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Case Report / Приказ болесника

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Cryptogenic organizing pneumonia – wrongfully neglected disease

Криптогена организујућа пнеумонија – неправедно занемарена болест

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SUMMARY

Introduction Cryptogenic organizing pneumonia (COP) is a type of organizing pneumonia with unknown primary etiology. Diagnosis of COP requires exclusion of any other possible cause. The disease is manifested by non-specific symptoms and clinical findings resembling respiratory infection. Diagnosis of COP should be considered after the radiographic signs of pneumonia persist despite applied therapy, or have a migrating effect. Due to diverse differential diagnostic palette, concluding the right diagnosis is often prolonged, resulting in delaying the administration of adequate therapy.

Case outline In this paper, we presented three female patients diagnosed with COP in our clinic. We presented all challenges in the diagnostics paths, from managing initial symptoms, over the all necessary laboratory tests and diagnostic procedures performed, to concluding the diagnosis and starting treatment. After presenting radiological findings before and after starting the corticosteroid treatment, we also reevaluated clinical response to administrated treatment in the beginning and in the next follow up period.

Conclusion To diagnose COP, first, we must frequently remind ourselves to consider this diagnosis when treating patients with repeated pneumonia. When COP is finally diagnosed, the quality of life of these patients is improved, avoiding excessive use of antimicrobial therapy and repeated hospitalizations. A multidisciplinary approach is needed, both diagnosing and treating patients, due to following comorbidities and necessity to exclude any other potential cause of organizing pneumonia. Corticosteroid treatment provides fast resolution of symptoms followed by long remission periods.

Keywords: cryptogenic organizing pneumonia; diagnosis; differential

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 симтомима 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, самим тим је и примена одговарајуће терапије одложена.

Приказ болесникâ У раду су приказане три болеснице којима је постављена дијагноза криптогене организујуће пнеумоније у нашој установи. 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 можемо 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 потенцијалних узрочника организујуће пнеумоније. Примена кортикостероидне терапије доводи до брзог изостанка тегоба праћеног дугим периодима ремисије.

Кључне речи: криптогена организујућа пнеумонија; диференцијална; дијагноза

INTRODUCTION

Cryptogenic organizing pneumonia (COP) is an idiopathic form of organizing pneumonia, formerly called bronchiolitis obliterans organizing pneumonia or BOOP. It is presented as a type of diffuse interstitial lung disease that affects distal bronchioles, respiratory bronchioles, alveolar ducts, and alveolar walls without disrupting lung architecture. Other than cryptogenic form, secondary organizing pneumonia (SOP) is a form of organizing pneumonia with known triggering factor and mainly caused by connective tissue diseases, autoimmune diseases, infections,

malignancies and drug-induced, with an increasing prevalence in correlation with new biological therapies, interferon, monoclonal antibodies. [1, 2, 3] To diagnose COP, it is required firstly to diagnose organizing pneumonia, then to exclude any possible cause. [1]

COP is commonly presented with relatively short duration (up to two months) of pseudo-flu-like symptoms, persistent, nonproductive cough, dyspnea, fever, malaise, weight loss and chest pain [1, 2, 4]. Physical examination can show normal pulmonary finding in one-fourth of patients [5]. Chest radiograph and computed tomography manifestations of COP are commonly presented as peripheral bilateral consolidative or ground-glass lung opacities, with tendency in recurrency and migratory effect. [6] There are no laboratory tests specific for COP, but when evaluating laboratory findings, results showed leukocytosis, elevated level of C reactive protein and erythrocyte sedimentation rate [2, 7]. Treatment for COP requires administration of corticosteroid therapy in prolonged period of time. Initial dose depends on the severity of disease and following 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 patients [1].

