CrossMark

ORIGINAL ARTICLE

IgG4-related disease involving polyserous effusions with elevated serum interleukin-6 levels: a case report and literature review

Xiang Tong[1] · Min Bai[1] · Weiya Wang[2] · Qingbing Han[1] · Panwen Tian[1,3] · Hong Fan[1]

Abstract Immunoglobulin G4-related disease (IgG4-RD) is a recently described immune-mediated fibroinflammatory disease with a characteristic histopathologic appearance that can affect various organs. We report a 43-year-old Chinese female patient with IgG4-RD involving polyserous effusions with reports of worsening exertional dyspnea for 3 months. Laboratory blood tests revealed that serum interleukin (IL)-6, carbohydrate antigens (CA-199 and CA-125), and alpha-fetoprotein levels were significantly increased, but serum IgG4 levels were normal. Repeat pleural effusion and ascite analysis showed lymphocyte-predominant exudates. In addition, computed tomography scan showed massive pleural effusion in the right pleural cavity, abdominal effusion, and some pericardial effusion with a partial compression atelectasis. Further, medical thoracoscopy was performed to examine the pleural cavity and found multiple nodules on the pleura and partly thickened pleura with a reddish color. Histopathologic and immunohistochemical examination revealed marked lymphocytes and IgG4-positive plasma cell infiltration. The patient was finally diagnosed with IgG4-RD according to the comprehensive diagnostic criteria, although the patient presented similar serological and pathological manifestations of Castleman disease (CD). Our case suggests that IgG4-RD may be one of the causes of polyserous effusions and shows the difficulties in differentiating between IgG4-RD and CD.

Keywords IgG4-related disease · Polyserous effusions · Interleukin-6 · Castleman disease

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a chronic, immune-mediated fibroinflammatory disease with a tendency to form tumefactive lesions in almost every organ or system, occurring in a synchronous or metachronous fashion [1, 2]. The pathologically characteristic features of the disease include a diffuse lymphoplasmacytic infiltration with abundant IgG4-positive plasma cells, mild-to-moderate eosinophilia, storiform fibrosis, and obliterative phlebitis [3, 4]. In addition, most patients with IgG4-RD show elevated serum IgG4 levels [5].

Castleman disease (CD), also known as angiofollicular lymph node hyperplasia, includes unicentric CD and multicentric CD (MCD) subtypes [6]. Interestingly, patients with MCD also sometimes have elevated serum IgG4 concentrations and abundant infiltration of IgG4-positive cells in affected organs [7]. Previous studies suggested that CD has a predominant inflammatory background with high levels of circulating interleukin (IL)-6, C-reactive protein (CRP), vascular endothelial growth factor, and gammaglobulin [8, 9]. Hence, serum levels of these inflammatory parameters appear particularly important when differentiating between CD and IgG4-RD because a significant increase in these factors (such as IL-6 levels) is less likely to be observed in patients with IgG4-RD [10, 11].

✉ Panwen Tian
13550351753@163.com

✉ Hong Fan
fanhongfan@qq.com

1 Department of Respiratory and Critical Care Medicine, West China Hospital/West China School of Medicine, Sichuan University, Guoxuexiang 37, Chengdu, Sichuan 610041, China

2 Department of Pathology, West China Hospital/West China School of Medicine, Sichuan University, Chengdu 610041, China

3 Lung Cancer Center, West China Hospital/West China School of Medicine, Sichuan University, Chengdu 610041, China

We report a case of IgG4-RD involving polyserous effusions (effusions in multiple serous cavities) with high serum IL-6 levels and show the difficulties in diagnosing and differentiating between IgG4-RD and CD.

