

Rapidly progressive organising pneumonia associated with cytomegalovirus infection in a patient with psoriasis

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ABSTRACT: *Rapidly progressive organising pneumonia associated with cytomegalovirus infection in a patient with psoriasis. M. Messina, N. Scichilone, F. Guddo, V. Bellia.*

A 63-year-old woman experienced progressive respiratory distress and psoriatic plaques. The radiographic images showed diffuse interstitial infiltrates. The surgical open lung biopsy revealed an obliteration of the alveolar spaces by plugs of connective tissue distributed within the terminal bronchioles, alveolar ducts and spaces. No relevant cause was determined, and she was diagnosed with idiopathic organising pneumonia. The patient was discharged with oral

glucocorticosteroid and supplemental oxygen therapy. One month later, the patient's pulmonary status had progressively worsened, and she was re-admitted. She required higher oxygen concentrations and mechanical ventilation. Pharmacological therapy included high-dose steroids and cyclophosphamide. Serological assays revealed high antibodies titers (both IgM and IgG) to cytomegalovirus. Therefore, ganciclovir was added to the regimen. Despite the therapy, she died as a result of the disease. The review of the current literature on the topic is also presented. *Monaldi Arch Chest Dis 2007; 67: 3, 165-168.*

Keywords: *Interstitial pneumonia, cytomegalovirus infection, psoriasis.*

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Bronchiolitis obliterans organising pneumonia (BOOP), is a distinct clinical and pathologic syndrome characterised by a pneumonia-like illness. Symptoms resemble those of an upper respiratory tract infection, usually followed by cough, dyspnoea, and crackles, with or without wheezing. The radiological presentation is variable: the most common findings include bilateral patchy alveolar opacities, which show peripheral and bilateral distribution, and tend to migrate spontaneously. Histologically, the lung injury exhibits anastomosing plugs ('buds') of granulation tissue, termed *Mason bodies*, that fill bronchiolar lumina ('*bronchiolitis obliterans*') and extend into the alveolar ducts and spaces ('*organising pneumonia*') [1].

Organising pneumonia (OP) can be of unknown aetiology or secondary to various conditions and/or insults [2], such as bacterial or viral infections, toxic exposures, cocaine abuse, connective tissue diseases, radiation therapy, myelodysplastic syndrome, human immunodeficiency virus infection, gastrointestinal disorders and pharmaceutical drugs. Therefore, a careful clinical history is required to differentiate the idiopathic from secondary forms of OP.

Although idiopathic OP has been described as having an indolent course with good prognosis [3], recent evidences report acute, fulminating, and life-threatening cases [4, 5]. Among those, cytomegalovirus pneumonia-associated organising pneumonia (OP) has only been described in lung

transplant recipients [6]. Herein, we present a patient with psoriasis who developed OP associated with cytomegalovirus infection. The aim of the presentation of this clinical case is to alert the physicians that a subset of patients with OP can also present with a fulminant course, characterized by poor prognosis and increased mortality.

Case Report

A 63-year-old female presented with fever (maximum temperature of 38.6°C), exertional dyspnoea and dry cough. She also complained of diffuse arthralgia and reduced exercise tolerance. Psoriatic plaques on her legs and arms were detected. She denied having any history of smoking. She had no occupational exposure to known organic or inorganic agents. The chest x-ray showed diffuse reticulo-nodular interstitial infiltrates. As a consequence, she was referred to our Pulmonary Department for further evaluation.

