IgG4 inflammatory pseudotumor mimicking primary lung cancer: a case report

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ABSTRACT

Introduction: IgG4 related disease (IgG4-RTD) is an infrequent disease with possible multiple organ involvement. It is characteristic to find inflammatory nodules with IgG4 positive plasma cell infiltration, storiform fibrosis and obliterative phlebitis. We present a patient with an inflammatory pseudotumor in the right upper lobe, mimicking a primary lung tumor. **Case report:** Our patient, a 48-year old heavy smoker (25 pack/year) with no relevant medical background, referred chest pain, non-productive cough and sporadic nightly fever. Image findings revealed a mass in the right upper lobe, with increased SUV in PET-scan, and mediastinal lymphadenopathies. Primary lung tumor was suspected and right upper lobectomy was performed. Due to absence of cellular atypia and the intense plasmacytic activity in the lesion, immunohistochemical analysis was performed: abundant IgG4 plasma cells were identified, with a IgG4/IgG relation of 74%. Diagnosis of IgG4- inflammatory pseudotumor was made. **Discussion:** After an extensive bibliographic review, we found just one similar case reported with an IgG4-lung pseudotumor without systemic disease. Due to the broad spectrum of clinical features of IgG4-RTD, and the potential multiple organ involvement, it is hard to find a classification and diagnostic criteria with high sensitivity and specificity, nevertheless they can be useful in clinical practice. **Conclusion:** There are several benign inflammatory diseases which can mimic a primary lung tumor. Although incidence is low, IgG4 pseudotumor should be considered as a differential diagnosis in the absence of malignancy.

Keywords: immunoglobulin g4-related disease; plasma cell granuloma; lung neoplasms.

Reporte de caso: pseudotumor inflamatorio por IgG4 simulando cáncer de pulmón

RESUMEN

Introducción: La enfermedad relacionada con IgG4 (IgG4-RTD) es una enfermedad poco frecuente con posible afectación multiorgánica. La presencia de infiltrados linfoplasmocitarios con células plasmáticas positivas para IgG4, fibrosis y flebitis obliterante. Presentamos el caso de un paciente con un pseudotumor inflamatorio en el lóbulo superior derecho, con presentación clínica compatible con tumor primario de pulmón. **Caso clínico:** Nuestro paciente de 48 años de edad, tabaquista severo (25 paquetes / año) sin antecedentes médicos relevantes, consulta por dolor torácico, tos no productiva y registros subfebriles aislados. Presenta una masa en el lóbulo superior derecho en estudio por imagen, con aumento de la captación en el PET, asociado a adenopatías mediastínicas. Con diagnóstico inicial de cáncer de pulmón, se realizó lobectomía superior derecha. Debido a la ausencia de atipia celular y la presencia de infiltrados linfoplasmocitarios en la lesión, se realizó análisis inmunohistoquímico: se identificaron abundantes células plasmáticas positivas para IgG4, con una relación IgG4 / IgG del 74%. Se realizó el diagnóstico de pseudotumor inflamatorio por IgG4. **Discusión:** Tras una extensa revisión bibliográfica, sólo encontramos un caso similar, de una paciente con un pseudotumor pulmonar IgG4 sin enfermedad sistémica. Debido a la variabilidad de la presentación clínica de la enfermedad relacionada a IgG4, y su potencial afectación multiorgánica, es difícil encontrar una clasificación y criterios diagnósticos con alta sensibilidad y especificidad, sin embargo estos suelen ser útiles en la práctica clínica. **Conclusión:** Múltiples enfermedades inflamatorias son diagnóstico diferencial de tumor primario de pulmón. Si bien la incidencia es baja, el pseudotumor IgG4 debe considerarse como un diagnóstico diferencial cuando no hay evidencia de enfermedad neoplásica.

Palabras claves: granuloma de células plasmáticas; enfermedad relacionada con inmunoglobulina g4; neoplasias pulmonares.