Case report

A 43-year-old Chinese female was referred from a local hospital with reports of worsening exertional dyspnea for 3 months, but no cough, chest pain, or fever. She had never smoked and had no history of diabetes, hypertension, tuberculosis, or autoimmune diseases. On physical examination, she showed decreased breath sounds in the lower lobe of the right lung. During hospital admission, the test results of complete blood cell count, alanine aminotransferase, bilirubin, renal function test, erythrocyte sedimentation rate, antinuclear antibody, extractable nuclear antigen, antineutrophil cytoplasmic antibodies, toxoplasma, rubella, cytomegalovirus, herpes (TORCH) test, tuberculosis-interferon gamma release assay, immunoglobulin G (IgG), IgA, IgE, and κ and λ light chain were unremarkable. CRP, procalcitonin, and aspartate aminotransferase were mildly elevated (7.64 mg/l, 0.06 ng/ml, and 97I U/l, respectively), and complement (C3 and C4) in blood serum was mildly decreased (0.725 g/l and 0.111 g/ml, respectively). Laboratory blood tests also revealed that serum carbohydrate antigens (CA-199 and CA-125) and alpha-fetoprotein (AFP) were increased (52.24 U/ml, 1065 U/ml, and 157.2 ng/ml, respectively), but the serum carcinoembryonic antigen (CEA) level was normal. Hepatitis B surface antigen (HbsAg), HbeAb, and HbcAb were positive, and hepatitis B virus (HBV)-DNA test result was 8.95×10^4 IU/ml. Moreover, serum IgG4 levels of 1.25 g/l (normal range 0.035–1.50 g/l) were normal, but serum IL-6 levels of 264 pg/ml (normal range 0–7 pg/ml) were obviously increased (Table 1). Computed tomography (CT) scan showed massive pleural effusion in the right pleural cavity, abdominal effusion, and some pericardial effusion with a partial compression atelectasis (Fig. 1). Additionally, the CT scan found a reduction in liver volume, but the liver parenchyma remained unchanged (no hepatic fibrosis).

Repeat pleural effusion and ascite analysis showed lymphocyte-predominant (range 80 to 97%) exudates on the basis of Light's criteria. The adenosine deaminase levels of pleural effusion and ascites were low (range 4.6–7.0 IU/l), while the values of CA125 and AFP were high (range 514.5–1035.0 U/ml, 88.16–110.5 ng/ml, respectively), and CEA levels were normal. The TB-DNA, microbiology, and exfoliocytology examination in pleural effusion and ascites were also negative.

The pleural biopsy result at the local hospital was chronic inflammation, which did not suggest any specific disease. To further diagnose the disease, medical thoracoscopy of the right thoracic side under local anesthesia was performed, and the pleural cavity was examined. Multiple nodules were observed on the pleura, which were partly thickened with a reddish color (Fig. 2). Biopsy specimens retrieved from the nodules revealed lymphoplasmacytic infiltration and follicular lymphoid hyperplasia with abundant plasma cells. Immunohistochemistry staining showed that plasma cells were positive for IgG4 (80 cells per high-power field, Ki-67/MIB-1 (5%), and a high ratio of IgG4-positive/IgG-positive cells (>40%) (Fig. 3). Additionally, κ and λ chain-positive plasma cells were partly discovered by immunohistochemistry. According to the criteria [12] and combined with these test results, we diagnosed the patient with probable IgG4-RD involving polyserositis, but with suspected CD because of the significantly elevated concentrations of serum IL-6 and normal levels of serum IgG4. Thus, the patient underwent glucocorticoid therapy (prednisone, 30 mg/day), which quickly improved her difficulty in breathing. Additionally, with the recommendation of the infectious disease physician, anti-HBV therapy (entecavir, 1 mg/day) was administered. Follow-up CT scan and laboratory tests conducted 4 months after treatment indicated an obvious absorption of pleural effusion and ascites (Fig. 4), and the value of IL-6 significantly decreased (Table 1). At present, the patient has continued prednisone 10 mg/day and maintains a good quality of life.

Discussion

Here, we report a woman involving polyserous effusions, mainly with reports of worsening exertional dyspnea, who was finally found to have IgG4-RD according to the histopathologic and immunohistochemical examination. This recently identified fibroinflammatory disease can involve virtually all organs, including the pancreas, biliary tree, lacrimal and salivary glands, periorbital tissues, lung, liver, kidney, lymph nodes, prostate, retroperitoneum, arteries, thyroid, pericardium, meninges, and skin [4, 13] However, it is not a novel disease because a wide variety of diseases previously considered "idiopathic" sclerosing lesions are now included in the clinical IgG4-RD spectrum, such as Mikulicz's disease, Ormond's disease, autoimmune pancreatitis, Küttner's tumor, Riedel's thyroiditis, multifocal fibrosclerosis, and subsets of interstitial lung disease [1, 4]. In light of previous literature, IgG4-RD is characterized by several features, including marked lymphoplasmacytic infiltration, abundant IgG4-positive plasma cell infiltration, storiform fibrosis, phlebitis, and frequently elevated serum IgG4 level [14, 15]. Unfortunately, thus far, only little is known about the epidemiology, pathogenesis, and treatment of IgG4-RD.

