The organizing pneumonias: an update and review

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Purpose of review

Basic information as well as more recent concepts regarding cryptogenic organizing pneumonia and secondary forms of the disease.

Recent findings

More recently described and less well recognized illnesses associated with organizing pneumonia, such as organizing pneumonia associated with radiation, are enumerated. In vitro studies from separate laboratories are integrated to create a proposed model of the pathogenesis and repair mechanisms that occur in organizing pneumonias. Using current criteria, we note other interstitial lung processes, in addition to organizing pneumonia, are present in some earlier reports.

Summary

Cryptogenic organizing pneumonia has been reported to respond to corticosteroids with clinico-radiographic resolution in 70–80% of cases. Treatment duration is lengthy, and despite this, recurrences and late recurrences are common. Rapidly progressive, steroid resistant and poor prognostic forms of organizing pneumonia have been described and have been reported more frequently with secondary organizing pneumonia. Since other histologic interstitial patterns often coexist with organizing pneumonia, tissue sampling error or an incorrect morphologic diagnosis can be the reason for aggressive clinical behavior. Steroid nonresponsive patients have been treated with secondary non-steroidal agents. Good clinical outcomes have been reported. Inhaled antigens stimulate GM-CSF-mediated airway inflammation in organizing pneumonia. Repair requires the following: granulation tissue, upon which re-epithelialization occurs; a favorable stromal ratio of matrix metalloproteinase to tissue inhibitors of metalloproteinase; concurrent resolution of inflammation; and stromal fibroblast ingestion of collagen produced earlier in repair, reversing the initial fibrosis.

Keywords

cryptogenic organizing pneumonia, repair mechanisms, secondary organizing pneumonia, steroid nonresponsive, treatment

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Abbreviations

ATS	American Thoracic Society
BALT	bronchus-associated lymphoid tissue
BOOP	bronchiolitis obliterans organizing pneumonia
COP	cryptogenic organizing pneumonia
CTD	connective tissue disease
ECM	extra-cellular matrix
ERS	European Respiratory Society
GERM'O'P	Groupe d'Études et de Recherche Maladies 'Orpheline' Pulmonaires
HRCT	high-resolution computed tomography
IIP	idiopathic interstitial pneumonia
MMP	matrix metalloproteinase
NSIP	nonspecific interstitial pneumonitis
OP	organizing pneumonia
TIMP	tissue inhibitors of metalloproteinase
UIP	usual interstitial pneumonitis

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Introduction

The concept of organizing pneumonia, whether cryptogenic or secondary, has a long and complicated history. It was Epler *et al.* [1] in 1985 who provided a classic description of the disease under the term 'bronchiolitis obliterans organizing pneumonia' (BOOP). Still, the features of the disease were recognized 150 years earlier. The histology had been previously described by Réynaud in 1835 [2,3]. In 1901, the clinicopathologic entity of an organizing pneumonia that involved the bronchioles and alveoli was re-described by Lange [4]. In 1975, similar histologic lesions were described once more by Averill Liebow, who proposed the term 'bronchiolitis obliterans interstitial pneumonia' [5]. Finally, in Frazer and Paré's 1979 reference textbook of pulmonary medicine, 34 patients with organizing pneumonia-type pulmonary illnesses were presented using the term 'bronchiolitis obliterans' [6].

An organizing pneumonia pattern of disease is frequently a manifestation of, or is associated with, other medical conditions. In Frazer and Paré's text, all 34 patients had associated medical conditions, predominantly connective tissue diseases (CTDs) [6]. Since then, the list of known associated conditions has continued to grow (Table 1). In more recent series, 31–44% of the organizing pneumonia cases were linked with other medical conditions [7–10]. However, in Epler's 1985 series, the idiopathic form was stratified out as a separate entity that comprised 85% of their reviewed cases [1]. The rarity of the idiopathic form is underscored by noting its inclusion as an 'orphan' disease by the French collaborative study group Groupe d'Études et de Recherche Maladies 'Orpheline' (orphan) Pulmonaires (GERM'O'P) [11].

