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CASE REPORT

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IgG4-related disease: Case report and 6-year follow-up of an elusive diagnosis mimicking malignancy

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Key Clinical Message

IgG4-related disease is a rare and emerging pathology, characterized by the appearance of pseudotumors. Due to the ability to mimic other pathologies, it is essential to consider it as a differential diagnosis in multisystemic processes. The diagnosis is challenging, requiring a multidisciplinary approach, to minimize the associated morbidity and mortality.

Abstract

IgG4-related disease (IgG4-RD) is a rare, emerging, systemic and chronic pathology, characterized by the appearance of pseudotumors resulting from tissue infiltration by IgG4-positive plasma cells that promote eosinophilic inflammation of the tissue with subsequent fibrosis. We present the case of a male, 45-year-old patient, with marked weight loss and skin pallor detected by his family doctor during a child health consultation of his daughter. When questioned, the patient referred complaints of postprandial discomfort in the left hypochondrium with a feeling of fullness, weight loss, chronic fatigue and hyperhidrosis that had lasted for a month. On physical examination, he was pale, and had pain at palpation of the left hypochondrium. Laboratory data showed increased inflammation markers, abdominal ultrasound and CT demonstrated numerous enlarged lymph nodes in the upper quadrants, raising concern for a malignant lymphoproliferative process. Serological, imaging, clinical and laparoscopic excisional biopsy revealed features of IgG4-related disease and excluded malignant lymphoproliferative disease. The immediate response to treatment with oral prednisolone 30 mg/day also contributed for diagnosis confirmation. Due to refractory disease after gradual prednisolone reduction, second-line therapy with rituximab was initiated. Over the 6 years of follow-up, the patient presented multiple exacerbations characterized by the emergence of systemic symptoms, being maintained under close clinical and imaging follow-up by reumathology, infectious diseases, and family medicine specialists.

KEYWORDS
chronic, IgG4-related disease, immune-mediated, pseudotumor, systemic

1 | INTRODUCTION

IgG4-related disease (IgG4-RD) is a rare, chronic and progressive clinical entity characterized by tissue infiltration through IgG4+ plasma cells that lead to eosinophilic inflammation and consequent storiform fibrosis, with the appearance of pseudotumor lesions.[1,2] It is an immune-mediated and multisystemic inflammatory disease that can affect virtually any organ or tissue.[2,3] A Japanese study estimated an incidence of 0.28–1.08 per 100,000 population, affecting mostly males over 50 years of age with a male/female ratio of 3:1.[3]

The disease may mimic other prevalent pathologies due to the subacute development of a mass or organomegaly, leading to possible delayed diagnosis and unnecessary medical or surgical treatment.[4,5] Although almost any organ can be affected, common sites include the pancreato-biliary system, kidneys, retroperitoneum/aorta, thorax, and salivary/lacrimal glands.[4] IgG4-RD also involves lymphadenopathy in approximately 80% of patients, occasionally as the first manifestation disease, most commonly affecting the mediastinal and intraabdominal lymph nodes.[6]

The knowledge regarding IgG4-RD pathogenesis is still limited, but some authors suggest that adaptive immune cells, including different types of T and B cells, and cytokines secreted by these cells play a vital role in the pathogenesis of this pathology. Antigen-presenting cells are stimulated by pathogens contributing to the activation of naive T cells and differentiation of different T cell subtypes, including helper T cells (Th1 and Th2), regulatory T cells, and T follicular helper cells. B cells are activated and transformed to plasma cells by T cell secreted cytokines. Moreover, macrophages, and some important factors, such as TGF-β promote target organ fibrosis.[1]

IgG4-RD diagnosis was officially confirmed in 2010[7] and the first consensus guideline on the approach and treatment of this entity was published in 2015.[8] Diagnosis is based on clinical, serological, radiological, and histological findings.[2,6–8] Timely diagnosis and treatment are essential to slow disease progression, preserve organ function, and prevent irreversible damage caused by chronic inflammation and fibrosis. Therefore, it is recommended to initiate treatment early for any symptomatic and active IgG4-RD patient.[2] Due to the elevated response rates around 97%–100% and a significant decrease of serum IgG4 levels, treatment with glucocorticoids is the preferred first-line medication for active IgG4-RD. Consequently, response to glucocorticoids has become part of the diagnostic criteria.[9] Corticosteroid therapy (CCT) is quickly effective, but disease outbreaks are common after gradual dose reduction.[2] Second-line therapy consists of conventional immunosuppressants such as azathioprine, mycophenolate mofetil and cyclosporine or CD20 depletion with rituximab.[2,10]

The ability of IgG4-RD to mimic infective, inflammatory and neoplastic processes compels the medical community to consider IgG4-RD as a differential diagnosis in multisystemic processes, especially in patients with atypical presentations.

