Review Article

Organising Pneumonia

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Abstract

Introduction : Organising pneumonia(OP) is characterised by presence of intraalveolar buds of granulation tissue progressing from fibrin exudates to loose collagen containing fibroblasts. OP may occur in the absence of aetiologic context in which case it is known as Cryptogenic Organising Pneumonia(COP) or in association with a known causative agent or inflammatory disorder such as connective tissue disease, where it is called secondary organizing pneumonia.

Clinical feutures : Men and women are affected equally in most series and are usually aged between 50 and 60 years. The onset of symptoms is usually subacute with fever, non-productive cough, malaise, anorexia, and weight loss. The most frequent and typical imaging profile of COP is of multiple patchy alveolar opacities with a peripheral and bilateral distribution.

Treatment : The response to corticosteroids is impressive. Clinical manifestations improve within 48 hours but complete resolution of radiographic pulmonary infiltrates usually takes several weeks.

Conclusions : COP is now a well recognised entity with characteristic clinical and radiological features and pathological diagnostic criteria. Although treatment with corticosteroids is very effective, relapse is common.

Key words : cryptogenic, organising pneumonia, bronchiolitis obliterans, buds of granulation.

Introduction

Organising pneumonia(OP) is a histopathological diagnosis defined by a well recognised pattern of changes underlying a characteristic clinicopathologic entity . OP may occur in the absence of aetiologic context in which case it is known as Cryptogenic Organising Pneumonia (COP) or in association with a known causative agent or inflammatory disorder such as connective tissue disease, where it is called secondary organizing pneumonia . OP is characterised by presence of intraalveolar buds of granulation tissue progressing from fibrin exudates to loose collagen containing fibroblasts[1]. The lesions occur predominantly within the alveolar spaces but are often associated with buds of granulation tissue occupying the bronchiolar lumen (bronchiolitis obliterans). This pathological pattern is not specific for any disorder or cause, but reflects one type of inflammatory process resulting from lung injury. It may also be a feature of the organising stage of adult respiratory distress syndrome and may be an accessory finding in other inflammatory disorders such as vasculitis. However, organising

pneumonia is the particular pathological hallmark of a characteristic clinicoradiological entity called cryptogenic organising pneumonia. This terminology is preferred to the other name used for this condition namely, idiopathic bronchiolitis obliterans with organising pneumonia (BOOP), which may be confused with other types of bronchiolar disorders, particularly constrictive bronchiolitis obliterans which is mainly characterised by airflow obstruction. COP is included in the ATS/ERS international consensus classification of idiopathic interstitial pneumonias, because of its idiopathic nature and occasional similarities with interstitial pneumonias[2].

Aetiology

Organising pneumonia may be classified into three categories according to its cause (Box-1): organising pneumonia of determined cause; organising pneumonia of undetermined cause but occurring in a specific and relevant context; and cryptogenic (idiopathic) organising pneumonia. Several possible causes and/or associated disorders may coexist in the same patient. There are no clear distinguishing clinical and radiological features between cryptogenic and secondary organising pneumonia[3].

Box - 1 Causes of Organising Pneumonia

Identified causes
Infections, Drugs, Distal to airway obstruction, Fumes and toxic exposure

Clinical settings
Occult aspiration pneumonia, Connective tissue diseases, Primary biliary cirrhosis, Inflammatory Bowel disease, Organ or marrow transplantation, Haematological malignancies, Thoracic radiotherapy, Common variable immunodeficiency, Sweet syndrome, Behcet disease, Thyroid disesese, vasculitis and Sarcoidosis

Idiopathic
Cryptogenic organising pneumonia

Pathogenesis

OP is a unique condition characterized by intra alveolar accumulation of intermixed fibroblasts and connective matrix especially collagen, that is reversible with corticosteroids. The first sequence of events leading to the formation of intra alveolar buds is alveolar epithelial injury with necrosis of pneumocytes. Injury to epithelial basal laminae and capillary endothelium results in flooding of the alveolar lumen with plasma proteins leading to accumulation of fibrin deposits that are soon populated by migratory inflammatory cells and fibroblasts[1]. Fibroblasts differentiate into myofibroblasts that organise and represent the predominant cell of fibroinflammatory buds. Inflammatory cells and fibrin are progressively replaced by aggregated fibroblasts and myofibroblasts intermixed with a loose connective matrix tissue rich in collagen and fibronectin (Fig. 1). Over all OP may be considered as a model of normal wound repair in contrast to UIP where there is uncontrolled repair and fibrosing process. Though the mechanism is unclear corticosteroids facilitate rapid resolution of OP indicating reversible nature of the lesion[12].

