CASE REPORT

Surgical management of isolated mesenteric autoimmune disease: addressing the spectrum of IgG₄-related disease and sclerosing mesenteritis

Alissa Greenbaum,¹ Nour Yadak,² Steven Perez,³ Ashwani Rajput³

¹Department of Surgery, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA

²Department of Pathology, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA

³Comprehensive Cancer Center, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA

Correspondence to
Ashwani Rajput,
Arajput@salud.unm.edu

Accepted 9 May 2017

SUMMARY

IgG₄-related disease (IgG₄-RD) is a rare form of autoimmune sclerosing disease, characterised by elevated serum IgG₄ and tissue IgG₄ levels, specific histopathological findings, multiorgan involvement and adequate response to glucocorticoid treatment. The low incidence and the heterogeneous nature of the disease has made consensus on diagnostic criteria for IgG₄-RD difficult. Whether sclerosing mesenteritis (SM) is considered a manifestation of IgG₄-RD is strongly debated. We present the case of a patient with a history of rheumatoid arthritis who presented with a calcified abdominal mass. She was found to have an isolated, pedunculated mesenteric mass positive for IgG₄ and concurrently elevated serum IgG₄ levels. Clinical features did not classify her disease as either SM or IgG₄-RD as currently described in consensus statements. Concurrent diagnoses of IgG₄-RD, SM and other autoimmune disorders, as well as postoperative recommendations for resected isolated IgG₄-positive masses, are discussed.

BACKGROUND

IgG₄-related disease (IgG₄-RD) is a rare process characterised by systemic sclerosing disease and IgG₄-positive plasma cell and lymphocyte infiltration of various organs.^{1–3} A cardinal feature entails signs of single or multiple organ inflammation, often raising concern for malignancy before diagnosis.⁴ Clinical manifestations can vary greatly and mimic other inflammatory or immunological disorders, resulting in major diagnostic challenges.² Current expert consensus defines IgG₄-RD as consisting of four characteristics features: (1) high-serum IgG₄ levels, (2) tissue IgG₄ elevation with characteristic histopathological findings, (3) multiorgan involvement and (4) effective response to glucocorticoid treatment.^{5–6} More than 90% of patients with IgG₄-RD have at least one of five clinical manifestations, including pancreatitis, sialadenitis, interstitial nephritis, dacryoadenitis and periaortitis,⁷ with the most common overall presentation being autoimmune pancreatitis.^{8–9} Surgical resection plays a minimal role in treatment of IgG₄-RD once diagnosed. Intervention should be reserved for obtaining tissue diagnosis and treatment of disease-related complications.⁸

Sclerosing mesenteritis (SM), also referred to as mesenteric fibrosis, mesenteric lipodystrophy or retractile mesenteritis,¹⁰ is non-specific, benign

inflammatory process with a variety of aetiologies. The specific cause of SM is difficult to determine in the majority of cases,¹¹ though is hypothesised to originate from an autoimmune or paraneoplastic process. SM usually affects the root of the small bowel mesentery, though retroperitoneal, peripancreatic and colonic mesentery could also be potentially involved.¹¹ Histologically, SM includes degeneration of fat cells leading to areas of calcification, occasional infiltration with lipophages, macrophages, plasma cells and a proliferative of fibroblasts. While IgG₄-RD can affect any organ,⁴ many investigators purport that IgG₄-RD, if ever, affects the small bowel mesentery.⁵ However, cases of SM in patients with elevated IgG₄-RD have been reported.^{10–12–13}

We present the case of a mesenteric mass resected for concerns of malignancy, found to be positive for IgG₄-subclass plasma cell infiltration and concurrently elevated serum IgG₄. The diagnoses of IgG₄-RD and SM are discussed as a possible spectrum of sclerosing disease.

