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Immunoglobulin g4-related disease, presented with retroperitoneal fibrosis and monoclonal gammopathy: case report and mini review

Abstract

Immunoglobulin G4-related disease (IgG4-RD) is a new entity, which comprise a group of conditions, sharing common clinical, serologic and pathologic features-mainly tumor-like swelling of involved organs, lymphoplasmacytic tissue in filtration with the predominance of IgG4 positive plasma cells and CD4 positive T lymphocytes, modest tissue eosinophilia, and so-called "storiform" fibrosis with cartwheel appearance of the arranged fibroblasts and inflammatory cells. The pathogenesis of IgG4-RD is not fully understood, and the pathogenic role of IgG4 is still under discussion. The pathology process may involve pancreas, bile ducts, gallbladder, liver, thyroid, salivary and lacrimal glands, orbits, lungs, mediastinum, pericardium, aortae and arteries, kidneys, prostate and testes, breast, lymph nodes, skin, hypophysis etc., but one of the most common manifestations is retroperitoneal fibrosis. Several case series data showed that IgG4-RD is responsible for a majority of cases of retroperitoneal fibrosis, previously regarded as "idiopathic". The diagnosis of IgG4-RD requires pathology data; lymphoplasmacytic tissue infiltration with mainly IgG4+ plasma cells and lymphocytes is confirmatory. Serum IgG4 levels should be measured and isolated IgG4 elevation is a significant aid in diagnosis, although it is not diagnostic. Elevated IgG4 in patients with IgG4-RD were shown to be usually polyclonal First-line treatment for symptomatic IgG4-RD is prednisone. Here we present a pathology proven case of IgG4-RD, manifested as retroperitoneal fibrosis and monoclonal gammopathy, successfully treated with corticosteroids.

Keywords: immunoglobulin g4, lymphoplasmacytic infiltration, retroperitoneal fibrosis, monoclonal secretion, prednisone

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Abbreviations: ANCA, anti-neutrophil cytoplasm antibodies; BP, blood pressure; C, complement; CD, classification determinant; CRP, c-reactive protein; CT, computer tomography; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ECHO-CG, echocardiography; ESR, erythrocytes sedimentation rate; Hb, hemoglobin; HBs Ag, hepatitis b serum antigen; HCV, hepatitis c virus; HEENT, head, eyes, ears, nose, throat; HIV, human immunodeficiency virus; HPF, high power field; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; La/SS-B, sjögren's syndrome related antigen B; Plt, platelets; PTH, parathyroid hormone; RBC, red blood cells; RF, rheumatoid factor; Ro/SS-A, sjögren's syndrome related antigen A; RPR-test, rapid plasma regain test; RR, respiratory rate; SG, specific gravity; T3, tri-iodothyronine; T4, thyroxin; TSH, thyroid stimulating hormone; WBC, white blood cells

Introduction

Immunoglobulin G4-related disease, previously also described as IgG4-syndrome, IgG4-related systemic sclerosing disease, IgG4 autoimmune disease, systemic IgG4-related plasmacytic syndrome, IgG4-positive multiorgan lymphoproliferative syndrome, multifocal idiopathic fibrosclerosis etc, is a new entity, which comprise a group of conditions, sharing common clinical, serologic and pathologic features. Main changes, characteristic for IgG4-RD are tumor-like swelling of involved organs, lymphoplasmacytic tissue infiltration with the predominance of IgG4 positive plasma cells and CD4 positive T lymphocytes, modest tissue eosinophilia, and so-called "storiform" fibrosis with cartwheel appearance of the arranged fibroblasts and inflammatory cells; 60-70% of patients demonstrate also elevated IgG4 serum concentrations.[1–9] IgG4-RD is regarded as a fibro inflammatory condition, which pathogenesis is not fully understood, and the pathogenic role of IgG4 is still under discussion. IgG4 is a unique bivalent blocking immunoglobulin; it does not fix complement and does not bind efficiently to Fcγ receptors, suggesting its role as an immuno modulator, rather than inflammatory antibody. Recent insights into the pathophysiology of IgG4-RD also suggest that one of the major drivers of the disease appear to be plasmablasts. Oligoclonal expanded plasmablasts with extensive somatic hyper mutation were found to be increased in IgG4-RD patients with active disease.[9–12]

The process may involve pancreas, bile ducts, gallbladder, liver, thyroid, salivary and lacrimal glands, orbits, lungs, mediastinum, pericardium, aortae and arteries, retroperitoneum, kidneys, prostate and testes, breast, lymph nodes, skin, hypophysis etc. Clinical manifestations, actually regarded in the setting IgG4-RD, include broad variety of conditions.[3–5,13–30]

i. Type 1 autoimmune pancreatitis (IgG4-related pancreatitis).