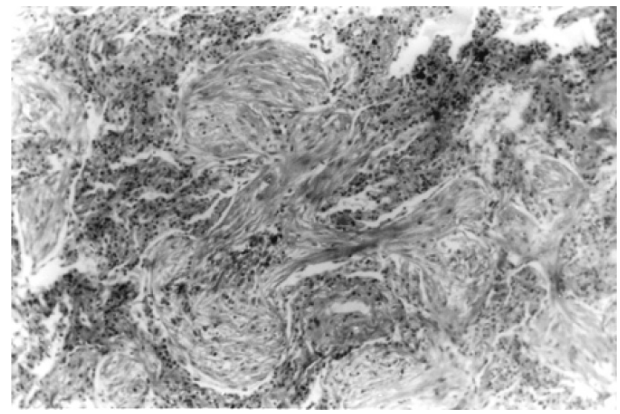

Figure 1
Buds of granulation tissue in the lumen of alveoli.

Clinical and Imaging Features

Cryptogenic organising pneumonia

Although organising pneumonia may result from numerous causes or occur in the context of systemic disorders, it remains cryptogenic and solitary in many cases. The recognition of cryptogenic organising pneumonia (COP) as a clinicopathological entity was long delayed for several reasons. Pathologists used to consider organising pneumonia as a non-specific finding of little, if any, interest, and merely a consequence of previous unrecognised infection. When mentioned in pathological reports it was not accorded attention by clinicians. With the increased use of lung biopsies, organising pneumonia was identified more often but included in the vast group of interstitial lung disorders. COP was therefore only recognised as a distinct disorder in the early 1980s after the reports of Davison and Epler. Further studies in the

1980s described its characteristic features, and COP is now accepted as a rare but very characteristic clinicopathological entity in pulmonary medicine[4].

Clinical features

Men and women are affected equally in most series and are usually aged between 50 and 60 years. Occasional cases in adolescents have been reported. No predisposing factors have been identified and, in particular, organising pneumonia is not related to smoking (most patients are non-smokers or ex-smokers). Seasonal cases (late February to early May) with biochemical cholestasis were found in one study, but this has not been further reported. The onset of symptoms is usually subacute with fever, non-productive cough, malaise, anorexia, and weight loss. Haemoptysis, bronchorrhoea, chest pain, arthralgia, and night sweats are uncommon. Severe haemoptysis is exceedingly rare. Dyspnoea is usually mild and only on exertion but it is occasionally severe in some acute and life threatening cases. In most cases symptoms develop over a few weeks after a viral like illness and diagnosis of COP is usually made after 6–10 weeks. Physical examination may be normal, but sparse crackles are commonly found over affected areas. Finger clubbing is usually absent. In many patients, the diagnosis is usually considered after they have received antibiotics for presumed infectious pneumonia without improvement[5].

Imaging features

Imaging features of COP may consist of variety of HRCT findings, some of which are highly suggestive of the diagnosis. Three main imaging patterns may be distinguished. The most frequent and typical imaging profile of COP is multiple patchy alveolar opacities with a peripheral and bilateral distribution (fig 2). These opacities often migrate spontaneously. Their size is variable, ranging from a few centimeters to a whole lobe. On the CT scan the density of the opacities varies from ground glass to consolidation; an air bronchogram may be present in consolidated areas (fig 3). This imaging pattern, although highly suggestive of COP, is not specific and the differential imaging diagnosis comprises conditions such as the chronic eosinophilic pneumonias (which can occur with COP), primary low grade pulmonary lymphomas, and bronchioloalveolar carcinoma[6]. Patchy ground glass opacities are frequently observed, which are usually associated with consolidation. The reverse halo sign or atoll sign, consisting of a circular consolidation pattern surrounding an area of ground glass opacities is also highly suggestive of the diagnosis, although not specific. The two other common imaging patterns of COP are less characteristic. Some patients present with a diffuse bilateral infiltration usually associated with interstitial opacities and small superimposed alveolar opacities. These patients show a greater degree of interstitial inflammation in addition to intra-alveolar organisation on pathological examination. Since intra-alveolar organisation is a non-specific feature that may be found in a variety of interstitial disorders, some cases may overlap with the organising stage of diffuse alveolar damage, non-specific interstitial pneumonia, or cryptogenic fibrosing alveolitis.

