with a high level of serum IgG4 and discuss the relationship between HUVS and IgG4-related disease.

Case Report

A 58-year-old Japanese woman was admitted to Aichi Medical University Hospital for upper abdominal pain. Thirteen years prior to this hospitalization, she was diagnosed with rheumatoid arthritis at a neighboring hospital and subsequently administered 15 mg/day of prednisolone and 6 mg/week of methotrexate. After one year, her symptoms disappeared and the medications were stopped. One year before being admitted to our hospital, she visited a local doctor because of severe upper abdominal pain. Intensive examinations, including fiberoptic examinations of her upper and

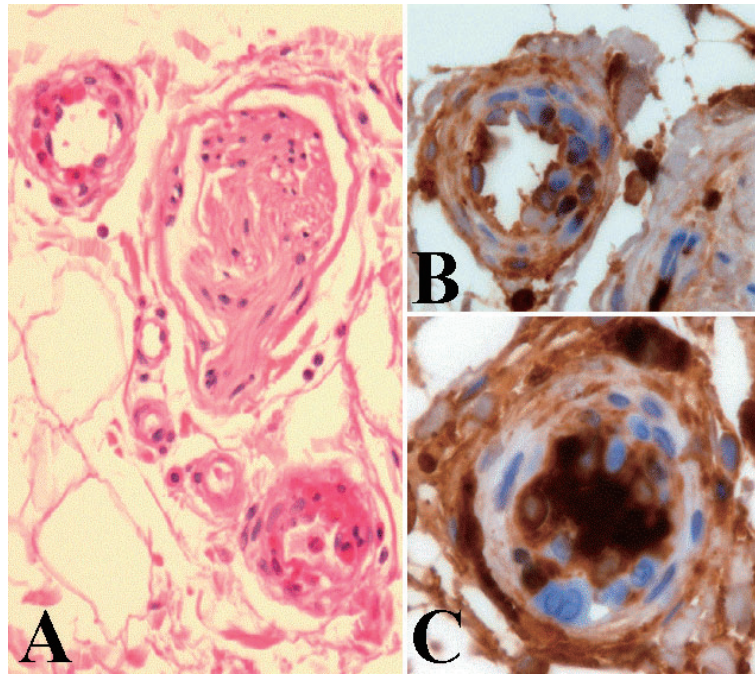


Figure 1. Light microscopic examination of a skin biopsy specimen. A: Leukocytes infiltrated the walls of a small artery, and fibrinoid changes were observed in the small artery (Hematoxylin and Eosin staining $\times 400$). B: IgG4-positive cells infiltrated the wall of the upper small artery (IgG4 enzyme immunostaining $\times 1000$). C: IgG4-positive cells also infiltrated the wall of the lower small artery, and strong staining was detected in the lumen of the small artery (IgG4 enzyme immunostaining $\times 1000$).

lower alimentary tracts, an enhanced CT scan, and ERCP, revealed no abnormal findings. She was treated with antibiotics and fluid supplementation for suspected chronic pancreatitis. Three months prior to admission, she visited the pain clinic at Aichi Medical University Hospital because of post-herpetic neuralgia in her left lower abdomen.

Upon admission, she was fully alert and oriented. A physical examination confirmed a high fever (38.7°C), hepatomegaly (2qfb), splenomegaly (3qfb), axillary lymph node swelling on both sides, urticaria in her upper extremities, and petechiae and edema in her lower extremities.

Laboratory studies revealed 1+ proteinuria (0.6 g/day), negative urine occult blood, total serum protein of 9.4 g/dL, albumin of 2.6 g/dL, blood urea nitrogen of 19.4 mg/dL, serum creatinine of 0.54 mg/dL, and total cholesterol of 102 mg/dL. Her C-reactive protein was 4.06 mg/dL and rheumatoid factor was 787.5 IU/mL (normal range, below 20). The patient was negative for anti-nuclear antibodies, anti-SS-A and SS-B antibodies, Hepatitis B antigen, Hepatitis C virus antibodies, and cryoglobulin. Her IgG, IgA, and IgM levels were 4,448 mg/dL (normal range, 870-1,700 mg/dL), 59 mg/dL (normal range, 110-410 mg/dL), and 200 mg/dL (normal range, 35-220 mg/dL), respectively. M-protein and Bence Jones protein were not detected in the serum or urine. Her C3, C4, and CH50 levels were 29.1 mg/dL (normal range, 65-135 mg/dL), 2.5 mg/dL (normal range, 13.0-35.0 mg/dL), and below 10 U/mL (normal range, 30.0-40.0 U/mL), respectively. The level of C1q immune complexes was 26 $\mu\text{g/dL}$ (normal range, 8.8-15.3 $\mu\text{g/dL}$), the C1 inactivator

activity was 65% (normal range, 70-130%), and the level of soluble IL-2 receptor was 3,890 U/mL (normal range, 220-530 U/mL).

