Multiple myeloma is characterized by >10 % bone marrow infiltration by plasma cells that secrete MC in serum and/or urine, along with cytokines that can cause bone lesions. Incidence is 3–5 cases/100,000 inhabitants/year, and the average age of patients is 65 years. Symptomatic multiple myeloma is defined as the presence of MC in serum and/or urine, plasma cell infiltration of the bone marrow or plasmacytoma and evidence of organ damage (CRAB), while asymptomatic multiple myeloma is defined as the presence of MC in serum and/or urine and plasma cell infiltration in bone marrow/plasmacytoma with no organ damage (CRAB).[1–4]

The patient received 5 sessions of stereotactic radiation therapy to the lung lesion (total dose: 55 Gy). He remained disease-free at 15 months, and subsequently initiated treatment with curative intent with lenalidomide and dexamethasone, achieving complete MM remission after 12 cycles of treatment.

In conclusion, patients with a history of MGUS who present bone lesions (although initially attributed to metastatic origin) and who remain asymptomatic should undergo guided bone biopsy, whenever possible, to rule out metastatic disease and/or progression to MM, since the therapeutic approach and the prognosis of the disease vary greatly, ranging from proposed palliative treatments to curative attempt. In these cases, multidisciplinary study and follow-up of patients is essential in order to optimize the diagnostic and therapeutic procedures.

References

1. Swerdlow SH, Campo E, Lee Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO classification of tumours of hematopoietic and lymphoid tissues, 2, 4th edition; 2017.
2. Baldini L, Guffanti A, Cesana BM, Colombi M, Chiorboli O, Damilano I, et al. Role of different hematologic variables in defining the risk of malignant transformation in monoclonal gammopathy. Blood. 1996;87:912–8.
3. Mateos MV, Bladé J, Lahuerta JJ, San Miguel J. Tratamiento del mieloma múltiple asintomático: recomendaciones del Grupo Español de Mieloma. Med Clin (Barc). 2017;148:517–23.
4. Go R, Rajkumar S. How I manage monoclonal gammopathy of undetermined significance. Blood. 2018;131:163–73.

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Not Cancer After All: Two Rare Cases of IgG4-Related Lung Disease

Al final, no era cáncer: dos casos infrecuentes de enfermedad pulmonar relacionada con IgG4

Dear Editor,

IgG4-related disease (IgG4-RD) is an uncommon systemic disorder characterized by sclerosing lesions that can affect almost any anatomical site.[1] Pulmonary involvement has highly variable clinical and radiological presentations.[2] Although IgG4-related lung disease is usually preceded or accompanied by multi-organ involvement,[3] rare cases of solely lung involving IgG4-RD have been described.[4–6] Herein, we report two biopsy-proven cases of IgG4-RD with lung mass as the sole radiographic presentation.

64-Year-old man with a 27 mm spiculated mass in the right upper lobe on computed tomography (CT) in the setting of chronic cough with hemoptoic sputum. He was a previous smoker (100 pack-year of smoking). Bronchoscopy showed neither signs of bleeding nor morphological anomalies and bronchoalveolar lavage (BAL) was negative for malignant cells and acid-fast bacilli. Further investigation with positron emission tomography (PET) demonstrated a right upper lobe nodule with standardized uptake value (SUV) max of 2.6. Due to the high suspicion of primary lung malignancy, biopsy of the nodule was performed by transthoracic needle aspiration (TTNA), documenting a fibrocollagenous lesion with lymphoplasmacytic infiltration and wall thickening of venous-type vessels. On immunohistochemistry, the number of IgG4-positive plasma cells was >20 per high power field (HPF) and immunostaining for CD20 and CD3 was positive. The serum concentrations of total IgG and IgG4 were normal.

71-Year-old man who presented with posterior upper thoracic pain for 2 years. He is an active smoker with 50 pack-year of smoking. Chest CT detected a 35 mm spiculated mass in the right upper lobe, which was biopsied by TTNA. Histological examination demonstrated a nodular lesion with total architectural distortion due to fibrosis and lymphoplasmacytic infiltration. On immunohistochemistry, the number of IgG4-positive plasma cells was >30 per HPF. Given the suspicion of IgG4-RD further workup was performed, showing elevated serum concentrations of IgG4 and normal concentrations of total IgG. PET demonstrated a right upper lobe nodule with SUV max of 3.1 and BAL pathological analysis was negative for malignant cells. Hence, in both cases the diagnosis of IgG4-RD was established based on clinico-pathological correlation.

