CRYPTOGENIC ORGANIZING PNEUMONIA – IDIOPATHIC BRONCHIOLITIS OBLITERANS ORGANIZING PNEUMONIA

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SUMMARY – Cryptogenic organizing pneumonia is a rare pulmonary disease with characteristic clinical, radiologic and histologic features. The radiologic presentation, and ventilatory and respiratory lung functions reflect the presence of intra-alveolar buds of granulation tissue occurring within the alveoli and alveolar ducts but rarely occupying the bronchiolar lumen. Therefore, it has been accepted that the diagnosis of these characteristic but not specific presentations of cryptogenic organizing pneumonia requires histologic confirmation. The terms cryptogenic organizing pneumonia and idiopathic bronchiolitis obliterans organizing pneumonia are synonyms. There is also secondary organizing pneumonia casually related to various conditions. Presentation is made of two patients with different clinical manifestations of cryptogenic organizing pneumonia: one with low-grade chronic clinical course and migratory inflammatory lung infiltrates, and the other with severe acute clinical manifestations of the disease. In both patients with cryptogenic organizing pneumonia, corticosteroids showed high efficacy for both primary disease and relapses.

Key words: Bronchiolitis obliterans organizing pneumonia – diagnosis; Bronchiolitis obliterans organizing pneumonia – therapy

Introduction

Cryptogenic organizing pneumonia (COP) is defined as a rare inflammatory lung disease with characteristic clinical-radiologic and histopathologic manifestations. COP has been recognized as a distinct clinicopathologic entity by our clinicians1. No predisposing factors have been identified3. COP is also classified into interstitial inflammatory lung diseases of unknown cause2-4. The term COP is preferred to its synonyms such as primary or idiopathic bronchiolitis obliterans organizing pneumonia (BOOP)5-6. The characteristic radiologic pattern and lung function disorders reflect typical inflammatory lesions determined by the presence of buds of granulation tissue occurring within alveolar spaces and alveolar ducts but rarely occupying the bronchiolar lumen. Therefore, this characteristic clinicoradiologic entity of unknown cause with a particular pathologic hallmark of organizing pneumonia (OP) may be appropriately called COP to distinguish it from other types of bronchiolar diseases6-9. This pathoanatomical pattern of OP is not specific for COP but represents various mechanisms of the inflammatory reparatory process resulting from lung injury5,6,7. Although corticosteroids have been considered highly effective therapy for COP, the dosage and duration of treatment to recovery have not yet been clearly established9,10. Furthermore, relapses of COP are quite frequent after reducing or stopping the treatment with corticosteroids11.

COP accounts for 50% of OPs, and the remaining 50% of OPs comprise of secondary organizing pneumonia (secondary BOOP), which is outlined herein4. It has been known that secondary OP may be found in association with certain drugs, infections, organ transplantation, following radiation therapy for breast cancer, connective tissue diseases, and many other causes6,7,12-21. There are no histologic, clinical or radiologic features to distinguish between COP and secondary OP. Corticosteroids are considered standard therapy for both COP and secondary OP. Therapeutic strategy for secondary OP depends on the nature of the underlying disorder. It has been generally accepted that the...
first aim of treatment for secondary OP is removal of the offending agent or cause. The prognosis in secondary OP is usually worse than in COP.

Case Reports

**Patient No. 1**

A 72-year-old female presented with a one-month history of intermittent fever, cough and left-sided thoracic pain. She was a non-smoker. Chest radiography showed infiltrative opacity in the left inferior lung lobe (Fig. 1A). However, she did not improve with antibiotics administered for presumed infective pneumonia. Then she was admitted to the hospital. On admission, she appeared well, febrile, with crackles in the left subscapular lung region on auscultation. The erythrocyte sedimentation rate (ESR) rose to 51 m/h and C-reactive protein (CRP) was

