Pulmonary pseudotumor in granulomatosis with polyangiitis (GPA). Pulmonary cancer and/or GPA? Diagnostic implications of pulmonary nodules

Gabriel Horta-Baas1*, Esteban Meza-Zempoaltecatl2, Mario Pérez-Cristóbal2 and Barile-Fabris Leonor Adriana2
1Rheumatology Department, Hospital General Regional 220, IMSS, Toluca; 2Rheumatology Department, Hospital de Especialidades, Centro Médico Nacional Siglo XXI, IMSS, Mexico City, Mexico

Abstract
Granulomatosis with polyangiitis (GPA), formerly known as Wegener’s granulomatosis, is a systemic necrotizing vasculitis, which affects small and medium sized blood vessels and is often associated with cytoplasmic anti-neutrophil cytoplasmic antibodies (ANCA). Inflammatory pseudotumor is a rare condition characterized by the appearance of a mass lesion that mimics a malignant tumor both clinically and on imaging studies, but that is thought to have an inflammatory/reactive pathogenesis. We report a patient with a GPA which was originally diagnosed as malignancy. (Gac Med Mex. 2016;152:468-74)

Corresponding author: Gabriel Horta-Baas, gabho@hotmail.com

KEY WORDS: Granulomatosis with polyangiitis. Pseudotumor. Malignancy.

Introduction
According to the 2012 revised Chapel Hill classification, granulomatosis with polyangiitis (GPA), previously known as Wegener’s granulomatosis (WG), is an autoimmune systemic disease of unknown etiology, characterized by necrotizing granulomatous inflammation of the respiratory tract and vasculitis affecting medium-sized and small vessels1. Clinical manifestations can be very heterogeneous, but it characteristically affects the upper and lower respiratory tract and the kidneys. Pulmonary involvement is one of GPA’s main features, it is the initial manifestation in 45% of patients, and up to 87% develop it in the course of the disease. There is an atypical manifestation of GPA, where initial clinical data, imaging studies and histopathology report are suggestive but not diagnostic of lung cancer.
scleritis, right eye visual acuity of 20/30 and right eye 20/60, nasal septum perforation, one lingual ulceration and another on the first premolar vestibular wall, bilateral hearing loss, paresthesias on the feet and cutaneous vasculitis on the legs were documented. The visual field test reported temporal hemianopia. His laboratory tests showed globular sedimentation rate and C-reactive protein elevation, proteinuria in the urinalysis, reduced creatinine clearance, positive cytoplasmic-pattern anti-neutrophil cytoplasmic antibodies (c-ANCA) and positive anti-proteinase 3 antibodies (74.7 mU/ml; negative < 5 mU/ml).

Mononeuropathy of the peroneal nerve was documented by neurophysiological study. Skin biopsy histopathology report confirmed leukocytoclastic vasculitis; sural nerve biopsy reported minimal isolated demyelination foci, blood vessels without significant microscopic changes and very scarce perineural lymphocytes.

GPA diagnosis was concluded, with 26 points on the Birmingham Vasculitis Activity Score (BVAS). The patient was treated with intravenous methylprednisolone 1 g every 24 h for 3 consecutive days, followed by prednisone 1 mg/kg/day. Induction scheme with intravenous cyclophosphamide was started according to the British Society for Rheumatology guidelines\(^2\).

A large parahilar mass was appreciated on chest X-ray (Fig. 1); computed tomography (CT) showed a solid tumor of 12 cm in diameter with ill defined margins on the right lung, with mediastinal adenopathies and bilateral pulmonary nodules with malignant characteristics (Fig. 2). A pleural biopsy was obtained, with histopathology report of poorly-differentiated malignant neoplasm.

In December 2010, due to the suspicion of lung cancer, the patient was assessed by the medical oncologist, with the diagnosis of Unknown Primary Cancer, with poor-prognosis factors, ECOG 2, and a survival expectancy of 6 to 7 months being concluded. A new biopsy was practiced, with no signs of malignancy being found.

With the cyclophosphamide induction scheme, remission of systemic activity and reduction of the size of the lesion was achieved (Figs. 3 A and B), and the patient continued with prednisone 20 mg/day and azathioprine 2 mg/kg/day. At follow-up, 4 years after hospitalization, activity remission and pulmonary lesions resolution was achieved (Figs. 3 C and D), with the patient remaining on maintenance treatment with azathioprine 75 mg/day and prednisone 5 mg/day.
Figure 2. Pulmonary high-resolution CT. Ovoid-shaped (*), well-defined lesion with lobulated borders, located at the medial segment of right lung middle lobe, of heterogeneous density, with 120 x 82 mm diameter and attenuation values between 60 and 28 UH, same side pleural recess fluid occupation. At the level of the left pulmonary parenchyma, multiple hyperdense (arrowheads), amorphous images with spiculated borders, calciﬁc density, are identiﬁed, the largest of 10 x 11 mm and the smallest of 5.5 mm in diameter; at lower lobe, stellate-appearing lesion, with pleural tail of 1.65 x 1.65 mm in diameter and attenuation values of 48 UH. Ovoid, hypodense right paratracheal lesions are identiﬁed with 19 x 10 mm and 17 x 10 mm dimensions in relation to adenopathies.

