Eur Radiol (2011) 21:2244–2254
DOI 10.1007/s00330-011-2191-6

CHEST

Organizing pneumonia: a kaleidoscope of concepts and morphologies

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Received: 17 January 2011 / Revised: 13 April 2011 / Accepted: 6 May 2011 / Published online: 10 July 2011

Abstract The basic histopathological pattern of organizing pneumonia (OP) is well recognized, but the contexts in which it is encountered continue to increase. In parallel with an appreciation of new causes and associations of OP, an understanding of OP in the spectrum of lung injury and repair has evolved. There is an increasing array of HRCT manifestations of OP, some of which have only recently been described. This article concentrates on new concepts surrounding OP and highlights newly described imaging patterns.

Keywords Organizing pneumonia · Cryptogenic organizing pneumonia · Bronchiolitis obliterans organizing pneumonia · BOOP

Introduction

Organizing pneumonia (OP) can be considered as one stage of a non-specific response to lung injury and is characterized by inflammatory cells and a connective tissue matrix within the distal airspaces. The histopathological entity of OP is encountered in many conditions, including infection, drug reaction and connective tissue diseases. OP also occurs as an idiopathic and well-characterized clinicopathological disorder, cryptogenic organizing pneumonia (COP). The CT signs of OP are many and varied and the classic and more recently reported imaging patterns of OP are reviewed, in addition, practical diagnostic issues for the radiologist are emphasized.

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What is organizing pneumonia?

- A *histopathological* pattern characterised by whorls of myofibroblasts and inflammatory cells in a connective tissue matrix within the distal airspaces.
- A non-specific response to lung injury associated with infection, drugs, inflammatory, and other conditions. (see Table 1).
- As a primary clinical entity, it is termed cryptogenic OP.

History, terminology and classification

Early references to OP can be found in the late nineteenth century literature [1], but the first detailed histopathological descriptions come from the early twentieth century [2]. These were largely based on autopsy studies performed on patients with non-resolving bacterial pneumonia, before the advent of antimicrobial therapy [3, 4]. It was established early on that OP occurred as a result of infection, but during the course of the twentieth century OP began to be recognized in such varied conditions as interstitial diseases [5], drug toxicity [6] and connective tissue disorders [7].

Reports of OP with no known cause or association appeared in 1983, when Davidson coined the term cryptogenic organizing pneumonia [8]. Two years later, Epler et al. described the same entity, which they named bronchiolitis obliterans organizing pneumonia (BOOP)[9]. These two names for the same condition resulted in much confusion [10]. The term BOOP emphasized the histological airspace predominance, but the semantic similarity to obliterative bronchiolitis (bronchiolitis obliterans), an unrelated condition, muddied the waters [11, 12].

The disorder had become firmly established as a distinct clinicopathological entity by the 1990s, and at that time it

Table 1 Causes and associations of secondary organizing pneumonia

Cause/association:	Example:
Drugs:	
Antibiotics	nitrofurantoin
Antiepileptics	carbamazepine
Antiarrythmics	amiodarone
Immuno-modulatory	interferon
Infections:	
Bacteria	*Streptococci*
Viruses	*Influenza*
Parasites	*Plasmodium vivax*
Fungi	*Cryptococci*
Inflammatory:	
Connective tissue diseases	poly/dermatomyositis
Vasculitis	Wegener's granulomatosis
Malignancy	lung cancer
Transplantation	bone marrow
Interstitial lung disease	UIP
Miscellaneous lung injury	radiotherapy

was more frequently referred to (certainly in North America) as BOOP, which was also the preferred term at the first international congress on organizing pneumonia in 1992 [13, 14]. In 1998, Katzenstein and Myers' landmark paper on the clinical relevance of the pathologic classification of idiopathic pulmonary fibrosis, the term BOOP was used; however, the condition was not included in their classification of interstitial disorders owing to its intraluminal rather than interstitial distribution and radiographic appearance of air space consolidation [15]. These issues were further explored in 2002, when a working group sponsored by the American Thoracic Society and the European Respiratory Society settled on the term COP for the clinical entity [16]. They also included the condition in their classification of idiopathic interstitial pneumonias because a) it may be confused with other interstitial disorders, b) the histopathological features include an element of interstitial inflammation and c) in some cases interstitial fibrosis is an obvious component (see later). The term COP remains preferred to BOOP as it conveys the characteristics of the condition and avoids confusion with airway-centered diseases; the trend towards the use of COP is reflected in its proportionately greater use over recent years, although the now abandoned term BOOP is still surprisingly frequently used in the literature.