2 | CASE HISTORY & EXAMINATION

We present the case of a male patient, 45 years old, caucasian, surf instructor, with no relevant medical, surgical or family history, no chronic medication or drug allergies. He has maintained a vegetarian diet for several years and referred sporadic smoking and an alcohol consumption of 20 g/day. In March 2017, he went to his health family unit with his daughter for her child health appointment. During this consultation, his family doctor noticed that he revealed marked weight loss and skin pallor in comparison to his normal physical features. When questioned, he reported complaints of postprandial discomfort on the left hypochondrium with a feeling of fullness, weight loss, chronic fatigue and hyperhidrosis during the last month. On physical examination, he revealed cutaneous paleness and pain on palpation of the left hypochondrium, with no other relevant alterations. Analysis showed increased inflammation markers and iron deficiency anemia (Table 1). Abdominal ultrasound, and subsequent computed tomography (CT) showed numerous enlarged lymph nodes in the upper quadrants, raising concerns about a malignant lymphoproliferative process, so referral to a hematology consultation was made.

3 | DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS & TREATMENT

Bone marrow biopsy was performed, revealing mild reactive plasmacytosis, without evidence of a lymphoproliferative process. However, endoscopic ultrasound (Figure 1A,B), CT scan (Figure 1C), and FDG PET-CT

TABLE 1 Analytical results obtained after first Primary Care Unit consultation (A) and during follow-up in Second Care Unit (B).

Parameter	A (2017)	B (2018–2023)
Hemoglobin (g/dL) [13–18]	11.7 [↓]	15.2[a]
Hematocrit (%) [40–52]	38.1 [↓]	45.4[a]
Mean corpuscular volume—MCV (fL) [80–100]	75.1 [↓]	87.6[a]
Mean corpuscular hemoglobin—MCH (pg) [26–34]	23.1 [↓]	29.3[a]
Mean corpuscular hemoglobin concentration—MCHC (g/dL) [32–36]	30,7 [↓]	33.5[a]
Reticulocytes ($\times 10^6$/μL) [0.8–2.5]	0.037 [↓]	-
Leukocytes ($\times 10^3$/μL) [3.8–10.6]	7.68	7.37[a]
Neutrophils ($\times 10^3$/μL) [1.3–8.8]	4.85	5.56[a]
Lymphocytes($\times 10^3$/μL) [1.0–4.8]	2.14	1.08[a]
Platelets ($\times 10^3$/μL) [150–440]	366	256[a]
Peripheral blood smear	Mild anisocytosis, microcytosis and anisochromia; erythrocyte stacking	-
INR	1.32	-
Urea (mg/dL) [13–43]	35	24[a]
Creatinin (mg/dL) [0.67–1.17]	0.91	0.82[a]
AST (U/L) [4–33]	16	16[a]
ALT (U/L) [4–50]	24	14[a]
Iron (μg/dL) [59–158]	17 [↓]	-
Ferritin (ng/mL) [30–400]	209,7	-
Lactate dehydrogenase (U/L) [135–225]	129 [↓]	-
Erythrocyte sedimentation rate (mm/h) [0–15]	120 [↑]	16[a]
C-Reactive protein (mg/L) [0–0.5]	7.90 [↑]	0.64[a]
IgG (mg/dL) [680–1450.0]	1830 [↑]	603[a]
IgG4 (mg/dL) [3.0–201.0]	649.5 [↑]	7.5[a]
Complement (mg/dL)		
C3 [75–135]	-	190.0 [↑]
C4 [9–36]	-	34.8
Auto-antibodies		
Anti-CCP, ANA, ANCA, Anti-dsDNA, rheumatoid factor, Anti-cardiolipin, Anti-β2 Glicoprotein, Anti-Sm, Anti-RNP, Anti SS-A (Ro), Anti SS-B (La)	-	Negative
Summary urine analysis	-	Erythrocyturia of 4.6/μL and urobilinogen of 2.0 mg/dL
Serology		
HIV 1+ 2	Negative	Negative
VDRL	Negative	Negative
HAV	IgG+; IGM−	IgG+; IGM−
HBV	Ag Hbs−; Ac HBc−; Ac HBs+	Ag Hbs−; Ac HBc−; Ac HBs+
HCV	Negative	Negative
Rubella virus	IgG+; IGM−	IgG+; IGM−
Toxoplasmosis	IgG+; IGM−	IgG+; IGM−
Cytomegalovirus	-	IgG−; IGM−
Epstein–Barr Virus	-	IgM VCA−; IgG EA/VCA+; IgG EBNA+

