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Organising pneumonia: a growing concern

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Abstract

English:

Organising pneumonia (OP), a rare form of interstitial lung disease (ILD), is frequently misdiagnosed as community-acquired pneumonia, leading to delays in appropriate treatment. While the cryptogenic form (cryptogenic organising pneumonia [COP]) has no identifiable cause, secondary organising pneumonia (SOP) has been associated with infections, drug reactions, autoimmune diseases, radiation exposure and, increasingly, the use of monoclonal antibodies. Following a thorough literature review, we concluded that an accurate diagnosis is best achieved through a combination of clinical and biological data, computed tomography (CT) imaging and, when possible, histological analysis. Corticosteroids have shown high efficacy; however, the relapse rate remains significant, emphasising the need for close patient monitoring as a standard of care.

Keywords

cryptogenic organised pneumonia • secondary organised pneumonia • interstitial lung disease

Pneumonita în organizare – o problemă emergentă

Rezumat

Romanian:

Pneumonita în organizare (OP), o formă rară de boală interstițială pulmonară (ILD), este frecvent diagnosticată eronat ca pneumonie comunitară, ceea ce duce la întârzieri în inițierea tratamentului adecvat. În timp ce forma criptogenică (COP) nu are o cauză identificabilă, pneumonia secundară în organizare (SOP) a fost asociată cu infecții, reacții adverse la medicamente, boli autoimune, expunere la radiații și, tot mai frecvent, cu utilizarea anticorpilor monoclonali. Un diagnostic corect se obține cel mai bine printr-o combinație de date clinice, biologice, imagistică de înaltă rezoluție și, atunci când este posibil, analiză histologică. Corticosteroizii s-au dovedit eficienți, însă rata de recădere rămâne semnificativă, subliniind necesitatea monitorizării atente.

Cuvinte-cheie

boală pulmonară interstițială • pneumonită criptogenică în organizare • pneumonită secundară în organizare

Introduction

Diffuse interstitial lung diseases (DILDs), often referred to simply as interstitial lung diseases (ILDs), encompass a heterogeneous group of pulmonary disorders that primarily affect the lung interstitium – a network of connective tissue that supports the alveolar walls and blood vessels. Historically, the recognition of DILDs dates back to the early 20th century,

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when advancements in radiographic imaging allowed for the identification of diffuse pulmonary infiltrates. Initial classifications were rudimentary, often grouping these disorders under broad terms such as *chronic interstitial pneumonia*. Over subsequent decades, with the advent of high-resolution computed tomography (HRCT) and histopathological techniques, a more nuanced understanding emerged, leading to the separation of specific entities within the DILD spectrum (1). Notably, the identification of *idiopathic pulmonary fibrosis* (IPF) as a distinct clinical entity marked a significant milestone in the field. Regarding the classification process, several systems have been proposed over time to categorise these diseases based on clinical, radiological and histopathological features. Initially, DILDs were broadly categorised into known and idiopathic causes. Known causes included occupational exposures, drug-induced lung diseases and connective tissue diseases. *Idiopathic interstitial pneumonias* (IIPs) were recognised as a subset without identifiable aetiology. In 2002, the American Thoracic Society (ATS)/European Respiratory Society (ERS) provided a more detailed classification of IIPs, dividing them into *major*, *rare* and *unclassifiable* categories (2, 3). The latter 2018 classification developed by the Fleischner Society described a new system, which focuses on the progression of fibrosis in ILDs. This framework delineates two primary categories: IIPs and progressive fibrosing interstitial lung diseases (PF-ILDs). Within the IIPs, IPF is characterised by a Usual Interstitial Pneumonia (UIP) – leading to a relentless decline in lung function – while idiopathic non-specific interstitial pneumonia (NSIP) presents with a more uniform interstitial involvement and generally has a more favourable prognosis compared with IPF. The PF-ILDs category encompasses non-IPF-ILDs that exhibit a progressive fibrosing phenotype. Examples include fibrotic hypersensitivity pneumonitis, which arises from an exaggerated immune response to inhaled antigens, and connective tissue disease-associated ILDs, where systemic autoimmune disorders contribute to pulmonary fibrosis (4).

