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IgG4-Related Disease (IgG4-RD) Autoimmune Pancreatitis (AIP) as an Initial Presentation of Systemic Lupus Erythematosus (SLE)

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ABSTRACT

Acute pancreatitis stemming from IgG4-Related Disease (IgG4-RD) seldom coincides with Systemic Lupus Erythematosus (SLE), highlighting the importance of investigating autoimmune conditions in patients with IgG4-RD. We present the case of a 57-year-old male with a medical history notable for hypertension, photosensitivity, arthritis, and malar rash, who presented with 6 weeks of persistent epigastric pain. Computed Tomography (CT) of the abdomen revealed hallmark features such as fat stranding around the pancreatic tail and gallbladder wall thickening, confirming the diagnosis of acute pancreatitis and cholecystitis. Post-cholecystectomy, histopathological examination of the gallbladder displayed IgG4-positive staining in multiple vessels, accompanied by perivascular inflammation and fibrinoid necrosis infiltrated by lymphocytes and neutrophils, confirming the diagnosis of IgG4-RD. Subsequent evaluation prompted by systemic manifestations revealed an ANA titer of 1:5120 and a dsDNA titer of 1:80, leading to the diagnosis of SLE. The patient later developed mononeuropathy, which improved upon initiation of immunosuppressive therapy. This case underscores the intricate interplay between IgG4-RD and SLE, an association documented to a limited extent in literature, thereby emphasizing the imperative of considering alternative autoimmune diseases with manifestations akin to IgG4-RD.

1 | Introduction

Immunoglobulin G4-related disease (IgG4-RD) represents an intriguing facet of immune-mediated disorders characterized by fibroinflammatory processes that can affect multiple organs. This condition manifests as chronic systemic inflammation, characterized by elevated serum IgG4 levels, infiltration of IgG4-positive plasma cells, dense lymphoplasmacytic infiltrates, and subsequent fibrosis within affected organs. Initially recognized primarily in autoimmune pancreatitis (AIP), its systemic nature became apparent in 2003, when extrapancreatic manifestations were observed alongside pancreatic involvement [1, 2].

Since then, a spectrum of conditions has been linked to IgG4-RD, including Kuttner tumor, Reidel thyroiditis, retroperitoneal fibrosis, sclerosing aortitis, inflammatory abdominal aortitis, orbital pseudotumor, and various inflammatory pseudotumors affecting diverse anatomical sites such as the kidney, brain, lung, breast, and lymph nodes [3, 4]. Despite its wide-ranging impact, IgG4-RD has rarely been associated with systemic lupus

Summary

- This case highlights IgG4-RD autoimmune pancreatitis as an initial presentation and association with SLE, emphasizing a potentially underrecognized link.
- The rarity of mononeuritis in both conditions and the need for elucidative diagnostics and comprehensive treatment strategies highlight the importance of heightened clinical awareness and proactive management to optimize patient care.

erythematosus (SLE), with fewer than 10 reported cases of this co-occurrence documented in the medical literature [5–11].

In this case report, we present a case of IgG4-RD, specifically AIP, shedding light on the complex interplay between IgG4-RD and autoimmune phenomena like SLE.

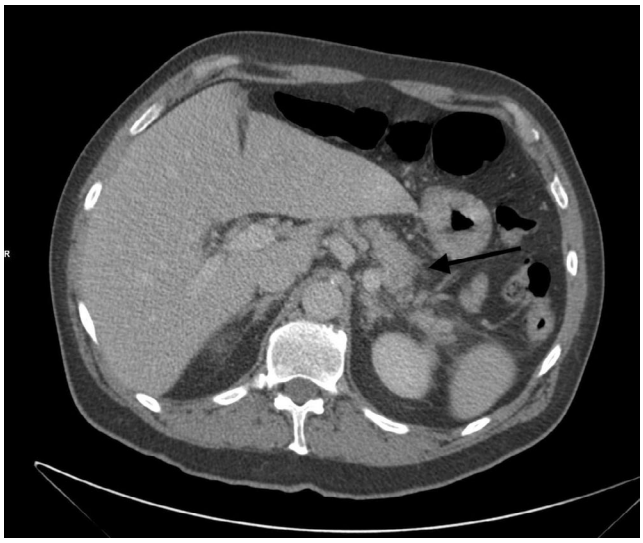

FIGURE 1 | CT of the abdomen with intravenous contrast shows increased peripancreatic fat stranding and fluid (arrow) concerning acute interstitial edematous pancreatitis.