Histopathology

At a histopathological level, OP is characterized by intraluminal plugs of inflammatory debris (predominantly within the alveolar ducts and surrounding alveoli), consisting of buds of granulation tissue, whorls of fibroblasts and myofibroblasts in a connective matrix (Masson bodies [17]) (Fig. 1). These buds may extend from one alveolus to the next through the narrow pores of Kohn (butterfly pattern). Alveoli may also contain foamy macrophages and there is often mild interstitial inflammation of the surrounding lung [16, 18]. In its purest form, background features of diffuse alveolar damage or fibrosis are absent. However, these components are increasingly recognized in specific situations or variant forms of organizing pneumonia, which are discussed later.

The initial trigger leading to intra-alveolar OP is a degree of alveolar epithelial injury, causing the death of pneumocytes and the formation of gaps in the basal lamina. Crucial to the development of OP is leakage of plasma proteins (including clotting factors) into the airspaces [18].

The process of organization then takes over, both the coagulation and fibrinolytic cascades are activated in the airspaces; the coagulation cascade predominates causing fibrin deposition. The first stage of organization of the exudate involves the formation of fibrinoid inflammatory cell clusters (lymphocytes, neutrophils and some eosinophils). In the second stage, inflammatory cells are less numerous, fibroblasts migrate through gaps in the basal lamina then proliferate and undergo phenotypic modification to become myofibroblasts, and an extracellular reticulin framework is laid down. Mature fibrotic buds characterize the final stage; inflammatory cells are increasingly scarce, concentric rings of myofibroblasts alternate with layers of collagen (predominantly type III), fibronectin and proteoglycans [18].

Cordier has proposed an interesting analogy for organizing pneumonia by comparing it to the granulation tissue of skin wounds, another example of a reversible fibroinflammatory process [18]. OP lesions share a few characteristics with granulation tissue which may shed light on the reversible nature of the lesion; these include

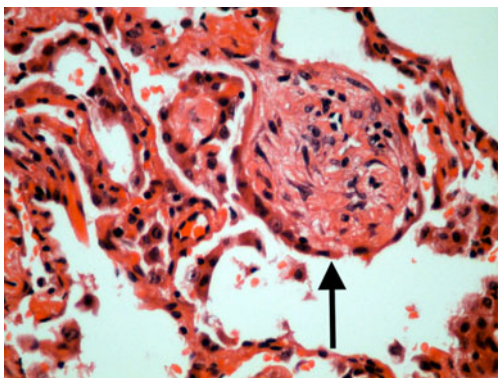

Fig. 1 Histopathology of organizing pneumonia. A surgical lung biopsy specimen stained with haematoxylin and eosin shows a Masson body (*arrow*); organized granulation tissue within the alveolar space, consisting of myofibroblasts and inflammatory cells within a connective tissue matrix

prominent capillarization of the intra-alveolar buds [19] and a predominance of type III collagen, which occurs in a loose matrix and is relatively susceptible to degradation (as opposed to irreversible type I collagen which is encountered in fibrotic lung disease such as UIP) [18, 20–22].

Histopathogenesis of organizing pneumonia:

- Alveolar epithelial injury leads to pneumocyte cell death forming gaps in the basal lamina. Plasma proteins (including clotting factors) and inflammatory cells leak into the airspace. ***(Leakage)***
- Activation of coagulation cascade leading to fibrin deposition. ***(Coagulation)***
- Organization into intra alveolar fibro-inflammatory buds involving whorls of myofibroblasts in a connective tissue matrix. ***(Organization)***
- Inflammatory component recedes, resorption of matrix in most cases. ***(Resorption)***

Epidemiology and clinical features

The incidence of the clinical entity of OP is not well documented, however one Icelandic study reported a mean annual incidence of just under 2 per 100,000 [23]. They also found the idiopathic clinical syndrome, COP, was commoner than OP associated with an underlying disease, such as a connective tissue disease (1.10 vs. 0.87/100,000)[23].

COP has an equal sex distribution. Most patients are non-smokers and it is not clear whether smoking has a protective role, or if this simply reflects the relative prevalence of smokers and non-smokers [18]. The mean age of onset is 58 years (range 15–87); COP has only rarely been reported in children and does not seem to occur in the neonatal period [23–25].

COP typically presents as a relatively short duration illness with fever, malaise, cough and dyspnoea, which may be severe [24]. A history of multiple courses of antibiotics is common and diagnosis is often delayed. There may be a history of a preceding viral-type illness [16] and a seasonal (early spring) relapsing pattern of occurrence has been described [26]. Inflammatory markers are elevated and there is frequently a peripheral neutrophilia. Lung function tests demonstrate a restrictive defect with a moderately reduced transfer factor, [13, 24, 27]. Resting and exercise induced arterial hypoxaemia is common [24] and may be surprisingly severe.

