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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Cryptogenic organizing pneumonia – wrongfully neglected disease

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SUMMARY
Introduction Cryptogenic organizing pneumonia (COP) is a type of organizing pneumonia with an unknown primary etiology. Diagnosis of COP requires exclusion of any other possible cause. The disease manifests with nonspecific symptoms and clinical findings resembling respiratory infection. Diagnosis of COP should be considered after the radiographic signs of pneumonia persist despite applied therapy, or show a migratory pattern. Due to a diverse differential diagnostic palette, establishing the correct diagnosis is often delayed, resulting in delayed administration of adequate therapy.
Outlines of cases In this paper, we present three female patients diagnosed with COP in our clinic. We outline all challenges in the diagnostic pathways, from managing initial symptoms, through all necessary laboratory tests and diagnostic procedures, to establishing the diagnosis and starting treatment. After presenting radiological findings before and after starting corticosteroid treatment, we also reevaluated the clinical response to the administered treatment initially and during the subsequent follow-up period.
Conclusion To diagnose COP, we must first remind ourselves to consider it when treating patients with recurrent pneumonia. When COP is finally diagnosed, the quality of life of these patients improves, as this avoids excessive antimicrobial therapy and repeated hospitalizations. A multidisciplinary approach is needed, both in diagnosing and treating patients, owing to comorbidities and the need to exclude any other potential cause of organizing pneumonia. Corticosteroid treatment provides rapid resolution of symptoms followed by long remission periods.
Keywords: cryptogenic organizing pneumonia; diagnosis; differential diagnosis

INTRODUCTION

Cryptogenic organizing pneumonia (COP) is an idiopathic form of organizing pneumonia, formerly called bronchiolitis obliterans organizing pneumonia. It is a type of diffuse interstitial lung disease that affects distal bronchioles, respiratory bronchioles, alveolar ducts, and alveolar walls without disrupting lung architecture. Apart from the cryptogenic form, secondary organizing pneumonia is an organizing pneumonia with known triggering factors and is mainly caused by connective-tissue diseases, autoimmune diseases, infections, malignancies, and drug exposure, with an increasing prevalence related to new biological therapies, interferons, and monoclonal antibodies [1, 2, 3]. To diagnose COP, clinicians must first identify organizing pneumonia and then exclude every possible cause [1].

COP commonly presents with a relatively short duration (up to two months) of pseudo-flu-like symptoms, persistent non-productive cough, dyspnea, fever, malaise, weight loss, and chest pain [1, 2, 4]. Physical examination can show normal pulmonary findings in one-quarter of patients [5]. Chest radiograph and computed-tomography manifestations of COP commonly appear as peripheral bilateral consolidations or ground-glass opacities, with a tendency to recur and to migrate [6]. There are no laboratory tests specific for COP, but results may show leukocytosis and elevated levels of C-reactive protein (CRP) and erythrocyte-sedimentation rate [2, 7]. Treatment for COP requires prolonged administration of corticosteroids. The initial dose depends on the disease severity, clinical symptoms, potential progression, and radiological findings [2, 4]. When treated with corticosteroids, recovery with complete clinical and physiologic improvement and normalization of chest radiographs is found in two-thirds of patients [1].

We present three cases of COP diagnosed and treated at the Clinic for Pulmonology, University Clinical Center of Serbia, in the previous three years.

REPORTS OF CASES

Case No. 1

A female patient, 52 years old, was repeatedly hospitalized in a regional secondary medical center over five months under the diagnosis of pneumonia, presenting with high fever, fatigue, chest pain, and generalized myalgia. She was a former smoker with known chronic illnesses and therapy for diabetes mellitus and

