CASE REPORT – OPEN ACCESS

International Journal of Surgery Case Reports 50 (2018) 100–105

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

IgG4-related disease mimicking pancreatic cancer: Case report and review of the literature

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ARTICLE INFO

Article history:
Received 12 July 2018
Accepted 26 July 2018
Available online 31 July 2018

Keywords:
IgG4 related disease
Pancreas lesions
Autoimmune pancreatitis
Case report

ABSTRACT

INTRODUCTION: Most patients with pancreatic masses pose a diagnostic challenge when a benign lesion is suspected, and often, resection is needed before a benign diagnosis is confirmed.
PRESENTATION OF CASE: A 57 years old male patient presented with a pancreatic head mass, obstructive jaundice and submandibular lymph node enlargement. He also had a history of recurrent eye pain and redness, skin lesions, and benign prostatic hypertrophy. MRI showed a pancreatic head mass with double duct sign, aortic thickening, bilateral renal lesions, diffuse lymph node enlargement, and prostatic enlargement. FDG-PET/CT demonstrated abnormal uptake corresponding to the MRI lesions, and there were elevated IgG4 levels on blood investigations. Biopsy of an inguinal lymph node revealed infiltrates with IgG4 plasma cells, consistent with the diagnosis of IgG4 disease. The patient was treated with IV steroids and showed significant improvement.
DISCUSSION: IgG4 related disease is a rare entity that is characterized by lesions that show heavy infiltration with IgG4 positive plasma cells, storiform fibrosis, and obliterative phlebitis. The pancreas is the most commonly involved organ, but several other organ systems are involved, and this helps in clinical suspicion of the diagnosis. A biopsy from any easily accessible site that shows the characteristic histological features is sufficient for diagnosis. Patients respond quickly to steroids, but recurrence is frequent.
CONCLUSION: IgG4 related disease is a rare cause of pancreatic tumorous lesions that need a high index of suspicion for diagnosis and should be differentiated from pancreatic neoplastic lesions.

1. Introduction

Most patients with a pancreatic mass pose a diagnostic challenge when a benign lesion is suspected, and often, resection is needed before a benign pathology is confirmed. IgG4 Related Disease (IgG4-RD) is a rare cause of pancreatic mass lesions that should be kept in the differential diagnosis, as a pancreatic biopsy may be avoided if the disease is suspected and identified.

The patient in this case report was treated at our General Hospital, which is an academic medical center and part of a Medical Corporation. This manuscript has been reported following the SCARE guidelines [1].

2. Presentation of the case

We are presenting the case of a 57 years old male patient who was referred to us with a pancreatic head mass and obstructive jaundice. He is a known case of hyperuricemia, gouty arthritis, chronic renal impairment, Diabetes Mellitus, and hypertension.

His condition started about two years before this presentation with recurrent nasal obstruction and eye dryness and itching, with multiple visits to the emergency department. He was diagnosed as allergic rhinitis and conjunctivitis and was maintained on antihistamines and eye drops. Six months after onset, he devel-

Abbreviations: IgG4, immunoglobulin-G4 related disease; FNAC, fine needle aspiration cytology; IgG, immunoglobulin G; BPH, benign prostatic hyperplasia; AST, aspartate aminotransferase; ALT, alanine aminotransferase; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangio-pancreatography; GFR, glomerular filtration rate; AFP, alfa feto protein; CEA, carcinoembryonic antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; EUS, endoscopic ultrasound; FDG-PET, fluorodeoxyglucose positron emission tomography; AIP, autoimmune pancreatitis.

