

Conflict of Interests

The authors declare that they have no conflict of interests directly or indirectly related with the contents of this manuscript.

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Immunoglobulin G4-Related Lung Disease as an Incidental Finding After Surgical Resection of Lung Cancer[☆]



Enfermedad pulmonar relacionada con inmunoglobulina G4 como hallazgo incidental tras resección quirúrgica de carcinoma pulmonar

To the Editor,

Immunoglobulin G4-related disease (IgG4-RD) is a recently recognized systemic autoimmune process that brings together a series of diseases that share certain pathological, serological, and clinical characteristics.¹ Although it most often affects the pancreas, salivary glands and lymph nodes, almost any structure of the body can be involved. Isolated pulmonary involvement is rare,² yet the greatest range of clinical and radiological presentations occurs in the lung. IgG4-related lung disease can manifest in the form of bronchovascular thickening, pleural thickening, interstitial involvement, solitary pulmonary nodule, or ground glass opacities that sometimes mimic lung cancer, so differential diagnosis is required.¹ However, the coexistence of pulmonary

IgG4-RD and lung cancer in the same lesion has only rarely been described.^{3–5}

We report the case of a patient diagnosed with lung cancer and mediastinal lymph node involvement who was treated with surgical resection; the pathology study of the lesion also revealed pulmonary IgG4-RD.

This was 70-year-old woman, former smoker of 50 pack-years, with a clinical history of discoid lupus and atrial fibrillation, who was referred to our department due to an incidental finding of a lung mass on chest X-ray. The patient did not report any respiratory symptoms. Computed tomography (CT) showed a mass with spiculated borders, measuring 6 cm, contiguous with the parietal pleura, in addition to hilar and mediastinal lymphadenopathies measuring 10 mm (Fig. 1A). Positron emission tomography showed an increased accumulation of fluorodeoxyglucose-F18 in the mass with a SUVmax of 9.2 (Fig. 1B), in addition to hypermetabolic lymphadenopathies in the right upper (SUVmax 4) and lower (SUVmax 6.7) paratracheal, subcarinal (SUVmax 5.4) and right pulmonary hilar (SUVmax 4.4) regions. Endobronchial ultrasound biopsy was obtained from the ipso and contralateral hilar and mediastinal lymphadenopathies: the subcarinal mass was positive for metastatic adenocarcinoma (TTF1+). Magnetic resonance imaging ruled out the presence of brain metastasis. Spirometry revealed forced vital capacity 111%, forced expiratory volume in 1 s 87%, and diffusing capacity of carbon monoxide 66%. Stair climb test was >22 m. After discussion in the multidisciplinary meeting, it was considered a case of locally advanced lung adenocarcinoma with N2 single station involvement, confirmed histologically

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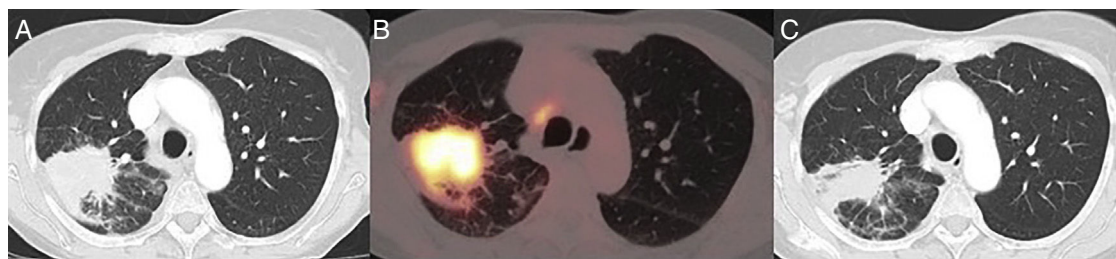


Fig. 1. (A) CT image on diagnosis, showing a 6 cm spiculated lesion in the right upper lobe. (B) Positron emission tomography-CT showing an increased accumulation of fluorodeoxyglucose-F18 in the mass with a SUVmax of 9.2. (C) CT image of the re-evaluation CT showing a decreased lesion size after anti-inflammatory therapy.

