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Organizing Pneumonia: Three Case Reports

Organize Pnömoni: Üç Olgu Sunumu

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Abstract

Organizing pneumonia is characterized histopathologically by the accumulation and proliferation of fibroblasts, myofibroblasts and collagen within the alveolar and bronchiolar lumens, with such potential causes as drug reactions, radiation therapy, collagen vascular diseases and infections. In cases with a specific cause, the condition is referred to as secondary organizing pneumonia, and cryptogenic organizing pneumonia when no cause is apparent. Radiologically, nodules or mass lesions accompanied by air bronchograms may be observed together with patchy peripheral alveolar consolidations. Although not present in every case, the reverse halo sign is an important radiological finding. While clinical-radiological diagnosis is possible, it must be confirmed histopathologically. When steroids appropriate dosages and durations are applied, the results are usually outstanding.

Keywords: *Bronchiolitis Obliterans, organising pneumonia, halo sign.*

Öz

Histopatolojik tanım olarak Organize Pnömoni (OP), alveolar alanlar ve bronşiol lümen içinde fibroblastların, miyofibroblastların ve kollagenin toplanması aynı zamanda proliferasyonu ile karakterize bir akciğer hastalığıdır. OP'ye başta ilaç reaksiyonları, radyasyon tedavisi gibi etkenler olmak üzere, kollajen vasküler hastalıklar, enfeksiyonlar gibi birçok hastalık neden olabilir. Radyolojik olarak hava bronkogramlarının eşlik ettiği nodül veya kitle lezyonlar ile birlikte periferik, yamalı alveolar konsolidasyonlar görülebilir. Her olguda görülmemekle birlikte ters halo işareti önemli bir radyolojik bulgudur. Tanısı klinik-radyolojik ve histopatolojik yöntemler ile konulur. OP tedavisinde uygun doz ve sürede kullanılan glukokortikoid tedaviye yanıtları çok iyidir.

Anahtar Kelimeler: *Bronşiolit Obliterans, organize pnömoni, halo işareti.*

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Organizing pneumonia (OP), referred to previously as bronchiolitis obliterans organizing pneumonia (BOOP), is a histopathological condition characterized by an accumulation and proliferation of fibroblasts, myofibroblasts and collagen within the alveolar and bronchiolar lumens. In cases where the underlying etiology is unclear, the condition is classified as cryptogenic organizing pneumonia (COP). Conversely, if a causative factor is identified, it is referred to as secondary organizing pneumonia (SOP). SOP in particular has been associated with autoimmune diseases, infections, malignancies, specific medications and radiation exposure (Table 1) (1-3).

This report contributes to OP literature by presenting three cases diagnosed during outpatient evaluation in a pulmonary clinic, two of which were confirmed through histopathological examination, while the third was diagnosed based on clinical and radiological findings.

CASE

Case 1: A 65-year-old female patient with a known history of hypertension (HT) and asthma presented to the pulmonary clinic with complaints of cough, sputum production, back pain, night sweats and weight loss (10 kg over 2 months). A posteroanterior chest X-ray (PA CXR) revealed an irregularly marginated opacity in the paracardiac area of the right lower zone (Figure 1A), while physical examination findings were unremarkable. Laboratory tests produced the following results: WBC: 7.5 x $10^3/\mu l$, serum C-reactive protein (CRP): 67 mg/dL and erythrocyte sedimentation rate: 18 mm/hour, and spirometry and carbon monoxide diffusion capacity (DLCO) measurements were as follows: FEV1/FVC: 98 %, FEV1: 1.26 L (80%), FVC: 1.97 L (72%), DLCO: 24.72 mL/min/mmHg (73%), and DLCO/VA: 4.55 mL/min/mmHg/L (82%). A thoracic computed tomography (CT) scan performed after 1 week of oral 2x500 cefuroxime axetil and 2 weeks of 2x500 oral clarithromycin revealed a consolidated area with air bronchograms in the paravertebral region of the superior segment of the right lower lobe (Figure 1B).

The persistency of the findings on follow-up PA CXR led us to carry out a CT-guided tru-cut biopsy (CT-TCB), and a histopathological examination of the sample revealed a fibroblastic proliferation within the alveolar lumens and interstitial areas with a loose fibromyxoid matrix. The alveolar lumen was filled with a histiocytic infiltration, accompanied by prominent lymphoid aggregates, and chronic inflammatory cell infiltration was identified along with mild fibrosis in the bronchial wall. The patient was diagnosed with OP and started on methylprednisolone 40 mg daily.