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https://doi.org/10.1016/j.ijscr.2018.07.030

oped bilateral submandibular swellings, more on the left side, and cervical ultrasound examination showed enlargement of multiple cervical lymph nodes with an appearance most likely representing proliferative lymphadenopathy. Fine needle aspiration cytology (FNAC) did not show any evidence of malignancy, and the diagnosis of reactive lymphadenopathy was confirmed. A few months later, the patient presented to the dermatology clinic with hyperpigmented skin lesions in the groin and hyperkeratotic lesions in both feet and received topical treatments with no improvement. He was kept on regular follow up and was seen by hematology to rule out the possibility of malignancy, and multiple investigations were done, including a serum immunoglobulin levels that showed a high IgG level of >2000, but no diagnosis was reached at that time. The patient again frequently presented to the emergency department with recurrent symptoms of eye pain and redness and was treated with antihistamines and antibiotics. He also developed obstructive urinary symptoms, and was diagnosed with benign prostatic hypertrophy (BPH) and was started on tamsulosin.

One month before his presentation, routine lab tests showed high AST and ALT levels, and he was referred to Gastroenterology. By the time he was seen he had developed jaundice, dark urine, and pale stools, with 8 Kg unintentional weight loss (over four weeks) and mild dilatation of the biliary system on ultrasound examination. MRI/MRCP (Fig. 1) revealed dilated biliary and pancreatic ducts (double duct sign) with a pancreatic head mass, multiple wedge-shaped lesions in both kidneys, significant aortic thickening suggestive of aortitis/Peri-aortitis, and cervical, mediastinal and intra-abdominal lymph node enlargement. His liver function tests were significantly abnormal (total bilirubin: 151, direct bilirubin: 113, ALP: 251, ALT: 30, AST: 50), and renal functions tests still showed renal impairment with a GFR of 51 ml/min, but the blood cell counts were normal. Serology for HBV and HCV were negative, and his AFP, CA 19-9, CA 15.3, and CEA were within normal. Total IgG was elevated at 2560, with elevation in all the subclasses as follows: IgG1: 1420, IgG2: 831, IgG3: 265, IgG4: 1980 (mg/dl). C3 and C4 were within normal, and his urine analysis showed no proteinuria. Endoscopic ultrasound (EUS) showed enlarged mediastinal lymph nodes and a bulky pancreatic head suggestive of pancreatic malignancy or autoimmune pancreatitis, and EUS guided FNAC samples taken from both sites showed only a few atypical cells, with no evidence of malignancy or metastatic carcinoma. An FDG PET/CT scan (Fig. 2) showed intense circumferential uptake in the abdominal aorta corresponding to the MRI findings, and suggestive of aortitis. Hypermetabolic enlarged lymph nodes were seen above and below the diaphragm as well as an irregular small pulmonary infiltrate, and the lacrimal and major salivary glands were also hypermetabolic. The pancreatic head mass and the renal cortical lesions seen on MRI showed intense FDG uptake as well, and the overall picture was suggestive of lymphoma.

The patient was discussed in the hepatobiliary multidisciplinary meeting with the principal differential diagnoses reached being lymphoma or Immunoglobulin-4 related disease (IgG4-RD), and lymph node biopsy was recommended. He underwent inguinal lymph node biopsy. Histopathological examination of the lymph node, which measured 1.8 cm in maximum dimension, showed many lymphoid follicles with prominent germinal centers consistent with reactive follicular hyperplasia. In addition, there was a marked expansion of paracortical areas with a dense plasma cell infiltrate. Areas of fibrosis including fibrotic thickened blood vessels were noted. The inflammatory infiltrates extended into para-nodal tissue. Immunohistochemistry studies confirmed a reactive nature of the lymphoid follicles (CD10+, BCL6+, and BCL2-). The plasma cells-infiltrate was CD138+, most of which were IgG positive cells and more than 30 IgG4 positive cells were seen per high power field. Kappa and Lambda immunohistochemical stains showed no light chain restriction. The overall morphology and Immunohistochemistry were consistent with IgG4-related disease (Fig. 3).

These findings confirmed the diagnosis of IgG4-RD with multiple manifestations including a pancreatic lesion, aortitis and peri-aortitis, bilateral renal lesions, diffuse lymph node involvement, lacrimal and salivary gland lesions, and cutaneous manifestations, with a possible pulmonary lesion. The patient was started on intravenous pulsed steroids (Methylprednisolone 500 mg daily) for three days, followed by oral prednisolone 40 mg daily and he showed a rapid clinical response. The bilirubin level dropped to 54 mmol/l at four weeks. Eight months after the onset of treatment, the patient was asymptomatic, with complete resolution of the lymphadenopathy, jaundice, skin lesions, allergic and conjunctival manifestations, and the obstructive urinary symptoms.