COP may also present on imaging as a solitary focal lesion associated usually with subacute or chronic inflammatory illness. This is often a pathological diagnosis after surgical excision of a lesion suspected to be a lung cancer on a routine chest radiograph; it usually occurs in the upper lobes and may cavitate. Some cases probably correspond to unresolved pneumonia. Less common radiological findings in patients with COP include multiple or cavitary nodules or masses, pneumatocele, peripheral irregular subpleural bands in parallel with the pleural surface, and bronchial dilatation (in association with opacities). Large nodules may have irregular or spiculated margins and a relatively broad pleural tag. Pleural effusion is generally uncommon although it was present in 22% of patients in one series.

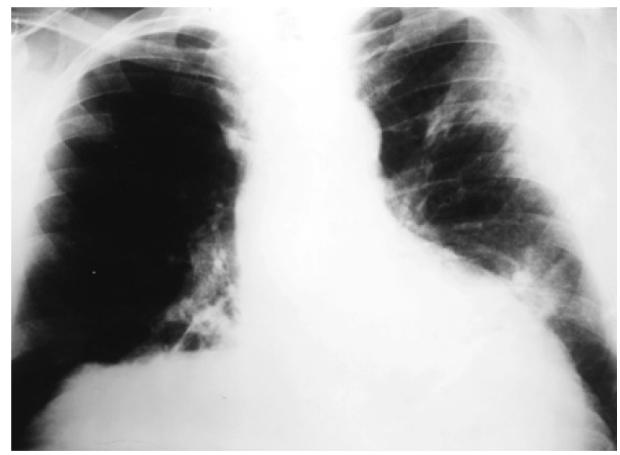

Figure 2
Chest radiograph showing the typical imaging pattern in COP.

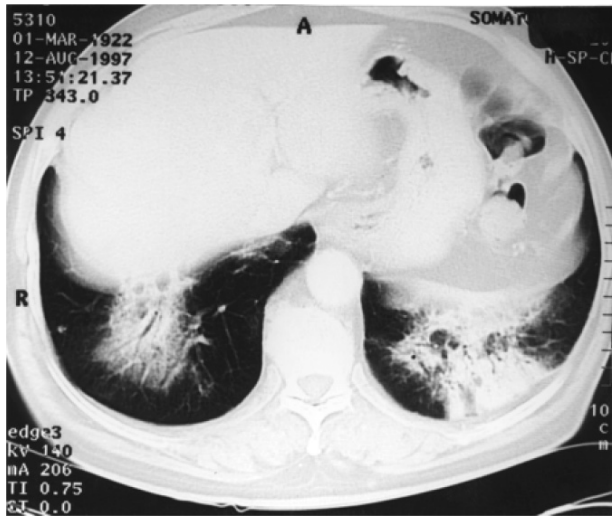

Figure 3
HRCT features of typical COP. Patchy bilateral consolidation with peripheral predominance and air bronchogram associated with ground glass opacities

Lung function tests

The most common finding on lung function testing in patients with COP is a mild or moderate restrictive ventilatory defect. Airflow obstruction may be present in smokers but is not a characteristic of COP (in contrast with the often severe airflow obstruction found in constrictive bronchiolitis obliterans). The transfer factor for carbon monoxide is reduced, but the transfer coefficient may be normal. Mild hypoxaemia at rest and/or on exercise is common[7]. Hypoxaemia is occasionally severe and correlates with right to left shunting as shown by increased alveolar-arterial oxygen difference while breathing 100% oxygen. Severe hypoxaemia in COP may reflect widespread and severe pulmonary disease or shunting in more limited lesions, or both.

Bronchoalveolar lavage and laboratory findings

Bronchoalveolar lavage may be used to exclude other disorders or causes of COP, particularly infections. The differential white cell count may show a characteristic "mixed pattern" with increased lymphocytes (20–40%), neutrophils (about 10%), and eosinophils (about 5%), sometimes with some plasma cells or mast cells. The lymphocyte CD4/CD8 ratio is decreased. There are no specific laboratory findings in COP. The erythrocyte sedimentation rate and C reactive protein levels are increased . There is a moderate leucocytosis, with an increased proportion of neutrophils[8].