and potentially resectable (cT3N2M0, stage IIIB), so trimodality treatment was planned with surgical resection and lymphadenectomy, followed by chemotherapy and radiotherapy.⁶ However, during the week prior to surgery, the patient developed pericarditis and pericardial effusion that forced us to postpone the intervention. The pericardial effusion was drained percutaneously and pericarditis treated with colchicine and nonsteroidal anti-inflammatory drugs. Following resolution of this syndrome, a new CT for re-evaluation was performed that showed a significant decrease in the size of the lesion, which now measured 36 mm (Fig. 1C). The patient finally underwent surgery, with right upper lobectomy plus systematic lymphadenectomy via video-assisted thoracoscopy. The pathology report was consistent with adenocarcinoma with a lepidic, acinar and papillary growth pattern, measuring 8 mm in diameter, and adenocarcinoma metastases in the subcarinal lymph node (pT1aN2M0, Stage IIIA). The tumor-free lung showed extensive inflammatory lymphoplasmocytic infiltrate with formation of germinal centers, storiform fibrosis, obliterative phlebitis, pulmonary parenchymal atrophy, and alveolar trapping with a marked pneumocytic reaction. The immunohistochemical study showed IgG4-positive cells in more than 10 plasma cells per field. These findings were conclusive for the diagnosis of pulmonary IgG4-RD. The postoperative course of the patient was satisfactory and she was discharged on postoperative day 5 without complications.

IgG4-RD has been recently defined as a single autoimmune disease that unites multiple fibroinflammatory diseases previously considered independent entities. It has been described as the new great mimicker, since it imitates the behavior of tumors, inflammatory diseases, and infectious diseases, making it difficult to diagnose and to treat correctly, leading to disease progression.⁷ The gold standard for diagnosis, apart from manifestations in the affected organ, is the identification of typical histopathological features (lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis) in the context of a significant infiltration of IgG4-positive plasma cells.¹ It is associated in 60%–80% of patients with raised IgG4 levels in serum.⁸

Some studies suggest that patients with IgG4-RD have an increased risk of developing tumors, including cancer of the lung, pancreas, and colon, and lymphomas.⁹ However, the coexistence of lung cancer and pulmonary IgG4-RD in a lung mass is extremely rare. In contrast, several cases of IgG4-RD lesions simulating lung tumors have been published.^{10–13}

In the 3 cases published in the literature,^{3–5} and in our case, the pattern on pathology study was adenocarcinoma.

It is of interest to note that on the diagnostic tests, despite the fact that the tumor component of the mass was only 8 mm, the metabolic measurement of the lesion was 5.2 cm, suggesting that pulmonary IgG4-RD is associated with an increase in glu-

cose metabolism.^{10–13} The measurement of early- and late-phase FDG uptake can be useful for differentiating benign and malignant lung lesions. Decreased late-phase uptake of radiomarker has been described in inflammatory processes.¹⁴

Most recommendations advocate early treatment of IgG4-RD with immunosuppressive therapy. However, spontaneous resolution of lung disease has also been reported.¹⁵ In the case described above, the pulmonary lesion initially measured 60 mm, but its size reduced considerably following anti-inflammatory therapy.

We believe that, although lung cancer must be included in the differential diagnosis of pulmonary IgG4-RD, the possibility that both diseases coexist must be considered, so we propose a comprehensive evaluation of patients with suspected IgG4-RD that includes histological confirmation.

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Surgical Resection of Endobronchial Glandular Papilloma[☆]



Resección quirúrgica de papilomatosis glandular endobronquial

To the Editor,

Papillomas of the respiratory tract are rare epithelial neoplasms. They occur most commonly in children and young adults in the form of multiple lesions located in the upper airway, usually the larynx, sometimes extending to the lower respiratory tract. This type of papillomatosis usually consists of squamous papillomas and is associated with human papilloma virus (HPV) infection.¹ Isolated endobronchial papillomatosis, especially the glandular variant, is rare.² We report the case of an adult patient with glandular endobronchial papillomatosis, limited to the lower respiratory tract, resected by lower right lobectomy via video-assisted thoracoscopy.