The majority of patients with COP respond rapidly and completely to a course of oral corticosteroids. A proportion relapse, often when the steroid dose is reduced, however relapses do not appear to be associated with increased mortality or long-term functional morbidity [18, 28]. The reported relapse rate ranges from 13% to 58% [28, 29], likely due to the heterogeneity of the groups studied. Treatment for at least 6 months is usually advised [9, 24], but Cordier has proposed low dose and short duration of treatment, with informed patients accepting a higher relapse rate whilst avoiding steroid side effects [18]. Overall, the prognosis is good, however, a proportion of patients will progress to fibrosis, respiratory failure and death [18]; this challenging subgroup is discussed later.

One study has suggested that there is no obvious difference between cryptogenic and secondary OP in terms of symptomatology, physical signs, laboratory and pulmonary function tests, radiologic or pathologic findings [29]. However, the authors also reported that secondary OP leads to more respiratory related deaths than COP and has a lower 5-year survival; although, the secondary OP group included patients with hematological malignancies and connective tissue disorders, which may partly account for the difference [29].

Characteristic clinical and imaging features may indicate the diagnosis of organizing pneumonia, but labeling it definitively as the cryptogenic form requires the exclusion of a cause or association. More specifically, serological testing for a connective tissue disorder and exclusion of, amongst others, infection or a relevant drug history are required. Bronchoalveolar lavage (BAL) can be useful, in that it may yield organisms or neoplastic cells and help obviate the need for lung biopsy. If tissue confirmation is required, the options for biopsy include transbronchial, video assisted thoracoscopy and CT guided percutaneous approaches, the appropriate technique depending on the distribution of the disease.

Imaging considerations

What follows is a brief summary of the well recognized and more recently described imaging patterns of OP. Extrapulmonary findings occur in a minority of patients and include small pleural effusions [30, 31] and mild to moderate mediastinal lymph node enlargement [32].

Classic imaging patterns of OP

Changing multifocal peripheral consolidation

Approximately three quarters of patients with COP exhibit this radiographic pattern (68–81% in the three largest series) [9, 25, 31], consisting of multifocal consolidation, usually peripheral, changing in location over a matter of weeks (Fig. 2) [11–13, 30, 33]. The zonal distribution is frequently described as preferentially affecting the lower zones, but a recent series

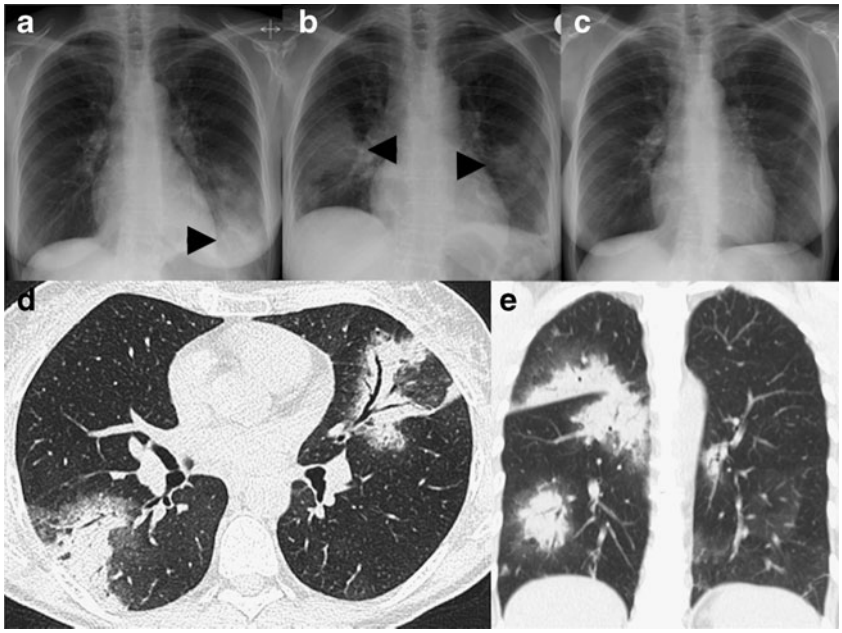

Fig. 2 Changing multifocal consolidation typical of COP. A 58-year-old woman presented with cough and pyrexia. **a, b.** Serial radiographs over a 6-month period show the classical radiographic pattern of changing multifocal consolidation (*arrowheads*), which resolved following oral corticosteroid treatment (**c**). **d., e.** HRCT axial section and coronal reconstruction before treatment show multiple foci of consolidation

from Ujita et al. found an equal distribution through all zones [34]. Migration over time and spontaneous regression of consolidation are important pointers, which narrow a potentially wide differential diagnosis to a significantly shorter list, which includes COP, eosinophilic pneumonia, pulmonary haemorrhage and pulmonary vasculitis.

High-resolution computed tomography (HRCT) findings reflect these changes with patchy consolidation containing air bronchograms, some with associated areas of ground glass opacification [31, 34].

