Organizing Pneumonias

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Abbreviations

AFOP   Acute fibrinous organizing pneumonia
BAL   Bronchoalveolar lavage
BO   Bronchiolitis obliterans
BOOP   Bronchiolitis obliterans organizing pneumonia
COP   Cryptogenic organizing pneumonia
COPD   Chronic obstructive pulmonary disease
CT   Computed tomography
DAD   Diffuse alveolar damage
DNA   Desoxyribonucleic acid
GPA   Granulomatosis with polyangiitis
NSIP   Nonspecific interstitial pneumonia
NYHA   New York Heart Association
OP   Organizing pneumonia
SOP   Secondary organizing pneumonia
TBB   Transbronchial biopsy

Definition and Terminology

Organizing pneumonia is a particular type of inflammatory and fibroproliferative process of the lung leading to a clinico-pathological syndrome. It is characterized clinically by symptoms and signs resulting from inflammation and consolidation of the lung parenchyma, and histologically by the presence of buds of granulation tissue filling the distal airspaces as a reparative process following damage to the alveolar epithelium. Although its histological features were known since the beginning of the twentieth century, the clinico-pathological syndrome of organizing pneumonia has only been described in the early 1980s [1, 2].

Although the term *bronchiolitis obliterans with organizing pneumonia* (*BOOP*) used in the original description [2] became rapidly popular, it led to confusion with *bronchiolitis obliterans* (*BO*), a clinically and histologically distinct entity characterized by bronchiolar involvement and airflow obstruction, whereas BOOP mainly affects the alveolar spaces and bronchiolitis, if present, is only an ancillary feature. To clarify this issue, the term BOOP has now been replaced by the more accurate term of *organizing pneumonia* (*OP*) [3]. If OP occurs in association with an identified cause or clinical condition, it is called *secondary* organizing pneumonia (SOP). If no cause is identified, OP is termed *cryptogenic* organizing pneumonia (COP). COP has been integrated in the international classification of idiopathic interstitial pneumonias in 2002 [3], and further confirmed in the 2013 update of this classification [4]. The term "organizing pneumonia" has been used both by pathologists to designate a particular but otherwise unspecific histopathological lesion, and by clinicians to describe a specific clinico-pathological syndrome. To clearly identify these two distinct but overlapping concepts, the term *organizing pneumonia* is now used for the clinico-pathological syndrome, whereas the term *organizing pneumonia pattern* designates the histopathological lesion [3].

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Epidemiology

OP represents 2–10 % of all interstitial lung diseases [5–7]. In the only epidemiological study available so far, performed in Iceland, the mean annual incidence of OP was 1.97/100,000, with 1.10/100,000 for COP and 0.87/100,000 for secondary OP [8], meaning that more than half of cases
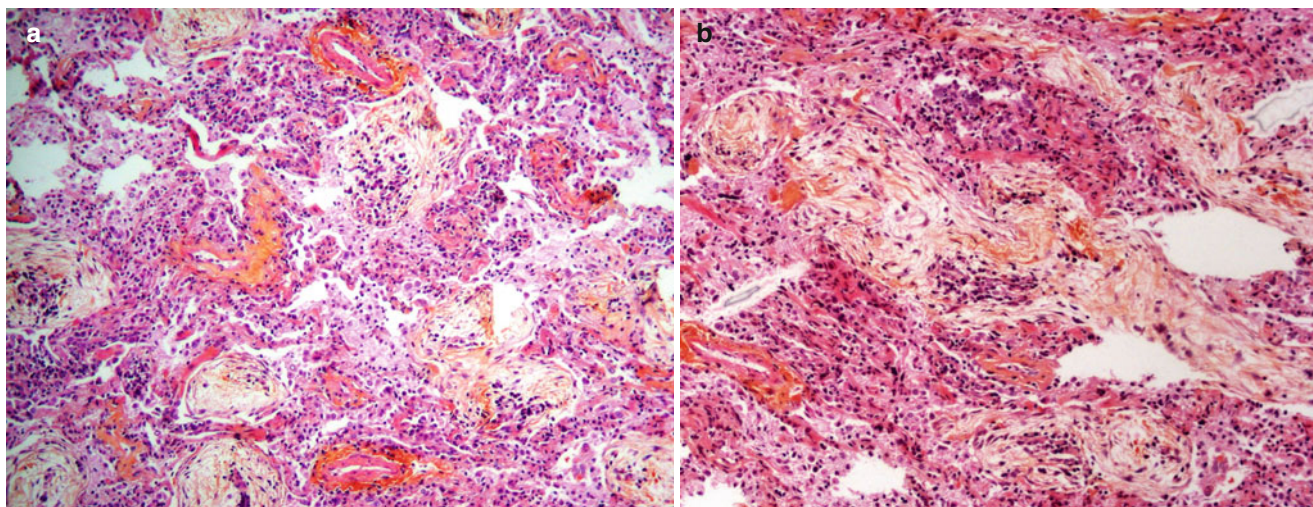
Fig. 24.1 (**a**, **b**) Histopathological pattern of organizing pneumonia at surgical lung biopsy: buds of granulation tissue containing myofibroblasts and inflammatory cells embedded in a loose connective matrix, and filling the alveolar spaces without disruption of the parenchymal architecture. Mild inflammatory infiltrates of the alveolar interstitium

of OP were idiopathic. Men and women were equally affected, at a mean age of 60–70 years. Smoking has not been found a risk factor for OP occurrence.

Pathogenesis

OP is initiated by an injury to the alveolar epithelium leading to necrosis and shedding of epithelial cells. Denudation and formation of gaps in the basal membranes lead to increased alveolar permeability, and exudation of plasma proteins and coagulation factors into the alveoli [9, 10]. In contrast with diffuse alveolar damage (DAD), there are no hyaline membranes. The endothelium appears only mildly damaged.

The first step of intra-alveolar organization is characterized by activation of the coagulation cascade in the alveolar spaces leading to accumulation of fibrin clots containing lymphocytes, some polymorphonuclear neutrophils, and occasionally mast cells and plasma cells [9, 11, 12]. In the second step, fibroblasts from the alveolar interstitium migrate through gaps in the injured epithelial basal membranes and colonize the fibrin residues in the alveolar spaces. Fibroblasts proliferate and transform into myofibroblasts, which produce an extracellular myxoid matrix replacing the fibrin residues. Inflammatory cells infiltrate the alveolar interstitium, while type II pneumocytes proliferate to restore the epithelial lining of the basal membranes. During the third step, the intra-alveolar granulation tissue undergoes progressive organization into mature fibrotic collagen-rich bundles or "buds" filling the alveoli, alveolar ducts, and distal bronchioles without altering the overall parenchymal architecture (Fig. 24.1) [2, 11–14].

Intraalveolar fibrosis resulting from organization of inflammatory exsudates in OP is characterized by dramatic reversibility with corticosteroids, in sharp contrast with fibrosis in the other fibrosing idiopathic interstitial pneumonias, especially usual interstitial pneumonia (UIP), which is irreversible. The mechanisms governing the disappearance of myofibroblasts and fibroblasts from alveolar spaces in OP (spontaneously or with corticosteroids) are poorly understood. Apoptosis may play a role, as apoptotic activity is increased in the newly formed connective tissue in OP [15]. Intraalveolar buds in OP are also characterized by prominent capillarization resembling granulation tissue in cutaneous wound healing [16]. Vascular endothelial growth factor and basic fibroblast growth factor are widely expressed in intraalveolar buds, and angiogenesis mediated by these growth factors could contribute to the reversal of buds in OP [17].