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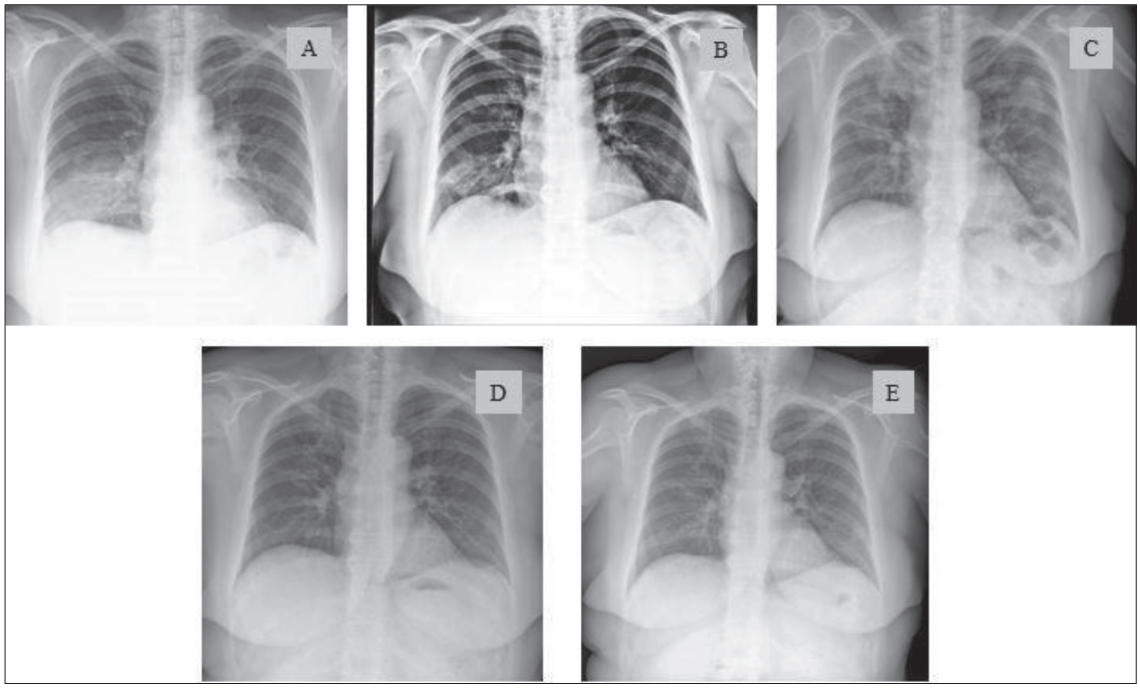

Figure 1. Chest radiographs from Case No. 1 patient chronologically, from the first manifestation of the disease during the first hospitalization at the regional medical center (RMC) (A), after initial empiric antibiotics treatment at RMC (B), when admitted to our clinic due to developing deterioration of the general condition (C), 10 days after initial corticosteroid treatment (D), and on the second follow-up after hospital discharge (E)

arterial hypertension. Her symptoms were accompanied by CRP levels up to 220 mg/L and chest-radiograph findings of lung-parenchyma consolidations at different sites. Each time she was treated with empiric parenteral antibiotics and corticosteroids, resulting in almost complete radiographic regression and lowered CRP levels. No infectious agents were detected in serum or sputum. After each discharge, she gradually redeveloped the symptoms, with escalating myalgia and fatigue. During a prehospital ambulatory episode, a chest CT showed a 70 × 60 mm irregular consolidation of the right upper lobe with a negative bronchus sign and several smaller consolidations of the left lower lobe. After significant clinical deterioration of general condition followed by dyspnea and fever of 38.3°C, she was referred to our institution. Laboratory findings at the beginning of hospitalization showed elevated level of CRP (107 mg/L) and leukocytes (12.2×10^9/L), with slight predominance of neutrophils in the leukocytic formula (7.7×10^9/L) and normal levels of eosinophils. Physical examination showed normal pulmonary findings.

During hospitalization at our clinic various diagnostic procedures and tests were performed. Immunology testing excluded autoimmune diseases, including myositis, systemic connective-tissue disease, and vasculitis (negative ANA-Hep-2, ANCA, normal creatine kinase). Bronchoscopy with transbronchial biopsy and bronchoalveolar lavage (BAL) showed normal endoscopic findings. Tuberculosis was excluded by negative microscopy and Löwenstein cultures of sputum and fiber-aspirate (FA). Additional tests of blood, FA, and sputum excluded fungal, bacterial, and viral infective agents.