Both patients started corticosteroid therapy with an initial prednisolone dosing of 0.6 mg/kg/d for 4 weeks. Patient 1 had a poor compliance to the treatment and presented no improvements after 2 months (Fig. 1). Patient 2 showed clinical improvement and a reduction of the mass' dimensions on CT imaging after 3 months of treatment (Fig. 2). The prednisolone dose was tapered by 10 mg/kg/d after the first and third month of therapy, maintaining 10 mg/d at the present time.

Although the epidemiology of IgG4-related lung disease (IgG4-RLD) remains poorly described,[7] it usually occurs in male adults with an average age of 69 years.[8] Its clinical presentation depends on the location of the lesion, nonetheless half of patients present nonspecific respiratory symptoms, whereas the remaining present abnormalities on imaging studies in the absence of symptoms.[2,8]

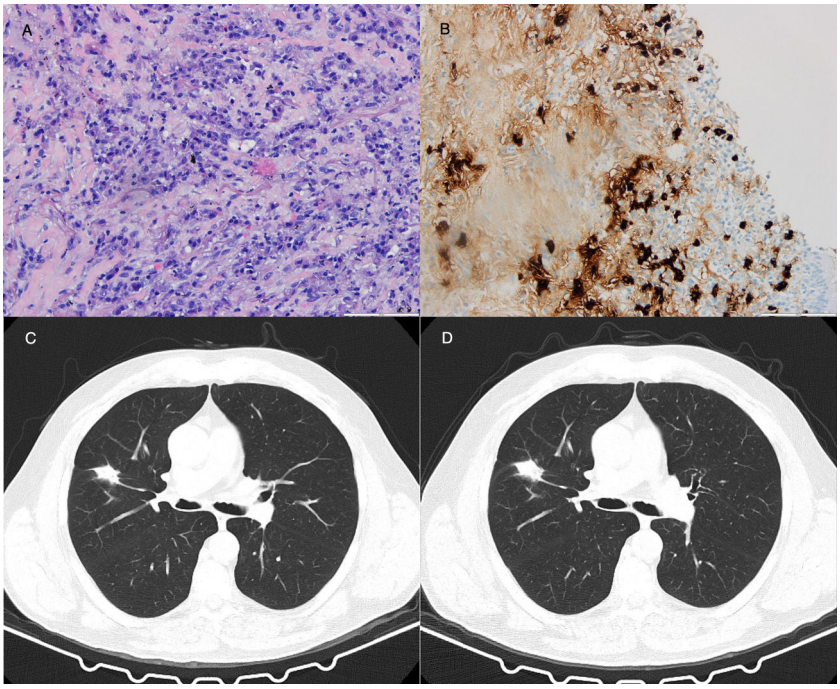

Fig. 1. Histological and radiological results from case 1: (A′) hematoxylin and eosin stain, (B′) immunohistochemistry for IgG4-positive plasma cells, (C′) CT images at the time of diagnosis, and (D′) CT images after 2 months of therapy with poor compliance.

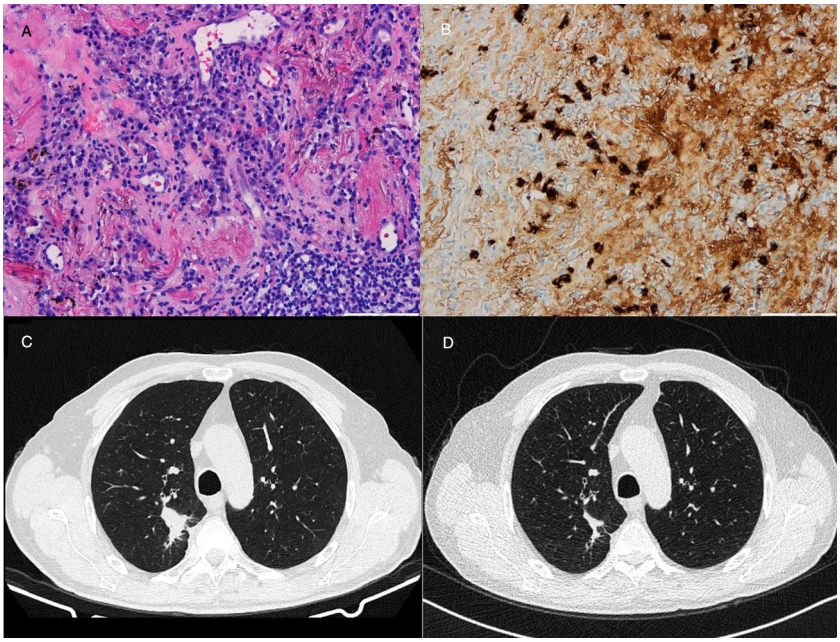

Fig. 2. Histological and radiological results from case 2: (A) hematoxylin and eosin stain, (B) immunohistochemistry for IgG4-positive plasma cells, (C) CT images at the time of diagnosis, and (D) CT images after 3 months of therapy.

