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IgG4-related disease manifesting as pericarditis with adenosine deaminase and IL-10 elevation in pericardial fluid

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Running title

IgG4-related pericarditis with ADA and IL-10 elevation

Abstract

A 78-year-old female with massive pericardial effusion fulfilled diagnostic criteria for IgG4-related disease. Although the adenosine deaminase level in the pericardial effusion was high, all the tests for tuberculosis infection were negative. Immunostaining of the pericardium biopsy specimen revealed remarkably increased IgG4-positive cells. This is the first report describing IgG4-related pericarditis with elevated ADA. We also demonstrate the elevated IL-10 level in pericardial fluid and IL-10-producing T cells in the pericardium.

Keywords

IgG4-related disease, pericarditis, adenosine deaminase(ADA), IL-10

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a recently recognized systemic fibroinflammatory disease of unknown etiology with multiorgan involvement, including pancreas, bile ducts, lacrimal glands, salivary glands, central nervous system, thyroid, lungs, liver, gastrointestinal tract, kidneys, prostate, retroperitoneum, arteries, lymph nodes, and skin [1]. However, pericarditis is a rare manifestation of IgG4-RD.

The pathogenesis of IgG4-RD is largely unknown, while recent studies have put forward a theory that IgG4 and IgE production is induced preferentially in the setting of Th2 cells, and that IL-10 shifts the balance between IgG4 and IgE, favoring IgG4 production. Here we report a case of IgG4-RD manifesting as pericarditis with adenosine deaminase (ADA) and IL-10 elevation in pericardial fluid.

Case report

A 78-year-old Japanese female presented to a local hospital with progressive exertional dyspnea in April, 20XX. She had a medical history of pulmonary tuberculosis, bronchial asthma and hypertension. Computed tomography (CT) scan and ultrasonography revealed marked pericardial effusion (Figure 1a). Gallium-scintigraphy showed abnormal accumulation in the pericardium (Figure 1b). Pericardiocentesis was performed by fine needle aspiration, and 800 milliliters of hemorrhagic pericardial fluid was removed. No malignant cells were found on cytology, and the pericardial fluid culture was negative. ADA activity in pericardial fluid was elevated to 107 U/ml. CT scan and gallium-scintigraphy showed multiple lymphadenopathy in the mediastinum, para-aorta, abdominal cavity, and inguinal region.

She was admitted to our hospital for evaluation of pericardial effusion and multiple lymphadenopathy in June, 20XX. Physical examination revealed mild lymphadenopathy in the bilateral supraclavicular and inguinal regions, and fine crackles in the lungs. The salivary glands and lacrimal glands were not palpable. Laboratory findings were as follows: WBC 5800 /μl, hemoglobin 13.8 g/dl, platelet count 11.6×10^4 /μl, total protein 9.2 g/dl, albumin 3.6 g/dl, BUN 19 mg/dl, creatinine 0.9 mg/dl, AST 74 U/l, ALT 39 U/l, amylase 100 U/l, CRP 0.22 mg/dl, IgG 3817 mg/dl, soluble interleukin 2-receptor 2230 U/ml and IgE 281 IU/ml (normal level: 173 IU/ml). Rheumatoid factor (101 IU/ml) and anti-nuclear antibody (×640, homogeneous pattern) were positive, while anti-SS-A/Ro and anti-SS-B/La antibodies and anti-neutrophil cytoplasmic antibodies were negative. Serum level of IgG4 was significantly elevated at 921 mg/dl (normal range: 4.5-105 mg/dl). The urinary examination was normal. Chest radiograph showed cardiomegaly. A contrast enhanced CT scan revealed marked

pericardial effusion, bilateral bronchial wall thickness, multiple lymphadenopathy, diffuse enlargement of the pancreas, and bilateral hydronephrosis.