Bronchocentric pattern

A pattern of consolidation forming conspicuous cuffs around larger bronchovascular bundles, with a lower lobe predilection occurs in up to one third of patients (Fig. 3b) [30, 31, 35]. This pattern can extend to the lung periphery and sometimes co-exists with subpleural consolidation, (there may also be associated ground glass opacification or a nodular pattern) (Fig. 3) [30].

Unusual imaging patterns of OP

Solitary focal mass or nodule

An early series of patients with COP reported that up to a third of patients present with a solitary focal mass [27], but this pattern is less frequently represented elsewhere in the literature. Of note, these lesions are often located in the upper lobes. Radiological distinction from lung cancer, in the absence of relatively rapid serial change, is often impossible; although, such foci of OP are often rhomboid in shape, in contrast to the spherical mass typical of a lung cancer (Fig. 4). Low grade FDG PET activity may be seen with OP [36], which can further cloud the issue.

Asymptomatic patients with OP may present following incidental discovery of a mass on a radiograph; the diagnosis is usually made following excision or biopsy of the suspicious lesion [37, 38]. Recurrence following excision of a solitary focus of OP is not usual and, as with more classical COP, complete spontaneous resolution has been described [18, 39].

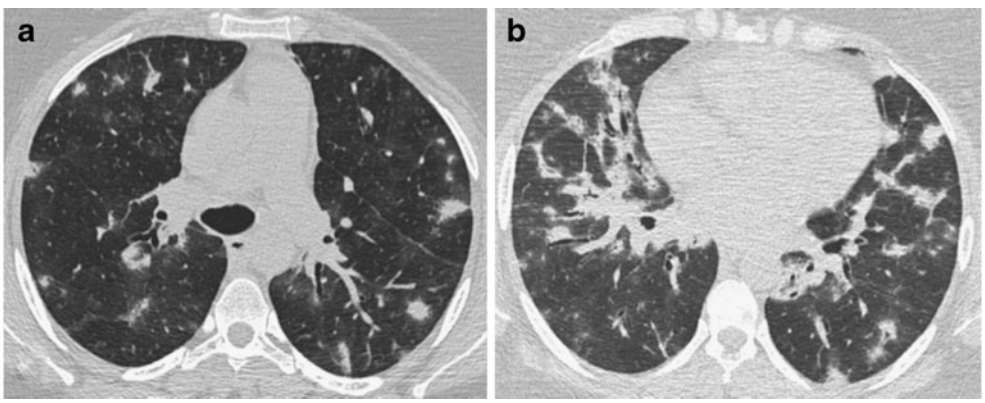

Fig. 3 Co-existent bronchocentric and nodular patterns. A 44-year-old woman with polymyositis presented with progressive breathlessness. **a.** HRCT image though the upper lobes show multiple irregular nodular opacities of various sizes. **b.** Axial images through the mid zones show bronchocentric consolidation in the middle lobe. A surgical lung biopsy confirmed organizing pneumonia

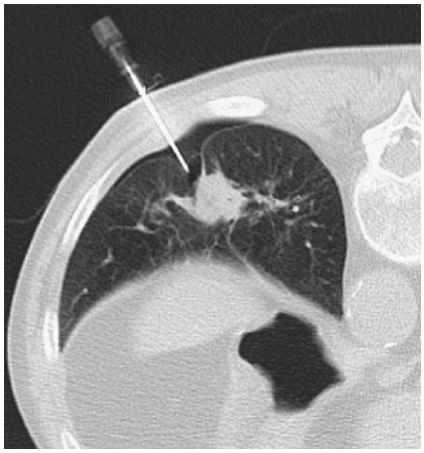

Fig. 4 Solitary focal mass. A 68-year-old man with COPD presented with worsening breathlessness on exertion. A chest radiograph showed opacification at the left lung base. A CT demonstrated a spiculated mass in the left lower lobe suspicious of lung cancer. Histological examination of a CT-guided biopsy specimen revealed organizing pneumonia, with no evidence of malignancy. The lesion resolved spontaneously without treatment

Nodular patterns

A nodular pattern may be a pronounced feature in up to a third of patients and coexist with other CT patterns (Fig. 3a and 5a) [31]. Nodules have been reported ranging in size from micronodular (≤4mm) (Fig. 5b) to larger "acinar" type nodules (up to 10 mm) (Fig. 5a).

Acinar type nodules, reported by Müller et al. [30], may occur on a background of ground glass opacification [40] and may be peribronchovascular or peripheral in distribution [30, 41]; when found in a peripheral distribution, nodules are said to be a useful discriminating feature distinguishing OP from chronic eosinophilic pneumonia [41]. An ill-defined micronodular pattern with peribronchial or centrilobular distribution is a less common manifestation of OP (Fig. 5b) [30, 35, 42] as is a tree-in-bud pattern resembling an exudative bronchiolitis [43].

