Case report

Hoarseness as the presentation of immunoglobulin G4-related disease with vocal cord and mediastinal infiltration

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ABSTRACT

Immunoglobulin G4-related disease is a rare fibroinflammatory infiltrative condition with heterogeneous clinical manifestations. We present the case of a 64-year-old man that presented with hoarseness due to vocal cord involvement, a particularly rare manifestation. A large mediastinal mass compressing thoracic large vessels was also identified. The patient was initially treated with glucocorticoids but had relapses during glucocorticoid tapering. Rituximab was started after a careful pre-treatment evaluation of the infectious risk and treatment of comorbidities.

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a fibroinflammatory infiltrative condition characterised by a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and elevated serum IgG4 concentrations (1). With its growing recognition, the diagnosis is made using increasingly small biopsy samples that frequently do not demonstrate the full spectrum of pathological findings (2).

Clinical vignette

A 64-year-old man presented to the oto-rhinolaryngology clinic in December 2016 complaining of increasingly worse hoarseness and asthenia in the previous 18 months. He had a history of smoking habits, alcoholism and *Helicobacter pylori*-positive gastritis. Considering the smoking history and the slow onset of symptoms, lung cancer was suspected. A chest computed tomography (CT) showed an infiltrative mediastinal mass (Fig. 1), and the patient was referred to the Pulmonology clinic. Between 2017 and 2018, six chest CTs and four biopsies (one endobronchial ultrasound-guided biopsy, one video-assisted thoracoscopic biopsy and two open-surgery biopsies) were performed. The first three biopsies were reported as inconclusive or non-specific. The fourth biopsy revealed fibro-adipose tissue with local lymphoplasmacytic infiltrate and hyalinised fibrous tissue fragments with inflammatory infiltration composed of lymphocytes, some eosinophils and abundant plasmacytes. A whole-body fluorodeoxyglucose positron emission tomography (FDG-PET)/CT performed in 2018 showed hypermetabolic foci in the right vocal cord (maximum SUV 8.21) and the aortopulmonary window (maximum SUV 5.9).

The patient was then referred to the Haematology clinic of our tertiary-care hospital for lymphoma *versus* IgG4-RD differential diagnosis. A revision of the biopsied tissues was requested for immunohistochemical evaluation. The sample was negative for Reed-Sternberg cells ($CD30^+$ $CD15^+$), and IgG4 immunostaining revealed more than 50 IgG4-positive plasma cells per high-power field and a ratio of IgG4- to IgG-bearing plasma cells higher than 40%. Serum IgG4 was 521 (normal range 3–201) mg/dL, serum C3 was 84 (normal range >90) mg/dL, and the peripheral blood eosinophile count was within the normal range in all available complete blood counts. The antinuclear antibody HEp-2 indirect immunofluorescence assay and the extractable nuclear antigen antibodies panel were both negative. The diagnosis of IgG4-RD was made, and the patient started 20 mg of prednisolone daily in May 2018. The hoarseness and asthenia resolved and an FDG-PET/CT performed in July 2019 showed marked improvement of the previously described hypermetabolic foci. The prednisolone dose was then slowly tapered from 20 mg to 5 mg daily.

In May 2020, the patient reported a

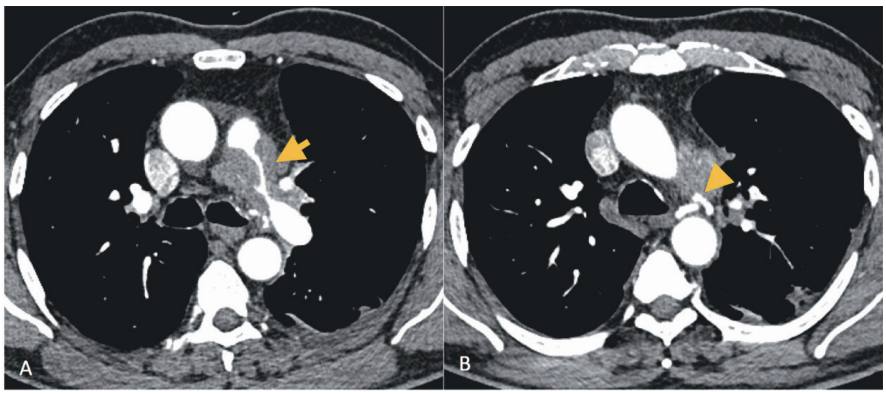

Fig. 1. CT pulmonary angiography axial images showing an infiltrative soft-tissue mass encasing the pulmonary trunk bifurcation and the left pulmonary artery. In panel A, a significant narrowing of the left pulmonary artery is seen (arrow), associated with collateral circulation seen anteriorly to the thoracic aorta in panel B (arrowhead). There are scarce minimal foci of calcification inside the mass (not shown).

recurrence of hoarseness and asthenia and an unintended weight loss of 3 kg in the previous month. A re-evaluation with FDG-PET/CT confirmed relapse of the disease in the right vocal cord and mediastinum (Fig. 2).