By analyzing cytology of BAL, the pathologist concluded that, with elevated percentage presentation of macrophages (half of them were foamy macrophages), lymphocytosis 30% with CD4/CD8 lymphocytes ratio of 0.3, and 10% of neutrophils, findings support the diagnosis of COP. Pathohistology of transbronchial biopsy was inconclusive for interpretation due to the small tissue sample.

A radiologist performed additional interpretation of chest CT scan and concluded that consolidations by appearance and distribution, considering the migratory effect, are suggestive of COP.

During the hospitalization at our clinic, the patient was treated initially with empiric parenteral antibiotics in accordance with the established guidelines for community-acquired pneumonia (CAP), taking into consideration the patient's clinical status, risk factors, and local epidemiology. Control laboratory tests showed lower CRP but control chest radiograph showed progression in the size of lung consolidation and developing new lesions. The administration of antibiotics was discontinued, and after excluding all potential causes of bilateral progressive consolidations of the lung, continuous corticosteroid therapy was initiated on June 7, 2024. Firstly, parenteral administration of methylprednisolone at a dose of 60 mg/day was performed. The patient showed significant improvement in general condition, followed by absence of high body temperature and dyspnoea. Control chest radiograph showed almost complete regression of previously visualized lesions (Figure 1). With control laboratory tests showing a CRP level of 14.5 mg/L, the patient was discharged from clinic and continued corticosteroid therapy in tablet form (60 mg/day of prednisone).

At the first follow-up visit two weeks after discharge from our hospital, with control chest radiograph showing complete regression, the dose of prednisone was lowered

to 40 mg/day, and, due to the previously known condition of diabetes mellitus as a comorbidity, the patient was referred to an endocrinologist in case of need for correction of doses of metformin, due to known effects of corticosteroids on serum glucose levels. In the next follow-up control six weeks after the first one, another de-escalation of the dose of prednisone was done, lowered to 30 mg/day. The patient was under regular follow-ups by a pulmonologist at intervals of 6–8 weeks. Follow-up chest radiographs were performed, and corticosteroid therapy was gradually tapered. On February 19, 2025, based on comprehensive clinical assessment, corticosteroids were discontinued, and a subsequent follow-up was scheduled in six months.

Case No. 2

Female patient, 63 years old, was in the period of eight months several times hospitalized in a regionally affiliated secondary medical center due to high fever, elevated CRP levels, and chest radiographic signs of repeated bilateral pneumonia. With no other comorbidities than periodical episodes of vertigo, each time she was treated with empiric antibiotic therapy in accordance with the established guidelines for CAP, resulting only in lowering the levels of CRP and body temperature, without complete radiographic regression. Three CT chest scans were performed during that period, showing only consolidations with ground-glass opacifications. She was admitted to our clinic with high fever and bilateral lung consolidations (described this time in the left lobe and right lower lobe) verified by the latest CT chest scan. CRP level was 44.2 mg/L, immunology tests were all negative. Bronchoscopy was performed, finding only endoscopic signs of inflammation (hyperemic mucosa of the tracheo-bronchial tree with pus, dominantly in the left lower lobe). Results of cytological and microbe analysis of the FA of bronchi were nonspecific (classic BAL was not performed). Radiologist performed additional interpretation of all three CT scans. Because of the nature of described irregular, organizing consolidations with dominantly migrating effect, refractory to any other applied treatment, we suspected the presence of COP. After the numerous laboratory and invasive diagnostics were performed, excluding any autoimmune or systemic and soft-tissue disease, malignant or infectious etiology of described consolidations, we started treatment with oral corticosteroids. Continuous parenteral corticosteroid therapy was initiated on 22 October 2022, starting with a 40 mg dose of methylprednisolone. The first follow-up was two weeks after hospital discharge, when the first de-escalation of dose of corticosteroids was done (from 40 mg to 30 mg of prednisone). At the time of first control after the discharge from our clinic, control chest radiograph showed complete regression of previously registered consolidations, followed by normal levels of CRP (Figure 2). She was treated with oral corticosteroids in de-escalating doses for seven months, without signs of relapse of the disease. After the corticosteroid treatment was stopped in May 2023, the patient still showed no signs of disease relapse in the total period of two years; she is regularly scheduled for annual check-ups.