The following are interesting findings in the present case. First, serum IgG4 levels were not elevated, while major histopathologic features, including abundant lymphocytes and

Table 1 Summary values of parameters in pretreatment and post-treatment over time

Parameters	Pretreatment	Post-treatment (7 days)	Post-treatment (4 months)	Reference value
IgG4	1.25 g/l	1.08 g/l	1.16 g/l	0.035–1.50 g/l
IL-6	264.0 pg/ml	173.0 pg/ml	47.0 pg/ml	0–7.0 pg/ml
WBC	3.36×10^9/l	6.62×10^9/l	4.53×10^9/l	3.9–9.5×10^9/l
HGB	129.0 g/l	120.0 g/l	136.0 g/l	115.0–150.0 g/l
ESR	17.0 mm/h	6.0 mm/h	8.0 mm/h	<26.0 mm/h
ALT	13.0 IU/l	6.0 IU/l	11.0 IU/l	<40.0 IU/l
AST	97.0 IU/l	25.0 IU/l	27.0 IU/l	<35.0 IU/l
CRP	7.64 mg/l	4.32 mg/l	3.23 mg/l	<5.0 mg/l
CA-199	52.24 U/ml	37.30 U/ml	21.43 U/ml	<22.0 U/ml
CA-125	1065.0 U/ml	780.0 U/ml	135.0 U/ml	<35.0 U/ml
AFP	157.2 ng/ml	88.0 ng/ml	37.6 ng/ml	<8.0 ng/ml

IgG4 immunoglobulin G4, *IL* interleukin, *WBC* white blood cell, *HGB* hemoglobin, *ESR* erythrocyte sedimentation rate, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CRP* C-reactive protein, *CA* carbohydrate antigen, *AFP* alpha-fetoprotein

IgG4-positive plasma cell infiltration, were noted. Previously, some studies reported that serum IgG4 levels were increased in only about 30% of patients with IgG4-RD, and the range varies widely, which lacks sufficient clinical value [15, 16]. Recently, Inoue et al. collected data from 235 patients with IgG4-RD and found that the serum IgG4 levels in 88% of patients were more than 135 mg/dl and that 71% of patients had levels elevated to >270 mg/dl [17]. On the other hand, Carruthers et al. indicated that the cutoff value of serum IgG4 levels of more than 135 mg/dl had a low sensitivity and specificity for the diagnosis of IgG4-RD [18]. In contrast, a recent meta-analysis showed that a sensitivity of 87.2% and a specificity of 82.6% were produced for a cutoff value of IgG4 and ranged from 135 to 144 mg/dl [19]. Interestingly, some studies also found that the diagnostic value of serum IgG4 levels strongly depends on the underlying population (the retrospective diagnostic value of serum IgG4 levels seems to be even worse among biopsy-proven patients, while studies using databases of patients with any IgG4 elevation usually report a high sensitivity and specificity for IgG4-RD) [20]. Additionally, elevated serum IgG4 concentrations have been observed in several other diseases, including autoimmune diseases and malignancies [21, 22]. Therefore, serological examination alone is not sufficient, and increased serum IgG4 levels also did not serve as a specific marker for IgG4-RD. If IgG4-RD is suspected, pathologic examination that includes immunohistochemical staining should be considered. In addition, more rigorous and uniform studies are needed to evaluate the value of serum IgG4 levels in IgG4-RD, especially in biopsy-proven patients.

Second, IgG4-RD can involve virtually every organ, but isolated polyserositis (pleuritis and peritonitis) involvement of the disease is still rare. Interestingly, in our case, the polyserous effusions were the only pulmonary manifestation.