Diagnosis of cryptogenic organising pneumonia

For COP to be diagnosed the organising pneumonia should be the main pathological feature and not merely an accessory to other well defined lesions such as vasculitis, eosinophilic pneumonia, hypersensitivity pneumonitis, or non-specific interstitial pneumonia. Furthermore, a careful search for a possible cause of organising pneumonia is necessary, including special stains to detect infectious agents. Because the pulmonary lesions are often migratory and may resolve spontaneously, a chest radiograph just before the biopsy is necessary. Video-assisted thoracoscopic lung biopsy is the currently preferred technique for diagnosing organising pneumonia since it provides quite large lung specimens which allow the diagnosis to be made with confidence and makes it easy to search for other pathological features. Transbronchial lung biopsy specimens may show organising pneumonia in many cases but they do not adequately allow the exclusion of associated lesions or disclose clues to a cause for the process[13]. Therefore the diagnosis of organising pneumonia by transbronchial biopsy may be accepted only in typical cases and requires careful patient follow up to prompt a surgical biopsy if the initial diagnosis has to be reconsidered because the evolution of the illness is unusual. Most cases require a surgical lung biopsy specimen to be taken before starting treatment[1].

The diagnosis of COP without a biopsy is seldom justified. It may be considered in patients who are critically ill (particularly older patients) or if the clinical diagnosis is considered as highly probable by an experienced physician. Particularly careful follow up would be necessary in such patients and lack of improvement with corticosteroids or relapses despite relatively high doses of corticosteroids should lead the clinician to suspect other diagnoses, particularly lymphomas.

Secondary Organising Pneumonia

Most cases of OP occurs as a reaction pattern and are considered to represent secondary OP, resulting from a determined cause, often infectious, or occurring in the context of systemic disorder or other specific conditions. The clinical, laboratory, and imaging features and outcome of secondary OP are similar, with minor differences[14].

Secondary organizing pneumonia of known cause

Infection is a common cause of organising pneumonia. Indeed, the concept of organising pneumonia as a distinct pathological entity emerged at the beginning of the 20th century with its recognition at necropsy in patients dying from bacterial pneumonia, especially pneumococcal pneumonia. It was interpreted as the failure of the usual resolution of pneumonia. Organising pneumonia has since been found in association with many other infections, mainly bacterial, but also in viral, parasitic and fungal infections (Box-2). In bacterial infections organising pneumonia occurs mostly in non-resolving pneumonia where, despite control of the infectious organism by antibiotics, the inflammatory reaction remains active with further organisation of the intra-alveolar fibrinous exudate. Rheumatic pneumonia occurring during the course of rheumatic fever was recognised as a typical organising pneumonia with intra-alveolar buds described as "bourgeons conjonctifs" or Masson's bodies[5].

Box - 2 Infectious agents associated with OP

Bacteria
Clamydia pneumonia, Coxiella burnetti, Legionella pneumophila, Mycoplasma pneumonia, Nocardia asteroids, Staphylococcus aureus, Streptococcus pneumonia, Serratia marcescens and Pseudomonas aeruginosa

Viruses
HIV, Influenza virus, Parainfluenza virus, Herpes virus, Hepatitis C virus

Parasites
Plasmodium vivax

Fungi
Cryptococcus neoformans, Penicillium janthinellum and Pneumocystis jiroveci

With drug induced organising pneumonia (Box -3) it is sometimes difficult to determine causality since organising pneumonia may also be associated with the underlying disease (Eg:-connective tissue disease). Resolution of organising pneumonia after stopping the drug is obviously the best clue to establish causality. In many cases, however, it is not possible to determine whether the drug is responsible or not—for example, in patients with cancer or haematological malignancies who may be treated with several drugs that are able to induce organising pneumonia. Serious diagnostic pitfalls may occur with drug induced organising pneumonia—for example, bleomycin induced organising pneumonia which may present as pulmonary nodules resembling metastases in patients treated for aggressive and potentially metastatic cancers.

