Immunoglobulin G4-Related Disease Presenting with Clinical Similarity to Churg-Strauss Syndrome

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Immunoglobulin G4-related disease (IgG4-RD) and Churg-Strauss syndrome (CSS) have different clinical and pathological features. However, in some cases characteristics of both conditions coexist, making diagnosis and treatment difficult. We report a case with a challenging diagnosis and discuss the common features of IgG4-RD and CSS.

PATIENT DESCRIPTION

A 67-year-old male presented to our hospital with persistent purulent cough, fever of 3 weeks, and 3 days of petechial rash over his left foot, back and buttocks. His medical background was significant for chronic sinusitis, obstructive lung disease (never smoked) treated with inhalers and preventive azithromycin, and prostatic neoplasm previously treated with radiation.

On admission, his vital signs were normal. Laboratory studies revealed elevated C-reactive protein, marked eosinophilia up to 4 K/μl, as well as mild anemia, hypoalbuminemia, and mild elevation in liver function tests. Urinalysis showed some erythrocytes and protein. Renal function was preserved.

Chest X-ray, echocardiography and total body computed tomography (CT) scan demonstrated bilateral pleural effusions, pericardial effusion, and thickening of the esophageal wall. A biopsy of the skin lesions was compatible with leukocytoclastic vasculitis. Pulmonary function tests demonstrated a mixed obstructive and restrictive pattern with decreased DLCO. Ear, nose and throat examination revealed laryngeal signs of reflux. Preliminary serology studies came back weakly positive for anti-myeloperoxidase (MPO) and negative for P- and C-ANCA (perinuclear and cytoplasmic antineutrophil cytoplasmic antibodies).

In light of the clinical presentation, combined with marked eosinophilia and anti-MPO, a diagnosis of Churg-Strauss vasculitis was suggested and treatment with high-dose corticosteroids was initiated. The patient was also treated with broad-spectrum antibiotics for respiratory infection. The treatment resulted in clinical and laboratory improvement.

Further laboratory studies revealed increased levels of immunoglobulins with the IgG4 fraction higher than four times the upper limit of normal and IgE levels higher than 10 times the upper limit of normal. These laboratory findings, combined with the esophageal involvement, were also compatible with a diagnosis of IgG4-related disease. A blood plasmablast concentration test demonstrated highly elevated levels, compatible with active IgG4-related disease.

The patient then underwent a positron-emission tomography (PET)-CT scan which demonstrated a medium-sized left pleural effusion with mild uptake, intense uptake at lymph nodes in the mediastinum, thickened pericardium, and pericardial effusion. Gastroscopy showed mild erythema and edema of the gastric mucosa. Treatment with proton pump inhibitors was initiated.

After tapering of the high-dose steroids, the patient remained clinically asymptomatic. A second test for ANCA including anti-MPO was negative, and levels of IgG4 decreased by half. Repeat echocardiography and chest X-ray showed resolution of pleural and pericardial effusions.

Six months after diagnosis, he continues on low dose prednisone (5 mg/day) and is asymptomatic.

COMMENT

IgG4-related disease (IgG4-RD) is a systemic fibro-inflammatory condition that may involve any organ. It is characterized by lymphoplasmacytic infiltrates abundant in IgG4-positive plasma cells. Elevated levels of interleukins 4, 5, 10 and 13 contribute to eosinophilia and to elevated serum IgG4 and IgE levels in many patients. Up to 50% of patients with IgG4-RD have allergic diseases such as bronchial asthma or chronic sinusitis [1].

Features of allergic disease, combined with elevated levels of IgE and eosinophilia, are also characteristic of Churg-Strauss syndrome (CSS). This is a systemic necrotizing vasculitis involving the lungs and a wide variety of other organs. Elevated serum levels of IgG4 have also been reported in CSS. Yamamoto et al. [2] found no significant difference in IgG subclasses between CSS and IgG4-RD.

Although CSS and IgG4-RD are clinically different, occasionally it is hard to differentiate between the two. Several case reports have been published describing

patients who presented with clinical features of both conditions, and it has been suggested that they are related. Whether the two diseases share a common pathophysiological pathway or coexist due to another reason is yet to be determined.

While others have struggled with the dilemma between these two diagnoses, none of the cases described had esophageal involvement as our patient did. Gastrointestinal involvement occurs frequently and is one of the major causes of death associated with CSS. Nonetheless, eosinophilic vasculitis-related esophagitis is very rare and has seldom been reported [3]. Esophageal involvement in IgG4-RD is also rare, but some recent studies have suggested it to be a more common, underdiagnosed condition [4].

Our patient was initially suspected to have CSS due to allergic symptoms, leukocytoclastic vasculitis on skin biopsy, fever, elevated CRP, eosinophilia and weakly positive anti-MPO. However, high levels of IgG4, esophagitis and gastro-esophageal reflux disease directed us towards the diagnosis of IgG4-RD. It has been reported that blood plasmablast concentrations correlate better with disease activity than do serum IgG4 levels [5]. We found highly elevated serum concentration of plasmablasts, which strengthened our belief that the diagnosis of IgG4-RD was more appropriate. Some of the clinical features of these diseases and their prevalence are shown in Table 1.

Table 1. Clinical aspects of IgG4-RD and CSS

Aspect	IgG4-RD	CSS
Esophagus	+/-	-
Skin	+	+
Pericardium	+	+
Lungs	+	+
Fever + inflammatory markers	+/-	+
Elevated serum IgG4	+	+/-
Elevated serum IgE	+	+
Eosinophilia	+	+

IgG4-RD = immunoglobulin G4-related disease, IgE = immunoglobulin E

Nonetheless, histopathological analysis remains the cornerstone of the diagnosis of IgG4-RD. However, since tissue was not obtained from our patient, we cannot rule out atypical CSS or coexistence of both conditions.

In conclusion, the current patient had clinical features of both CSS and IgG4-RD. He represents an intriguing example of the common findings of these two conditions – allergic symptoms as well as eosinophilia, high IgE and IgG4 levels. Esophageal involvement is rare in both cases but is more typical in IgG4-RD. Blood plasmablast concentrations can provide further information and help guide the diagnosis.

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Capsule

A defined commensal consortium elicits CD8 T cells and anti-cancer immunity

There is a growing appreciation for the importance of the gut microbiota as a therapeutic target in various diseases. However, there are only a handful of known commensal strains that can potentially be used to manipulate host physiological functions. **Tanoue** et al. isolated a consortium of 11 bacterial strains from healthy human donor feces that is capable of robustly inducing interferon-γ-producing CD8 T cells in the intestine. These 11 strains act together to mediate the induction without causing inflammation in a manner that is dependent on CD103+dendritic cells and major histocompatibility (MHC) class Ia molecules. Colonization of mice with the 11-strain mixture enhances both host resistance against *Listeria monocytogenes* infection and the therapeutic efficacy of immune checkpoint inhibitors in syngeneic tumor models. The 11 strains primarily represent rare, low-abundance components of the human microbiome, and thus have great potential as broadly effective biotherapeutics.

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Eitan Israeli

"Life isn't about finding yourself. Life is about creating yourself"

George Bernard Shaw (1856–1950), Irish playwright, critic, and political activist, and Nobel Prize laureate for Literature

"Change your life today. Don't gamble on the future, act now, without delay"

Simone de Beauvoir (1908–1986), French writer, intellectual, existentialist philosopher, political activist, feminist, and social theorist