CASE PRESENTATION

A 56-year-old G0 woman initially presented to the gynaecology–oncology service for consultation of a calcified right adnexal mass. She had a history of hypothyroidism, rheumatoid arthritis (RA) in remission for nearly 30 years, hyperlipidaemia and a past occlusion of her left anterior descending artery requiring stenting 9 years prior. Family history was significant for a paternal aunt diagnosed with endometrial cancer, though no ovarian or breast cancers were noted. She underwent flat plate X-rays of the spine at a referring institution to evaluate for osteoarthritis and was incidentally found to have a calcified mass in the right lower quadrant of her abdomen. She subsequently underwent an ultrasound which was of limited value secondary to shadowing from the calcifications in the mass. CT scan of the abdomen and pelvis with intravenous contrast confirmed a 4 cm diameter calcified mass in the right lower quadrant.

However, on careful review of the imaging with our cancer centre radiologist, the mass did not appear to be adnexal in origin. The mass was located more centrally, just lateral to the right side of the sacral promontory and close to the bifurcation of the right external and internal iliac arteries. The mass appeared to be involved with mesenteric

CrossMark

To cite: Greenbaum A, Yadak N, Perez S, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-220400

Figure 1 CT scan of the abdomen and pelvis with intravenous contrast with (A) axial and (B) coronal views demonstrates an approximately 4 cm in diameter, well-circumscribed and calcified right pelvic mass.

components of the small bowel. No carcinomatosis or other intra-abdominal lesions were noted, with all other anatomy appearing normal. The patient was subsequently referred to surgical oncology for the evaluation of an isolated, intrapelvic mesenteric mass of unknown aetiology.

At the time of her surgical consultation, she complained of mild fatigue and intermittent constipation, though was otherwise asymptomatic. Specifically, she denied abdominal pain or increasing girth, unintentional weight loss, constitutional symptoms, nausea, vomiting or diarrhoea. Abdominal examination was unremarkable and pelvic examination revealed a normal cervix, uterus and no palpable adnexal masses. The patient was agreeable to undergo surgical resection of the mass to obtain definitive pathological diagnosis.

INVESTIGATIONS

Cancer antigen 125 was 6 U/mL, further decreasing suspicion of an adnexal malignancy. Papanicolaou testing was normal with cytology negative for human papillomavirus. A repeat CT scan of the abdomen and pelvis with intravenous contrast demonstrated a 4.1×3.2×2.9 cm partially calcified right pelvis mass, unchanged in size and appearance to initial imaging 3 months prior (figure 1 A,B).

DIFFERENTIAL DIAGNOSIS

Partially calcified masses in an adnexal location in a postmenopausal woman must be ruled out for ovarian serous or mucinous cystadenoma, ovarian adenocarcinoma, simple ovarian cyst, teratoma and uterine fibroid. However, in this case, careful

Figure 2 (A) Histological analysis of the nodule with H&E stain (10×) shows dense sclerosis. (B) Further magnification (20×) of the mass revealed sclerosis with lymphoplasmic cellular infiltrate. (C) IgG₄ immunostaining showing an increase in IgG₄-positive plasma cells (40×).

review of advanced imaging revealed the mass likely originated from pelvic retroperitoneal soft tissue or the small bowel mesentery. Differential diagnosis for a mesenteric mass is broad and includes SM, lymphoma, peritoneal carcinomatosis, carcinoid tumour, mesenteric fibromatosis, sequelae of inflammatory bowel disease, inflammatory pseudotumour and adenocarcinoma infiltration from adjacent small bowel.

TREATMENT

The patient underwent diagnostic laparoscopy. A 5 cm calcified mass was found in the right pelvis, attached to the small bowel mesentery by a thin pedicle. There was no involvement of the mesenteric root or vasculature. The remainder of the abdominal cavity and intra-abdominal organs appeared normal, except for some mild fibrotic changes in the liver. The mass was excised laparoscopically using an electrothermal bipolar tissue sealing device and removed using a plastic retrieval bag through the umbilical port site. She recovered well from the operation and was discharged from the hospital the following day.

OUTCOME AND FOLLOW-UP

The histopathological analysis of the intra-abdominal mass revealed a densely sclerotic nodule with areas of calcification and lymphoplasmic cellular infiltrate (figure 2A,B). No evidence of malignancy identified. Ancillary immunohistochemical staining of IgG and IgG₄ was performed (figure 2C) and highlighted the increased positivity of IgG₄-positive plasma cells. IgG₄ plasma cells were scattered throughout densely sclerotic tissue (thus a diffuse distribution) though not uniformly. The number of plasma cells was described as focally measuring up to 33 plasma cells/high power field (HPF). Although it was difficult to assess the classic features of IgG₄ disease (eg, obliterative phlebitis) because of the sclerotic nature of the specimen, the overall features were suggestive of IgG₄ disease.

