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Case Report

Onset of granulomatosis with polyangiitis obscured by heart disease in an elderly man

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ABSTRACT

We describe a case of 85-year-old man who presented to the Emergency Department with sudden dyspnea. He had a past medical history of cardiomyopathy and radiography and nonenhanced computed tomography (CT) of the chest showed pulmonary edema. Despite intravenous diuretic therapy, there was no clinical improvement. Cardiac CT was then performed showing a solid pulmonary nodular lesion with intralesional cavitations, ground-glass opacities, and peripheral vascularization. CT-guided needle lung biopsy yielded a diagnosis of granulomatosis with polyangiitis (Wegener granulomatosis). Medical treatment with cyclophosphamide and prednisone produced rapid symptomatic improvement and complete resolution of the radiological findings. This case demonstrates the challenges in making this diagnosis in an elderly patient with heart disease. We found very few documented cases where there was onset of granulomatosis with polyangiitis at this age.

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Background

Granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis, is a systemic inflammatory chronic disease characterized by necrotizing vasculitis of small arteries and veins. Its main manifestation is the necrotizing granulomatous inflammation of the respiratory tract.

It is a rare disease with an incidence of 2 cases per 12 million and a prevalence of 1/42,000–1/6200 people [1].

There is no sex predilection—males and females are equally involved. The typical age of onset is between 40 and 60 years and the average age of 45 years [1,2], is rare in children (3.3%–7%) [3] and elderly and it's most frequently reported in men of 45–65 years of age [4].

The respiratory system, the kidneys (necrotizing extracapillary glomerulonephritis), the ear, the nose, and the throat

Abbreviations: ANCA, antineutrophil cytoplasmatic antibodies; ESR, erythrocyte sedimentation rate; CT, Computed Tomography.

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Fig. 1 – Chest radiography with one projection AP in sitting position which showed diffuse inhomogeneous opacity.

(chronic nasal obstruction, deafness, and nasal bone defects) are most commonly affected. Typical clinical manifestation includes lungs involvement with necrotizing granulomas and hemorrhagic alveolitis [5].

The diagnosis is difficult, and it is suggested from the clinical manifestations and from the detection of antineutrophil cytoplasmic antibodies (ANCA). C-ANCA, in particular antiproteinase 3 (anti-PR3), is more common than P-ANCA [6]. ANCA are autoantibodies directed against antigens present in the cytoplasmic granules of neutrophils and monocytes. ANCA indirect immunofluorescence (IIF) patterns include cytoplasmic granular fluorescence with central interlobular accentuation (the classical “C-ANCA”), flat homogeneous cytoplasmic fluorescence (“C-ANCA (atypical)”), perinuclear fluorescence with nuclear extension (“P-ANCA”), perinuclear fluorescence without nuclear extension (usually described as ‘P-ANCA’12 but sometimes called “P-ANCA (atypical)” or even atypical ANCA) and other less usual patterns, including the combination of cytoplasmic and perinuclear staining (“atypical”) [7]. ANCA are typically found in GPA, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg- Strauss syndrome [8], which are all forms of small-vessel vasculitis. In ANCA-associated vasculitis, ANCA specifically bind to 2 proteins that are normally found in the neutrophil cytoplasm PR3 and myeloperoxidase (MPO). Patients with ANCA-associated vasculitis usually have autoantibodies against PR3 (PR3-ANCA) or MPO (MPO-ANCA) but not both. In GPA, 95% of patients are ANCA positive at diagnosis, and GPA is most commonly associated with PR3-ANCA (~65% patients). In microscopic polyangiitis 90% of patients are ANCA positive at diagnosis, typically with MPO-ANCA (~55% patients) [9]. However, in EGPA, only 40% of patients are ANCA positive at diagnosis, usually MPO-ANCA [10]. In GPA, biopsy of lung, kidney, or nose can be performed.