Fig. 1 Contrast-enhanced CT scan showed massive pleural effusion in the right pleural cavity and abdominal effusion with a partial compression atelectasis
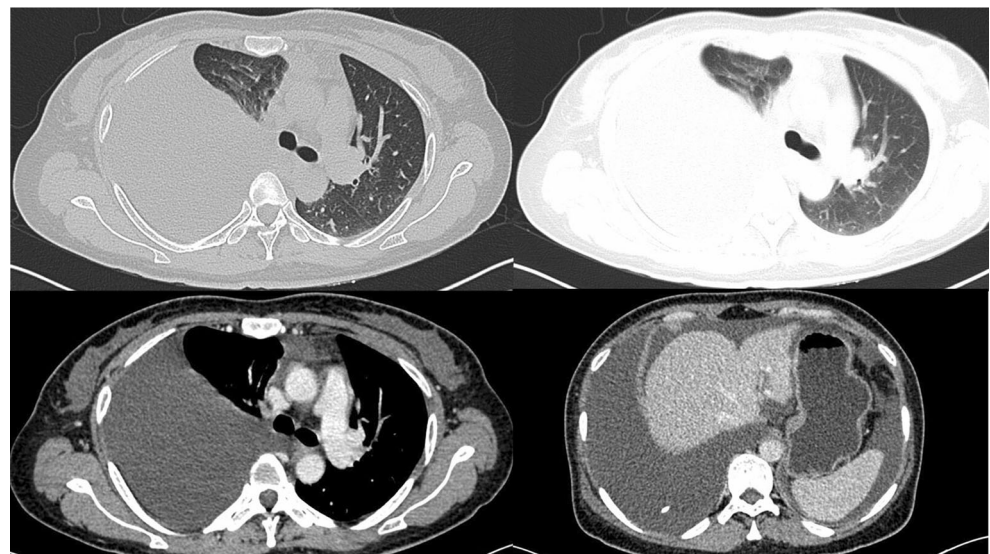
Fig. 2 Medical thoracoscopy of the right pleural cavity found multiple nodules on the pleura and partly thickened pleura with a reddish color

Thus far, few epidemiologic studies on the IgG4-related lung and pleural diseases have been reported. Zen et al. identified 21 cases of IgG4-RD and found pleural lesions in five patients [23]. The two most recent studies indicated that pleural involvement has been reported in 28% of patients with IgG4-related lung disease [24, 25]. Moreover, a previous study

Fig. 3 Histopathologic examinations of biopsy samples from the nodules on the pleura showed lymphoplasmacytic infiltration and follicular lymphoid hyperplasia with abundant plasma cells (**a** hematoxylin and eosin (H&E) stain, ×100; **b** H&E stain, ×200). Immunohistochemical staining (**c**, **d** ×200) showed that plasma cells were positive for IgG4 (80 cells per high-power field, Ki-67/MIB-1 [5%]) and a high ratio of IgG4-positive/IgG-positive cells (>40%)

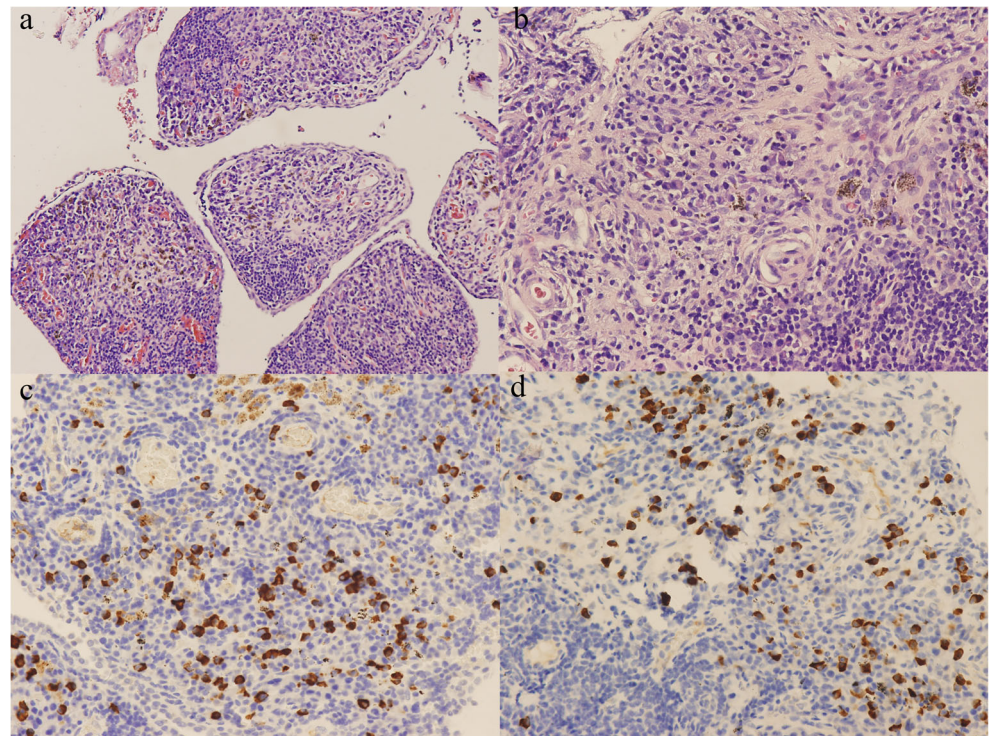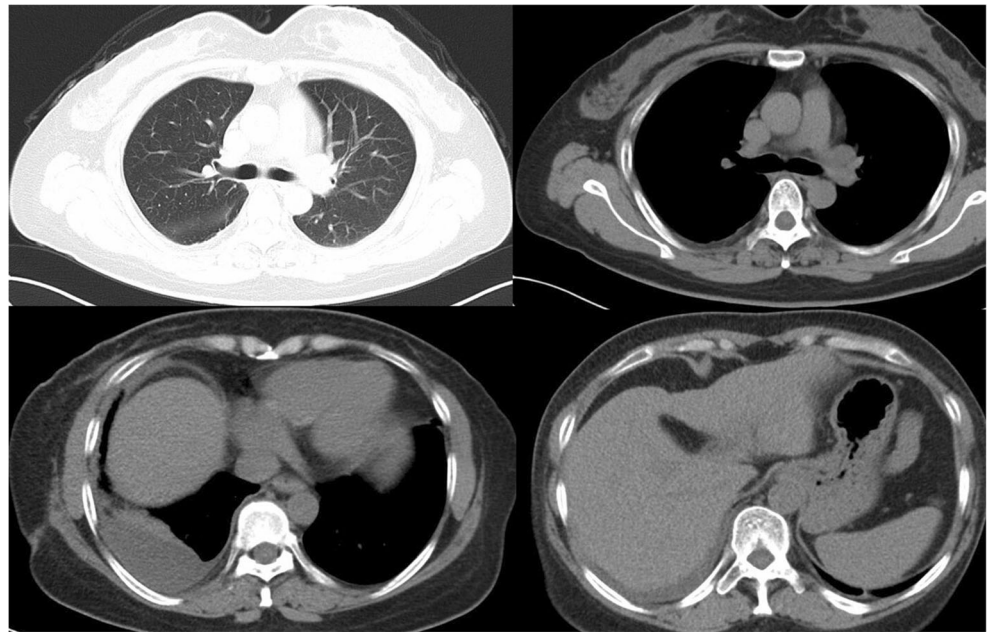**Fig. 4** Follow-up (after 4 months) computed tomography scan showed that massive pleural effusion and abdominal effusion were obviously reduced except for a small amount of encapsulated effusion