Multiple masses or larger nodules

When a patient presents with multiple large nodules, exclusion of neoplastic disease including lymphoma and multicentric adenocarcinoma is important [44, 45]. Akira et al. described a series of 59 consecutive patients with biopsy proven COP, 20% of whom had this pattern (often in combination with other patterns); most of these lesions had an irregular or spiculated margin and nearly half contained air bronchograms; pleural tags, pleural thickening, interlobular septal thickening and parenchymal bands were also a feature [44]. This pattern can mimic invasive fungal disease in immunocompromised leukaemia patients [46].

Progressive fibrotic pattern

In this pattern, basal reticulation and architectural distortion co-exist with, or follow, regions of consolidation (Fig. 6); ground glass, acinar nodules and more occasionally honeycombing may also occur [11]. This pattern occurs in up to about a quarter of patients according to Ujita et al. [34] and seems to convey a poorer prognosis.

Recently described imaging patterns of OP

Perilobular pattern

The perilobular pattern was described by Murata et al. [47] and later by Johkoh et al. [48]; it describes disease involving structures bordering the pulmonary lobule (the interlobular septa). It is a useful corroborative sign of OP, and is seen on HRCT as poorly defined (or fuzzy) arcade-like or

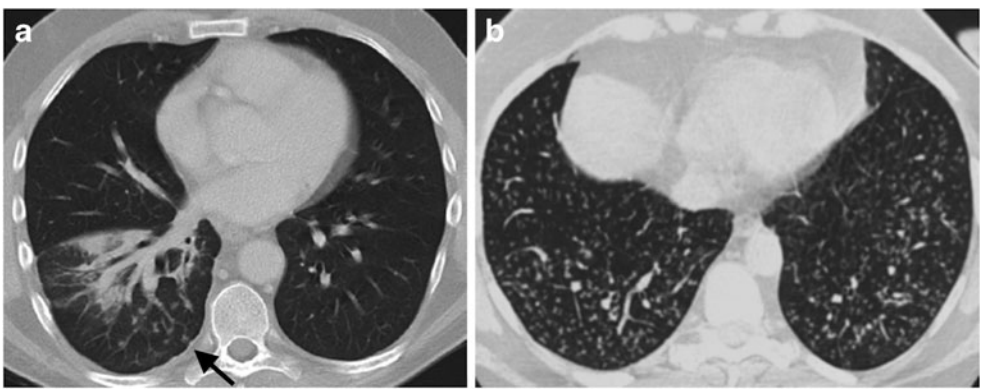

Fig. 5 Nodular patterns. **a.** A 48-year-old man presented with fever, cough and breathlessness; HRCT reconstruction show multiple acinar nodules (*arrow*) adjacent to an area of bronchocentric consolidation. A biopsy demonstrated OP; the patient was treated successfully with steroids. **b.** HRCT section showing diffusely distributed micronodular opacities in a patient with biopsy proven organizing pneumonia, courtesy of Dr Stefan Diederich, Düsseldorf

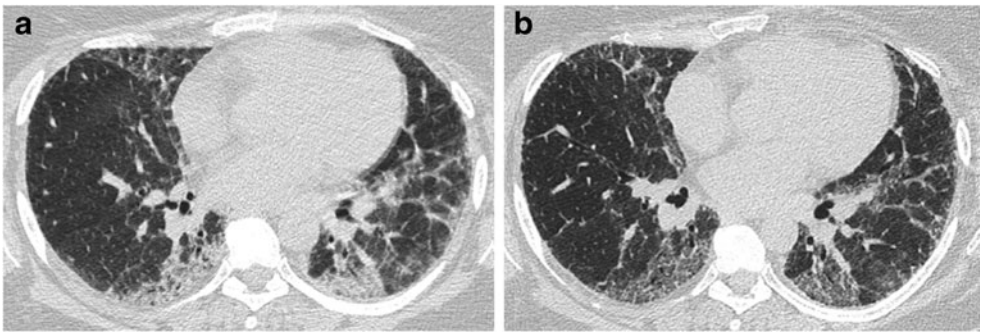

Fig. 6 Progressive fibrotic pattern. HRCT images at the same level in a 54-yearold woman with rapidly deteriorating exercise tolerance. **a.** Shows patchy lower lobe consolidation and a perilobular pattern characteristic of OP. **b.** six months later there is progression to reticulation, parenchymal distortion and traction bronchiectasis indicating fibrosis. Fibrotic organizing pneumonia was diagnosed at a MDT; the patient was stabilized with steroids and immuno-modulatory treatment

polygonal structures, usually abutting the pleural surface and surrounded by aerated lung parenchyma [37] (Fig. 7). In the series reported by Ujita et al., this pattern was present in 57% of patients with COP and did not appear to be indicative of established fibrosis [34]. It is generally not an extensive pattern, usually a few arcades are identified in conjunction with the more typical features of consolidation.

