Surgical and Experimental Pathology

CASE REPORT Open Access

IgG4-related lymphadenopathy – a difficult diagnosis

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Abstract

Background: The IgG4-related disease (IgG4-RD) is a systemic immune-mediated non-neoplastic disease associated with IgG4 positive plasma cells and fibrosis that often presents as a mass lesion. Although the disease could affect virtually any anatomical site, there are strong predilections for certain organs. IgG4-related lymphadenopathy can exhibit a broad morphologic spectrum. We describe a patient with IgG4-related lymphadenopathy with overlapping histological features that proved to be a diagnostic red herring.

Case presentation: A 58-year-old gentleman with multiple co-morbidities presented with obstructive jaundice, elevated transaminases, and bilateral inguinal and left axillary lymphadenopathy. Imaging of the abdomen and pelvis showed circumferential soft tissue thickening resulting in luminal narrowing of common and proximal bile duct with upstream intrahepatic biliary radicle dilatation, multiple enlarged lymph nodes, and homogenous soft tissue lesions in the tail of the pancreas and bilateral renal cortical parenchyma with perinephric soft tissue extension. Left inguinal, and axillary lymph node excision biopsies were suggestive of IgG4-RD. Serum IgG4 levels performed subsequently, were markedly elevated. The patient was treated with prednisone which led to resolutions of his symptoms, reduction in the size of the lesions, and reversal of abnormal laboratory parameters.

Conclusion: The diagnosis of IgG4-RD in lymph node excision biopsy is a difficult call to make and needs a multidisciplinary team. An early diagnosis renders timely intervention and prevents the progression of the disease and its complications.

Keywords: IgG4-related disease, IgG4-related lymphadenopathy, Biopsy, Immunohistochemistry

Background

The IgG4-related disease (IgG4-RD) was first described as a systemic immune-mediated non-neoplastic disease associated with IgG4 positive plasma cells and fibrosis (Kamisawa et al. 2003; 2006). It often presents as a mass lesion and can be confused with malignancy (Bledsoe et al. 2018). Although the disease could affect virtually any anatomical site, there are strong predilections for certain organs. These include the major salivary gland, the orbit, lacrimal glands, the pancreaticobiliary system, lung, kidney, aorta, retroperitoneum, meninges, and thyroid gland (Mahajan et al. 2014). Generalized lymphadenopathy is reported in up to 80% of patients with IgG4-RD on imaging (Hamano et al. 2006). IgG4-related lymphadenopathy can exhibit a broad morphologic spectrum, with the various histologic patterns being designated types I (multicentric Castleman disease-like), II (follicular hyperplasia), III (interfollicular expansion), IV (progressive transformation of germinal centers), and V (inflammatory pseudotumor-like) (Cheuk and Chan 2012). We describe a patient with overlapping and rare histological features that proved to be a diagnostic red herring.

Case presentation

A 58-year-old gentleman, a known diabetic, hypertensive, and coronary artery disease patient presented with nausea, poor appetite, abdominal pain, and dark-colored urine for the past 1 month. There was no history of reflux disease or vomiting. On examination, the patient had jaundice