suggested that the serum IgG4 concentrations did not increase in all patients with IgG4-related pleural disease [23]. However, it is interesting that IgG4 levels of pleural effusion were higher than the serum levels in some case reports [26, 27]. To date, it is unclear whether levels of serosal IgG4 could have more diagnostic specificity than serum IgG4 concentrations, but it is undeniable that the serosal IgG4 levels were a useful and potential biomarker to diagnose IgG4-related pleural or polyserous disease.

Finally, we observed significantly elevated serum IL-6 levels in our patient. Generally, abundant infiltration of lymphoplasmacytic and IgG4-positive cells is considered a pathological feature of IgG4-RD, but these characteristics are not sufficiently specific to diagnose IgG4-RD [28]. In fact, CD's clinical and pathological characteristics were partially similar to or overlapping IgG4-RD, including elevated serum IgG4 levels and marked IgG4-positive cell infiltration [29, 30]. Previous studies found that 72.7% of patients with plasma cell-type infiltrates were accorded with the diagnostic criteria for IgG4-RD, which could easily cause a misdiagnosis [31]. However, some studies showed that the elevated serum IL-6 and CRP levels were obviously more frequently observed in patients with CD compared to IgG4-RD [7, 10]. Brandt et al. found that IL-6 transgenic mice constitutively secrete IL-6, which induced an MCD-like condition, including multifocal lymphadenopathy, splenomegaly, hypergammaglobulinemia, and plasmacytosis [32]. The other studies showed that the nuclear factor kappa B pathway activation may lead to IL-6 overproduction [33], and IL-6 causes a systemic response by stimulating CRP production; it also promotes the expression of vascular endothelial growth factor, resulting in angiogenesis [34–36]. This may contribute to the prominent capillary

proliferation and inflammatory background, which are histologic characteristics of CD. Moreover, many studies indicated that therapy with anti-IL-6/IL-6 receptor antibodies resulted in improved symptoms and biochemical abnormalities associated with CD [37, 38].