This was a 53-year-old woman, never-smoker with a history of invasive ductal carcinoma of the breast, operated 10 years previously with quadrantectomy and treated with chemotherapy and radiation therapy. The patient was initially examined for a respiratory infection with productive cough associated with wheezing, dyspnea on exertion, and oppressive chest pain. Chest computed tomography (CT) revealed a polylobulated pulmonary nodule in the right parahilar lower lobe measuring 2.1 cm, that showed weak to moderate metabolic activity on positron emission tomography (PET-CT) (SUVmax: 2.68) (Fig. 1). Clinical laboratory results and lung function tests were normal. Bronchoscopy showed a pinkish exophytic vascularized mass of soft consistency with necrotic areas that occluded practically the entire basal lobe bronchus, and appeared to originate from an accessory bronchus in the posterior wall.

An incisional biopsy was not diagnostic, with a report of predominantly plasmocytic inflammatory infiltrate. The case was presented to the multidisciplinary committee, and in view of the lack of diagnosis and the impossibility of performing a complete resection by endoscopy, we decided on surgical treatment. In view of the location of the lesion, right lower lobectomy was performed by videothoracoscopy. The postoperative course was favorable and the patient was discharged after 4 days.

The final diagnosis was endobronchial papillomatosis, with three glandular papillary lesions, the largest measuring 2.5 × 1.6 cm, along with two millimetric lesions, one of which occurred in continuity with the larger one. The lesions extended from the lobar bronchus to the bronchioles. Histological changes

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consisted of papillomatous proliferations with a respiratory-type epithelial lining, mucosecretory cell hyperplasia, squamous metaplasia, and cuboidal cells. Of note in the stroma was the presence of a lymphoplasmocytic infiltrate, and foamy histiocytes. No cell atypia was detected, and mitosis was scant.

The patient has continued to attend periodic check-ups with follow-up CT and bronchoscopy, and has shown no signs of recurrence after 18 months.

Respiratory tract papillomas consist of rare epithelial neoplasms that may be classified according to the number of lesions, location, and histology.² The lesions may present in multiple forms, and generally appear in the upper respiratory tract, although they may affect any point of the airway, extending to the lower respiratory tract in up to 30% of cases.³ They tend to recur, hence the name “recurrent respiratory papillomatosis”.⁴ This is the most common form in children and young people, although an adult form with similar characteristics has been described.⁵ It is caused by HPV, mainly serotypes HPV-6 and HPV-11. Treatment is based on the resection of lesions usually with laser, combined with antiviral drugs.⁶

The isolated form is less frequent, although the actual incidence is unknown. This is the most common form of presentation in adults, occurring usually in the fifth or sixth decade of life with a greater incidence in men.⁷ It usually presents as a polypoid nodule in the trachea, or the lobar or segmental bronchus. We can differentiate between central or peripheral papillomas, depending on site, and this will also affect the form of clinical presentation. The most common symptom of endobronchial papillomas is cough, which may lead to atelectasis and postobstructive infections. Other possible symptoms are fever, hemoptysis, and dyspnea. Peripheral papillomas are usually asymptomatic and discovered incidentally.²

Three histological forms have been described: squamous, glandular, and mixed. The squamous variant is the most common, and is believed to be caused by HPV.⁸ This type has been associated with a potential risk of malignant transformation, which ranges between 8% and 40%, depending on the series.⁹ This risk increases with exposure to tobacco¹⁰; moreover, the serotypes HPV-16 and HPV-18 are associated with a higher risk of malignant transformation.^{11,12}

The glandular variant is less common. In the largest series published in the literature, Tryfon et al.¹¹ described 32 cases of lower airway papillomas, of which only 6 were glandular. This article also includes a review of published cases, and of a total of 69 cases, only 14 were glandular. It is generally thought to affect older patients, is unassociated with smoking, and usually occurs in a peripheral location. Malignant transformation of glandular papilloma has not been described.¹³

As for differential diagnosis on pathology examination, it can be sometimes difficult to distinguish between the secondary changes