

Churg-Strauss Syndrome with a Clinical Condition Similar to IgG4-Related Kidney Disease: A Case Report

Nobuhiro Ayuzawa^{1,4}, Yoshifumi Ubara^{1,5}, Sumida Keiichi¹, Yamanouchi Masayuki¹, Eiko Hasegawa¹, Eriko Hiramatsu¹, Noriko Hayami¹, Tatsuya Suwabe¹, Junichi Hoshino¹, Naoki Sawa¹, Masateru Kawabata², Kenichi Ohashi³ and Kennmei Takaichi^{1,5}

Abstract

A 68-year-old Japanese woman with asthma of recent onset and a long history of membranous glomerulonephropathy (MN) was admitted because of multifocal pulmonary infiltrates, marked eosinophilia, mild renal dysfunction, a rash on her feet, and right median nerve paralysis. Although MPO- and PR3-ANCA were negative, skin biopsy demonstrated leukocytoclastic vasculitis and Churg-Strauss Syndrome (CSS) was diagnosed. She also had salivary gland swelling and a high serum IgG4 level. Renal biopsy revealed MN with eosinophil-rich tubulointerstitial nephropathy. Her symptoms resolved after the start of corticosteroid therapy. The present case shows that ANCA-negative CSS can have a clinical condition similar to IgG4-related kidney disease.

Key words: IgG4-related kidney disease, Churg-Strauss syndrome, ANCA negative, membranous nephropathy, tubulointerstitial nephritis

(Intern Med 51: 1233-1238, 2012)

(DOI: 10.2169/internalmedicine.51.6074)

Introduction

Churg-Strauss syndrome (CSS) was first described in 1951; it is a rare systemic disorder in which eosinophil-rich granulomatous inflammation involves the respiratory tract along with necrotizing vasculitis of small to medium-sized vessels, and it is associated with both asthma and eosinophilia (1, 2). Three phases of CSS can usually be recognized. Allergies such as asthma and rhinitis may precede the onset by some months, and sometimes by several years, after which eosinophilic infiltrative disease develops along with eosinophilic pneumonia or gastroenteritis, and this is followed by the vasculitis phase (3-6). The American College of Rheumatology (7) has proposed the following 6 criteria for the diagnosis of CSS: asthma, eosinophilia>10%, paranasal sinusitis, pulmonary infiltrates, histologic proof of vasculitis, and mononeuritis multiplex. Although CSS is

considered to be one of the antineutrophil cytoplasmic antibody-associated systemic vasculitides (AASVs) (8, 9), the actual detection rate of antineutrophil cytoplasmic antibodies (ANCA) in CSS patients is variable, ranging from 40 to 70% (10, 11). IgG4 only accounts for 3 to 6% of the total serum IgG in normal persons, but it is increased in patients with a recently proposed novel clinicopathological entity known as IgG4-related disorders (12-14).

In this report, we discuss the possible relation between CSS and IgG4-related disorders, including membranous nephropathy and tubulointerstitial nephropathy.

Case Report

In mid-September 2008, a 68-year-old Japanese woman was admitted to our institution with productive cough, exertional dyspnea, a rash on the dorsum of both feet, polyarthralgia, polymyalgia, and paralysis of the right upper limb.

¹Nephrology Center, Toranomon Hospital, Japan, ²Department of Respiratory Medicine, Toranomon Hospital, Japan, ³Department of Pathology, Toranomon Hospital, Japan, ⁴Department of Nephrology & Endocrinology, Graduate School of Medicine, The University of Tokyo, Japan and ⁵Okinaka Memorial Institute for Medical Research, Toranomon Hospital, Japan

Received for publication June 27, 2011; Accepted for publication February 6, 2012