Table 1. Clinical findings associated with an organizing pneumonia pattern

Drug reactions
Cocaine abuse
Collagen vascular diseases
Extrinsic allergic alveolitis
Organized bacterial infection
HIV infection
Mycoplasma infection
Viral pneumonitis
Malignancy (solid tumor and hematologic)
Organ transplantation
Nonspecific reaction adjacent to localized lesions (e.g. infarcts, tumors, necrotizing granulomas, resolving pneumonias)
Postradiation (outside radiation ports)
Toxic fume or smoke inhalation
Anthrax vaccination (new)

Nomenclature

The term 'cryptogenic organizing pneumonia' (COP) was introduced by Davison and associates in 1983 [12], but was supplanted in the American literature by the term 'BOOP.' However, in 2002, the American Thoracic Society/European Respiratory Society International Consensus Panel for the Classification of Idiopathic Interstitial Pneumonia (ATS/ERS) recommended that the term 'COP' be used as the preferred clinical term for idiopathic cases, emphasizing the cryptogenic nature of the process. At the same time, it was appreciated that organizing pneumonia patterns of injury could be seen in secondary forms of disease (which we shall term secondary organizing pneumonia or organizing pneumonia). Since pathologists often lack relevant clinical information to distinguish COP from secondary organizing pneumonia, the panel recommended that pathologists use the descriptor 'organizing pneumonia pattern' to report the morphologic pattern of injury that they see under the microscope [13,14]. This recommendation conforms to the common panel recommendation for all idiopathic interstitial pneumonias (IIPs) that the predominant histomorphologic finding(s), followed by the word 'pattern' be used in the final pathologic (as opposed to the clinical) diagnosis (Table 2).

With all due respect, it should be noted that there has been inconsistent use of this terminology even at the highest of academic levels. Examples are use of the terms 'primary COP' (a redundancy) and 'secondary COP' (an oxymoron) [13]; and the statement that 'the clinicopathologic diagnosis of BOOP is appropriate, with mention of the underlying disease' (italics ours) [14]. This assertion implies that the term 'BOOP,' used in conjunction with an appropriate disease modifier, is an acceptable rendering of both the final clinical and pathologic diagnoses. As such, it is our opinion that purging the term 'BOOP' from the medical lexicon might well prove to be difficult.

Table 2. ATS/ERS nomenclature for organizing pneumonia

Clinical diagnosis	Pathologic diagnosis
Cryptogenic organizing pneumonia	Organizing pneumonia pattern [etiology undetermined]
Organizing pneumonia associated with underlying disease (e.g. rheumatoid arthritis) or secondary organizing pneumonia	Organizing pneumonia pattern

ATS/ERS, American Thoracic Society/European Respiratory Society.

Clinical characteristics

Cryptogenic organizing pneumonia 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. The caveat is that COP is a diagnosis of exclusion. Patients usually experience a 2–10 week prodrome prior to seeking medical attention [1], and often describe a specific and abrupt time of onset [15]. There is no sex predilection. COP occurs most commonly in the sixth decade [16], although pediatric COP [17] and organizing pneumonia associated with juvenile rheumatoid arthritis [18] have also been reported. Although organizing pneumonia is uncommon, it should be included in the differential diagnosis in any patient with bilateral airspace disease that is unresponsive to antibiotics [10]. As few large studies of COP or organizing pneumonia exist, the available series [7–10] will be referenced frequently. These reports provide a critical mass of patients that is difficult to obtain with smaller patient cohorts.

Clinical outcome often is better in COP than in other idiopathic or secondary interstitial pneumonias (IIP), even secondary organizing pneumonia. Approximately 70–80% of patients have complete clinical and radiographic resolution of their symptoms with steroid treatment. However, it is important to remember that not all patients respond. A small number respond to antibiotics [1,19–21]; others require supplemental non-steroidal agents, which are almost always used in addition to steroids (discussed as a separate section). Patients with focal nodular organizing pneumonia, usually radiographically detected during follow-up for cancer, are often cured by surgery and need no additional treatment [8,21,22]. Some improve with no treatment [10,21,23]; others have been reported to die from or become incapacitated by progressive disease [9,24,25]. Yousem *et al.* observed that approximately 10–15% of cases are progressive. In nonprogressive forms, relapses often occur when therapy is stopped too rapidly or even during initial treatment [11], further indicating that COP is an inflammatory process that may persist for prolonged periods [26].

