SN Comprehensive Clinical Medicine (2022) 4:162
https://doi.org/10.1007/s42399-022-01247-5

CASE REPORT

IgG4-Related Disease in a Rheumatoid Arthritis Patient — a Coincidence or Possible Association? A Case Report

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Accepted: 6 July 2022 / Published online: 19 July 2022

Abstract

Immunoglobulin G4-related disease (IgG4-RD) is a newly emerging disease entity. IgG4-RD is a systemic disease characterized by swelling or masses in the involved organs, elevated serum immunoglobulin G4 (IgG4), and marked IgG4-positive plasma cell infiltration and fibrosis. The serum concentration of IgG4 increases not only in IgG4-RD but in a broad spectrum of rheumatologic and non-rheumatologic diseases. Elevated serum levels of IgG4 were demonstrated in some patients with rheumatoid arthritis (RA). Interestingly, it was suggested that RA patients who have elevated serum IgG4 levels are more prone to have higher disease activity, higher levels of autoantibodies, and poor response to methotrexate and leflunomide therapy. However, the association between RA and IgG4-RD remains elusive. Herein, we describe a case of a 64-year-old man with a known history of RA and RA-associated interstitial lung disease (RA-ILD) presented with unintentional weight loss and a speculated lung nodule mimicking lung malignancy. As a result, he underwent a computer tomography (CT)-guided biopsy of the lung nodule. Histological analysis revealed fibrous tissue with dense lymphoplasmacytic infiltrates; immunostaining indicated the presence of IgG4-positive plasma cells; serum IgG4 levels were elevated; and a definitive diagnosis of IgG4-related disease was confirmed. He was started on prednisone initially and then on rituximab as a steroid-sparing agent.

Keywords Rheumatoid arthritis · Immunoglobulin G4 · IgG4-related disease · Lung nodule · Case report

Introduction

IgG4 is the least common of the 4 IgG subclasses and is associated with several autoimmune diseases. IgG4-RD is a newly recognized immune-mediated fibroinflammatory condition characterized by elevated serum IgG4 levels and abundant IgG4-bearing plasma cell infiltration. Since the recognition of IgG4-RD, interest has shifted toward IgG4 level in various autoimmune diseases. Several studies have reported elevated serum IgG4 levels in a subset of RA patients. Here, we describe a case of a patient with RA who was years later diagnosed with IgG4-RD raising the question of a possible association.

This article is part of the Topical Collection on *Medicine*

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Case Report

A 64-year-old man with a known history of seropositive rheumatoid arthritis (RF > 600 IU/ml and anti-cyclic citrullinated peptide (anti-CCP) > 250 at time of diagnosis 6 years ago) and RA-ILD, well-controlled on hydroxychloroquine. This patient was hospitalized for a syncope workup. Review of systems revealed unintentional weight loss of 30 lbs over a 2-month period prior to admission. He also noted chills and night sweats but no fevers. He denied any cough, shortness of breath, sputum production, or hemoptysis. Further review of systems was negative. He had a 30-pack year smoking history and has been working as a chef for the past 40 years. Family history is significant for malignancy (brother with prostate cancer; mother, two uncles, and an aunt with colon cancer; another aunt with pancreatic cancer; a cousin with lung cancer). A review of his records revealed that 3 years prior to this admission, he presented to the ED complaining of chest pain; a CT pulmonary angiogram was done which showed no PE but revealed bilateral emphysematous changes, scattered

subpleural fibrotic changes within the upper lobes, as well as left upper lobe pulmonary nodule measuring 5.7 mm (Fig. 1), for which a close follow-up was recommended; however, the patient lost to follow-up due to financial issues. At presentation, vital signs were within normal limits. Physical examination demonstrated bibasilar inspiratory fine crackles on lung auscultation; otherwise, there were no other significant findings. Laboratory examination revealed normal white cell count, elevated total protein at 9.2 g/dl (6.1–7.9 g/dl), normal albumin, elevated globulin at 5.2 g/dl (2.6–3.2 g/dl), increased ESR at 54 mm/h (1–10 mm/h), and increased CRP: 2.7 mg/dl (0–1 mg/dl). Serum plasma electrophoresis was done and showed polyclonal gammopathy.