Diagnosing DILDs presents significant challenges due to their heterogeneous nature and non-specific clinical manifestations. Patients often experience an insidious onset of symptoms such as dyspnoea and cough, which are easily attributed to more prevalent respiratory or cardiovascular conditions. This symptom overlap frequently leads to initial misdiagnoses, with conditions such as asthma, pneumonia and bronchitis being common erroneous attributions (5). The diagnostic process is further complicated by the necessity for a comprehensive evaluation, including detailed medical history, physical examination, serologic testing, imaging studies, pulmonary function tests and even biopsies. Although in many pathologies, a biopsy is the ultimate investigation that gives the microscopic clues, in terms of DILDs, it is only a part of the process, given the rather generic type of inflammation. Despite advancements in imaging modalities, such as high-resolution computed tomography (HRCT), no single test can definitively diagnose DILDs. Consequently, patients often undergo multiple diagnostic procedures, leading to delays in establishing an accurate diagnosis. Studies have highlighted the extent of these delays. For instance, a survey revealed that 43% of patients waited over a year from symptom onset to receive a correct diagnosis, with 19% experiencing delays of ≥3 years. Additionally, more than half of the patients reported at least one misdiagnosis during their diagnostic journey (6).

Recent studies have provided complex insights into the prevalence and incidence. Globally, the incidence and prevalence of DILDs vary significantly. A systematic literature review published in 2023 highlighted the variability in reported prevalence and incidence rates of DILDs worldwide. This variability is attributed to differences in study designs, diagnostic criteria and healthcare infrastructure across regions (7). In the United States, data from the 2021 Global Burden of Disease study estimated more than 650,000 cases of ILDs, with an age-standardised prevalence ranging from 101 to 156 cases per 100,000 people among different states. This study also noted a higher prevalence among females, with an age-adjusted prevalence of 131.4 per 100,000, compared with 121.3 per 100,000 in males (8).

The first descriptions of organising pneumonia (OP) were made by pathologists who observed the presence of intra-alveolar fibrosis and inflammatory infiltrates in lung tissue. These changes were frequently found in patients with infections or lung injuries but were not recognised as a distinct clinical entity (9, 10). In 1985, Epler et al. (1) introduced the term bronchiolitis obliterans organising pneumonia (BOOP) to describe a specific clinical syndrome characterised by the presence of fibroblastic plugs (Masson bodies) in alveolar spaces and bronchioles, significant pulmonary inflammation without extensive fibrosis and a favourable response to corticosteroids. This term was widely used throughout the 1980s and 1990s as more cases were documented and better understood (11). In 2002, the ATS and the ERS updated the classification of ILDs, replacing the term BOOP with cryptogenic organising pneumonia (COP) (12). The decision to move from the term BOOP to COP had several underlying motivations. One of them was the fact that BOOP included bronchiolitis obliterans, a condition characterised by irreversible obstruction of the small airways, a term that does not reflect the reality of the condition, namely organised pneumonia, without significant obstruction at the level of the bronchioles, but rather an inflammatory process and associated fibrosis at the level of the bronchioles and alveoli. The term COP reflects more the cryptogenic (idiopathic) nature of the condition, in opposition to the secondary form, which can be associated with an infection, some drugs, autoimmune

diseases or radiation exposure. Bronchiolitis obliterans is a distinct condition characterised by irreversible obstruction in the small airways, unlike COP, which has a favourable evolution and a good prognosis when corticotherapy is administered (12).

COP occurs without an identifiable cause, considered idiopathic and classified under IIPs, typically responds well to corticosteroid therapy but may relapse after treatment discontinuation (11). Secondary organising pneumonia (SOP) develops in response to various triggers, such as infections (bacterial, viral, fungal, parasitic), drugs (amiodarone, methotrexate, nitrofurantoin, etc.), connective tissue diseases (rheumatoid arthritis, systemic lupus erythematosus, scleroderma), toxic exposures (chemical fumes, radiation), neoplasms (associated with lung cancer or metastases) and transplant-related lung disease. Some biological therapies, monoclonal antibodies, interferon or anti-interleukin antibodies may also induce OP. Differentiating between COP and SOP is essential, as identifying and addressing the underlying cause in secondary cases significantly influences treatment and prognosis (13).

