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Cryptogenic organising pneumonia – a continuous challenge. Case report

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Abstract

English:

Cryptogenic organising pneumonia (COP) is an interstitial lung disease, with an unknown aetiology. Treatment is based on oral corticotherapy, starting with attack doses given for 2–6 weeks, followed by gradual tapering over a period of 3–6 months. Relapses are common, especially in the first year. A 51-year-old patient, former smoker, without exposure to noxious substances, presented to the hospital in January 2020 with fever, dry cough and malaise. On chest radiography, lesions suggestive of bronchopneumonia were revealed and antibiotic treatment was started. The patient did not respond to treatment and chest Computed tomography (CT) was performed, which detected pulmonary condensations, predominantly with a subpleural disposition, predominantly in the lower lobes, as well as pleural effusion and minimal pericarditis. Due to the unfavourable disease evolution despite treatment and according to other investigation results, COP diagnosis was raised and oral corticotherapy was prescribed, with a favourable response. The patient complained of reappearance of the initial symptoms at dose weaning and she was reassessed by CT in June 2020. The Coronavirus Disease 2019 (COVID-19) pandemic raised the suspicion of a severe acute respiratory syndrome coronavirus-2 (SARS-COV2) infection, which was infirmed later. Corticotherapy was resumed, and at a check-up after 10 months, broncho-alveolar lavage was performed, with results within normal limits. The evolution of the patient was favourable. In conclusion, in the case of a pneumonia in which there is a discrepancy between the clinic, biologic and imagistic (possibly with a migratory pattern) and the response to treatment, COP must also be considered. Relapses are relatively common, and may occur both during corticotherapy dose reduction and after the end of treatment.

Keywords

broncho-alveolar lavage • corticotherapy • relapses

Pneumonita criptogenica în organizare – o continuă provocare. Prezentare de caz

Rezumat

Romanian:

Pneumonita criptogenică în organizare (COP) face parte din pneumoniile interstițiale difuze și are o etiologie necunoscută. Tratamentul are la baza corticoterapia orală, începând cu doze de atac administrate timp de 2-6 săptămâni, urmată de descaladare treptată pe o perioadă de 3-6 luni. Recăderile sunt frecvente în primul an de la debut. Pacientă în vârstă de 51 de ani, fostă fumătoare, fără expunere la noxe inhalatorii, s-a prezentat la spital în luna ianuarie 2020 acuzând: febră, tuse seacă și o stare generală influențată. Pe radiografia toracică efectuată la internare s-au evidențiat leziuni sugestive pentru bronhopneumonie, motiv pentru care s-a inițiat tratament antibiotic. Răspunsul la tratament nu a fost favorabil, astfel că se efectuează un CT toracе nativ, care decelează focare de condensare pulmonară cu o dispoziție predominant subpleurală, în special la nivelul lobilor inferiori, pleurezie și pericardită minimă. Din cauza evoluției nefavorabile a bolii în ciuda tratamentului și în urma investigatiilor, s-a ridicat suspiciunea diagnostică de COP, începându-se corticoterapia orală la care răspunsul este favorabil. Pacienta acuză reapariția simptomelor inițiale în momentul descaladării dozelor, efectuându-se o reevaluare clinico-imagistică în iunie 2020. Contextul epidemiologic legat de pandemia de COVID-19 a ridicat suspiciunea infecției cu SARS-CoV-2, infirmată prin investigații suplimentare. S-a reluat corticoterapia iar reevaluarea de 10 luni de la debut, s-a putut efectua și lavajul bronho-alveolar, cu rezultate în limite normale. Evoluția ulterioara a pacientei a fost favorabilă. În situația unei pneumonii la care se constată o discrepanță între tabloul clinic, biologic și imagistic (posibil cu aspect migrator) respectiv răspunsul la tratament, trebuie luat în considerare și diagnosticul de pneumonite criptogenică în organizare. Recăderile sunt relativ frecvente, putând apărea atât în timpul descaladării corticoterapiei, cât și după terminarea tratamentului.

Cuvinte-cheie

lavaj bronho-alveloar • corticoterapie • recăderi

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Introduction

Cryptogenic organising pneumonia (COP) is a diffuse interstitial pneumonia that mainly affects the distal bronchioles, respiratory bronchioles, ducts and alveolar walls. These changes are caused by an inflammatory and proliferative process whose aetiology is unknown. The average age of onset is 58 years and the extents of severity with which it affects women and men are similar (1).