Plain and enhanced abdominal CT scans revealed that the anterior wall of the stomach and small intestine were enlarged with edematous changes and that multiple lymph nodes in the abdominal cavity were swollen. A ^{67}Ga scintigram showed hot spot lesions between the stomach and spleen and in the bilateral axillar area. Fiberscopic examinations of the upper and lower alimentary tracts revealed erosive gastritis and non-specific inflammation, respectively.

An analysis of the IgG subclasses revealed that the IgG1, IgG2, IgG3, and IgG4 levels were 1,730 mg/dL (normal range, 320-740 mg/dL), 1,780 mg/dL (normal range, 208-754 mg/dL), 59 mg/dL (normal range, 66-88 mg/dL), and 1,050 mg/dL (normal range, 48-105 mg/dL), respectively. The ratios at the upper limit for each IgG subclass were 2.3, 2.3, 0.7, and 10.0, respectively. The ratios of IgG1, IgG2, IgG3, and IgG4/the total IgG were 0.38, 0.39, 0.013, and 0.22 (normal range, 0.02-0.05), respectively.

A skin biopsy showed findings of leukocytoclastic vasculitis with an increased number of cells in the capillary walls and degenerative changes in part of the capillary walls. Enzyme immunostaining with an anti-IgG4 antibody revealed that IgG4-positive cells had infiltrated into the arterial walls and the area surrounding the small artery, and showed strong positive staining that resembled IgG4 emboli in the arterial lumen (Fig. 1).

A lymph node biopsy showed that the essential structure

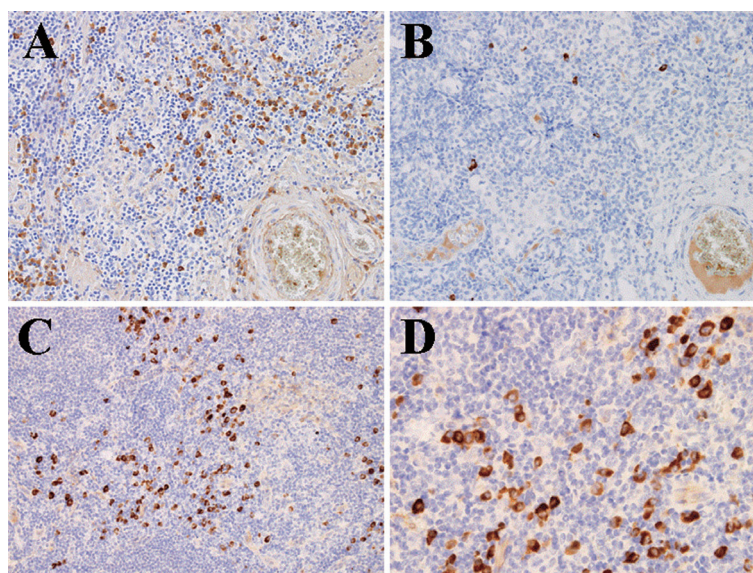


Figure 2. Light microscopic examination of a lymph node biopsy specimen. A: IgG immunostaining of the lymph node from a control patient with reactive lymphadenitis. There were many IgG-positive cells in the area surrounding the follicles (IgG enzyme immunostaining $\times 20$). B: IgG4 immunostaining in the above patient. There were scant numbers of IgG4-positive cells in the area surrounding the follicles (IgG4 enzyme immunostaining $\times 20$). C: IgG4 immunostaining in the present patient. Many IgG4-positive cells were present in the area surrounding the follicles (IgG4 enzyme immunostaining $\times 20$). D: An enlarged photograph of the above figure (IgG4 enzyme immunostaining $\times 40$).

of the lymph node was conserved, but that there was an increased number of cells, consisting of macrophages, lymphocytes, and plasma cells, in the area surrounding the follicles. These findings were comparable with reactive lymphoid hyperplasia due to autoimmune diseases (8), but were different from that of angioimmunoblastic T-cell lymphoma or B-cell lymphoma, as determined by Dr. Shigeo Nakamura, Department of Clinical Pathophysiology/Clinical Pathology, Nagoya University Graduate School of Medicine. Enzyme immunostaining with an anti-IgG4 antibody demonstrated that there were many IgG4-positive cells surrounding the follicles but not in the center of the follicles compared with a control case of reactive lymphadenitis (Fig. 2).