On presentation, the patient presented tachypnoea and tachycardia with body temperature of 37.5°C. The respiratory rate was 28/min, heart rate was 87/min, and systemic blood pressure was 110/70 mmHg. Oxygen saturation was 89%, in room air. Lung examination revealed diffuse bilateral basal crackles, which were more evident in the basilar areas. The white blood count (WBC) was $10.0 \times 10^3/\text{mL}$, with 8% eosinophils on differential count, and erythrocyte sedimentation rate (ERS)

was 58 mm/h. Her autoimmune workup, including ANA, RA factor and ANCA, was negative. Arterial blood gas showed the following findings: pH, 7.46; PO₂, 69 mm Hg; PCO₂, 37.5 mm Hg; HCO₃⁻, 27.3 mEq/L, on room air. Pulmonary function tests showed a restrictive pattern; a severe reduction in the carbon monoxide diffusing capacity (DLCO) was recorded (DLCO: 14% of predicted). The high-resolution computed tomography (HRCT) scan demonstrated an alveolar consolidation, pleural-based, with air bronchogram of the posterior segment of the right lower lobe, there was also a smaller, adjacent, nodular-like opacity (figure 1).

A bronchoscopy with bronchoalveolar lavage (BAL) was performed. The bronchoscopic specimens were negative on microbiological and cytological examinations. The BAL contained 19x10⁹/L WBCs with a differential count of 2.9% neutrophils, 38.3% macrophages, 1.4% eosinophils, and 57.4% lymphocytes.

Since the observations were not conclusive for a definite diagnosis, the patient underwent open lung biopsy. Histopathological examination re-

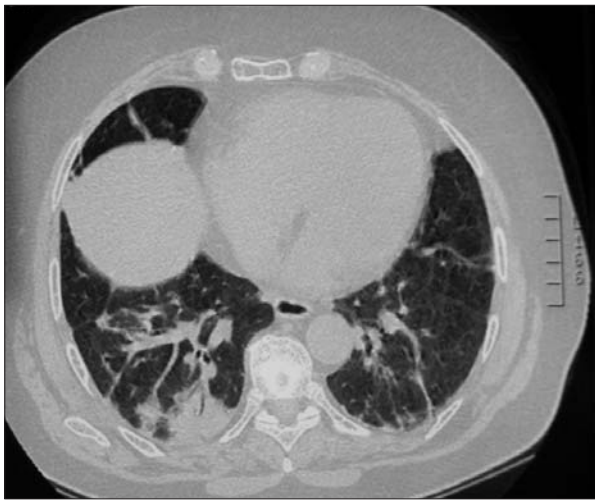


Fig. 1. - HRCT scan of the chest demonstrating an alveolar consolidation, pleural-based, with air bronchogram of the posterior segment of the right lower lobe, there was also a smaller, adjacent, nodular-like opacity.

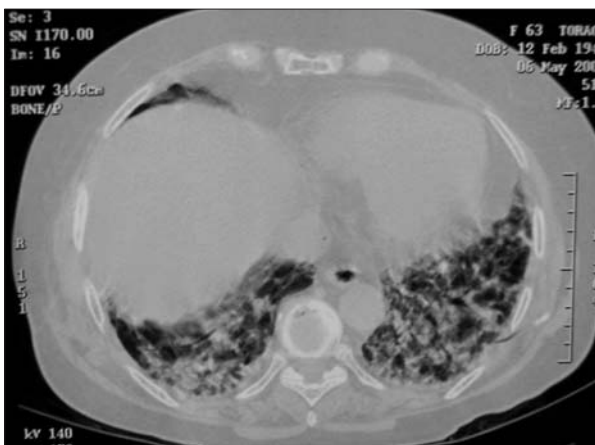


Fig. 2. - HRCT scan of the chest demonstrating extensive bilateral diffuse reticular pattern with associated distortion, honeycombing, and traction bronchiectasis predominantly in the bases.

vealed obliteration of the alveolar spaces by plugs of connective tissue distributed within the terminal bronchioles, alveolar ducts and spaces, with associated areas of fibrous scarring and fibrous peribronchiolar thickening. Hyperplasia of type II pneumocytes was also detected. Taken together, these findings were consistent with a “*forme fruste*” of diffuse alveolar damage.

The patient was discharged with instructions for oral prednisone 37.5 mg daily, and supplemental oxygen via a nasal cannula. One month later, the patient’s pulmonary status had worsened, requiring oxygen supplementation at continuous low flow. She was, then, re-admitted to our Pulmonary Department. On presentation, the patient showed shortness of breath at rest. Arterial blood gas level analysis performed under supplemental oxygen revealed a pH of 7.5, PO₂ of 55 mmHg, PCO₂ of 34.9 mmHg, and a haemoglobin oxygen saturation of 90.4%. Laboratory studies were normal, except for ERS of 78 mm/h. The HRCT scan showed an extensive bilateral diffuse reticular pattern with associated distortion, honeycombing, and traction bronchiectasis predominantly in the bases (figure 2). The patient’s condition deteriorated, requiring higher oxygen concentrations and mechanical ventilation. Methylprednisolone at doses of 1000 mg intravenously was administered for three days, followed by oral prednisolone 60 mg/day and cyclophosphamide 100 mg/die orally. One week later, the WBC was 60.30x10³/mL, with 4.3% lymphocytes on differential count and the ERS was 58 mm/h. The histological revision of the bioptic specimens obtained before the immunosuppressive treatment showed the presence of viral inclusions (figure 3). Serological assays revealed high titres of antibodies (both IgM and IgG) to CMV. The HIV-test was negative. Ganciclovir was immediately added to the regimen. A chest radiograph showed bilateral interstitial opacities (figure 4). The patient’s condition did not improve despite the antiviral therapy. She was scheduled for lung transplant. Unfortunately, she died as a result of the disease. An autopsy was not performed.

Discussion

Organising pneumonia is a non-specific pathologic pattern, first described by Epler and colleagues in 1985 as “bronchiolitis obliterans organising pneumonia” (BOOP) [7]. However, in 2002, the American thoracic Society/European Respiratory Society International Consensus Panel for the Classification of Idiopathic Interstitial Pneumonia (ATS/ERS) recommended the term “COP” to be used as the preferred clinical term for idiopathic cases, emphasising the cryptogenic nature of the process. It was also accepted that the organising pneumonia pattern could be seen in secondary forms of disease [7]. Cryptogenic organising pneumonia (COP) is the most common presentation [8]. It is a heterogeneous disease with insidious onset, non-specific physiologic findings, and variable radiographic patterns, but with typical histopathologic findings that are *sine que non* for diagnosis [1].

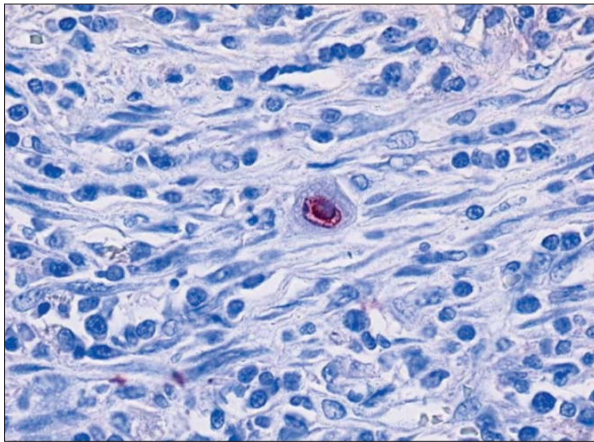


Fig. 3. - Histologic section. Immunohistochemical demonstration of viral inclusion. New fuchsin alkaline phosphatase method. (Original magnification, x40)

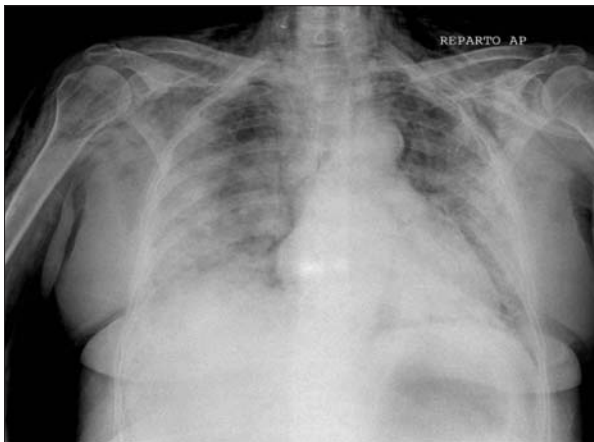


Fig. 4. - Chest radiograph performed in the end-stage revealing bilateral interstitial opacities.

Although organising pneumonia is uncommon, it should be included in the differential diagnosis in any patient with bilateral airspace disease that is unresponsive to antibiotics [2]. Post-infectious OP can develop after a variety of infectious pneumonias, including agents such as *Streptococcus pneumoniae* [9], *Chlamydia* [10], *Legionella* [11] and *Mycoplasma pneumoniae* [12] and viruses such as human immunodeficiency virus [13] and Parainfluenza virus [14]. Parasitic infection including *Plasmodium vivax* [15] and fungal infection, including *Cryptococcus neoformans* [16] and *Pneumocystis Jieroveci* [17], have also been reported as a cause of OP. BAL may be used to exclude other causes of OP, particularly infections [18]. In our case, BAL was negative for micro-organisms, although viral culture was not carried out.

Cytomegalovirus pneumonia-associated OP has only been described in lung transplant recipients [6] and in a case-report associated with systemic lupus erythematosus [19]. OP has been reported with connective tissue diseases [20]. Patients usually respond well to corticosteroid therapy and have a good prognosis. In our patient, psoriasis was under control on maintenance topic corticosteroids. Psoriasis is an inflammatory and proliferative disease of the skin that results in a rapid turnover of the skin cells. The association of inter-

stitial pneumonia with psoriasis is rare. To our knowledge, the development of OP associated with CMV pneumonia in patients with psoriasis has never been reported; a case of constrictive bronchiolitis obliterans has been described [21], and interstitial pneumonia following gold therapy for psoriatic arthritis has also been demonstrated [22].

Initial reports suggested that more than 80% of patients with OP showed rapid and complete resolution of the disease on steroids, although relapse could have occurred as the dose was reduced [3,7]. However, some patients show acute symptoms like acute interstitial pneumonia (AIP), and they have a rapidly-progressive disease, which is refractory to steroids and associated with a high mortality [4-5, 23-25]. On the other hand, patients may improve in the absence of treatment [26]. Yousem *et al.* observed that approximately 10-15% of cases are progressive [25]. Cohen *et al.* reported a series of 10 patients with 70% mortality [4]. Nizami *et al.* described 5 cases of progressive OP with 40% mortality [27]. Our patient was given prednisolone at doses and duration within which clear improvement would be seen in the vast majority of patients [28]. Instead, she progressively worsened; perhaps, the addition of cyclophosphamide should have been anticipated. The use of cyclophosphamide in association with prednisolone in OP has been successful in early phases of the disease and should be considered in patients who fail to respond to steroids [29]. Recent cases have reported a good response to cyclosporine and corticosteroid therapy in rapidly progressive OP variant [30], but the utility of immunosuppressive drugs such as cyclophosphamide or azathioprine has not been established. In agreement with Chang *et al.* [23], we believe that OP could be a precursor of alveolar septal inflammation and honeycombing lung, and might represent an early phase of the temporal spectrum of interstitial lung disease. Therefore, a sampling error or an incorrect morphologic diagnosis may be the reason for clinical steroid unresponsiveness, rapidly progressive and poor prognostic forms [1].

The final question is whether CMV infection was present at the presentation or whether CMV infection was secondary to immunosuppressive therapy. The question can be refuted histologically for the presence of viral inclusions on bioptic specimens before the immunosuppressive therapy. CMV infection and CMV disease are frequent complications in immunocompromised patients. Tamm *et al.* [31] showed that the incidence of CMV infection and the development of CMV disease in patients with lung fibrosis under immunosuppressive treatment were not any different to those of immunocompromised patients with other diseases. However, the possibility that, in our patient, the immunosuppressive regimen had contributed to worsen the clinical picture associated with the CMV infection cannot be excluded. As a consequence, the late diagnosis of CMV infection could be responsible for rapid and fatal course of the disease. We propose to add the CMV infection to the list of the most severe infectious conditions associated with OP.

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