Contrasted CT chest, abdomen, and pelvis were obtained to look for malignancy, given recent unintentional weight loss. CT abdomen and pelvis revealed no acute abdominal or pelvic process, no suspicious masses, and no lymphadenopathy within the abdomen or pelvis. CT chest revealed an interval increase in the size of the previously noted left upper lobe nodule measuring 2.6 × 1.5 × 1.3 cm (Fig. 2), severe centrilobular paraseptal emphysema, unchanged bilateral

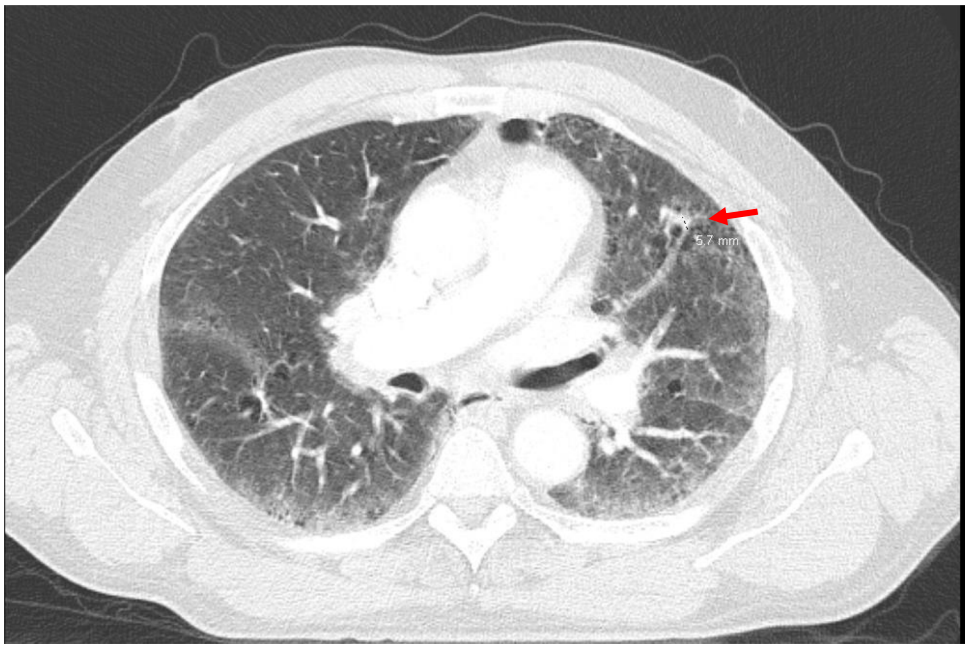

Fig. 1 CT pulmonary angiogram showing a 5.7-mm-solid left upper lobe pulmonary nodule (red arrow), bilateral peripheral predominant reticular and ground-glass opacities, and centrilobular and paraseptal emphysema