In addition, some studies suggested that responses to corticosteroids and prognoses were different between IgG4-RD and CD. Patients with IgG4-RD may often be receptive to corticosteroid treatment, but patients with CD may be aggressive or smoldering, and this treatment has been associated with a high mortality rate [12, 23, 29]. Interestingly, in our present patient, the immunohistochemical staining showed almost 80 IgG4-positive plasma cells per high-power field, and follow-up indicated satisfactory response to corticosteroids, which strongly suggests IgG4-RD with high specificity. However, significantly increased serum IL-6 levels were not compatible with the previous results. Recently, two studies also indicated that patients' IgG4-RD was associated with high serum levels of IL-6 [39, 40]. Even though the mechanism remains unclear, we speculate that IL-6 might play an important role in the pathogenesis of IgG4-RD, similar to that of CD. Moreover, it is still unknown whether an association exists between clinical severity of IgG4-RD and the serum levels of IL-6. Therefore, serum IL-6 levels may be difficult to use to distinguish between the IgG4-RD and CD. More studies on the biomarkers, including serum IL-6 levels in IgG4-RD and CD, are required in the future.

Additionally, it is interesting to note that the CA-125 and AFP levels of serum and serosal fluid were significantly increased, but the CEA was normal. Many previous studies found that the CA125 and AFP levels were high in patients with HBV infection [41, 42]. Moreover, a series of studies

revealed that these tumor biomarkers were increased in patients with inflammation [43, 44]. Considering the patient's current condition was also combined with HBV, the substantially elevated CA125 and AFP may be appropriately explained. However, we must note that IgG4-RD is a chronic fibroinflammatory disease, which may also lead to an increase in these tumor biomarkers. Besides, clinicians need to be vigilant that a patient might have a malignancy when patients have severe polyserous effusions and elevated tumor biomarkers. Therefore, we should closely monitor the change of these indicators during the course of treatment.

In conclusion, we report a case of IgG4-RD presenting as polyserous effusions with elevated serum IL-6 levels. This paper mainly highlights through analysis some difficulties in differentiating between IgG4-RD and CD because no strongly specific laboratory or histopathologic findings exist that could appropriately diagnose IgG4-RD. We suggest that researchers design and report more studies to explore the pathological and clinical features of IgG4-RD in the future, which may help differentiate these diseases and may influence their prognoses.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. Mod Rheumatol. 2012;22(1):1–14. doi:10.1007/s10165-011-0508-6.

2. Martinez-Valle F, Fernandez-Codina A, Pinal-Fernandez I, Orozco-Galvez O, Vilardell-Tarres M. IgG4-related disease: evidence from six recent cohorts. Autoimmun Rev. 2017;16(2):168–72. doi:10.1016/j.autrev.2016.12.008.

3. Cheuk W, Yuen HK, Chan JK. Chronic sclerosing dacryoadenitis: part of the spectrum of IgG4-related Sclerosing disease? Am J Surg Pathol. 2007;31(4):643–5. doi:10.1097/01.pas.0000213445.08902.11.

4. Mahajan VS, Mattoo H, Deshpande V, Pillai SS, Stone JH. IgG4-related disease. Annu Rev Pathol. 2014;9:315–47. doi:10.1146/annurev-pathol-012513-104708.

5. Culver EL, Vermeulen E, Makuch M, van Leeuwen A, Sadler R, Cargill T, et al. Increased IgG4 responses to multiple food and animal antigens indicate a polyclonal expansion and differentiation of pre-existing B cells in IgG4-related disease. Ann Rheum Dis. 2015;74(5):944–7. doi:10.1136/annrheumdis-2014-206405.

6. Inada K, Hamazaki M. Localized mediastinal lymph-node hyperplasia resembling thymoma; a case report. Ann Surg. 1958;147(3):409–13.

7. Sato Y, Kojima M, Takata K, Morito T, Mizobuchi K, Tanaka T, et al. Multicentric Castleman's disease with abundant IgG4-positive cells: a clinical and pathological analysis of six cases. J Clin Pathol. 2010;63(12):1084–9. doi:10.1136/jcp.2010.082958.

8. Cervantes CE, Correa R. Castleman disease: a rare condition with endocrine manifestations. Cureus. 2015;7(11):e380. doi:10.7759/cureus.380.

9. D'Souza A, Hayman SR, Buadi F, Mauermann M, Lacy MQ, Gertz MA, et al. The utility of plasma vascular endothelial growth factor levels in the diagnosis and follow-up of patients with POEMS syndrome. Blood. 2011;118(17):4663–5. doi:10.1182/blood-2011-06-362392.

