Clinical significance of complement as a biomarker of disease activity in 4 cases of IgG4-related disease with retroperitoneal fibrosis

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ABSTRACT

Hypocomplementaemia is frequently observed in IgG4-related diseases, however the clinical significance is unclear. We describe herein the clinical courses of 4 patients with IgG4-related disease with hypocomplementaemia. Our cases showed autoimmune pancreatitis, retroperitoneal fibrosis, Mikulicz's disease, interstitial lung disease, lymphadenopathy and mesenteric fibrosis around the aorta. A decrease in serum complement preceded deterioration of the disease and clinical improvement was observed in accordance with normalisation of serum complement. These clinical courses suggest that serum complement is a biomarker of the disease activity.

Introduction

It has been recently reported that Mikulicz's disease, autoimmune pancreatitis (AIP), and retroperitoneal fibrosis are all IgG4-related diseases (1-3). Elevated serum IgG4 concentration and IgG4-positive plasma cell infiltration in tissues are characteristic of IgG4-related diseases. The pathogenesis is considered to be a lymphoproliferative disease with remarkable infiltration of IgG4 positive plasma cells in a wide variety of organs. Hypocomplementaemia is frequently observed in IgG4-related diseases (2-4). However, the clinical significance of that is unclear. There have been no previous reports of a relationship between alteration of complement and disease activity in IgG4-related diseases. We describe herein the clinical courses of 4 patients with IgG4-related disease in which serum complement was clinically useful as a surrogate marker to evaluate the disease activity.

Case 1. A 63-year-old male was referred to our hospital with pancreatitis, widespread soft tissue masses around the aorta and bilateral parotid masses. Laboratory studies revealed an increase in IgG4 and immune complexes determined by C1q or monoclonal rheumatoid factor (mRF) assay with hypocomplementaemia (Table I). Radiological findings showed a localised enlargement of the pancreas and a constriction of the main pancreatic duct. These findings were consistent with a diagnosis of definite IgG4-related disease with autoimmune pancreatitis (AIP), retroperitoneal fibrosis and Mikulicz's disease (5). Histopathologic examination was not done. Treatment was commenced with 30 mg of oral prednisolone (PSL) daily, which subsequently alleviated symptoms, and serum amylase and complement returned to normal levels (Fig. 1A). After PSL was tapered, the patient showed progressive decrease of CH50, preceding the development of AIP. Total IgG and IgG4 were not elevated in the recurrence (Fig. 1A). The PSL dose was increased to 30 mg/day and azathioprine (AZA) and methylprednisolone pulse therapy was added, but AIP recurred and hypocomplementaemia persisted. However, after intravenous cyclophosphamide was initiated, there was a marked improvement of clinical signs in accordance with normalisation of serum complement (Fig. 1A), and the PSL was tapered to 5mg/day.

Case 2. An 87-year-old male was referred to our hospital with soft tissue masses around an abdominal aortic aneurysm. Hypocomplementaemia and hypergammaglobulinaemia were not found at the first visit. However, serum CH50 decreased and total IgG increased progressively over two years with elevation of IgG4 and immune complexes (Table I; Fig. 1B). This preceded the development of bilateral enlargement of the submandibular glands, interstitial lung disease, mediastinal lymphadenopathy and bilateral hydronephrosis with increasing soft tissue around the abdominal aorta (Fig. 2A-B). He also developed esophagitis. Biopsy specimens of the esophageal mucosa showed abundant IgG4-positive cells (IgG4 cells/high-power field>10). Thus, this patient was diagnosed with definite IgG4-related disease (5). After treatment with 20mg/day of PSL, his clinical signs and symptoms improved and serum complement returned to normal levels (Fig. 1B).

Case 3. A 75-year-old male came to our hospital with bilaterally enlarged salivary glands, mesenteric fibrosis,

and retroperitoneal fibrosis. Laboratory studies showed hypocomplementaemia and an increase in IgG4 and immune complexes in the serum (Table I; Fig. 1C). Submandibular gland biopsy showed infiltration of IgG4-positive plasma cells (Fig. 2D). He was diagnosed with definite IgG4-related disease (5). After the commencement of 50mg/day of PSL, serum CH50 and IgG4 returned to normal levels following normalisation of glandular size and shrinkage of the soft tissue masses around the aorta (Fig. 1C).

Case 4. A 51-year-old male was referred to our hospital with bilaterally enlarged submandibular glands for 2 years and bilaterally enlarged cervical lymph nodes, which showed infiltration of IgG4-positive plasma cells (6). Computed tomography scan showed retroperitoneal fibrosis and interstitial pneumonia. Laboratory studies revealed hypocomplementaemia and increase of IgG4 (Table I; Fig. 1C). Thus, this patient was diagnosed with definite IgG4-related disease. CH50 immediately returned to normal levels after initiation of 50 mg of oral PSL daily followed by a striking clinical improvement. IgG4 had decreased after the treatment, but were not normalised (Fig. 1C).