ii. IgG4-related sclerosing cholangitis.

iii. Mikulicz's disease (IgG4-related dacryoadenitis and sialadenitis).

iv. Sclerosing sialadenitis (Küttner's tumor, IgG4-related submandibular gland disease).

v. Inflammatory orbital pseudotumor (IgG4-related orbital inflammation or orbital inflammatory pseudotumor).

vi. Chronic sclerosing dacryoadenitis (lacrimal gland enlargement, IgG4-related dacryoadenitis).

vii. A subset of patients with "idiopathic" retroperitoneal fibrosis (Ormond's disease) and related disorders (IgG4-related retroperitoneal fibrosis, IgG4-related mesenteritis).

viii. Chronic sclerosing aortitis and periaortitis (IgG4-related aortitis or periaortitis).

ix. Riedel's thyroiditis (IgG4-related thyroid disease).

x. IgG4-related interstitial pneumonitis and pulmonary inflammatory pseudotumors (IgG4-related lung disease).

xi. IgG4-related kidney disease (including tubulointerstitial nephritis and membranous glomerulonephritis secondary to IgG4-RD).

xii. IgG4-related hypophysitis.

xiii. IgG4-related pachymeningitis.

xiv. Skin disease, including a subset of cutaneous pseudolymphoma, typically involving scalp, face, neck, and pinna of the ear.

xv. IgG4-hepatopathy, resembling autoimmune hepatitis, and hepatic inflammatory pseudotumor.

xvi. Lymphoplasmacytic gastritis associated with autoimmune pancreatitis.

xvii. Sclerosing mastitis and inflammatory pseudotumors of the breast.

xviii. CNS involvement, with hypopituitarism associated with IgG-4-related hypophysitis and pachymeningitis being the most common manifestations.

xix. Prostatitis.

xx. Constrictive pericarditis.

xxi. Nasopharyngeal disease.

xxii. Midline-destructive lesion.

Thus, the diagnosis of IgG4-RD should be at least considered in patients with one or more of the above listed characteristic patterns of organ/tissue involvement. Given the most often involved target organs, the specific diagnostic search is strictly needed in the patients with:

a. Pancreatitis of unknown origin.

b. Sclerosing cholangitis.

c. Bilateral salivary and/or lacrimal gland enlargement.

d. Orbital pseudotumor or proptosis.

e. Retroperitoneal fibrosis.

Retroperitoneal fibrosis is one of the most common manifestations of IgG4-RD. Several case series data showed that IgG4-RD is responsible for a majority of cases of retroperitoneal fibrosis, previously regarded as "idiopathic". IgG4-related retroperitoneal fibrosis (RPF) involves particularly the infrarenal aorta, iliac arteries and ureters, causing obstructive uropathy, and may present as isolated RPF, or in some cases may be accompanied by IgG4-related pancreatitis, sialadenitis, lymph node sclerosis, hypophysitis, mediastinal periaortitis, sclerosing mesenteritis, sclerosing mediastinitis, and multifocal fibrosclerosis.[31–39] On the other hand, RPF may present as a "secondary" form, major causes of which are.[40]

A. Drugs: Methysergide, Pergolide, Bromocriptine, Ergotamine, Methyldopa, Hydralazine, Analgesics, Beta blockers, Barium

B. Malignancies: Carcinoid, Hodgkin's and non-Hodgkin's lymphomas, sarcomas, carcinomas of the colon, prostate, breast, stomach

C. Infections: Tuberculosis, histoplasmosis, actinomycosis

D. Autoimmune and inflammatory diseases: Histiocytosis, Erdheim-Chester disease, amyloidosis, ANCA-associated vasculitis, polyarteriitis nodosa, hepatitis C virus-associated cryoglobulinemia, systemic lupus erythematosus, rheumatoid arthritis

E. Others: Trauma, surgery, radiotherapy

Given multiple conditions, which may lead to RPF, differential diagnostics demand screening for above mentioned diseases and factors. Confirmation of the diagnosis of IgG4-RD requires pathology data, such as lymphoplasmacytic tissue infiltration of mainly IgG4 positive plasma cells and lymphocytes, accompanied by fibrosis that has "storiform" features, and often by obliterative phlebitis and modest tissue eosinophilia. Serum IgG4 levels should be measured, and isolated IgG4 elevation is a significant aid in diagnosis, although it is not diagnostic.[41,42]

Treatment for IgG4-RD is not yet established, International consensus statement tells that prednisone should be the first-line treatment in patients with symptomatic IgG4-RD, unless contraindicated, and recent studies confirm benefit of corticosteroids in patients with IgG4-related kidney disease. There are also increasing data in favour of rituximab usage for IgG4-RD, mostly in patients not responding to prednisone.[43–46]

Case presentation

Caucasian lady 57years old, admitted to nephrology unit May 5 2015

Main complains

General weakness, moderate back pain, decreased appetite, and weight loss.