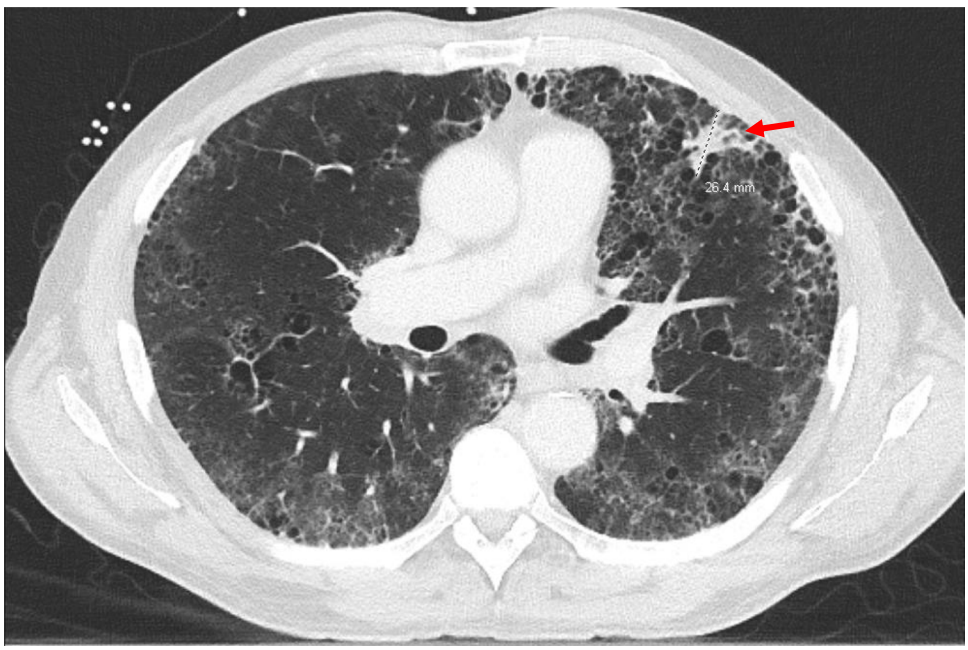

Fig. 2 CT chest with contrast showing interval increase in the size of speculated left upper lobe nodule measuring 2.6 × 1.5 × 1.3 cm (red arrow)

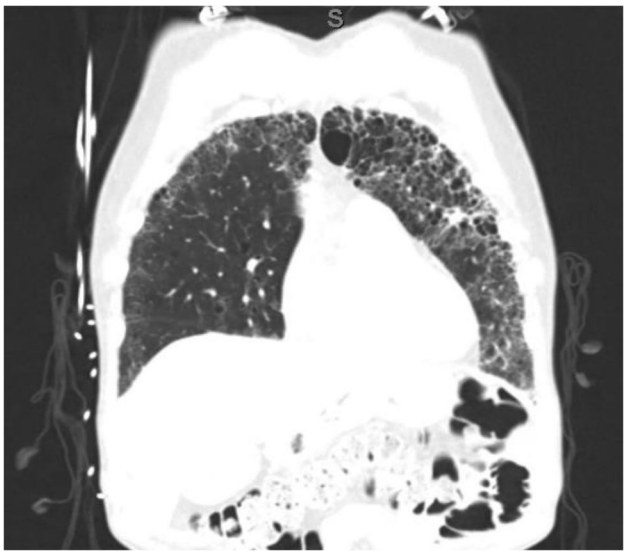

Fig. 3 CT chest with contrast showing subpleural peripheral and apical predominant reticular opacities, fibrosis, and honeycombing which predominantly visualized in the left upper lobe. Severe centrilobular paraseptal emphysema is also evident

subpleural peripheral and apical predominant reticular and ground-glass opacities, fibrosis, and honeycombing (Fig. 3).

Given high suspicion for malignancy, a CT-guided lung biopsy of the left upper lobe nodule was performed, and histopathological examination showed fibrous tissue with dense lymphoplasmacytic infiltrates; the infiltrate consists predominantly of mature appearing plasma cells. There were some scattered admixed lymphocytes. No atypical lymphocytes, diffuse areas of large cells, or lymphoepithelial lesions were identified (Fig. 4). An immunohistochemical stain was performed to evaluate the infiltrate, which revealed increased IgG4 positive plasma cells (50% of total), which were in clusters of up to 20 cells. Based on these findings, serum IgG and serum IgG4 were subsequently checked. The serum concentrations of IgG (2601 mg/dl; normal range: 600–1540 mg/dl) and IgG4 (216.3 mg/dl; normal range: 4.0–86.0 mg/dl) were elevated.

IgG4-related lung disease (IgG4-RLD) was confirmed. The patient was discharged with an outpatient referral to rheumatology and pulmonary clinics. By the time he was seen in the rheumatology clinic, he was complaining of exertional dyspnea. His dyspnea at that time was thought to be