Correspondence to Dr. Yoshifumi Ubara, ubara@toranomon.gr.jp

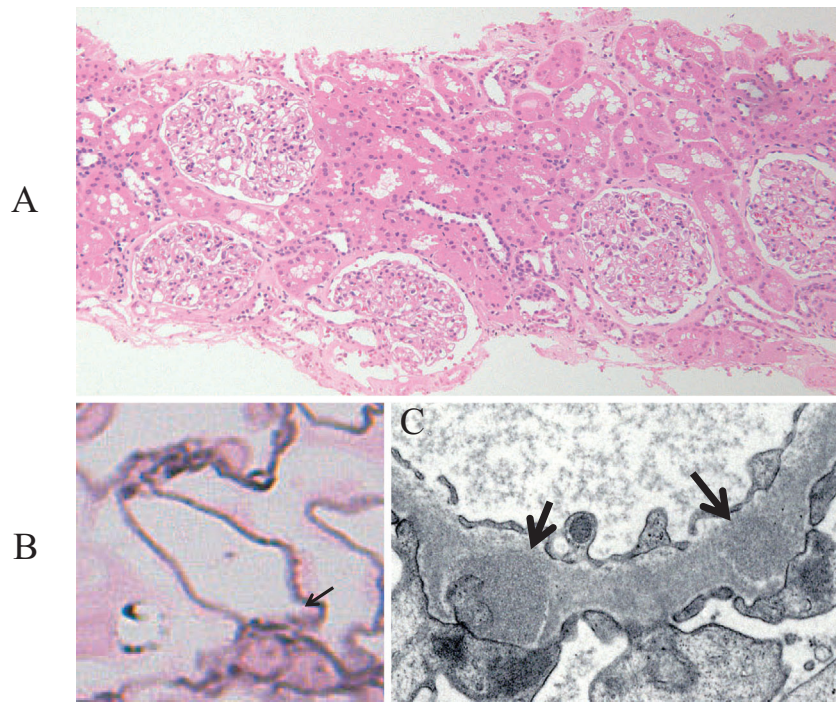


Figure 1. A: Light microscopic examination of a renal biopsy specimen containing 16 glomeruli does not reveal collapse (Hematoxylin and Eosin staining). A few inflammatory cells are scattered in the tubulointerstitium (negative for IgG and IgG4 staining). B: Mild thickening of the capillary walls with spike formation (arrow) (periodic acid methenamine silver stain). C: Electron microscopy reveals electron-dense deposits (arrows) on the subepithelial surface of the glomerular capillary walls.



Figure 2. Chest X-ray film shows multifocal patchy non-segmental consolidation, which is more prominent in the upper lung fields, and blunting of the bilateral costophrenic angles.

Renal biopsy had been performed in 1996 because of proteinuria (1.2 g daily) and hypertension (170/90 mmHg). Membranous glomerulonephritis associated with nephrosclerosis was diagnosed. There were scanty inflammatory cell infiltrates in the tubulointerstitium (negative for IgG and IgG4) (Fig. 1A-C). She was being treated with a calcium channel blocker, an angiotensin-receptor antagonist, cyclosporine, and mizoribine. Although normal renal function

and blood pressure had been maintained, mild proteinuria and occult hematuria were still detected.

Approximately 6 months prior to admission, she had developed asthma. Treatment was started with salmeterol/fluticasone, fexofenadine, and pranlukast and her symptoms subsided. However, asthma relapsed after 5 months and gradually became resistant to treatment. She also developed an itchy red rash on the dorsum of both feet. After several days, her wheezing and productive cough became markedly worse along with dyspnea on exertion and various other symptoms, including migratory polyarthralgia and polymyalgia. Finally, in mid-September 2008, she developed paralysis/paresthesia of the right upper limb and presented to our institution.

On admission, she was 156 cm tall and weighed 53.6 kg. Her blood pressure was 142/102 mmHg, her pulse rate was 92/min, her temperature was 35.5°C. Slight tachypnea was observed with an oxygen saturation of 94% while breathing room air. The salivary glands were enlarged and tender. Prominent coarse crackles and wheezing were heard in both lungs. A red rash was seen on the dorsum of both feet. Neurological examination revealed paralysis of the right median nerve with so-called ape hand. The chest X-ray film showed multifocal patchy areas of nonsegmental consolidation that were more prominent in the upper lungs, as well as blunting of the bilateral costophrenic angles (Fig. 2). Chest CT scans showed multifocal patchy areas of ground-glass opacity around the sites of patchy consolidation (i.e., the halo sign),