Previous medical history

Duodenum ulcer for manyyears, last time symptomatic in 2014 and treated with omeprazole; uterine fibroid (uterine extirpation in 2004); inguinal hernia (hernioplasty in 2011).

History of current disease

January 2015 she developed unexplained weakness, thirst and weight loss. Outpatient work-up found anemia (Hb 8.8g/dL) and decreased renal function (serum creatinine 240μmol/L). Abdomen ultrasound showed bilateral hydronephrosis, gastroscopy found nothing but duodenum cicatricle deformity, colonoscopy findings were unremarkable.

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March 2015 she was admitted to urology clinic with her serum creatinine raised up to 450μmol/L, CT confirmed bilateral ureterohydronephrosis, and found right kidney enlargement and retroperitoneal mass with bilateral ureteral compression (Figure 1). She was diagnosed with retroperitoneal fibrosis, underwent right kidney percutaneous nephrostomy and left ureteral stenting, her creatinine lowered to 241μmol/L and she was referred to our clinic for further evaluation.

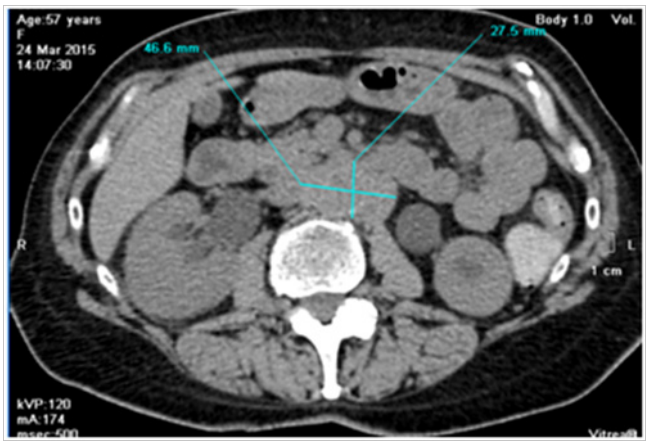

Figure 1 CT scan, showing retroperitoneal mass.

At admission

Conscious, alert, oriented, slightly depressed. Body temperature 36.9°C, RR 18 per minute, pulse regular 84 per minute, BP 140/80mm Hg. Pale, undernourished. No peripheral oedema, neither palpable peripheral lymph nodes.

Joints: No swelling, movements not restricted. HEENT and neck otherwise normal.

Lungs: No dullness to percussion, any rhonchi, wheezes or rubs.

Heart: Regular rhythm, no murmur. Abdomen soft, non-tender, bowel sounds normal. Liver +1cm below rib arch, non-painful, spleen and kidneys not felt. Right kidney urine drainage functioning well, urine output via drainage 1000 mL/day, spontaneous urine output 900mL/day, urine normally colored, slightly opaque.

Work up

Total blood count: Hb 11.0g/L, WBC 8.2x109/L with normal formula, Plt 166x109/L, ESR 35mm/h.

Blood chemistry: creatinine 225μmol/L, urea 20.1mmol/L, uric acid 560μmol/L, total protein 82g/L, serum iron 6.7μmol/L; electrolytes, glucose, albumin, cholesterol, bilirubin, liver enzymes - within normal range.

Urinalysis: SG 1012, protein 0.4g/L - 0.69g/day, RBC 3-5, WBC >200hpf.

Urine culture: Klebsiella species 1x108/mL.

Infections screening: RPR-test for Treponema Pallidum, HBsAg, anti-HCV and anti-HIV-antibodies negative, tuberculin skin test-all negative.

Autoimmune screening: RF, anti-DNA antibodies, anti-Ro/SS-A, anti-La/SS-B antibodies, C3, C4, pANCA, cANCA, IgG, IgA, IgM and CRP-all within normal range, cryoglobulines negative.

Hormones: T3, T4, TSH and PTH within normal range.

Serum protein high resolution electrophoresis: Mild IgG-κappa monoclonal secretion, confirmed by immunofixation and immunophenotyping.

Urine protein electrophoresis: Mild tubular proteinuria.

IgG subclasses: Total IgG 12.7g/L, IgG1 60.5%, IgG2 34.0%, IgG3 3.2%, IgG4 2.3% (all within normal range).

ECG; chest and skeletal X-Ray; ECHO-CG and aortae; pelvis and peripheral lymph nodes ultrasound: Unremarkable.

Abdomen and kidneys ultrasound: Gallbladder lithiasis, liver and pancreas otherwise normal, mild splenomegaly (140x65mm).

Kidneys: Right 116x47, left 101x45mm, with hyperechoic parenchyma 17-20mm.