Case presentation

A 51-year-old-female patient, former smoker (5PY), with no professional exposure to allergens or inhalatory noxious substances, is admitted to a regional hospital in January 2020 with a fever (38°C), dry cough and malaise symptoms which had debuted 5 d earlier. The patient has a medical history of partial thyroidectomy with post operatory hypothyroidism, for which she is being treated with Levothyroxine. Clinical examination reveals the presence of basal bilateral crackles. On the initial chest X-ray, only bilateral basal infiltrates and a right subclavicular infiltrate are detected (Figure 1).

Biologically, an inflammatory syndrome is standing out (erythrocyte sedimentation rate (ESR) = 64 mm/h, C-reactive protein (CRP) = 62.19 mg/L), with a white blood cells (WBC) within normal values. Treatment is initiated with cefoperazone/sulbactam 1000/1000 mg, for 1 week. After this period, the patient stays feverish, with an influential general condition, and inflammatory syndrome persists. Blood culture reveals an *Escherichia coli* infection while bacteriological examination of sputum shows only commensal flora. Therapeutical regime is changed according to antibiogram: meropenem 3 × 1 g/d, vancomicine 2 × 1 g/d, moxifloxacine 400 mg/d, fluconazol 100 mg/d, and hemisuccinate of hydrocortisone 100 mg, 2 × 1/d associated with symptomatics. After 3 d, biological exam is repeated and shows persistency of the inflammatory syndrome (ESR = 25 mm/h, CRP = 37 mg/L, Hb = 9.8 mg/dL, leukocytes: 10,980/L with neutorphiles 81% and lymphocytes 14.1%). At 10 d from the initial chest X-ray, a native chest CT was performed, which detected the presence of condensation foci with air bronchogram predominantly in the inferior lobes, but also the presence of small condensation areas in the superior lobes, accompanied by a small bilateral pleural effusion and a minimal pericardial fluid reaction (Figure 2).

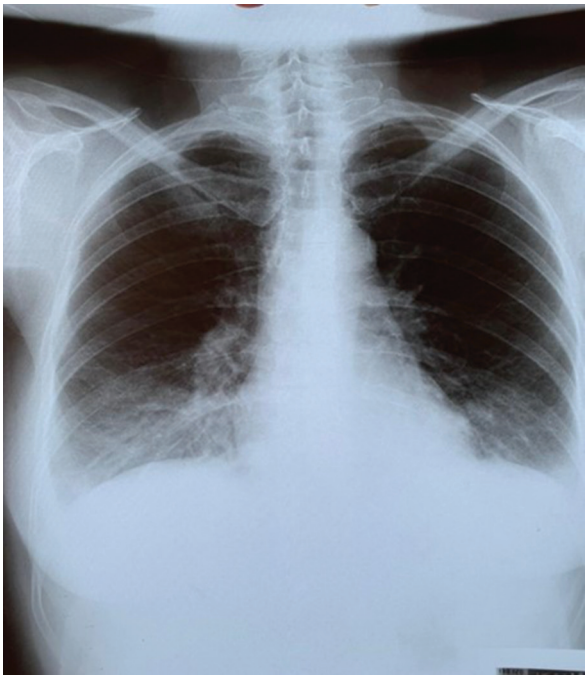


Figure 1. First chest X-ray: right subclavicular and bilateral basal infiltrates.

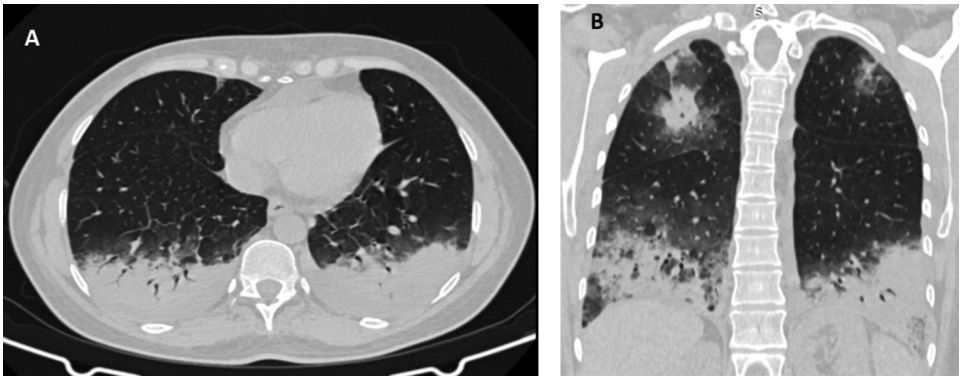


Figure 2. First chest CT scan shows the presence of consolidations with air bronchogram in both inferior lobes, but also the presence of small consolidations in the superior lobes, accompanied by a small bilateral pleural effusion and a minimal pericardial fluid reaction.

Consequent to the extension of pulmonary condensations under antibiotic treatment, transfer of the patient to the Respiratory Diseases Department of 'Victor Babeș' Hospital, Timișoara was considered appropriate. The initial treatment was continued and the dose of hydrocortisone hemisuccinate was increased to 300 mg/d, for 9 d. A series of investigations were performed, such as a bronchoscopy with bronchial aspirate that did not detect any pathological modifications, a spirometry with a bronchodilation test and diffusion capacity of lung for carbon monoxide (DLCO), which both showed normal values, and cardiac ultrasound that showed no pathological modifications. Two weeks after the chest CT, a control chest X-ray was done, detecting bilateral subclavicular focal infiltrative lesions and right perihilar lesions (Figure 3).

Since the clinical and radiological evolution, under initial treatment, had been stationary, with a mild improvement with the increased dosage of corticosteroids, the suspicion of COP was raised.

A series of differential diagnoses (bacterial bronchopneumonia, eosinophilic pneumonia, connective tissue disease with pulmonary determinations, hypersensitivity pneumonitis or pulmonary tuberculosis) was ruled out by carrying out specific investigations: mycobacteriological examination from sputum, procalcitonin, antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), rheumatoid factor, etc. After establishing the diagnosis of COP, treatment was initiated with prednisone 45 mg/d, for 6 weeks, and then decreased by 5 mg every 2 weeks, until a 15 mg/d dose was reached. At a check-up after 6 months, the patient reported the recurrence of the initial symptoms (dry cough, feverish state, night sweats) concomitant with decreasing the dose of prednisone to the maintenance dose. Biologically, WBC was in the normal range, but the systemic inflammatory syndrome reappeared (ESR = 20 mm/H, CRP = 5.25 mg/L). Chest CT was repeated, detecting the occurrence of infiltrates and ground glass opacities in inferior and superior lobes, but with a different topography from anterior examination (Figure 4). In the current epidemiological context,



Figure 3. Second X-ray: bilateral subclavicular focal infiltrative lesions and right perihilar lesions.