We performed biopsy of the right inguinal lymph node. The specimen revealed lymphadenopathy with proliferation of lymphoplasmacytes. There were few eosinophils in the lymph node. Immunostaining revealed an increased absolute count of IgG4-positive cells and the ratio of IgG4/IgG-positive cells was 53%. Our patient met all clinical (organ enlargement and organ dysfunction), serological (serum IgG4 concentration >135 mg/dl), and histopathological (>10 $IgG4^+$ cells per HPF and an $IgG4^+$:IgG^+ cell ratio >40%) diagnostic criteria for IgG4-RD. She also satisfied international consensus diagnostic criteria for autoimmune pancreatitis (typical parenchymal imaging, IgG4, >2× upper limit of normal value, other organ involvement). Then she was diagnosed as IgG4-RD. The bilateral hydronephrosis might be also manifestations of IgG4-RD.

In order to determine the cause of the pericardial effusion, we performed a biopsy of the pericardium and drainage of the pericardial effusion. The majority of cellular fractions of pericardial effusion were lymphocytes and plasmacytes (Figure1c). There were few eosinophils in the effusion. The fluid was hemorrhagic, and the findings were as follows: TP 7.6 g/dl, albumin 3.1 g/dl, IgG 3911 mg/dl, IgG4 1070 mg/dl, ADA 74.2 U/ml, and IL-10 9.99 pg/ml. Polymerase chain reaction of tuberculosis DNA and culture of mycobacterium tuberculosis were negative, and Ziehl-Neelsen staining of the pericardium was negative. A specimen of the pericardium revealed diffuse fibrous thickening, and patchy lymohoplasmacytic infiltration with few eosinophils (Figure 2a, b). The accumulation of monoclonal kappa or lambda free light chains were not observed. Immunostaining revealed increased absolute count of IgG4-positive cells (86 per high-power field on average) and the ratio of

IgG4/IgG-positive cells was 51% (Figure 2c, d). Consequently, we concluded that the pericardial effusion was caused by IgG4-RD, not by tuberculosis.

Because IL-10 concentration was increased in the pericardial effusion, we performed the immunostaining for CD3 and IL-10 of the pericardium (Figure 3a, b). It showed that a part of CD3-positive cells expressed IL-10.

We administered oral prednisolone (30mg/day), and rapid improvement was achieved, including the pericarditis.

Discussion

Pericarditis caused by IgG4-RD is rare, and only a few cases with biopsy-proven IgG4-related pericarditis are reported in literature. Table 1 summarizes the clinicopathological features of the previously reported cases of IgG4-related pericarditis as well as present one [3, 4, 5, 6, 7, 8, 9]. Sugimoto et al. reported a first case with IgG4-related pericarditis in 2008. Only Rossi G et al. examined ADA in the pericardial fluid, and the result was not elevated. In contrast, ADA activity was elevated in our case. Komsuoglu, et al reported that specificity for tuberculosis pericarditis was 91% with a cutoff level for ADA activity of 70 U/ l [2]. The presence of ADA in pericardial fluid reflects the cellular immune response in the fluid compartment, especially the activation of T cells. The finding in this case suggests that IgG4-RD should be considered as a differential diagnosis when ADA activity is elevated in the pericardial effusion.

Recent studies have put forward a theory that IgG4 and IgE production is induced preferentially in the setting of Th2 cells, and IL-10 shifts the balance between IgG4 and IgE, favoring IgG4 [10]. We found that IL-10,

which can be produced by Th2 cells as well as Treg cells, was elevated in the pericardial fluid in IgG4-RD. To examine if the IL-10 is produced by T cells, we performed the immunostaining for CD3 and IL-10 of the pericardium. It showed that a part of CD3-positive cells expressed IL-10. This result supports that infiltrating Th2 or Treg cells might produce IL-10, but other type of cells, such as monocytes and B cells, are also involved in elevated IL-10 levels in pericardial effusion.

To our knowledge, our case is the first report describing IgG4-related pericarditis with elevated ADA and IL-10 in pericardial fluid. The case indicates that T cells are activated in IgG4-RD and may express ADA in pericardium, and that activated T cells are partially involved in elevated IL-10 in the pericardium, presumably leading to IgG4 production.

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We have no acknowledgement.

Conflict of interest

None.

