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# AMIODARONE - OTHER PULMONARY MANIFESTATIONS

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***Abstract***

***Introduction.*** *Cryptogenic organizing pneumonia (COP), first described in 1985 as BOOP bronchiolitis obliterans organizing pneumonia, is an acute inflammatory disease characterized histopathologically by intracellular granulomas formed by connective tissue and miofibroblasts (Masson bodies).*

***Case presentation****. 62-year-old female patient, known with type 2 DZ, ICC, CIND (paroxysmal FiA) and HTAE, under treatment with Amiodarone, is hospitalized with acute respiratory symptomatology. Laboratory tests show bilateral basaltic crepitation risers, biological inflammatory syndrome, and radiologically multiple opacities with ½ inferior condensation appearance for which empiric antibiotic treatment was initiated. Evolution of the patient was unfavourable, despite antibiotic treatment. Therefore, it is decided to do a fibrobronchoscopic examination (bronchial aspiration for cytology and BK), thoracic CT followed by thoracoscopy and pulmonary biopsy.*

*The diagnosis of COP was based on the typical radiological appearance of bronchopneumonia but that is not responding to antibiotic treatment. The bronchoalveolar lavage revealed nonspecific inflammatory infiltration with lymphocytes and polymorphonuclear cells, the histopathological examination revealed the presence of Masson bodies, alveolar fibroblast polyps and bronchiolar polyps. As amiodarone is known to have pulmonary adverse effects, among which COP was very rarely quoted, treatment with amiodarone was discontinued and cortisone treatment with prednisone 70 mg/day was initiated, with rapid progressive improvement of symptomatology and slow improvement of imaging. In treatment month 3, after the decrease in prednisone to 30 mg/day, the general condition of the patient worsens in parallel with the biological and imaging parameters secondary to the reintroduction of the amiodarone treatment, an event treated as a recurrence of drug-induced obliterans pneumonia. The evolution of the patient was favourable, with the remission of clinical symptoms and radiological appearance, in the absence of relapses one and a half years after the end of the treatment.*

***Conclusions.*** *This paper presents a complete case of cryptogenic organizing pneumonia in a patient undergoing amiodarone treatment, which has a complete response to cortisone treatment only after the trigger factor has been removed.*

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## Clinical cases

### Introduction

Cryptogenic organizing pneumonia (COP), first described in 1985 as BOOP [1] bronchiolitis obliterans organizing pneumonia, is an acute inflammatory disease affecting the distal bronchiole, alveolar ducts and alveolar walls, characterized histopathologically by intracellular granulomas formed by connective tissue and miofibroblasts (Masson bodies) [2].

The exact pathogenesis of cryptogenic pneumonia is unknown; however, the corticoid treatment rapidly improves the clinical and imaging aspect, and COP fibrosis is completely reversible under corticotherapy, unlike idiopathic interstitial pneumonias (IIP). [3].

### Case presentation

62-year-old, overweight, non-smoker, non-occupational exposed female patient with type 2 diabetes insulin-dependent and essential stage II hypertension JNC 8, painless ischemic cardiopathy - paroxysmal arterial fistulae history under treatment with amiodarone, sartan, nitrate, diuretic, B blocker, insulin therapy and oral anticoagulant. The patient is hospitalized for: dyspnoea in moderate efforts, irritable dry cough, fever (39 °C), loss of appetite, nocturnal sweating, 2 weeks of onset symptomatology.

Clinical examination reveals bad general condition, dyspnoea, tachypnoea (30 res/min.), Pulmonary presence of rhythm crepitation in 2/3 inferior bilateral, rhythmic heart rhythm noises, without murmurs, 90/60 mmHg blood pressure, 120 b/min heart rate, skin dehydration signs: dry mucous membranes, persistent abdominal skin fold.

Laboratory analysis reveal leukocytosis (16,000/mm$^3$) with neutrophilia (14.240/mm$^3$), inflammatory syndrome present (reactive C protein =127,8 mg/dl, VSH =120 mm/h, Fibrinogen = 686 mg/dl), slight nitrogen retention (urea = 70 mg/dl, creatinine =1,5 mg/dl), international normalized ratio (INR) therapeutically modified, hyperglycaemia (150 mg/dl). The rest of the laboratory tests: transaminases, amylases, lipases, electrolytes, pro Calcitonin, natriuretic atrial peptide were within normal range, haemocultures and sputum were collected.

The patient's electrocardiograph was at sinus rhythm, with ventricular alveolar of 75/min, with no terminal phase changes. Radiologically, it presents multiple optic reticulonodular opacities with a tendency to confluence in 1/3 inferior bilateral, cardiomegaly (Img.1)Spirometry - the patient has mild restrictive ventilator dysfunction

with a decrease in total pulmonary capacity (TPC) to 75% of the predicted volume, and the maximum expiratory volume per second at 67% (2.01 L).