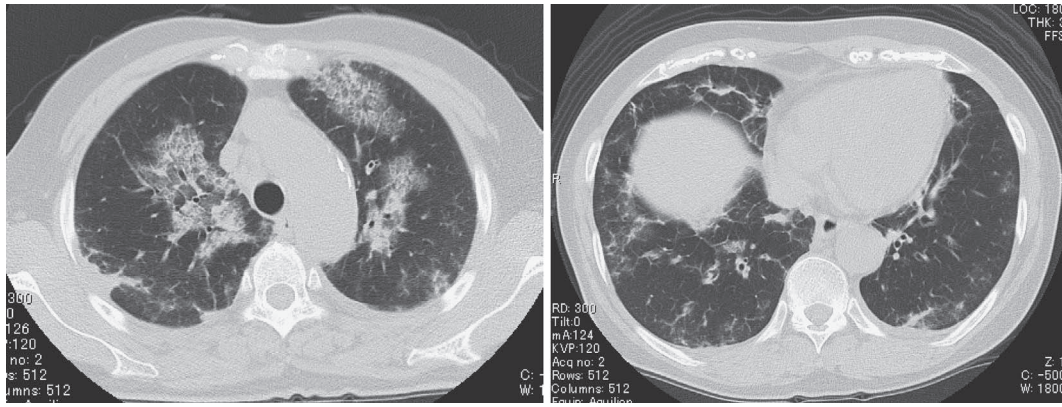


Figure 3. Chest CT scan shows multifocal patchy ground glass opacities around the areas of patchy consolidation (halo sign), evident thickening of bronchial walls and intralobular septa, and a medium-sized pleural effusion.

as well as thickening of the bronchial walls and intralobular septa, and a medium-sized pleural effusion (Fig. 3). The electrocardiogram showed no abnormalities. Laboratory tests revealed leukocytosis ($2.0 \times 10^4/\text{mL}$) with marked peripheral eosinophilia ($1.35 \times 10^4/\text{mL}$) and a high serum IgE titer (5,398 U/mL). Serum IgG was 1,997 mg/dL, IgA was 288 mg/dL, and IgG4 was 275 mg/dL. She also had mild normocytic normochromic anemia (Hb 11.3 g/dL), hypoalbuminemia (2.0 g/dL), hyponatremia (120 mEq/L), and nephrotic range proteinuria (9.9 g/day) with urinary sediment containing numerous erythrocytes per high power field. In addition, there was elevation of CRP (8.1 mg/dL), an increase of the ESR (110 mm/hr), and hypocomplementemia (CH50: 9 U/mL; C4: 13 mg/dL). Mild renal dysfunction was noted with a serum creatinine of 0.9 mg/dL. Blood gas analysis (on 3 L/min of oxygen) was within the normal range. Serological tests were negative for myeloperoxidase (MPO)-ANCA, proteinase 3 (PR3)-ANCA, antinuclear antibody, antidouble-stranded DNA antibody, and anti-SS-A/Ro antibody. However, rheumatoid factor was positive at a low titer (66 U/mL). Tests for bacteria were negative, although the soluble interleukin-2 receptor level was elevated to 3,301 U/L (normal <566 U/L). Nerve conduction studies showed severe neuropathy of the right median nerve. No abnormalities of the paranasal sinuses were detected by MRI. Cytologic examination of bronchoalveolar lavage fluid indicated the presence of severe nonspecific inflammation with marked elevation of the eosinophil count (total nucleated cells were $6.3 \times 10^3/\text{mL}$ and 86% were eosinophils), but there was no malignancy or hemorrhage. Plain abdominal CT did not show any abnormalities of the renal or pancreatic parenchyma. Percutaneous renal biopsy and skin biopsy (at the rash) were performed on the day of admission, but salivary gland biopsy was not done.

Renal biopsy

Light microscopic examination of the renal biopsy specimen identified 17 glomeruli, with collapse of 2 and segmental sclerosis of 1. Most of the other glomeruli were enlarged