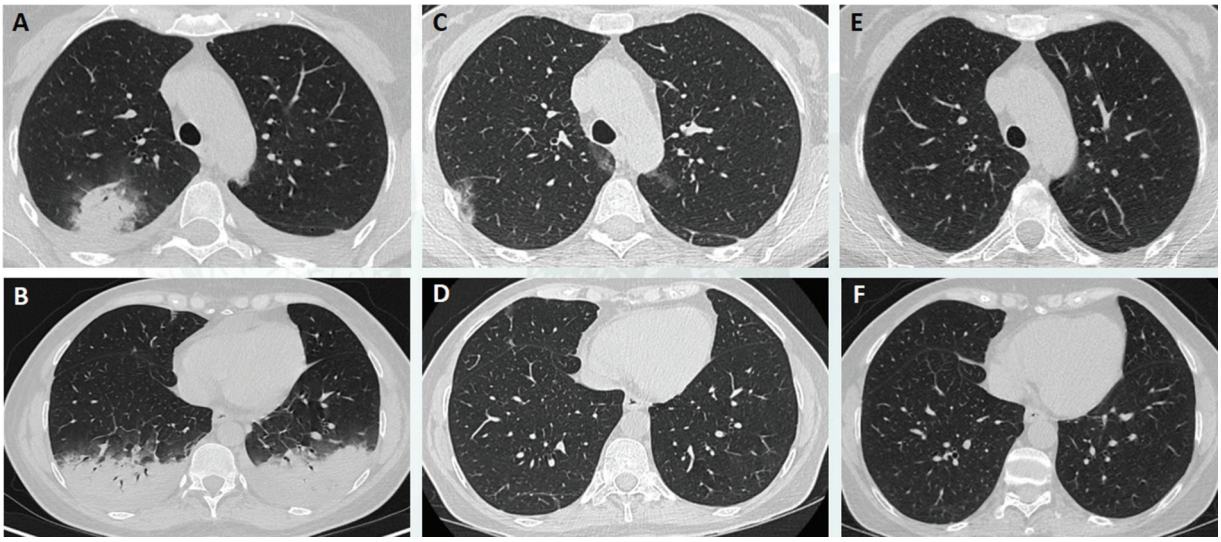


Figure 4. A,B - First chest CT; C,D second chest CT at 6 month; E,F third chest CT at 10 month. Compared to the first chest CT, the second and third also show infiltrates and ground glass opacities in inferior and superior lobes, but with a different topography from anterior examination.

an RT-PCR test for SARS-CoV-2 was performed from nasal and pharyngeal exudate, in order to rule out COVID-19, which resulted negative. A decision was made to increase the dose of prednisone to 20 mg/d, which was followed by a remission of symptoms. At a check-up after 10 months, clinical and biological examination showed normal values, and spirometry and bronchoscopy with bronchoalveolar lavage did not indicate any pathological changes, but a slight decrease of DLCO cor to 77% was noticed. Continuation of corticosteroid treatment was recommended up to 1 year, with gradual dose reduction.

Discussion

The unspecific clinical presentation of COP that includes flu-like symptoms (cough, fever, dyspnoea, asthenia) often results in a delayed diagnosis. The clinical examination frequently reveals bilateral basal crackles. COP patients are commonly associated with a systemic inflammatory syndrome characterised by raised levels of ESR, fibrinogen and CRP (1). Respiratory functional tests often reveal a restrictive ventilatory dysfunction, but there are studies showing that up to 30% of the patients can have spirometric results within the normal range, as is the case in this patient. Rather specific is the impairment of DLCO, also observed in this case (1).

In this report, the imaging was suggestive for COP. Guidelines present the COP typical high resolution computed tomography (HRCT) pattern as peripheral consolidations with air bronchogram often limited by ground glass opacities or multiple air spaces opacities. Furthermore, detecting an annular consolidation with a ground glass opacity in the centre is called an Atoll sign or a reversed halo, and is considered a distinctive sign for COP. However, some studies have shown that this sign might also show up in various infections, granulomatosis or neoplasms. However, this sign appears only in about 20% of patients, and thus the lack of it cannot rule out COP. The case presented here was not associated with this type of lesion. On the other hand, the HRCT presentation of COP can also be atypical with a nodular pattern, crazy paving, infiltrative opacities or progressive fibrosis. The association between a suggestive clinical presentation and a compatible HRCT imaging of COP is enough to establish the diagnosis in 80% of cases. Due to the fact that this entity has multiple radiological patterns, it is important to correlate the initial presentation of the disease and migratory evolution in time and under treatment, in order to avoid misdiagnosis. In 20% of the cases, a multidisciplinary approach and extensive investigations might be necessary, including bronchoscopy with bronchoalveolar lavage, as well as pulmonary biopsy (2).

One of the particularities in this case was the association with both pleural effusion and pericarditis. Whereas pleural involvement is seen in about 10% of cases, pericarditis is very rarely associated with this pathology. These serositis rapidly went into remission after initiating treatment with corticosteroids.

Bronchoscopy with broncho-alveolar lavage is important for ruling out differential diagnostics. The lavage reveals a mixed cellularity pattern: lymphocytes (20%–40%) with a CD8 predominance, neutrophils (10%) and eosinophils (5%). In the context of the COVID-19 pandemic, the bronchoscopy guidelines recommend that all non-urgent endoscopic investigations should be delayed. Thus, the bronchoscopy with broncho-alveolar lavage was postponed for this patient until the 10th month of treatment, when, due to her relapse, she was investigated and the cytological results were found to be in the normal range (1).

