An Unusual Cause of Nonresolving Pneumonia

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Introduction

Non-resolving pneumonia is a challenging clinical problem, with etiological, patient-related, and treatment-related factors to be considered during evaluation. When adequate treatment has been administered, other unusual causes of non-resolving pneumonia need to be considered (Table 1). Primary pulmonary lymphomas are very rare and represent only 3–4% of extra-nodal non-Hodgkin's lymphoma and only 0.5–1% of primary pulmonary malignancies. Herein we report a patient with persistent cough and bilateral consolidation despite appropriate antibiotic therapy, who was diagnosed with primary pulmonary lymphoma, to illustrate the evaluation of this common and challenging clinical scenario.

Case Report

A 40-year-old female presented to our clinic with persistent non-productive cough for 3 months and worsening breathlessness for a month. There was no associated fever, atopy, anorexia, or weight loss. She did not smoke or abuse alcohol. She denied a preceding viral prodrome, chest trauma, epistaxis, arthritis, dry eyes, oral ulcers, or photosensitivity. She was a homemaker and did not raise any pets. Oral levofloxacin had been administered for 12 days prior to evaluation in our hospital. On evaluation she was pale, afebrile, and normotensive, with a respiratory rate of 18 breaths/min, pulse rate of 80 beats/min, and body mass index of 19 kg/m^2. Lymph nodes were not enlarged. Oral, ophthalmological, and sinus examinations were normal. Pulmonary examination revealed bronchial breath sounds and coarse mid-inspiratory and expiratory crackles in the infra-scapular areas bilaterally, with bronchophony and egophony. The remainder of the physical examination was unremarkable.

Table 1. Differential Diagnoses to be Considered in Non-resolving Pneumonia

Antimicrobial failure
Patient non-compliance
Improper dosing regimen
Resistant pathogen
Unusual or unsuspected pathogen
Complications
Infectious
Empyema
Endocarditis
Super-infection
Non-infectious
Congestive cardiac failure
Renal failure
Acute respiratory distress syndrome
Pulmonary thromboembolism
Drug fever
Incorrect diagnosis
Tuberculosis
Endemic fungal diseases (cryptococcosis, histoplasmosis)
Cryptogenic organizing pneumonia
Lipoid pneumonia
Pulmonary infarction
Pulmonary contusion
Pseudo-alveolar sarcoidosis
Bronchoalveolar carcinoma
Primary pulmonary lymphoma
Metastases (rarely colorectal carcinoma, etc)
Pulmonary alveolar proteinosis
Chronic eosinophilic pneumonia
Vasculitis (Wegener's granulomatosis)

Chest radiograph (Fig. 1) revealed sharply defined multilobar consolidation in the bilateral lower zones and the right mid-zone. Contrast-enhanced and high-resolution computed tomography (CT) (Fig. 2) revealed segmental consolidation with air bronchograms in the right upper lobe (anterior segment) and bilateral lower lobes, without any lymphadenopathy or cavitation. Two blood cultures and sputum cultures were sterile. Induced sputum for acid-fast bacilli was negative on 3 occasions. Complete blood count revealed hemoglobin of 10 g/dL, leukocyte count of

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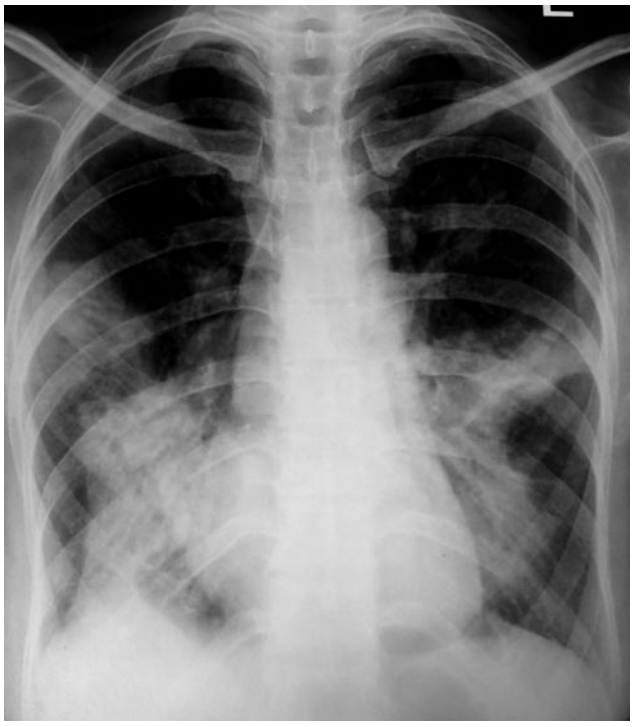

Fig. 1. Chest radiograph reveals multi-lobar consolidation in bilateral lower lobes and the right mid-zone, which are sharply demarcated.

7,800 cells/μL, with 68% neutrophils, 27% lymphocytes, and 2% eosinophils, absolute eosinophil count of 50 cells/μL, and microcytic hypochromic anemia. Serum electrolytes, renal and liver function tests were normal. Further microbiological and hematological investigations are summarized in Table 2.