3. Discussion

IgG4 related disease is a recently described entity, first designated in 2003, that includes variable organ manifestations, many of which used to have different groupings and nomenclatures [2]. The diagnosis relies on the characteristic pathological features that are identical in all of the involved organs and include: heavy plasmacytic infiltrates with IgG4 producing plasma cells, storiform fibrosis, and obliterative phlebitis [3]. The possible mechanisms for etiology and pathogenesis include autoimmunity (whether being an autoimmune disorder itself or a down-regulatory mechanism for another autoimmune entity), and allergy, but this is still not fully understood [3,4].

The disease affects many organs and organ systems in the body, and this leads to variable presentations that may seem nonspecific or unrelated, contributing to the long delay before diagnosis, as seen in this patient who was diagnosed after two years of follow up and investigations. However, the most common manifestations are autoimmune pancreatitis, salivary gland disease, orbital/lacrimal gland disease, and retroperitoneal fibrosis [5,6]

This patient presented at the age of 57 years, which is consistent with the epidemiology of the IGG4-RD as it mainly affects middle-aged and elderly males, except in limited cervicofacial disease, where men and women are affected equally [7]. At presentation, multiple organ involvement is present in 60–90% of the cases, and most of the patients have lymphadenopathy, most frequently involving the cervical, mediastinal, and retroperitoneal lymph nodes. However, some patients may present initially with lymphadenopathy only, as seen in this patient, making the diagnosis difficult, even with a biopsy. Weight loss is common and progressive during the long workup stage despite the patient being generally well with no systemic manifestations, as evident in this patient. Allergic symptoms were also noted in this patient and as have been described in many patients with IGG4-RD [7,8].

Autoimmune pancreatitis is the typical and most common manifestation. It can present with diffuse enlargement of the gland or as in our case, with a pancreatic mass, making differentiation from pancreatic cancer difficult [9]. Closely associated is IgG4 related sclerosing cholangitis, which should be distinguished from primary sclerosing cholangitis and cancer. The diagnosis is challenging but is mainly based on identifying the characteristic histological features in other organs due to the difficulty in obtaining adequate biopsies from the bile ducts [10].

Salivary and lacrimal gland involvement is also common in IgG4-RD. It may present with dryness, enlargement, and tumors, and is one of the causes of proptosis and orbital pseudotumor [11]. Lacrimal gland involvement most likely explains the recurrent eye symptoms in our patient, especially that the PET scan showed