Rapidly progressive and poor-prognosis forms of organizing pneumonia

Rapidly progressive forms [27], steroid nonresponsive forms [26] and organizing pneumonia with a fulminant course [9,24,25] have been described. In Cordier's 1989 study, the 7 Group 3 patients had diffuse pulmonary

involvement and radiographic interstitial opacities, not usually present in organizing pneumonia. Four were steroid-nonresponsive, while the other 9 patients with COP did respond [22]. Under the current ATS/ERS classification, some Group 3 patients would likely be re-classified, e.g. as nonspecific interstitial pneumonitis (NSIP) or as unclassified interstitial pneumonitis in which an organizing pneumonia pattern is superimposed upon other interstitial lung processes [25]. Patients with rapidly progressive and lethal organizing pneumonia have been found at autopsy to have more severe interstitial inflammation, alveolar exudate and/or septal fibrosis and fibrotic honeycombing than identified in pre-mortem tissue samples [9,24]. Therefore, sampling error or an incorrect morphologic diagnosis may be the reason for clinical steroid unresponsiveness, rapidly progressive and poor prognostic forms.

Some reports indicate that worse clinical outcomes occur in smokers [25,27]. In these patients, the organizing pneumonia pattern is probably superimposed on pre-existing interstitial and airway abnormalities that prevent a well regulated repair process and are unaffected by steroids. Organizing pneumonia linked with CTD is more likely to be steroid nonresponsive [23,25]. Patients with organizing pneumonia in the setting of hematologic malignancies, especially post bone marrow transplant, develop more severe pulmonary disease and have a higher mortality rate [21], although the underlying condition likely is a strong contributing factor.

Recently recognized associated illnesses

The discussion here is limited to a few more recently described and less well known clinical associations. As various reports attest, secondary forms of organizing pneumonia occur in both solid organ and bone marrow transplant recipients [23,28,29]. There is even one report of occurrence in a syngeneic bone marrow recipient [30]. Organizing pneumonia has long been linked to the use of a variety of drugs. More recently, reports from the transplant literature focus on the relation of posttransplant organizing pneumonia to specific immunosuppressive drugs, such as sirolimus [31], and tacrolimus [32]. The relation is defined by resolution of organizing pneumonia following cessation of the suspected offending agent and re-initiation of steroid treatment with resultant clinical improvement [31–34]. A similar history of drug-related secondary organizing pneumonia was reported in a patient with rheumatoid arthritis [35]. In the pulmonary transplant literature, a histologic organizing pneumonia pattern may be seen with cytomegalovirus infection, aspiration, proximal airway obstruction or even acute rejection [29,36,37].

The syndrome of post-radiation BOOP was clinically defined by GERM'O'P in 1998. The criteria include radiotherapy within 12 months, symptom duration of at least 2 weeks, lung infiltrates outside the radiation ports and exclusion of other causes. This entity is distinguished from radiation pneumonitis by its migratory radiographic pattern [38], although it can follow typical radiation pneumonitis [39,40]. Organizing pneumonia has been reported following thoracic radiation for other malignancies including lung cancer [40,41] and in a thymoma [42]. Organizing pneumonia always should be considered in the differential diagnosis of respiratory symptoms following thoracic radiation. Patients respond to steroids, but often experience relapses and require maintenance dosing [12].

Postradiation organizing pneumonia was reported to occur in 4 of 157 (2.5%) women treated for early stage breast cancer [43]. A similar study demonstrated an identical 2.5% frequency, with post-radiation organizing pneumonia occurring in 5 of 206 breast cancer patients [44•]. Although this syndrome was described relatively recently, the prevalence under close surveillance suggests that this complication may be under recognized [45]. Since the condition is not yet well known, diagnosis may be delayed [39], and the patient may have already returned to her community physician for follow-up [46].

Organizing pneumonia occurred in a 39-year-old U.S. serviceman 1 day after receiving the first in a series of 6 doses of anthrax vaccine. This was an isolated adverse event that occurred following a mass vaccination of US military personnel [47]. Currently, anthrax vaccination is restricted; however, the United States is stockpiling 50% of its anthrax vaccine supplies for civilian use during an emergency [48], raising the finite possibility that organizing pneumonia associated with vaccine use might be seen again. The above is the only known report of organizing pneumonia occurring in association with any type of vaccination.

One report describes 'COP' manifesting as an air-leak syndrome with massive pneumothorax [49], although we favor that the organizing pneumonia response seen here was probably of a reactive nature, rather than a primary cause. Organizing pneumonia has also been described in a canine [50].