The best treatment approach includes cyclophosphamide and corticosteroid for induction of remission and

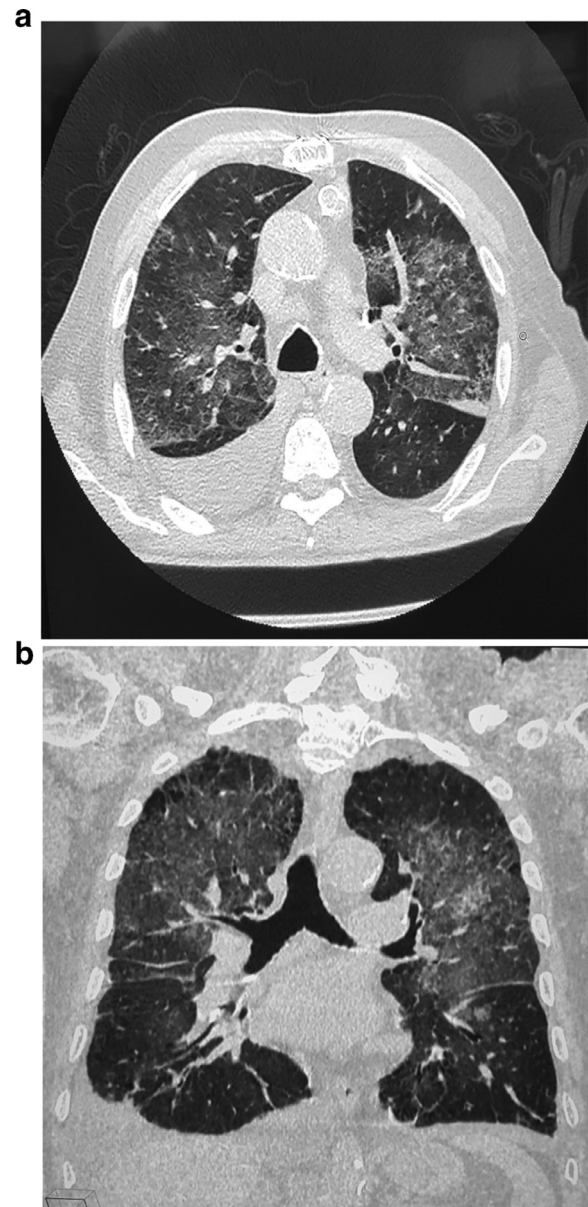


Fig. 2 – CT without contrast agent lung filter (a) axial, (b) coronal: showing a diffuse density alteration, clearest/most striking in the upper lobe and bilateral pleural effusion, more evident on the right lung.

immunosuppressive agents for its maintenance (azathioprine, methotrexate) [11,12].

Case presentation

We describe a case of 85 year-old man was admitted to the Emergency Depart because of sudden dyspnea. We performed a chest radiography which showed diffuse radiopacity (Fig. 1). Since the patient had a cardiomyopathy history, a pulmonary subedema was suspected but, despite of intravenous diuretic therapy, there was no clinical improvement. Moreover, the