The patient was then referred to the Rheumatology clinic. The prednisolone dose was increased to 0.6 mg/kg/day (40 mg) for four weeks, followed by a taper every two weeks (10 mg every two weeks until 20 mg/day, then 5 mg every two weeks until 10 mg/day, and finally 2.5 mg every two weeks). The symptoms quickly regressed, and the patient recovered his prior weight. It was decided that treatment with rituximab should ensue, and the patient was assessed for neoplasia, dental health condition, vaccination status, latent tuberculosis, HIV and viral hepatitis. Several dental procedures were deemed necessary, as well as anti-pneumococcal vaccination and prophylaxis of both tuberculosis (nonspecific calcifications in the chest CT) and hepatitis B infection reactivation (anti-HBc positive), with isoniazid and tenofovir, respectively. An episode of multidermatomal herpes zoster, successfully treated with oral valaciclovir and topical fusidic acid, further delayed rituximab initiation. Still before rituximab treatment, in December 2020, immediately after tapering the prednisolone dose from 7.5 to 5 mg/day, the patient presented with another clinical relapse, characterised again by hoarseness, asthenia and weight loss of 4 kg in a month.

In February 2021, rituximab (1000 mg + 1000 mg 2 weeks apart) was started. Rituximab successfully depleted B cells (flow cytometry with no CD19+ cells at 1 and 3 months after the infusion) and diminished the serum IgG4 levels to as low as 274 mg/dL. Clinically, asthenia and weight loss quickly resolved, but hoarseness persists.

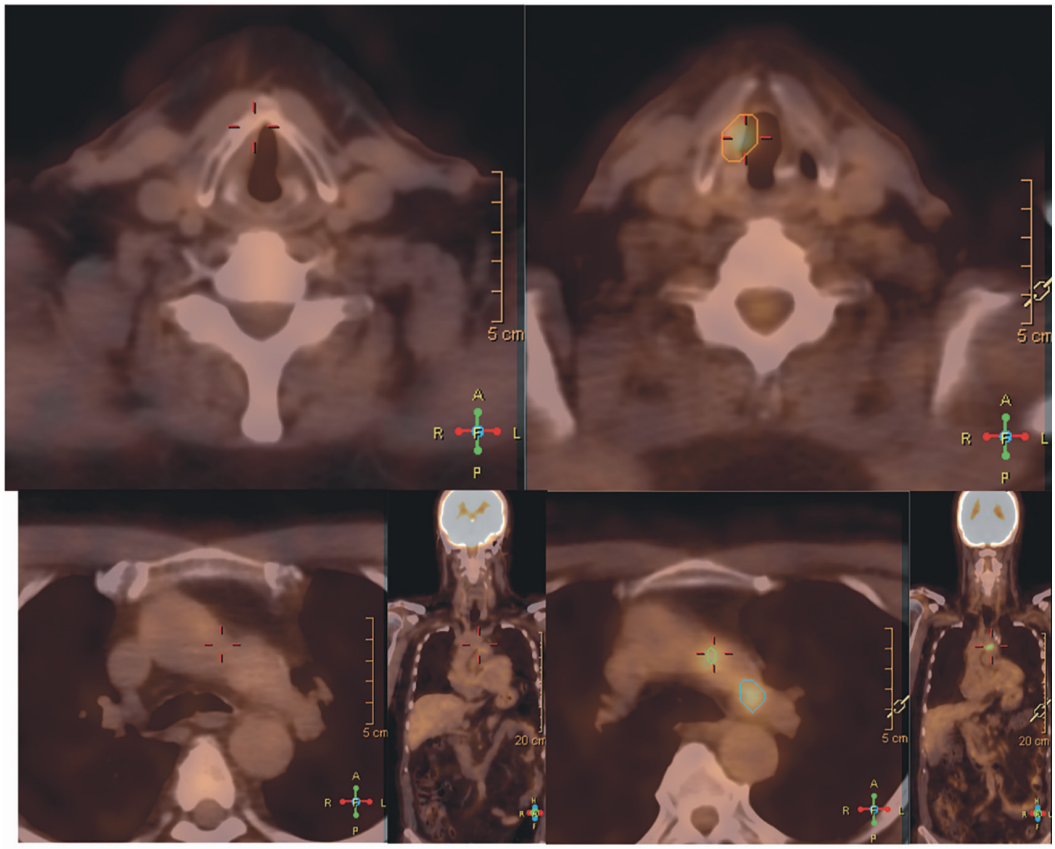

Fig. 2. Comparison of the whole-body FDG-PET/CT imaging from July 2019 (under treatment with prednisolone 20 mg/day; panels A, C and D) and May 2020 (under treatment with prednisolone 5 mg/day; panels B, E and F) at the level of the vocal cords, showing *de novo* increased FDG uptake at the right vocal cord with a maximum SUV of 5.45 (panel B), and at the aortopulmonary window (panels E and F), showing two foci of *de novo* increased FDG uptake with maximum SUVs of 5.89 and 5.44.

Discussion

This patient fulfils the 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-RD (2). Laryngeal involvement as a primary feature represents an extremely infrequent expression of this uncommon disease (3), and vocal cord involvement is even rarer (3). Relapses were formally detected by increases in IgG4-RD responder index (4) and FDG-PET/CT imaging.

If left untreated, this patient's prognosis is poor, considering the risks of upper airway obstruction and haemodynamic complications from the mediastinal involvement. Considering these hazards and the disease relapsing course, treatment with a steroid-sparing agent was indicated (5). Treatment with conventional disease-modifying antirheumatic drugs was considered, but lack of consistent evidence of efficacy (5, 6) and the severity of the involvements prompted the use of rituximab. Even with rituximab treatment, this patient's prognosis is unclear. Hoarseness persists, and relapse may occur in more than one-third of patients treated with rituximab (7), particularly in those with high serum IgG4 at baseline (7). The infectious risk is also a concern (8), especially considering that this patient has hypocomplementaemia, a common clinical feature of patients with IgG4-RD with thoracic involvement (9).

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