2 | Case History/Examination

A 57-year-old male with a past medical history of hypertension sought medical attention due to persistent epigastric abdominal discomfort spanning 6 weeks. The pain was described as an achy sensation exacerbated by food intake, accompanied by intermittent bouts of nausea, vomiting, and loss of appetite, and weight loss ranging between 18 and 22 kg. Additionally, he reported experiencing chills and night sweats without fever, diarrhea, or constipation. Furthermore, he detailed a concurrent 6-week history of persistent numbness in his right foot, accompanied by pain but no discernible weakness.

Upon further inquiry, the patient disclosed a history of photosensitivity and recurrent joint pain and swelling affecting his wrists and ankles before the onset of abdominal pain. Physical examination revealed a faint malar rash, subtle tenderness in his wrists, and tenderness in the right upper quadrant of the abdomen. Ultrasound examination of the right upper quadrant exhibited signs indicative of gallbladder wall edema and thickening, raising concerns for calculous cholecystitis. Subsequent imaging via CT scan of the abdomen and pelvis with intravenous contrast demonstrated increased peripancreatic fat stranding and fluid accumulation, suggestive of acute interstitial edematous pancreatitis (Figure 1). A nerve conduction study (NCS) showed sensory and motor peripheral neuropathy with mixed axonal and demyelinating features. Magnetic resonance imaging of the arteries of the abdomen was unremarkable.

3 | Differential Diagnosis, Investigation, and Treatment

Subsequently, he was referred to our institution for comprehensive diagnostic evaluation. A detailed array of laboratory investigations was conducted, yielding the following results as in Table 1.

Cholecystectomy was performed, and subsequent examination of the excised gallbladder unveiled a distinctive histopathological profile. Noteworthy observations included multiple vessels exhibiting perivascular inflammation, fibrinoid necrosis, storiform patterns, and infiltration by lymphocytes and neutrophils. Hematoxylin and eosin at 10x magnification revealed fibrinoid necrosis with perivascular inflammation and lymphocytic infiltration (Figure 2).

Further immunohistochemical analysis, specifically IgG and IgG4 staining, provided crucial insights. These stains highlighted the augmented presence of perivascular plasma cells (Figure 3A,B).

Quantitative assessment through immunohistochemical (IHC) staining revealed 140 IgG-positive plasma cells per high-power field (HPF) and 80 IgG4-positive plasma cells per HPF, with the IgG4: IgG ratio of 57% and ≥ 51 IgG4+ cells/high power field. These findings strongly indicated evidence of IgG4-RD, consolidating the diagnostic impression [12].

The patient fulfilled the 2019 ACR/EULAR IgG4-RD criteria with histopathological and immunostaining criteria. As IgG4-RD AIP emerged as the favored diagnosis, a comprehensive approach was undertaken, given the potential involvement of other autoimmune pathways. Recognizing this, a rheumatologic panel was ordered to explore broader autoimmune implications. Results from these investigations revealed a significant elevation in antinuclear antibody (ANA) levels at 1:5120 (reference range < 1:80) and anti-double-stranded DNA (dsDNA) levels at 1:80 (reference range < 1:10), prompting further investigation.

Per the 2019 SLICC classification criteria, the constellation of findings led to the definitive diagnosis of SLE [13]. Specifically, the patient fulfilled the entry criterion with an ANA titer of ≥ 1:80 and accrued more than 10 points, meeting the clinical criterion of acute cutaneous lupus (6 points) and the laboratory criterion of dsDNA 1:80 (6 points). This marked the onset of a diagnostic journey encompassing an overlap between IgG4-RD and SLE.

TABLE 1 | Laboratory data.