Diagnosis

Plain chest radiographic findings are classically described as patchy alveolar opacities predominantly in the lower lobes, often subpleural, with or without ground-glass opacities. The infiltrates may be migratory [7,51–53]. Air bronchograms or feeding vessels and pneumonic-type consolidations are common. The histologic correlate of these radiographic findings is the classic organizing pneumonia pattern, i.e. bronchiolar and alveolar fibrous plugging. The occasional finding of peripheral subpleural reticular opacities may correlate with the histologic and clinical presence of other IIPs and/or fibrosis in addition to organizing pneumonia [51]. Organizing pneumonia presenting as upper lobe

infiltrates, both bilateral [54] and unilateral [3] and as cavitary infiltrates mimicking tuberculosis (2 cases) [55] have also been described.

High-resolution CT may demonstrate bilateral patchy and asymmetric areas of consolidation and ground glass attenuation [56,57,58] and sometimes with small nodular or irregular linear opacities. Bronchial wall thickening and dilatation and/or small pleural effusions may be present. Pathologically, the nodules and areas of consolidation represent different degrees of inflammatory involvement in the bronchiolo-alveolar zone [59]. Consolidation may be present in a sub-pleural or peribronchial distribution. Immunocompromised patients may have atypical radiologic findings and lack areas of consolidation [14]. HRCT occasionally will allow a precise diagnosis of bronchiolar pathology but often it only permits a differential range of possibilities [57,60]. Both usual interstitial pneumonitis (UIP) and non-specific pneumonia (NSIP) may also exhibit ground glass opacities, albeit in different zones of the lungs. The ground glass opacities in organizing pneumonia should remain in a peribronchial distribution, whereas the ground glass opacities in NSIP are usually noted in the bases and subpleural zones and they are often accompanied by reticular opacities. In UIP, the presence of restructuring and honeycombing should yield the correct radiographic diagnosis [61••].

Specimens

The favored diagnostic method for IIPs is the video-assisted thoracoscopic wedge biopsy. Transbronchial biopsies are prone to sampling error in patchy interstitial processes. Wedge biopsies should be obtained from at least 2 lobes and from areas with distinct degrees of radiographic involvement. Preoperative HRCT may permit precise localization of possible biopsy sites. HRCT can also be used as a tracking parameter for treatment response [60]. Even though specimens from the lingula are technically easy to obtain, sampling from this site alone is unsuitable for diagnostic biopsy in interstitial pneumonias, since there can be clinically insignificant fibrosis and inflammation because of its anatomic location. It should only be used to confirm results from other sites, as interstitial processes may not involve this segment of the upper lobe to the same degree [14]. Adequate specimen volume and samples from more than one area will help to avoid possible sampling or interpretation errors.

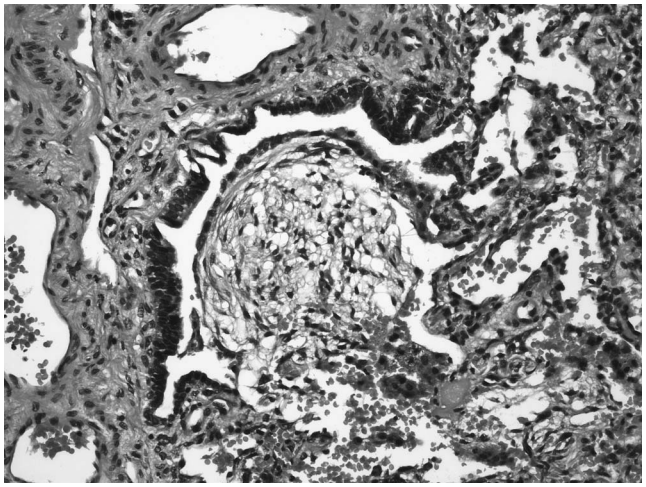
A compelling reason for pathologic examination of lung tissue in interstitial pneumonias, rather than empiric treatment, is the frequency of other primary or secondary processes. In particular, subclinical infection can impact a decision regarding steroid use. Also, since treatment of organizing pneumonia requires rather lengthy administration of corticosteroids, pretreatment tissue evaluation and confirmation is strongly indicated, if clinically feasible [10].