Insights into the clinical, imaging and histological appearance of OP

OP is a well-defined clinicopathological condition characterised by an inflammatory process affecting the lung parenchyma. Histologically, OP is distinguished by the presence of intra-alveolar proliferations of granulation tissue (Masson bodies), which occlude alveolar ducts, air sacs and small bronchioles. The idiopathic variant is commonly termed COP, whereas secondary OP can arise due to infections, adverse drug reactions, connective tissue diseases or following radiation therapy. In recent years, growing research has refined our comprehension of its clinical manifestations, diagnostic approach and optimal therapeutic strategies. OP is regarded as COP when the causative factor has not been identified, and it is regarded as SOP when the possible cause of the disease is known (14, 15).

The clinical onset of OP is typically subacute, with symptoms developing over weeks or even months. A predominantly non-productive cough is reported in approximately 65%–70% of patients (16). Progressive exertional dyspnoea is a hallmark, often leading to significant functional impairment. Low-grade fever, fatigue and weight loss may occur in up to 40% of cases. Some patients present with flu-like symptoms or are initially misdiagnosed with community-acquired pneumonia, especially when empirical antibiotics fail to elicit improvement. Inspiratory crackles are frequently noted, although digital clubbing is uncommon. However, this phenomenon is evident in patients with overlap syndromes such as usual interstitial pneumonia or NSIP; it may also be present in patients with underlying diseases (e.g. circulatory insufficiency, neoplastic). The absence of significant infectious findings (negative cultures and unresponsiveness to antibiotics) should prompt further evaluation for OP. Rarely, OP progresses to a severe form with features of respiratory failure. Its main histological counterpart is Acute Fibrinous and Organizing Pneumonia (AFOP), which is characterised by a richly fibrinous inflammatory exudate in the alveoli, respiratory tract and bronchioles; this exudate comprises spherical conglomerates, observed as diffuse bilateral shadows on radiographic imaging. AFOP is most often secondary to lung transplantation, allergic alveolitis, reactions to pneumotoxic agents, connective tissue diseases and infections. AFOP has a high mortality rate, particularly in transplant patients (11, 16).

Laboratory and functional studies in OP are generally nonspecific but contribute to the overall diagnostic framework. Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are common findings. In suspected secondary OP (e.g. related to connective tissue diseases), serological assays for antinuclear antibodies (ANAs), rheumatoid factor (RF) and other autoantibodies can be informative (11). Most patients exhibit a reduction in total lung capacity (TLC) and a decreased diffusing capacity for carbon monoxide (DLCO), findings that correlate with the extent of parenchymal involvement. Bronchoalveolar lavage (BAL) fluid in OP often reveals a lymphocyte-predominant inflammatory profile, sometimes with increased neutrophils and eosinophils. Recent work has emphasised the utility of BAL in differentiating OP from other ILDs. In a prospective cohort study, Wang et al. (13) demonstrated that BAL findings, when combined with radiologic features, significantly enhance the diagnostic accuracy for OP. A tissue biopsy with adequate sampling is considered by many experts to be essential for diagnosis (14). An adequate biopsy specimen allows other causes of OP (such as malignancy) to be ruled out and other forms of IIP to be differentiated from COP. Important and useful clues may often be obtained from HRCT imaging patterns, and bronchoscopic investigations can support a confident diagnosis without resorting to tissue sampling with surgical lung biopsy (SLB). Although transbronchial biopsy (TBB) may retrieve diagnostic tissue, its diagnostic adequacy remains somewhat controversial (17).

HRCT remains the imaging choice and consists of the appearance of several characteristic features of semiology. Patchy, bilateral consolidations are typically observed, with a predilection for peripheral or subpleural areas. Air bronchograms are often present within these opacities (15). Serial imaging may demonstrate shifting or ‘migratory’ opacities, a pattern that can help to distinguish OP from other causes of consolidation. Ground-glass opacities (GGO) frequently coexist with areas of consolidation, suggesting

regions of active inflammation or partial resolution. Although less common, small nodular opacities may be noted. The 'reverse halo sign' (central GGO surrounded by a denser ring of consolidation) has been reported as a suggestive insight, though not pathognomonic, feature (16). Follow-up imaging is made with repetitive HRCT, useful in monitoring therapeutic response but also in identifying relapses. For example, a study by Garcia et al. (4) highlighted a series of patients in whom HRCT demonstrated classic subpleural consolidations that resolved with corticosteroid treatment, correlating with clinical improvement (10, 11, 14, 17).