Box - 3 Drugs causing Organising Pneumonia

5-Aminosalicylic acid	Minocycline
Amiodarone	Nilutamide
Amphotericin B	Nitrofurantoin
Beta blockers	Penicillamine
Bleomycin	Phenytoin
Busulfan	Statins
Carbamazepine	Rituximab
Dihydroergocryptine	Sirolimus
Everolimus	Sulfasalazine
Interferon-a	Tacrolimus
Interferon-ß	Thalidomide
Mesalazine	Trastuzumab
Methotrexate	

It has long been known that radiation therapy to the chest may induce radiation pneumonitis, an inflammatory reaction within the radiation field with some pathological features of organising pneumonia. However, a syndrome similar to cryptogenic organising pneumonia has been identified recently in women receiving radiation therapy to the breast after removal of a malignant tumour. It differs strikingly from usual radiation pneumonitis in that the pulmonary infiltrates occur or migrate outside the radiation fields and in the good response to corticosteroid treatment. The pathological findings are typical of organising pneumonia. Bronchoalveolar lavage (BAL) fluid differential cell counts show an increase in lymphocytes in particular, but also in neutrophils, eosinophils, and mast cells. Although corticosteroid treatment is usually necessary, spontaneous improvement

may occur. Interestingly, unilateral breast irradiation, whether or not it results in pneumonitis, has been shown to induce bilateral lymphocytic alveolitis with activated CD4+ T cells; however, this does not result in organising pneumonia in the majority of patients. An additional genetically determined host factor and / or trigger acting on radiation "primed" lymphocytes may be necessary to induce the organising pneumonia syndrome.

Organising pneumonia of unknown cause occurring in a specific context

The connective tissue disorders often involve the pulmonary parenchyma. Infiltrative lung disease in this context varies and may include usual interstitial pneumonia, non-specific interstitial pneumonia, or organising pneumonia. The idiopathic inflammatory myopathies may cause a characteristic organising pneumonia syndrome. Organising pneumonia also occurs in rheumatoid arthritis and Sjögren's syndrome but, in contrast, is uncommon in systemic lupus erythematosus and systemic sclerosis. In addition to organising pneumonia, bronchiolitis obliterans may occur in connective tissue disorders (particularly in rheumatoid arthritis). Pathological features of organising pneumonia may occur with Wegener's granulomatosis. These usually consist of small foci of organising pneumonia at the periphery of otherwise typical granulomatous lesions, but in some cases they are the major histological finding although the patients do not differ clinically or radiologically from those with classical Wegener's granulomatosis. Organising pneumonia has been reported occasionally in polyarteritis nodosa.

It is well established that both lung transplantation and bone marrow grafting may be complicated by constrictive mural bronchiolitis with airflow obstruction. This is generally interpreted as a manifestation of chronic rejection and graft versus host disease, respectively, and it often results in severe chronic obstructive respiratory failure. Less commonly, organising pneumonia occurs in transplanted lungs. Organising pneumonia in this setting may result from preservation injury, infection or aspiration, or it may be a manifestation of lung rejection and it may be associated with chronic rejection associated bronchiolitis obliterans. In lung transplant patients the combination of constrictive obliterative bronchiolitis and organising pneumonia appears to be associated with a poorer prognosis than constrictive obliterative bronchiolitis alone. Organising pneumonia also occurs after allogeneic bone marrow grafts where it is considered to be a manifestation of graft versus host disease. Other disorders that have been reported to be associated with organising pneumonia include Sweet's syndrome, ulcerative colitis, Crohn's disease, polymyalgia rheumatica, thyroiditis, Behçet's disease, mesangiocapillary glomerulonephritis, myelodysplasia, leukaemia, myeloproliferative disorders, cancer, common variable immunodeficiency, and hepatitis C. Since only single or small numbers of cases have been reported, it is unclear whether these represent a true association or whether the organising pneumonia results from other causes such as undiagnosed infection or drug induced reaction[5].