(Fig. 4A). Some glomeruli showed an increase of mesangial matrix, but there was no evident increase in the number of mesangial cells. Diffuse thickening of the capillary walls was observed, as well as a bubbly appearance and spike formation (Fig. 4B). Immunofluorescence microscopy showed granular deposition of IgG (Fig. 4C) and C3 along the capillary loops. IgG subclass analysis revealed that these granular deposits were predominantly composed of IgG1 (Fig. 4D) with some IgG4 (Fig. 4E), while IgG2 and IgG3 were negative. Patchy infiltration of inflammatory cells, including lymphocytes, plasma cells, and eosinophils, was observed in the tubulointerstitium (Fig. 4F). Eosinophils were also seen in the glomerular capillaries (Fig. 4G). IgG4-positive plasma cells (Fig. 4H) accounted for about 10% of all IgG-positive plasma cells (Fig. 4I). Electron microscopy detected electron-dense to electron-lucent deposits on the subepithelial surface of the glomerular capillary walls (Fig. 4J). Membranous glomerulonephritis (stages III-IV) and tubulointerstitial nephritis with eosinophilia were diagnosed, but necrotizing or crescentic glomerulonephritis was not evident.

Skin biopsy

Focal infiltration of neutrophils, eosinophils, lymphocytes, and histiocytes with nuclear fragmentation was seen around the small vessels in the dermis, and extravasation of erythrocytes was also observed (Fig. 5). Eosinophils were predominant. Both IgG4-positive plasma cells and IgG-positive plasma cells were scant in the skin biopsy specimen. Leukocytoclastic vasculitis was diagnosed, but granulomatous angiitis was not observed.

Clinical course

We discontinued all of the patient's medications that had been prescribed before admission. Immunosuppressive therapy with high-dose intravenous methylprednisolone (1 g daily for 3 consecutive days) was followed by oral prednisolone (40 mg daily). After several days, her respiratory symptoms improved, and repeat CT showed marked reduction of both the pulmonary opacities and pleural effusion. Polyar-