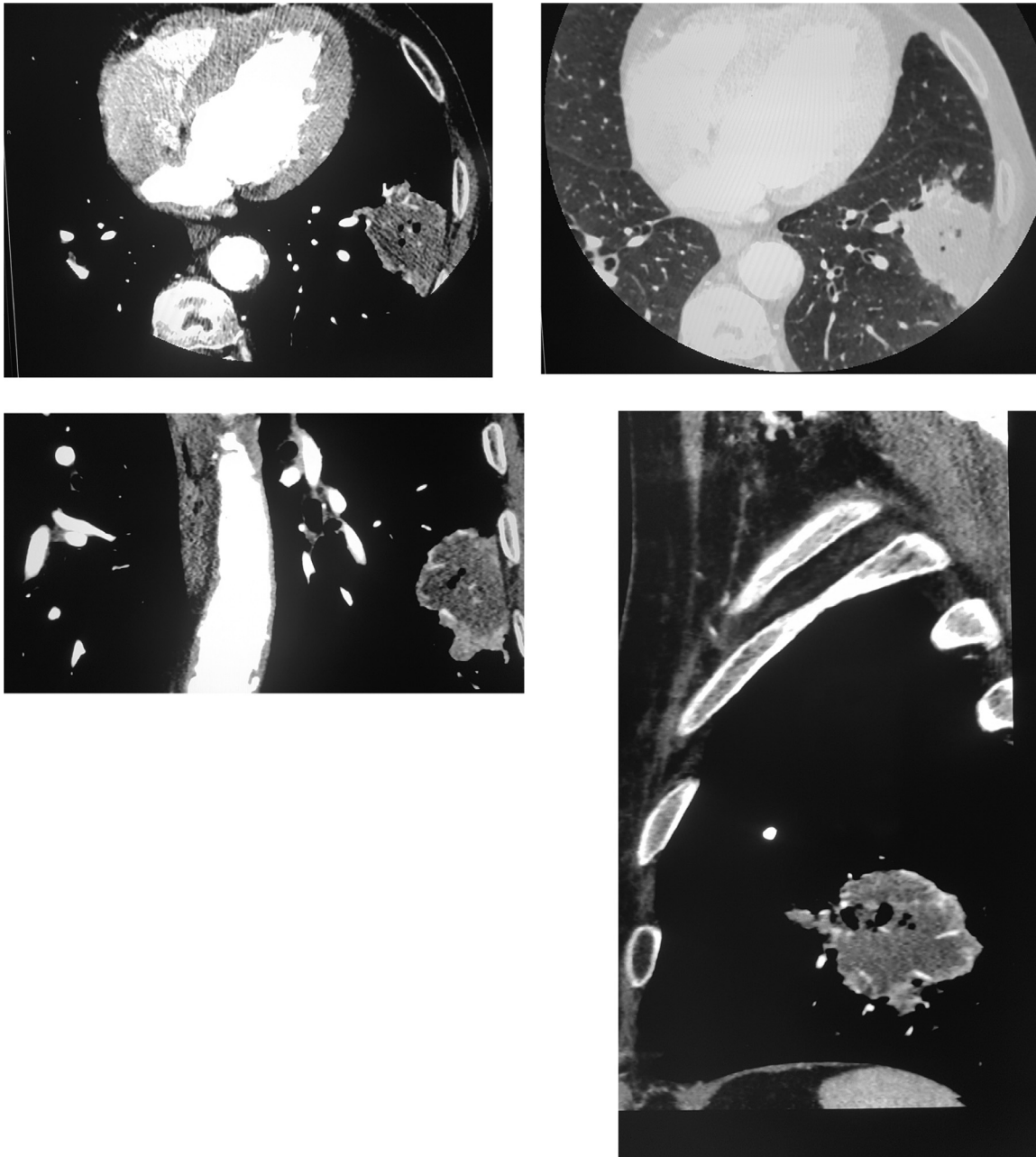


Fig. 3 – Cardiac-CT on 3 plans with mediastinal and lung filter after the contrast agent injection showing a solid nodular lesion (53 × 45 × 40 mm) in the upper segment of lower left lobe, with intralesional cavitations and peripheral vascularization.

patient had a progressive anemia, high erythrocyte sedimentation rate and worsening of the renal function, therefore it was decided to perform a chest CT showing a diffuse density alteration, clearest/most striking in the upper lobe and bilateral pleural effusion, more evident on the right lung (Fig. 2). Despite medical therapy, patient's respiratory symptoms increased, therefore, a Cardiac-CT was performed showing a new finding—a solid nodular lesion (53 × 45 × 40 mm) in the upper segment of the lower left lobe, with intralesional cavitations and with ground-glass opacities and peripheral vascularization, after administration of iodine contrast medium

(Fig. 3). Differential diagnosis was challenging and included granulomatous lung diseases. Since pneumonia is common in the elderly, in the first instance it was considered an infectious nature, such as tuberculosis, nontuberculous mycobacteria and fungal infection; secondly, not infectious lung disease, such as sarcoidosis, GPA, and other vasculitis (Goodpasture syndrome). However, it should be emphasized that our case report patient had no history of hemoptysis. Subsequently a thoracentesis with pleural fluid culture test was performed, demonstrating absence of bacterial growth after 5 days.