Histology

Bronchiolitis is a generic term indicating the presence of inflammation within and around small airways $\leq$2 mm in diameter. Histologically, the organizing pneumonia pattern of lung injury exhibits anastomosing plugs ('buds') of granulation tissue, the Masson bodies, that fill bronchiolar lumina ('bronchiolitis obliterans') (Fig. 1) and extend into the alveolar ducts and spaces ('organizing pneumonia') (Fig 2). The latter component is usually more noticeable, and the bronchiolitis obliterans component may be minor or not present in the sample. Observed at low power, the process is patchy, but the organizing pneumonia foci are temporally uniform and bronchiolocentric with extension into the immediately adjacent parenchyma. Interstitial lymphocytic inflammation with plasma cells is variable but usually mild, to at most, moderate. In common with all interstitial processes that result in distal airway obstruction, intra-alveolar collections of foamy macrophages (endogenous lipoid pneumonia) may be present. The architecture in the adjacent uninvolved lung is normal with no significant fibrosis or alveolar remodeling [14,16].

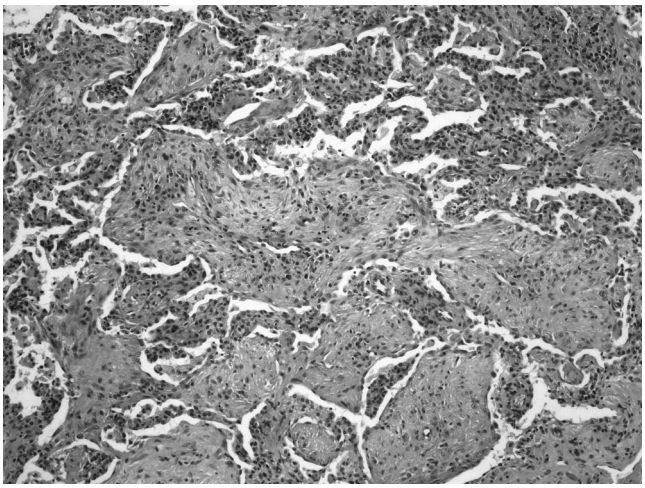
As stated previously, the histologic organizing pneumonia pattern can be superimposed on any of the other interstitial pneumonia patterns. These entities are distinguishable with the caveat that the biopsy tissue must be entirely representative of the pathologic process. The following discussion applies only to wedge biopsies. Certain features, when present, should suggest the presence of interstitial pneumonias other than organizing pneumonia. Interstitial fibrosis is not a component of organizing pneumonia, and if it is present the differential diagnosis of the interstitial process should widen to include UIP, fibrosing NSIP patterns, or limited pre-existing pulmonary fibrosis

Figure 1. Organizing pneumonia histologic pattern



This view shows one of the components of the pattern, namely bronchiolitis obliterans, in which a Masson body is present within a bronchiolar lumen.

Figure 2. Organizing pneumonia histologic pattern



Here a Masson body is present with an alveolar lumen.

with superimposed organizing pneumonia, among others. The interstitial inflammatory infiltrate in organizing pneumonia should remain in a bronchiolocentric distribution immediately surrounding the organizing pneumonia process, not in remote uninvolved lung. Diffuse significant interstitial inflammation associated with edema should suggest alternate possibilities, such as NSIP pattern.

Pathogenesis and mechanisms of disease

Several authors propose that COP may result from undetected viral infection [16,62,63], cryptic antigens [31], or capsid proteins [64]. If this is the case, immune system stimulation by cryptic antigens could mirror immune stimulation by identifiable infectious or noxious agents. Clinical reports of a 'viral-type' prodrome for organizing pneumonia support this concept. The lack of case reports describing organizing pneumonia in association with vaccine use (other than anthrax) is of interest. Although vaccines have a high antigen load, probably higher than other stimuli leading to organizing pneumonia, it is possible that the development of organizing pneumonia requires an immune response that follows antigen inhalation or presentation within the lungs, something that does not occur during vaccination.

The role of the pulmonary immune system in the pathogenesis of organizing pneumonia is still speculative. Bronchial lymphocytes, although sparsely distributed in the lung, are more numerous at the bifurcations of bronchi and near the distal bronchioles [65], where high concentrations of exogenous antigens deposit [66]. Exposure to inhaled antigens stimulates inflammation and lymphokine production in bronchus-associated lymphoid tissue (BALT). This mechanism is known to occur in constrictive bronchiolitis [67]. It is possible that a similar mechanism may initiate the immune response in the other forms of bronchiolitis. We speculate that variation in patient immune systems might tip the direction of response to injury toward a specific type of bronchiolitis. Prolonged sub-clinical immunologic injury that eventually resolves might be the reason for the lengthy clinical course and final recuperation in patients with organizing pneumonia.