Discussion

Recent reports have revealed that a substantial percentage of idiopathic retroperitoneal fibrosis cases are associated with IgG4-related diseases (7). These are also associated with SLE or hypocomplementaemia in some cases (8, 9). Our cases of retroperitoneal fibrosis were classified as IgG4-related diseases due to the diagnostic criteria, and hypocomplementaemia can be related with IgG4-related diseases.

Biomarker for disease activity and prediction of relapse is not established in IgG4-related diseases. Serum IgG4 and IgG are decreased after the immunosuppressive treatment, as with our cases and other reports (10, 11). Previous report showed re-elevation of serum IgG4 was observed in 4 relapsed patients with AIP (6). The clinical course of case 1 showed re-elevation of serum IgG4 was not detected in the relapse of

Table I.

Case	Age years, sex	IgG (mg/dl)	IgG4 (mg/dl)	C3 (mg/dl)	C4 (mg/dl)	CH50 (U/ml)	IC-C1q[a] (pg/ml)	IC-RF[a] (pg/ml)
1	63, M	3110	240	79	<detection limit	<10	4.7	28.4
2	87, M	3209	975	28	<detection limit	<10	1.5	7.7
3	75, M	4469	1350	51	<detection limit	5	5.4	25.7
4	51, M	8586	4280	22	1	<10	4.3	NA

[a]Immunocomplex (IC) was measured by C1q assay or monoclonal rheumatoid factor(RF) assay. The normal values of each parameters are following. IgG: 870~1700 mg/dl, IgG4: 4.8~105 mg/dl, C3: 86.0~160.0 mg/dl, C4: 17.0~45.0 mg/dl, CH50: 30.0~40.0 U/ml, IC-C1q: <3.0 pg/ml, IC-RF: <4.2 pg/ml.

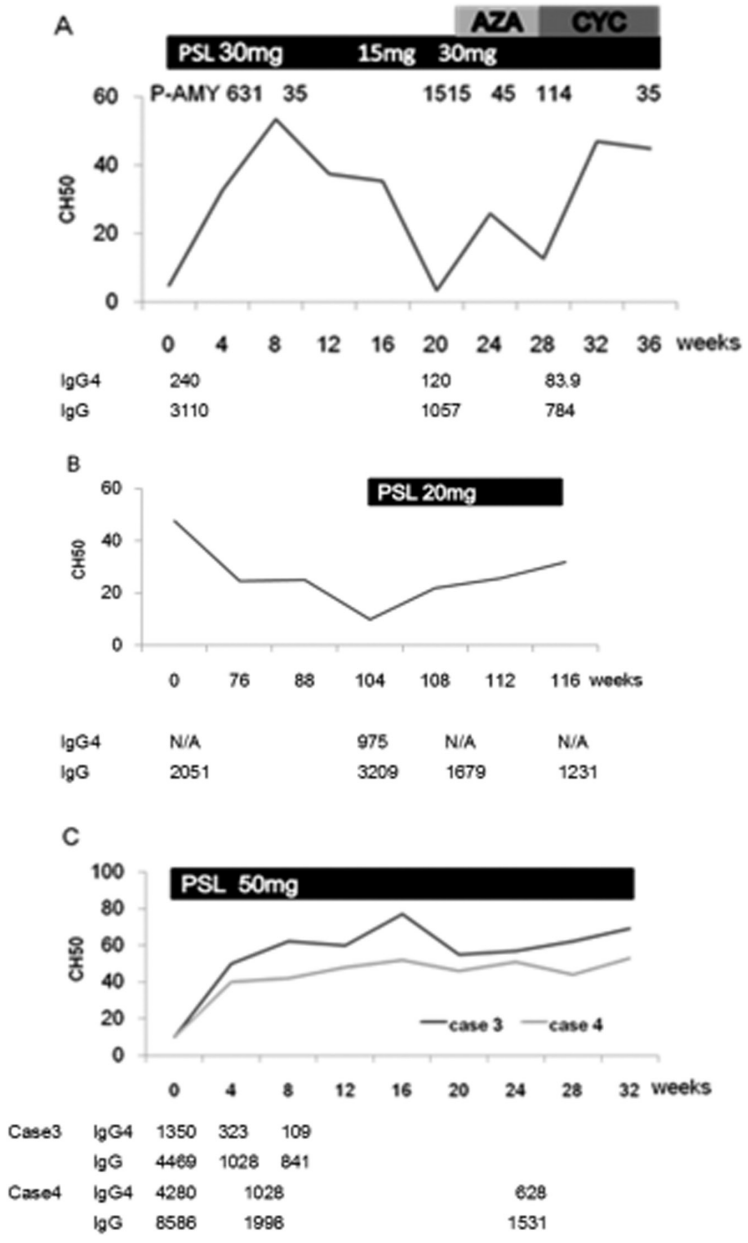

Fig. 1. Clinical courses and serum complement levels.
Clinical courses of case 1 (**A**), case 2 (**B**) and cases 3 and 4 (**C**) were shown. A decrease of serum complement could predict the relapse (**A**) or worsening (B) of the IgG4-related diseases, and complement increased in accordance with clinical improvement after cyclophosphamide (**A**) or prednisolone (**B**, **C**) therapy.
AZA: azathioprine; CYC: cyclophosphamide; PSL: prednisolone.