Discussion

Primary vasculitis are complex pathologies, with varied clinical manifestations that can be common to those occurring in multiple conditions. Pulmonary manifestations are one of the main ﬁndings in GPA, with the most common symptoms being cough, hemoptisis and pleuritis. Vasculitis that produce pulmonary granulomatous disease are characterized by the presence of ANCA-type antibodies, and produce a granulomatous inﬂammation of the respiratory tract with necrotizing vasculitis and renal involvement with hematuria and proteinuria. In most cases, antibodies are directed against cytoplasmic proteinase 3. In the pathogenesis of this type of pulmonary condition, an inﬂammatory cell-response has been implicated, which leads to the generation of granulomas formed by an inﬂammatory infiltrate composed of neutrophils, lymphocytes, plasma cells, histiocytes and eosinophils.

Radiological manifestations of lung involvement in GPA are varied, both at initial presentation and in the course of the disease, not offering data that can be considered speciﬁc, although within the clinical context they are highly useful. Most common ﬁndings are pulmonary inﬁltrates and nodules. Nodules in most patients are often multiple, with well-deﬁned margins, occurring with no zonal predilection, and normally add-up to less than 20; with variable diameter, they usually measure between 2 and 4 cm, but they can measure from a few mm to 10 cm and in 50% they are accompanied by cavitation. In up to 25% of cases, nodules can be isolated. Hilar and mediastinal adenopathies are rare manifestations. Since pulmonary nodules are the main radiological manifestation at the pulmonary
level, the initial study is often made with more prevalent diagnoses such as: infectious processes by micobacteria and fungi, malignant tumors or metastases of solid neoplasms\textsuperscript{4-6}. Very large sized nodules are infrequent, and can be easily mistaken for primary or metastatic malignant tumors, especially when accompanied by adenopathies, and differential diagnosis with neoplastic processes is essential.

In our case, the initial X-ray showed a large unilateral nodular lesion, and CT documented a very large pulmonary nodule with lesions consistent with metastases, which are unusual findings in GPA and, therefore, there was no diagnostic difficulty in view of the possibility of a malignant disease. From the radiological point of view, benign nodules are considered to normally have well-defined margins and smooth contour, whereas malignant nodules have poorly-defined or spiculated margins and irregular or lobular contour\textsuperscript{7}, as in our case. However, there is considerable overlapping between benign and malignant nodules with regard to borders and contour. The spiculated image with adjacent bronchovascular bundles distortion is highly suggestive of malignant tumors, with a predictive value of 90%; however, nodules due to infection or inflammation may also show this appearance\textsuperscript{7}.

Inflammatory pseudotumor association is described in a wide spectrum of rheumatologic and autoimmune diseases, including GPA (Table 1). Blennerhassett et al.\textsuperscript{8} reported 4 cases with limited WG variety where pulmonary resection was performed due to suspected cancer. In the thoracotomy procedure, extensive fibrosis and the relatively poorly defined margins of the lesion also suggested an infiltrating neoplasm\textsuperscript{8}. Fouad-Rabahi et al.\textsuperscript{9} reported the case of a pseudotumor in WG in a 61-year old male smoker who had respiratory symptoms and chest X-ray showed a nodular opacity at the right hemithorax lower third, chest CT-scan revealed a 4.2 cm x 3.1 cm lesion, contiguous to the parietal pleura and positive c-ANCA.
Table 1. Characteristics of patients with pulmonary pseudotumor due to granulomatosis with polyangiitis