10. Ogoshi T, Kido T, Yatera K, Oda K, Kawanami T, Ishimoto H, et al. Assessment of pathologically diagnosed patients with Castleman's disease associated with diffuse parenchymal lung involvement using the diagnostic criteria for IgG4-related disease. Lung. 2013;191(6):575–83. doi:10.1007/s00408-013-9497-x.

11. Soumerai JD, Sohani AR, Abramson JS. Diagnosis and management of Castleman disease. Cancer Control. 2014;21(4):266–78.

12. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol. 2012;22(1):21–30. doi:10.1007/s10165-011-0571-z.

13. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol. 2012;25(9):1181–92. doi:10.1038/modpathol.2012.72.

14. Tanaka A, Tazuma S, Okazaki K, Tsubouchi H, Inui K, Takikawa H. Nationwide survey for primary sclerosing cholangitis and IgG4-related sclerosing cholangitis in Japan. J Hepatobiliary Pancreat Sci. 2014;21(1):43–50. doi:10.1002/jhbp.50.

15. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med. 2012;366(6):539–51. doi:10.1056/NEJMra1104650.

16. Sah RP, Chari ST. Serologic issues in IgG4-related systemic disease and autoimmune pancreatitis. Curr Opin Rheumatol. 2011;23(1):108–13. doi:10.1097/BOR.0b013e3283413469.

17. Inoue D, Yoshida K, Yoneda N, Ozaki K, Matsubara T, Nagai K, et al. IgG4-related disease: dataset of 235 consecutive patients. Medicine (Baltimore). 2015;94(15):e680. doi:10.1097/md.0000000000000680.

18. Carruthers MN, Khosroshahi A, Augustin T, Deshpande V, Stone JH. The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. Ann Rheum Dis. 2015;74(1):14–8. doi:10.1136/annrheumdis-2013-204907.

19. Hao M, Liu M, Fan G, Yang X, Li J. Diagnostic value of serum IgG4 for IgG4-related disease: a PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore). 2016;95(21):e3785. doi:10.1097/md.0000000000003785.

20. Lang D, Zwerina J, Pieringer H. IgG4-related disease: current challenges and future prospects. Ther Clin Risk Manag. 2016;12:189–99. doi:10.2147/tcrm.s99985.

21. Su Y, Sun W, Wang C, Wu X, Miao Y, Xiong H, et al. Detection of serum IgG4 levels in patients with IgG4-related disease and other disorders. PLoS One. 2015;10(4):e0124233. doi:10.1371/journal.pone.0124233.

22. Yu KH, Chan TM, Tsai PH, Chen CH, Chang PY. Diagnostic performance of serum IgG4 levels in patients with IgG4-related disease. Medicine (Baltimore). 2015;94(41):e1707. doi:10.1097/md.0000000000001707.

23. Zen Y, Inoue D, Kitao A, Onodera M, Abo H, Miyayama S, et al. IgG4-related lung and pleural disease: a clinicopathologic study of 21 cases. Am J Surg Pathol. 2009;33(12):1886–93. doi:10.1097/PAS.0b013e3181bd535b.

24. Matsui S, Hebisawa A, Sakai F, Yamamoto H, Terasaki Y, Kurihara Y, et al. Immunoglobulin G4-related lung disease: clinicoradiological and pathological features. Respirology. 2013;18(3):480–7. doi:10.1111/resp.12016.

25. Inoue D, Zen Y, Abo H, Gabata T, Demachi H, Kobayashi T, et al. Immunoglobulin G4-related lung disease: CT findings with pathologic correlations. Radiology. 2009;251(1):260–70. doi:10.1148/radiol.2511080965.

26. Yamamoto H, Suzuki T, Yasuo M, Kobayashi O, Tsushima K, Ito M, et al. IgG4-related pleural disease diagnosed by a re-evaluation of chronic bilateral pleuritis in a patient who experienced occasional acute left bacterial pleuritis. Intern Med. 2011;50(8):893–7.

27. Gonzalez-Moreno J, Losada-Lopez I, Gallego-Lezaun C, Garcia-Gasalla M, Gomez Bellvert C, Ortego CN. Serosal involvement in IgG4-related disease: report of two cases and review of the literature. Rheumatol Int. 2016;36(7):1033–41. doi:10.1007/s00296-016-3501-8.

28. Strehl JD, Hartmann A, Agaimy A. Numerous IgG4-positive plasma cells are ubiquitous in diverse localised non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders. J Clin Pathol. 2011;64(3):237–43. doi:10.1136/jcp.2010.085613.