Mild bilateral collecting system dilatation: Right pelvis 15mm, calices 12mm, left pelvis 14mm, calices 8mm. Urine drainage in the right pelvis, stent in the left ureter. No visible retroperitoneal lymph nodes. Stringy hypoechoic retroperitoneal masses, 6x12x15 mm, surrounding aorta and both ureters.

Thyroid gland ultrasound: Right lobe 50x17x17mm, left lobe 45x17x15mm, isthmus 4mm. Echogenicity uneven, texture irregular, multiple nodules maximum 11x6mm. Regional lymph nodes enlarged up to 12-14mm with normal structure.

Bone marrow biopsy: No changes, specific for lymph proliferative disease found.

Diagnostic considerations and further work-up

At that point patient with retroperitoneal fibrosis was evaluated for aortic aneurism, Riedel's thyroiditis, ANCA-associated vasculitis, systemic lupus erythematous, cryoglobulinemia, rheumatoid arthritis, infections and solid tumors, and no proof for these disorders was found. On the other hand, presence of low-grade paraproteinemia and splenomegaly was suggestive for extra-organ lymphoma and demanded pathology evaluation of retroperitoneal masses. Ultrasound-guided biopsy was technically unachievable. Patient was treated with antibiotics for urinary tract infection, then urine drainage was removed and right ureter stent placed instead, after that she was referred to the surgical unit for endoscopic biopsy of retroperitoneal mass.

Biopsy of retroperitoneal mass: pathology evaluation (Figures 2–4) by light microscopy sections of formalin fixed paraffin embedded tissue, stained with periodic acid-Schiff and Haematoxylin-Eosin, represented mostly coarse fibrous tissue with prominent desmoplastic changes, and focal lymphoid infiltration with substantial admixture of plasma cells. Fine focal lymphocyte and plasma cell aggregates were found also per vascular in the depth of fibrous tissue. Immunohistochemistry on formalin fixed paraffin embedded tissue with immuno peroxidase staining for IgG4, CD138, CD3 and CD20 showed diffuse (80%) prominent expression of CD20+, diffuse multifocal (40%) prominent expression of CD138+, and focal (<20%) moderate expression of CD3+. Vast majority of CD138 positive cells showed also diffuse moderate expression of IgG4 (up to 15-20 IgG4 positive plasma cells per field with magnification x400).

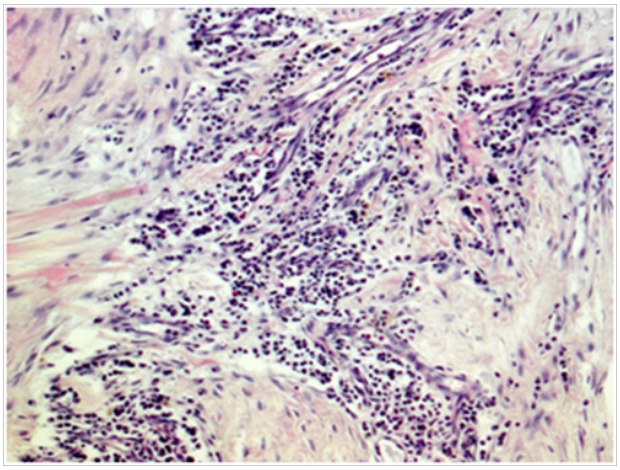

Figure 2 Light microscopy showing patchy perivascular, predominantly plasma cell infiltration in the fields of irregular fibrosis (H&Ex100).

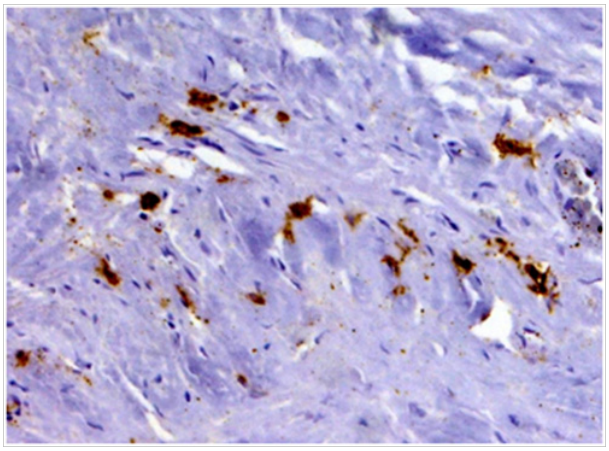

Figure 3 Immuno histo chemistry revealing patchy clusters of CD138-positive plasma cells in the fields of coarse fibrosis. (Immunoperoxidasex100).