Materials and methods

We conducted an extensive review using PubMed, MEDLINE and Google Scholar to identify the principal epidemiological, clinical, histological and imaging aspects of OP and its various forms. Another main objective of this review was to identify case reports on OP, with a particular focus on rare and unusual cases. The key search terms included 'cryptogenic organizing pneumonia', 'secondary organizing pneumonia' and, importantly, 'case reports of organizing pneumonia'. A wide range of publications was included, encompassing epidemiological analyses and case reports, meta-analyses and reviews, to describe the clinical presentation and forms of OP.

The many faces of OP

As previously mentioned, diagnosing OP remains a clinical challenge. Yao et al. (18) reported a case of a 70-year-old man who presented with a 1-month history of cough with haemoptysis. Initially, an infectious process was suspected. However, the lack of response to antibiotics, the absence of an identifiable aetiological agent, and the presence of a patchy, dense shadow (approximately 2.7 cm × 2.2 cm) with irregular margins in the upper lobe, just below the pleura, raised concerns about the reliability of the initial diagnosis and led to suspicion of malignancy. A percutaneous needle biopsy under computed tomography (CT) guidance was performed, revealing a multifocal centrilobular distribution of fibromyxoid polyps of granulation tissue within the lumen of distal airspaces and small bronchioles. These histopathological findings confirmed a diagnosis of focal COP. The patient was started on oral prednisone at a dosage of 0.5 mg/kg/day, leading to a complete resolution of symptoms and radiological findings after 6 months of treatment.

A rare acute/subacute form of OP, characterised by fibrin deposits in the alveoli, known as acute cryptogenic fibrinous and OP, was described in another case report involving a 58-year-old woman. She was initially diagnosed with community-acquired pneumonia based on radiological findings of consolidation in the right lower lobe. Despite multiple rounds of antibiotics, no pathogen was isolated, and her clinical condition continued to deteriorate. A repeat CT scan revealed that the initial consolidation had expanded, with new lesions appearing in both the upper and lower lobes of the left lung. Given the lesion distribution, a CT-guided percutaneous needle biopsy was performed. Histopathological analysis showed thickened alveolar spaces, scattered fibroblast and lymphocyte infiltration, and massive fibrinous exudates with organisation in the alveolar cavities – findings consistent with OP with acute fibrinous deposits. The patient was initially treated with methylprednisolone at 40 mg/day for 1 week, followed by prednisone at 25 mg/day, which was gradually tapered >5 months. Notably, significant absorption of the consolidations was observed within 1 week of methylprednisolone therapy (19).

Another case involved a 55-year-old man, who presented a 2.7 cm left retrocardiac density, as shown on a chest radiography, associated with right subcostal pain and low-grade fever that persisted. The lesion was further characterised using a CT scan, revealing multiple subpleural lesions in the bilateral lower lobes, some of which had small necrotic areas. Despite completing a course of oral antibiotics, the fever continued to spike and the histological findings showed recurrent alveolar haemorrhage, alveolar and capillary fibrin deposits, and mild to moderate focal interstitial and perivascular lymphocytic infiltrate, supporting the diagnosis of acute fibrinous OP, which responded well to prednisone administration in a dosage of 1 mg/kg, with the resolution of the CT findings after 2 months of treatment (20).

Acute fibrinous and OP can be associated with several autoimmune diseases, such as Sjögren's syndrome, and it can be a presenting feature of primary Sjögren's syndrome. This was observed in the case of a 51-year-old man who was initially treated for community-acquired pneumonia, a presumed diagnosis based on chest radiography findings – basal reticular opacities without areas of consolidation. Due to the persistence of symptoms, the patient sought consultation at an outpatient clinic, where a severe decrease in DLCO (up to 26% of the predicted value) was detected. A subsequent rheumatological evaluation was conducted under the assumption that pulmonary involvement was the presenting feature of Sjögren's syndrome. The patient tested positive for ANAs, ENA, anti-Ro and anti-La antibodies. To further assess the extent of the lesions seen on chest radiography, a CT scan was performed, revealing thickening of inter- and intralobular septa associated with GGO predominantly in the lung bases, as well as multiple foci of multilobar consolidation areas and bronchiolectasis, without evidence of honeycombing – findings suggestive of unspecified interstitial pneumonia. A bronchoscopy with transbronchial biopsies was performed,

and histological examination showed pulmonary parenchyma with altered architecture due to the presence of collagen foci and young fibroblasts, which, in some areas, protruded into the alveolar spaces – findings consistent with OP. Treatment included methylprednisolone pulses for 3 days, alongside intravenous cyclophosphamide (500 mg/m²). Upon discharge, oral corticosteroids were recommended (21).