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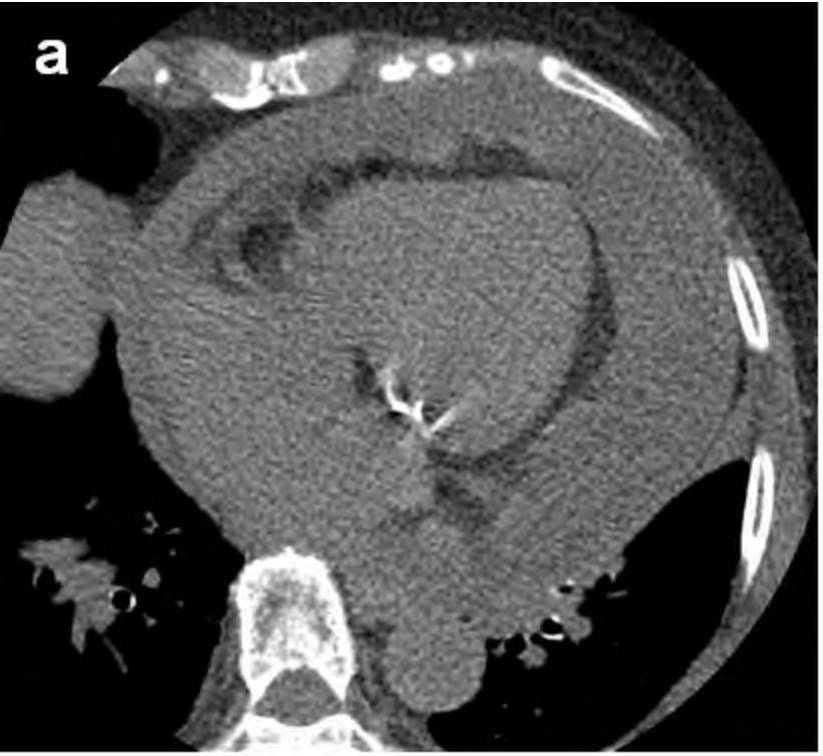
Figure legends

Figure 1. **a** Chest CT scan showed marked pericardial effusion. **b** Gallium-scintigraphy showed abnormal accumulation in the pericardium. **c** Cytological specimen obtained from pericardial effusion.

Figure 2. A specimen of the pericardium: Hematoxylin-eosin staining: ×100 (**a**), ×400 (**b**). Immunostaining for IgG (**c**) and IgG4 (**d**), ×100.