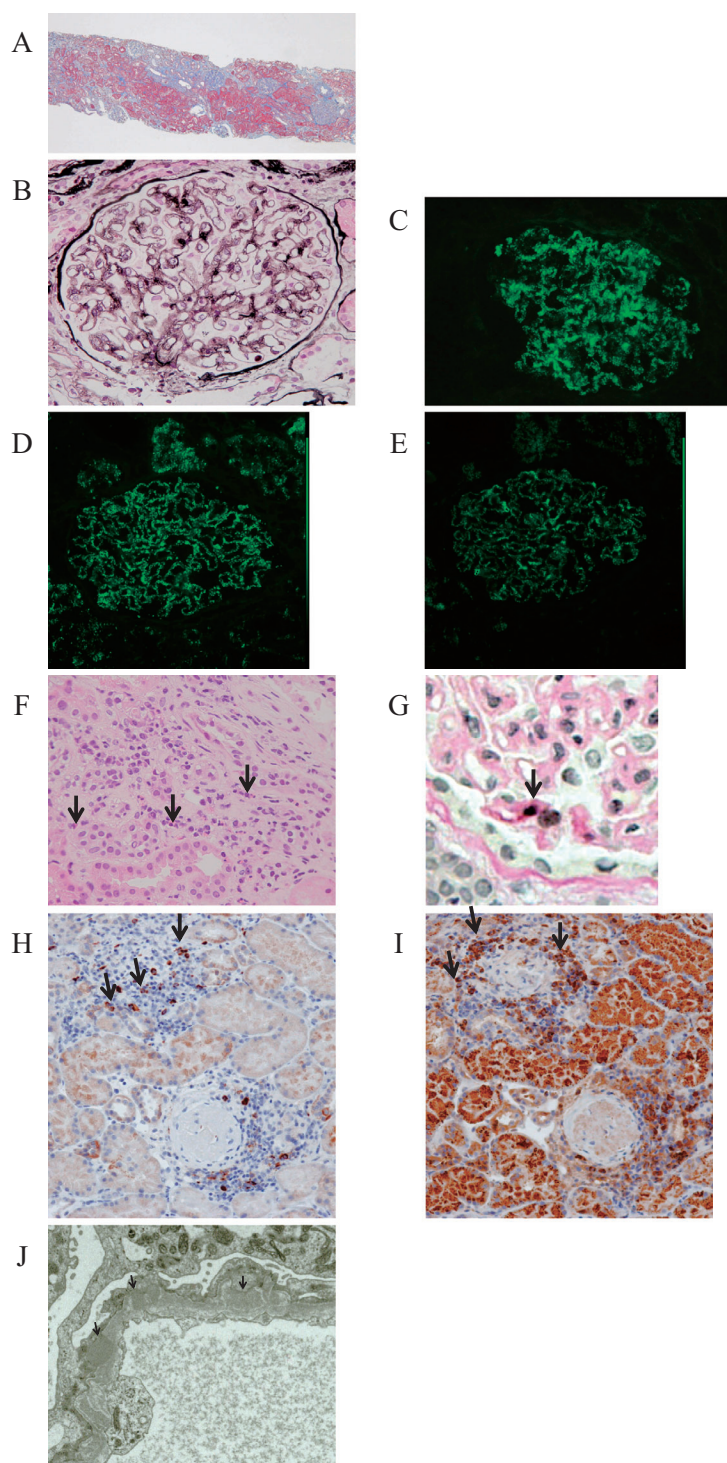


Figure 4. A: Light microscopic examination of a renal biopsy specimen containing 17 glomeruli reveals collapse of 2 and segmental sclerosis of 1. Most of the other glomeruli are enlarged (Masson's trichrome stain). B: Some glomeruli show an increase of mesangial matrix, but there is no evident increase in the number of mesangial cells. Diffuse thickening of the capillary walls can be observed. Bubbling and spike formation are also observed (periodic acid methenamine silver stain). C: Immunofluorescent microscopy shows granular deposition of IgG. D: IgG subclass analysis reveals granular deposition of IgG1. E: IgG subclass analysis demonstrates granular deposition of IgG4. F: There is patchy infiltration of inflammatory cells, lymphocytes, plasma cells, and eosinophils (arrows) around the tubules. Eosinophils are predominant, and are also seen in the capillaries. Although there is mild intimal thickening of interlobular arteries, no angiitis is observed (Hematoxylin and Eosin staining). G: Arrow shows an eosinophil. H: Arrows show IgG4-positive plasma cells. I: Arrows show IgG-positive plasma cells. J: Electron microscopy reveals electron-dense to electron-lucent deposits (arrows) on the subepithelial surface of the glomerular capillary walls.

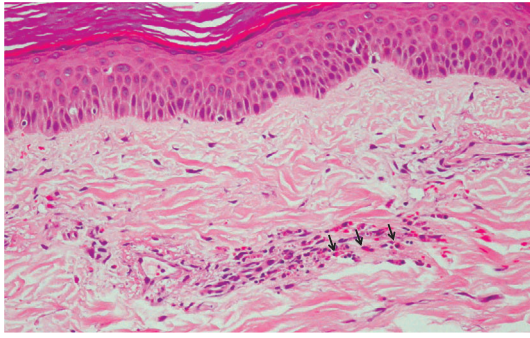


Figure 5. Focal infiltration of neutrophils, eosinophils (arrows), lymphocytes, and histiocytes can be seen, along with nuclear fragmentation and extravasation of erythrocytes around the small vessels in the dermis (Hematoxylin and Eosin staining).

thralgia was completely resolved. On the other hand, the rash on her feet persisted for about 1 month, and right median nerve paralysis only began to improve after 6 months. The eosinophil count was reduced to 362/mL after 17 days of treatment and serum IgE fell to 766 U/mL after 14 days. Serum creatinine decreased again to 0.6 mg/dL after 17 days along with the reduction of proteinuria and hematuria. Prednisolone was tapered carefully and gradually. The patient was doing well as of November 2011.

Diagnosis

In the current patient, the presence of asthma, eosinophilia, mononeuropathy, pulmonary opacities on imaging, and biopsy-proven leukocytoclastic vasculitis with accumulation of eosinophils fulfilled the criteria for a diagnosis of CSS. On the other hand, her salivary gland swelling was atypical. The combination of salivary gland swelling, asthma with interstitial pneumonia, tubulointerstitial nephritis with membranous glomerulonephropathy, a high serum IgE level, and a good response to steroid therapy, along with marked elevation of the serum IgG4 level (275 mg/dL) suggested a diagnosis of IgG4-related disorder. However, IgG4-positive plasma cells in the tubulointerstitium accounted for about 10% of all IgG-positive plasma cells.