Taking into account the clinical and laboratory data, the diagnosis of bronchopneumonia, essential stage II hypertension JNC 8, painless ischemic cardiopathy - a past history of paroxysmal heart disease, NYHA class III congestive heart failure, Type II diabetes - insulin-dependent, acute renal failure through the prerenal mechanism.

Taking into account the high degree of severity of pneumonia (Score CURB65 = 3) and the presence of comorbidities (diabetes, heart failure), according to the Guidelines of treatment of the antibiotic empiric community-acquired pneumonia [4] it was initiated the empiric antibiotic cephalosporin generation III treatment (Ceftriaxone 1 g every 12 hours) and macrolide (Clarithromycin 500 mg every 12 hours), with 2 l/min oxygen therapy, hydro-electrolytic re-balancing, anti-thermic, antiarrhythmic (amiodarone 300 g/day), slow release nitrate, warfarin anticoagulant - with maintaining INR within therapeutic limits, and insulin therapy.

At 72 hours after admission, the patient's progression was unfavourable with fever persistence (38.5° C), cough persistence, increased dyspnoea (30-35 rpm), increased creaking rhythm, normalization of blood pressure. Biologically: remission of nitrate retention, with the maintenance of the inflammatory syndrome (CRP 120,8 mg/dl, VSH 122 mm/h, fibrinogen 550 mg/dl), leukocytosis (14 000 $mm^3$); radiologically: progression of reticulo-demographic images compared to the previous examination (Img. 2).

Taking into account the absence of response to the treatment, it is decided to change the antibiotic regime so that there is coverage for the resistant Staphylococcus aureus methicillin and the multi-resistance gram negative bacteria to antibiotics, to opt for Imipenem / cilastatin 500 mg /500 mg at 6 hours associated with Vancomycin 1g at 12 hours; without improving clinical symptoms after 48 hours of treatment.

Considering that after five days of empiric antibiotic treatment the patient's progression was unfavourable with persistence of fever, sputum culture and hemocultures are negative, it is decided to perform chest computed tomography (CT) and bronchial aspirated fibrobronchoscopy for cytology and bacteriology. CT of the thorax indicates multiple condensation zones / matt glass with peribronhiolar distribution and peripleural nodular formations with confluence tendency (Img. 3). The fibrobronchoscopic examination does not reveal proliferative or specific active lesions, and the cytological examination reveals nonspecific inflammatory infiltration with lymphocytosis (18.3%), macrophages (61.8%), polymorphonuclear (18.2%), bronchial cells (1.8% ), with no neoplastic cells and negative cultures.

Collaborating clinical and laboratory data to establish a diagnosis in a patient with acute respiratory symptomatology that presents biological persistent inflammatory syndrome, imaging with multiple condensation outbreaks not improved by empirical antibiotic therapy and in which bronchoalveolar lavage reveals nonspecific inflammatory infiltration, the following diagnostic possibilities are assessed : bronchopneumonia, pulmonary lymphoma, idiopathic interstitial pneumonia, and eosinophilic pneumonia, (Table1).

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In order to establish the diagnosis with certainty, the histopathological examination is necessary, since it is a patient with multiple comorbidities and the thoracoscopy brings an additional risk, a transthoracic biopsy, a choice motivated also by the existence of the peripleural nodule. Histopathological examination reveals alveolar and perilobular interstitial thickening by predominantly lymphocytic diffuse infiltration, moderate fibrosis degree with lymphocytic micro nodules, some alveoli containing macrophage agglomerations, and rare fibro-mixoid polymorphic structured formations infiltrated with rare lymphocytes and alveolar epithelial wall (Masson bodies – specific for COP). Also described are nodular formations of varying sizes on the alveolar and bronchiolar walls, which occupy the space of several adjacent alveoli. In conclusion, suggestive aspect of cryptogenic pneumonia organized with acute fibrosis component.

Thus, the diagnosis with certainty of organized cryptogenic pneumonia is established. Because of the known causes of organized cryptogenic pneumonia, drug-induced cases (amiodarone) have been reported [5] [6], it is decided to interrupt treatment with amiodarone and antibiotic treatment and initiate corticosteroid therapy with prednisone 1 mg / kg body (70 mg / day) for 6 weeks, followed by a gradual decrease in the dose by 20 mg per month associated with the patient's background therapy. Rheumatoid factor and antinuclear antibodies were also dosed, being negative.

The progression of the patient under corticotherapy was favourable with the rapid progressive improvement of clinical symptomatology beginning with the first 48 hours by improving dyspnoea, cough, affectivity and normalization of biological parameters (inflammatory syndrome), but also radiological appearance at the end of the first month of treatment.