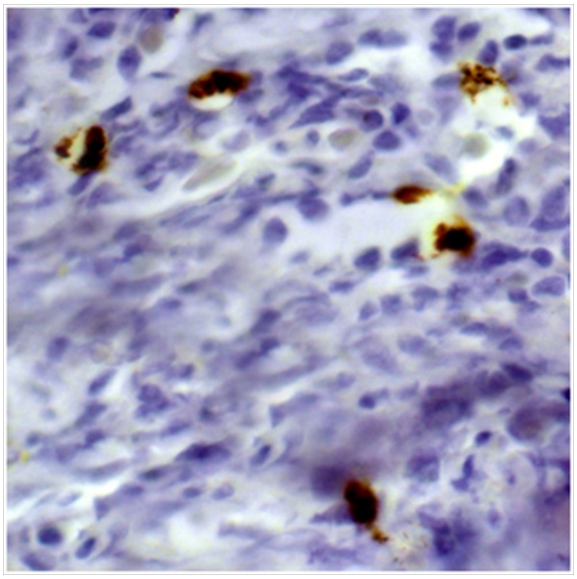

Figure 4 Immuno histo chemistry showing seven IgG4-positive plasma cells per HPF (Immunoperoxidasex400).

Pathology conclusion*:* IgG4-associated retroperitoneal damage with massive desmoplastic fibrosis and focal, mainly B-cell lymphoid infiltration with plasma cell transformation (CD20+, CD138+, IgG4+).

Final diagnosis and further treatment: Patient was diagnosed with IgG4-related retroperitoneal fibrosis and started on prednisone 40mg/day.

At last evaluation

2months later (October 2015) she is doing well, no complains, gained 4 kilos weight, BP 120/80mm Hg, urine output 1500ml/day, and physical examination unremarkable. Hb 144g/L, WBC 6.6x109/L, Plt 184x109/L, ESR 4mm/h; creatinine 160µmol/L, urea 16.7mmol\L, other blood chemistry tests within normal range. Urinalysis: protein absent, RBC 30-40, WBC 10-20hpf. Abdomen ultrasound showed partial regression of previously seen retroperitoneal masses. She was retreated with antibiotics for asymptomatic urinary tract infection and advised slowly taper prednisone to 30mg/day.

Discussion

Patient presented with clear retroperitoneal fibrosis and bilateral ureterohydronephrosis with impaired renal function. After the restoration of her urine passage, the question of the cause for RPF was raised. As a first step, screening for the diseases and conditions, which may lead to the "secondary" RPF was carefully performed. Patient denied usage of any medications but omeprazole; she also denied traumas, exposure to radiation and surgery, except uterine extirpation and inguinal hernioplasty. The results routine labs, infectious and autoimmune screening, thyroid and parathyroid hormones tests, chest X-Ray, gastro copy and colonoscopy, ECHO-CG, aortae, neck, abdomen, kidneys, pelvis and peripheral lymph nodes ultrasound allowed us to rule out autoimmune systemic and inflammatory diseases, viral hepatitis, tuberculosis and solid tumors. The only findings, beyond retroperitoneal masses, were thyroid nodules, gallbladder lithiasis, mild splenomegaly and low-grade IgG-kappa paraproteinemia.

That turned us to the differential diagnostics between extra organ B-cell lymphoproliferative disorder and IgG-related disease. Bone marrow biopsy did not reveal any proof for lymphoproliferative disease, and IgG4 serum level was found to be normal, thus none of these two conditions were not confirmed neither excluded and we need pathology confirmation of the diagnosis. Endoscopic retroperitoneal mass biopsy provided the clue to the diagnosis. Pathology examination with immunohistochemistry found massive desmoplastic fibrosis and focal, mainly B-cell lymphoid infiltration with plasma cell transformation (CD20+, CD138+, IgG4+), which is characteristic for IgG4-RD.[41,42]

Based on these findings, IgG4-related retroperitoneal fibrosis was diagnosed. Taking into consideration that elevated serum levels of IgG4 are observed only in 60-70% of patients with IgG4-RD and not necessarily needed to confirm the diagnosis.[7,41,42] normal level of IgG4 don't rule out this diagnosis. We believe that RPF in this particular case is the solely one manifestation of IgG4-RD, as we did not find any data in favor of aortic aneurism, pericarditis, Riedel's thyroiditis and pancreatitis or any other typical for IgG-RD organ involvement. Gallbladder lithiasis without signs of holecystitis or cholangitis is probably comorbid condition rather than IgG4-RD

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manifestation, as well as small thyroid nodules not accompanied by thyroid dysfunction. Patient was treated with prednisone according to International consensus statement,[41] which resulted in the resolution of clinical symptoms and partial regress of retroperitoneal masses.