Tissue repair requirements

The sequential process of repair includes coagulation, formation of granulation tissue, and the re-establishment of parenchyma-stromal cell interrelationships. Normal repair of acute lung injury results in the restoration of tissue integrity and function that is the end result of complex interactions between cellular and humoral factors and the extracellular matrix (ECM) [68]. The presence of granulation tissue plugs (the Masson bodies) is a prerequisite for re-epithelialization and restoration of the basement membrane. These events occur during bronchiolar intraluminal repair in organizing pneumonia [69]. By contrast, in experimental lung fibrosis, granulation tissue does not form; instead, production, deposition and remodeling of ECM occur within alveolar spaces [69] with resultant parenchymal restructuring [70].

Inflammation

The epithelial cells surrounding Masson bodies carry granulocyte/macrophage colony-stimulating factor (GM-CSF) on their surfaces. This cytokine is thought to play a role in inflammatory recruitment [71]. Resolution of inflammation and removal of inflammatory cells are critical to normal repair. The ability of cells such as neutrophils to undergo apoptosis, followed by macrophage phagocytosis, is important to cell clearance. This process requires CD44 expression on the macrophage surface. CD44 binds hyaluronan, an adhesion molecule found on the surface of apoptotic cells. By contrast, the lack of CD44 may result in a macrophage burst of proinflammatory chemokines [68].

The roles of metalloproteinases

The matrix metalloproteinases (MMPs) (gelatinases, collagenases) are a family of highly regulated, zinc-dependent endopeptidases that mediate ECM remodeling through degradation and re-synthesis of its components. Each enzyme has its own latent and active forms and specific inhibitors, the tissue inhibitors of metalloproteinase (TIMP) [72]. These are present in low levels in normal adult tissues, but are up-regulated in many pathologic processes. Tightly regulated MMP/TIMP balance and homeostasis are crucial for normal repair and remodeling [68,70,72].

Inflammation

Macrophages, eosinophils and neutrophils are the major sources of matrix metalloproteinase (MMP-9) within the airways [68]. Higher absolute concentrations of MMP-9 and TIMP-1 are found in BAL specimens from patients with COP compared with those from UIP patients. The

molar ratio of MMP-9 to TIMP-1 is also higher. In turn, BAL samples from patients with UIP have higher MMP-9/TIMP-1 concentrations than those from normal control subjects. Probably more importantly, UIP patients have low MMP-9/TIMP-1 ratios, and therefore less ability to degrade ECM. Thus, a quantifiable imbalance within at least one MMP/TIMP pair is noted in a fibrotic as opposed to reparative response [73]. Regenerating epithelial cells in organizing pneumonia have high levels of MMPs -1, -2, -9 and TIMP-2. In addition, the ratio of active to latent MMP-2 forms is significantly higher than in control lungs [70].

Granulation tissue formation and fibroblast repair

It is somewhat of a tradition, for good reason, that IIPs are not discussed in isolation. The disease from which organizing pneumonia must be separated in terms of pathobiology is UIP. UIP is predominantly a fibroproliferative process that results in scarring and alveolar parenchymal restructuring rather than the resolution that usually occurs in organizing pneumonia.

Several different tissue responses to lung injury may occur. The first, relevant in organizing pneumonia, is the formation of intra-alveolar fibroblastic buds that partially fill the airspaces and develop into collagen globules. The globular surfaces are lined by alveolar epithelium with discontinuous basement membranes, readily identified by decoration of the epithelial cells with antibody to keratin (Fig. 3). The collagen globules also have an unusual ECM milieu, not present in UIP, which leads to repair [74]. Ultrastructurally, spiraling collagen fibrils and numerous microfibrils are found beneath the regenerating epithelium. Myofibroblasts within the Masson bodies express MMP; these myofibroblasts are able to phagocytize collagen fibrils, reversing early fibrosis. Neovascularization occurs within the connective tissue only in organizing pneumonia, not UIP, and the regenerating endothelial cells are also positive for MMP-2 [70]. This process appears to be stimulated by vascular endothelial growth factor (VEGF) and its receptors Flt-1 and Flk-1 [75].