(Continues)

TABLE 1 (Continued)

Parameter	A (2017)	B (2018–2023)
Herpes varicella zoster	-	IgG+; IGM−
Herpes simplex 1	-	IgG+; IGM−
Herpes simplex 2	-	IgG+; IGM−
Latent TB screening	-	Mantoux 0 mm; IGRA indetermined

Note: Normal ranges are presented between square brackets, when applicable: [↓]—decreased value in comparison to the normal range; [↑]—increased value in comparison to the normal range.

[a]Analytical study performed on September of 2023.

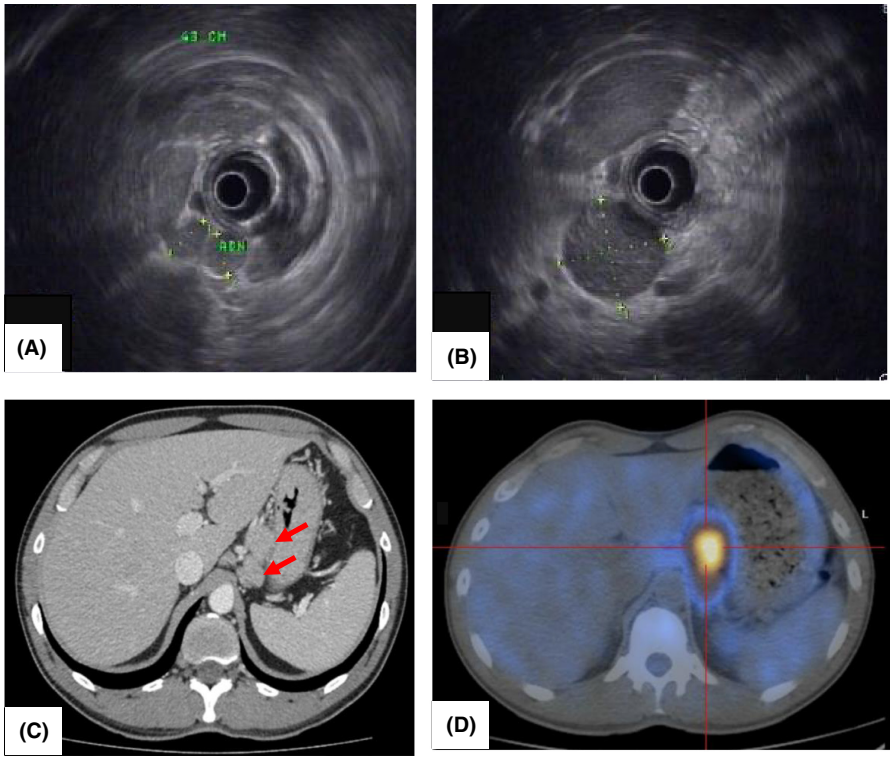

FIGURE 1 Perigastric adenopathic conglomerate in the region of the lesser gastric curvature and the celiac trunk shown in endoscopic ultra-sound (A, B) and contrast-enhanced CT (C), with high metabolic activity on PET/CT (D), performed in 2017.

(Figure 1D) demonstrated a perigastric adenopathic conglomerate in the region of the lesser gastric curvature and the celiac trunk, raising the possibility of malignancy. First laparoscopic excisional biopsy of the lymph nodes was inconclusive, so a second one was performed. The pathological study revealed lymph nodes with reactive changes, without evidence of a neoplastic process (lymphoproliferative or other). Histological examination showed lymph node parenchyma with reactive follicular hyperplasia, intact sinuses and abundant mature plasma cells in interfollicular areas. The immunohistochemical study confirmed the preservation of lymph node architecture, with B and T cell populations in their respective territories, and identified plasma cells expressing both lambda and kappa immunoglobulin light chains. Regarding the heavy chains, it was observed predominance of plasma cells with IgG expression and numerous plasma cells IgG4 positive (Figure 2). Though not specific, these features raise the hypothesis of IgG4-related lymphadenopathy, consistent with type II pattern. These findings combined with increased serum IgG and IgG4 (Table 1) supported the possible diagnosis of IgG4-RD.