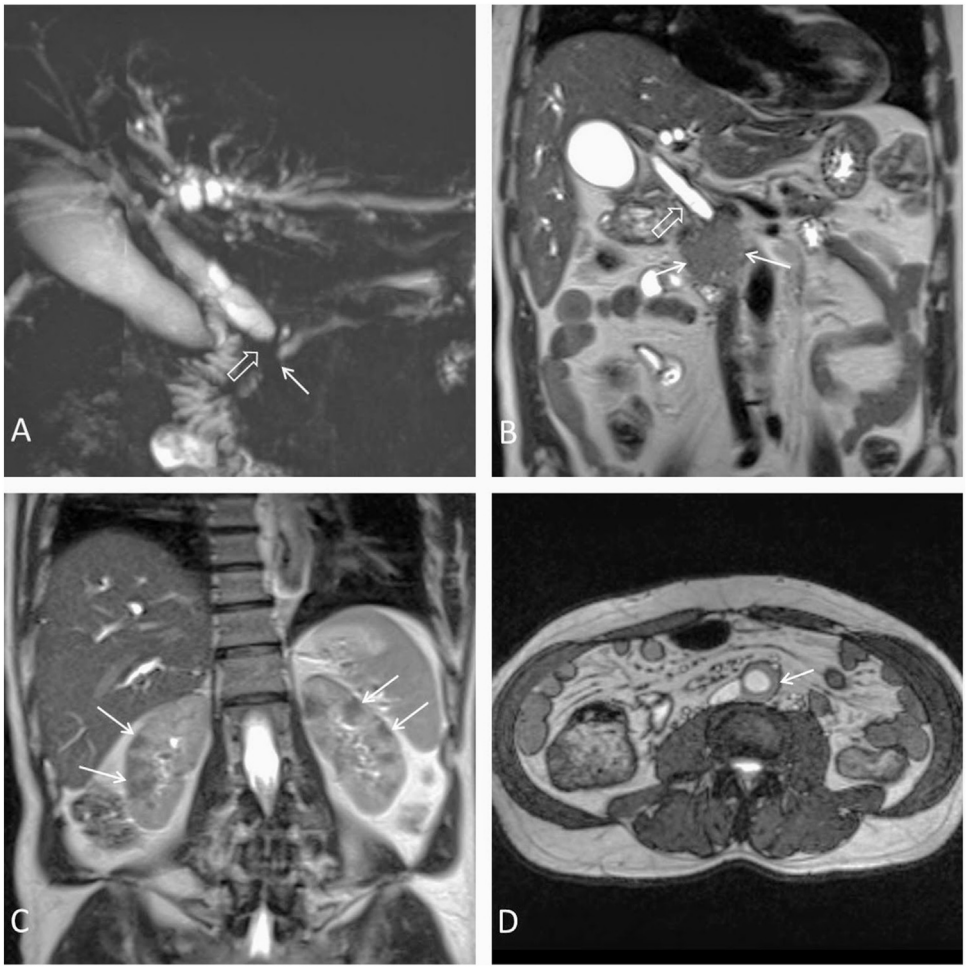

Fig. 1. MR imaging of the abdomen in IgG4-related disease.
A) Magnetic resonance cholangiopancreatography (MRCP) shows interruption of the dilated pancreatic duct (arrow) and the common bile duct (hollow arrow) at the pancreatic head (double duct sign).
B) Coronal T2-weighted MR image shows a pancreatic head lesion (arrow) obstructing the common bile duct (hollow arrow).
C) Coronal T2-weighted MR image shows multiple bilateral renal lesions.
D) Transverse steady-state free precession MR image shows thickening of the wall of the abdominal aorta (arrow).

lacrimal gland uptake, although pure allergic conjunctivitis and rhinitis could also be the cause as they are common in IgG4-RD. Our patient's images showed impressive aortitis and peri-aortitis seen as a thickening in the MRI and increased uptake in the FDG-PET scans, and this is one of the features of the disease, where the infrarenal aorta is most frequently involved. Aortitis and peri-aortitis can lead to dissection or aneurysms as a complication, and this is more likely with pre-existing aneurysms [12]. The disease may also affect other parts of the retroperitoneum resulting in fibrosis.

This patient had renal involvement evident as wedge-shaped lesions on the MRI and focal cortical uptakes on PET-CT, and this is consistent with the diagnosis. Renal involvement in IgG4-RD includes tubulointerstitial nephritis, glomerulonephritis, and membranous nephropathy [13]. Ureteric involvement in retroperitoneal fibrosis can also result in obstruction and hydroureter and hydronephrosis. Skin manifestations have also been described, and this includes macules, papules, plaques, and bullae, and these cutaneous manifestations can sometimes be mistaken for lymphoma. The skin lesions in this patient (bilateral foot macules and desquamation) could be part of the disease process, supported by the resolution of the lesion on steroid treatment, but this needs to be confirmed by skin biopsy. Other organs that can be involved include the pericardium, the breasts, and the central nervous system [7]. Of note is that prostatitis has also been described as part of the disease, and whether the prostatic enlargement and increased FDG uptake in this patient is part of IGG4-RD remains to be proved, but the improvement of symptoms upon steroid treatment is in support of this.