In the case of a 47-year-old man who was initially treated for community-acquired pneumonia, a CT scan revealed irregular patchy opacities in the lower lobe of the left lung. Despite treatment, there was no improvement in his symptoms. Of note, the patient had a 7-year history of dry mouth and dry eyes, which had not been previously evaluated or treated. Upon admission to a specialised hospital, follow-up imaging showed that the patchy opacities in the left lower lobe had progressed compared with the previous CT scan, and new small patches had appeared in the right middle lobe. After testing positive for *Legionella* urine antigen, antibiotic therapy was initiated. However, his symptoms persisted. Immunological testing revealed positive results for ANAs, anti-SSA/Ro60, anti-SSA/Ro52, anti-SSB/La and anti-histone antibodies. Additionally, a tear secretion test was positive, and salivary gland emission CT dynamic imaging demonstrated impaired uptake in both the submandibular and parotid glands. Lung biopsy findings showed the formation of fibrin balls in the alveolar cavities, along with changes associated with OP. Treatment with oral prednisone (10 mg daily) was initiated, and at a 1-month follow-up, complete resolution of the pulmonary lesions was observed (22).

Huang et al. (23) presented the case of a 56-year-old woman who was initially treated for community-acquired pneumonia based on CT findings (multiple flake-like lesions) and laboratory results. She received broad-spectrum antibiotics, leading to moderate clinical improvement. Notably, the lesions in the right lower lung and the posterior segment of the left lower lung resolved, but those in the apical segment of the left lower lung and the lateral segment of the middle lobe worsened, despite extensive efforts to identify a pathogen. To further investigate, a percutaneous lung biopsy was performed on a new lesion in the left lower lung. The pathology report revealed striated lung tissue, chronic inflammation with widened alveolar septa and focal areas with Masson bodies – characteristic of OP. After multiple unsuccessful attempts to isolate a pathogen from lung tissue samples, *Mycobacterium tuberculosis* was detected using an advanced microbial detection method based on ultra-sensitive polymerase chain reaction (PCR) and second-generation sequencing. This technique allowed for simultaneous pathogen identification and drug resistance analysis. Given the diagnosis of both tuberculosis and OP, the patient was started on isoniazid, rifampin, ethambutol and pyrazinamide, along with prednisone (40 mg daily). Over the following months, CT findings and clinical symptoms showed significant improvement.

When myelodysplastic syndrome is present, both diagnosis and therapeutic management become more complex. A 38-year-old man was admitted to the haematology department with intermittent fever of unknown origin. CT imaging revealed small nodules and patchy consolidations in the right lung, the left upper lobe and the basal regions of the lower lung. Initial bone marrow smears were unremarkable. Given the clinical presentation, elevated biological markers of infection, and PET findings suggestive of a malignant condition, a diagnosis of hemophagocytic lymphohistiocytosis was considered and treatment with dexamethasone (10 mg daily) was initiated. Despite receiving broad-spectrum antibiotics for nearly a month, the fever persisted. Initially, dexamethasone led to fever remission and improvement in lung abnormalities, but high fever recurred after dose reduction. To further investigate the pulmonary findings, a percutaneous fine-needle biopsy was performed, revealing alveolar spaces filled with abundant inflammatory fibrin exudate with immature organisation. Subsequent bone marrow biopsies and the identification of the *ASXL1* gene mutation confirmed the diagnosis of myelodysplastic syndrome with multilineage dysplasia. Following this, treatment with methylprednisolone (80 mg daily) and immunoglobulin was initiated. However, the fever persisted and the lung abnormalities remained unchanged. The patient later returned to the haematology unit, where he ultimately succumbed to gastrointestinal and pulmonary bleeding due to immunosuppression (24).