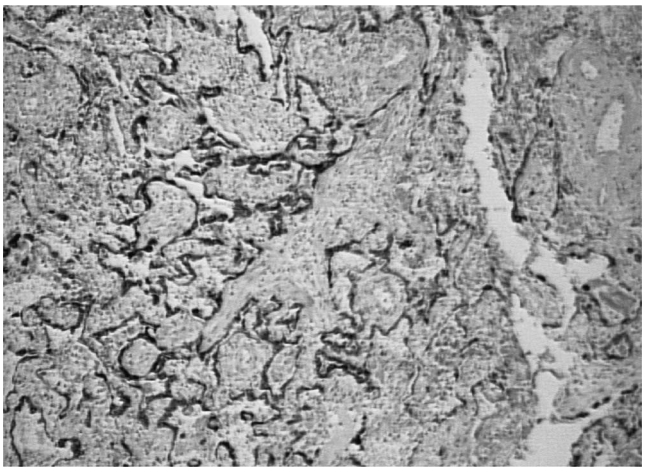
In contrast, changes that occur in UIP include complete obliteration of air space lumina by connective tissue and subsequent mural incorporation of this connective tissue. Ultrastructurally, the regenerative epithelial basement membranes in UIP are continuous, rather than discontinuous [74]. Myofibroblasts in UIP have high levels of TIMP-2 that inhibit MMP activity, tipping the balance toward ECM deposition [70]. The matrix contains bundles of normal collagen fibrils and small elastic fibers, but phagocytosis of this collagen does not occur, nor does neovascularization. This is the 'default' process, and the ECM milieu present is the 'usual type' [74]. The end result is alveolar wall coalescence, luminal obliteration and in the extreme form, 'honeycombing' [70].

In vitro, under basal conditions, fibroblast cell lines derived from human lungs produce little collagenase. However, under induction, different cell lines have varying potentials to synthesize and secrete collagenases. Fibroblast cell lines with low collagenase production have been cultured from UIP patients, and these low levels are thought to contribute to development of fibrosis [76]. Conversely, in organizing pneumonia, cell lines with higher collagenase levels are present, which serves to prevent or inhibit fibrosis [70].

Summary

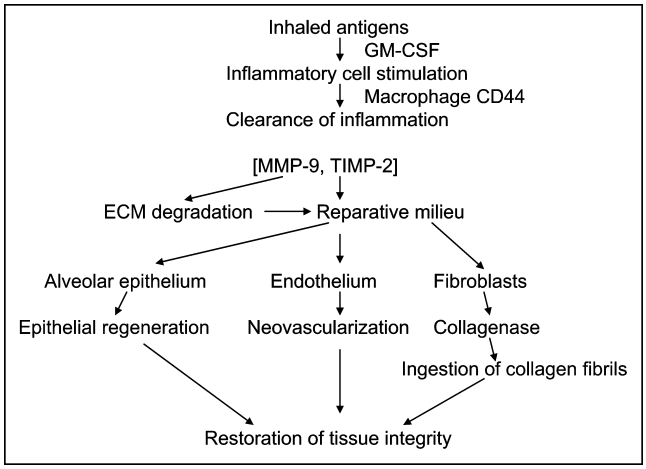
A few of the currently known intracellular and extracellular mechanisms involved in the organizing pneumonia

Figure 3. Low-power micrograph of diffuse epithelial repair in organizing pneumonia pattern, accentuated by Keratin AE1/3 stain



The epithelium is cuboidal and electron microscopy demonstrates fenestrations between the cells (not shown).

Figure 4. Summary of proposed subcellular repair processes occurring during resolution of organizing pneumonia



inflammatory response and tissue repair are summarized in Figure 4. The process is initiated by inhaled antigens, whether of viral or bacterial origin, exogenous material or other noxious stimuli, sometimes undetectable, and may involve BALT amplification of the response. What follows is a simplified outline of the regulated repair response to injury that occurs in organizing pneumonia: (1) stimulation of inflammatory cells mediated by epithelial GM-CSF; (2) clearance of inflammation mediated by macrophage CD44; (3) higher concentrations and molar ratios of MMP-9 and TIMP-2 present in the epithelium, fibroblasts, and endothelium within Masson bodies resulting in a reparative milieu; (4) regenerative neovascularization; (5) high collagenase levels produced by fibroblasts and fibroblast ingestion of collagen fibrils. The result is clearance of inflammatory cells and ECM degradation that culminates in restoration of tissue integrity.