Fig. 1A, 1B

Fig. 1C-E
increased (84.5 mm/L). The white blood cell (WBC) count was normal, with mild neutrophilia. There was mild arterial hypoxemia with normal spirometry and single-breath carbon monoxide diffusion capacity. Electrocardiography (ECG) and heart ultrasound (US) were normal. Bronchoscopic evaluation showed a normal tracheobronchial tree. Transbronchial lung biopsy specimen histology showed very thickened and fibrotic alveolar septa, some of them consisting of mononuclear infiltrations and accumulation of anthracotic pigment. Granulation tissue and foamy cells filled alveolar spaces. Bronchoalveolar lavage (BAL) predominantly showed lymphocytes (72%) and macrophages (18%), followed by eosinophils (6%) and granulocytes (4%). The patient remained clinically stable. Control chest radiography revealed infiltrates in the left lung base that regressed in size as compared with previous radiography findings, however, a new right lung infiltrative opacity occurred progressing in size despite antibiotic therapy administration (Fig. 1B). Therefore, the clinical and radiologic patterns as well as histologic findings pointed to COP as the most likely diagnosis. However, the patient refused the recommended corticosteroid therapy. Two months later, she was readmitted to the hospital for persistent cough, while clinically appearing unchanged. Radiographic control revealed partial dissolution of the inflammatory infiltrate in the right lung base and a new infiltrate in the left parahilar lung zone (Fig. 1C). The remainder of findings were not significantly changed. At this stage, the patient accepted corticosteroids and the treatment started with prednisolone, 40 mg. After 5 days of this therapy, her cough resolved. Radiographic controls initially showed partial dissolution of the lung infiltrates followed by complete dissolution in the further course of the disease. The dose of prednisolone was tapered to the maintenance dose. Corticosteroid therapy was discontinued after 7 months.

Relapses associated with symptom recurrence and radiographic finding of the left upper lung lobe infiltrate (Fig. 1D) corresponding to computed tomography (CT) finding of ground-glass attenuation (Fig. 1E) occurred two months of corticosteroid discontinuation. The patient received oral methylprednisolone, 24 mg, which resulted in rapid symptom disappearance and complete infiltrate dissolution on chest radiography. The dose of corticosteroid was tapered to the maintenance dose. Corticosteroid therapy was discontinued after 11 months.

**Patient No. 2**

A 28-year-old female, a smoker, was referred to our hospital with a history of one-month malaise, generalized fatigue, backpain, cough, body temperature up to 38 °C, and infiltrative opacities in both upper lobes on chest radiography. Prior to hospitalization, she was treated at outpatient department but did not respond to antibiotics and antituberculotics. Then she was admitted to the hospital in extremely poor condition. She was treated with alternative antibiotics and antymycotic fluconazole for oral candidiasis. On examination, she presented with bilateral bronchial breath sounds in the upper lung regions and audible left-sided crackles.

Chest radiography showed consolidations containing air bronchograms in both upper lobes and apical segments of lower lobes, and possibly in lateral segment of the middle lobe (Fig. 2A). CT scan showed bilateral lung infiltrates with peripheral consolidated areas containing air bronchograms (Fig. 2B). Laboratory findings: ESR 124 mm/h; CRP 176 mg/L; WBC count 10.0x10⁹/L; and mild neutrophilia. On spirometry, she showed a severe restrictive ven-
tialatory defect and pronounced arterial hypoxemia. Bronchoscopy findings revealed normal appearance of the lar-
ynx and tracheobronchial tree, with bilateral purulent se-
cretion within the lumen and traces of hemorrhage from the
left sixth segmental bronchus. BAL was inadequate for
histologic and immunocytologic examination. Sputum
and BAL specimens referred for bacteriologic analysis were
sterile, and cultures were negative for Mycobacterium tuber-
culosis. Histologically, transbronchial biopsy specimen of the
sixth left segmental lung area showed alveolar spaces of
normal size with some thickening of the alveolar septa and
multiple intra-alveolar loose granulation tissues. There
were some eosinophilic deposits within the alveoli and a
minor accumulation of granulocytes predominated by eosi-
nophils and some mononuclear cells in the alveolar walls.

Based on the clinical presentation and these histologic
findings, the diagnosis of COP was made and treatment with
prednisolone, 60 mg per day, was initiated. Despite
the dramatic onset of symptoms, this corticosteroid ther-
apy led to rapid clinical response. Good clinical response
including improved laboratory findings and partial dissolu-
tion of radiographic lung lesions was observed after a few
days of corticosteroid therapy. Prednisolone was followed
by methylprednisolone, 40 mg, with a rapid dose tapering
to 32 mg, then slowly to the maintenance dose. After two
months of corticosteroid therapy, the patient achieved full
recovery. The follow-up imaging studies showed complete
disappearance of lung lesions with mildly reduced total gas
transfer and normal other laboratory findings. Corticoster-
oid therapy was discontinued after ten months.

A relapse occurred two months of corticosteroid discon-


tinuation. The patient presented with a mild clinical pic-
ture and identical but less numerous pulmonary lesions on
chest radiography. Spirometry revealed a restrictive lung
function defect of a higher degree and mild obstructive
ventilatory defect. Total gas transfer was markedly reduced
(46%), with arterial normoxemia. Corticosteroid therapy
(32 mg methylprednisolone) with slow dose tapering was
reintroduced with good clinical response. After six months
of methylprednisolone (5 mg), the patient was clinically
well and laboratory findings were normal except for a re-
duced total gas transfer (64%). It should be noted that the
patient did not stop smoking.