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

REPORTS OF CASES

Case No. 1

Female patient, 52 years old, was repeatedly hospitalized in regionally affiliated secondary medical center in the period of five months under the diagnosis of pneumonia, presented with high fever, fatigue, chest pains and general muscle pain. She was a former smoker, with previous known chronic illness and therapy for diabetes mellitus and arterial hypertension. Her symptoms were followed by elevated levels of C reactive protein (CRP) up to 220 mg/L and variety of chest radiographic findings presented as different localizations of lung parenchyma consolidations. Each time she was treated with empiric parenteral antibiotics and corticosteroid therapy resulting almost complete regression in radiographic findings and lowering levels of CRP. During this time, there were no infectious agents detected or isolated from additional tests of serum and sputum. After each discharge from hospital, she was gradually developing previous symptoms with significant escalation of intensity of muscle pain and fatigue. In prehospital episode of ambulatory treated pneumonia, computed tomography (CT) of chest was performed.

It showed 70 × 60 mm irregular consolidation of upper right lobe with negative bronchi sign and few smaller consolidations od lower left lobe. After developing significant deterioration of general condition followed by dyspnoea and high fever 38.3°C, she was referred to our institution by a regional pulmonologist and administrated to our hospital. Laboratory findings at the beginning of hospitalization showed elevated level of CRP (107 mg/L) and leukocytes (12.2 × 10^9), with slight predominance of neutrophils in leukocytic formula (7.7 × 10^9) and normal levels of eosinophils. Physical examination showed normal pulmonary findings.

During hospitalization at our clinic various diagnostic procedures and tests were performed. Immunology test excluded presence of autoimmune diseases including myositis, systemic disease of soft and connective tissue and vasculitis [negative tests for ANA Hep2, ANCA, normal levels of creatine kinase (CK)]. Bronchoscopy was performed, sampling transbronchial biopsy (TBB) and bronchoalveolar lavage (BAL), endoscopic findings were normal. Tuberculosis infection was excluded by negative findings of direct microscopy and Löwenstein cultures of sputum and fiberaspirate (FA) of bronchi. Additional test of blood, FA of bronchi and sputum excluded infective agents from group of fungi, bacteria and viruses.

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

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

During the hospitalization at our clinic, 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 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 lung, continuous corticosteroid therapy was initiated on June 7, 2024. Firstly, parenteral administration of methylprednisolone in doses of 60 mg per 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 level of CRP

14.5mg/L, she was discharged from clinic and continued corticosteroid therapy in tablet form (60 mg/per day of prednisone).

At the first follow-up visit two weeks after discharge from our hospital, with control chest radiograph showing complete regression, dose of prednisone was lowered to 40 mg/per day, and due to previous known condition of diabetes mellitus comorbidity, she was referred to 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 descalation of dose of prednisone was done, lowered to 30 mg/per 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 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 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 tracheobronchial 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 on 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 October 22, 2022, starting with 40mg dose of

methylprednisolone. The first follow up was two weeks after hospital discharge, when the first descalation 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 descalating 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 relapsing disease in the total period of two years, so she is regularly scheduled for annual check-up.

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 oxygen blood 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 lung. She was discharged home, and scheduled for pulmonologist control in two months with control CT chest 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 up to 40°C, and again elevated CRP level to 170 mg/L, she was admitted to Institute for rheumatology, then treated with parenteral empiric antibiotic therapy in accordance with the established guidelines for CAP. After numerous laboratory tests, arthritis and other soft tissue diseases were excluded. During the beginning of that hospitalization, control CT chest 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, 30mg per day), and with clinical improvement she was discharged from clinic with gradually descalation in oral doses of corticosteroids (deflazacort).

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

After considering all clinical manifestations and improvement, both clinical and in general condition, developed after the initiation of corticosteroids into treatment, she was diagnosed as COP (Figure 3). She continued oral corticosteroid therapy as previously advised. During the next follow up period she had one relapse of disease two months after 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.

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 of them showed significant time delay in making the right diagnosis. With 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 ambulatory with antibiotics. Repeated hospitalizations with intensive medication treatment resulting lack of expected response, can harm quality of patients' lives in many ways.