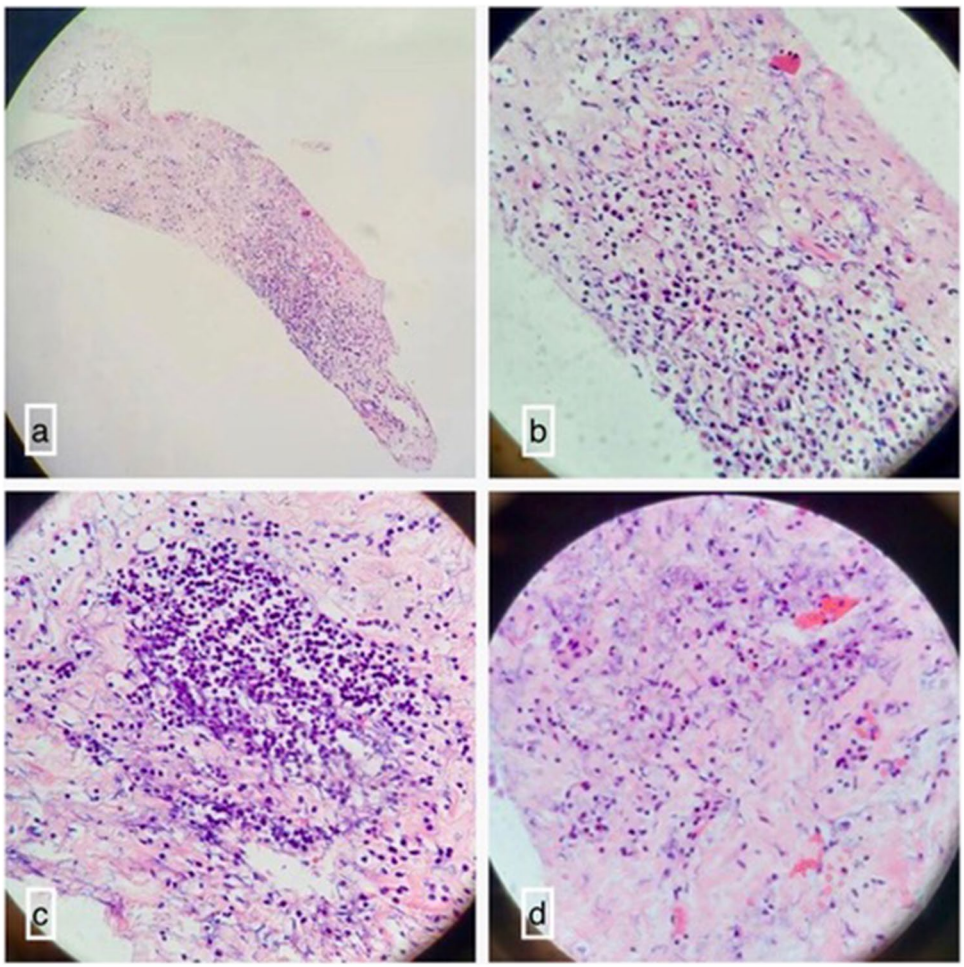

Fig. 4 The microscopic findings of the lung biopsy show fibrous tissue with dense lymphoplasmacytic infiltrates (**a**). The infiltrate cells are mainly composed of mature appearing plasma cells (**b**, **c**, and **d**)

due to a combination of his underlying RA-ILD and IgG4-RLD, as a result he was started on prednisone 40 mg daily, his appetite improved, and started to gain weight; however, dyspnea persisted despite 6 weeks of prednisone therapy. As a result, rituximab (1 g once every 2 weeks for 2 doses) was added as a second immunosuppressive agent. His exertional dyspnea improved significantly after the addition of rituximab, and he regained most of his weight back. A follow-up CT chest 3 months later showed stable size of the speculated left upper lobe nodule, and similar subpleural reticulation/fibrosis (Fig. 5). Repeat serum IgG4 levels showed a decrease to normal levels. Prednisone was eventually tapered down slowly to a maintenance dose of 5 mg daily, and the patient remained on rituximab therapy.

Discussion

IgG4-RD is a recently described disorder that involves lymphoplasmacytic infiltrates causing fibrotic and tumor-like lesions that can affect multiple organ systems [1]. IgG4 elevation in association with autoimmune pancreatitis was first recognized in 2001 [2]. In 2003, the term systemic IgG4-related disease was proposed [3]. Before its recognition as a unified disease, the different organ manifestations of this disorder had been presumed to be unrelated, single-organ disorders [4–7].

Despite RA not being considered an IgG4-RD, several studies have investigated the role of serum IgG4 in RA. It was found that serum IgG4 levels were higher in RA patients compared to healthy population [8]. A few studies have demonstrated that serum IgG4 level was elevated in a subset of RA patients [9–11]. Furthermore, it was suggested that elevated serum IgG4 levels may be associated with a specific clinical phenotype of RA, which is characterized by higher disease activity, higher level of autoantibodies, and poor response to methotrexate and leflunomide therapy [12]. However, there is no clear association between RA and increased risk of developing IgG4-RD.