29. Terasaki Y, Ikushima S, Matsui S, Hebisawa A, Ichimura Y, Izumi S, et al. Comparison of clinical and pathological features of lung lesions of systemic IgG4-related disease and idiopathic multicentric Castleman's disease. Histopathology. 2017; doi:10.1111/his.13186.

30. Jindal N, Yadav D, Passero C, Krasinskas A, Craig F, Bastacky S, et al. Membranous nephropathy: a rare renal manifestation of IgG4-related systemic disease. Clin Nephrol. 2012;77(4):321–8.

31. Manabe A, Igawa T, Takeuchi M, Gion Y, Yoshino T, Sato Y. Immunohistochemical analysis of IgA expression differentiates IgG4-related disease from plasma cell-type Castleman disease. Med Mol Morphol. 2017;50(1):34–41. doi:10.1007/s00795-016-0145-4.

32. Brandt SJ, Bodine DM, Dunbar CE, Nienhuis AW. Dysregulated interleukin 6 expression produces a syndrome resembling Castleman's disease in mice. J Clin Invest. 1990;86(2):592–9. doi:10.1172/jci114749.

33. Schwarz M, Murphy PM. Kaposi's sarcoma-associated herpesvirus G protein-coupled receptor constitutively activates NF-kappa B and induces proinflammatory cytokine and chemokine production via a C-terminal signaling determinant. J Immunol. 2001;167(1):505–13.

34. Bonekamp D, Hruban RH, Fishman EK. The great mimickers: Castleman disease. Semin Ultrasound CT MR. 2014;35(3):263–71. doi:10.1053/j.sult.2013.12.005.

35. Aoki Y, Jaffe ES, Chang Y, Jones K, Teruya-Feldstein J, Moore PS, et al. Angiogenesis and hematopoiesis induced by Kaposi's sarcoma-associated herpesvirus-encoded interleukin-6. Blood. 1999;93(12):4034–43.

36. Chan KL, Lade S, Prince HM, Harrison SJ. Update and new approaches in the treatment of Castleman disease. J Blood Med. 2016;7:145–58. doi:10.2147/jbm.s60514.

37. van Rhee F, Fayad L, Voorhees P, Furman R, Lonial S, Borghaei H, et al. Siltuximab, a novel anti-interleukin-6 monoclonal antibody, for Castleman's disease. J Clin Oncol. 2010;28(23):3701–8. doi:10.1200/jco.2009.27.2377.

38. Nishimoto N, Kanakura Y, Aozasa K, Johkoh T, Nakamura M, Nakano S, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. Blood. 2005;106(8):2627–32. doi:10.1182/blood-2004-12-4602.

39. Ikeura T, Horitani S, Masuda M, Kasai T, Yanagawa M, Miyoshi H, et al. IgG4-related disease involving multiple organs with elevated serum interleukin-6 levels. Intern Med. 2016;55(18):2623–8. doi:10.2169/internalmedicine.55.6919.

40. Yamamoto M, Takahashi H, Hasebe K, Suzuki C, Naishiro Y, Hayashi T, et al. The analysis of interleukin-6 in patients with systemic IgG4-related plasmacytic syndrome—expansion of SIPS to the territory of Castleman's disease. Rheumatology (Oxford). 2009;48(7):860–2. doi:10.1093/rheumatology/kep098.

41. Assmar M, Yeganeh S, Mansourghanaei F, Amirmozafari N. Combined evaluation of AFP, CA15-3, CA125, CA19-9, and CEA tumor markers in patients with hepatitis B and C. Iran J Public Health. 2016;45(12):1645–51.

42. Zhu M, Guo J, Li W, Lu Y, Fu S, Xie X, et al. Hepatitis B virus X protein induces expression of alpha-fetoprotein and activates PI3K/mTOR signaling pathway in liver cells. Oncotarget. 2015;6(14):12196–208. doi:10.18632/oncotarget.2906.

43. Berger Y, Nevler A, Shwaartz C, Lahat E, Zmora O, Gutman M, et al. Elevations of serum CA-125 predict severity of acute appendicitis in males. ANZ J Surg. 2016;86(4):260–3. doi:10.1111/ans.13128.

44. Mizejewski G. Alpha-fetoprotein (AFP) and inflammation: is AFP an acute and/or chronic phase reactant? J Hematol Thrombo Dis. 2015;3(1):191. doi:10.4172/2329-8790.1000191.