Apart from the many forms of OP described in this paper, autoimmune illnesses such as scleroderma associated with polyarthritis can also be linked to OP. A case involved a 43-year-old man previously diagnosed with polyarthritis, for which he had not received treatment. He presented with breathlessness persisting for 3 years, a productive cough over the past month, skin hardening and thickening and itchy lesions on his face and back, which had been misdiagnosed by a dermatologist. Findings suggestive of scleroderma were confirmed by nailfold capillaroscopy, leading to a treatment plan that included oral corticosteroids (prednisone 30 mg daily, with gradual tapering), methotrexate (15 mg) and folic acid (5 mg). HRCT revealed patchy consolidations with pleural thickening in the lateral segment of the left lower lobe, pleural thickening in the lateral segment of the right middle lobe, basal segments of both lower lobes, the superior segment of the left upper lobe and multiple centrilobular nodules in the left lower lobe. Extensive investigations aimed at identifying a pathogen were unsuccessful. A treatment strategy was then established, incorporating prednisone (60 mg), methotrexate (15 mg), folic acid (5 mg) and nintedanib (150 mg), which led to significant clinical and radiological improvements (25).

Lee and Kim (26) presented the case of a 35-year-old woman, 11 weeks pregnant, who had a history of community-acquired pneumonia. She was initially treated with antibiotics, with only mild improvement. Over the next 4 weeks, her symptoms worsened. Radiologic examination, including a chest radiograph, revealed patchy opacities in the right lower lobe. Further characterisation with CT showed patchy lobular consolidation and peripheral GGO in the posterior and lateral basal segments of the right lower lobe. A BAL was performed, revealing an increased lymphocyte count (40%) and a decreased CD4/CD8 ratio, with macrophages comprising 25% and neutrophils 8% – findings suggestive of OP. Treatment with prednisolone (0.5 mg/kg daily) was initiated. The patient delivered at 39 weeks without complications. Subsequent histological analysis of specimens obtained via transbronchial lung biopsy showed proliferation of granulation tissue into the bronchioles and alveolar ducts, confirming a diagnosis of COP.

A large number of substances have been correlated with OP, and it is important to consider this association in clinical practice. A case involved a 75-year-old man diagnosed with osteomyelitis, requiring surgery and subsequent vancomycin administration for 41 days. The patient developed a fever the following day, and CT revealed irregular GGO and consolidation in the right upper lobe. At the time, the findings were attributed to hospital-acquired pneumonia, though no pathogen was isolated, and meropenem was prescribed. Despite normal laboratory results and the resolution of fever, the right upper lung lesions persisted. Given the clinical course and imaging findings, a diagnosis of OP secondary to vancomycin was suspected. Prednisolone (60 mg daily for 4 weeks) was initiated, leading to the complete resolution of the lesions. Sertraline, a selective serotonin reuptake inhibitor commonly used in antidepressant therapy, was associated with OP in a 63-year-old man with a long-standing diagnosis of depression. The patient initially presented with symptoms, laboratory findings and a chest X-ray suggestive of community-acquired pneumonia. Despite treatment with broad-spectrum antibiotics, his condition deteriorated significantly, ultimately requiring mechanical ventilation. Further imaging revealed multiple bilateral consolidations, predominantly in the right lung, with a subpleural and peribronchial distribution, along with diffuse patchy bilateral GGO. A SLB identified intra-alveolar buds of granulation tissue composed of fibroblasts, confirming the diagnosis of OP. Intravenous methylprednisolone (1 mg/kg/day) led to initial clinical improvement. However, multiple attempts to taper the corticosteroid dose resulted in relapses, raising suspicion of a secondary cause. This prompted a reassessment of the patient's chronic medications. Noteworthy, discontinuation of sertraline led to a rapid and sustained clinical improvement, which remained stable over the following 4 months. This coincided with a gradual resolution of radiological abnormalities, suggesting a causal link between sertraline use and OP (27).

Trimethoprim-sulfamethoxazole (TMP-SMX) is a commonly used antibiotic with well-established and recognised cutaneous side effects. However, lung toxicity induced by its use is an unusual condition. Nevertheless, TMP-SMX can act as a triggering factor for OP, as demonstrated in the case of an 8-year-old girl who had been treated with TMP-SMX for 25 days for *Group D Salmonella* bacteraemia and osteomyelitis. On the 19th day of treatment, fever reemerged, accompanied by a maculopapular rash and vomiting. An infection with *Rickettsia* was suspected, leading to the addition of doxycycline to her treatment. After completing 25 days of TMP-SMX, she was admitted to the hospital due to persistent fever and acute respiratory distress. CT revealed a tear in the left hypopharynx and anterior chest wall of the upper trachea, leading to pneumomediastinum, bilateral pneumothoraces, and lower cervical and thoracic subcutaneous emphysema. Additionally, parenchymal changes were observed, characterised by diffuse pulmonary GGO with an apicobasal gradient. Following this scan, the patient deteriorated rapidly, developing acute respiratory distress that required emergency intubation. Several differential diagnoses were considered, including infectious causes, autoimmune diseases and underlying immunodeficiencies. However, after gradually excluding other potential causes, TMP-SMX remained the only likely trigger for OP. Based on the CT findings, treatment with methylprednisolone (2 mg/kg daily) was initiated on the sixth day of mechanical ventilation, leading to gradual improvement. After 22 days of mechanical ventilation, she was successfully extubated and completed a 32-day course of corticosteroid therapy. Following a prolonged hospital stay and rehabilitation, she recovered. At the 9-month follow-up, chest radiography revealed only fine reticular opacities in the bilateral lower lung zones (28).