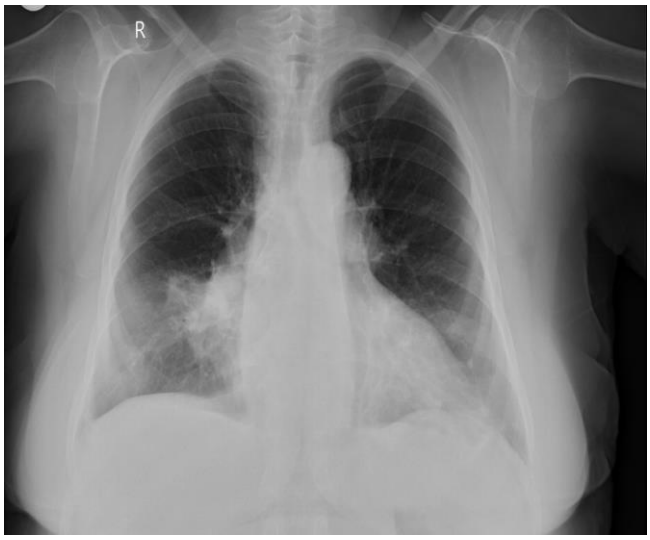

Figure 1a: *An irregularly bordered, non-homogeneous increased density in the paracardiac area of the right lower lung zone*

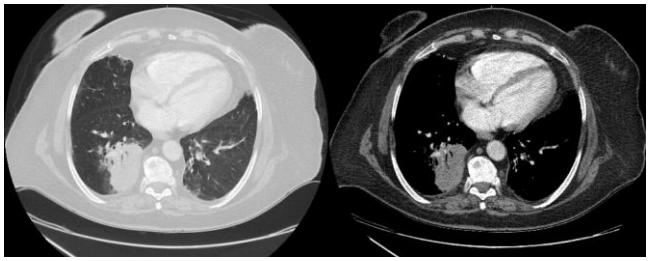

Figure 1b: *An irregularly bordered, non-homogeneous increased density in the paracardiac area of the right lower lung zone*

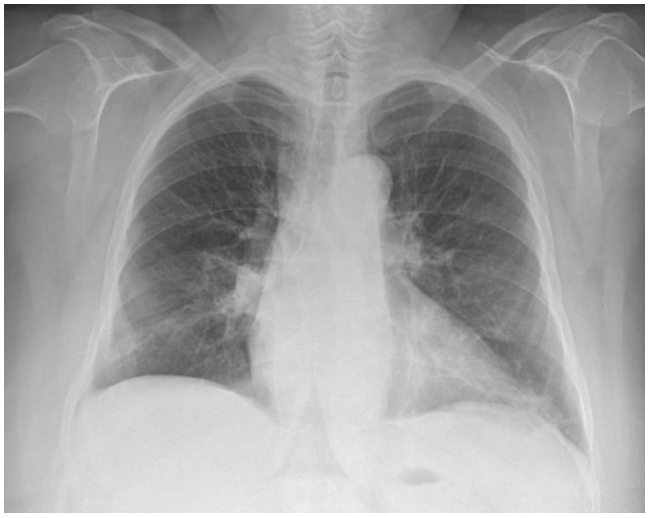

Figure 1c: *Significant regression noted on follow-up chest X-ray*

The methylprednisolone treatment was gradually reduced and terminated after a total of 3 months. Significant regression was observed following the first month of treatment (Figure 1C).

Table 1: Causes of Cryptogenic Organizing Pneumonia and Secondary Organizing Pneumonia

Diseases	Diseases that can cause Organizing Pneumonia
Autoimmune Diseases	•RA, DM-PM, SS, SD, AS, SLE •Behcet Disease, Mixed Cryoglobulinemia, PAN •Inflammatory Bowel Diseases
Other Diseases	• ARDS, Chronic Eosinophilic Pneumonia • SIP-UIP, Cystic Fibrosis, CVID • Emphysema, Bronchiectasis, Sarcoidosis • CHF - CKD, Coronary Bypass Grafts
Neoplasms	• Lung and GI malignancies • Hematological Malignancies
Infectious Diseases • *Viral* • *Bacteria* • *Fungal* • *Others*	• HIV, Adenovirus, Influenza and Parainfluenza • SARS-CoV-2, SARS-CoV, MERS-CoV • Mycoplasma sp, Chlamydia sp, Legionella pneumophila • Streptococcus pnumoniae, Staphylococcus aureus • Actinomyces israelii, Serratia sp, Nocardia sp. • Aspergillus sp, Pneumocystis jirovecii • Cryptococcus neoformans, Penicillium sp. • Plasmodium vivax
Transplantation	• Solid organ transplants (includes lungs)
Others	•Toxic gases, Cocaine-Cannabis Inhalation, electronic cigarette
Drugs	**Drugs that can cause Organizing Pneumonia**
Antibiotics	• Minocycline, Nitrofurantoin • Cephalosporins, Amphotericin
Antiarrhythmics	• Amiodarone, Beta blockers • Phenytoin, Hydralazine, Timolol
Biological Agents	• Interferons, Trastuzumab, Rituksimab • Bortezomib, Ceritinib • Tosilizumab, Etanersept, Infliximab, Ipilimumab
Kinase Inhibitors	• Sirolimus, Everolimus • Anti EGFR, Anti ALK inhibitors
PD-1/PD-L1 Inhibitors	• Pembrolizumab, Atezolizumab, Nivolumab
CT-RT	• Azathioprine, Chlorambucil, Cladribine • Bleomycin, Busulfan, Mitomycin • Methotrexate, Doxorubicin, Daptomycin • Oxaliplatin, Thalidomide
Others	• Statins, Dihydroergocryptine, Penicillamine • Propylthiouracil, Carbamazepine

Case 2: A 48-year-old female patient with a history of pancreatic cancer surgery approximately 10 years earlier, followed by one year of chemotherapy, presented with complaints of cough, hemoptysis and chest pain. A posteroanterior chest X-ray (PA CXR) obtained at the referring center revealed a peripheral density in the right upper zone (Figure 2A). Physical examination findings were unremarkable. Laboratory test results were as follows WBC: 12 x 10^3/μL, hemoglobin (Hb): 10.7 g/dL, CRP: 37.1 mg/dL and erythrocyte sedimentation rate: 16 mm/hour.

Spirometry revealed FEV1/FVC: 77 %, FEV1: 2.08 L (79%), and FVC: 1.98 L (67%). The patient was unable to cooperate with the DLCO test. Thoracic computed tomography (CT) scans from two different centers with a short interval between revealed migratory and transient lesions (Figure 2B). Metastatic disease was initially suspected given the patient's history of pancreatic cancer, and so a CT-guided tru-cut biopsy (CT-TCB) was performed. The pathology report described intraluminal granulation tissue within the bronchioles, cellular infiltration in the interstitium, alveolar septal inflammation, and intra-alveolar cellular desquamation with a small amount of granulation tissue, and histopathological findings were consistent with OP. The patient was started on methylprednisolone at a dose of 0.5 mg/kg, but she opted to discontinue the treatment on the third day. Follow-up chest X-rays revealed a significant regression of the lesions. The patient was subsequently managed without treatment and followed up with a diagnosis of OP exhibiting spontaneous regression (Figure 2C).

Case 3: A case with known nodular sclerosis Hodgkin lymphoma (NSHL) who was undergoing chemotherapy was referred to the Chest Diseases outpatient clinic due to new-onset shortness of breath and cough complaints. The PA CXR revealed peripheral opacities in the bilateral upper zones and widespread non-homogeneous opacities in the middle and lower zones (Figure 3A). A physical

examination identified crackles in the bilateral lower fields, and the laboratory parameters showed WBC: $3.1x10^3/\mu l$, CRP: 2 mg/dl, and Sedimentation: 12 mm/hour. The patient was subsequently started on oral 2x500 cefuroxime axetil and oral 2x500 clarithromycin, however, the patient's symptoms did not improve following the first week of antibiotic therapy. A direct examination of sputum for acid-resistant bacilli (ARB) yielded a negative result, and no growth was observed in the culture. Thoracic CT revealed widespread nodular opacities in the bilateral lungs (Figure 3B) and opacity compatible with a reverse halo sign in the right lung (Figure 3C). Spirometry findings were FEV1/FVC: 77 %, FEV1: 3.42 L, 118%, FVC: 3.88 L, 131%, DLCO: 21.30 L, 76%, and DLCO/VA: 5.05 L, 99%. The case was started on 40 mg of methylprednisolone treatment with a clinical radiological diagnosis of OP, and complete regression was observed by the third month of treatment (Figure 4).

DISCUSSION

Organizing pneumonia (OP) is a benign condition that, due to its radiological and histological characteristics, often requires differentiation from lung malignancies. OP is a rare clinical entity that, by nature, is diagnostically challenging. The diagnostic process for OP begins with suspicion of the disease based on the patient's clinical presentation and the clinician's judgment, and should be considered in differential diagnosis.

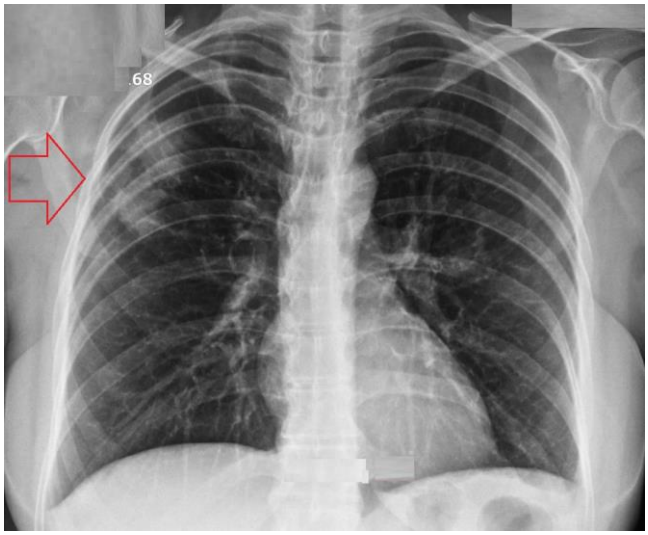

Figure 2a: *Non-homogeneous density located peripherally in the upper zone of the right lung*

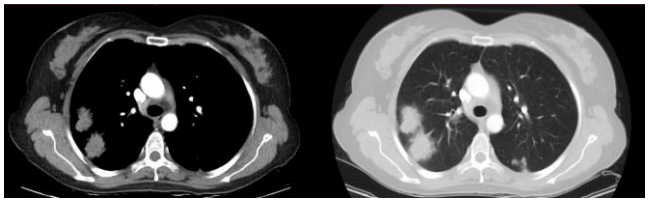

Figure 2b: *Thoracic CT showing two lesions with soft tissue densities in the right upper lung lobe*