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and bilateral inguinal and left axillary lymphadenopathy. Liver function tests revealed conjugated hyperbilirubinemia (total bilirubin: 2.72 mg/dL, reference range: 0–1.0 mg/dL; direct bilirubin: 2.41 mg/dL, reference range: 0–0.2 mg/dL; indirect bilirubin: 0.31 mg/dL, reference range: 0–0.8 mg/dL), elevated alkaline phosphatase (503 U/L, reference range: 40–130 U/L), elevated aminotransferases (aspartate aminotransferase: 207 U/L, reference range: 0–40 U/L; alanine aminotransferase: 319 U/L, reference range: 0–41 U/L). Erythrocyte sedimentation rate (ESR) was increased (74 mm/hr., reference range: 5–25 mm/hr). Serum total protein, albumin, globulin, creatinine, electrolytes, CA19–9, and lactate dehydrogenase were within the reference range. His blood counts did not reveal any significant abnormality. Ultrasonographic examination of the abdomen and pelvis revealed dilated intrahepatic biliary radicles and bilateral renal cortical echos. Contrast-enhanced computed tomography (CECT) of the abdomen and pelvis showed circumferential soft tissue thickening causing luminal obliteration of common and proximal bile duct with upstream intrahepatic biliary radicle dilatation. There were multiple enlarged homogenous non-necrotic lymph nodes in the pericholecystic, common hepatic, left gastric, precaval, para-aortic, interaortocaval, bilateral common iliac, external and internal iliac, and inguinal regions. Also, homogenous soft tissue lesions were noted in the tail of the pancreas and bilateral renal cortical parenchyma with perinephric soft tissue extension. Positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with computed tomography (18F-FDG PET/CT) showed metabolically active lesions corresponding to the abdominopelvic CECT lesions, cervical, mediastinal, and bilateral axillary lymph nodes. With the working clinical diagnosis of lymphoma, left inguinal, and axillary lymph node excision biopsies were performed and subjected to TB Gene Xpert and histopathological examination. The TB Gene Xpert test was negative. Histopathological examination of both the lymph nodes had similar morphology. There was marked capsular thickening. The cortex showed hyperplastic lymphoid follicles with germinal center formation (Fig. 1). The mantle zone was relatively well preserved. Prominent wreath-like perifollicular granulomas were noted (Fig. 2). The CD2, CD3, CD4, CD8, CD20, and PAX5 immunostains highlighted the non-neoplastic nature of the disease process. The subcapsular sinus was obliterated by marked expansion of the paracortex, interfollicular and perifollicular area by cellular infiltrates dominated by plasma cells (Fig. 3) with admixed lymphocytes and few immunoblast-like cells. The plasma cell expansion was chiefly IgG4 dominant (> 100/HPF) and the CD138+/IgG4+ plasma cell ratio was found to be > 40% (Fig. 4a and b). Ziehl–Neelsen stain was negative for acid-fast bacilli and Periodic acid–Schiff stain was negative for fungal profiles. A final

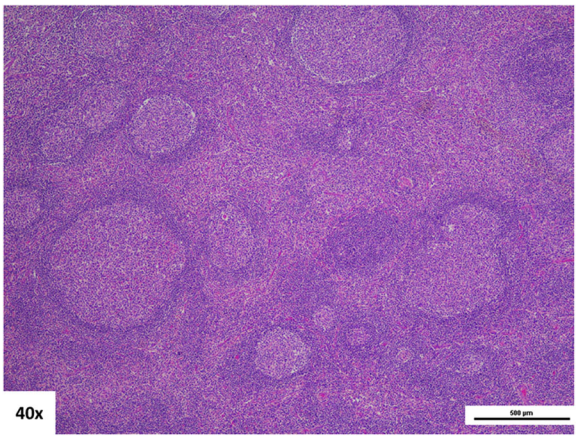

Fig. 1 (H&E stain): Follicular hyperplasia with germinal center formation

histopathological diagnosis of IgG4 related-disease was rendered and correlation with serum IgG4 levels was suggested. Serum IgG4 levels performed subsequently, were markedly elevated (22 g/L, reference range: 0.03 to 2 g/L). The patient was treated with prednisone 40 mg per day for 4 weeks and gradually tapered over 3 months. During the current visit (after 5 months), the patient was asymptomatic and the previously deranged laboratory parameters viz. direct bilirubin, aspartate and aminotransferases, alkaline phosphatase, and ESR were back to the normal range. A repeat 18F-FDG PET/CT revealed a significant resolution of the lesions.

Discussion

IgG4-related lymphadenopathy is a common but under-recognized manifestation of IgG4-RD (Cheuk and Chan 2012). It can be the initial manifestation of systemic IgG4-RD or can occur in the due course of the illness.