La enfermedad relacionada a IgG4 es una entidad autoinmune infrecuente de compromiso multiorgánico con posible afectación pulmonar. Suele presentarse en el sexo masculino a edades avanzadas. Presentamos el caso de una paciente con una masa pulmonar en el lóbulo superior derecho, de características clínicas e imagenológicas similares a un tumor primario de pulmón. El diagnóstico definitivo se realizó con los hallazgos de la histopatología, en la cual se evidenciaron infiltrados linfoplasmocitarios con predominio de células plasmáticas IgG4 positivas.

Por esto consideramos que, en los casos de masa pulmonar sin evidencia de atipias celulares la enfermedad por IgG4 es un diagnóstico diferencial a tener en cuenta.

CONCEPTOS CLAVES:

Qué se sabe sobre el tema

La enfermedad relacionada con IgG4 fue descrita en los años '90 y se caracteriza por su compromiso multiorgánico y presentación clínica variable, por lo cual se establecieron múltiples criterios diagnósticos y clasificaciones. A nivel pulmonar se puede presentar como neumonía intersticial, adenopatías mediastinales y pulmonares o pseudotumor inflamatorio. El diagnóstico se confirma con el estudio histopatológico por la presencia de infiltrados de células plasmáticas y tiene buena respuesta al tratamiento con corticoides.

Qué aporta este trabajo

El caso presentado a continuación es de un paciente con un pseudotumor inflamatorio en el vértice pulmonar derecho sin compromiso sistémico que simula un tumor primario de pulmón. Si bien constituye una presentación clínica atípica, consideramos que se debe tener en cuenta al pseudotumor por IgG4 como diagnóstico diferencial de masa pulmonar, una vez descartada la causa neoplásica.

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Pseudotumor inflamatório IgG4 simulando câncer de pulmão: relato de caso

RESUMO

Introdução: A doença relacionada com IgG4 (IgG4-RTD) é uma doença infrequente com possível envolvimento de múltiplos órgãos. É característico encontrar nódulos inflamatórios com infiltração de células plasmáticas positivas para IgG4, fibrose estoriforme e flebite obliterativa. Apresentamos um paciente com pseudotumor inflamatório no lobo superior direito, simulando ser um tumor primário de pulmão. **Relato de caso:** Nosso paciente, fumador, faz mais de 48 anos (25 maços / ano) sem história médica relevante, referia dor no peito, tosse não produtiva e febre noturna esporádica. As imagens revelaram uma massa no lobo superior direito, com SUV aumentado no PET-scan e linfadenopatias mediastinais. Suspeitou-se de um tumor primário de pulmão e realizou-se lobectomia superior direita. Devido à ausência de atipia celular e à intensa atividade plasmocítica na lesão a peça foi estudada com análise imunoistoquímica: foram identificados plasmócitos IgG4 + abundantes, com relação IgG4 / IgG de 74%. Chegou-se ao diagnóstico de pseudotumor inflamatório por IgG4. **Discussão:** Após uma extensa revisão bibliográfica, encontramos apenas um registro semelhante relatado com um pseudotumor de pulmão IgG4 sem doença sistêmica. Devido ao amplo espectro de características clínicas do IgG4-RTD e ao potencial envolvimento de múltiplos órgãos, é difícil encontrar uma classificação e critérios diagnósticos com alta sensibilidade e especificidade; no entanto, eles podem ser úteis na prática clínica. **Conclusão:** Existem várias doenças inflamatórias benignas que podem mimetizar um tumor pulmonar primário. Embora a incidência seja baixa, o pseudotumor de IgG4 deve ser considerado como diagnóstico diferencial na ausência de malignidade.

Palavras-chave: doença relacionada a imunoglobulina g4; granuloma de células plasmáticas; neoplasias pulmonares.

INTRODUCTION

IgG4 related disease (IgG4-RTD) is an infrequent disease which most commonly affects elderly male patients, originally described in the 1990s. Several reports show evidence of multiple organ involvement, such as salivary glands, orbital structures, pancreas and kidneys, among others. It is characteristic to find inflammatory nodules with IgG4 positive plasma cell infiltration, storiform fibrosis and obliterative phlebitis[1]. In the year 2019 a new classification was proposed by the American College of Rheumatology and the European League Against Rheumatism[2].