Parameters	Value	Normal range
White blood cell count (K/μL)	7.2	4.5–11.0
Red blood cell count (M/μL)	4.2	4.5–6.0
Hemoglobin (g/dL)	12.8	13.5–18.0
Platelet count (K/μL)	277	140–440
Glucose (mg/dL)	92	70–99
Creatinine (mg/dL)	0.70	0.7–1.30
Total protein (g/dL)	6.7	6.4–8.2
Total bilirubin (mg/dL)	0.6	0.2–1.0
Alkaline phosphatase (U/L)	58	45–117
AST (U/L)	15	15–37
ALT (U/L)	20	16–61
Sed Rate (mm/h)	48	0–20
CRP (mg/dL)	9.4	0.0–0.3
Creatine kinase (U/L)	37	35–232
Lipase (U/L)	281	73–393
Magnesium (mg/dL)	2.0	1.8–2.4
TSH (uIU/mL)	1.01	0.36–3.74
ANA	1:5120 homogenous	<1:40
Anti-dsDNA	1:80	<1:10
C3 (mg/dL)	127.7	90.0–180.0
C4 (mg/dL)	28.2	12.9–39.2
Immunoglobulin G (mg/dL)	1251	650–1600
IgG subclass 4 (mg/dL)	96	(2–121)
B2glycoprotein (IGG/M/A)	<9	<20
Anticardiolipin ab IgG (U/mL)	1.4	0.0–15.0
Anticardiolipin IgM (U/mL)	9.8	0.0–15.0
Lupus anticoagulant	Not detected	
HIV	Not detected	
Hepatitis B surface antigen	Not detected	
Hepatitis C antibody	Not detected	

Treatment initiation was tailored to address the dual pathology, with a regimen comprising 1 mg/kg of oral prednisone at 60 mg daily, hydroxychloroquine at 400 mg daily, and mycophenolate at 500 mg twice daily. The selection of mycophenolate as the steroid-sparing agent was based on evidence from a randomized controlled trial, underscoring the importance of evidence-based therapeutic decisions in managing complex autoimmune disorders [14].

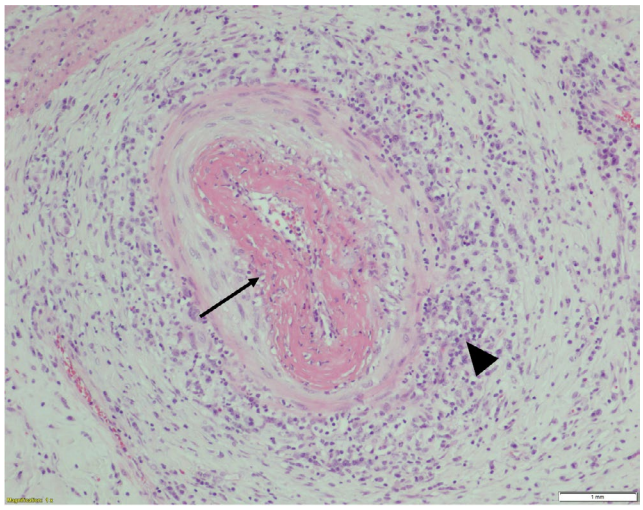

FIGURE 2 | Hematoxylin and eosin stain (10× magnification) demonstrates fibrinoid necrosis with perivascular inflammation (arrow) and infiltration by lymphocytes (arrowhead).

He showed remarkable improvement, evidenced by the resolution of his abdominal pain, rash, arthritis, and numbness. Subsequently, he was effectively maintained on a regimen comprising hydroxychloroquine at 400 mg daily, mycophenolate at 3 g daily, and low-dose prednisone (<5 mg), resulting in sustained symptom relief.

However, a setback occurred with the emergence of a severe sinus infection after 2 months, necessitating the temporary discontinuation of mycophenolate. During this period, he developed right-sided foot drop and peroneal mononeuropathy, an uncommon manifestation within the realm of SLE. NCS revealed moderate generalized length-dependent axonal sensorimotor neuropathy and severe right tibial and peroneal neuropathies with actual denervation changes. Nevertheless, these neurological complications improved with high-dose prednisone, gradually tapered down to 5–10 mg over several months, alongside the reinstatement of mycophenolate.

Over the ensuing months, a marked improvement was observed in his foot drop, indicative of the efficacy of the therapeutic interventions. Notably, his journey was punctuated by a positive dsDNA, persisting until 2022, alongside a gradual decline in ANA titer over the years, with the most recent measurement registering at 1:320. This dynamic clinical course underscores the complexities of managing overlapping autoimmune disorders and highlights the importance of vigilant monitoring.