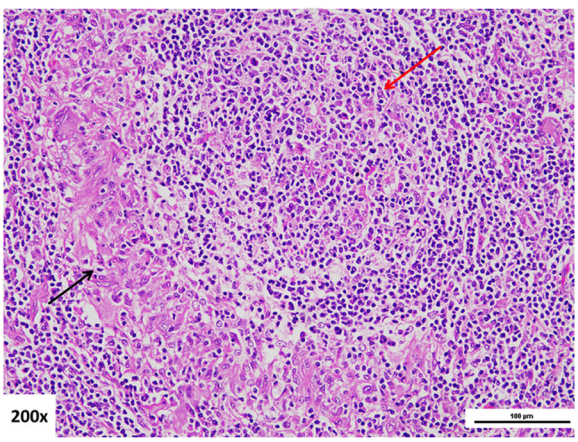

Fig. 2 (H&E stain): Wreath-like granuloma (black arrow) around the reactive follicles (red arrow)

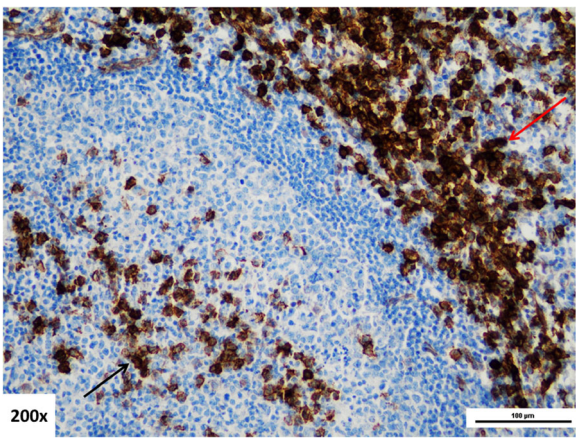

Fig. 3 (CD138 immunostain): Highlights intrafollicular (black arrow) and perifollicular plasma cells (red arrow)

Most often, multiple lymph node groups are commonly involved and unlike lymphomas, constitutional symptoms are generally absent (Wallace et al. 2020). Characteristic histopathological features of IgG4-RD have been established for extranodal sites. However, most of the studies with regards to IgG4-related lymphadenopathy have documented mainly nonspecific histopathological features (Rollins-Raval et al. 2012; Martinez et al. 2014). A recent study has focussed on this issue (Bledsoe et al. 2020). In this retrospective study of 46 lymph node excision specimens of 41 patients with an established diagnosis of IgG4-RD, features that are specific for IgG4-RD in lymph nodes were identified. These include an extrafollicular increase in IgG4+ plasma cells and IgG4+/IgG+ ratio, comprising of 2 major histopathologic patterns: (1) nodal fibrosis with increased IgG4 parameters specifically within the regions of fibrosis, and (2) marked interfollicular expansion associated with increased interfollicular IgG4+ plasma cells. The identification of eosinophils in regions with increased IgG4+ plasma cells was also confirmed to be a characteristic finding in lymph nodes of IgG4-RD, and both perifollicular or wreath-like granulomas and phlebitis were occasionally seen. Established morphologic patterns of IgG4-related lymphadenopathy include Castleman disease-like, follicular hyperplasia, interfollicular expansion, progressive transformation of germinal centers (PTGC), and inflammatory pseudotumor (IPT)-like patterns. Their study has shown that the IPT-like and interfollicular expansion patterns of IgG4-related lymphadenopathy are highly specific for IgG4-RD. An increase in IgG4+ plasma cells of > 100/HPF in 3 HPFs had a sensitivity and specificity of 62 and 73%, respectively for detecting IgG4-RD. When the threshold for IgG4+ plasma cells was decreased to 50/HPF, the sensitivity was increased (82%) but specificity was decreased (58%). A significant proportion (38%) of their patients did not have an increase in IgG4+ plasma cells. Our index case had follicular hyperplasia, interfollicular expansion by IgG4+ plasma cells, wreath-like perifollicular granulomas, IgG4+ plasma cells > 100/HPF and the CD138+/IgG4+ plasma cell ratio was > 40%. Our case had mixed features that could not be categorized in any of the five established morphological types of IgG4-related lymphadenopathy. The 2019 ACR/EULAR IgG4-RD criteria for the diagnosis of IgG4-RD has recently been published (Wallace et al. 2020). This is an integrated approach with scoring system that incorporates clinical, serological, radiological and pathological parameters to arrive at a confident diagnosis. A case meets the classification criteria for IgG4-RD if the entry criteria are met, no exclusion criteria are present, and the total points is ≥20. The IgG+ plasma cells can be identified using either IgG staining or CD138 staining. Assigned weight is 0 if the IgG4+:IgG+ ratio is 0–40% or indeterminate and the number of IgG4+ plasma cells/HPF is 0–9. Assigned weight is 7 if: (1) the IgG4+:IgG+ ratio is ≥41% and the number of IgG4+ plasma cells/HPF is 0–9 or indeterminate or (2) the IgG4+:IgG+ ratio is 0–40% or indeterminate and the number of IgG4+ plasma cells/HPF is ≥10 or indeterminate. Assigned weight is 14 if: (1) the IgG4+:IgG+ ratio is 41–70% and the number of IgG4+ plasma cells/HPF is ≥10 or (2) the IgG4+:IgG+ ratio is ≥71% and the number of IgG4+ plasma cells/HPF is 10–50. Assigned weight is 16 if the IgG4+:IgG+ ratio is ≥71% and the number of IgG4+ plasma cells/HPF is ≥51. Biopsies from lymph nodes, mucosal surfaces of the gastrointestinal tract and skin are not acceptable for use in weighting the immunostaining domain. Hence, the diagnosis of IgG4-related lymphadenopathy becomes more challenging when the 2019 ACR/EULAR IgG4-RD criteria is