The patient was subsequently referred to a rheumatology consultation, for treatment and follow-up. In May 2018, he initiated treatment with oral corticosteroid (CCT), starting with prednisolone 40 mg, with subsequent reduction to 30 mg and then 25 mg, over a 3-month period. Immediate improvement in symptoms was noticed, but aggravation was reported after reducing CCT dose. The analytical study revealed an increase in inflammatory parameters which continued to grow. Due to refractory disease, two cycles of rituximab were given, with symptoms resolution. One year later, the patient had a new crisis that motivated the administration of rituximab every 30 weeks.

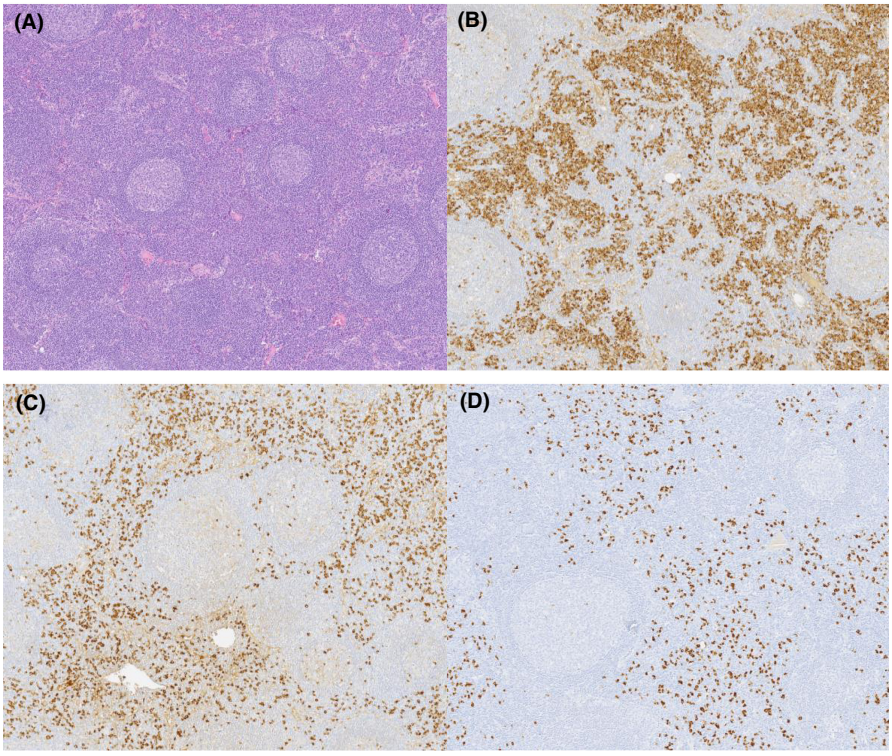

FIGURE 2 The excisional lymph node biopsy shows reactive follicular hyperplasia with preserved sinuses and abundant plasma cells in interfollicular areas (A) (HE, original magnification ×60). Polytypic/policlonal plasma cells expressing both kappa (B) and lambda (C) light chains (kappa and lambda immunostaining, original magnification ×70). Numerous IgG4+ plasma cells in the interfollicular zone (D) (IgG4 immunostaining, original magnification ×70).