Not suspecting the COP in patients with progressive migratory lung lesions followed by deterioration of general condition can result in quickly administrating a wide spectrum of antibiotics (including reserve antibiotics), or antifungal medications. Uncritical widespread use of antibiotics can cause antimicrobial resistance, especially by providing 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 clinical and systematic approach to the problem, with good organized algorithm in the process of excluding the differential diagnoses. This is often impracticable in many hospitals and healthcare centers due to insufficient availability to invasive diagnostics and many 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 three patients had bronchoscopy, but only one showed confirmation of the disease by analyzing the BAL. Analyzing the FA of bronchi to exclude infectious disease is also very important. When resources are scarce, it is not always necessary to conduct invasive diagnostics, but its preferable, considering 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 risk of cumulative steroid dosage and negative or 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 disease potential for relapses, which would require correction of medication doses. Routine follow-up with chest radiographs and pulmonary function tests every 2-3 months is recommended during the 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 a 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 multidisciplinary approach (considering radiologists, immunologists, allergologists) is necessary to exclude any known factors that can cause organizing pneumonia [15]. 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 wrongfully neglected disease, not enough considered as a possible diagnosis. Suspecting on presence of COP is first step in diagnostic process. With the right diagnostics algorithm that excludes any other cause and at the same time exhibits 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 having the patient with migratory lung lesions, clinically presented like bacterial pneumonia.

Conflict of interest: None declared.

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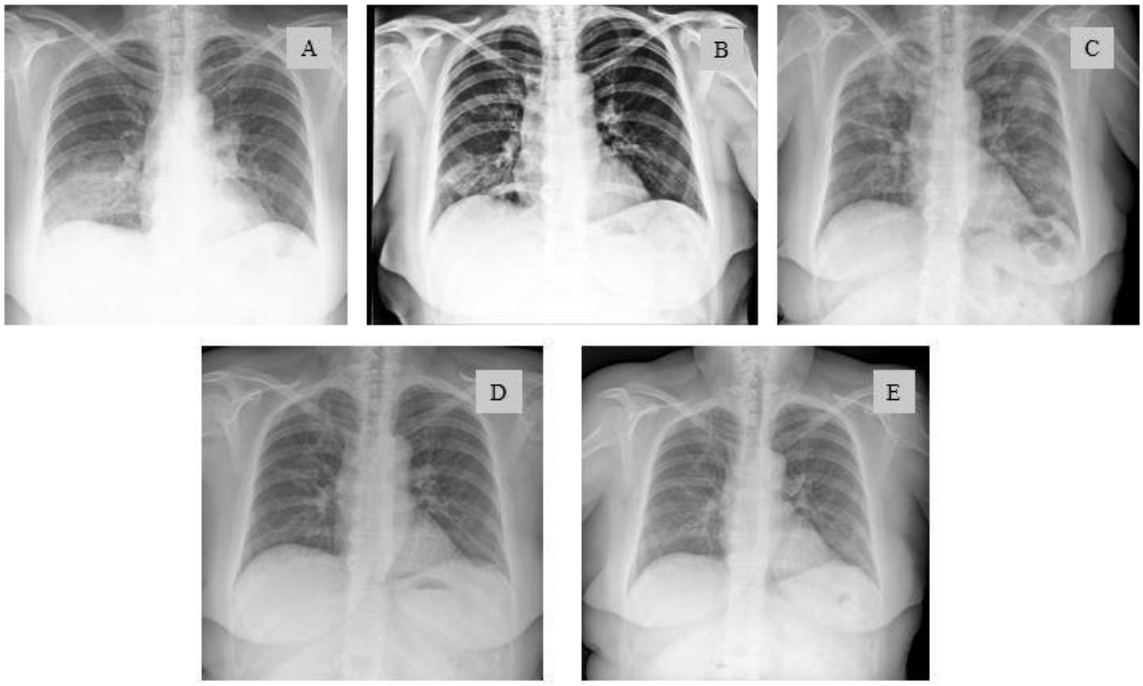