We also mention here that the patient had been offered to have a pulmonary biopsy with histopathological examination done, which she refused. In cases in which the clinical and imagistic presentation are atypical and the broncho-alveolar lavage does not provide additional information, the pulmonary biopsy is necessary. This is also recommended for patients with an inadequate response to treatment (1).

In clinical practice, most frequently the differential diagnosis is made with community acquired pneumonia. A useful, common instrument in differentiating the two entities is procalcitonin, a marker that seems to be more accurate than the presence of leucocytosis or of a systemic inflammatory syndrome. Moreover, in COP, there is no remission of symptomatology and imagistic under antibiotic treatment. According to the clinical, biological and imagistic presentation, the diagnostic algorithm has to rule out also other entities such as eosinophilic pneumonia, neoplasms, connective tissue diseases, hypersensitivity pneumonitis or pulmonary tuberculosis. Once the diagnosis of organising pneumonia (OP) has been set, one has to analyse whether it is cryptogenic or induced by certain drugs (forming part of the regimens of chemotherapy, immunotherapy etc.), radiotherapy, bacteria, fungus, sarcoidosis, connective tissue disease, occupational exposure or organ transplant. Older studies have shown that 50% of OP are idiopathic, but more recent data shows that only 15% of OP are cryptogenic, while the rest are secondary forms. Thus, it is important to respect diagnostic algorithms that are meant to rule out forms induced by certain medication or other pathologies (3).

In this case, diagnostic algorithm had been influenced by the COVID-19 pandemic context. SARS-CoV-2 pneumonia has a similar clinical presentation (fever, dry cough, fatigue, dyspnaea, malaise) and imagistic pattern as COP (ground glass opacities with subpleural distribution, consolidations or mixed pattern with bilateral distribution, crazy paving and even

reversed halo sign). Thus, the clinician should not ignore this differential diagnosis, taking into consideration the potential severe/fatal evolution of this infection. Our patient was repeatedly tested by both reverse transcription polymerase chain reaction (RT-PCR) and IgM/IgG antibodies for SARS-CoV-2 infection, with negative results every time (4).

On the other hand, several reviews of COVID-19 HRCT along with autopsies indicate that the vast majority of COVID-19 patients with pulmonary involvement also have a secondary OP. Furthermore, the results of RECOVERY (randomised controlled trial which compared dexamethasone with placebo in COVID-19) suggest that corticosteroid therapy should be the first-line treatment in patients with COVID19-OP (5).

Although at present there is no consensus about administering corticotherapy, most guidelines recommend a treatment with prednisone 0.75–1 mg/kg/d, for 6 weeks, and weaning over 6–12 months; this regimen was also followed by our patient. The severity of disease, the initial clinical presentation and the comorbidities should be considered when choosing the appropriate regimen and treatment duration. When facing a relapse, re-escalation of corticosteroids dose is recommended, and this strategy was also applied in our case. After returning to the dose of 20 mg/d, the patient's symptoms went into remission. For patients that are corticoresistant or with contraindications, other therapeutic classes can be used, such as azathioprine, mycophenolate mofetil, cyclophosphamide or cyclosporine A (6). Since the administration of corticotherapy or other immuno-suppressing treatment is prolonged (6–12 months) and associated with significant side effects, other therapeutic classes are being studied. Another alternative proposed by a researcher is clarithromycin for patients with normal spirometric values. The advantage of this therapy is the shorter period of administration (3 months) and a lower relapse rate, but more randomised studies are needed to validate this approach (1,7).

Disease relapse when tapering or stopping corticosteroid therapy is common: between 30% and 65% of cases experience at least one episode. There have been identified risk factors for COP relapse such as bilateral shadow pattern, traction bronchiectasis, partial remission, a high neutrophil percentage in the bronchoalveolar lavage and higher levels of fibrin deposition in lung biopsy specimens. However, the 5-year survival rate of COP patients is 83%–98.3%. (8–13).

Conclusions

In the case of a pneumonia in which there is a discrepancy between the clinical, biological and radiological images (possibly with a migratory pattern) and the response to treatment, the diagnosis of COP must be considered. Relapses are relatively common, and may occur during the reduction of corticosteroid dosage and also after the end of treatment.

Consent for publication

Written informed consent was obtained from the patient for publication of this report.

Conflict of interest statement

The authors declare that they have no competing interests.

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