The diagnosis of IGG4-RD relies on clinical evaluation, laboratory tests, and imaging, but the gold standard remains biopsy and histopathology. Diagnostic criteria that classify the diagnosis based on these findings into definite, possible and probable have been described by Umehara and colleagues [14]. Thorough clinical history and examination are very important given the broad patterns of organ involvement, and clinical findings are sufficient if the biopsy is positive in one site. Biopsies are best obtained from the affected organs by core needle from the obvious lesions, and fine needle aspiration cytology is not useful for the diagnosis [15]. The characteristic histological features include: dense lymphoplasmacytic infiltrates with high levels of IgG4 producing plasma cells, storiform fibrosis, obliterative phlebitis, and eosinophilic infiltrates. Recent diagnostic guidelines suggest that more than 30–50 IgG4 staining cells per high power field (HPF) are needed for diagnosis [16,17]. Plasma IgG4 levels are usually elevated (>135 mg/dl), but they are not diagnostic alone as they may be raised in other

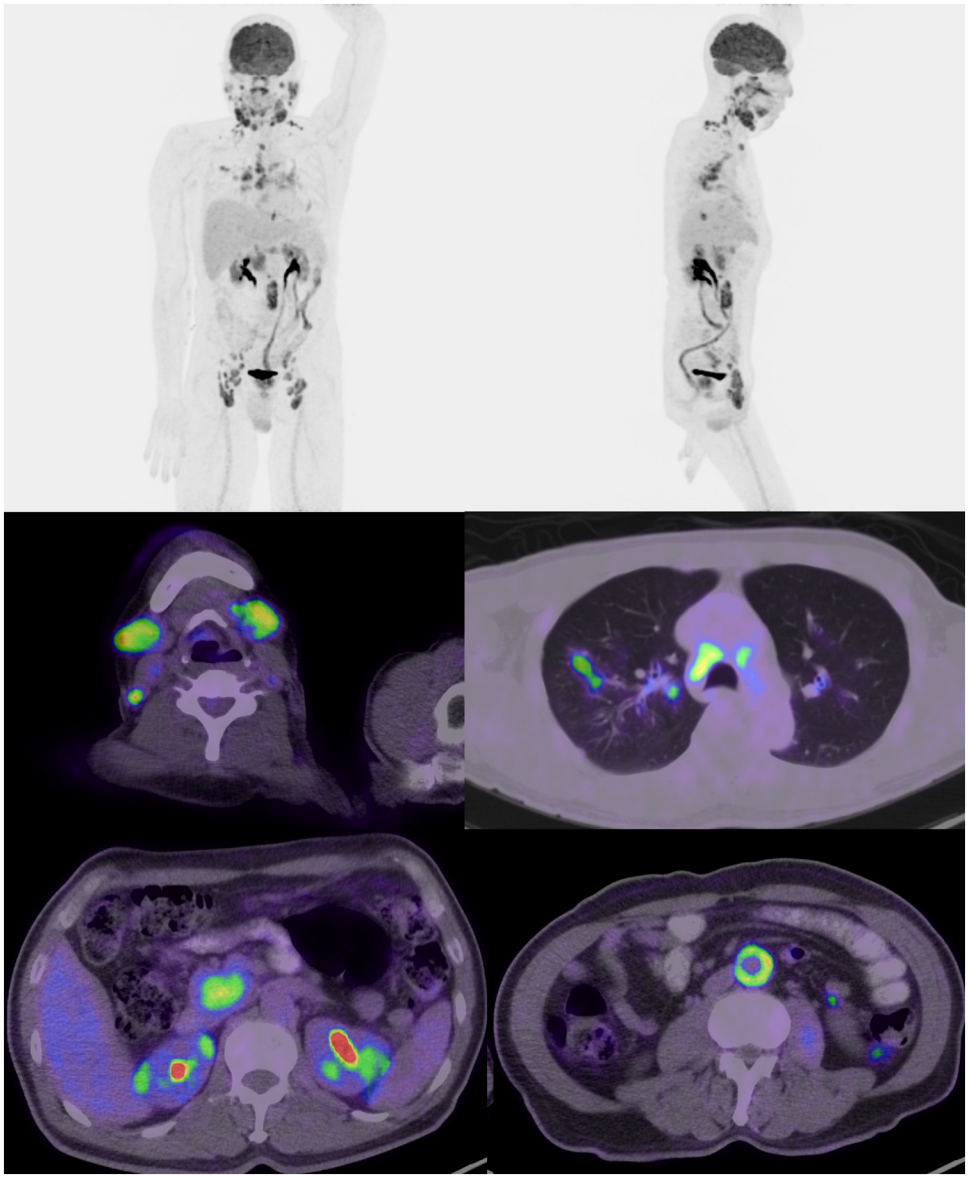

Fig. 2. FDG PET/CT: FDG PET/CT maximum intensity projection (upper row) and fused trans-axial images (lower row) showing multiple lymph nodal involvement, lacrimal/salivary gland uptake, a right pulmonary focus, a hypermetabolic pancreatic head lesion, renal cortical lesions, and intense circumferential uptake in the abdominal aorta.

conditions. IgG4 levels also do not correlate with the activity of the disease. Blood plasmablast levels are characteristically elevated, and they correlate well with the activity of the disease; however the tests are not widely available. Recently, Hubers and Beuers demonstrated that measuring the serum IgG/IgG4 RNA ratio with PCR can