Discussion

Males and females are equally affected with COP, usu-
ally at the age between 40 and 60 years. Our two patients
were both of atypical age, one of them older and the other
one younger than the age most frequently associated with
the disease occurrence. The typical onset of symptoms is
subacute with fever, nonproductive cough, exertional dys-
pnea, anorexia and weight loss. The characteristic pulmo-
nary infiltrates are typically present on chest radiography.
Pleural effusion is rare. Medical history frequently reveals
unsuccessful treatment with antibiotics administered for
presumed infective pneumonia. On physical examination,
inspiratory crackles may be present. The clinical presen-
tation of COP may be typical and focal in about 80% and
10% of COP patients, respectively. The focal variant of
COP may present radiographically as a solitary node or
multiple nodular lesions, and clinically often with pleural
pain. The diagnosis of COP is usually made histologi-


ally2,22. The fibrotic progressive and nonprogressive forms are
rare, and fulminant form is extremely rare5,21. Clinically,
the fulminant variant of COP may be similar to acute intersti-
tial pneumonia and adult respiratory distress syndrome
(ARDS) followed by acute respiratory failure over a few
days2,24.

Both of our patients had fever, cough and pulmonary
infiltrates that did not resolve with antibiotic therapy. Pati-
ent No. 1 was in good condition and presented with a
slowly progressive clinical course. Patient No. 2 was in
extremely poor condition with a rapidly progressive form
of the disease. On physical examination, patient No. 1
typically presented with audible crackles over the radio-
logically detected lung infiltrate, whereas patient No. 2
presented with bronchial breath sounds such as those
heard in bacterial pneumonia.

Although laboratory findings are not specific for the
diagnosis of COP, accelerated ESR and increased CRP
values are commonly found. Moderate leukocytosis with
variable neutrophilia may be present in 15%-35% of pa-
tients4. Both of our patients had accelerated ESR, in-
creased CRP values and mild neutrophilia, however, with-
out any major increase in total leukocyte count. Radiog-
raphic findings may show bilateral inhomogeneous alve-
olar consolidations in peripheral lung areas and lower lung
lobes. Other radiographic patterns include reticular in-
terstitial opacities or fibrotic lesions. The size of consoli-
dations varies from a few centimeters to a whole lobe. Rare
unilateral and migratory infiltrates may be found in about
25% of COP patients2,20,25. The progressive form of COP
typically shows slow enlargement of infiltrates, which may
also occur at another localization. Central colliquations are
rarely found, and may be seen in the focal form of COP1.
Pleural effusion is rarely observed. It has been generally
accepted that the characteristic CT findings in association
with typical clinical presentation suggest the diagnosis of
COP. Ground-glass attenuation and inhomogeneous alveolar consolidations are most often reported (90%-100% and 83%-91%, respectively). The consolidations typically have a triangular appearance with the basis on the pleural side and the apex turning on the hilus. The consolidations usually contain air bronchograms such as those seen in pneumonia. CT scans may also show linear opacities and rarely reticulonodular opacities. The characteristic radiographic presentations of COP were detected in both of our patients: patient No. 1 presented with migratory pulmonary infiltrates, and patient No. 2 with extensive progressive infiltrates.

As expected, no characteristic bronchoscopic findings related to COP were found in either of our patients. It has been usually reported that cytologically BAL may show a “mixed pattern” with obligatorily increased lymphocyte count (20%-40%) and mild granulocytosis (<15% of neutrophils and <7% of eosinophils). Moreover, plasma cells, foamy macrophages may be found in more than 50% of COP cases. The CD4/CD8 ratio is mostly decreased. Mast cell count may also be increased. In our patient No. 1, the BAL finding was compatible with the diagnosis of COP, whereas in patient No. 2 the BAL specimen was inadequate for additional analysis.

The histologic pattern of COP shows buds of granulation tissue into alveolar spaces and alveolar ducts that may spread continuously into bronchioles. The buds usually consist of fibroblasts, myofibroblasts, and loose connective tissue. The fibroblasts are characteristically “onion-like” arranged. Granulation tissue may spread through the pores of Kohn to the adjacent alveoli with preserved alveolar architecture. The chronic inflammatory reaction of the surrounding alveolar septa is recognizable by active pneumocytes type 2, dense lymphocyte infiltrates and foamy macrophages into the alveolar lumen. Occasionally, there may be elements of interstitial fibrosis with a honeycomb structure. It is known that COP predominantly occurs as an acinar process in which terminal bronchioles show intact bronchiolar walls and occasionally are occupied by granulation tissue but are not obliterated. This variant of OP correlates pathoanatomically with the clinicoradiologic entity of COP. Transbronchial lung biopsy specimens revealed a characteristic histologic pattern of COP in both of our patients.