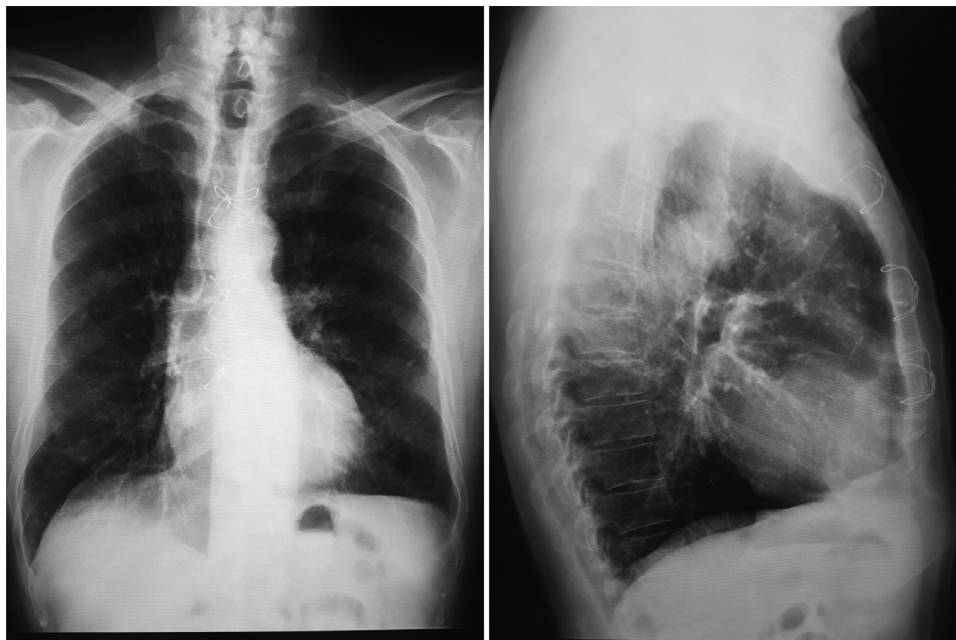


Fig. 4 – Radiographs findings (with 2 projections in orthostatism) after treatment that show a complete resolution except for the presence of some fibrotic- scarring striae.

Then a CT-guided needle lung biopsy with an “Ultra low dose radiation protocol (80 Kv, 3 Mas)” [13] was performed yielded a GPA pattern (1) Inflammatory component with neutrophils, located in central place and giant Langerhans-like cells in the periphery; (2) Vasculitis that involves the arteries and veins, but also the venules and capillaries (capillaritis); (3) Necrosis is basophilic and with an irregular contour (“geographical map”). Subsequently, the immunoglobulins rate revealed a hypergammaglobulinemia (with prevalence of IgA class) and a positive evaluation of ANCA antibodies with cytoplasmic pattern (c-ANCA) was observed at indirect immunofluorescence on neutrophils fixed in ethanol, due to the presence of antibodies against PR3. These findings, as well as the presence of anemia, the increase of erythrocyte sedimentation rate, and the increase of creatinine level as glomerulopathy index, are hematochemical typical indices of this pathology. Instead, the patient tests negative for rheumatoid factor. Therefore, the diagnosis of GPA was confirmed and a medical treatment was established: cyclophosphamide at a dosage of 2 mg/kg/day per os for 1 year, initially associated with prednisone at a dosage of 1 mg/kg/day per os for the first month, then every other day, followed by a gradual reduction until suspension. An improvement in symptoms was observed in 1 week, with associated remission within 1 month, and a complete resolution of the radiological finding except for the presence of some fibrotic-scarring striae, mostly in the segment of the previously lesion area (Fig. 4).

Discussion

The peculiarity of this clinical case is the age of the patient, in fact, to the best of our knowledge, very few cases of GPA

reported in the medicine literature [4,14] have such an elderly onset (85 years). This is what probably led us to a misleading diagnosis like cardiopulmonary disease, due to the overload of pulmonary circle, which is generally more frequently observed in elderly patients with a previously cardiological surgery history, and pneumonia. Moreover, biopsy-proven GPA in the elderly is rare, so that is the value of this case. Another particular characteristic of our case report is that our patient had no other GPA systemic symptoms, except for a slight worsening of renal function, although this pathology is often associated with multiorgan damage, as reported in the literature [15].

Focusing on the diagnosis, we can now understand that the alterations reported as diffuse inhomogenous opacity at the radiographic examination and the “ground glass” areas at CT scan were the signs of an alveolar hemorrhage associated to the necrotizing vasculitis that led to intraparenchymal bleeding events with consensual blood loss through vascular hemorrhage causing dropping Hemoglobin leading to anemia. As reported by Green [16] anemia resulting from blood loss is a common finding in patients with Pulmonary Capillaritis and Alveolar hemorrhage, although it can also be due to the underlying chronic disease or renal failure. The appearance of a nodule in a few days is frequent in this pathology—it represents the “granuloma,” that is the extra vasal inflammation and necrosis, typical manifestation of GPA, and the most common pulmonary radiographic and CT finding. In fact, in adults the most common radiological appearance is represented by multiple nodules, randomly distributed throughout the lung [3]—they can range from few millimeters to more than 10 cm in maximum diameter and become cavitated. The cavities usually have thickened walls and are characterized by an irregular inner margin and the absence of calcifications [17].

Conclusion

This case allows us to understand how it's easy to miss the diagnosis in an elderly patient. In these patients with sudden dyspnea and the appearance of a nodule with intralesional cavitations, all diagnostic hypotheses should be considered, although rare for this age group, such as GPA. It should never be excluded and always keep in mind in the diagnostic and therapeutic process.

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