Appropriate diagnosis can be challenging, as it relies upon the integration of clinical, laboratorial and histopathologic findings. The consensus statement on the pathology of IgG4-RD mentions that the final diagnosis requires both an appropriate histologic appearance and increased numbers of IgG4+ plasma cells.[1] Such statement suggested >50/HPF and >20/HPF as the cut-off value for increased IgG4+ cells in surgical and nonsurgical biopsies, respectively.[1] Additionally, it underlines that diagnosis should be based primarily on morphological appearance and less importantly on tissue IgG4+/IgG+ ratio, since various conditions can course with elevated IgG4+/IgG+ ratio.[1,2] While pathologic findings represent the cornerstone for a definite diagnosis, the interpretation of lung biopsy for any fibroinflammatory condition is challenging due to the fact that the lung tends to undergo stereotypic morphologic responses regardless of the type of injury.[8] The characteristic histologic findings of IgG4-RLD are fairly common in lung samples afflicted by severe infection or organizing injury of various causes,[8] highlighting the importance of a careful correlation with clinical and laboratorial data.

Elevation of IgG4 serum concentration is used to support the diagnosis of IgG4-RD.[2] However, recent studies have demonstrated that up to half of patients with biopsy-proven and clinically active

IgG4-RD may have normal serum concentrations[9] and only a minority of patients with high IgG4 levels have IgG4-RD.[10] Thus the current trend is to deemphasize excessive reliance on serum IgG4, which is neither specific nor sensitive of IgG4-RD.[11]

PET has been advocated as it can detect unforeseen localizations of the disease and assess the extent of systemic disease.[6] In both patients, PET confirmed that the disease is confined to the lung. Two other case reports documented pulmonary, hilar and mediastinal lesions with SUV max from 2.1 to 11.0,[6,12] yet there is no demonstrated range for SUV that can either gauge disease activity or guide treatment decisions.[7]

The natural course of the disease is not completely known and there are no formal treatment guidelines. However, it is agreed among experts that the threshold for initiating treatment is low, in order to prevent fibrosis and its irreversible damage on organs.[7] The consensus statement on the treatment of IgG4-RD recommends glucocorticoids as the first-line agent for remission induction in all patients with active and untreated disease.[7] Prednisolone at an initial dosage of 0.6 mg/kg/d for 2–4 weeks is recommended,[13] which may be adjusted if the disease appears to be particularly aggressive.[7] Immunossupression with rituximab is indicated in the steroid refractory disease.[2] There is no consensus regarding the tapering regimen and maintenance therapy however.

In cases of isolated pulmonary disease, it is imperative to ensure a regular follow-up with screening of multi-systemic involvement and malignancies. Although the association of lung cancer with IgG4-RLD remains unclear, a small number of adenocarcinoma-associated cases have been reported.[14]

In conclusion, IgG4-RLD is a rare condition that may be diagnosed after the unexpected result of a biopsy in the setting of suspected lung malignancy. Awareness of IgG4-RD is of utmost importance, as the pathologist must perform a specific immunostaining and the clinician must exclude other differential diagnoses. Increasing recognition and further studies will enlighten our understanding of the pathogenesis, diagnostic criteria and standardized therapy for this disease.