Band-like pattern

This distinctive and under-recognized pattern involves thick radial bands (≥8mm width), which curve towards the (non-thickened) pleura, often containing a single prominent air bronchogram (Fig. 8), which distinguishes such bands from linear atelectasis [11, 49].

Reversed halo or atoll patterns

Crescentic and ring-shaped opacities surrounding areas of ground glass attenuation (Fig. 9) were first reported in two patients with OP in 1996 [50]. More recently the terms "reversed halo sign" or "atoll sign" have been coined [51, 52]. In 2003, Kim et al. found this sign in 19% of patients with OP and suggested that it was relatively specific for COP [51], however it has now been described in numerous other conditions including sarcoidosis [53] and Wegener's granulomatosis [54]. This sign is not to be confused with the "halo sign" describing a halo of ground glass surrounding a nodule, which is also non-specific and encountered in fungal infection or malignancy [55].

Crazy paving

Ground glass opacification is seen in the majority of patients with COP, but is not an obligatory feature [34], interlobular septal thickening away from areas of parenchymal opacification is also well described, but is not usually a prominent feature [41]. It is therefore not surprising that patients may occasionally exhibit a combination of ground glass and superimposed interlobular septal thickening (the crazy paving sign); this pattern has been reported in OP secondary to bleomycin [56].

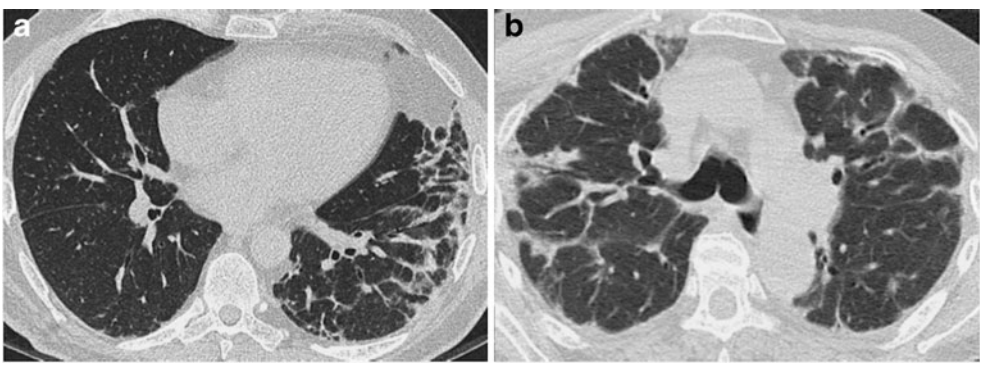

Fig. 7 Perilobular pattern. **a.** A 47-year-old man developed breathlessness, cough and malaise over 2 months. HRCT image through the lower lobes demonstrated arcade-like curvilinear opacities forming irregular polygons. Identification of this perilobular pattern led to a diagnosis of organizing pneumonia and the patient responded promptly to oral steroid treatment. **b.** A 74-year-old women diagnosed with nitrofurantoin induced lung disease. HRCT image through the upper lobes demonstrates a perilobular pattern consistent with organizing pneumonia; the patient responded to withdrawal of nitrofurantoin and steroid treatment

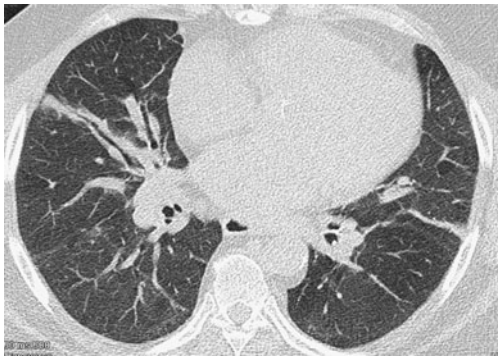

Fig. 8 Band like pattern. A 70-year-old woman presented with breathlessness, HRCT image through the mid zones demonstrates band like opacities extending to the pleura, some containing prominent air bronchograms. OP was diagnosed and the symptoms resolved following steroid treatment

Organizing pneumonia: concepts and uncertainties

Causes and associations of OP

The numerous causes and associations of secondary OP are well documented and continue to increase [11]; the most frequent are shown in Table 1, which is by no means a complete list. A wide range of infective agents have been incriminated, from pneumococcus through a host of atypical bacteria, viruses, parasites and fungi. Recently, biopsy proven organizing pneumonia has been reported in two patients with swine-origin Influenza A H1N1 flu [57]. It is likely that some cases of OP are considered "cryptogenic", when, in fact, the causative organism is simply never identified.

OP is a relatively common histopathological pattern in drug-induced lung disease [18, 58]; numerous compounds are implicated including many immuno-modulatory drugs and antibiotics (notably nitrofurantoin [59]). OP is well documented following lung transplantation or bone marrow grafting, in these situations the pathogenesis is likely to be multifactorial, involving altered immunity, inflammation, infection and drugs [18].