The most controversial issue is the significance of mild IgG-kappa paraproteinemia. Elevated IgG4 in patients with IgG4-RD were shown to be polyclonal.[5,9] On the other hand, patients with IgG4-RD have a 3.5 times higher risk of cancer than the general population. Reported cases are predominantly extranodal marginal zone lymphomas (MALT lymphomas), which either may arise in the background of a pre-existing non-clonal IgG4-related chronic sclerosing lesion, or have evidence of plasmacytic differentiation with IgG4-positive monoclonal plasma cells.[47–50] Few cases of the association of IgG4-RD, POEMS and Castleman disease also are reported.[51–53] Several studies of subclass distribution in IgG monoclonal gammopathy of undetermined significance and myeloma, performed back in the 1980s, showed that IgG4 myeloma represented 2-8% of IgG plasma cell neoplasms.[54–57]

The recent study of more that 150 patients with IgG plasma cell myeloma found that IgG4 myeloma represented 4% of cases (6 out of 158). Remarkable, that two of six patients had a documented phase of monoclonal gammopathy of undetermined significance or smoldering myeloma before developing overt plasma cell myeloma. None of these 6 patients met criteria for IgG4-RD, but one of them had an episode of pancreatitis, another had chronic sinusitis, and two patients presented with necrotizing fasciitis. Authors postulate that IgG4 myeloma should be considered in the differential diagnosis of patients with high serum levels of IgG4.[58] Another recent study found that the focal band, detected by electrophoresis in sera from patients with IgG4-RD, can be in fact polyclonal while tested by immunofixation or immunosubtraction.[59] Our patient with IgG4-RD does not fulfill criteria for myeloma, but she has a monoclonal gammopathy IgG-kappa, confirmed by immunofixation and immunophenotyping. This demands follow-up and annual serum immunochemistry tests, evaluating putative progression to myeloma.

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Conflict of interest

Author declares that there is no conflict of interest.

References

1. Umehara H, Okazaki K, Masaki Y, et al. A novel clinical entity, IgG4–related disease (IgG4RD): general concept and details. *Mod Rheumatol.* 2012;22(1):1–14.
2. Cheuk W, Chan JK. IgG4–related sclerosing disease: a critical appraisal of an evolving clinicopathologic entity. *Adv Anat Pathol.* 2010;17(5):303–332.
3. Khosroshahi A, Stone JH. A clinical overview of IgG4–related systemic disease. *Curr Opin Rheumatol.* 2011;23(1):57–66.
4. Okazaki K, Uchida K, Koyabu M, et al. Recent advances in the concept and diagnosis of autoimmune pancreatitis and IgG4–related disease. *J Gastroenterol.* 2011;46(3):277–288.
5. Stone JH, Zen Y, Deshpande V. IgG4–related disease. *N Engl J Med.* 2012;366(6):539–551.
6. Kamisawa T, Zen Y, Pillai S, et al. IgG4–related disease. *Lancet.* 2015;385(9976):1460–1471.
7. Wallace ZS, Deshpande V, Mattoo H, et al. IgG4–Related Disease: Clinical and Laboratory Features in One Hundred Twenty–Five Patients. *Arthritis Rheumatol.* 2015;67(9):2466–2475.
8. Deheragoda MG, Church N, Rodriguez–Justo M, et al. The use of immunoglobulin G4 immunostaining in diagnosing pancreatic and extrapancreatic involvement in autoimmune pancreatitis. *Clin Gastroenterol Hepatol.* 2007;5(10):s1229–1234.
9. Carruthers MN, Stone JH, Khosroshahi A. The latest on IgG4–RD: a rapidly emerging disease. *Curr Opin Rheumatol.* 2012;24(1):60–69.
10. Sthoeger Z, Asher I, Rosenberg–Bezalel S, et al. Immunoglobulin G4 and related diseases. *Isr Med Assoc J.* 2012;14(10):642–645.
11. Mattoo H, Mahajan VS, Della–Torre E, et al. De novo oligoclonal expansions of circulating plasmablasts in active and relapsing IgG4–related disease. *J Allergy Clin Immunol.* 2014;134(3):679–687.
12. Wallace ZS, Mattoo H, Carruthers M, et al. Plasmablasts as a biomarker for IgG4–related disease, independent of serum IgG4 concentrations. *Ann Rheum Dis.* 2015;74(1):190–195.
13. Cheuk W, Lee KC, Chong LY, et al. IgG4–related Sclerosing disease: a potential new etiology of cutaneous pseudolymphoma. *Am J Surg Pathol.* 2009;33(11):1713–1719.
14. Miyagawa–Hayashino A, Matsumura Y, Kawakami F, et al. High ratio of IgG4–positive plasma cell infiltration in cutaneous plasmacytosis– is this a cutaneous manifestation of IgG4–related disease?. *Hum Pathol.* 2009;40(9):1269–1277.
15. Ikeda T, Oka M, Shimizu H, et al. IgG4–related skin manifestations in patients with IgG4–related disease. *Eur J Dermatol.* 2013;23(2):241–245.
16. Umemura T, Zen Y, Hamano H, et al. IgG4 associated autoimmune hepatitis: a differential diagnosis for classical autoimmune hepatitis. *Gut.* 2007;56(10):1471–1472.
17. Zen Y, Fujii T, Sato Y, et al. Pathological classification of hepatic inflammatory pseudotumor with respect to IgG4–related disease. *Mod Pathol.* 2007;20(8):884–894.
18. Uehara T, Hamano H, Kawa S, et al. Chronic gastritis in the setting of autoimmune pancreatitis. *Am J Surg Pathol.* 2010;34(9):1241–1249.
19. Cheuk W, Chan AC, Lam WL, et al. IgG4–related sclerosing mastitis: description of a new member of the IgG4–related sclerosing diseases. *Am J Surg Pathol.* 2009;33(7):1058–1064.
20. Zen Y, Kasahara Y, Horita K, et al. Inflammatory pseudotumor of the breast in a patient with a high serum IgG4 level: histologic similarity to sclerosing pancreatitis. *Am J Surg Pathol.* 2005;29(2):275–278.
21. Shimatsu A, Oki Y, Fujisawa I, et al. Pituitary and stalk lesions (infundibulo–hypophysitis) associated with immunoglobulin G4–related systemic disease: an emerging clinical entity. *Endocr J.* 2009;9(56):1033–1041.
22. Haraguchi A, Era A, Yasui J, et al. Putative IgG4–related pituitary disease with hypopituitarism and/or diabetes insipidus accompanied with elevated serum levels of IgG4. *Endocr J.* 2010;57(8):719–725.
23. Joshi D, Jager R, Hurel S, et al. Cerebral involvement in IgG4–related disease. *Clin Med.* 2015;15 (2):130–134.

24. Uehara T, Hamano H, Kawakami M, et al. Autoimmune pancreatitis–associated prostatitis: distinct clinicopathological entity. *Pathol Int.* 2008;58(2):118–125.

25. Sugimoto T, Morita Y, Isshiki K, et al. Constrictive pericarditis as an emerging manifestation of hyper–IgG4 disease. *Int J Cardiol.* 2008;130(3):100–101.

26. Takikita–Suzuki M, Ishida M, Okabe H. Re–evaluation of IgG4 in systemic fibro inflammatory disease with intracardiac involvement. *Hum Pathol.* 2010;41(3):458–459.

27. Fatemi G, Fang MA. IgG4–related pharyngitis–an addition to the nomenclature of IgG4–related disease: comment on the article by Stone et al. *Arthritis Rheum.* 2013;65(8):2217–2217.

28. Carruthers MN, Miloslavsky EM, Stone JH. Reply: To PMID 22736240. *Arthritis Rheum*. 2013;65(8):2217–2217.

29. Della–Torre E, Mattoo H, Mahajan VS, et al. IgG4–related midline destructive lesion. *Ann Rheum Dis*. 2014;73(7):1434–1436.

30. Pieringer H, Parzer I, Wöhrer A, et al. IgG4– related disease: an orphan disease with many faces. *Orphanet J Rare Dis*. 2014;9:110–124.

31. Neild GH, Rodriguez–Justo M, Wall C, et al. Hyper–IgG4 disease: report and characterization of a new disease. *BMC Med*. 2006;4:23–41.

32. Zen Y, Onodera M, Inoue D, et al. Retroperitoneal fibrosis: a clinicopathologic study with respect to immunoglobulin G4. *Am J Surg Pathol.* 2009;33(12):1833–1839.

33. Hamano H, Kawa S, Ochi Y, et al. Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. *Lancet.* 2002;359(9315):1403–1404.

34. Stone JR. Aortitis, periaortitis, and retroperitoneal fibrosis, as manifestations of IgG4–related systemic disease. *Curr Opin Rheumatol*. 2011;23(1):88–94.

35. Khosroshahi A, Carruthers MN, Stone JH, et al. Rethinking Ormond's disease: "idiopathic" retroperitoneal fibrosis in the era of IgG4–related disease. *Medicine (Baltimore)*. 2013;92(2):82–91.

36. Zen Y, Sawazaki A, Miyayama S, et al. A case of retroperitoneal and mediastinal fibrosis exhibiting elevated levels of IgG4 in the absence of sclerosing pancreatitis (autoimmune pancreatitis). *Hum Pathol*. 2006;37(2):239–243.

37. Chen TS, Montgomery EA. Are tumefactive lesions classified as sclerosing mesenteritis a subset of IgG4–related sclerosing disorders?. *J Clin Pathol.* 2008;61(10):1093–1097.