Discussion

Two disorders (ANCA-negative CSS and IgG-related disorder) coexisted in the present case. There are three main classifications of CSS, which are Lanham's criteria (15), the American College of Rheumatology criteria (7), and the Chapel Hill Consensus Conference criteria (2). In a study of 93 consecutive patients with CSS (16), ANCAs were present in 35 patients (37.6%), with perinuclear (p)-ANCA being found in 26 patients (74.3%) and p-ANCA that showed specificity for MPO being identified in 24 patients. In addition, cANCA specific for PR3 was found in 3 patients (8.6%) and unclassifiable ANCAs were detected in 6 patients (17.1%). A CSS-like syndrome has been reported to

occur in patients who are being treated with leukotriene receptor antagonists (including zafirlukast, montelukast, and pranlukast), and this may be relevant to the present case (17). The US Food and Drug Administration recently reported that 146 patients had developed CSS in association with leukotriene receptor antagonist therapy (18).

In a study of 116 patients with CSS (19), renal abnormalities were present in 31 patients (26.7%). Rapidly progressive glomerulonephropathy (13.8%) and urinary tract abnormalities (12.1%) were the main clinical syndromes. Pauci-immune necrotizing crescentic glomerulonephritis was the prevailing histological pattern, with positivity for MPO-ANCA. Other histological patterns were also seen, such as eosinophilic tubulointerstitial nephritis, focal mesangial proliferative glomerulonephritis, and focal segmental glomerular sclerosis. There have been only a few reports which discuss membranous glomerulonephropathy as a pattern of renal involvement in CSS. In a study of 96 patients with CSS, 25 had renal involvement, but only 4 underwent renal biopsy and among them, 1 patient had focal membranous proliferation (4).

Recently, the presence of a high serum level of IgG4 in combination with marked eosinophilia, high serum IgE, salivary gland swelling, asthma, interstitial pneumonia, and tubulointerstitial nephritis has been reported as IgG4-related disorder. This proposed clinicopathological entity was first described as autoimmune pancreatitis (AIP) by Yoshida in 1995 (20). Subsequent reports have gradually revealed its clinical, radiological, serological, and histopathological characteristics, indicating that AIP is only one of the IgG4-related disorders. This systemic disease is characterized by a high serum IgG4 level, as well as by extensive infiltration of IgG4-positive plasma cells and T lymphocytes into various organs (12-14). Clinical manifestations involve the pancreas, biliary tree, gallbladder, salivary glands, retroperitoneum, kidneys, lungs, and prostate. The renal lesions of patients with IgG4-related disorders are known to include tubulointerstitial nephritis or sometimes a renal pseudotumor (21, 22). Takahashi et al. (22) reported that 14 out of 40 AIP patients (35%) had renal involvement. There have been several case reports of tubulointerstitial nephritis associated with a high serum IgG4 level and almost all of these patients showed infiltration of IgG4-positive cells into the renal interstitium (21, 23-25). On the other hand, it is interesting that decreased levels of complement and membranous glomerulonephropathy have been found in some cases of interstitial nephritis associated with IgG4-related disorders (25, 26).

A high serum IgG4 level has also been reported in some other conditions, such as atopic dermatitis (27), asthma (28-30), and some parasitic diseases (31). In patients with these conditions, the IgG4 subclass is usually categorized as a pathologic antibody. High serum levels of IgE and IgG4 are a direct response to an exogenous antigen (27, 31), and an increase of serum IgG4 has been postulated to block the access of soluble antigen to IgE-coated mast cells (31).

Recently, Kawano et al. proposed useful diagnostic criteria for IgG4-related kidney disease (32).

In conclusion, the present patient had typical clinical features of CSS with three sequential phases (the prodromal phase, eosinophilic, and vasculitic phases), even though she was negative for both MPO-ANCA and PR3-ANCA by ELISA. This patient also had salivary gland swelling, tubulointerstitial nephropathy, and pre-existing membranous glomerulonephropathy without typical necrotizing crescentic nephritis, as well as a high serum IgG4 level. However, the ratio of IgG4-positive plasma cell to all IgG-positive plasma cells was 10% (less than 40%) which is atypical of IgG4-related disorder. This case shows that CSS can have a clinical condition similar to IgG4-related kidney disease.

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

Grant support

This study was funded by the Okinaka Memorial Institute for Medical Research.

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