Case No. 3

Female patient, 74 years old, with symptoms of prolonged pain in body joints and high body temperature up to 38.3°C, high level of CRP (175 mg/L) and radiographic signs of bilateral pneumonia, started oral antibiotics treatment (cefixime, levofloxacin) suggested by her physician. After developing shortness of breath and extreme fatigue, elevation of CRP level to 257 mg/L, registered low blood-oxygen level and progression of radiological findings, she was admitted to our clinic, where she was treated with parenteral antibiotics (meropenem, levofloxacin). The patient showed clinical improvement after the treatment. CT chest scan after finished antibiotics treatment showed presence of bilateral consolidation of lung in lower lobes and upper right lobe with lesions of interstitium of the lung. She was discharged, and scheduled for pulmonologist control in two months with control chest CT scan. Bronchoscopy was advised, but was never conducted as the patient refused the proposed diagnostic procedure.

In the following period, due to repeated joint pains, followed by high fever of up to 40°C, and again elevated CRP level to 170 mg/L, the patient was admitted to the Institute for Rheumatology, where she was treated with parenteral empiric antibiotic therapy in accordance with

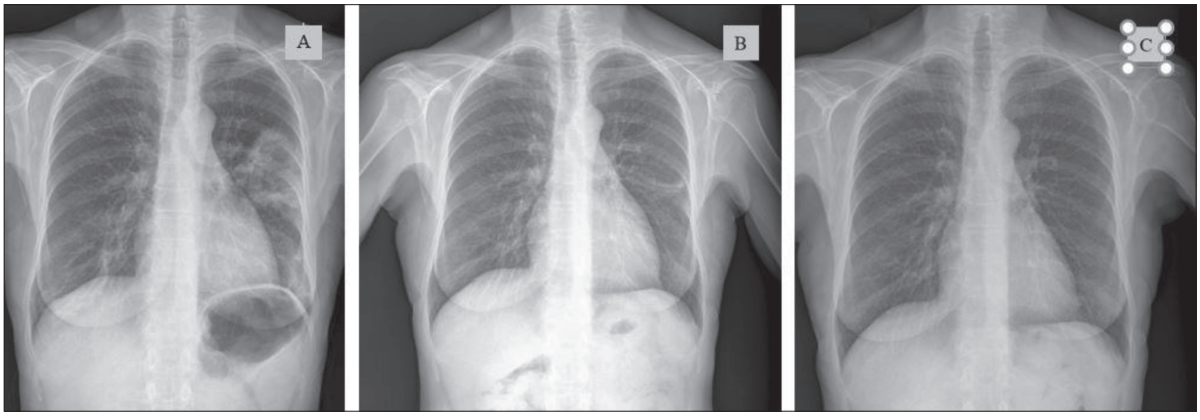

Figure 2. Chest radiographs from patient Case No. 2, before administering corticosteroid therapy (A), one month after corticosteroid treatment started (B), and one year after starting treatment of COP (C)

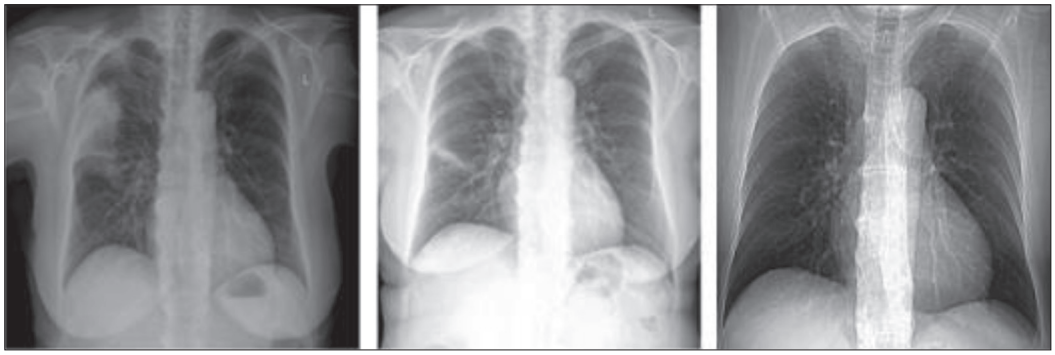

Figure 3. Chest radiographs of Case No. 3 patient, before (on the left), one month after starting corticosteroid therapy (in the middle), and on the annual follow up control (on the right)