A 79-year-old woman with severe asthma developed chronic eosinophilic pneumonia (CEP). After CEP was resolved with oral prednisolone at 30 mg/day, prednisolone was tapered and discontinued under the introduction of benralizumab for her severe asthma. However, 8 weeks later, symptoms and bilateral patchy infiltrates on chest radiography appeared. Lymphocytosis without eosinophilia was seen in BAL fluids, and TBB indicated OP. COP was diagnosed and resolved with prednisolone at 30 mg/day. Prednisolone was tapered to 3 mg/day without relapse of CEP or COP (29).

At the beginning of 2020, a 76-year-old man presented with symptoms and a chest radiograph showing extensive alveolar opacities in the posterior segment of the right lower lobe and the anterior segment of the left upper lobe, findings suggestive of COVID-19 infection. Notably, he had been on

amiodarone for 1 year to manage frequent ectopic beats and extrasystoles. Despite signs of infection requiring broad-spectrum antibiotics, RT-PCR testing for COVID-19 was negative, and no bacterial pathogens were identified. Further investigations included HRCT, which revealed bilateral subpleural consolidations with air bronchograms, surrounded by GGO. BAL showed a marked increase in lymphocytes, with a mild elevation in neutrophils and eosinophils. These findings supported a diagnosis of OP, likely induced by amiodarone. Six weeks after initiating prednisone (0.5 mg/kg) with a gradual taper over 6 months, follow-up chest radiography showed complete resolution of the right lower lobe opacity and a residual area of parenchymal thickening in the left upper lobe, which resolved over the remaining treatment period. At 6 months, CT confirmed remission, allowing for steroid discontinuation (30).

Epidemiological data suggest that OP secondary to radiotherapy is a syndrome affecting approximately 1.4%–3% of patients treated for breast cancer. Among the recorded cases, one involved a 71-year-old woman with clinical stage T1N0M0 ER+/PR–/HER2– breast cancer, who underwent surgery followed by adjuvant radiotherapy. Eight weeks after surgery, she began radiotherapy targeting the left breast, completing the treatment without major side effects, aside from mild erythema. After starting adjuvant chemotherapy, she developed left breast tenderness, erythema and warmth but remained afebrile. She was diagnosed with radiation recall dermatitis and responded well to treatment with oral corticosteroids and sulfadiazine, allowing her to continue both chemotherapy and letrozole therapy. At her 6-month follow-up after radiotherapy, symptoms and chest radiography revealed a consolidation in the left middle lobe. Despite a course of antibiotics, her condition did not improve. She later developed shortness of breath, and a CT scan showed infiltrates in both the upper and left lower lobes. BAL findings revealed elevated lymphocytes (73%), monocytes (2%) and neutrophils (12%), suggesting radiation pneumonitis. She was treated with oral corticosteroids, initially at 60 mg, which were gradually tapered over a month. However, 1.5 months later, she was readmitted with worsening symptoms. A follow-up CT scan revealed bilateral multifocal rounded consolidations and airspace disease. A biopsy of the right lung confirmed OP, leading to the initiation of prednisone therapy (31).