Pulmonary IgG4 related disease has a wide spectrum, and may present itself as nonspecific interstitial pneumonia, inflammatory pseudotumor or lymphadenopathies[1]. We present a patient with an inflammatory pseudotumor in the right upper lobe, with no evidence of extrapulmonary involvement, clinically indistinguishable from a primary lung tumor.

CASE REPORT

We present a 48-year old heavy smoker (25 pack/year) with no relevant medical background. His chief complaint was a low intensity, constant chest pain, with non-productive cough and sporadic nightly fever.

Chest x-ray revealed a radiopaque mass in the right upper lobe without pleural effusion, pneumotorax or lung consolidation (figure 1). SARS-Cov2 infection was ruled out by polymerase-chain-reaction. CT-scan showed an irregular mass with spiculated edges of 47 x 50.5 mm and pleural retraction, along with pathological mediastinal lymph nodes (over 10 mm) (figure 2).

Tumor staging studies were performed: PET-scan showed increased uptake of the lung mass (SUV 10) and mediastinal and hilar lymph nodes with a slightly increased uptake (2.8 and 3.9 SUV respectively) (figure 3). There was no evidence of disseminated disease in the PET-Scan or brain-MRI. Given the patient's history and imagenological findings, locally advanced primary lung tumor was suspected. Esophageal ultrasound (EUS) was performed, with no evidence of esophageal infiltration.

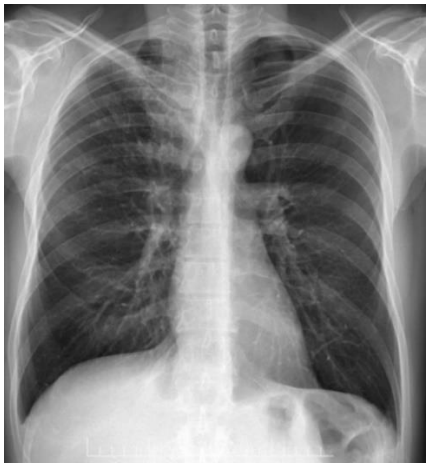

Figure N°1. Initial chest x-ray. X-ray showing an area of increased density in the upper right lobe, near the vertex, with no evidence of associated pleural effusion or pneumothorax.

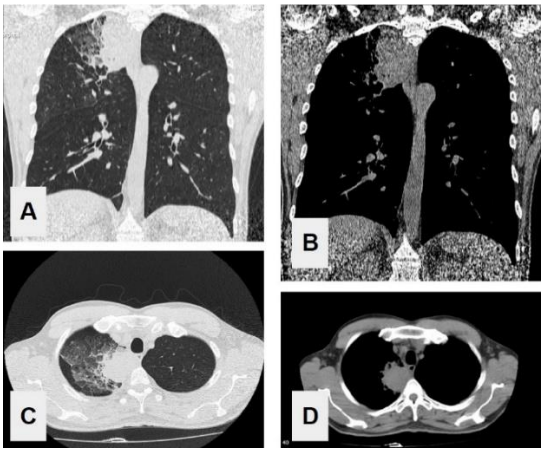

Figure N°2. Preoperative non-enhanced computed tomography showing mass of 47 x 50.5 mm in axial (C, D) and coronal (A, B) planes, which is in intimate contact with the esophagus.

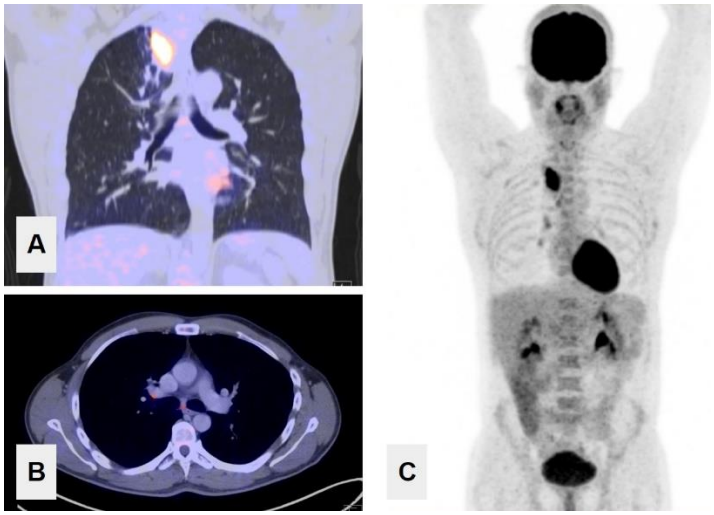

Figure N°3. Pet-scan showing increased SUV in already known mass in right upper lung vertex (SUV 10) (A, C) and mediastinal and right hilar subcentimeter lymph nodes (SUV 2.8 and 3.9) (B). No other organs with pathological findings were evidenced by this method.

