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Pulmonary and Orbital Bifocal IgG4 Disease: Case Report and Literature Review

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Abstract

Introduction: IgG4 disease is an orphan, fibro-inflammatory autoimmune disease of recent discovery whose thoracic involvement is rarer. We report a case of Pulmonary and orbital bifocal IgG4 disease with a review of the literature. **Observation:** This is a 71-year-old patient with a history of hypertension, dyslipidemia, smoking cessation at 15 PA, with progressive dyspnoea, weight loss of 4 kg with PS = 0 for 2 months. The thoracic CT scan revealed 3 pseudotumoral lung lesions of the LIG, LID and LM. The histology of the two CT-guided lung biopsies and the LIG wedge had objectified inflammatory lesions without signs of malignancy. The evolution was marked by the occurrence of a right orbital edema. The cerebral scanner found a voluminous right orbital inflammatory pseudotumor. Biopsy with histology found fibroinflammatory lesions with lymphoplasmacytic infiltrates and positive immunolabeling with anti-IgG4 antibodies. The PET scanner had objectified pulmonary and pleural parenchymal consolidations and moderately hypermetabolic mediastinal ADP with max SUV between 3 and 6. The patient was put on corticosteroid therapy with a favorable outcome. **Conclusion:** IgG4 disease is rare and difficult to diagnose despite well-defined and consensual diagnostic criteria and classification. The discovery of new biomarkers facilitates the diagnosis and monitoring of patients. Well-codified corticosteroid therapy is effective but possibility of recurrence. The current challenge remains the lack of data on the follow-up of these patients to assess the risk of neoplasia (lymphoma).

Keywords

Orphan Disease, Thoracic IgG4 Disease, Autoimmunity

1. Introduction

IgG4 disease is a rare and recently discovered autoimmune disease. It is an inflammatory and fibrosing disease affecting one or more organs. It is characterized by clinical signs, tumor lesion(s), sometimes an elevation in the serum IgG4 level, and positivity of anti-IgG4 antibodies. The diagnosis of IgG4 disease is very difficult, hence diagnostic criteria and an ACR/EULAR classification were established, thus facilitating the diagnosis [1]. The diagnosis of thoracic IgG4 disease is even more rare and difficult. This thoracic involvement is very difficult to distinguish from pulmonary neoplasia both clinically and visually [2]. The definitive diagnosis is based on immunohistochemistry of fragments of the affected organ. We report a case of bifocal pulmonary and orbital IgG4 disease with a review of the literature.

2. Case Report

This was a 71-year-old patient, smoking at 15 PA who had stopped smoking, who had progressively worsening dyspnea over the past 2 months, weight loss of 4 kg with PS = 0. Chest CT highlighting 3 pseudo pulmonary lesions tumors of the left lower lobe (LIG), the right lower lobe (LID) and the middle lobe (LM) (**Figure 1**).

The standard biological assessment was normal. MPO type ANCAs = 80 IU/ml. Two CT-guided lung biopsies of the LID and LM lesions were performed with objective histological examination of subacute inflammatory and necrotic lesions, without signs of malignancy. The patient underwent an atypical pulmonary resection (wedge) of the LIG with histological examination revealing fibrous and inflammatory changes without granulomatosis or neoplasia. CT of the skull and abdominopelvic was normal. Bronchial endoscopy and histology of bronchial biopsies were normal. EFRs were normal. The evolution was marked

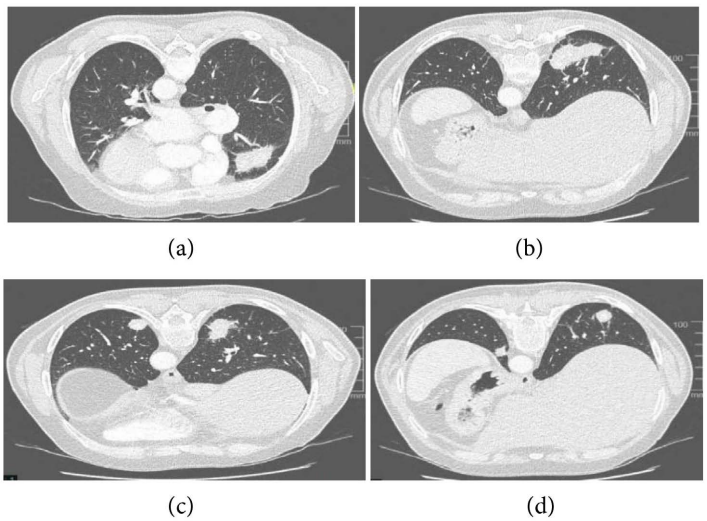

Figure 1. Thoracic CT appearance of multiple parenchymal condensations. pulmonary: (a) (Middle lobe), (b) (Lower right lobe), (c) (both lower lobes), (d) (left subpleural nodule with right lower lobe condensation).

by the occurrence of right orbital edema with on cerebral CT a voluminous expansive process intra orbital supero-temporal right retro, latero bulbar intra conal infiltrating the lacrimal gland, the external oculo motor muscle and extended to the region upper eyelid taking moderate contrast with exophthalmos related to an inflammatory pseudotumor. Biopsy of the orbital mass was performed. Histology revealed fibroinflammatory lesions, with lymphoplasmacytic infiltrates. On PET scan the lung lesions and hilar lymph nodes were moderately hypermetabolic with SUV max of hilar ADP between 3.2 and 3.6, SUV max of LM = 4.2, SUV max of LID = 6 and SUV max of LIG = 4.1. Immunostaining with anti-CD138 antibodies revealed numerous plasma cells. Immunostaining with anti-IgG4 antibodies marked 30% of CD138 plasma cells. The diagnosis of IgG4 disease was retained. The patient was put on long-term corticosteroid therapy with favorable progress.