In the third month of treatment, when the dose of prednisone was 30 mg / day, the patient is present in the emergency room in the area for palpitations, dyspnoea with orthopnoea, electrocardiography is attributed to atrial fibrillation, left undiluted ventricle under ultrasound with moderately diminished systolic function (left ventricular ejection is 40%) without significant valvulopathy, for which amiodarone drug cardioversion is decided. Approximately two weeks after reintroduction of amiodarone treatment, the patient comes in with dyspnoea and coughing during the last 5 days, a febrile episode (38.5° C), biologically she presents moderate inflammatory syndrome (CRP 50,8 mg/dl, VSH 90 mm/h ), and the imaging features multiple condensation areas with a predominantly

apical matt glass appearance. (Img. 4) . Respiratory symptomatology is interpreted as a recurrence episode of amiodarone-induced obstructive pneumonia, it is decided to discontinue the treatment with amiodarone and to increase the dose of Prednisone from 30 to 70 mg per day - 6 weeks followed by a gradual decrease of 20 mg per month to the dose of 20 mg maintenance per day; the duration of treatment being 1 year. Evolution of the patient was favourable with remittance of clinical symptomatology and radiological appearance in the absence of relapse at 1 year and a half after the end of treatment.

**Discussions**

Obliterant pneumonia is a diagnostic challenge with regard to acute respiratory symptomatology associated with persistent inflammatory syndrome, multiple imaging condensation outbreaks that may suggest an infectious context and that do not improve under antibiotic therapy, and bronchio-alveolar lavage bronchoscopy only showing non-specific inflammatory appearance. The diagnosis with certainty is only histopathologic.

The prevalence and incidence of the disease is unknown, but an incidence of 6-7 cases per 100,000 admissions has been reported in a Canadian hospital [7].

Most commonly, the aetiology of the disease is unknown, 50% of cases are considered cryptogenic [12] among the causes of organized pneumonia are collagen diseases, drug causes, where besides amiodarone [5, 6] can be enumerated bleomycin, interferon, carbamazepine, [8] methotrexate and acetylsalicylic acid [9], legionella infections, M pneumonia, staphylococcus aureus [5]. There are also cases reported in patients with exposure to benzocaine, [10], in cocaine users, [10], and a case of cryptogenic pneumonia in a pregnant, HIV positive patient [11].

Evolution of the disease is favourable with complete regression of intracellular fibrosis under corticoid treatment, but cases of unfavourable development (respiratory distress and exitus) have been reported in patients where corticoid diagnosis and treatment have been delayed or associated with immunosuppressive therapy or suspicion of resistance to corticosteroids [4].

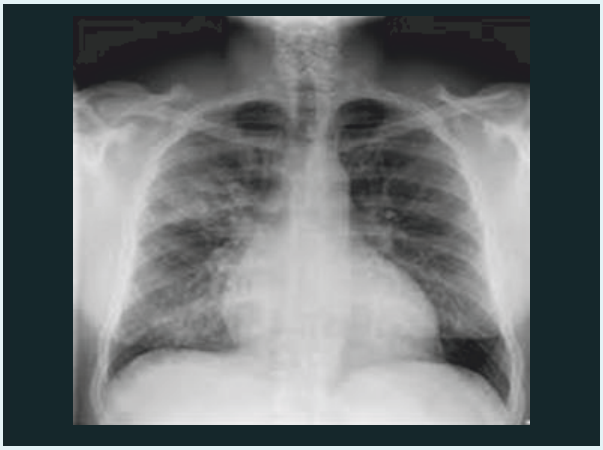

***Image 1*** *Posterior-anterior thoracic radiography upon admission presents multiple reticulmonodular opacities of subcostal intensity with tendency to confluence in 1/3 lower bilateral*

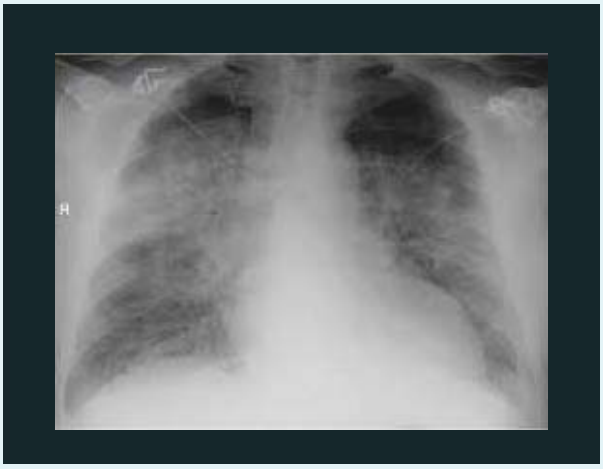

***Image 2*** *Posterior-anterior thoracic radiography at 72 hours from admission indicates the progression of reticulmonodular opacity compared to the previous radiological exam.*