<table>
<thead>
<tr>
<th>Age (years)/ Gender/ Reference</th>
<th>Findings on imaging studies</th>
<th>Findings on histopathological study</th>
<th>Clinical manifestations</th>
<th>Treatment employed</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>50/Female³</td>
<td>Basal bilateral radiographic opacities. On TC, 1 more solid opacity at pulmonary base, 3 small rounded intrapulmonary lesions. No evidence of calcification or cavitation.</td>
<td>Sputum cytology showed atypical cells, but no neoplastic cells. Necrosis and extensive infiltration by lymphocytes and plasma cells, large numbers of multinucleated giant cells and giant cell-granulomatous vasculitis were found in pulmonary tissue.</td>
<td>Cough and chest pain.</td>
<td>Anti-TB drugs Lobectomy</td>
<td>Not reported</td>
</tr>
<tr>
<td>64/Male³</td>
<td>Opacity at upper left lobe apical segment.</td>
<td>Atypical cells reported on sputum cytology. No malignant cells were observed on bronchial aspirate. Same findings of previous case. Giant cells were found in lymph nodes, but without vasculitis.</td>
<td>Productive cough, weight loss, anorexia. Pneumonectomy</td>
<td>Symptom resolution</td>
<td></td>
</tr>
<tr>
<td>68/Female³</td>
<td>Left upper lobe poorly defined opacity</td>
<td>Granulomatous vasculitis without extended necrosis. Perivascular and peribronchial infiltration with lymphocytes and plasma cells.</td>
<td>Weight loss Lobectomy</td>
<td>At 6 months, symptomatic relapse treated with prednisone and cyclophosphamide with improvement.</td>
<td></td>
</tr>
<tr>
<td>64/Male³</td>
<td>CT showed solid lesion at the right lung lower portion axillary segment, and the rest of the lobe with honeycomb appearance due to cavities. Hilary lymphadenopathy</td>
<td>Mucosal biopsies showed normal bronchial mucosa. Loss of lung architecture due to a granulomatous process where many multinucleated cells were observed. Small areas of necrosis were observed. Presence of pulmonary vasculitis characterized by chronic inflammatory cells, predominantly lymphocytes.</td>
<td>Weakness, weight loss, chest pain. Pneumonectomy</td>
<td>Symptom resolution.</td>
<td></td>
</tr>
<tr>
<td>71/Female¹⁵</td>
<td>Multiple pulmonary nodules, absence of lymphadenopathy</td>
<td>Sputum cytology showed a three-dimensional cluster of cells with intra-cytoplasmic vacuoles, increased nucleus-to-cytoplasm, and prominent nucleoli, suggestive of adenocarcinoma.</td>
<td>Productive cough, hemoptisis, general malaise, anorexia and weight loss. Prednisone Cyclophosphamide</td>
<td>Pulmonary lesions resolution.</td>
<td></td>
</tr>
<tr>
<td>70/Female¹¹</td>
<td>CT showed 3 pulmonary nodules with irregular margins.</td>
<td>Lung biopsy: presence of foamy histiocytes, epithelioid cells, and some groups of cells with higher nucleus/plasma ratio. Prominent nucleoli were identified, which were suggestive of adenocarcinoma diagnosis, were identified.</td>
<td>Productive cough, chest pain, saddle nose. Prednisolone Cyclophosphamide</td>
<td>Good treatment response.</td>
<td></td>
</tr>
</tbody>
</table>

continue
As in our case, there are 3 reported cases where GPA was initially considered to be a metastatic lung adenocarcinoma\textsuperscript{10,11}. In the described cases, localized symptoms were found at the pulmonary level with imaging studies suggestive of malignant pulmonary lesions and, therefore, WG diagnosis was not considered.

Campainha et al.\textsuperscript{6} describe the case of a 45-year old male smoker initially diagnosed with stage IV non-small cell lung cancer, owing to the fine needle aspiration cytology result. The patient underwent chemotherapy cycles with carboplatin and gemcitabine and achieved a complete remission after 3 cycles, which led to diagnostic reassessment; c-ANCA and anti-proteinase were determined to be positive, with WG limited variety diagnosis being concluded. Diagnostic confusion was attributed to the fact that the patient had only pulmonary involvement and the lesions were suggestive of metastatic disease and ANCA values were not initially determined\textsuperscript{6}.

ANCA have shown to be highly useful, they constitute a sensitive and specific biomarker and they test positive in between 40 and 95\% of GPA patients. However, they are not pathognomonic and can appear in other conditions, including different forms of cancer; in these patients, most cases occur with an atypical ANCA pattern, not associated with any specific antigen (proteinase 3 or myeloperoxidase)\textsuperscript{12}. Small et al.\textsuperscript{13} reported the case of a primary T cell lung lymphoma, which was initially diagnosed as WG owing to a right parahilar mass, positive c-ANCA and bronchial mucosa biopsy with lymphoid lymphocytic infiltrate and perivascular mononuclear cells with necrosis areas suggestive, but not diagnostic of WG.