Clinical Vignette

A 77-year old woman presented because of progressive dyspnea stage NYHA II, cough, fatigue, night sweats, anorexia, and loss of 10 kg over 1 year. A chest X-ray showed a left basal infiltrate. A course of antibiotic therapy had no effect, and the patient was referred to a respiratory physician. A chest CT-scan revealed multiple alveolar opacities with air bronchogram in the lingula, middle lobe, and left lower lobe. Bilateral crackles were present. The patient had never smoked, did not take any medication, had no symptoms of connective tissue disease, and no environmental exposure. C-reactive protein was 38 mg/dL. Hemoglobin was 114 g/L. Leucocytes differential count was normal. Antinuclear antibodies were positive at 1/320 but rheumatoid factor, anti-cyclic citrullinated peptide, anti-

double strand DNA and anti-nucleoprotein antibodies were negative. BAL differential count showed 52 % lymphocytes, 6 % neutrophils, and 4 % eosinophils. Cultures were negative. Transbronchial biopsies showed mild chronic interstitial inflammation and intraalveolar fibroblastic buds. Cryptogenic organizing pneumonia was diagnosed. Because of old age, prednisone was started at only 0.5 mg/kg/day (25 mg/day). After 3 days, cough and general symptoms had completely resolved, and dyspnea was markedly reduced. After 2 weeks, chest X-ray was improved. Prednisone was well tolerated and maintained at the same dose for 2 more weeks then tapered over 6 months. The patient was informed about the risk of relapse.

Table 24.1 Frequency of symptoms and signs in organizing pneumonia

No symptoms (incidental finding at chest X-ray)	6 %
General	
Fever	43 %
Malaise	53 %
Night sweats	4 %
Respiratory	
Cough	60 %
Dyspnea	53 %
Pleuritic pain	20 %
Hemoptysis	2 %
Inspiratory crackles	59 %
Wheezing	8 %

Adapted from Ref. [27]

Clinical Features

The clinical features of OP are unspecific and mimic other pulmonary diseases especially infections and malignancies. Many patients initially receive one or more courses of empirical antibiotic therapy, and it is only when this treatment proves ineffective that further investigations are performed. The diagnosis of OP is thus frequently delayed by weeks or even months [2, 14, 18–23].

Disease onset is usually subacute with flu-like symptoms, dry cough, mild dyspnea, fatigue, fever, and weight loss [2, 14, 20, 24]. Productive cough, chest pain, night sweats, arthralgias and myalgias, are less frequent features. Hemoptysis is rare in most large series [23, 25–27], although it has been reported in up to 50 % of cases in one study [28]. Finger clubbing is absent. At chest auscultation, sparse inspiratory crackles are usually heard over the affected areas [26, 27]. Wheezing is uncommon in OP. The frequency of clinical symptoms and signs in a large recent series of OP is summarized in Table 24.1 [27]. No significant difference was found between the clinical presentations of COP and SOP in this series, except for more common crackles in the latter [27]. On rare occasions, OP is incidentally discovered at chest X-ray in an asymptomatic patient [22, 23, 27].

At pulmonary function testing, OP is characterized by mild to moderate restrictive ventilatory defect. Airflow obstruction is found in only a minority of patients, usually smokers [2], and probably reflects preexisting chronic obstructive pulmonary disease unrelated to the OP pathologic process. Carbon monoxide diffusion capacity is usually moderately reduced. Mild to moderate hypoxemia is common [2, 13, 14, 18, 19]. Severe hypoxemia is rare and may result from right-to-left blood shunting through densely consolidated lung parenchyma [29].

Blood cell count usually discloses moderate leucocytosis and neutrophilia [22, 26, 27]. C-reactive protein level and erythrocyte sedimentation rate are usually increased [14, 26, 27, 30]. Bronchoalveolar lavage (BAL) typically shows a mixed pattern alveolitis [14, 20, 21, 23, 24, 31], with predominance of lymphocytes (20–40 %), and a moderate increase of neutrophils (~10 %) and eosinophils (~5 %). Mast cells (~2 %) may be found in one fourth of cases and plasma cells are occasionally present [23]. The lymphocyte CD4/CD8 ratio is usually decreased [14, 21, 23, 24, 31], but it has no specific diagnostic value for OP and is therefore not useful in the diagnostic process. Predominance of eosinophils over lymphocytes is uncommon [31] and suggests the diagnosis of eosinophilic pneumonia rather than OP (cases with overlapping features of eosinophilic pneumonia and OP have occasionally been reported).

Imaging

The imaging characteristics of OP are variable, but can be broadly classified into four patterns: (1) multifocal alveolar opacities, (2) isolated nodule, (3) diffuse infiltrative opacities, and (4) others.

Multifocal Form

The multifocal form is the most typical presentation of OP and accounts for 40–70 % of all cases [22, 23, 26, 32]. It is characterized by multiple bilateral alveolar opacities predominating in the subpleural regions and the lower lung zones, often containing an air bronchogram (Fig. 24.2) [14, 18, 19, 32–34]. A chest computed tomography (CT) is a useful non invasive procedure if OP is suspected, as it often shows more opacities than the chest X-ray, and this multifocal pattern provides an important diagnostic clue for OP. Spontaneous disappearance of some opacities over time and appearance of new infiltrates in other sites occurs in 25–50 % of cases of OP [23, 31], either before treatment or when a relapse occurs (Fig. 24.3). This phenomenon called
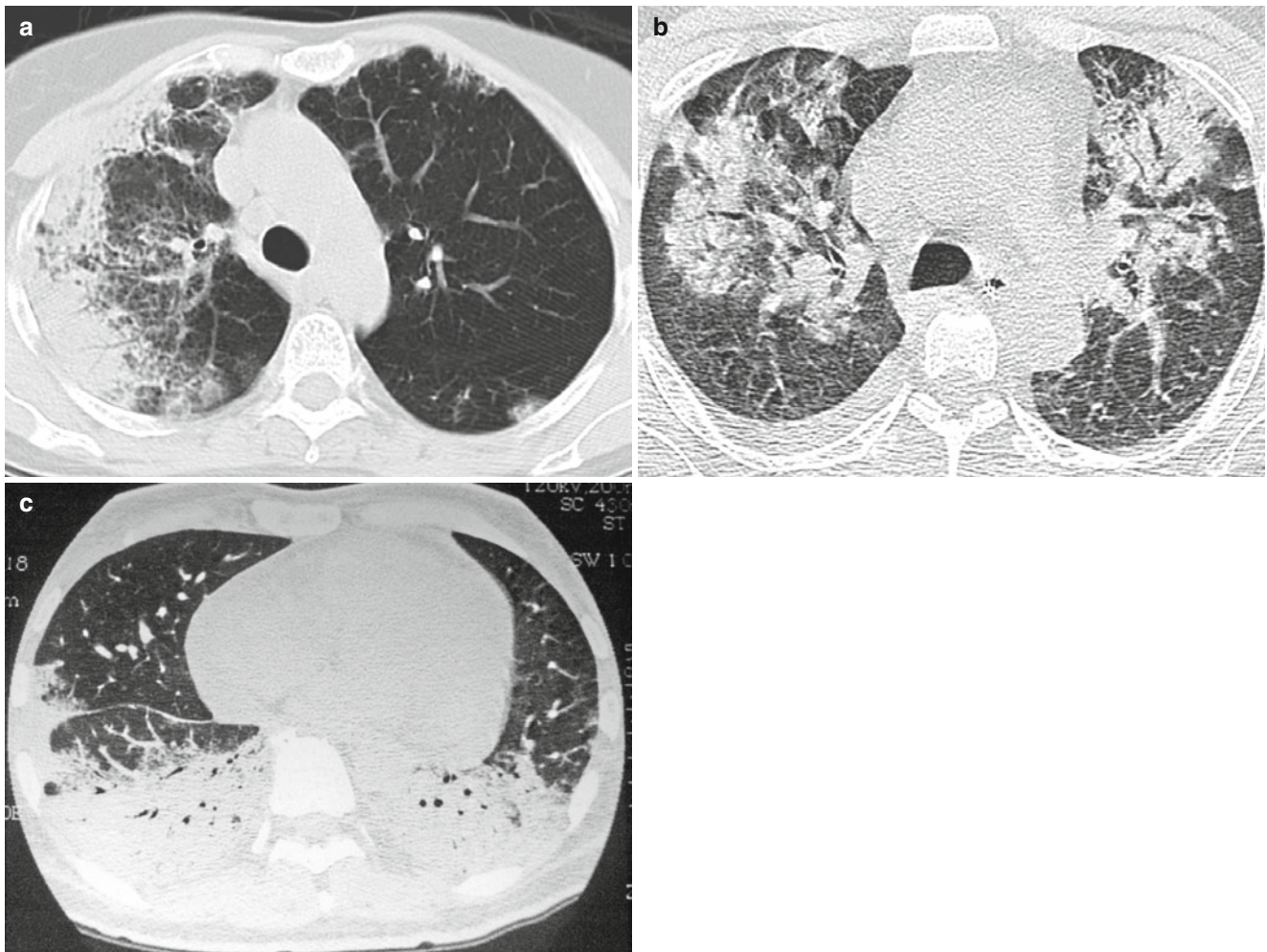
Fig. 24.2 (**a–c**) Chest CT scan in the classical multifocal form of organizing pneumonia in three patients: multiple bilateral alveolar opacities with an air bronchogram, mainly located in the subpleural areas and the lung bases
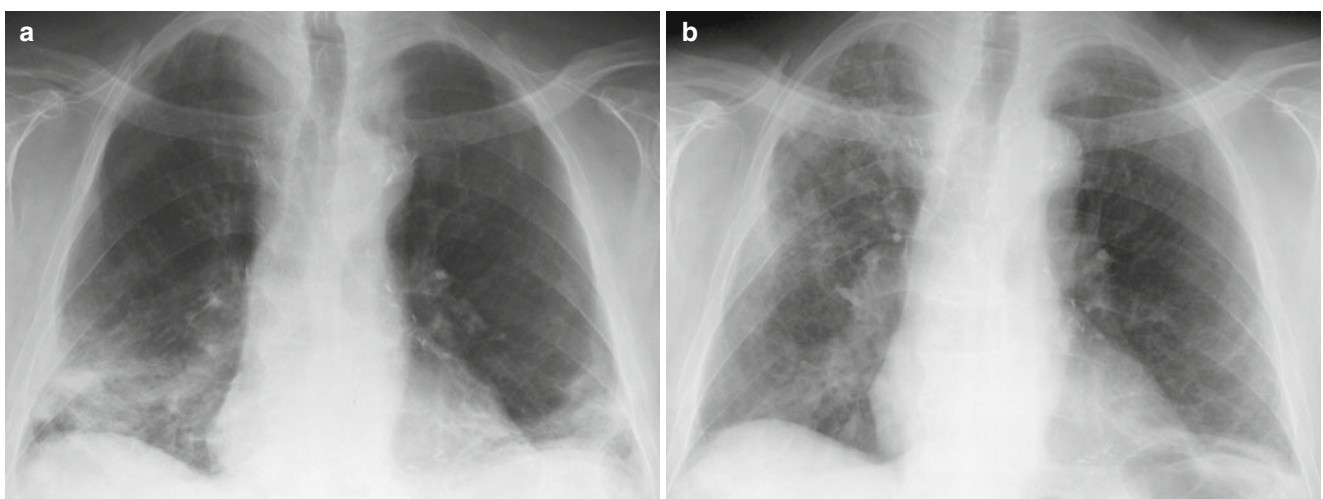
Fig. 24.3 Migratory opacities in organizing pneumonia. (**a**) Bilateral basal subpleural consolidations. (**b**) Three weeks later, spontaneous healing of right basal consolidation and partial regression of left basal consolidation, but appearance of new ground-glass opacities in the middle and upper fields of the right lung (reproduced with permission of Elsevier from Rev Pneumol Clin 2005;61:193-202)

"migratory opacities" provides another important diagnostic clue for OP, as the differential diagnosis is relatively narrow (Table 24.2). Positron emission tomography has shown a significant fluorodeoxyglucose uptake in OP presenting with parenchymal consolidation [35], but this procedure is not part of the routine assessment of OP. Pleural effusion has usually been reported as uncommon in OP [19, 23], although a small effusion has been found in up to 35 % of cases in one series [28]. A moderate enlargement of mediastinal lymph nodes may be found in about 14 % of cases [36].

Isolated Nodular Form

This form has been termed "localized", "solitary", "nodular", or "focal" OP, and represents 5–20 % of cases [14, 22, 26]. It appears as a solitary nodule or mass with smooth or irregular margins [14, 37–41] (Fig. 24.4a). In around half of patients, the lesion is found incidentally [39–42].
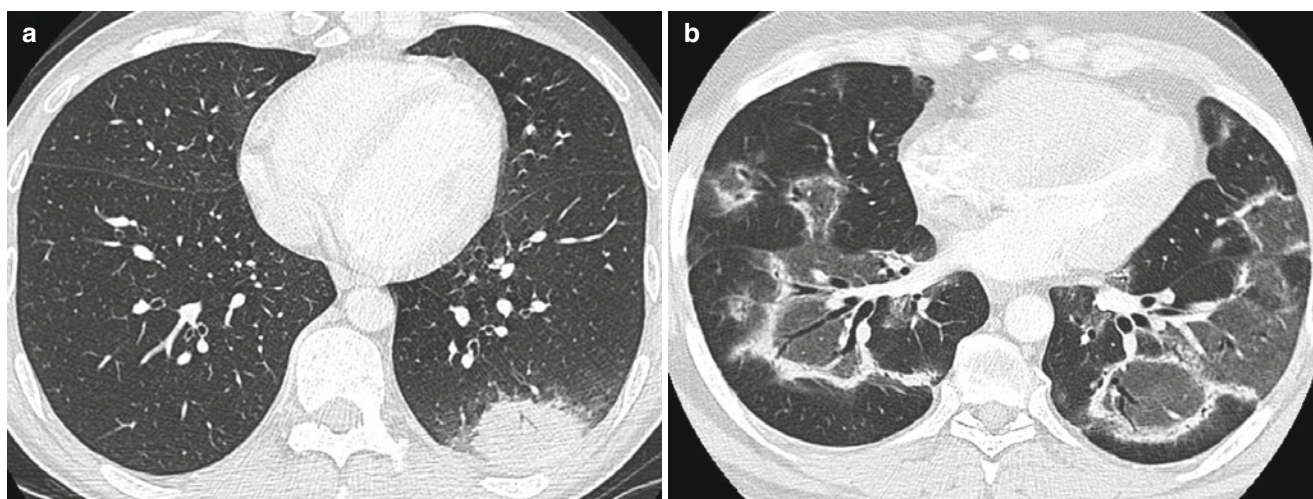
In pooled data from five series of nodular OP totaling 105 cases [39–43], 69 % were men (range across series 56–100 %) and 74 % were smokers or ex-smokers (range

Table 24.2 Differential diagnosis of migratory pulmonary infiltrates

Organizing pneumonia (cryptogenic or secondary)
Chronic idiopathic eosinophilic pneumonia
Secondary eosinophilic pneumonias due to parasitic infections, drug toxicity, etc.
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
Allergic bronchopulmonary aspergillosis
Granulomatosis with polyangiitis (Wegener's)
Lupus pneumonitis
Hypersensitivity pneumonitis
Others (thromboembolic pulmonary manifestations, psittacosis)

57–72 %, n=87). Only 47 % were symptomatic (range 17–77 %). A history of recent infection was found in 29 % (range 12–57 %). The upper lobes were affected in 45 % of cases (range 29–58 %, n=47). The mean size of the nodular opacity was 21 mm (range 6–68 mm). Irregular, lobulated or spiculated margins were present in 72 % (range 54–94 %). An air bronchogram was found in 18 % of cases (n=47). Satellite nodules were found in 40 % (range 29–56 %, n=65) and mediastinal lymphadenopathy in 7 % (range 0–19 %, n=73).

Isolated nodular OP presents with contrast enhancement on CT and positive tracer uptake on positron emission tomography [40, 41], and cannot be confidently distinguished from primary or metastatic malignancy at imaging. This tumor-like appearance frequently leads to surgical resection, and the diagnosis of OP is made retrospectively at pathological examination. In one report, lung resections for isolated nodular OP represented 0.8 % of 1,612 thoracic surgical procedures performed in a 3-year period at one institution [40]. In 105 patients with nodular OP from five series, preoperative transthoracic or transbronchial biopsy was performed in only 23 % of patients (range 0–83 %), whereas 70 % underwent a wedge resection or a segmentectomy (range 17–100), and 7 % had a lobectomy (range 0–24 %). The surgical procedure was curative in most cases without the need for subsequent corticosteroid therapy [40, 41]. Of note, in all of 17 non-operated cases, a spontaneous improvement of the opacity was observed [39, 43]. One practical difficulty in the management of nodular OP is thus to avoid unnecessary lobectomy in this benign disorder mimicking lung cancer. The causes of nodular OP are discussed later in this chapter.

Fig. 24.4 (**a**) Isolated nodular form of organizing pneumonia: unique dense rounded mass with irregular margins located in the left lower lobe. (**b**) Reverse halo sign in organizing pneumonia: multifocal opacities characterized by dense margins and central ground glass opacities with air bronchogram. This feature is not specific and may be found in other inflammatory and infectious disorders

Diffuse Infiltrative Form

A diffuse infiltrative imaging pattern has been reported to occur in 10–40 % of cases in several series of OP [2, 10, 22, 26, 33, 44], some presenting with severe, rapidly progressive disease and respiratory failure [23, 45–51]. Some cases were associated with drugs, connective tissue diseases, or toxic exposure [50–52], whereas other appeared cryptogenic [23, 46, 47, 52].

Diffuse infiltrative OP probably represents a heterogeneous group. It has mainly been reported in early series of OP, suggesting misclassification or overlap with other entities which were unknown at that time. Some early descriptions of diffuse infiltrative OP would probably be now better classified as nonspecific interstitial pneumonia (NSIP), an idiopathic interstitial pneumonia described in the 1990s and characterized histologically by homogeneous chronic interstitial inflammation and/or fibrosis with preserved lung architecture, in which intra-alveolar buds of granulation tissue are a common ancillary finding. Hence, OP pattern representing usually less than 10 % (but sometimes up to 20 %) of the total abnormalities is found in half of cases of NSIP at surgical lung biopsy [53, 54]. Sampling of such focal OP lesions by transbronchial biopsies might thus have led to misdiagnose NSIP as diffuse infiltrative OP. It has also been suggested that a continuum exists between OP and NSIP [54], and that OP/NSIP overlap might explain part of the diffuse infiltrative cases of OP [55]. Hence, patients presenting at imaging with both interstitial changes (histologically corresponding to NSIP) and consolidations (histologically corresponding to OP) have been reported [56]. In a large series of NSIP, the distinction between OP and NSIP has been based upon whether OP pattern represents more or less than 10 or 20 % of the total abnormalities at surgical lung biopsy, an arbitrary criterion [54]. In support of the concept of overlap between OP and NSIP, one study of 22 patients with OP proven by surgical lung biopsy and prolonged CT follow-up reported the evolution of OP consolidations into reticular changes resembling NSIP pattern in a subset of patients [57]. The coexistence of OP and NSIP histological patterns at surgical lung biopsy has been especially observed in idiopathic inflammatory myopathies, in contrast with other autoimmune diseases [58], but more histological data are needed to support the concept of OP/NSIP overlap as a distinct entity.

Other cases diagnosed as diffuse infiltrative OP may actually have had acute interstitial pneumonia, with OP being only a minor histopathological feature or overlapping with DAD at the organizing stage. Other cases could correspond to "acute fibrinous and organizing pneumonia" (AFOP), a recently described entity combining clinical and pathological features of DAD and OP [59] (see below).

Finally, other cases initially reported as diffuse OP may have had acute exacerbation of interstitial lung disease, a recently described acute event occurring in the natural history of idiopathic pulmonary fibrosis, NSIP and other fibrotic interstitial disorders [60]. Acute exacerbations of interstitial lung disease have been associated with histological patterns of either OP or DAD at lung biopsy, the former being associated with a much better short term prognosis [61].

Although genuine diffuse infiltrative OP probably exists, it still awaits better characterization and distinction from similarly appearing entities. Meanwhile, the above-mentioned disorders need to be considered in the differential diagnosis.

Other Imaging Patterns

Rarely, OP may present as multiple, sometimes cavitary nodules [62–65], a micronodular pattern, with multiple small well- or poorly- defined nodules, or nodules with an air bronchogram [66]. Other variants include a bronchocentric pattern, a perilobular pattern resembling thickened interlobular septas, circumferential subpleural linear opacities, and radial opacities [32, 62, 66–69]. A "ring-like", "reversed halo" or "atoll" pattern has rarely been reported in OP, consisting of a focal round area of ground glass surrounded by a crescent or ring of consolidation (Fig. 24.4b) [66]. Contrary to early beliefs, this sign is not specific to OP and may also be found in Churg-Strauss syndrome, granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), chronic eosinophilic pneumonia, lymphomatoid granulomatosis, tuberculosis, and various fungal infections [70].

Histopathological Diagnosis of OP Pattern

Buds of granulation tissue (Masson's bodies) consisting of fibroblasts embedded in a myxoid matrix filling the distal airspaces (alveoli, alveolar ducts, and less commonly distal bronchioles) constitutes the histological hallmark of OP (Fig. 24.1). Associated features include mild interstitial inflammatory infiltrate, type II cell hyperplasia, and intraalveolar foamy macrophages [2, 11, 13]. However, buds of granulation tissue are not specific and may be seen as an ancillary feature in many other disorders such as infections, tumors, pneumonia distal to airway obstruction, hypersensitivity pneumonitis, NSIP, chronic idiopathic eosinophilic pneumonia, or GPA (Wegener's) [11, 12, 71] (Table 24.3). For instance, OP pattern has been found in the vicinity of tumoral tissue in up to 40 % of resected lung cancers [72]. Thus, a confident histopathological diagnosis of OP pattern requires: (1) the presence of buds of granulation tissue within distal airspaces as the dominant histopathological lesion and not only a minor feature, and (2) the absence of features suggesting another diagnosis such as prominent eosinophilic or neutrophilic inflammation, granulomas, hyaline membranes, acute bronchiolitis, or necrosis (see Box 24.1) [3, 11]. The main differential diagnosis of OP pattern at histopathology includes NSIP and the organizing stage of DAD [3].

Table 24.3 Disorders in which organizing pneumonia pattern may be found as an ancillary histopathological feature

Neoplasms
Pulmonary infections
Organization distal to airway obstruction
Aspiration pneumonia
Nonspecific interstitial pneumonia
Hypersensitivity pneumonitis
Desquamative interstitial pneumonia
Chronic idiopathic eosinophilic pneumonia
Secondary eosinophilic pneumonias
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
Granulomatosis with polyangiitis (Wegener's)
Primary pulmonary lymphoma
Diffuse alveolar damage
Drug reactions and toxic exposures
Others

Clinicopathological Diagnosis of OP Syndrome

The clinicopathological diagnosis of OP requires the combination of clinical, imaging and histopathological features. Thus, OP is essentially a multidisciplinary diagnosis. BAL is recommended in virtually all cases presenting with multiple or diffuse opacities at imaging in which a diagnosis of OP is suspected. It allows to exclude an active infectious process and to differentiate OP from other inflammatory disorders having a similar picture such as eosinophilic pneumonias. A histological proof of OP should be obtained whenever possible [73]. Transbronchial lung biopsy (TBB) is the most commonly used method, whereas surgical lung biopsy is now performed in a minority of cases, although it can be considered as the gold standard for histological diagnosis of OP.

The diagnostic value of BAL and TBB to diagnose COP has been analyzed in one study [74]. In 37 consecutive patients presenting with clinical features suggestive of COP and bilateral patchy infiltrates at chest X-ray, BAL with >25 % lymphocytes combined with 2 out of 3 other criteria (foamy macrophages >20 %, neutrophils >5 %, or eosinophils >2 % and <25 %) had a sensitivity of 63 % and a specificity of 57 % to diagnose COP [74]. A sensitivity of 20 % and a specificity of 89 % were found in another study using the same criteria [36]. Transbronchial biopsies showing buds of granulation tissue in distal airspaces, chronic inflammation of the alveolar walls, and preserved lung architecture were 64 % sensitive and 86 % specific for the diagnosis of COP [74]. Although generalization of these data is questionable, expert opinion-based current international guidelines consider that if the clinical and imaging picture is typical with multifocal opacities, a TBB showing also typical intraalveolar buds of granulation tissue is sufficient to confidently diagnose OP [3, 55].