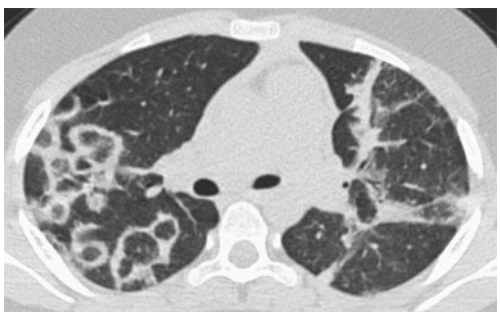

Fig. 9 Reversed halo (atoll) pattern. A 24-year-old man developed a cough and breathlessness on exertion. HRCT image through the upper zones shows a classic reversed halo pattern. An underlying cause was not found, cryptogenic organizing pneumonia was diagnosed and the patient responded well to immunosuppressive treatment

OP is frequently reported as occurring in lung parenchyma adjacent to a variety of localized lesions including lung cancer [18, 60, 61], lymphoma, lung abscess and pulmonary infarction. Many inflammatory conditions including autoimmune diseases, inflammatory bowel disease and systemic vasculitides are associated with OP [18].

The histopathological features of Wegener's granulomatosis include necrotizing granulomatous vascular inflammation, but an OP like variant has also been reported. In this entity, the histopathological features are consistent with OP, with the superimposition of subtle clues to the underlying condition including peri-vascular neutrophilic infiltration, tiny necrotic zones, microabscesses and multinucleated giant cells [62].

Histopathological patterns reminiscent of OP may also be found in other pneumonic entities including eosinophilic pneumonia and acute exacerbations of hypersensitivity pneumonitis [11, 63], in these instances, the presence of clusters of eosinophils or occasional loosely formed granulomas, respectively, are the only features distinguishing the pattern from pure OP [11]. In patients with connective tissue diseases, OP may coexist with NSIP or even be the dominant pattern (especially in dermatomyositis-polymyositis).

Radiotherapy-induced OP is an interesting entity, which occurs with an incidence of approximately 2.5% following radiotherapy, usually for breast cancer, [18, 64]. It seems to be distinct from the common sequelae of radiotherapy, which are radiation pneumonitis and radiotherapy induced fibrosis. Radiotherapy-induced OP is clinically and radiographically reminiscent of COP, it is steroid responsive and can affect any part of the lung, often being seen outside the irradiated area of lung. It seems that, despite irradiating a small part of the lung, the radiotherapy beam "primes" lymphocytes throughout the lungs, which leads to a more diffuse lymphocytic alveolar infiltrate [64] and can eventually result in the classic imaging features of migratory peripheral (Fig. 10) or bronchocentric consolidation [65]. The rarity of this condition suggests that the radiotherapy alone is not sufficient for the progression to OP and that further, perhaps multiple, triggers are required to then precipitate the development of OP. These might include endogenous factors such as genetic predisposition and environmental factors such as infection and drugs [64].

OP has numerous causes and associations and often coexists with other histopathological and imaging patterns of lung injury; it is the position of OP in the spectrum of manifestations of lung injury that is now considered.

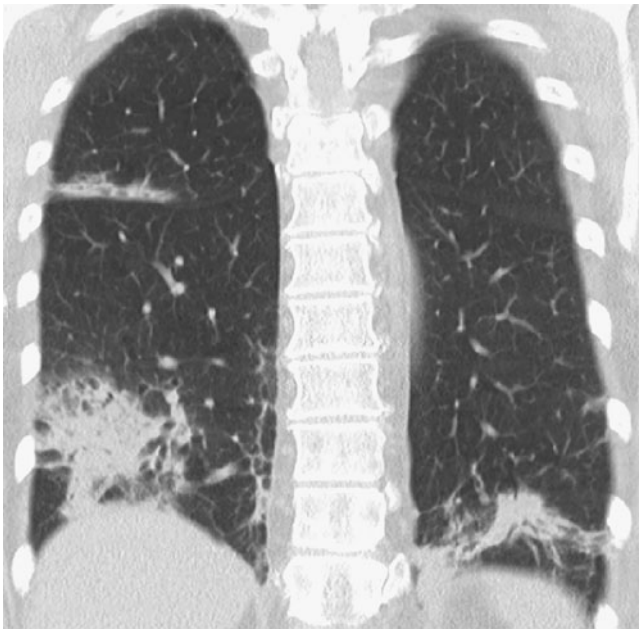

Fig. 10 Radiotherapy induced OP. A 65-year-old woman with breast cancer underwent lumpectomy and radiotherapy to the right breast, seven months later she was referred with a persistent cough. A coronal reformat CT image demonstrates multifocal consolidation, involving both lungs