Six weeks postoperatively, the patient was evaluated by medical oncology in outpatient clinic. Serum IgG₄ levels were mildly elevated at 134 mg/dL (normal range 1–123 mg/dL). The patient was recommended to follow-up with her rheumatologist for further recommendations. Laboratory evaluation ordered by the patient's rheumatologist revealed

a negative antinuclear antibody screen, normal rheumatoid factor (<10 IU/mL), erythrocyte sedimentation rate (14 mm/hour) and C reactive protein (<0.3 mg/dL). Serum IgG₄ was again elevated at 164 mg/dL. During a clinic visit with surgical oncology 5 months postoperatively, she reported doing well overall, with good appetite, normal bowel movements and mild weight gain. She currently has no other manifestations of IgG₄-related disease. A CT scan of the abdomen and pelvis will be performed 1 year postoperatively for surveillance.

DISCUSSION

IgG₄-RD is a rare autoimmune, systemic sclerosing disease.^{14 15} The majority of literature regarding IgG₄-RD has originated from Japan, where prevalence is estimated to be 6 in 100 000 patients. IgG₄-RD should be suspected in patients presenting with unexplained inflammation or enlargement of one or more organs⁴; however, the diagnosis must be confirmed with histopathological and serum IgG₄ subclass analysis. Secondary to the rarity and heterogeneous nature of the disease, diagnostic and treatment guidelines have been difficult to determine. Investigators have recently discussed the creation of an international multicentre registry to gather a comprehensive dataset. In the meantime, current clinical and histopathological guidelines are based on patterns observed in a relatively small number of cases.^{3 4}

The patient presented in this case met some, but not all, currently accepted diagnostic criteria of IgG₄-RD. She demonstrated tissue IgG₄ elevation within the mass, characteristic histopathological findings of sclerosis, lymphocyte and plasma cell infiltration and high-serum IgG₄ levels. However, she did not have histological obliterative phlebitis or multiorgan involvement. In fact, the sole organ manifestation in her case was found in a pedunculated mesenteric mass of the small bowel. The patient underwent surgical resection to obtain tissue diagnosis. IgG₄-RD was not suspected prior to surgery. She never exhibited clinical signs or symptoms consistent with IgG₄-RD organ involvement commonly described such as pancreatitis.^{1 2} Therefore, she did not receive glucocorticoid treatment as the remainder of her abdominal organs appeared normal. Her response to immunosuppression therefore was not assessed.

Debate about the current diagnostic standards of IgG₄-RD continue. While multiorgan involvement is included as one of the four criteria, 42% of patients with IgG₄-RD present with an isolated lesion.⁷ In addition, the definition of elevated serum IgG₄ is also unclear. From ROC curves calculated by Yamamoto *et al*¹⁴, the optimal cut-off value of serum IgG₄ for diagnosing IgG₄-RD in patients with autoimmune pancreatitis was 144 mg/dL. Other authors have advocated that serum IgG₄ levels >135 mg/dL demonstrate a sensitivity of 97% and specificity of 79.6% in diagnosing IgG₄-RD. As the sensitivity and specificity of various IgG₄ serum levels remains controversial, histological criteria are crucial to solidify the diagnosis of IgG₄-RD.^{1 3} Cut-off values of tissue IgG₄-positive plasma cells per HPF may vary by organ because of different levels of fibrosis predominance. Deshpande *et al*³ suggest cut-off values of tissue IgG₄-positive plasma cells (per HPF) to confirm IgG₄-RD, ranging from >10 in liver biopsy specimens to >200 in skin tissue samples. While attempts to reach consensus have been recently made, there remains an ongoing discussion about the exact diagnostic criteria for IgG₄-RD. No studies have provided mesenteric-specific cut-off values, further adding to difficulty in obtaining a definitive IgG₄-RD diagnosis in this organ.