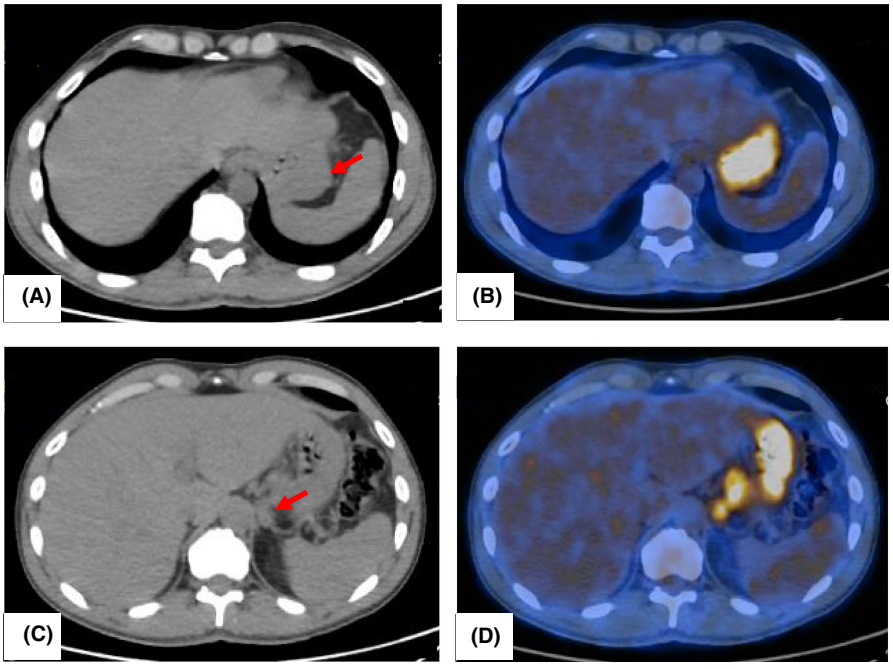

FIGURE 3 Intense contrast uptake diffusely involving the gastric body and fundus (A), and hypermetabolic adenopathies in the hepato-gastric ligament (C), shown in contrast-enhanced CT, with high metabolic activity on PET/CT (B, D), performed in 2022.

4 | OUTCOME & FOLLOW-UP

CT scan and FDG PET-CT performed in October 2022 revealed intense contrast uptake diffusely involving the gastric body and fundus and hypermetabolic adenopathies in the hepato-gastric ligament (Figure 3). The gastric findings raised the hypothesis of gastritis or neoplastic disease, so an urgent upper digestive endoscopy with biopsy was performed, revealing a chronic pangastritis with activity, atrophy and intestinal metaplasia, associated with *Helicobacter pylori*, enabling to exclude the possibility of gastric malignancy. *H. pylori* eradication was subsequently performed with success.

Over the 6 years of follow-up, the patient had six aggravation periods, with fever, anorexia, weight losses of 7–12 kg in 1 week, hyperhidrosis, dorsal pain, arthralgias, extreme prostration, and fatigue. The administration of rituximab every 30 weeks plus a maintenance

treatment with daily oral prednisolone 5 mg, improved the systemic complaints, and no adverse reactions were reported.

During the follow-up, the patient underwent for annual screening of latent tuberculosis and viral serologies (Table 1). He also was vaccinated with Pneumovax 23, but refused vaccines against flu and COVID-19.

In September 2023, upon reassessment by his family doctor, the patient denied constitutional symptoms, or any other complaints. Physical examination did not reveal palpable adenopathies or abdominal changes, and cardiopulmonary auscultation was unremarkable.

He is currently medicated with rituximab every 6 months and prednisolone 5 mg/day, maintaining close clinical and imaging follow-up by reumathology, infectious diseases and family medicine specialists.

5 | DISCUSSION

The clinical picture reported here was characterized by sudden appearance of systemic and nonspecific symptoms, associated to perigastric adenopathies in the lesser gastric curvature and the celiac trunk that then evolved to the hepato-gastric ligament. The most common sites of abdominal involvement include the pancreas and bile ducts, although involvement of the liver, gallbladder, and gastrointestinal tract has been described.[4] This case reflects an IgG4-related lymphadenopathy, characterized by elevated serum levels of IgG4 and IgG. The impaired gastric emptying function reflected by the feeling of fullness reported by the patient, may be attributed to tumor-like adenopathies leading to compression of adjacent organs, strictures, and, eventually, organ dysfunction,[9] affecting in this case, the stomach. A multicentric study, the European Guideline and a recent systematic review and meta-analysis regarding the risk of malignancy, reported a higher risk of overall cancer, especially pancreatic and gastric cancer and also lymphoma in patients with IgG4-RD.[9,11,12]

Multiple laboratory abnormalities can be found in IgG4-RD, typically related to the specific organ involved.[2,10] In this case, the analytical study revealed an iron deficiency anemia probably due to the impaired iron intake associated with chronic inflammation, as the patient had maintained a vegetarian diet for several years and blood tests showed a small cell hypochromic anemia with decreased reticulocytes without decreased ferritin, with elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The anemia was improved by iron supplementation, and after starting treatment with prednisolone and rituximab. During the follow up, hematuria was often detected, without renal disfunction, allowing to discard kidney involvement, as this scenario presents mostly with elevated serum creatinine, with 50% showing mild proteinuria and/or hematuria.[4]

IgG4 serum level alone lacks sensitivity and specificity, but in IgG4-RD lymphadenopathy, elevated serum and tissue levels of IgG4 are important diagnostic criteria, and therefore should be measured.[6] In former studies, serum IgG4 >135 mg/dL demonstrated a sensitivity of 97.0% and a specificity of 79.6% in diagnosing IgG4-RD, and serum IgG4/IgG ratios >8% had a sensitivity and specificity of 95.5% and 87.5%, respectively.[13] According to the European guidelines, diagnostic criteria involve an elevation of serum IgG4 above 1.5 times the upper limit of normal.[9] In our patient, this parameter was of 649.5 mg/dL, approximately threefold the upper normal limit (3.0–201 mg/dL) and fivefold higher than the cuttoff value of 135 mg/dL. Additionally, an elevated IgG level of 1830 mg/dL was found in our patient (Table 1), originating an IgG4/IgG ratio of 35.5%, which supported the IgG4-RD diagnosis.

Although serum IgG4 levels are not an accurate tool for monitoring the course of the disease, since they do not correlate sufficiently with the development of complications or disease recurrence, research has indicated a positive correlation between elevated serum IgG4 levels and the number of affected organs and disease severity.[2,8,12] Patients with infiltration of more than one organ and/or aggressive conditions show elevation of acute phase markers, such as ESR and CRP, which constitute the main markers of disease activity or relapse.[14] Our patient presented high values of these inflammatory parameters at the presentation of the first symptoms, and also at exacerbations, with subsequent reduction after institution of treatment.

The most accurate assessment of IgG4-RD is based on a full clinical history, physical examination, selected laboratory investigations and appropriate radiologic studies, but diagnostic confirmation by biopsy is strongly recommended for the exclusion of malignancies and other IgG4-RD mimics. International consensus guidelines outline the histopathologic and immunohistochemistry features that support the diagnosis of IgG4-RD and, in proper clinical context, can establish diagnosis.[8] Furthermore, IgG4 plasma cells and histological staining along with an IgG4+/IgG plasma ratio >40% both increase specificity of IgG4-RD diagnosis,[10] being therefore, an important diagnostic criterion.[5,6,9] However, previous studies have shown that IgG4-RD lymphadenopathies are histologically distinct from the effects of IgG4-RD on other organs, presenting five subtypes based on the histological

diversity: (I) multicentric Castleman's disease-like, (II) reactive follicular hyperplasia-like, (III) interfollicular expansion and immunoblastosis, (IV) progressively transformed germinal center (PTGC-type), and (V) inflammatory pseudotumor like IgG4-related lymphadenopathy.[6] Storiform fibrosis and obliterative phlebitis are usually absent, and an IgG4+/IgG plasma ratio >40% is only present in Type IV.[6] Moreover, according to the 2019 classification criteria for IgG4-RD, the immunostaining domain of biopsies from lymph nodes, mucosal surfaces of the gastrointestinal tract, and skin are not acceptable as a diagnosis criterion.[5] In the presented case, biopsy was crucial to exclude neoplastic disease, and the histological and immunocytochemistry were suggestive of IgG4-associated lymphadenopathy (Type II pattern), characterized by reactive follicular hyperplasia-like on histology, with interfollicular distribution of IgG4+ plasma cells and localized lymphadenopathy.[6]