38. Taniguchi T, Kobayashi H, Fukui S, et al. A case of multifocal fibrosclerosis involving posterior mediastinal fibrosis, retroperitoneal fibrosis, and a left seminal vesicle with elevated serum IgG4. *Hum Pathol*. 2006;37(9):1237–1239.

39. Hamed G, Tsushima K, Yasuo M, et al. Inflammatory lesions of the lung, submandibular gland, bile duct and prostate in a patient with IgG4–associated multifocal systemic fibrosclerosis. *Respirology*. 2007;12(3):455–457.

40. Vaglio A, Salvarani C, Buzio C. Retroperitoneal fibrosis. *Lancet.* 2006;367(9506):241–251.

41. Khosroshahi A, Wallace ZS, Crowe JL, et al. International Consensus Guidance Statement on the Management and Treatment of IgG4–Related Disease. *Arthritis Rheumatol.* 2015;67(7):1688–1699.

42. Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4–related disease. *Mod Pathol.* 2012;25(9):1181–1192.

43. Saeki T, Kawano M, Mizushima I, et al. The clinical course of patients with IgG4–related kidney disease. *Kidney Int*. 2013;84(4):826–833.

44. Khosroshahi A, Stone JH. Treatment approaches to IgG4–related systemic disease. *Curr Opin Rheumatol*. 2011;23(1):67–71.

45. Khosroshahi A, Bloch DB, Deshpande V, et al. Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4–related systemic disease. *Arthritis Rheum*. 2010;62(6):1755–1762.

46. Khosroshahi A, Carruthers MN, Deshpande V, et al. Rituximab for the treatment of IgG4–related disease: lessons from 10 consecutive patients. *Medicine (Baltimore)*. 2012;91(1):57–66.

47. Yamamoto M, Takahashi H, Tabeya T, et al. Risk of malignancies in IgG4–related disease. *Mod Rheumatol.* 2012;22(3):414–418.

48. Kim T, Grobmyer SR, Dixon LR, et al. Autoimmune pancreatitis and concurrent small lymphocytic lymphoma: not just a coincidence?. *J Gastrointest Surg.* 2008;12(9):1566–1570.

49. Cheuk W, Yuen HK, Chan AC, et al. Ocular adnexal lymphoma associated with IgG4+ chronic sclerosing dacryoadenitis: a previously undescribed complication of IgG4–related sclerosing disease. *Am J Surg Pathol.* 2008;32(8):1159–1167.

50. Takahashi N, Ghazale AH, Smyrk TC, et al. Possible association between IgG4–associated systemic disease with or without autoimmune pancreatitis and non–Hodgkin lymphoma. *Pancreas.* 2009;38(5):523–526.

51. Gatti–Mays ME, Kardon D, Chieu TT, et al. Autoimmune Pancreatitis in the Setting of Multifocal Castleman Disease in an HIV–Negative, HHV–8–Negative, 70–Year–Old Man. *Clin Adv Hematol Oncol*. 2012;10(10):683–686.

52. Nicoli P, Guerrasio A. Autoimmune Pancreatitis, IgG4– Related Disease, and Castleman Disease: Is There a Link?. *Clin Adv Hematol Oncol.* 2012;10(10):687–688.

53. Starr JC, Rao A, Brasher GW, et al. IgG Subclass 4–Related Disease with Fluctuating Biclonal Gammopathy and Features of POEMS Syndrome: a Case Report. *Clin Exp Med Sci*. 2013;1(4): 177–188.

54. Aucouturier P, Preud'Homme JL. Subclass distribution of human myeloma proteins as determined with monoclonal antibodies. *Immunol Lett*. 1987;16(1):55–57.

55. Papadea C, Reimer CB, Check IJ. IgG subclass distribution in patients with multiple myeloma or with monoclonal gammopathy of undetermined significance. *Ann Clin Lab Sci.* 1989;19(1):27–37.

56. Tichy M, Hrncir Z, Mracek J. Subclasses IgG1–IgG4 in 84 sera with IgG paraprotein. *Neoplasma*. 1978;25(1):107–110.

57. Kyle RA, Gleich GJ. IgG subclasses in monoclonal gammopathy of undetermined significance. *J Lab Clin Med*. 1982;100(5):806–814.

58. Geyer JT, Niesvizky R, Jayabalan DS, et al. IgG4 plasma cell myeloma: new insights into the pathogenesis of IgG4–related disease. *Mod Pathol.* 2014;27(3):375–381.

59. Jacobs JF, Van der Molen RG, Keren DF. Relatively Restricted Migration of Polyclonal IgG4 May Mimic a Monoclonal Gammopathy in IgG4–Related Disease. *Am J of Clin Pathol.* 2014;142(1):76–81.

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