SM is also a rare but widely known sclerosing disease. The relationship of IgG₄-RD to SM has been a topic of intense

debate.^{5 10} The patient in our case had an incidentally found mass comprised of sclerosed mesentery and lymphocytic infiltrate on pathological examination, suggesting SM in the context of elevated IgG₄. However, SM characteristically involves a thickened, retracted mesentery with nodularity at the mesenteric root that encases and narrows the mesenteric vessels^{2 11 16} and has never been described as a peripheral, pedunculated mass. While the fat necrosis seen in SM could explain the calcification seen in this patient's tumour, no other common pathological SM findings such as fat cell degeneration, fatty necrosis or infiltration of lipophages were observed in her case.¹¹ Only 14 previously published cases are available to analyse the diagnosis of SM in the context of elevated IgG₄.¹⁵ While some authors have proposed the possibility of concurrent IgG₄-RD and SM,^{12 13} no cases of SM in this review were found to fulfil all four of the IgG₄-RD characteristic features. After examining the histopathological and clinical patterns in this limited cohort of patients, Avinsal *et al*⁵ concluded that while some cases of SM may mimic IgG₄-RD, IgG₄-RD rarely affects the mesentery. As conclusions from these small studies and expert opinions are highly variable, the question of whether IgG₄-RD can include the diagnosis of SM remains unknown.

Further confounding a definitive diagnosis of IgG₄-RD is the presence of serum IgG₄ elevation in other autoimmune disorders.^{9 16 17} Out of the 14 patients in the review by Yamamoto *et al*¹⁵, only one patient had a diagnosis of RA. The patient in our case had a previous history of RA, though was in remission for nearly 30 years and had a negative rheumatoid factor at the time of IgG₄-RD diagnosis. As her RA was dormant, this would not explain her elevated IgG₄ levels. In the context of multiple autoimmune processes, her remote history of a sudden cardiac event resulting in left anterior artery occlusion raises the question of a previous inflammatory event. However, she demonstrated no signs of aortitis and denied cardiac symptoms since stent placement 9 years prior, also decreasing the likelihood that this event represents an acute autoimmune inflammatory state.

After diagnosis of IgG₄-RD and organ involvement, current recommendations do not include routine surgical resection. However, a small subset of patients with IgG₄-RD will require surgical intervention secondary to intraperitoneal masses causing obstruction or abdominal pain.¹⁵ Surgical excision may be employed to rule out malignant aetiology, as in the case of our patient. While patients with IgG₄-RD have a relatively low prevalence of malignancy, ranging from 1.8% to 16% in the literature,^{7 18} there remains the question of whether IgG₄-RD may be a paraneoplastic process in some patients. In the largest study of IgG₄-RD performed to date, including 235 consecutive patients, 6% were diagnosed with cancer during follow-up, and 15% of patients had a diagnosis of malignancy prior to IgG₄-RD diagnosis. The involvement of a surgical oncologist is appropriate in cases of masses suspicious for autoimmune disease, but also with concern for malignancy. The provision of care at our cancer centre encouraged a comprehensive approach in conjunction with medical specialties, as well as close patient follow-up and disease surveillance.

In conclusion, IgG₄-RD and SM coexist on a spectrum of sclerosing disease. We present a patient case that could not be straightforwardly classified in either category. Patients presenting with multiorgan involvement and all four recommended diagnostic criteria of IgG₄-RD should be managed primarily by rheumatology or haematology/oncology specialists to decide on the appropriate course of immunosuppressive therapy. However, in a patient presenting with a resected

solitary mass positive for IgG₄-RD, mildly elevated IgG₄ and no other clinical manifestations of IgG₄-RD, a multidisciplinary approach including surgical oncology, medical oncology and rheumatology is appropriate. In addition, close clinical observation and advanced imaging surveillance comprises a viable option to manage asymptomatic and isolated disease.