Imaging evaluation by CT scan and FDG PET-CT performed at the disease onset, with annual surveillance revealed adenopathic progression from lesser gastric curvature and celiac trunk to the hepato-gastric ligament, 5 years after diagnosis. Though the advancements in IgG4-RD understanding, its pathogenesis remains incompletely clarified.[2] However, its chronicity, radiologic progression, high recurrence rates, and multiorgan fibroinflammatory involvement is well documented in previous literature.[3–5] Furthermore, despite the effectiveness of glucocorticoids, about one-third of patients experience disease relapse, which may occur in the same organ being treated or in formerly uninvolved organ systems.[10] Previous studies have suggested that elevated Th1 levels, changes of regulatory $CD4^+CD25^+$ T cells that primarily secrete the anti-inflammatory factor IL-10 and the fibrogenic factor TGF-ß and/or IgG4 production promoted by regulatory T-cell-mediated immune response might participate in the progression of IgG4-RD.[1] Considering the increased risk of cancer in patients diagnosed with IgG4-RD,[9,11,12] this progression raised the concern of a neoplastic transformation, prompting an urgent upper digestive endoscopy with biopsy, which was crucial to enable the exclusion of a gastric malignancy. The PET-CT gastric findings may be explained by the chronic inflammation due to the chronic pangastritis with activity found in the gastric biopsy. These outcomes urge the need to maintain the patient under close imaging monitoring, to enable early detection of neoplastic processes and/or chronic inflammation and fibrosis of other organs, and also adjust treatment to delay or prevent irreversible organ dysfunction.

The immediate response to treatment with oral CCT therapy with symptoms improvement was also a major contribution for diagnosis confirmation. The international consensus advocates an initial treatment regimen with oral prednisone 30–40 mg/day for 2–4 weeks, with subsequent reduction by 5 mg every 1–2 weeks, aiming to reach a daily dose of 5 mg over a period of 3–6 months, and further suspension.[8] Although initial remission rates are high after short-term immunization shocks with glucocorticosteroids, outbreaks, and relapses are common,[2,12,15] requiring other treatment possibilities, as demonstrated in this case. Rituximab, an anti-CD20 monoclonal antibody stands out as the earliest and most extensively researched B-cell targeted therapy, demonstrating unequivocal efficacy, especially as a long-term maintenance therapy for younger patients handling with the challenging aspects of the disease.[2] Over the 6 years of follow-up, our patient presented multiple exacerbations characterized by the emergence of systemic symptoms, requiring the administration of new cycles of rituximab, with good response and without adverse reactions.

6 | CONCLUSION

The description of this clinical case aims to highlight a rare diagnosis that presents a common symptomatic picture with a wide spectrum of clinical manifestations, recurrently nonspecific at presentation. The diagnosis was challenging, involving the clinical features, integrated with the serological, imaging, histological, and immunocytochemical findings, as well as the response to therapy, which met the multiple criteria defined by previous guidelines, allowing to confirm the diagnosis of IgG4-RD. We unraveled an autoimmune process which frequently associates with significant morbidity and mortality, demanding timely diagnosis and treatment. Malignancy must be excluded, while inflammatory manifestations and increased risk of lymphoproliferative disorder require periodic and long-term surveillance. Treatment is imperative to suppress inflammation, delay fibrotic progression, and prevent related complications by maintaining the disease in a latent state. Therefore, it is essential to raise awareness among the medical community about this differential diagnosis, as well as the importance of a multidisciplinary approach between Primary and Secondary Health Care for its diagnosis, guidance and follow-up.

This case also highlights the relevance of the doctor-patient relationship, emphasizing the benefit of a holistic

approach, facilitated by the recognition of patients in their usual state by their assistant physician. In the present scenario, the patient went to the health unit, just as an escort of his daughter for her child health consultation. The weight loss and skin pallor caught the attention of his family doctor, due to the marked contrast in relation to his typical appearance, triggering the initial study that led to the diagnosis. This recognition enabled treatment to be anticipated, thus minimizing the disease morbidity with consequent improvement of patient's life quality.

AUTHOR CONTRIBUTIONS

Sara Melo Oliveira: Conceptualization; data curation; writing – original draft. **Isabel Gomes:** Supervision; writing – review and editing. **Inês Trigo:** Conceptualization; data curation; writing – review and editing. **Elsa Fonseca:** Data curation; writing – review and editing. **Rita Neto Lopes:** Data curation; writing – review and editing. **Ana Sofia Oliveira:** Data curation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

All procedures performed in this case were in accordance with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

PATIENT PERSPECTIVE

The patient was anxious and worried about his health condition, mainly due to the possibility of a neoplastic disease. However, he felt calmer as soon as he was informed about the diagnosis and experienced symptomatic improvement after starting treatment. During the follow-up, he remained cooperative and assiduous in regular consultations.

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