**Box 24.1**

Diagnostic Criteria of Organizing Pneumonia

A. Compatible clinical picture, imaging and bronchoalveolar lavage (see text)

B. OP pattern at histopathology obtained by transbronchial, transthoracic, or surgical lung biopsy*, showing:

  (a) Presence of intraluminal organizing fibrosis in distal airspaces (bronchioles, alveolar ducts, and alveoli) as the predominant feature, patchy distribution of lesions, uniform temporal appearance, mild chronic interstitial inflammation, and overall preservation of lung architecture

  (b) Absence of other significant abnormalities such as interstitial fibrosis, granulomas, neutrophilic infiltration or abscesses, necrosis, hyaline membranes, prominent airspace fibrin, prominent eosinophilic infiltration, and vasculitis

*Modifying circumstances:

1. A diagnosis of OP without biopsy is acceptable if a typical clinico-radiological picture and a well-identified cause are present, and if an infectious process has been ruled out

2. If the patient is too frail or too old for a biopsy, an empirical treatment of corticosteroids may be acceptable, but the risk-benefit ratio of empirical therapy should be carefully weighted in individual cases. Mimics of OP should be ruled out by history and clinical examination, blood and/or urine analyses, and BAL, especially pulmonary infection, drug toxicity, environmental exposure, granulomatosis with polyangiitis (Wegener's), and lymphoproliferative disorder

3. If corticosteroids are administered empirically, a critical re-assessment of the diagnosis should be performed after 2–4 weeks. A rapid and complete response to corticosteroids provides an additional argument in favor of OP, although disorders mimicking OP may also initially respond to corticosteroids (see text). Lack of response to corticosteroids after 2–4 weeks should lead to reconsider the initial diagnosis of OP

Adapted from Ref. [3]

If the initial clinical and imaging features are atypical (solitary nodular opacity, diffuse infiltrative pattern) and if an infection or tumor have not been found at bronchoscopy, a video-assisted thoracoscopic surgical lung biopsy is recommended to make sure that OP is the dominant histopathological pattern and not just an ancillary finding in the frame of another pathological process (Fig. 24.5a) [73].
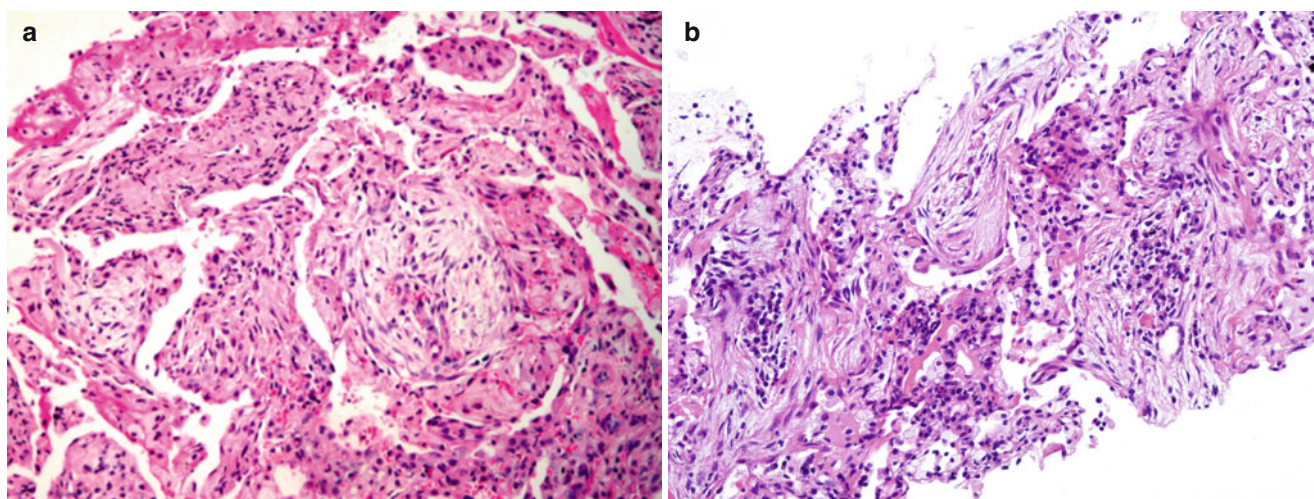
Fig. 24.5 (**a**) Transbronchial biopsy showing a few buds of granulation tissue filling alveolar spaces, with moderate lymphocytic inflammatory infiltrates of the alveolar walls, in a patient with diffuse parenchymal ground glass opacities. Organizing pneumonia was initially diagnosed, but surgical lung biopsy showed a pattern of nonspecific interstitial pneumonia, in which organizing pneumonia was only an ancillary feature. (**b**) CT-guided transthoracic needle biopsy in organizing pneumonia. Numerous intraalveolar buds of granulation tissue with fibroblasts and inflammatory cells embedded in a loose myxoid matrix are visible

Transthoracic CT-guided needle biopsy has been recently reported as a useful minimally invasive diagnostic method for OP with a high diagnostic yield [75, 76]. Most patients studied had unilateral or bilateral consolidations or tumor-like lesions, and only a few had a diffuse infiltrative pattern [75, 76]. The most frequent complications were subclinical pneumothorax and minor hemoptysis, occurring in around 30 % of cases. As transthoracic needle biopsy usually provides larger tissue samples than transbronchial biopsy, it may constitute an alternative to surgical lung biopsy in some cases (Fig. 24.5b). However, experience with this technique for the diagnosis of OP is currently insufficient to recommend it for routine clinical use.

Biopsy may be omitted in a minority of cases with typical clinico-radiological and BAL features, and a clearly identified causal agent of OP such as radiotherapy for breast cancer within the past year, recent documented infectious pneumonia, or obvious drug toxicity. In COP, a combination of typical BAL and multiple patchy parenchymal consolidations at imaging has been found diagnostic in half of cases in one series in the absence of a biopsy, and this strategy deserves further studies [36]. If the risk/benefit ratio of lung biopsy is considered unfavorable due to old age, frail patient or significant comorbidities, a presumptive diagnosis of OP and an empirical treatment of prednisone may be an acceptable strategy. However, the disadvantages of prolonged empirical corticosteroid therapy in the absence of a clear diagnosis, and the risk of false diagnosis of OP, should also been kept in mind. Hence, disorders mimicking the clinical and imaging features of OP may initially respond to corticosteroid treatment, including GPA (Wegener's), primary pulmonary lymphoma, NSIP, or hypersensitivity pneumoni-

tis. Therefore, if the disease follows an unusual course or the response to therapy is inadequate, the diagnosis of OP should be reconsidered, especially if the initial diagnosis was made without biopsy or with transbronchial biopsy only.

Differential Diagnosis

After having assessed the clinical, imaging and histopathological features which make OP a likely diagnostic hypothesis, one must consider other disorders presenting with similar features such as infections, tumors and other inflammatory lung diseases. Imaging could be a starting point to address the differential diagnosis.

In cases presenting with single or multiple areas of parenchymal consolidation, the main differential diagnosis includes infections, minimally invasive or invasive adenocarcinoma (formerly bronchoalveolar carcinoma), eosinophilic pneumonias (either idiopathic or secondary to a known cause), GPA (Wegener's), Churg-Strauss syndrome, and primary pulmonary lymphoma. The distinction between OP and GPA may be challenging in some cases, as GPA may present with clinical, imaging, and even histological features of OP pattern [11, 71]. Although the latter usually consist of small foci of OP at the vicinity of otherwise typical granulomatous lesions, OP pattern may occasionally be a prominent histological finding in GPA [11, 71].

In patients presenting with a solitary nodule or mass, lung cancer is the main working hypothesis until proven otherwise. When multiple nodules are present, the differential diagnosis includes metastatic tumors, lymphomas, and pulmonary infections including septic emboli.

If OP presents as a diffuse infiltrative disorder at imaging, the differential diagnosis mainly includes hypersensitivity pneumonitis, NSIP, acute interstitial pneumonia, other idiopathic interstitial pneumonias, and acute exacerbation of preexisting interstitial lung disease.

Etiological Diagnosis of OP

The next step in the diagnostic process of OP is to distinguish between SOP and COP. The search for a cause or associated condition should not be overlooked, as removal of an offending agent, such as a drug, is an essential part of therapy. Since there is no clinical, radiological, or histological characteristic allowing to confidently distinguish COP from secondary OP [27], the diagnosis of COP is made by exclusion, when the search for a cause remains negative.

SOP has been associated with numerous causal agents and clinical contexts (Table 24.4) [27, 73]. It frequently occurs in association with various infections mostly caused by bacteria, but occasionally also by viral, fungal, and parasitic agents. Another frequent cause of OP is a drug reaction [73]. A comprehensive and updated list of incriminated drugs is available on www.pneumotox.com. OP can also arise in the context of connective tissue diseases such as idiopathic inflammatory myopathies or rheumatoid arthritis, and in various types of solid cancers and hematologic malignancies, where it should not be mistaken for neoplasm progression or recurrence [77]. One example is provided by bleomycin toxicity: besides diffuse interstitial lung disease,

bleomycin can also occasionally induce OP manifesting as pulmonary nodules mimicking metastatic tumor [78–80]. OP can also occur during myelo- or lymphoproliferative syndromes, and after lung or bone marrow transplantation. In the latter, an association has been recently demonstrated between OP and both acute and chronic forms of graft-versus-host disease, suggesting that a causal relationship may exist between these two conditions [81].

OP may occur in women receiving radiation therapy for breast cancer [82–87], with a reported incidence of 1.8 % among 2,056 patients followed by chest-X-ray every 3 months for 1 year [86]. Affected patients are women treated by tumorectomy or mastectomy followed by chemotherapy or hormonal therapy, and radiation therapy of approximately 50 Gy on the tumoral site and homolateral lymph nodes. The clinical picture is identical to COP and starts on average 14 weeks after the irradiation, although it can occur up to 1 year later [82]. In contrast to classical radiation pneumonitis, which is limited to the radiation field, radiation-induced OP also affects the lung outside the radiation field and frequently involves the controlateral lung. Opacities may be migratory. BAL shows a typical mixed pattern alveolitis. The outcome is favorable under corticosteroid treatment [82]. Despite the frequent occurrence of relapses, a complete cure is usually observed. In milder cases, spontaneous disappearance without corticosteroids has been reported [88]. Interestingly, this variant of OP has been almost exclusively described in women irradiated for breast carcinoma, and only rarely in individuals of both genders irradiated for other types of tumors, especially lung cancer. The particular tangential

Table 24.4 Causes of secondary organizing pneumonia, with relative frequencies of main categories

Infections	**~45**%
Bacteria (*Chlamydia pneumoniae*, *Coxiella burnetii*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Nocardia asteroides*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Staphylococcus aureus*, *Streptococcus group B*, *Streptococcus pneumoniae*), **virus** (*herpes virus*, *human immunodeficiency virus*, *influenza*, *parainfluenza*, *adenovirus*, *cytomegalovirus*, *hepatitis C*), **parasites** (*Plasmodium vivax*), **fungi** (*Cryptococcus neoformans*, *Penicillium janthinellum*, *Pneumocystis jiroveci*)	
Drugs	**~20**%
5-Aminosalicylic acid, amiodarone, amphotericin, azathioprine, barbiturates, beta blockers, bleomycin, busulphan, carbamazepine, cephalosporin, clomipramine, cocaine, erlotinib, everolimus, gold salts, interferon, L-tryptophan, mesalazine, minocycline, nitrofurantoin, nilutamide, oxaliplatin, phenytoin, rituximab, sulfasalazine, tacrolimus, thalidomide, temozolomide, ticlopidine, transtuzumab. **See also** www.pneumotox.com	
Solid tumors and hematologic malignancies	**~15**%
Autoimmune/inflammatory disorders	**~11**%
Systemic lupus erythematosus, Behçet disease, rheumatoid arthritis, polymyalgia rheumatica, polymyositis and dermatomyositis, systemic sclerosis, mixed connective-tissue disease, Sjögren syndrome, ankylosing spondylitis	
Radiation therapy for breast carcinoma	**~9**%
Allografts (lung, bone marrow, kidney, liver)	
Inflammatory bowel diseases	
Toxic exposures (acramin FWN – an aerosolized textile dye, paraquat, sulfur dioxide, house fire, paraffinic mineral oil)	
Post-obstructive pneumonia and aspiration pneumonia	
Other	
IgA nephropathy, thyroiditis, primary biliary cirrhosis, mesangiocapillary glomerulonephropathy, Sweet's syndrome, common variable immunodeficiency, essential mixed cryoglobulinemia, coronary artery bypass graft surgery	

From Ref. [27]

irradiation fields used for breast cancer could play a role. A bilateral lymphocytic alveolitis has been reported to occur in 85 % of women receiving unilateral irradiation for breast cancer and, despite being asymptomatic in most cases, could be an early event in the occurrence of OP [89]. Hormonal factors could also be involved. Hence, in one study, age >50 and anti-estrogen therapy were significantly correlated with the occurrence of OP, with odd ratios of respectively 8.88 and 3.05 [87]. However, given the importance of hormonal therapy for tumor control in these patients, avoidance or interruption of hormonal therapy to prevent or cure OP cannot be recommended at the present time.

The cause and mechanisms of focal OP are probably different from the other forms of OP. Although some authors found focal OP to be idiopathic in most cases [41], others have reported underlying COPD in up to 67 % of cases, and recurrent respiratory infections in up to 57 % [40], suggesting that focal OP may be triggered and preceded by an infectious process. In support of this hypothesis, one study reported the occurrence of small neutrophil aggregates in the vicinity of localized OP (with otherwise typical OP pattern at histopathology) in 73 % of cases [42]. Aspiration of food particles may be another cause of focal OP [90]. In one retrospective study of 59 cases of aspiration pneumonia, OP pattern was the predominant histopathological pattern in 88 %, usually associated with particulate foreign material, multinucleated giant cells, acute pneumonia, bronchiolitis, or suppurative granulomas [90]. Twenty-two percent of these cases presented as solitary nodules suspect of lung cancer, whereas food aspiration was clinically suspected in less than 10 % [90]. Infraclinical particulate matter aspiration pneumonia may thus be a relatively common cause of lung nodules presenting with OP pattern at histopathology. Interestingly, the prevalence of active or former smoking appears high in series of isolated nodular OP (57–93 %) [39–43]. It is currently unknown whether smokers are more prone to develop this presentation of OP, or are simply more likely to undergo a surgical procedure for such nodular lesions resembling lung cancer.

In the majority of cases, OP has no recognizable cause [23] and is termed cryptogenic OP (COP). COP has been integrated in 2002 in the classification of idiopathic interstitial pneumonias [3], and maintained in the 2013 update of this classification in the category of major idiopathic interstitial pneumonias (acute/subacute disorders) [4].

Treatment

Corticosteroids are the current standard treatment of OP [2, 14, 20, 22, 26, 31, 34], although spontaneous improvement has occasionally been reported [2, 88]. Clinical improvement usually occurs within 2–3 days after treatment onset. Pulmonary infiltrates at chest X-ray usually markedly improve within a few days. On average, a >50 % improvement

at imaging usually occurs within 3 weeks of treatment, and complete cure is observed after around 3 months [21, 22]. The spectacular and reproducible response to corticosteroids can even be considered as an additional diagnostic feature of the clinical syndrome of OP, and if this response is poor, the initial diagnosis should be reconsidered. Besides corticosteroids, removal of the causing agent should be done whenever possible in secondary OP.