Figure 3. Immunostaining for CD3 (**a**) and IL-10 (**b**), ×400.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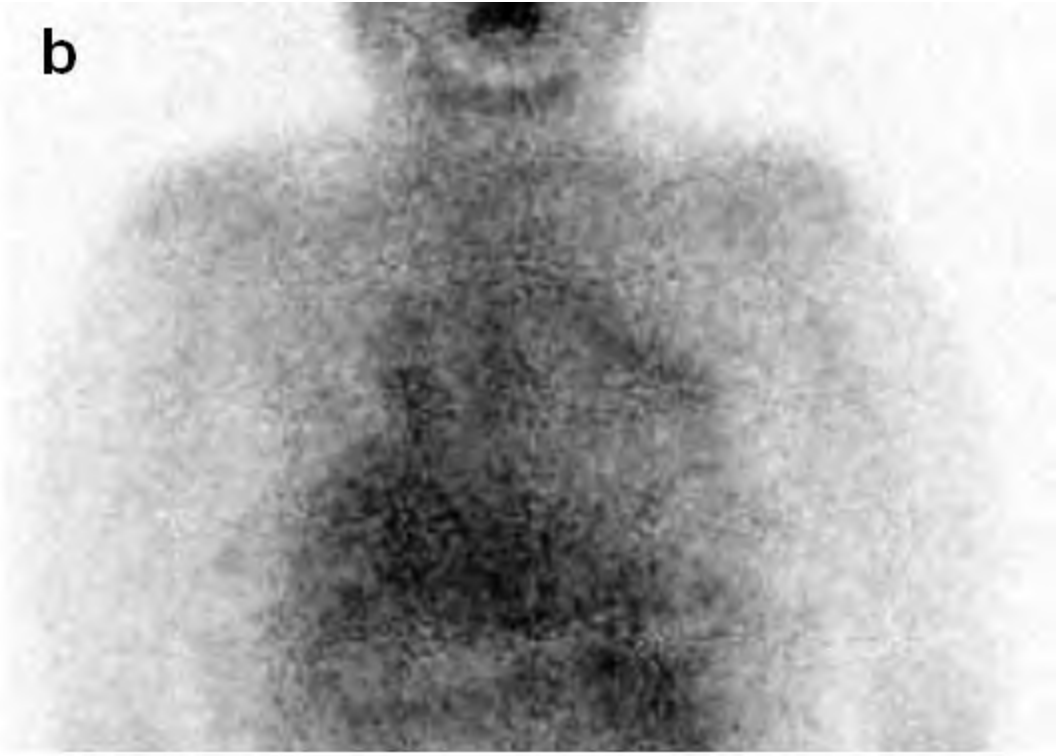
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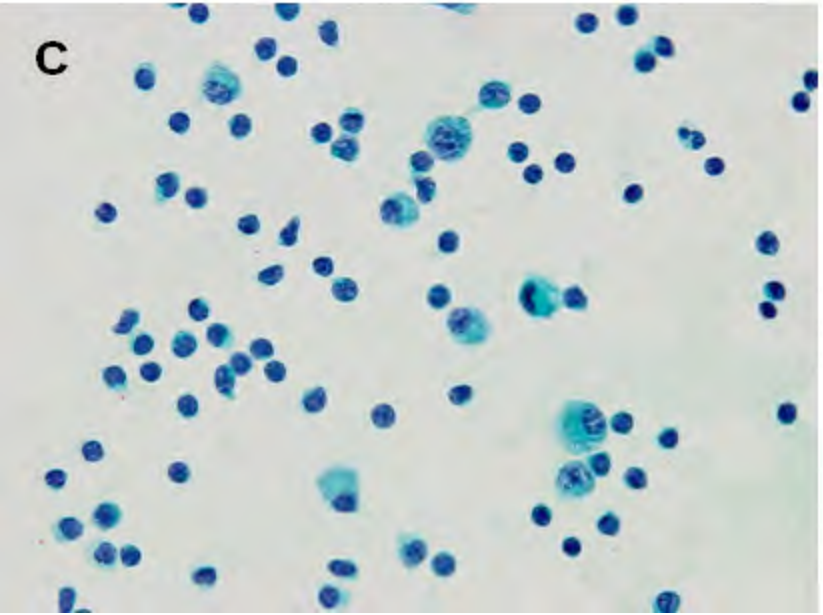
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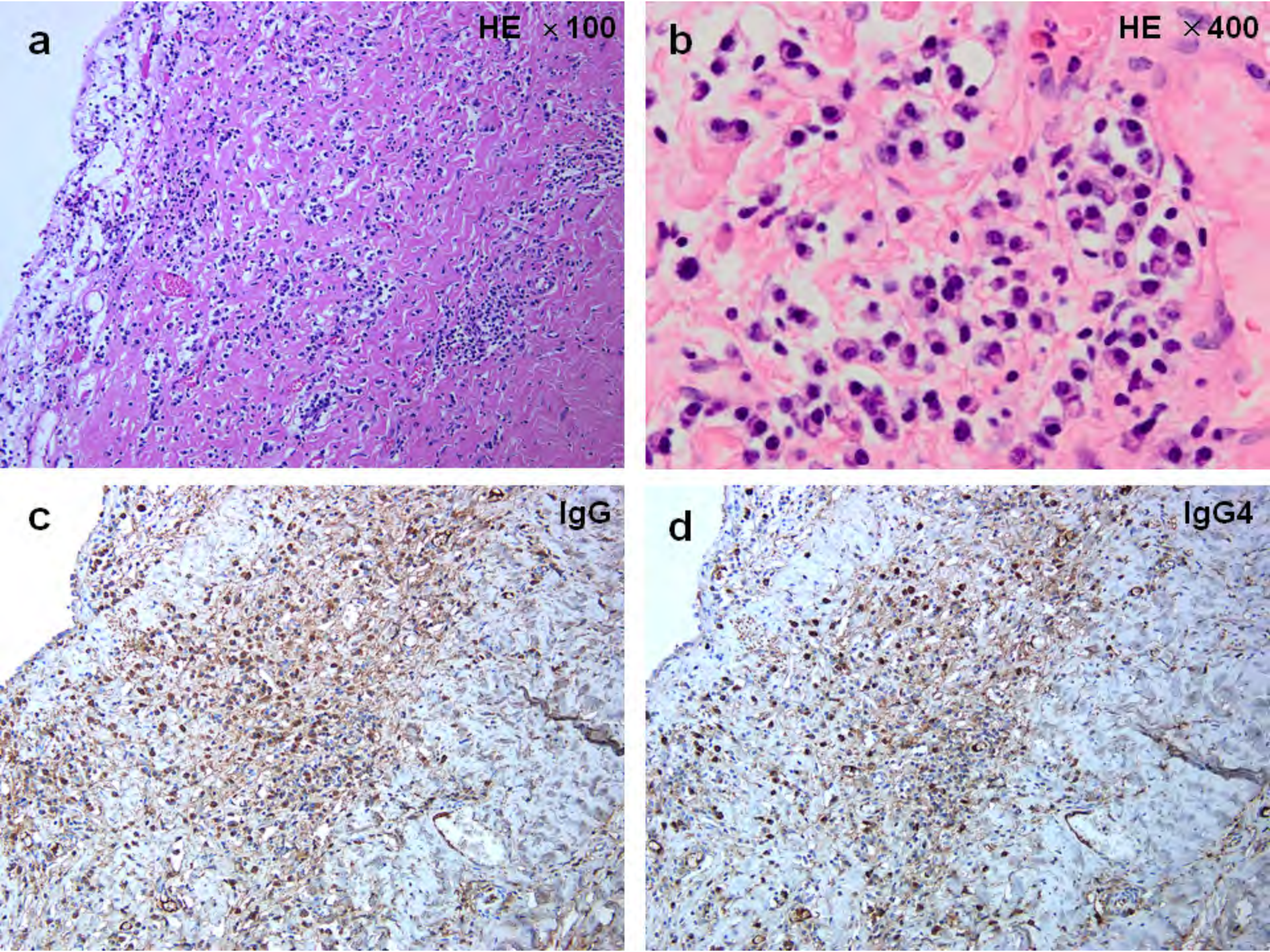
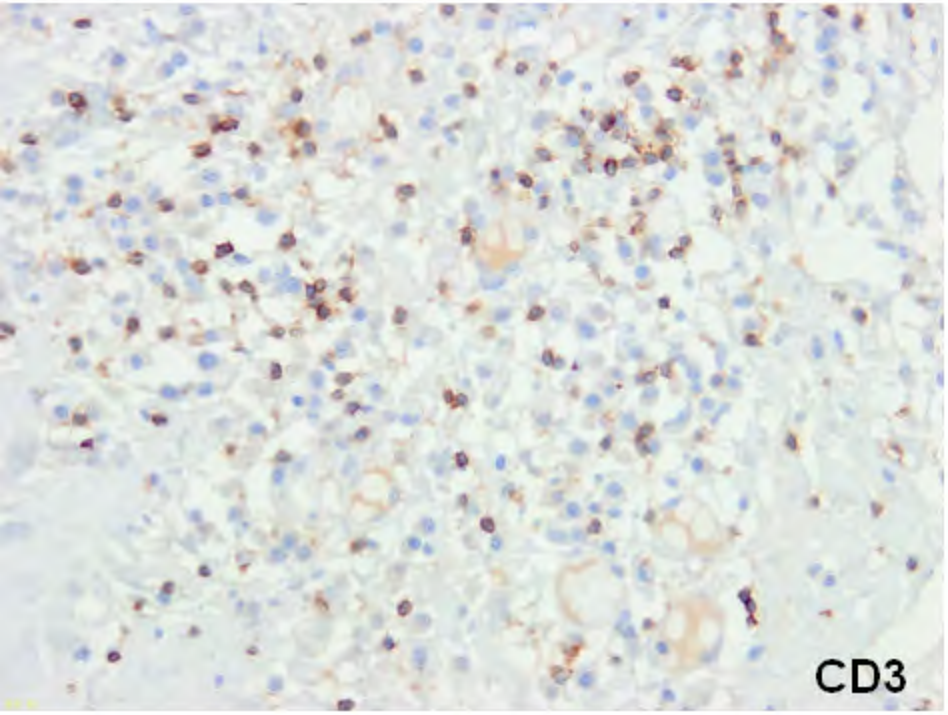