Prior to oncological resection, lymph node biopsy of groups 2R, 4R, 4L and 7 (which had high uptake on PEt-scan) was performed by videomediastinoscopy. Pathology results were positive for antracosis, with no signs of cellular atypia. The case was discussed in a multidisciplinary committee and surgical resection was decided.

Video assisted thoracoscopic right upper lobectomy with lymphadenectomy was performed. The patient had no immediate complications, and spent 72 hours in the intensive care unit for routine monitoring. The patient was discharged on day six. 15 days later, postoperative control showed no late complications.

Histopathologic study revealed an inflammatory process with necrotic areas and lymphoplasmacytic infiltration. The entire lung mass was thoroughly analyzed in his whole extension (4,5 x 3,2 cm) and no cellular atypia were found. Anthracosis and reactive changes were found at the lymph nodes.

Due to the absence of atypical cells and the intense plasmacytic activity in the lesion, immunohistochemical analysis was performed: 294 IgG positive plasma cells per high-power-field (HPF) and 219 IgG4 plasma cells per high-power-field were identified, with a IgG4/IgG relation of 74%. Figure 4.

With these findings, diagnosis of IgG4-inflammatory pseudotumor was made. Serum IgG4 levels were measured, with a total of 244 mg/dL, superior to reference range.

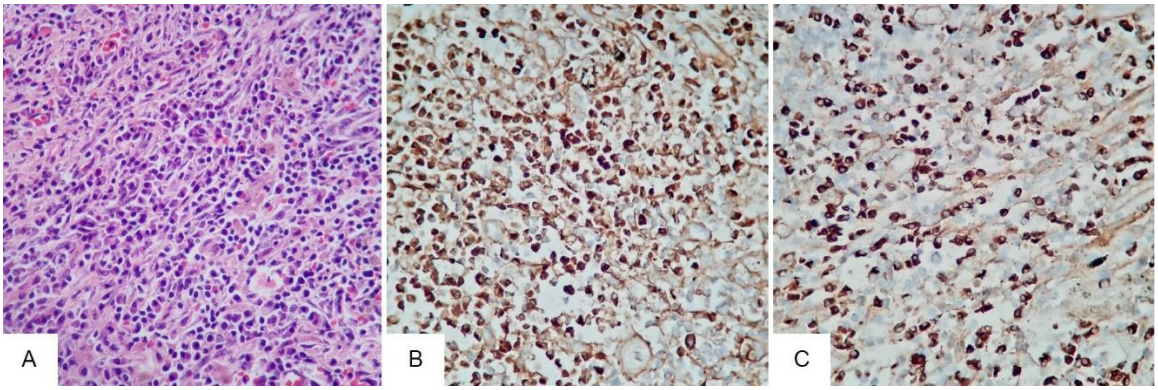

Figure N°4. Tissue samples of the lung mass. A: dense lymphoplasmacytic infiltration with eosinophils (Hematoxylin and eosin staining, original magnification x400). B: IgG positive plasma cells evidenced with immunostaining in a high power field (immunohistochemistry, original magnificaction x400). C: IgG4 positive plasma cells evidenced in a high power field (immunohistochemistry, original magnification x400).

DISCUSSION

IgG4 related disease with lung involvement is uncommon and is usually seen in cases of multiorganic affection[3]. After an extensive bibliographic review, we found but one similar case reported, of a japanese woman with an IgG4-lung pseudotumor without systemic disease[4].