A chromosomal analysis by G-band without phytohemagglutinin (PHA) stimulation showed that one in every three analyzed cells had abnormalities, such as 44, XX, -13, add (15)(p11), -17, -17, and mar. These findings indicate that this patient had a chimeric state of normal and abnormal lymphocytes. T-cell receptor rearrangement was not analyzed.

Clinical course

A dermatologist prescribed 0.5 mg/day of dexamethasone for leukocytoclastic vasculitis, after which her skin lesions and abdominal pain disappeared. However, after dexamethasone was withdrawn, the abdominal pain recurred. Prednisolone (10 mg/day) relieved these symptoms. After the patient was diagnosed with HUVS, the prednisolone dose was increased to 15 mg/day. Subsequently, the abnormal laboratory data, including the increased levels of IgG, complement,

rheumatoid factor, and circulating C1q-immune complexes as well as hepatosplenomegaly and lymph node swelling, were gradually improved.

Discussion

The patient presented in this report had symptoms that met the criteria for hypocomplementemic urticarial vasculitis syndrome (HUVS) proposed by Schwartz et al (9). This definition stipulates that the patient must meet at least two of the following six criteria: 1) vasculitis by skin biopsy, 2) arthralgia or arthritis, 3) uveitis or episcleritis, 4) recurrent abdominal pain, 5) glomerulonephritis, and 6) decreased C1q or increased C1q immune complexes. It was confirmed that the present patient had vasculitis based on a skin biopsy, recurrent abdominal pain, increased levels of C1q immune complexes, and suspicious glomerulonephritis as indicated by proteinuria. When diagnosing patients, acquired C1 esterase inhibitor deficiency (ACID) should be distinguished from HUVS. According to a review by Markovic et al (10), ACID is characterized by normal C3 levels, decreased C4 levels, and a significant decrease in C1 inactivator activity. The present patient did not meet these criteria because both her C3 and C4 levels were decreased and her C1 inactivator activity was close to normal at 65% (normal range, 70-130%).

Recently, IgG4-related disease or IgG4-positive multi-organ lymphoproliferative syndrome was proposed to be a novel disease entity (6, 7, 11), which includes sclerosing pancreatitis (12), sclerotic cholangitis (13), acute interstitial

nephritis (5, 14), retroperitoneal fibrosis (15), and Mikulicz's disease (16). These disorders are associated with significantly elevated serum IgG4 levels and the infiltration of IgG4-producing cells into several organs and numerous fibers. Thirty to forty percent of patients with IgG4-related disease have hypocomplementemia. An analysis of the IgG subclasses in the present patient revealed significantly elevated IgG4 at 1,050 mg/dL (normal range, 48-105 mg/dL), and an IgG4/total IgG ratio of 0.22 (normal range, 0.02-0.05). In the present case, no sclerotic changes were observed.

Regarding the role of IgG4 in IgG4-related disorders, it is well established that IgG4 does not activate the classical complement pathway (17) and that other IgG subclasses likely activate complement (18). It is still unknown whether high levels of IgG4 in the sera are indicative of the phenomenon or are a cause of IgG4-related disease.

In the present case, a chromosomal analysis of the patient's lymph nodes in the absence of PHA stimulation revealed abnormal clones such as 44, XX, -13, add(15)(p11), -17, -17, and mar. These abnormalities indicate that the patient had a chimeric state of normal and abnormal lymphocytes. Fetal microchimerism was proposed to have a role in the pathogenesis of autoimmune diseases (19). In the present case, a non-fetal gene mutation produced this chimeric state. Abnormal immune reactions are thought to occur due to a mixture of normal and abnormal clones in the lymph node, which may induce HUVS and high levels of serum IgG4. Because it is still possible that the present patient will develop malignant lymphoma in the future, we will continue to follow the progress of this patient. Identifying and studying similar cases, such as HUVS with clinical features that mimic IgG4-related disease, will further clarify the pathogenesis of this novel disease.

The authors state that they have no Conflict of Interest (COI).

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