Table 1. Characteristics of patients with pulmonary pseudotumor due to granulomatosis with polyangiitis (continued)

<table>
<thead>
<tr>
<th>Age (years)/Gender/Reference</th>
<th>Findings on imaging studies</th>
<th>Findings on histopathological study</th>
<th>Clinical manifestations</th>
<th>Treatment employed</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>52/Male\textsuperscript{11}</td>
<td>X-ray showed apical and left upper lobe irregular lesions. Absence of hilar lymphadenopathy.</td>
<td>Sputum cytology showed atypical cells, suspicious of bronchogenic carcinoma.</td>
<td>Cough, chest pain, weight loss, nocturnal diaphoresis, nasal mucosa ulcerations, cutaneous vasculitis and glomerulonephritis.</td>
<td>Prednisolone Cyclophosphamide</td>
<td>Pulmonary lesions resolution.</td>
</tr>
<tr>
<td>52/Male\textsuperscript{10}</td>
<td>X-ray with parahilar infiltrates, right pleural effusion. CT revealed bilateral pulmonary nodules, the largest with central cavitation</td>
<td>Renal biopsy showed fibrous crescents, diffuse glomerulosclerosis and extended interstitial fibrosis.</td>
<td>Dry cough, dyspnea, fever and glomerulonephritis.</td>
<td>Prednisone Cyclophosphamide</td>
<td>At 6 months, cavitated lesion resolution. Persistence of some small pulmonary nodules.</td>
</tr>
<tr>
<td>45/Male\textsuperscript{6}</td>
<td>Multiple nodules and masses on both lungs, with some of them displaying cavitation.</td>
<td>Fine needle aspiration biopsy with cellular detritus, consistent with tumor necrosis. Bronchial biopsies demonstrated extended necrosis and vasculitis, with no features of neoplastic nature.</td>
<td>Dry cough, dyspnea, anorexia, weight loss, oral ulcerations and cutaneous vasculitis.</td>
<td>Methylprednisolone Cyclophosphamide</td>
<td>Had a period of improvement. Subsequently, died of pneumonia complicated by acute renal failure.</td>
</tr>
<tr>
<td>61/Male\textsuperscript{9}</td>
<td>X-ray showed a nodular opacity at the right hemithorax lower third. CT revealed right hemithorax extended lesion, contiguous to the parietal pleura.</td>
<td>Aspiration biopsy: areas of fibrosis and areas of extensive necrosis associated with an inflammatory process.</td>
<td>Cough, dyspnea, fever, labyrinthitis, hypoaacusis.</td>
<td>Not reported</td>
<td>Pulmonary lesions resolution.</td>
</tr>
</tbody>
</table>
Sputum and fine needle aspiration cytology results can be problematic and mix up pathologists, since they can be misdiagnosed as cancer. On histopathology analyses, acute inflammation, necrotic detritus, multinucleated giant cells, reactive epithelial cells and histiocytes, and atypical bronchial cells, often present in GPA, can be misinterpreted as adenocarcinoma or even as squamous cell cancer. Although multinucleated giant cells and epithelioid histiocytes are considered relatively more specific in the cytology analysis, acute inflammation and necrosis are the most common histopathological findings in GPA. Two cases of WG with initial diagnosis of adenocarcinoma based on sputum cytology results have been described, as well two cases based on fine needle aspiration biopsy cytology results. In the described cases, cytological characteristics were suggestive, but not diagnostic, of adenocarcinoma. WG histological diagnosis requires for necrotizing vasculitis with predominant involvement of medium caliber arteries, and necrotizing granulomatous inflammation with geographic necrosis to be identified.

On the other hand, adding to diagnostic complexity, there are cases reported with an initial diagnosis of GPA that concluded in lung cancer and cases with presence of GPA and lung adenocarcinoma. Rimoldi et al. reported the case of a 69-year-old woman presenting with fatigue, anorexia, weight loss, arthralgias, peripheral neuropathy, acute renal failure, acute phase reactants elevation, positive perinuclear-pattern ANCA and positive anti-myeloperoxidase antibodies, chest and abdomen X-ray without abnormalities; with a diagnosis of ANCA-associated vasculitis, the patient received treatment with plasmapheresis and died at 14 days owing to hemorrhagic complications. In the autopsy examination, lung adenocarcinoma was demonstrated with no data of vasculitis.

Based on the above, the GPA relationship with cancer can be classified in 3 groups: Malignant tumors mimicking vasculitis; vasculitis mimicking malignant tumors and coexistence of a malignant tumor with vasculitis. GPA can be a difficult-to-diagnose condition, since sometimes it can mimic other pathologies’ symptoms, as well as overlapping them. Including it in the differential diagnosis is essential in order to establish an adequate treatment as soon as possible. Clinical suspicion is the most important element for diagnosis, and it requires adequate interpretation of clinical, imaging, laboratory and histopathological findings.

**Conclusion**

GPA diagnosis is not always easy for clinicians and pathologists, and can be mistaken with neoplastic processes. ANCA are useful biomarkers as diagnostic complementation that can support the diagnosis if a high pre-test probability is met, particularly in cases with atypical presentations. ANCA determination is recommended in patients with multiple pulmonary lesions, even in the absence of other clinical signs and symptoms of GPA, in order to employ the appropriate treatment and avoid complications.

**References**