Treatment intensity and duration have not been well defined. In patients with typical COP, an initial dose of prednisone of 0.75 mg/kg/day has been proposed for 2–4 weeks [22, 55]. Corticosteroids are then usually tapered over 6 months and stopped. However, this duration can extend up to 12 months or even longer due to relapses in a significant proportion of patients. Side effects of prolonged corticosteroid treatment occur in up to 25 % [22]. In an attempt to better define the corticosteroid treatment in COP, a standardized therapeutic regimen has been proposed by the French Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires (Table 24.5) [22]. A retrospective comparison of patients having received this standardized protocol with a group treated with other therapeutic regimens did not reveal any differences in terms of efficacy, delay to remission, occurrence of relapses, morbidity, or final outcome [22]. In contrast, cumulated doses of prednisone after 1 year were reduced twofold in the group having received the standardized treatment [22]. This therapeutic regimen may thus provide a framework to guide management and limit the burden of corticosteroid therapy, while maintaining the same efficacy on disease control as higher doses of prednisone. However, given the wide clinical expression and severity of the disease, a unique treatment regimen cannot cover all clinical situations and physicians need to adjust the prednisone dose to disease severity, response to therapy, and side effects. In severe OP, prednisolone IV boluses during 3 consecutive days [47–49] and immunosuppressive treatment with cyclophosphamide, azathioprine, or cyclosporin A have been used [46, 50, 51, 91, 92], especially in acutely ill patients who do not improve within a few days of corticosteroid treatment. However, the efficacy of these strategies is not established. Whether the patients requiring immunosuppressive drugs in addition to prednisone had more frequently a diffuse infiltrative pattern than a multifocal pattern at imaging is unclear, as detailed chest CT scan analysis was not available in most of these cases.

Whether SOP should be treated differently from COP is currently unclear. Some data suggest that SOP is associated with less frequent resolution of symptoms and higher mortality than COP [26], but no such difference was found in another recent large series [27]. In a recent comparison of COP and OP secondary to connective tissue disease, treatment modalities, improvement rate and mortality rate were similar, although complete recovery was slightly more frequent in COP [93]. Thus, at the present time, no data support the use of different treatment regimens for SOP and COP.

Not all cases of OP require treatment. In six large series totalizing 418 cases [2, 23, 27, 31, 52, 93], 12 % of patients (range across series 3–23 %) did not receive corticosteroids. Among 26 of these cases with reported outcome, spontaneous improvement was noted in 8/26 and complete cure in 16/26 [23, 52, 93]. In another study of 12 women with OP after radiation therapy for breast cancer detected by systematic chest X-ray, only 6 were symptomatic. Hormonal treatment was temporarily withheld in 9, and complete cure was observed in all without corticosteroids [88]. Thus, in asymptomatic patients with mild OP, corticosteroids may not be necessary, and careful clinical and chest-X-ray follow-up may be the best initial strategy.

Several macrolide antibiotics (erythromycin, clarithromycin, azithromycin) have been found to have anti-inflammatory properties, which have been first observed in Japanese panbronchiolitis. A significant clinical benefit of azithromycin has now been demonstrated by randomized controlled trials in several other airway diseases including cystic fibrosis, bronchiolitis obliterans syndrome after lung transplantation, bronchiectasis, and more recently COPD. A beneficial effect of erythromycin and clarithromycin has also been reported in small uncontrolled series of COP and OP secondary to radiation therapy for breast cancer [94–97]. In a retrospective series of 12 patients with mild or moderate OP, the administration of clarithromycin 1,000 mg/day for 3–4 months led to complete cure in 7 cases, and an improvement in 2, whereas 3 other patients did not respond and required prednisone as a rescue therapy [97, 95]. Altogether, in the cases reported so far, onset of clinical improvement with macrolides appeared much slower than with corticosteroids (weeks instead of days) and therapeutic response was less constant [94–97]. Given the current paucity of evidence, the use of macrolides for the treatment of OP is currently not recommended in the usual clinical setting.

Clinical Course and Outcome

In typical multifocal COP, the outcome is usually excellent with disappearance of symptoms and normalization of imaging in more than 80 % of cases [22]. In a minority of cases, some minor fibrous sequelae can persist at imaging. Overall mortality in COP is reported to be <5 % [22, 23]. It has been suggested that the prognosis could be less favorable in SOP than in COP [2, 13, 26, 50], but a recent formal comparison did not find any significant difference between COP and SOP in clinical features, response to therapy, relapses and outcome [27].

COP is characterized by the frequent occurrence of relapses when corticosteroid treatment is tapered or stopped [1, 2, 14, 22]. Single or multiple relapses have been reported in up to 58 % of cases [22]. Most relapses occur within the first year, while patients are still taking low-dose prednisone

(usually <10 mg/day) for the initial episode. A relapse occurring under higher doses (>20 mg/day) or >18 months after the initial episode is unusual and should prompt to carefully re-assess the diagnosis. The cause of relapses is unknown, but the initial episode of COP and the subsequent relapses may be viewed as a single pathological process, which progressively abates over time [22]. Relapses are not due to insufficient prednisone dose for the initial episode, but delayed treatment onset could be a risk factor [22]. Other factors associated with the occurrence of relapses include more severe hypoxemia at first examination [98], elevation of serum gamma-glutamyl-transferase and alkaline phosphatase [22], and the multifocal form of OP [99]. Importantly, relapses did not affect morbidity and mortality [22]. Therefore, preventing relapses by extending treatment duration appears unnecessary in most cases, and the strategy should rather aim at minimizing the adverse effects of corticosteroids. To avoid unnecessary concerns, the possible occurrence of relapses, and even multiple relapses, should be explained to the patient during tapering of prednisone for the initial episode. The occurrence of a relapse in OP should prompt to reconsider the hypothesis of a persisting causal agent, such as a drug, which has not been removed initially.

Aggressive treatment of relapses was initially recommended, but they now appear as a relatively benign phenomenon, which can usually be controlled with a moderate increase of corticosteroid treatment. Accordingly, a low-dose regimen of 6-month duration to treat relapses of COP has been proposed (Table 24.5), starting at 20 mg/day of prednisone [22]. In localized OP, relapses are less common [40, 41], but also respond to corticosteroids. Mild asymptomatic relapses detected at chest X-ray may be observed without treatment.

Severe Forms of OP with Respiratory Failure

Patients with severe OP have been reported in several small series and isolated cases [23, 46, 47, 50–52]. Some of these cases were secondary to collagen vascular diseases, drugs, or toxic exposure to an aerosol textile dye [50–52] and others were idiopathic [23, 46, 47, 52]. In the 44 cases from five series with available data [46, 47, 50–52], nearly all patients received high-dose corticosteroids, 32 % received immuno-

Table 24.5 Proposed therapeutic regimen for typical COP

Step	Duration (weeks)	Doses of prednisone for the initial episode	Doses of prednisone for the first relapse (mg/day)
1	4	0.75 mg/kg/day	20
2	4	0.5 mg/kg/day	20
3	4	20 mg/day	20
4	6	10 mg/day	10
5	6	5 mg/day	5

Adapted from Ref. [22]

suppressive drugs (mostly cyclophosphamide), and 43 % required mechanical ventilation. Twenty-seven percent recovered, 9 % evolved to chronic respiratory insufficiency or required lung transplantation, and 64 % died. Factors which have been associated with a poorer outcome in OP include presence of collagen vascular disease [50], diffuse infiltrative pattern at imaging [14, 100], absence of lymphocytosis at BAL [14, 50], and interstitial fibrosis with architecture remodeling of lung parenchyma at histopathology [46]. As several of these characteristics are atypical in OP, it is possible that some of these cases had in fact other disorders in which OP pattern was only an ancillary histological finding, such acute interstitial pneumonia, acute respiratory distress syndrome, acute exacerbation of interstitial lung disease, or acute fibrinous and organizing pneumonia (see below). Alternatively, some cases may have had a true overlap between OP and one of these entities. Hence, among ten patients with severe OP and characteristic OP pattern at lung biopsy, seven died and five of them had associated UIP pattern, honeycombing or DAD at autopsy [50]. In other cases, OP may have been the initial pathologic process, but lung injury may have occurred as a secondary event due to superimposed infection or drug toxicity. Both multifocal and diffuse infiltrative imaging patterns have been described in severe OP [52].