the established guidelines for CAP. After numerous laboratory tests, arthritis and other soft-tissue diseases were excluded. During the beginning of that hospitalization, control chest CT scan was performed, describing previously detected lung lesions/consolidations still present. After several days of hospitalization, treatment with corticosteroid therapy was introduced in February 2022 (deflazacort, 30 mg/day), and with clinical improvement she was discharged from the Clinic with gradually de-escalating oral doses of corticosteroids (deflazacort).

Considering the persistency of CT findings, during the next follow-up control by her pulmonologist, a radiologist was consulted and both previously performed CT scans were compared. The radiologist concluded that CT findings were highly suggestive of COP.

After considering all clinical manifestations and improvements, both clinical and in general condition, developed after the initiation of corticosteroids into treatment, she was diagnosed with COP (Figure 3). She continued oral corticosteroid therapy as previously advised. During the next follow-up period she had one relapse of the disease two months after the diagnosis of COP was made, which was regulated in short-term elevation of corticosteroid dose (the dose of deflazacort was increased to 45 mg in total duration of eight weeks). After remission, the dose of deflazacort was gradually tapered to the maintenance dose of 7.5 mg per day, and in the following year when she attended regularly follow-up appointments with the pulmonologist, she experienced no relapses of the disease.

Ethics: The authors declare that the article was written in accordance with ethical standards of the Serbian Archives of Medicine as well as ethical standards of institutions for each author involved. Written consent to publish all shown material was obtained from the patients.

DISCUSSION

Regarding all presented cases, all cases showed a significant time delay in making the right diagnosis. With a clinical presentation of infective disease, minimal respiratory symptoms but alarming radiological signs, it can be easily misleading to suspect yet another common case or pneumonia caused by infective agents. In our experience, patients underwent, on average, three hospitalizations until making the right diagnosis, not including the time between hospitalizations when they were treated as ambulatory patients with antibiotics. Repeated hospitalizations with intensive medication treatment resulting in a lack of expected response can harm patients' quality of life in many ways.

Not suspecting COP in patients with progressive migratory lung lesions followed by deterioration of general condition can result in the rapid administration of broad-spectrum antibiotics (including reserve antibiotics) or antifungal medications. Uncritical widespread use of antibiotics can cause antimicrobial resistance, especially by using reserve antibiotics [8]. Prolonged antibiotic exposure is also a major risk factor for *Clostridioides difficile* infection, as it reduces the population of non-pathogenic anaerobes that normally inhabit the gut, thereby allowing *C. difficile* to proliferate [9]. A patient with COP and a potential *C. difficile* infection who is scheduled to begin corticosteroid therapy, which suppresses the general immune response, is at increased risk of developing severe gastrointestinal complications, as immunosuppression may exacerbate the course of the infection.

It is crucial to emphasize the importance of a clinical and systematic approach to the problem, with a well-organized algorithm in the process of excluding differential diagnoses. This is often impracticable in many hospitals and healthcare centers due to insufficient availability of invasive diagnostics and laboratory and immunology tests.

The current diagnostic algorithm for COP includes histopathological confirmation of the disease. Although opinions vary, invasive diagnostic procedures are generally recommended in cases of unclear clinical or radiological presentation, or when there is an inadequate response to initial therapy. Surgical lung biopsy is necessary to establish a diagnosis when vasculitides are part of the differential diagnosis. However, histopathological confirmation of organizing pneumonia alone should not be considered a sufficient criterion for diagnosis [10, 11].

In our cases, two of the three patients had bronchoscopy, but only one showed confirmation of the disease by analyzing the BAL. Analyzing the FA of the bronchi to exclude infectious disease is also very important. When resources are scarce, it is not always necessary to conduct

invasive diagnostics, but it is preferable, considering the wide differential-diagnosis palette.

Clinical improvement is typically observed within 24–72 hours after the initiation of corticosteroid therapy in responsive patients, often manifesting as reduced symptoms and improved overall condition. Complete remission is generally confirmed after approximately three months [4].