Pulmonary involvement of IgG4-RD was first described in 2004 [13, 14]. Subsequently, several case reports have demonstrated that the lungs are a common target organ of IgG4-RD, with highly variable clinical and radiological manifestations [15–17].

Since the clinical and radiological manifestations of IgG4-RD are highly variable and non-specific, establishing the diagnosis of IgG4-RD requires a high index of suspicion. In most cases, tissue biopsy with histopathologic examination usually provides strong evidence for the diagnosis of IgG4-RD [18, 19]. Biopsies typically reveal lymphoplasmacytic tissue infiltration of IgG4-positive plasma call and lymphocytes, accompanied by fibrosis that has storiform features. However, histopathological findings are not diagnostic alone and must be interpreted in the context of clinical, serologic, and radiologic data. Similarly, serum IgG4 levels are a significant aid in diagnosis, but are neither sensitive nor specific for IgG4-RD. Ryu and colleagues [20] identified 3300 patients who had IgG subclass testing done, less than one-fifth of these patients manifested evidence for IgG4-RD. As a result, the diagnosis of IgG4-RD cannot be predicted entirely based on a single finding, and a collaborative approach between clinicians, radiologists, and pathologists is needed to arrive at a definite diagnosis.

Because of its recent recognition, international guidelines for the diagnosis, management, and treatment of IgG4-RD are limited. In 2011, Japanese experts have proposed comprehensive diagnostic criteria for this disease, which

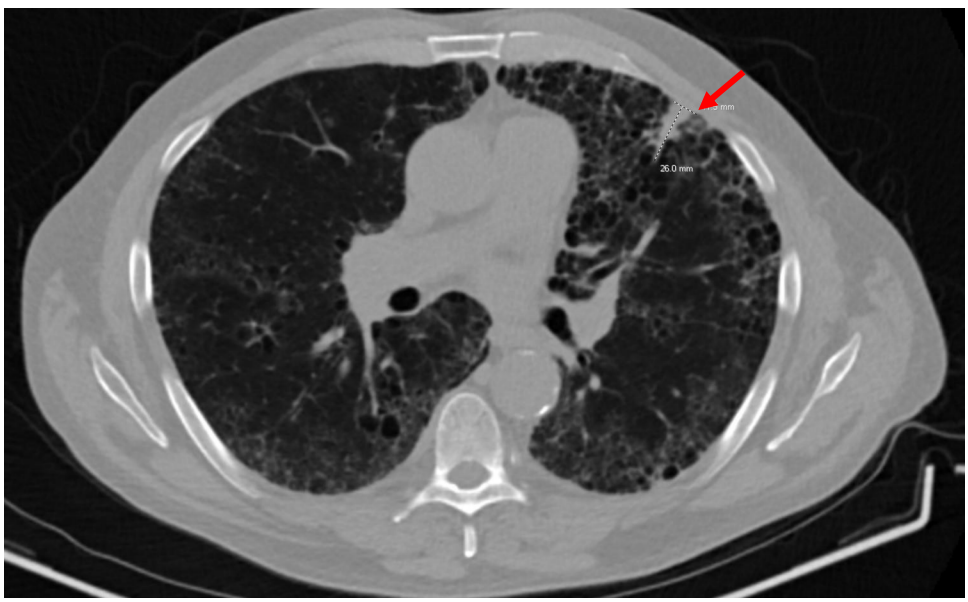

Fig. 5 Repeat CT chest (low-dose CT scan) showing that the previously biopsied left upper lobe nodule remained stable in size, measuring 2.6 × 1.2 × 1.3 cm (red arrow)

Table 1 The Japanese comprehensive diagnostic criteria for IgG4-RD

[1] Organ involvement such as diffuse/localized swelling
[2] Serum IgG4 levels greater than 135 mg/dl
[3] Histopathological examination shows: - Marked plasmacyte infiltration, defined as > 10 IgG4 + plasma cells/HPF and a > 40% ratio of IgG4 + /IgG + cells - Accompanied by fibrosis
Diagnosis: Definite: 1 + 2 + 3 Probable: 1 + 3 Possible: 1 + 2

Table 2 The 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD

[1] Clinical and radiological features: - One or more organs show diffuse or localized swelling or a mass or nodule characteristic of IgG4-RD. In single organ involvement, lymph node swelling is omitted
[2] Serological diagnosis: - Serum IgG4 levels greater than 135 mg/dl
[3] Pathological diagnosis: Two of the following three criteria: I. Dense lymphocyte and plasma cell infiltration with fibrosis II. Ratio of IgG4-positive plasma cells/IgG-positive cells greater than 40% and the number of IgG4-positive plasma cells greater than 10 per high-powered field III. Typical tissue fibrosis, particularly storiform fibrosis, or obliterative phlebitis
Diagnosis: Definite: 1 + 2 + 3 Probable: 1 + 3 Possible: 1 + 2

classified IgG4-RD into definite, probable, and possible (Table 1) [21].

The Japanese IgG4 team has updated the 2011 comprehensive diagnostic criteria for IgG4-RD and proposed the 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD (Table 2) [22].

According to the 2011 Comprehensive Diagnostic criteria as well as the revised comprehensive diagnostic criteria for IgG4-RD, our case has met 3 criteria (1 + 2 + 3) for a definite diagnosis. See Table 3.

In 2019, the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) formulated the 2019 ACR/EULAR IgG4-RD Classification Criteria for international use [23].

The optimal treatment for IgG4-RD has not been established. Majority of the literature regarding treatment of IgG4-RD is focused upon treatment modalities for type 1 autoimmune pancreatitis. The mainstay treatment for IgG4-RD is glucocorticoids. A prednisone dose of 0.6 mg/kg (or 30–40 mg) once daily has been suggested to treat active disease. Lung involvement tends to respond favorably to prednisone treatment, and improvement is noticed in both symptoms as well as imaging [24]. Immunosuppressive agents like rituximab, azathioprine, or mycophenolate can be utilized in patients who do not respond to glucocorticoid monotherapy or cannot be tapered to less than 5 mg daily, and in patients with contraindications to glucocorticoids. Regarding maintenance therapy, it is unclear whether IgG4-RD patients should receive maintenance therapy. The introduction of maintenance therapy is beneficial in patients who are at increased risk for relapse (e.g., multiorgan involvement) and in patients with recurrent disease. A low-dose glucocorticoid or glucocorticoid-sparing agent can act as maintenance therapy [19]. Additional studies are needed to define the duration of maintenance therapy.

The long-term prognosis of IgG4-RLD is uncertain. A favorable response to corticosteroid therapy is typical. However, relapses are common following discontinuation of therapy.

Conclusion

IgG4-RD is a recently described systemic fibroinflammatory disease that is characterized by elevated serum IgG4 level and abundant IgG4-bearing plasmacyte infiltration of

Table 3 Our case fulfilling diagnostic criteria for a "definite diagnosis," according to the RCD criteria for IgG4-RD

[1] Clinical and radiological features: + Presence of a localized nodule in the lung characteristic of IgG4-RD
[2] Serological diagnosis: - Serum IgG4 level of 216.3 mg/dl which is greater than 135 mg/dl
[3] Pathological diagnosis: Two out of 3 criteria were met: I. The histopathological examination of our case showed fibrous tissue with dense lymphoplasmacytic infiltrates II. An immunohistochemical stain revealed IgG4-positive plasma cell/IgG-positive cell ratio of 50% (greater than 40%), and number of IgG4-positive plasma cells were in clusters of up to 20 cells (greater than 10 per high-powered field)
Since 1 + 2 + 3 were met in our case, a definite diagnosis has reached per the RCD criteria

involved organs. On the other hand, studies have shown that serum IgG4 concentrations are elevated in a subset of RA patients but not all RA patients. Interestingly, it was suggested that these patients may represent a specific phenotype. In this case, IgG4-RD was diagnosed in a patient with a well-known history of RA, raising the question of a potential association between the two conditions. Indeed, further studies are necessary to elucidate this potential association.

Author Contribution All the authors were involved in case management. Literature search and first draft of the manuscript were done by MZ. A critical revision was done by RS. Approval of the final version was done by all the authors.

Data Availability Available upon request.

Code Availability Not applicable.

Declarations

Ethics Approval Ethics approval was waived, since it is not a human subject research.

Consent to Participate Not applicable.

Consent for Publication Written consent was obtained from the patient to publish this case.

Conflict of Interest The authors declare no competing interests.

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