Acute Fibrinous and Organizing Pneumonia

Acute fibrinous and organizing pneumonia (AFOP) has been first described in 2002 as an entity with overlapping features of DAD and OP [59]. Two very different clinical courses have been observed with the same histological picture, and the imaging characteristics have not been fully characterized. Therefore, in contrast with OP, AFOP cannot be currently viewed as a clinico-pathological syndrome but rather as a particular and uncommon histopathological pattern, which clinical significance needs to be further clarified. AFOP has been integrated in the 2013 classification of idiopathic interstitial pneumonias in the category of rare histopathological patterns [4].

In the original report of 17 cases of AFOP identified retrospectively from surgical biopsy files [59], disease onset followed an acute or subacute course with a mean time from first symptoms to lung biopsy of less than 2 months (mean 19 days). The most frequent symptoms were dyspnea (71 %), cough (24 %), fever (35 %), weakness (29 %), and thoraco-abdominal pain (29 %). One or more associated conditions were identified in two thirds of cases including history of environmental exposure, drug exposure, connective tissue disease, and co-morbidities resulting in altered immunity (Table 24.6). Other cases were idiopathic. Most frequent chest X-ray features included bilateral basal and diffuse

opacities, but detailed chest CT imaging characteristics were not available. Two distinct disease patterns and outcomes were identified, each affecting about half of cases: (1) severe rapidly progressive disease resembling classical DAD and leading to death within less than 1 month, and (2) mild subacute disease course resembling classical OP (Fig. 24.6a), and leading to recovery. The overall mortality rate was 53 %, which was similar to adult respiratory distress syndrome and much higher than classical OP. At lung histopathology, the dominant findings were prominent intra-alveolar fibrin balls filling around 50 % (range 25–90 %) of the alveolar spaces with a conspicuous patchy distribution and a relatively normal intervening lung parenchyma. OP pattern with buds of fibroblasts within airspaces was present in all cases, but was usually less abundant than the intra-alveolar fibrin (Fig. 24.6b). Associated features included mild to moderate interstitial infiltrate with edema, predominant lymphocytes, sparse neutrophils, and type 2 pneumocyte hyperplasia. There were no hyaline membranes, abcesses, or granulomas. No histological characteristics were found predictive of outcome. The histopathological features of AFOP are summarized in Table 24.7.

In its original description, AFOP was classified as a fibrinous variant of DAD, which however differs from classical DAD by several aspects: (1) organizing intra-alveolar fibrin was the dominant feature, whereas it is less prominent in classical DAD, (2) fibrin was organized into "balls" with a patchy distribution, as opposed to the widespread changes found in DAD, (3) intervening lung parenchyma appeared relatively normal in most cases, and (4) hyaline membranes were absent. AFOP differed from typical acute infectious

Table 24.6 Conditions associated with acute fibrinous and organizing pneumonia

Infections

Haemophilus influenzae, *Acinetobacter baumanii*, severe acute respiratory syndrome coronavirus, *Pneumocystis jiroveci*, human immunodeficiency virus

Drugs

Abacavir, amiodarone, busulfan, decitabine

Autoimmune disease

Polymyositis, dermatomyositis, ankylosing spondylitis, systemic lupus erythematosus, primary biliary cirrhosis

Tumors

Lymphoma, acute lymphocytic leukemia

Environmental exposures

Construction worker, animal exposure (zoologist), excessive hair-spray use, coalminer

Allografts

Hematopoetic stem cell transplantation

Other

Renal failure

Idiopathic

Adapted from Ref. [59] and pneumotox.com
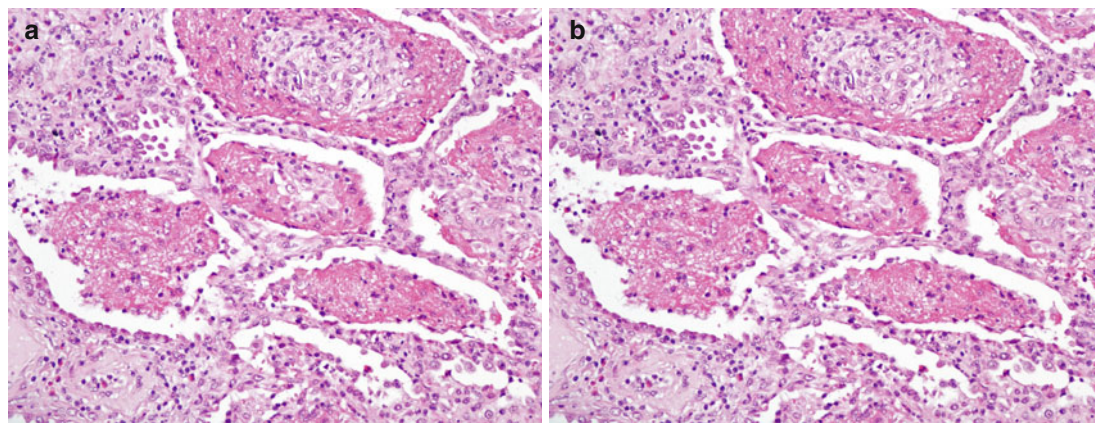
Fig. 24.6 Acute fibrinous and organizing pneumonia in a 68-old woman with symptoms of several month duration and lack of response to empirical antibiotic therapy. (**a**) Multifocal alveolar opacities with air bronchogram predominant at the lung bases. (**b**) Surgical lung biopsy showing prominent fibrin clusters filling alveolar spaces, with a lesser component of fibroblasts and inflammatory cells

Table 24.7 Histopathological features of acute fibrinous and organizing pneumonia

Major features
Organizing intra-alveolar fibrin "balls" as dominant finding
Organizing pneumonia pattern, less prominent than fibrin balls
Patchy distribution of lesions
Minor features
Mild to moderate acute and/or chronic interstitial inflammation
Alveolar septal expansion by myxoid connective tissue
Type 2 pneumocyte hyperplasia
Interstitial changes co-localized with patchy intra-alveolar fibrin lesions, with only minimal changes in the intervening parenchyma
Absence of:
Hyaline membranes
Prominent eosinophilic inflammation
Prominent neutrophilic inflammation or abcesses
Granulomatous inflammation

Adapted from Ref. [59]

pneumonia by the absence of significant neutrophilic inflammation. AFOP also markedly differed from classical OP by the predominance of intra-alveolar fibrin over intra-alveolar buds of granulation tissue. Besides histopathological differences, AFOP and classical OP were characterized by different disease course [59]. However, one cannot rule out that AFOP corresponds to a particular variant of severe OP, with lung biopsy performed at an early stage of the OP pathogenic process when fibrin fills the alveolar spaces before being colonized by proliferating fibroblasts to constitute the classical buds of granulation tissue. Further studies are needed to clarify this issue.

Similarly to the OP pattern, the histological AFOP pattern has been found as a minor nonspecific reaction in the vicinity of abcesses, necrotizing granulomas, GPA (Wegener's) lesions, and lung carcinomas [59]. For this reason, and until more data become available, transbronchial biopsies should not be considered adequate to diagnose AFOP, and this pattern can currently be identified only by surgical lung biopsy.

Treatment of AFOP is not codified. In the original report, most patients received antibiotics and/or corticosteroids, but no correlation was found between treatment modalities and outcome [59]. However, more than half of the patients did not receive corticosteroids, or received them late in the disease course. It therefore cannot be concluded that steroids are not effective in AFOP. Furthermore, significant and even dramatic improvement with corticosteroids has been reported by some authors [101]. The usefulness of cyclophosphamide and mycophenolate mofetil in addition to corticosteroids has been occasionally reported [102, 103]. Similarly to classical COP, relapses have been reported in AFOP [101].

Until the clinical significance of the AFOP pattern is further clarified, this histopathological finding should lead the clinician to consider the disease course as potentially more severe and life-threatening than classical OP. Similarly to OP, a cause or associated condition should be looked for in AFOP, and removed whenever possible. Corticosteroids seem effective in a number of cases and a steroid treatment should be attempted after having ruled out or treated an infectious process.

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