OP in the spectrum of manifestations of lung injury and repair

The histopathological entities of diffuse alveolar damage (DAD), OP and non specific interstitial pneumonia (NSIP) can coexist in a variety of situations including patients with the clinical syndromes of adult respiratory distress syndrome (ARDS), COP and patients with polymyositis related diffuse lung disease. In these contexts, DAD, OP and NSIP appear to represent different phases or manifestations of lung injury and repair. Histopathologically, they may be identified in adjacent areas of lung. DAD can be viewed as the initial and diffuse manifestation of injury (characterized by an acute exudative phase and accompanied by typical hyaline membranes): upon which focal regions of OP may develop (where plugs of cellular inflammatory debris spill into the distal airspace). Whether or not there is progression to NSIP is idiosyncratic and may be inhibited by steroid treatment when there are regions of OP, but such treatment is largely ineffective in the context of DAD alone [18, 66]. This has been corroborated by a group who studied patterns of DAD and OP in patients with ARDS; they found that those exhibiting DAD with OP had improved outcomes compared to those with DAD alone [67]. The reasons why one patient, or indeed one area of lung, develops florid OP in addition to DAD is not clear but studies in animal models (reovirus induced lung injury in mice) indicate that the severity of the initial may be influential and that T-cells may be required for the development of OP [18, 68].

DAD is the histopathological pattern that occurs in acute exacerbations of fibrotic interstitial pneumonias, notably usual interstitial pneumonia (UIP), but OP is also reported [69]. It has also been reported that those with a histologic predominance of OP had an improved outcome when compared with those with DAD [70]. The better prognosis associated with OP is echoed in data from Kondoh et al. who separated patients with rapidly progressive interstitial pneumonia into two groups, those who exhibited OP and/or NSIP and those with DAD and/or UIP, they reported a more favorable outcome in the OP/NSIP group [71].

In summary, OP should be considered as existing within the wide spectrum of manifestations of lung injury; further, it is important to identify as it implies the likelihood of a response to corticosteroid therapy.

Severe acute (rapidly progressive) OP and progressive fibrotic OP

There have been several reports of a subgroup of patients who present with severe OP with hypoxaemia, a few of whom fulfill criteria for ARDS, and who may require ventilation or progress rapidly to death, especially if prompt steroid therapy is not initiated [72]. The radiological findings in this group consist of prominent bilateral, predominantly basal consolidation. Cordier has suggested that most patients with fulminant OP are likely to fall into an overlap group with acute interstitial pneumonia (AIP) or ARDS (when a cause is present) [18]. However, another histopathological pattern has been reported in a series of 17 patients with a similar presentation: an acute fibrinous (AFOP) pattern with intra-alveolar fibrin balls in addition to organizing pneumonia (and without the hyaline membranes of DAD) has been described; the authors suggested this represents a histological subgroup, distinct from DAD and OP [73]; however, there have not been enough subsequent confirmatory reports to suggest that this is a frequent occurrence, or indeed a separate entity.

OP can occur in acute exacerbations of UIP but there also exists a small sub group of patients presenting with OP, who have a progressive fibrotic course with a poor prognosis. An early description of an admixture of organizing pneumonia and interstitial fibrosis was made in 1973 by Gosink et al. [74] and later Cordier et al. suggested the formation of a separate group of OP (essentially an overlap group with UIP), characterized by more interstitial involvement and a poorer outcome [27]. Further evidence to suggest a subset of patients with histological OP but an aggressive course and poor prognosis, was published in a series by Cohen et al. in 1994 [75]. Lee et al. also reported, in a series of 26 patients with histological OP, that reticular

opacification on HRCT is associated with a persistent or progressive disease [76].

Conclusion

Despite efforts to tighten the clinicopathologic definition of COP and clarify the situations in which the histopathological pattern is encountered, the term "organizing pneumonia" still means different things to different people. A clinician will attach different interpretations to the term "organizing pneumonia", depending on whether it is offered by a radiologist, or pathologist. If OP is mentioned in a pathological report of a lung biopsy specimen when the diagnosis of primary or secondary OP has not been entertained on the basis of clinical presentation or imaging features, then the extent of OP becomes crucial: a few Masson bodies on a biopsy may be dismissed as unrepresentative and a distraction. If OP is the dominant feature on a lung biopsy, then a checklist of alternative explanations or diagnoses should be considered. By contrast, if the radiology shows a sequence of multifocal changing consolidation then, with or without pathological corroboration, a clinician will (in the absence of contradictory clinical features) be receptive to the diagnosis of COP.

Effective management of these challenging cases requires the combined expertise of the clinician, radiologist and pathologist, united with an understanding of OP in the spectrum of manifestations of lung injury and repair and its diverse causes, associations and imaging patterns.

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