In the year 2011 the comprehensive Criteria for IgG4 related disease were proposed[5]. These include: a) swelling or masses in single o multiple organs, b) elevated levels of serum IgG4 (>135mg/dL), c) lymphocytic and plasmacytic infiltration and fibrosis in histopathologic analysis or presence of IgG4 plasma cells. When criteria A. and C. are met, the diagnosis of IgG4 related disease is probable. If the IgG4 serum levels are elevated, the diagnosis is definite. Our patient fulfilled all of the criteria: a lung mass with marked lymphoplasmacytic infiltration and fibrosis, associated with high IgG/IgG4 proportion (74%) and IgG4-serum levels of 244 mg/dL.

The American College of Rheumatology and the European League Against Rheumatism developed a new classification for IgG4-RTD in the year 2019. These criteria were proposed by a multispecialty group of 86 physicians based on a cohort of 1879 patients and the existing literature. Our patient patient would not be classified as having IgG4-RTD following this classification because of meeting some of the exclusion criteria (fever and radiological findings suspicious of malignancy) and not presenting the inclusion criteria of lung involvement (e.g. peribronchovascular or septal

thickening evidenced in cross-sectional image study or paravertebral band-like soft tissue). However the diagnosis was confirmed by histopathological and immunohistochemical analysis.

Due to the broad spectrum of clinical features of IgG4-RTD, and the potential multiple organ involvement, it is hard to find a classification and diagnostic criteria with high sensitivity and specificity. Even though the classifications published in the literature can be useful in clinical practice, one must take into account that some cases do not necessarily fulfill the criteria to be considered as IgG4-RTD, like our patient.

There are several benign inflammatory diseases (e.g. sarcoidosis, Castlemann disease) which can mimic a primary lung tumor. Although incidence is low, IgG4-RTD presenting as a lung pseudotumor without other organ involvement is a differential diagnosis to be considered in the case no malignancy is found. When IgG4-RTD is diagnosed, corticosteroids are the first line treatment, showing improvement of radiological findings and symptoms.

Conclusion

IgG4 related disease is an infrequent and variable disease which can mimic a primary lung tumor. Even though incidence is low it is a differential diagnosis to be considered, once malignancy is ruled out. Several classifications and diagnostic criteria published in the last years are useful to identify this disease. However, not all of them suited our patient and IgG4-RTD was confirmed upon/with pathological findings.

Conflict of Interest Statement

El estudio se llevó a cabo en total acuerdo con la normativa nacional e internacional vigente: Declaración de Helsinki de la Asociación Médica Mundial y las Normas de Buenas Prácticas Clínicas ICH E6.

La participación en el estudio fue en todos los casos voluntaria y certificada por el proceso de consentimiento informado. Se respetó en todo momento el derecho a la no participación en el estudio sin que esto implique en ningún caso algún tipo de discriminación, trato diferencial o maltrato. En todo momento se observó la protección de la identidad y los datos del paciente acorde a la normativa legal vigente ley nacional de protección de datos personales 25.326 (Habeas Data), en concordancia con la normativa internacional sobre registro de enfermedades y protección de datos personales y privados, de acuerdo con 18th World Medical Assembly de Helsinki (1964) cuando aplique. La confidencialidad de los datos estuvo garantizada ya que los datos identificatorios de los pacientes fueron separados de los datos clínicos obtenidos en el estudio, utilizando número de ID y no el nombre de los pacientes en lo que respecta al armado de planillas y bases de datos. Las técnicas utilizadas fueron no invasivas, se efectuó en la práctica cotidiana y no conllevó riesgos para el paciente, por lo que no se requirió la contratación de un seguro.

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Ethical Considerations

Informed consent was obtained from all individual patients described in this paper.

This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Limitaciones de responsabilidad:

La responsabilidad del trabajo es exclusivamente de quienes colaboraron en la elaboración del mismo.

Conflicto de interés:

Ninguno.

Fuentes de apoyo:

La presente investigación no contó con fuentes de financiación

Originalidad:

Este artículo es original y no ha sido enviado para su publicación a otro medio de difusión científica en forma completa ni parcialmente.

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Contribución de los autores:

Quienes participaron en la elaboración de este artículo, han trabajado en la concepción del diseño, recolección de la información y elaboración del manuscrito, haciéndose públicamente responsables de su contenido y aprobando su versión final.