When initiating corticosteroid therapy, consider possible risks of cumulative steroid dosage and side effects of prolonged therapy and refer patients to other subspecialties. At the beginning of treatment, patients need frequent follow-up controls, due to possible side effects of the therapy and the disease's potential for relapses, which would require correction of medication doses. Routine follow-up with chest radiographs and pulmonary function tests every two–three months is recommended during corticosteroid treatment [12].

Most relapses occur within the first year of treatment, often upon tapering or discontinuation of corticosteroids. Relapses typically respond well to corticosteroids. In the management of disease relapse, one study showed no difference in clinical outcomes between increasing prednisone to 20 mg/day versus higher doses, while higher doses were associated with more side effects. Reinitiating treatment at 20 mg/day with gradual tapering is suggested to be the most adequate approach [4, 13].

A recent retrospective observational study on clinical outcomes in COP patients aimed to identify predictors of relapse by comparing those who showed clinical improvement with those who did not. Elevated serum Krebs-von-den-Lungen-6 levels and chest CT findings indicative of pulmonary fibrosis were associated with poor clinical response. In contrast, markers of systemic inflammation, such as elevated CRP, increased neutrophil percentage, and decreased lymphocyte percentage, were linked to a shorter time to the first relapse among patients who initially responded to treatment [14].

The presence of nonspecific symptoms and radiologic features that mimic other pulmonary diseases complicates the diagnostic process so a multidisciplinary approach (considering radiologists, immunologists, allergologists) is necessary to exclude any known factors that can cause organizing pneumonia [15]. A multidisciplinary approach is also needed in managing potential negative effects of prolonged corticosteroid therapy in patients with comorbidities like diabetes mellitus, osteoporosis, arterial hypertension.

Our cases are examples that COP is often a wrongfully neglected disease, insufficiently considered as a possible diagnosis. Suspecting the presence of COP is the first step in the diagnostic process. With the right diagnostic algorithm that excludes any other cause and at the same time exhibits a characteristic CT pattern, once diagnosed, it is easily treated, resulting in complete regression and long remissions. Hence, it is important to always consider COP when treating a patient with migratory lung lesions, clinically resembling bacterial pneumonia.

Conflict of interest: None declared.