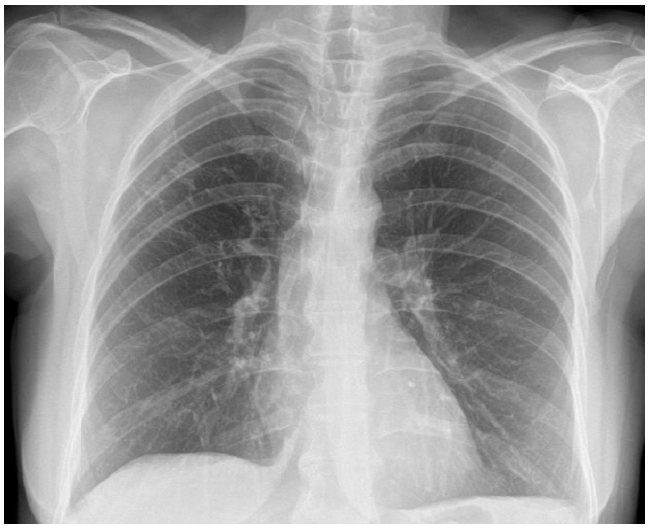

Figure 2c: *Significant regression noted on follow-up chest X-ray*

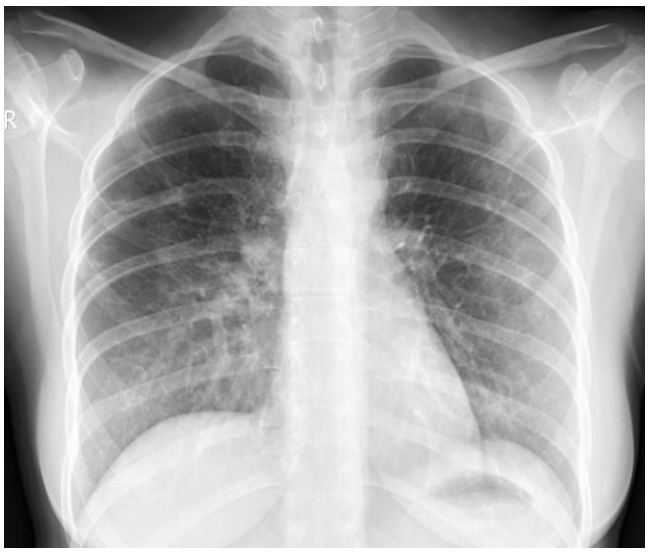

Figure 3a: *Chest X-ray revealing peripheral involvement in the bilateral upper zones and widespread non-homogeneous densities in the mid-lower zones*

The clinical findings, laboratory results, symptoms and signs of OP are typically non-specific. Physical examination (PE) may be normal in 25% of cases, although inspiratory rales are frequent findings. Laboratory markers specific to OP are lacking, although approximately 50% of cases show elevated levels of such non-specific inflammatory markers as white blood cell count, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Commonly observed symptoms in OP include dry cough, flu-like symptoms, exertional dyspnea, fever, fatigue and weight loss, while hemoptysis is less frequently seen. In cases where clinical and radiological findings align, spirometry and a diffusion capacity for carbon monoxide (DLCO) test may assist in diagnosis, often revealing mild-

to-moderate restrictive patterns and a reduction in diffusion capacity (4,5). Rales were identified only in the third of the presented cases, while the first two cases had normal physical examination findings. Cough was a common symptom in all three cases, while hemoptysis was noted in one case and weight loss in another, as symptoms that are less frequently reported in OP. Concurring with previous studies in the literature, the pulmonary functions test results of all cases indicated mild restriction, while mild reductions in diffusion capacity were identified in two of the presented cases.

OP is a disease that affects the lung interstitium, and so as would be expected, typically presents with mild decreases in FVC and DLCO. Studies have shown that SFT-DLCO values may not decrease dramatically in all cases despite radiological intervention, with 30% of OP cases exhibiting normal SFT-DLCO values, and mild reductions noted in 60–70% of cases (6). The most accurate radiological diagnoses of OP are through thoracic computed tomography (CT) or high-resolution CT (HRCT), multifocal consolidations with air bronchograms being apparent in the latter. Other possible findings include peripheral patchy alveolar consolidations, nodules, ground-glass opacities, bronchial wall thickening and reticular fibrous changes. One rare but significant finding on HRCT is the reverse halo sign (Atoll Sign), which was first described in OP referring to a focal ground-glass opacity surrounded by a ring-like consolidation (2,7,8). In the first of our cases, thoracic CT revealed characteristic air bronchograms, while the second case exhibited peripheral multifocal consolidations and the reverse halo sign was noted in the third case.