4 | Discussion

The literature review was conducted using the keywords "systemic lupus erythematosus," "IgG4-related disease," "autoimmune pancreatitis," "mononeuropathy," and "lupus," with English as the primary search language. The search was performed using PubMed and Google Scholar and included all relevant published articles to date. Both IgG4-RD and SLE represent significant autoimmune challenges capable of

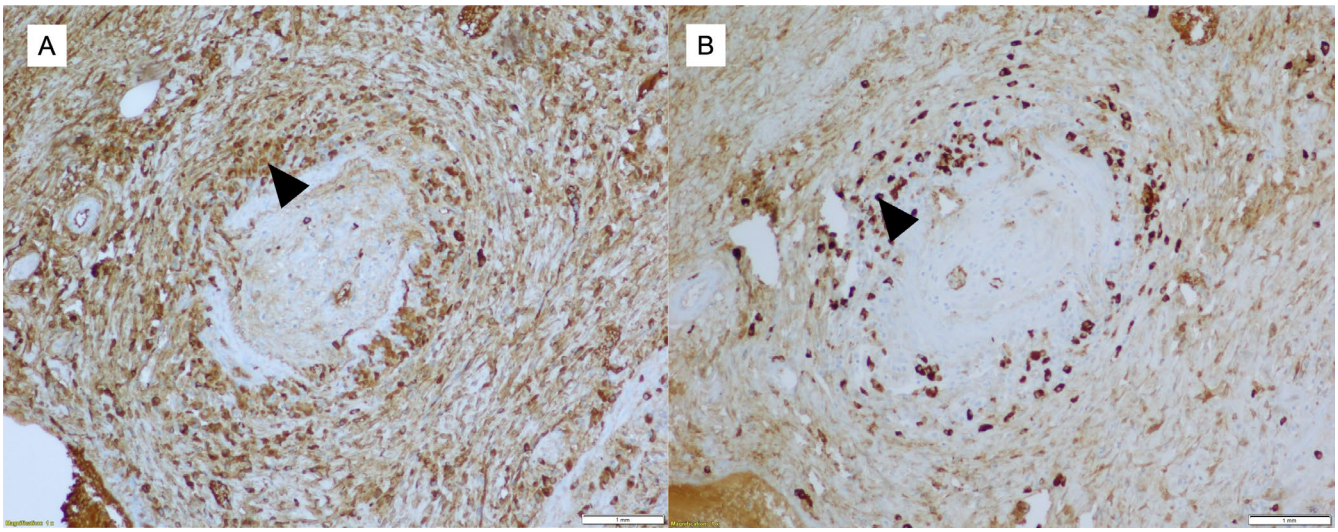

FIGURE 3 | IgG immunohistochemical stains (A) and IgG4 immunohistochemical stains (B) highlight the increased perivascular plasma cells.

TABLE 2 | Overlapping cases of SLE and IgG4-RD.

Case	Reference	SLE manifestations	IgG4-RD manifestations	Therapy
1	Arai et al. 2018 [10]	Arthritis serositis	Interstitial nephritis parotid swelling	Steroids
2	Naramala et al. 2019 [11]	Arthritis hair loss pleurisy	Cervical lymphadenopathy	Steroids, hydroxychloroquine
3	Yamamoto et al. 2019 [9]	Skin rash fever lupus nephritis	Renal disease	Steroids, belimumab
4	Fujita et al. 2022 [8]	Membranous nephropathy interstitial nephritis hair loss peripheral neuropathy retinopathy	Interstitial nephritis glomerulonephritis interstitial pneumonia	Steroids, hydroxychloroquine belimumab
5	Kobayashi et al. 2007 [18]	Lupus nephritis	Autoimmune pancreatitis	Steroids
6	Zaarour et al. 2015 [18]	Lupus nephritis	Renal disease	Steroids, mycophenolate
7	Takanashi et al. 2020 [18]	CNS lupus	Lymphadenopathy, sclerosing cholangitis	Steroids, cyclophosphamide
8	Present case	Malar rash, arthritis, mononeuropathy	Autoimmune pancreatitis	Steroids, mycophenolate

causing widespread organ damage. While SLE is characterized by inflammatory cell infiltration in organs, IgG4-RD typically presents with fibrosis and organ enlargement. Notably, approximately one-third of patients with IgG4-RD exhibit normal serum IgG4 levels, complicating diagnosis [15].