a
HE ×100
b
HE ×400
c
IgG
d
IgG4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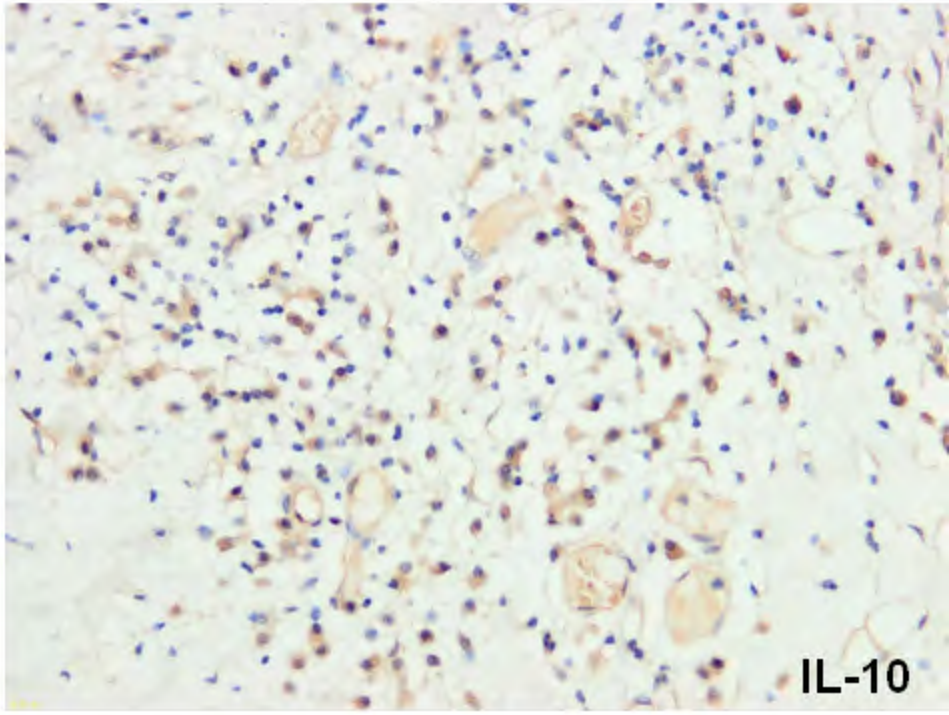
IL-10