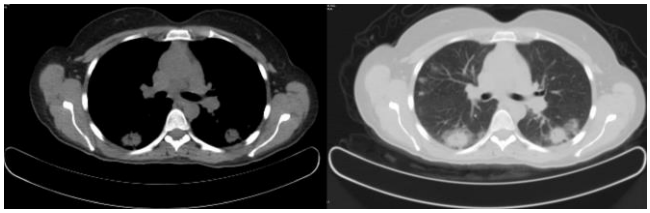

Figure 3b: *Thoracic CT showing widespread nodular opacities in both lungs*

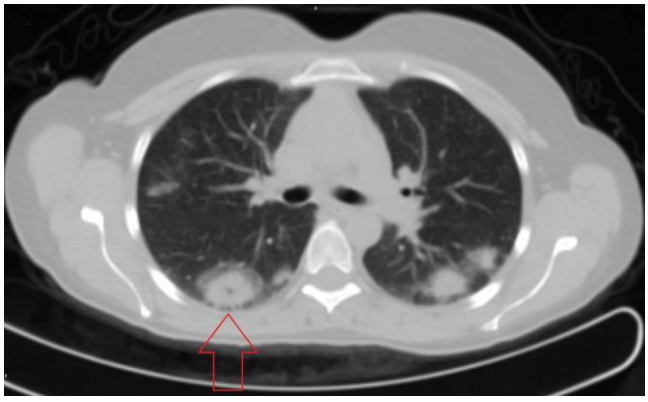

Figure 3c: *Thoracic CT showing widespread nodular opacities in both lung*

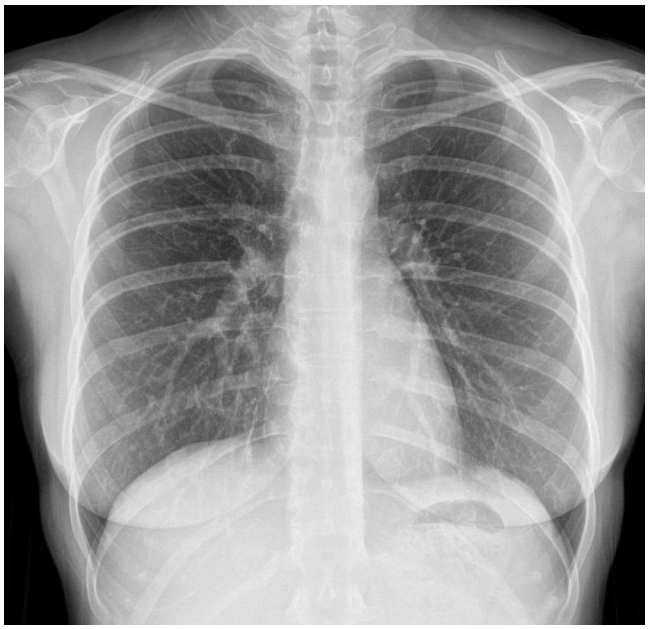

Figure 4: *Complete regression shown on Lung Radiograph*

An examination of the histopathological findings of cases with organizing pneumonia (OP) revealed the most common findings to be intraluminal granulation tissue (Masson bodies) within the bronchioles, which are small airways, mononuclear cell infiltration in the interstitium, and intra-alveolar cellular desquamation. The most common consolidations detected radiologically are, in fact, formed histopathologically from intra-alveolar fibroblastic granulation tissue, known also as Masson bodies. Similarly, ground-glass opacities observed radiologically correspond histologically to alveolar septal inflammation and areas of intra-alveolar cellular desquamation with small amounts of granulation tissue in the terminal airspaces (9). The diagnoses of our first two cases were established based on histopathological methods, as their histopathological findings were consistent with OP.

Today, the mainstay of treatment for OP is glucocorticoids, and response is typically rapid and favorable in patients without respiratory failure and with a good general clinical condition. The optimal glucocorticoid regimen and treatment duration have yet to be determined, but the most commonly approach is to administer prednisone at a dose of 0.5–1 mg/kg daily for 6–12 months, with tapered doses over time. In cases of severe OP with respiratory failure, high-dose/pulse steroids (e.g., 500–1000 mg of methylprednisolone followed by maintenance therapy with 1 mg/kg oral methylprednisolone) and other immunosuppressive agents may be used. Additionally, macrolide antibiotics may be employed due to their anti-inflammatory effects, and surgical treatment may be considered for localized OP (10,11). Spontaneous regression without treatment is observed in approximately 10% of

OP cases, and while the exact mechanisms behind this regression remain unclear, there are studies suggesting a link to specific clinical and laboratory results. Spontaneous regressions of OP may be attributable to such temporary factors as viral infections or inhalation injury, and to lower serum CRP levels and higher lymphocyte counts at the time of diagnosis (12). In our series, the first and third cases responded well to methylprednisolone treatment, while the second exhibited spontaneous regression.

In conclusion, OP is a disease with a typically subacute clinical course. The presence of such radiological features as nodules and masses can lead OP to be mistaken for lung malignancies, making it essential to consider it in differential diagnosis. The clinical and radiological characteristics of OP, as well as the treatment approaches presented in the three presented cases, emphasize the need to keep this condition in mind in clinical practice.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - C.D., G.M.; Planning and Design - C.D., G.M.; Supervision - C.D., G.M.; Funding - G.M.; Materials - G.M.; Data Collection and/or Processing - C.D.; Analysis and/or Interpretation - C.D.; Literature Review - G.M.; Writing - C.D.; Critical Review - C.D.

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