accurately distinguish IgG4-RD from primary sclerosing cholangitis and pancreatic and biliary malignancy [18]. After establishing the diagnosis, patients require imaging studies such as CT scans and FDG-PET of the neck, chest, abdomen, and pelvis, to determine the extent of the disease. Renal involvement is assessed by urine analysis for proteinuria and serum C3 and C4 levels (which are characteristically low in Tubulointerstitial Nephritis) [13].

Most of the current guidelines for the management of IGG4-RD are derived from observational trials with few RCTs addressing the issue [8]. The standard treatment is steroids (Prednisolone 40 mg/day), and a good response within 2–4 weeks is characteristic of the disease and may help to establish the diagnosis [8,19,20,15]. Non-response to steroids is unusual, and the diagnosis of IgG4-RD should be questioned in these cases. Induction steroid therapy is started on all symptomatic patients and in some asymptomatic patients, depending on the pattern of disease involvement (mild lymphadenopathy does not need treatment), and some patients may require maintenance steroid therapy. Relapse is treated either with further steroid courses or with steroid-sparing agents including azathioprine and mycophenolate mofetil. Rituximab, a B cell-depleting agent, also results in good response [21].

4. Conclusion

IGG4-RD is one of the causes of a pancreatic mass that should be kept in the differential diagnosis, especially in the setting of multiple organ involvement. Blood investigations help in detecting the disease, but the gold-standard for diagnosis is formal histopathology from any of the accessible lesions. The pancreatic lesion should not be biopsied if the diagnosis can be confirmed by biopsy from a more accessible peripheral site, and rapid response to steroids is characteristic.

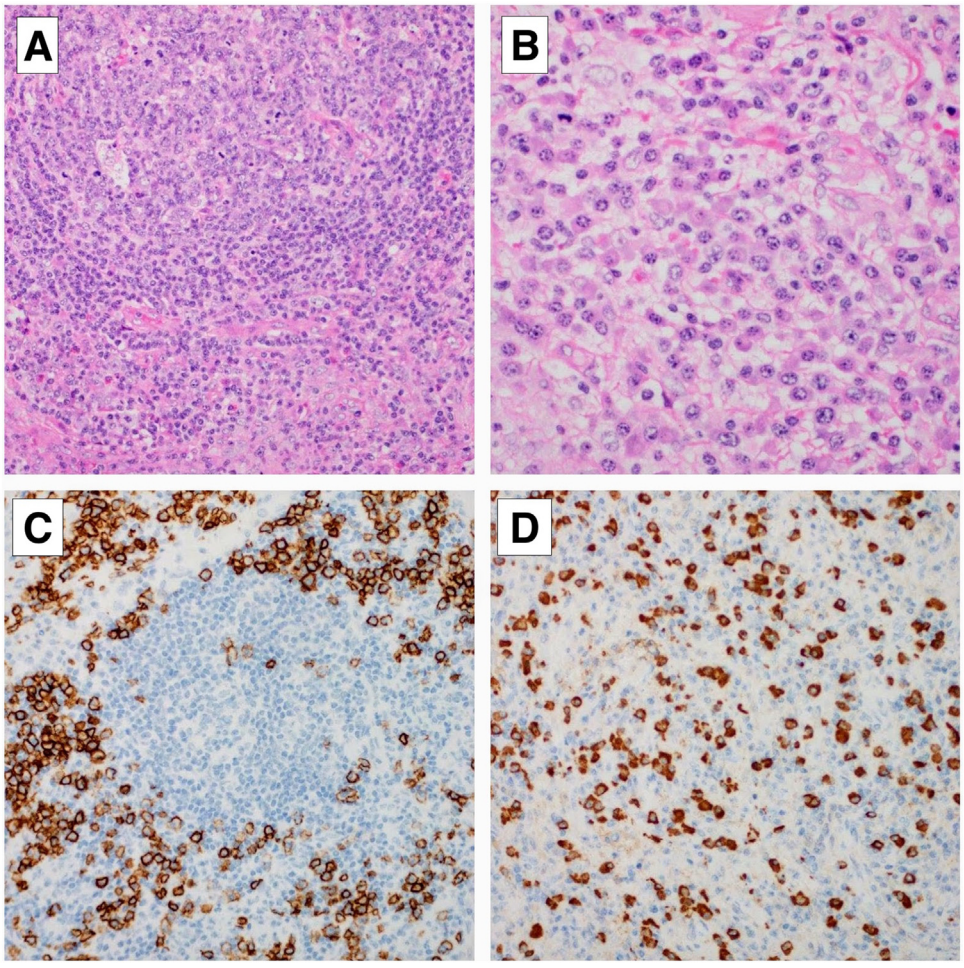

Fig. 3. Histopathology.
A) Low power examination of the lymph node showed a lymphoid follicle with a reactive germinal center and part of an expanded paracortical area with dense infiltrate.
B) High power examination showed a marked plasma cells infiltrate.
C) Immunohistochemical stain for CD138 highlighted many plasma cells, some of which are seen inside the germinal center.
D) IgG4 Immunohistochemical stain revealed more than 30 cells seen per high power field.

Conflict of interest

No conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

The case report was approved by the Medical Research Centre of Hamad Medical Corporation (ABHATH) on March 20, 2018.
Protocol ID **MRC-04-18-077**.

Consent

A written informed consent was obtained from the patient and is ready for review.

Author contribution

Ibnouf Sulieman: Main author. Contributed to the wiring of the case report, discussion and literature review, obtaining the required consents and ethical approvals, and the writing up of the manuscript.

Ahmed Mahfouz: Senior radiologist: Had major input in the diagnosis and interpretation of the images; provided the images for publication with the comments; reviewed and edited the manuscript.

Einas AlKuwari: Pathologist: Established the pathological diagnosis; Provided the histopathology slide images; reviewed and edited the manuscript.

Lajos Szabados: Nuclear medicine: Diagnosis and interpretation of the PET scan images; Provided the images for the PET scan for publication with the comments; reviewed and edited the manuscript.

Walid Elmoghazi: Surgeon: Reviewed and edited the manuscript.

Ahmed Elaffandi: Surgeon: Reviewed and edited the manuscript.

Hatem Khalaf: Surgeon: Main clinical care of the patient; Concept of the case report; Guidance and overall responsibility of the study; review and final approval of the manuscript.

Registration of research studies

HMC Medical Research Center Protocol ID MRC-04-18-077.

Guarantor

Dr. Hatem Khalaf.
Dr. Ibnouf Sulieman.

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