Table. Clinicopathological features of the cases of IgG4-related pericarditis.

No.	Age/ Gender	Constrictive pericarditis	Associated diseases	Serum IgG4(mg/dl)	Biopsy of pericardium	The ratio of IgG4/IgG-positive cells	ADA in pericardial fluid(U/ml)	Sterold treatment	Reference
1	68/M	+	Pleuritis	206	Performed	Increased (percentage is unclear)	Not available	Not available	Sugimoto T, et al.[3]
2	68/F	+	Pleuritis Autoimmune pancreatitis	420	Not performed	-	Negative	Performed (dose unclear)	Rossi G, et al.4)
3	69/M	+	Retroperitoneal fibrosis	408	Not performed	-	Not available	PSL50mg	Kabara M, e et al.[5]
4	29/F	+	Pleuritis	136	Not performed	(92% in pleural specimen)	Not available	PSL40mg	Sekiguchi H, et al.[6]
5	76/M	+	Pleuritis	Not available	Performed	34%	Not available	Not performed	Sekiguchi H, et al.[7]
6	83/M	+	Pleuritis, retroperitoneal fibrosis	812	Performed	Increased (percentage is unclear)	Not available	Not performed	Sakamoto A, et al.[8]
7	81/M	+	Pleuritis	196	Performed	68%	Not available	PSL30mg	Yanagi H, et al.[9]
Present case	78/F	+	Pericarditis Retroperitoneal fibrosis Autoimmune pancreatitis	921	Performed	51%	74.2-107	PSL30mg	