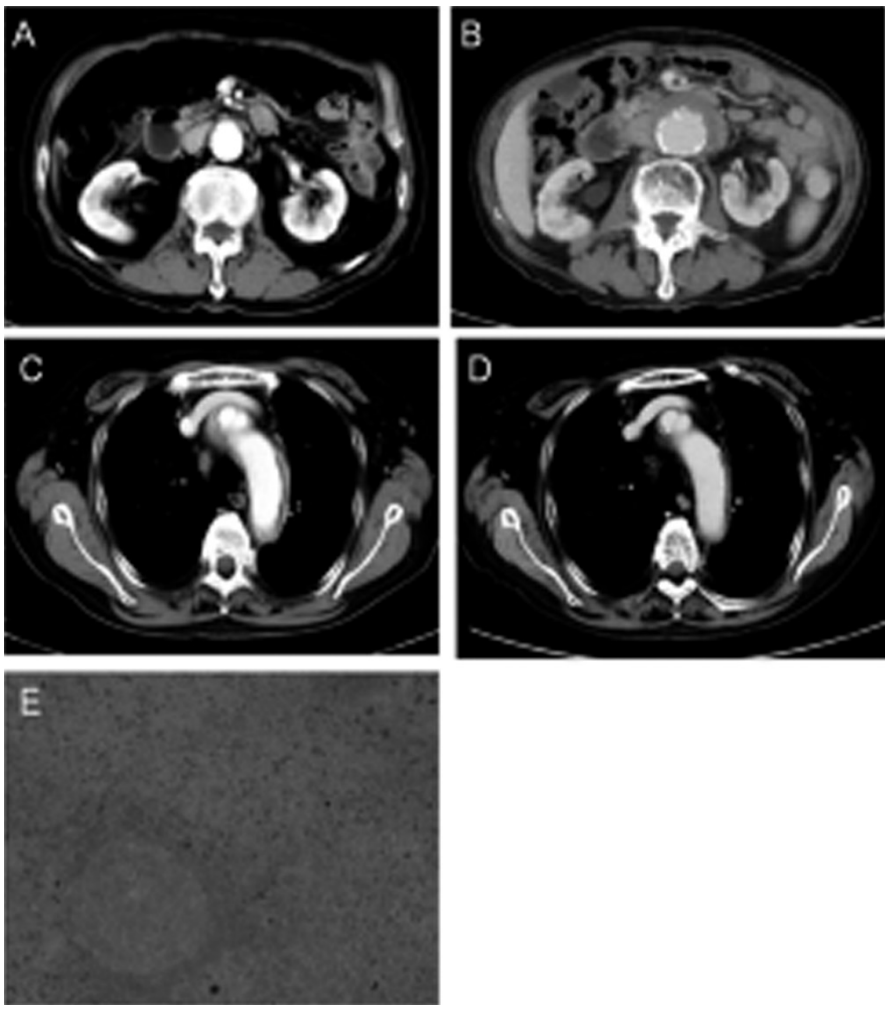

Fig. 2. Clinical images. Radiological findings on computed tomography scan in case 2 (**A** and **B**) and case 3 (**C** and **D**) are shown. Soft tissue around the abdominal aorta was seen at first visit (**A**), and bilateral hydronephrosis with increasing soft tissue around the abdominal aorta developed over two years (**B**). Soft tissue masses around the mescenteric vessels (**C**) and abdominal aorta (data not shown) were found. These findings improved after the initiation of prednisolone (**D**). IgG4 immunostaining of the submandibular gland of case 3 showed more than 50% of IgG positive cells were IgG4 positive cells (**E**).

the disease, and hypocomplementaemia was more sensitive marker of the relapse. In the case 2, hypocomplementaemia and hypergammaglobulinaemia progressed in accordance with the deterioration of the disease. These suggest that serial measurement of serum complement may be useful to evaluate the disease activity as well as serum IgG4 and IgG.

The possible causes of hypocomplementaemia are inherited complement deficiency, existence of complement inhibitors, reduced hepatic synthesis and increased consumption by immune complexes. Our cases showed normal protein synthesis and reversible reduction of both absolute amounts and biological activity of complements. It is unlikely that hypocomplementaemia is ascribed to the increased consumption of complement with IgG4 subclass of immune complexes (12). Immune complexes determined by C1q assay can be thought of as the cause of hypocomplementaemia (13), and were actually detected in our cases and in other reports (4, 12, 14, 15), however, the pathophysiologic role is unclear.

Our cases suggest that normalisation of serum CH50 suggests an amelioration of the disease and a decrease of CH50 may predict a deterioration of the disease. Further investigations in the larger group of patient are required to clarify the clinical significance of measurement of serum complement in IgG4-related diseases.

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