References

1. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol. 2012;25:1181–92, http://dx.doi.org/10.1038/modpathol.2012.72.
2. Campbell SN, Rubio E, Loschner AL. Clinical review of pulmonary manifestations of IgG4-related disease. Ann Am Thorac Soc. 2014;11:1466–75, http://dx.doi.org/10.1513/AnnalsATS.201403-128FR.
3. Patel M, Kumar B, Diep ML, Nandurkar D. IgG4 related lung disease. Can Respir J. 2016;2016:1409281, http://dx.doi.org/10.1155/2016/1409281.
4. Chen CF, Chu KA, Tseng YC, Wu CC, Lai RS. IgG4-related lung disease presenting as interstitial lung disease with bronchiolitis: a case report. Medicine. 2017;96:e9140, http://dx.doi.org/10.1097/MD.0000000000009140.
5. Zhang XQ, Chen GP, Wu SC, Yu S, Wang H, Chen XY, et al. Solely lung-involved IgG4-related disease: a case report and review of the literature. Sarcoid Vasc Diffuse Lung Dis. 2016;33:398–406.
6. Bertoglio P, Viti A, Paiano S, Assante LR, Bogina GS, Pomari C, et al. IgG4-related disease: a new challenging diagnosis mimicking lung cancer. Interact Cardiovasc Thorac Surg. 2019;28:410–2, http://dx.doi.org/10.1093/icvts/ivy279.
7. Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN, et al. International consensus guidance statement on the management and treatment of IgG4-related disease. Arthritis Rheumatol. 2015;67:1688–99, http://dx.doi.org/10.1002/art.39132.
8. Yi ES, Sekiguchi H, Peikert T, Ryu JH, Colby TV. Reprint of: Pathologic manifestations of Immunoglobulin(Ig)G4-related lung disease. Semin Diagnos Pathol. 2018;35:147–51, http://dx.doi.org/10.1053/j.semdp.2018.09.004.
9. Wallace ZS, Deshpande V, Mattoo H, Mahajan VS, Kulikova M, Pillai S, et al. IgG4-related disease: clinical and laboratory features in one hundred twenty-five patients. Arthritis Rheumatol. 2015;67:2466–75, http://dx.doi.org/10.1002/art.39205.
10. Ryu JH, Horie R, Sekiguchi H, Peikert T, Yi ES. Spectrum of disorders associated with elevated serum IgG4 levels encountered in clinical practice. Int J Rheumatol. 2012;2012:232960, http://dx.doi.org/10.1155/2012/232960.
11. Bledsoe JR, Della-Torre E, Rovati L, Deshpande V. IgG4-related disease: review of the histopathologic features, differential diagnosis, and therapeutic approach. APMIS. 2018;126:459–76, http://dx.doi.org/10.1111/apm.12845.
12. Kitada M, Matuda Y, Hayashi S, Ishibashi K, Oikawa K, Miyokawa N, et al. IgG4-related lung disease showing high standardized uptake values on FDG-PET: report of two cases. J Cardiothorac Surg. 2013;8:160, http://dx.doi.org/10.1186/1749-8090-8-160.
13. Kamisawa T, Okazaki K, Kawa S, Ito T, Inui K, Irie H, et al. Amendment of the Japanese Consensus Guidelines for Autoimmune Pancreatitis, 2013 III. Treatment and prognosis of autoimmune pancreatitis. J Gastroenterol. 2014;49:961–70, http://dx.doi.org/10.1007/s00535-014-0945-z.
14. Choi S, Park S, Chung MP, Kim TS, Cho JH, Han J. A rare case of adenosquamous carcinoma arising in the background of IgG4-related lung disease. J Pathol Transl Med. 2019;53:188–91, http://dx.doi.org/10.4132/jptm.2019.02.21.

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Pleuroparenchymal Fibroelastosis as Another Potential Lung Toxicity Pattern Induced by Amiodarone

Fibroelastosis pleuroparenquimal como posible patrón de toxicidad pulmonar inducido por amiodarona

Dear Editor,

Pleuroparenchymal fibroelastosis (PPFE) is a rare condition firstly described in 1992 by Amitani et al. under the name of upper lobe pulmonary fibrosis[1] and then in 2004 by Frankel et al. as pleuroparenchymal fibroelastosis.[2] Later in the updated 2013 American Thoracic Society/European Respiratory Society classification, idiopathic PPFE (IPPFE) was included as a new clinic-pathological entity.[3] In this condition, both radiology and histology show typically pleural thickening and subpleural fibrosis in the upper lobes, with the involvement of lower lobes being less marked or absent.[3–5] Besides the rarity of the idiopathic form, PPFE is often associated with a multiplicity of clinical entities namely other interstitial lung diseases (ILD) as Idiopathic Pulmonary Fibrosis (IPF) or Hypersensitivity Pneumonitis, bronchiectasis, connective tissue disorders, recurrent infections, bone marrow/organ transplant, or ambient exposure as silica or asbestos.[4,6,7] Interestingly, PPFE can also occur in a familiar context, and even a particular association with telomere length mutations have been described.[8] As other particular pulmonary radiologic/histologic pattern, PPFE can also be associated with toxicity induced by drugs.[4,9] At present, cases with chemotherapy either associated or not with radiation and methotrexate have been reported.[9]

Here we present a case of PPFE diagnosed in a patient under amiodarone prescription, an association not previously described.

A 68-year-old Caucasian woman was referred to ILD outpatient clinic with recurrent episodes of a dry cough for the past two years, significantly worsened in the last six months, and consolidations in both upper lobes in thoracic high-resolution computed tomography (HRCT) scan. She had atrial fibrillation diagnosed five years