Despite extensive research, the exact pathogenesis linking IgG4-RD and SLE remains elusive. However, there's speculation about the involvement of follicular helper T-cells implicated in both diseases. Additionally, detecting anti-Annexin V antibodies in IgG4-RD suggests potential shared pathways with SLE. A recent genome-wide association study on IgG4-RD has uncovered significant associations with HLA-DRB1 ($p = 1.1 \times 10^{11}$ for IgG4-RD, odds ratio of 2.4 for SLE) and FCGR2B ($p = 2.0 \times 10^{8}$ for IgG4-RD, odds ratio of 2.3–2.45 for SLE) [16]. Moreover, the interaction between CD40 and CD40L, crucial for class switching and diverse immunoglobulin production, has been strongly associated with the pathogenesis of SLE, hinting at a possible connection to IgG4-RD as well [17].

Our extensive literature review revealed limited case reports documenting an overlap between IgG4-RD and SLE, summarized in Table 2. Existing case reports have delineated instances where IgG4-RD contributed to various manifestations such as interstitial nephritis, cervical lymphadenopathy, pancreatic enlargement, and interstitial pneumonia. The details of these case reports are succinctly summarized in the table below. However, our case presents a distinct scenario, showcasing the manifestation of AIP as an IgG4-RD manifestation in a patient concurrently diagnosed with SLE, further complicated by the presence of mononeuropathy. It's noteworthy that the incidence of peripheral neuropathy

in neuropsychiatric SLE is estimated at 2.3%, with only two case reports to date documenting its occurrence in IgG4-RD [19–21].

This case report highlights the critical importance of recognizing overlap conditions linked with IgG4-RD, as it not only aids in accurate diagnosis but also informs long-term therapeutic strategies. Most previously reported cases presented with lupus nephritis as the primary organ manifestation. The distinctive presentation of our patient, characterized by both an acute episode of IgG4 autoimmune pancreatitis (AIP) and an unusual manifestation of mononeuropathy secondary to SLE, demonstrates the complexity of autoimmune disorders and the need for comprehensive evaluation and management.

5 | Conclusion and Results

Ultimately, this case serves as a compelling illustration of IgG4-RD autoimmune pancreatitis (AIP), serving as an initial presentation of SLE, shedding light on a potentially underrecognized association. This connection warrants further investigation, given the scarcity of documented cases linking IgG4-RD and SLE. Notably, the recognition of IgG4-RD as an independent diagnostic entity has only gained momentum in clinical medicine over the past two decades, contributing to the limited literature available regarding its associations with other pathologies.

Furthermore, this case underscores the rarity of mononeuritis in the context of both SLE and IgG4-RD, with only a handful of reports documenting such an association. Heightened clinical awareness of these overlapping presentations is crucial, mainly when patients present with symptoms suggestive of acute pancreatitis or neuropathy. In such scenarios, autoimmune conditions should remain at the forefront of differential diagnoses, even after establishing a diagnosis of IgG4-RD.

The management approach should prioritize agents capable of addressing IgG4-RD and concurrent autoimmune conditions, emphasizing the need for a comprehensive treatment strategy. In our patient's case, the decision to expand the rheumatologic workup during his cholecystectomy led to the identification of unique findings, thus broadening his treatment options and averting potential disease progression. This highlights the importance of vigilant clinical evaluation and proactive management in optimizing patient care.

Author Contributions

Srilatha Kothandaraman: conceptualization, formal analysis, supervision, validation, writing – review and editing. **Rithwik Terala:** conceptualization, data curation, methodology, writing – original draft.

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Ethics Statement

Ethics approval is not required for de-identified single case reports based on institutional policies.

Consent

Written informed consent was obtained from the patient to publish this case report per the journal's patient consent policy. A copy of the written consent is available for review by the editor-in-chief of this journal on request.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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