There are increasing reports in the literature of OP occurring secondary to radiotherapy. One such case involved a 73-year-old woman diagnosed with early-stage breast cancer – an invasive ductal carcinoma, grade 2 – who required adjuvant radiotherapy. Six months after completing treatment, she was admitted with respiratory symptoms and right lung opacities, while laboratory findings remained nearly normal. Given these findings, empirical antibiotic therapy was initiated; however, the patient showed a poor response and developed pyrexia. Corticosteroid therapy with methylprednisolone (1 mg/kg/day) was then introduced, leading to an initial improvement. However, 1 month into the corticosteroid tapering process, follow-up CT scans showed worsening lung findings, prompting a prescription of prednisolone at 30 mg daily. Two weeks after the prednisolone dose was tapered, the patient experienced extreme fatigue, and the disease relapsed, presenting with new pulmonary migratory infiltrates. At this point, a high-dose corticosteroid regimen was reintroduced. This cycle of relapse and corticosteroid re-escalation is repeated multiple times. Consequently, long-term maintenance therapy with prednisolone (5 mg/day) was initiated, alongside antibiotics and proton pump inhibitors. Over the following 10 years, the patient remained stable, with no disease relapses. To this day, she continues to receive 5 mg of prednisolone daily (32).

Ocrelizumab, a humanised anti-CD20 monoclonal antibody, has been used for both relapsing and primary progressive forms of multiple sclerosis. Apart from minor side effects, OP has been linked to other anti-CD20 antibodies, such as rituximab. This was the case of a 37-year-old woman who was diagnosed with multiple sclerosis and was using fingolimod as therapy for 7 years, but the disease followed a progressive course, leading to the initiation of ocrelizumab (300 mg). Three months later, respiratory symptoms began, and a chest X-ray showed lobar pneumonia with a consolidated area displaying a reversed halo appearance on thoracic CT. Empirical antibiotic therapy was started, but there was no clinical improvement. Subsequent CT scans showed lesion progression, with multiple consolidated areas and scattered GGO bilaterally, predominantly in the lingular segment of the right lower lobe. New lesions also emerged in the upper lobes of both lungs while the patient was still on antibiotics. With a preliminary diagnosis of OP related to ocrelizumab administration, methylprednisolone (32 mg) was initiated, leading to clinical and radiological improvements (33).

Conclusions

ILDs are a group of rare conditions, making their diagnosis a significant challenge in clinical practice due to limited day-to-day exposure. This review aims to serve a dual purpose: first, to provide a deeper understanding of the key epidemiological, clinical and imaging characteristics of OP; and second, to offer a practical tool for clinicians. Although rare, OP remains an important concern. In most of the case reports presented, initial lung CT or chest X-ray findings were misinterpreted as community-acquired pneumonia, leading to unnecessary broad-spectrum antibiotic treatment and delaying the correct diagnosis. A crucial aspect of these cases was the repeated use of CT imaging, which allowed for a thorough assessment of the lung parenchyma and a better understanding of the

diverse imaging features of OP, ultimately leading to an accurate diagnosis. One notable radiological hallmark of this condition is its 'migratory' pattern of lung modifications, which should be recognised as a key imaging characteristic for early and accurate diagnosis. Additional investigations, such as BAL fluid analysis, can provide valuable insights into the nature of potential OP. However, histopathological examination remains indispensable, as it allows for the detailed assessment of tissue changes associated with the disease. Despite its risks, it is regarded as the 'holy grail' of ILD diagnosis and should be considered standard practice whenever feasible. Clinically, symptoms are often non-specific, but a persistent and recurrent fever is a common finding in several cases. This pattern may serve as a key indicator of ineffective antibiotic therapy. Therefore, an ongoing, low-grade fever that does not respond to treatment should raise suspicion and prompt further investigation. Additionally, reviewing a patient's chronic medication regimen is essential, as an increasing number of drugs have been linked to OP. For example, sertraline, typically considered a 'benign' medication, has been associated with cases of drug-induced OP, highlighting the importance of careful evaluation. Moreover, the growing use of monoclonal antibodies raises further concerns, as more of these agents are being connected to lung abnormalities, underscoring the need for vigilant monitoring in clinical practice. In light of these new insights, pharmacological treatments should be reassessed whenever there is no clinical or imaging improvement. The administration of corticosteroids, either intravenously or orally, remains the main therapeutic strategy. However, the duration of treatment can vary from a few months to several years. As demonstrated in the case of a woman treated for OP, multiple unsuccessful attempts to taper or discontinue prednisone led to repeated relapses, highlighting the need for an individualised approach. Treatment duration should be tailored based on clinical, functional and imaging evolution.

The information provided in this review aims to serve as a practical tool for clinicians, pulmonologists and specialists in related medical fields to better assess and manage OP.

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