Figure 1. Chest radiographs from Case No. 1 patient chronologically, from the first manifestation of the disease during the first hospitalization at regional medical center (RMC) (A), after initial empiric antibiotics treatment at RMC (B), when admitted to our clinic due to developing deterioration of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

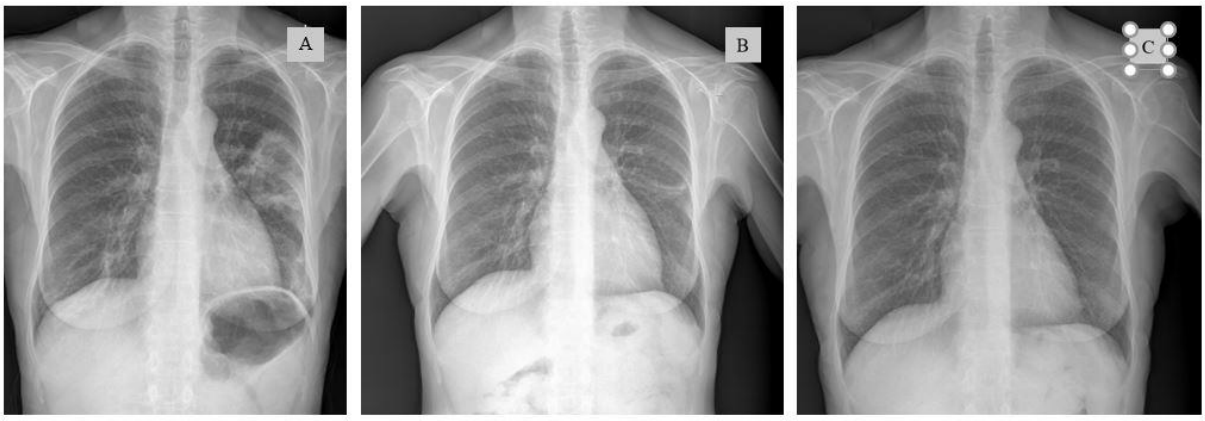

Figure 2. Chest radiographs from patient Case No. 2, before administrating corticosteroid therapy (A), one month after corticosteroid treatment started (B), and one year after starting treatment of COP (C)

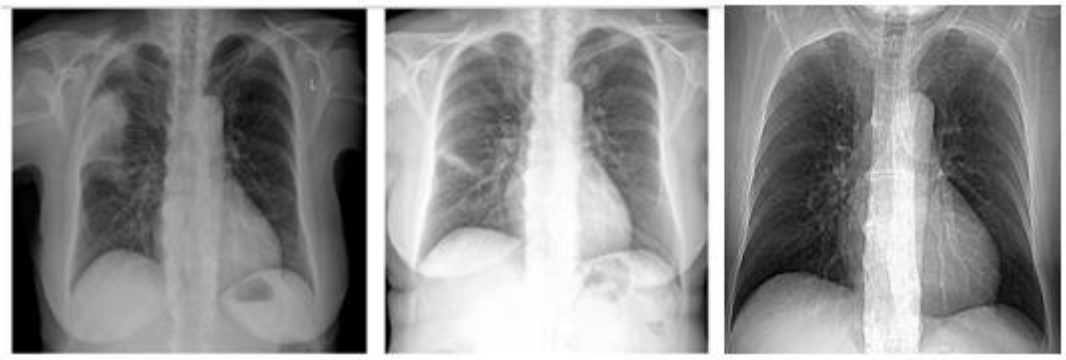

Figure 3. Chest radiographs of Case No. 3 patient, before (on the left), one month after starting corticosteroid therapy (in the middle), and on the annual follow up control (on the right)