Pharmacologic treatment

It is well known that steroids are the mainstay of treatment for organizing pneumonia; in fact, the terms COP and 'steroid responsive' are almost inseparable. Patients usually receive high-dose corticosteroids, with an initiation dose of 0.75 mg/kg/d based on ideal body weight [77]. Relapses usually occur if the patient is treated for less than 1 year [15,16]. In the only available longitudinal series, the GERM'O'P group stratified and collectively followed 48 COP patients treated with steroids alone. Fifty-eight percent of patients had at least 1 relapse, and of these, 68% relapsed while still undergoing initial treatment. Late relapses, after ≥2 years, occurred in one third of patients; and maintenance treatment was also required in one third. Relapses did not affect the final outcome of 80% clinical and radiographic resolution overall. [11] The findings confirm a high relapse rate even in patients with the 'excellent prognosis' idiopathic form of the disease.

Other treatment options for organizing pneumonia are infrequently used, and the limited world experience with these is summarized as follows [78]: The agents include cyclophosphamide (14 reports) [79–86]; azathioprine (6 reports) [87–92]; and cyclosporine A (5 reports) [18, 93–95]. Most of these reports come from outside the US. In each case these drugs were used in combination with reduced doses of corticosteroids. Most reports noted good responses, often within brief time spans, probably reflecting at least some degree of reporting bias.

Patients with secondary forms of organizing pneumonia also had good outcomes. However, in some of the texts [24,80,83,90,96], there is incidental mention of microscopic interstitial patterns other than, and in addition to, organizing pneumonia. Examples include the presence of acute lung injury pattern and honeycombing in one case [80], and positive immunofluorescence staining for immunoglobulins (lupus pattern) in another [24]. The presence of other histologic patterns removes theses cases from the 'pure organizing pneumonia' category. In most, mixed patterns of interstitial lung disease were present; the organizing pneumonia component was sometimes a secondary process. Mixed interstitial patterns are more common than pure interstitial patterns in CTD-associated pulmonary processes [97; personal observation, MNK].

Treatment experience with agents other than steroids in organizing pneumonia is necessarily anecdotal because of the rarity of the disease, as well as the inclusion of other types of interstitial lung diseases in some published reports. Therefore, small series or additional case reports, describing patient profiles and outcomes following the use of these agents are to be encouraged, but only when grounded in good pathologic evidence of the disease. Collectively, these reports might be helpful to those clinicians who treat this 'orphan' disease. Implementing a data registry similar to GERM'O'P in the US, a more populous country, might provide useful insights into these diseases. Many unanswered questions still remain in regard to optimal use of these agents.

Conclusion

Histologic organizing pneumonia pattern frequently coexists with, or is superimposed on, other interstitial pneumonitides. Thus, tissue sampling error or an incorrect morphologic diagnosis is sometimes the basis for the occurrence of organizing pneumonias that are clinically aggressive. For optimal diagnosis, we recommend use of the thoracoscopic wedge biopsy from more than one site, HRCT for preoperative selection of biopsy site, preferably expert pathology review, and good interdisciplinary communication. More precise stratification of the interstitial pneumonias using current ATS/ERS criteria will ultimately lead to a more accurate understanding of the prognoses occurring within this disease spectrum.

While COP often responds to steroids with complete clinical resolution of symptoms, the treatment duration is lengthy and recurrences requiring additional treatment occur in at least 60% of cases. Sparse reports from the world literature describe successful treatment of steroid nonresponsive, predominantly secondary, forms by use of second line agents including cyclophosphamide, cyclosporine A and azathioprine. However, other pulmonary disease processes were present in some cases, making it difficult to draw disease-specific conclusions from a compilation of these reports. However, good clinical responses have been noted following use of secondary pharmacologic agents, even in cases in which mixed pulmonary interstitial patterns were present.

The initiation of the organizing pneumonia tissue response in the bronchiolar and sub-bronchiolar location may be due to the presence of BALT. Airway inflammation and clearance, formation of granulation tissue, and a favorable ratio

of MMP to TIMP within the granulation tissue stroma results in a reparative milieu that allows ECM degradation and re-synthesis to occur. MMP-expressing fibroblasts are paradoxically stimulated to phagocytize collagen produced earlier in repair, reversing the initial fibrosis. If these complex interactions occur in an orderly manner, full tissue repair may ensue, as in organizing pneumonia. If not, interstitial fibrosis, the default process, is more likely to occur.

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- • of special interest
- •• of outstanding interest

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