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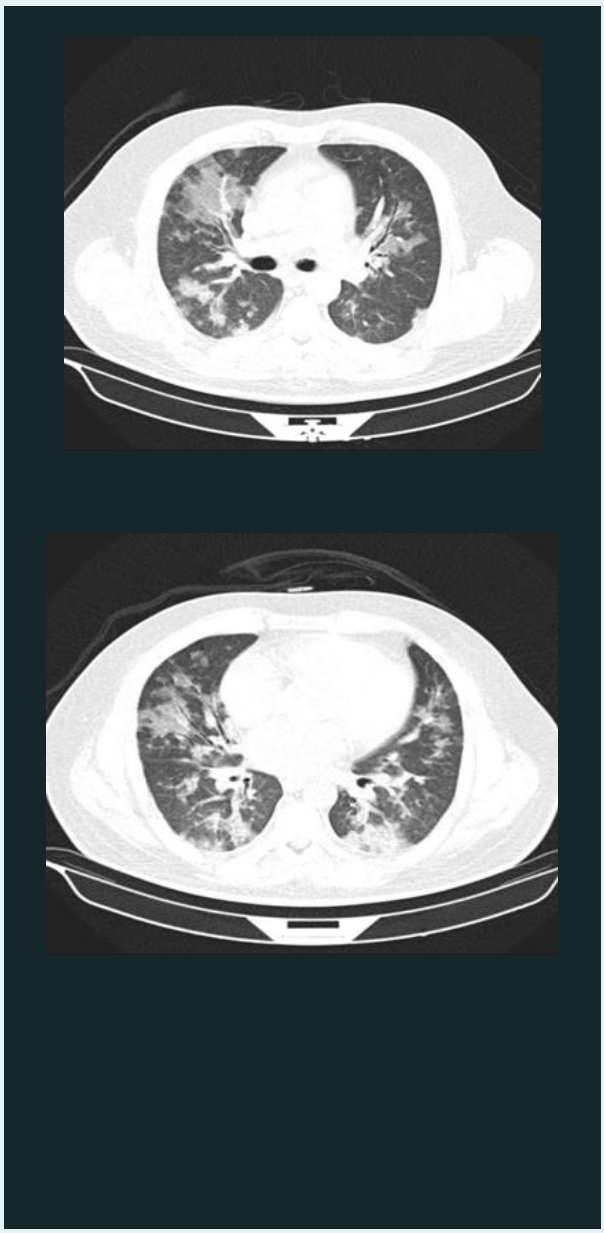

***Image 3*** *CT thorax on day 5 of admission: multiple condensation / matt glass areas with peribronthylar distribution and peripleural nodular formations with confluence tendency.*

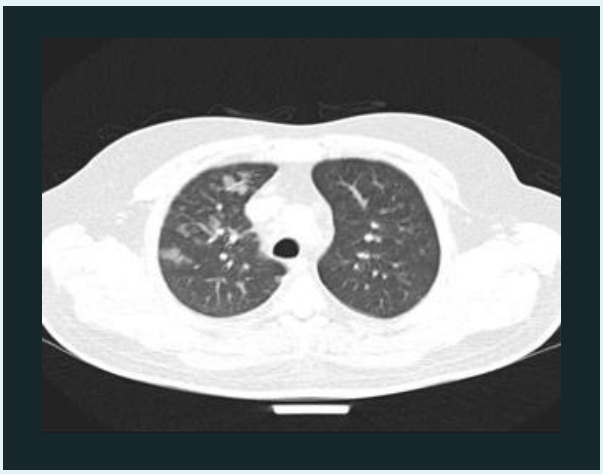

***Image 4*** *CT thorax in the 3rd month of treatment: Multiple condensation zones apical bilateral arranged - relapse of COP*

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| Arguments for: | Arguments against: |
|---|---|
| Bronchopneumonia | |
| - Clinically fever, cough, general altered state<br>- Imaging: Multiple condensation centres with a tendency to confluence | - No response to antibiotic treatment |
| Eosinophilic pneumonia | |
| - Clinically fever, cough, general altered state<br>- Imaging: Multiple condensation centres not responding to antibiotic treatment | - Absence of eosinophilia (Hemogram / bronchialveal lavage) |
| IID (idiopath ic interstitial pneumonia) | |
| - Clinically: fever, dyspnoea,<br>- Imaging: condensation centres/ matt glass | - Absence of destructive lesions: bronchiectasis, "honeycomb" |
| Pulmonary lymphoma | |
| - Clinically: cough, dyspnoea<br>- Imaging: bilateral alveolar condensation + aerosol bronchogram | - No hemogram modifications<br>- No mediastinal or peripheral adenopathies |

***Table no. 1.*** *Osteodensitometry*

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