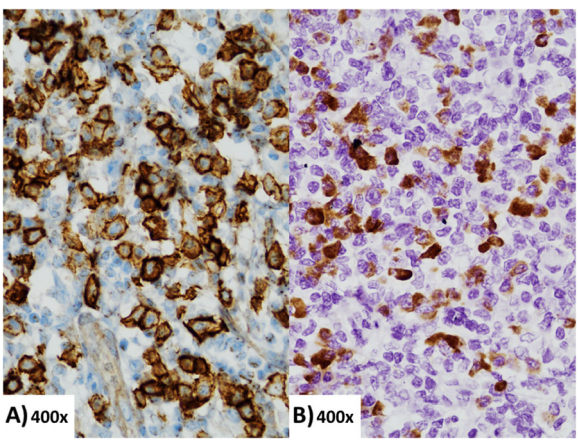

Fig. 4 **a** CD138 immunostain highlights the plasma cells and **b** IgG4 immunostain highlights the subset of CD138 plasma cells which are IgG4 positive. The overall there were > 100 IgG4 positive plasma cells/HPF and the ratio of CD138:IgG4 was > 40%

strictly applied. Another limitation of the 2019 ACR/EULAR IgG4-RD classification criteria is that there is no requirement of a biopsy or an elevated serum IgG4 level for the diagnosis of IgG4-RD. The diagnosis in our case was made by a high index of suspicious histopathological features, correlation with serum IgG4 levels, and clinico-radiological features.

Conclusion

The diagnosis of IgG4-RD in lymph node excision biopsy is difficult and cannot be solely based on morphology and immunohistochemistry. In an appropriate clinical setting and supportive investigations, the diagnosis can be made. An early diagnosis renders timely intervention and prevents the progression of the disease and its complications.

Abbreviations

IgG4-RD: IgG4-related disease; CECT: Contrast-enhanced computed tomography; PTGC: Progressive transformation of germinal centers; IPT: Inflammatory pseudotumor

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Author's contributions

GBL conceived the idea, was the sole contributor to the writing of the manuscript, and diagnosed the case. The author read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for. participation in the study.

Competing interests

The authors declare that they have no competing interests.

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