Treatment and prognosis of organising pneumonia

Spontaneous improvement occurs occasionally in organising pneumonia and slow improvement has been reported in some patients after prolonged treatment with erythromycin. However, corticosteroids are the current standard treatment, although the ideal dose and duration necessary for complete healing are less certain. The response to corticosteroids is impressive, although much less dramatic than in idiopathic chronic eosinophilic pneumonia. Clinical manifestations improve within 48 hours but complete resolution of radiographic pulmonary infiltrates usually takes several weeks (usually without significant sequelae). Most patients show a marked improvement after one week of treatment[4]. Although some authors recommend starting treatment with doses of prednisone of 1–1.5mg/kg/day for 1–3 months, in patients with typical COP a lower dose of 0.75mg/kg/day may be sufficient (Box-4). Relapses involving the initial sites or different locations occur frequently as the dose of corticosteroid is reduced. The final outcome is not significantly affected by the occurrence of relapses. The severity of hypoxaemia at first presentation has been reported to be a determinant of subsequent relapse but this has to be confirmed. The duration of treatment required varies considerably but is usually between six and 12 months. Some patients experience several relapses and require treatment for much longer. Because of the adverse effects of prolonged and high doses of corticosteroids, it is better to withdraw steroid after a few months and only prolong treatment in patients with relapsing disease[9].

Box-4 Proposed therapeutic regimen for typical COP

Steps	Duration	Prednisolone
	Treatment of initial episode	
1	4 weeks	0.75 mg/kg/day
2	4 weeks	0.5 mg/kg/day
3	4 weeks	20 mg/day
4	6 weeks	10 mg/day
5	6 weeks	5 mg/day
	Treatment of relapse	
1	12 weeks	20 mg/day
2	6 weeks	10 mg/day
3	6 weeks	5 mg/day

Adapted from Jean-Francois Cordier, Eur Respir J 2006

The prognosis in typical COP with patchy alveolar opacities is usually excellent following treatment with corticosteroids. The prognosis of organising pneumonia secondary to a determined cause or associated with a specific condition such as a connective tissue disease is more difficult to determine because of the heterogeneity of reported cases. The prognosis in COP is usually better than that seen in secondary organising pneumonia, probably due to the nature of the underlying disorders[11]. There are reports of patients with severe and rapidly progressive COP but interpretation of such reports is unclear. Of 10 patients with rapidly progressive organising pneumonia characterised by severe respiratory failure and organising pneumonia on the initial pulmonary biopsy, subsequent pathological examination of the lung at autopsy in six showed a fibrotic honeycomb pattern. In another series of patients with acute and life threatening organising pneumonia, organising adult respiratory distress syndrome (ARDS) was considered likely[10]. Acute fibrinous and organising pneumonia(AFOP) is a variant of OP characterized by abundant fibrin deposition in the alveoli with hyperplasia of type 2 pneumocytes, associated organising pneumonia and absence of hyaline membrane. Some cases with a poor outcome may represent an uncommon evolution of otherwise typical organising pneumonia, but most are likely to be either acute interstitial pneumonia or organising ARDS, widespread organising pneumonia resulting in respiratory failure, organising pneumonia associated with other chronic disease or lung injury either aggravated by lung biopsy or associated with delayed treatment. Some patients with severe disease requiring assisted ventilation may improve completely with corticosteroids. Factors that appear to be associated with a poor outcome in COP include a predominantly interstitial pattern on imaging, lack of a lymphocytosis on the BAL fluid differential cell count, associated disorders, and a finding on histological examination of scarring and remodelling of the lung parenchyma in addition to organising pneumonia[11].

Cytotoxic drugs, especially cyclophosphamide and azathioprine, are occasionally used to treat COP, but they have not been evaluated. The cytotoxic drugs are usually given in addition to corticosteroids so whether the observed improvement is due to the prolonged course of corticosteroids or to the cytotoxic drug is not known. Cyclophosphamide may be considered in severely ill patients who show no improvement with corticosteroid treatment within a few days and in patients who fail to improve despite a prolonged course of corticosteroids. In such acute and severe cases one to three intravenous boluses of cyclophosphamide may be tried, as in the initial treatment of Wegener's granulomatosis[9].

Conclusion

COP is now a well recognised entity with characteristic clinical and radiological features and pathological diagnostic criteria. Although treatment with corticosteroids is very effective, we are unable to predict which patients will relapse after reducing or stopping treatment, nor do we know the most appropriate dose with which to start treatment and how long patients should be treated. Some patients are probably over treated whereas others would benefit from longer treatment. There may not be a single cause of COP but histopathological studies are needed to identify the mechanisms whereby a limited wound healing reaction switches to an idiopathic persistent inflammatory process which is nevertheless very responsive to corticosteroids.

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