Learning points

- ▶ IgG₄-related disease (IgG₄-RD) is a systemic sclerosing disease with characteristic findings of elevated serum and tissue IgG₄ levels, multiorgan involvement and effective response to glucocorticoids. Sclerosing mesenteritis (SM) also a rare sclerosing disorder typically involving the mesenteric root and encasing the mesenteric vessels.
- ▶ Consensus on whether SM is a manifestation of IgG₄-RD has not been reached.
- ▶ In a patient presenting with a surgically resected, solitary mass positive for IgG₄ and mildly elevated serum IgG₄, a multidisciplinary approach including surgical oncology, medical oncology and rheumatology may be appropriate.
- ▶ If no other clinical manifestations of IgG₄-RD are present, close observation and surveillance with advanced imaging should be considered.

Contributors Study conception/design: AR, AG, NY. Analysis and interpretation of data: AR, AG, NY, SP. Drafting of manuscript: AG, NY, AR. Critical revision: AR, AG, NY, SP.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Fernández-Codina A, Martínez-Valle F, Pinilla B, *et al.* IgG4-related disease: results from a multicentre Spanish registry. *Medicine* 2015;94:e1275.
- 2 Al Zahrani H, Kyoung Kim T, Khalili K, *et al.* IgG4-related disease in the abdomen: a great mimicker. *Semin Ultrasound CT MR* 2014;35:240–54.
- 3 Deshpande V, Zen Y, Chan JK, *et al.* Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012;25:1181–92.
- 4 Briton-Zerón P, Ramos-Casals M, Bosch X, *et al.* The clinical spectrum of IgG4-related disease. *Autoimmun Rev* 2014;12:1203–10.
- 5 Avincsal MO, Otani K, Kanzawa M, *et al.* Sclerosing mesenteritis: a real manifestation or histological mimic of IgG4-related disease? *Pathol Int* 2016;66:158–63.
- 6 Umehara H, Okazaki K, Kawano M, *et al.* How to diagnose IgG4-related disease. *Ann Rheum Dis* 2017. Epub ahead of print.
- 7 Inoue D, Yoshida K, Yoneda N, *et al.* IgG4-related disease: dataset of 235 consecutive patients. *Medicine* 2015;94:3680.
- 8 Dasari BV, McElvanna K, Loughrey M, *et al.* IgG4-related systemic sclerosing disease: a diagnosis to be considered!! *BMJ Case Rep* 2013;2013:bcr2012007101.
- 9 Vasaitis L. IgG4-related disease: a relatively new concept for clinicians. *Eur J Intern Med* 2016;27:1–9.
- 10 Abe A, Manabe T, Takizawa N, *et al.* IgG4-related sclerosing mesenteritis causing bowel obstruction: a case report. *Surg Case Rep* 2016;2:120.
- 11 Wat SY, Harish S, Winterbottom A, *et al.* The CT appearances of sclerosing mesenteritis and associated diseases. *Clin Radiol* 2006;61:652–8.
- 12 Minato H, Shimizu J, Arano Y, *et al.* IgG4-related sclerosing mesenteritis: a rare mesenteric disease of unknown etiology. *Pathol Int* 2012;62:281–6.
- 13 Nomura Y, Naito Y, Eriguchi N, *et al.* A case of IgG4-related sclerosing mesenteritis. *Pathol Res Pract* 2011;207:518–21.
- 14 Masaki Y, Kurose N, Yamamoto M, *et al.* Cutoff values of serum IgG4 and histopathological IgG4+ plasma cells for diagnosis of patients with IgG4-Related disease. *Int J Rheumatol* 2012;2012:1–5.
- 15 Yamamoto M, Tabeya T, Naishiro Y, *et al.* Value of serum IgG4 in the diagnosis of IgG4-related disease and in differentiation from rheumatic diseases and other diseases. *Mod Rheumatol* 2012;22:419–25.
- 16 Dufay C, Abdelli A, Le Pennec V, *et al.* Mesenteric tumors: diagnosis and treatment. *J Visc Surg* 2012;149:e239–e251.
- 17 Soliotis F, Mavragani CP, Plastiras SC, *et al.* IgG4-related disease: a rheumatologist's perspective. *Clin Exp Rheumatol* 2014;32:724–72.
- 18 Wang Y, Zhu J. Caution is needed in diagnosing IgG4-related disease: a possible paraneoplastic syndrome. *Arthritis Rheumatol* 2017;69:681–2.

Copyright 2017 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow