D Rozenberg, S Shapera. What to do with all of these lung nodules? Can Respir J 2014;21(3):e52-e54.

Caplan syndrome is a rare entity that is specific to rheumatoid arthritis and presents with multiple, well-defined necrotic nodules in patients with occupational dust exposure. The present report describes a case of Caplan syndrome involving a 71-year-old man with a known diagnosis of seropositive rheumatoid arthritis who presented to the authors’ centre with a five-year history of multiple, bilateral cavitary lung nodules with mild dyspnea on exertion. He was an ex-smoker (30 pack-years) and had previously worked with silica. The case highlights the clinical, radiological and pathological features of this syndrome and outlines the importance of considering a broad differential in the management of pulmonary nodules, especially in patients with rheumatoid arthritis.

Key Words: Lung diseases; Nodules; Pneumoconiosis; Rheumatoid arthritis

Learning objectives
• To recognize that Caplan syndrome is a rare pulmonary manifestation of rheumatoid arthritis (RA) found in patients with occupational dust exposure.
• To be aware of the differential diagnosis and management of cavitary pulmonary nodules in Caplan syndrome.

CAN MEDS Competency: Medical Expert
Pretest
• What is the classic clinical and radiological presentation of Caplan syndrome?
• What is the differential diagnosis of cavitary pulmonary nodules in RA?
• How do you treat Caplan syndrome?

CASE PRESENTATION
A 71-year-old man was referred to the authors’ facility with a five-year history of multiple, bilateral cavitary lung nodules. He was asymptomatic from a respiratory standpoint, with only mild dyspnea over the past six months, with no weight loss, cough or hemoptysis. The patient described a 10-year history of polyarthritis consistent with his known diagnosis of seropositive rheumatoid arthritis (RA). His RA was previously well controlled with methotrexate and leflunomide for several years. Four years before presenting to the authors’ centre, his medications were changed to azathioprine and prednisone, given the concern of multiple lung nodules (Figure 1A). He also had ischemic cardiomyopathy, atrial fibrillation, type 2 diabetes and gastroesophageal reflux disease.

He was a retired construction worker who had significant exposure to rock dust as a result of rock drilling for 10 years and rock mining in graphite mines in the latter part of his career. He had no asbestos or sandblasting exposure. He was an ex-smoker (30 pack-year history) with no alcohol or recreational drug use. He described no tuberculosis exposures. His family history was noncontributory.

On examination, the patient appeared comfortable and in no respiratory distress. His cardiorespiratory examination was unremarkable aside from an oxygen saturation of 92% on room air. He had hand changes consistent with a diagnosis of RA with no digital clubbing. He had no subcutaneous nodules, rashes or joint swelling.

His pulmonary function tests demonstrated a mixed pattern with mild restriction (total lung capacity 5.0 L [70% predicted]) and post-bronchodilator obstruction (forced expiratory volume in 1 s [FEV1]/forced vital capacity [FVC] ratio 0.67; FEV1 1.46L [45% of predicted]) with a moderate reduction in his diffusing capacity for carbon monoxide (DLCO) (47%). His vital capacity (VC) was 2.2 L (49%) and his residual volume 2.8 L (110%). His rheumatoid factor (>650 kIU/L) and anticyclic citrullinated protein antibody (500 mg/L) were strongly positive; antinuclear antibody, extranuclear antigen panel and antinuclear cytoplasmic antibodies were negative; and erythrocyte sedimentation rate (73 mm/h) and C-reactive protein (77 mg/L) were elevated. His echocardiogram had shown a left ventricular ejection fraction of 40%, with no evidence of pulmonary hypertension.

Chest imaging demonstrated stable calcified mediastinal and hilar lymphadenopathy with numerous parenchymal nodules and cavities, which had waxed and waned over the past five years (Figures 1A to 1C). Cultures from a spontaneous sputum sample (culture and sensitivity, acid-fast bacilli and fungal) were negative six months before presentation at the authors’ centre. Subsequently, bronchoscopy demonstrated normal anatomy, cytology and a second set of negative cultures (culture and sensitivity, acid-fast bacilli and fungal). A left-sided video-assisted thoracic surgical biopsy revealed multiple nodules with necrosis surrounded by dust, with areas of surrounding inflammation and fibroblastic response (Figures 2A and 2B). A diagnosis of Caplan syndrome was made.

His referring physicians were advised to continue with the current extrapulmonary RA management. Tiotropium was started for his concomitant airflow obstruction with improvement in his pulmonary function tests (total lung capacity 5.4 L [78% of predicted]; FEV1/FVC ratio 0.90; FEV1 2.2 L [70%]). His VC was 2.5 L (56%), residual volume 2.9 L (116%) and DLCO (58%). The nodules remain unchanged over one year of follow-up.

DISCUSSION
With a prevalence of approximately 1% in Canada (1), RA has many pulmonary manifestations: necrobiosis nodules, interstitial disease, pleural abnormalities, bronchiolitis obliterans, vasculitis, drug-induced lung disease, upper airway disease, organizing pneumonia and Caplan syndrome (2,3).

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The prevalence of nodules in RA is difficult to estimate. In two older case series of RA patients with 253 and 702 patients screened using chest x-ray, no nodules were identified (4,5). However, one study demonstrated pulmonary nodules to be quite common, found in 13 of 40 (32%) patients who underwent biopsy for suspected lung involvement (6). Multiple cavitary pulmonary nodules can have malignant and benign etiologies, as outlined in Table 1.

In the present case, malignancy and infection (including mycobacterium) was believed to be unlikely given the indolent course, normal sputum cultures, negative bronchoscopy and video-assisted thoracic surgical biopsy. A diagnosis of Caplan syndrome was made based on the diagnostic criteria of multiple, well-defined pulmonary nodules and inorganic dust exposure in a patient with RA (7). An open-lung biopsy was not absolutely necessary, but was helpful to confirm this rare entity and exclude alternative diagnoses. Histopathology can be useful in patients without a diagnosis of RA because the nodules can precede the onset of RA symptoms.

Caplan (8) originally described this entity in 1953, having observed an increased prevalence of pulmonary manifestations in coal miners with RA who were exposed to mineral coal or silica dust. He observed well-defined rounded opacities 0.5 cm to 5 cm in size that were bilateral and predominantly peripheral on chest x-ray, a pattern different from progressive massive fibrosis (PMF), associated with coal worker's pneumoconiosis. Although most cases of Caplan syndrome have been reported in coal workers, some have been in patients exposed to asbestos or free silica (9,10), as in our case.

The majority of the literature regarding Caplan syndrome was published before the advent of chest computed tomography (CT), with reliance entirely on chest x-rays. Although a few case reports have described using chest CT, it has not been helpful in distinguishing Caplan syndrome from simple silicotic nodules (11,12). However, CT imaging can be useful in recognizing other forms of RA-associated lung disease. Typically, radiological findings of Caplan syndrome include benign-appearing nodules that can coalesce, cavitate or calcify in the periphery of the lung (7). Although uncommon, pulmonary complications can include pneumothorax, pleural effusions, hemoptysis and, most importantly, an increased prevalence of tuberculosis compared with other pneumoconioses (5). A more comprehensive overview of the clinical and radiological presentations can be found in a review article by Schreiber et al (7).

**Table 1**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Example</th>
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</thead>
<tbody>
<tr>
<td>Neoplasm</td>
<td>Bronchogenic carcinoma (synchronous primary tumours), metastatic disease</td>
</tr>
<tr>
<td>Infection</td>
<td>Bacterial (<em>Staphylococcus aureus</em>, * Klebsiella pneumoniae*, <em>Pseudomonas</em>)</td>
</tr>
<tr>
<td></td>
<td>Granulomatous (endemic fungi, mycobacterial, <em>Nocardia</em>)</td>
</tr>
<tr>
<td></td>
<td>Parasitic (<em>Paragonismus</em>, <em>Echinococcus</em>)</td>
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<tr>
<td>Inflammatory</td>
<td>Granulomatosis with polyangitis</td>
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<td></td>
<td>Langerhans cell histiocytosis</td>
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<tr>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Vascular</td>
<td>Pulmonary embolism with infarction</td>
</tr>
<tr>
<td>Pneumoconioses</td>
<td>Berylliosis, Caplan syndrome, coal-worker’s lung, silicosis</td>
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<tr>
<td>Developmental</td>
<td>Congenital pulmonary airway malformation, pulmonary sequestration</td>
</tr>
<tr>
<td>Drugs</td>
<td>Amiodarone, infliximab, bleomycin, carbamazepine, others</td>
</tr>
<tr>
<td>Other</td>
<td>Amyloidosis</td>
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Figure 1) A Computed tomography scan (coronal view) demonstrating bilateral nodules in the upper lung zones (blue arrows) and calcified hilar lymphadenopathy (white arrows) five years before presentation. B Computed tomography scan (axial images) illustrating calcified lymph nodes (white arrows) five years before presentation. C Computed tomography scan (axial view) illustrating cavitation of the pulmonary nodules (blue arrows).

Figure 2) A High magnification (∗100) view of a necrotic nodule (star marks area of necrosis) containing abundant dust particles (arrow). Hematoxylin and eosin stain. B High magnification (∗100) view of mixed dust nodule, with abundant silicotic and anthracotic dust particles (arrows), admixed with lymphohistiocytic cells and fibrosis (star). Hematoxylin and eosin stain
A few case reports have described pulmonary function tests in Caplan syndrome, which typically have shown mild airway obstruction (7,12). In the largest study to date, however, Constantinidis et al (13) retrospectively compared 24 patients with Caplan syndrome and 36 patients with PMF suggesting overlap in pulmonary function tests. When adjusted for age, smoking and mining exposure, patients with Caplan syndrome had less airflow obstruction than patients with PMF, but no other differences with respect to lung volumes and diffusion capacity were identified. In the present case, we speculate the reduced VC and DLCO could be due to the patient’s upper lobe cavitary fibrotic changes producing a physiological pattern of lung restriction that resembles mild PMF. There were no signs of diffuse interstitial lung disease, pulmonary vascular disease or history of diaphragmatic dysfunction.

The present case demonstrates the classic historical, radiological and pathological features of Caplan syndrome, a rare entity. The case outlines the importance of considering a broad differential in the management of cavitary pulmonary nodules, especially in patients with RA. Given there is no specific therapy for Caplan syndrome, the focus should be on management of extrapulmonary RA.

REFERENCES
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