On spirometry, the patients with COP usually exhibit mild to moderate restrictive ventilatory defects with reduced total gas transfer for carbon monoxide and commonly mild hypoxemia. Both of our patients showed similar laboratory findings.

The diagnosis of COP requires characteristic clinical, radiologic and histologic features, and absence of any recognizable cause or associated disease. The video-assisted thoracoscopic (VATS) lung biopsy is preferred to transbronchial lung biopsy for obtaining abundant lung specimen necessary to make the diagnosis. However, making the diagnosis of primary COP on the basis of characteristic clinicoradiologic pattern and BAL is acceptable in typical cases. Prior to making the diagnosis of COP, it is necessary to exclude any possible cause of secondary OP. On differential diagnosis, multifocal bronchoalveolar cancer and pulmonary lymphoma that may initially respond to corticosteroid therapy should firstly be considered. In addition, there are other rare disorders mimicking the features of COP, e.g., alveolar proteinosis, migratory eosinophilic infiltrates, chronic eosinophilic pneumonia, mycosis, pulmonary embolism with peripheral infarction, and tuberculosis. Both of our patients showed no features of secondary OP and presented with characteristic clinicoradiologic and histologic patterns of COP. Thus, the diagnosis of COP was made.

The prognosis of COP is good in the majority of patients treated with corticosteroids, although spontaneous improvement without therapy has also been reported. Corticosteroids are therapy of choice for both initial clinical manifestations of COP and its relapses. It is recommended to start with 40 mg prednisolone per day or with a dose of 0.5 or 0.75 mg/kg/day. After an improvement has been achieved, the dose can be reduced to 30 mg per day over two weeks, then gradually tapered by 10 mg monthly to the maintenance dose of 5 or 7.5 mg per day. Other authors suggest a similar therapeutic approach. Patients usually respond well to corticosteroids over a few days, whereas radiographic manifestations may take 2-3 months and lung function tests 3-6 months to resolve. The duration of treatment is usually between 6 and 12 months, and complete remission frequently occurs. However, some patients experience successive relapses and require long-term treatment. Relapses have been reported in 58% of COP patients. Definitive COP outcome is not affected by the frequency of relapses. The treatment with azathioprine and cyclophosphamide is rarely required. Both of our patients were treated with corticosteroids with initially good clinical responses but relapses occurred two months of treatment discontinuation. Similar to literature reports, the relapses in our patients responded favorably to corticosteroid therapy. Some authors suggest that relapses be treated with low initial doses of corticosteroids, i.e. a dose of 25 mg prednisone or less per day.
Generally, the prognosis of COP is good\textsuperscript{2,4}. The 5-year survival is 80\%\textsuperscript{2}. The factors that appear to be associated with poor outcome include a predominantly interstitial pattern on radiography, low lymphocyte count in BAL, histologic findings of scarring and remodeling of the lung parenchyma in addition to OP\textsuperscript{6}. The possible lethal outcome has been reported in patients with COP persisting despite corticosteroid treatment\textsuperscript{24,31}. However, we observed that both of our patients responded well to corticosteroid therapy.

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Sažetak

KRIPTOGENA ORGANIZIRAJUĆA PNEUMONIJA – IDIOPATSKA BRONHIOLITIS OBLITERANS ORGANIZIRAJUĆA PNEUMONIJA

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Kriptogena organizirajuća pneumonija je rijedak entitet u pulmologiji sa znakovitim kliničkim, radiografskim i histološkim manifestacijama. Radiografske manifestacije, kao i ventilacijsku i respiracijsku plućnu funkciju određuju pupoljci granulacijskog tkiva u alveolama i alveolarnih hodnicima, koji se mogu vidjeti i u bronhiolama. Zato je nužna histološka potvrda ovih promjena koje su znakovite, ali ne i specifične za kriptogenu organizirajuću pneumoniju. Kao sinonim za ovu bolest nepoznatog uzroka rabi se i izraz idiopatska (primarna) bronhiolitis obliterans organizirajuća pneumonija. Postoji i sekundarna organizirajuća pneumonija koja ima različite uzroke. Cilj ovoga prikaza je upozoriti na dvije različite manifestacije kriptogene organizirajuće pneumonije: jedna je polagana, kronična, s migrirajućim upalnim infiltratima i blagom kliničkom slikom, a druga akutna s teškom kliničkom slikom. U oba slučaja uslijedio je dobar odgovor na terapiju kortikosteroidima, ali se je javio recidiv koji je također dobro reagirao na ovo liječenje.

Ključne riječi: Bronhiolitis obliterans organizirajuća pneumonija – dijagnostika; Bronhiolitis obliterans organizirajuća pneumonija – terapija