REFERENCES

1. Cordier JF. Cryptogenic organising pneumonia. Eur Respir J. 2006;28(2):422–46. [DOI: 10.1183/09031936.06.00013505] [PMID: 16880372]
2. King TE Jr, Lee JS. Cryptogenic Organizing Pneumonia. N Engl J Med. 2022;386(11):1058–69. [DOI: 10.1056/NEJMra2116777] [PMID: 35294814]
3. Radzikowska E, Fijolek J. Update on cryptogenic organizing pneumonia. Front Med (Lausanne). 2023;10:1146782. [DOI: 10.3389/fmed.2023.1146782] [PMID: 37153105]
4. Lazor R, Vandevenne A, Pelletier A, Leclerc P, Court-Fortune I, Cordier JF. Cryptogenic organizing pneumonia: characteristics of relapses in a series of 48 patients. Am J Respir Crit Care Med. 2000;162(2 Pt 1):571–7. [DOI: 10.1164/ajrccm.162.2.9909015] [PMID: 10934089]
5. Epler GR, Colby TV, McLoud TC, Carrington CB, Gaensler EA. Bronchiolitis obliterans organizing pneumonia. N Engl J Med. 1985;312(3):152–8. [DOI: 10.1056/NEJM198501173120304] [PMID: 3965933]
6. Tiralongo F, Palermo M, Distefano G, Vancheri A, Sambataro G, Torrisi SE, et al. Cryptogenic organizing pneumonia: evolution of morphological patterns assessed by HRCT. Diagnostics (Basel). 2020;10(5):262. [DOI: 10.3390/diagnostics10050262] [PMID: 32365469]
7. Marwah V, Peter DK, Sharma N, Bhattacharjee S, Hegde A, Shelly D, et al. Clinico-etiological characteristics of organizing pneumonia: a retrospective study. Lung India. 2021;38(2):144–8. [DOI: 10.4103/lungindia.lungindia_105_20] [PMID: 33687008]
8. Maki G, Zervos M. Health care-acquired infections in low- and middle-income countries and the role of infection prevention and control. Infect Dis Clin North Am. 2021;35(3):827–39. [DOI: 10.1016/j.idc.2021.04.014] [PMID: 34362546]
9. Smits WK, Lyras D, Lacy DB, Wilcox MH, Kuijper EJ. Clostridium difficile infection. Nat Rev Dis Primers. 2016;2:16020. [DOI: 10.1038/nrdp.2016.20] [PMID: 27158839]
10. Raghu G, Meyer KC. Cryptogenic organising pneumonia: current understanding of an enigmatic lung disease. Eur Respir Rev. 2021;30(161):210094. [DOI: 10.1183/16000617.0094-2021] [PMID: 34407978]
11. Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax. 2008;63(Suppl 5):v1–58. [DOI: 10.1136/thx.2008.101691] [PMID: 18757459]
12. Saito Z, Kaneko Y, Hasegawa T, Yoshida M, Odashima K, Horikiri T, et al. Predictive factors for relapse of cryptogenic organizing pneumonia. BMC Pulm Med. 2019;19(1):10. [DOI: 10.1186/s12890-018-0764-8] [PMID: 30626371]
13. Jo YS, Park JS, Park SH, Joh JS, Jang HJ, Lee HK; Korean Interstitial Lung Disease Study Group. Korean guidelines for diagnosis and management of interstitial lung disease: cryptogenic organizing pneumonia. Tuberc Respir Dis (Seoul). 2025. Epub ahead of print. [DOI: 10.4046/trd.2024.0167] [PMID: 40078018]
14. Taniguchi Y, Arai T, Tsuji T, Sugimoto C, Tachibana K, Akira M, et al. Cryptogenic organizing pneumonia: clinical outcomes of 60 consecutive cases. J Thorac Dis. 2024;16(5):3129–41. [DOI: 10.21037/jtd-24-225] [PMID: 38883617]
15. Arı M. Current approaches in the diagnosis and treatment of organizing pneumonia. Anatolian Curr Med J. 2025;7(1):89–93. [DOI: 10.38053/acmj.1599119]

Криптогена организујућа пнеумонија – неправедно занемарена болест

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САЖЕТАК

Увод Криптогена организујућа пнеумонија (КОП) је тип организујуће пнеумоније непознатог примарног узрочника. Дијагноза КОП се поставља када се искључе сви други могући узрочници. Манифестује се неспецифичним тегобама и клиничким симптомима који иду у прилог респираторној инфекцији, а сумња на КОП се јавља када упркос примењеној терапији радиографски налази пнеумоније перзистирају, или добијају миграторни ефекат. С обзиром на широку диференцијалну дијагностичку палету, постављање дијагнозе је пролонгирано, па је самим тим и примена одговарајуће терапије одложена.

Приказ болесникâ У раду су приказане три болеснице којима је у нашој установи постављена дијагноза криптогене организујуће пнеумоније. Представљени су сви изазови и путеви сваке болеснице од почетка развоја симптома до постављања дијагнозе. Обрађене су све учињене лабораторијске анализе и дијагностичке процедуре на основу којих је закључено постојање ове болести. Уз илустрацију приказа радиолошких налаза пре и након започињања кортикостероидне терапије, обрађен је и клинички одговор на примењену терапију и начин на који су болеснице амбулантно праћене.

Закључак Да би се поставила дијагноза КОП, прво на њу треба посумњати. Уз правовремено постављање дијагнозе могуће је побољшати квалитет живота болесника, избегавањем екцесивне употребе антимикробне терапије и честих хоспитализација. Постављање дијагнозе али и само лечење често захтева мултидисциплинарни приступ, како због пратећих коморбидитета тако и због потребе елиминисања других могућих узрочника организујуће пнеумоније. Примена кортикостероидне терапије доводи до брзог изостанка тегоба праћеног дугим периодима ремисије.

Кључне речи: криптогена организујућа пнеумонија; дијагноза; диференцијална дијагноза