3. Discussion

IgG4 disease is little known and underdiagnosed. The positive diagnosis is guided by the association of characteristic criteria with imaging, serology, and histology. The diagnosis is confirmed by the predominance of plasma cells and the positivity of anti-IgG4 antibodies on immunohistochemistry [2]. Respiratory damage is generally discovered incidentally. The patient is male and 71 years old. Male predominance is reported in the literature in 60% of cases with an average age between 60 and 70 years. The patient presented with progressively worsening dyspnea and weight loss of 4 kg in 2 months. In the literature, respiratory symptoms are nonspecific and patients are asymptomatic in 75% of cases [3] [4] [5]. IgG4 disease can affect one or more organs with single organ involvement in 19% of cases. The involvement of several organs mainly concerns the salivary glands (70%), lacrimal glands (60%), lymph nodes (60%), pancreas (25%). Chest involvement is less common (23%) of cases. Our patient has bifocal thoracic and orbital involvement unlike other studies with bifocal thoracic and pancreatic involvement predominating in 50% of cases [4]. The chest scan lesions were pseudo-tumorous pulmonary parenchymal lesions of LIG, LID and LM. Among pulmonary locations, parenchymal involvement is most frequently found in studies with intra or interlobular reticulations, traction bronchiectasis, honeycombing and aspects of organizing pneumonia [5] [6]. Pulmonary vascular damage such as aneurysm, necrotizing angiitis or stenosis of the pulmonary arteries are also described [7]. Thoracic involvement of IgG4 disease was the subject of the ACR/EULAR classification [8] [9]. The standard biological assessment carried out in the patient was normal; notably neutrophils and eosinophils. The MPO type ANCA dosage was positive at 80 IU/ml without signs of vasculitis on the histology of the 2 CT-guided biopsies and the wedge. Serum IgG4 was 1.47 g/L (Normal ≤ 1.35 g/L). In the literature, the increase in plasma IgG4 level is not specific for IgG4 disease but constitutes a criterion for diagnostic guidance. Our patient had an IgG4/IgG plasma cell ratio > 50%. Several studies have shown that this IgG4/IgG ratio ≥ 40% seems to be a good argument in favor of

IgG4 disease [10]. New biological biomarkers have been identified for diagnosis and prognosis [11]. These are serum levels of IgG2, soluble IL-2 receptors and chemokine C-C motif ligand 18 [12]; eotaxin-3 [12]; circulating plasmablasts [5]. In our case, the histology associated with the immunohistochemistry of the biopsy of the lung lesions but especially the right orbit had made it possible to make the diagnosis of IgG4 disease as reported by some others [5] [13] [14] [15].

The clinical, paraclinical and histopathological characteristics of IgG4 disease were the subject of an international consensus adopted in 2011 and revised in 2020 [12]. The disease is considered confirmed, probable, or possible depending on the number of criteria met. In our patient, the criteria met were radiological, histological and immunohistochemical, therefore, criteria 1 + 2 + 3 of **Table 1** make the diagnosis definite. The histopathological features of G4 immunoglobulin-related disease are listed in **Table 2** [16].

These criteria were completed during an international consensus in 2012 [9]. The main differential diagnoses of IgG4 disease are ANCA vasculitis, Gougerot-Sjögren syndrome, sarcoidosis, organizing pneumonia, eosinophilic pneumonia, Castleman disease and cancers, particularly malignant lymphomas [5] [17].

Therapeutically, the management of IgG4 disease is mainly based on corticosteroid therapy. Our patient was placed on long-term corticosteroid therapy with good clinical progress.

There are several treatment regimens depending on the schools and authors. The following treatment consensus is the most used: starting dose, prednisolone at a dosage of 0.6 to 1 mg/kg per day for two to four weeks, then gradual reduction until stopping. The total duration is 12 weeks [18]. According to literature data, under this treatment regimen, recurrence is found in approximately 25% of patients [19]. In cases of corticosteroid dependence, immunosuppressants can be used [16]. IgG4 disease is a recently discovered disease and there is little data on its evolution. Indeed, IgG4 disease would be an increased risk factor for neoplasia, especially lymphoma [20], hence the importance of rigorous monitoring to assess this risk.

Table 1. Diagnostic criteria for immunoglobulin-related disease type G4 (IgG4).

Signs of organ(s) diffusely or partially enlarged, or in nodular form.
Serum IgG4 level > or equal to 1.35 g/l.
Histopathological examination: lymphoplasmacytic infiltrate with sclerosis IgG4+/IgG+ cell ratio > 40%, and > or equal to 10 IgG4+ plasma cells/HPF.
Confirmed diagnosis: 1 + 2 + 3; probable 1 + 3; possible 1 + 2 HPF: high power field.

Table 2. Histopathological characteristics of disease linked to immunoglobulin type G4 (IgG4).

Lymphocytic infiltrate with predominance of IgG4-positive plasma cells and CD4+ T lymphocytes;
Storiform fibrosis or fibrosis consisting of proliferating spindle-shaped cells around infiltrating lymphocytes;
Obstructive phlebitis;
Refers to a carcass wheel pattern with a sometimes spiral center, and bands of fibrosis emanating from it with an irregular tangled weave somewhat resembling that of a straw mat.

4. Conclusion

IgG4 disease is an orphan disease and pulmonary involvement remains little known in pulmonology. The clinical symptoms are non-specific. Imaging reveals pseudotumors. Diagnosis is based on immunohistochemistry. Corticosteroid therapy is effective. IgG4 disease appears to be a risk factor for lymphoma, hence the importance of rigorous monitoring.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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