Ultrasonographic evaluation of the abdomen did not reveal organomegaly, lymphadenopathy, or adrenal enlargement. Spirometry showed a restrictive ventilatory pattern, with a total lung capacity of 76% of predicted, vital capacity of 2.66 L (75% predicted), forced expiratory volume in the first second of 2.43 L (82% predicted), and reduced transfer factor of the lung for carbon monoxide (60% predicted). Fiberoptic bronchoscopy was normal, and the bronchoalveolar lavage fluid results are summarized in Table 1. Transbronchial lung biopsy showed evidence of necrosis and inflammation, with no malignant cells. CT-guided fine-needle aspiration from the right lower lobe consolidation showed chronic lymphocytic inflammation only. Surgical lung biopsies from the right upper and lower lobe revealed sheets of neoplastic lymphoid cells with vesicular nuclei and prominent nucleoli (Fig. 3), staining strongly for CD20, a B-cell marker (CD20 immunostain $\times$200, see Fig. 3 right), consistent with primary pulmonary non-Hodgkin's lymphoma, mucosal-associated lymphoid-tissue-associated type with transformation into large-cell B-cell lymphoma.

Discussion

Normal resolution of pneumonia is variable and depends on the causative agent and the host response to the invading pathogen. About 6–15% of hospitalized patients with community-acquired pneumonia have inadequate responses to initial therapy.[1] Non-resolving pneumonia must be distinguished from "progressive" and "non-responding pneumonia." Progressive pneumonia is an acute process defined as "clinical deterioration after 24 hours of treatment for community-acquired pneumonia, with an increase of 50% in the extent of the pneumonic opacity on radiographic images, respiratory insufficiency requiring mechanical ventilation or septic shock after 72 hours of treatment."[1,2] Non-responding pneumonia refers to absence of clinical response to antibiotic treatment after 3–5 days of treatment for community-acquired pneumonia.[1] Non-resolving pneumonia has been variably defined in the clinical literature. A widely used current definition is "the presence of focal infiltrates associated with symptoms of acute pulmonary infection and lack of clinical improvement or lack of resolution of infiltrates within 12 weeks despite a minimum of 10 days of antibiotic therapy."[3-5]

With changing host factors, such as advanced age, immunosuppression, and comorbidities (chronic obstructive pulmonary disease, alcoholism), the usual cause of non-resolving pneumonia is a slowly resolving community-acquired or nosocomial pneumonia secondary to inadequate or inappropriate therapy or patient-related factors. However, the differential diagnosis also includes subacute infectious processes and non-infectious diseases masquerading as pneumonia, which may be responsible for about 20% of cases[1] (see Table 2). The subacute onset of symptoms and lack of fever or toxemia in our patient suggested a non-infectious cause of consolidation at the onset of illness in the index patient. Atypical infections were negated by bronchoalveolar lavage fluid and sputum investigations. Non-infectious causes of subacute alveolar opacities are numerous (see Table 1), but most can be ruled out by examination and radiology.

Primary pulmonary lymphoma is defined as clonal lymphoid proliferation affecting one or both lungs, with no detectable extrapulmonary involvement at diagnosis or during the subsequent 3 months.[6] These tumors are very rare and represent only 3–4% of extra-nodal non-Hodgkin's lymphoma, and only 0.5–1% of primary pulmonary malignancies.[6] Histologically, primary pulmonary lymphomas are mostly mucosal-associated lymphoid-tissue lymphomas. Mucosal-associated lymphoid tissue is a lymphoid tissue specializing in mucosal defense that is physiologically absent from the lung. It arises under conditions of chronic antigenic stimulation, especially autoimmune, and primary pulmonary lymphoma (B-cell) has been linked etiologically to systemic lupus erythrematosus, Hashimo-

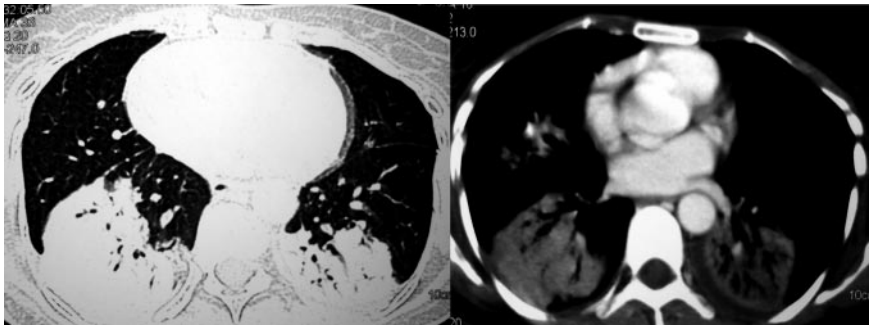

Fig. 2. Contrast-enhanced and high-resolution computed tomography shows segmental consolidation with air bronchograms, without any lymphadenopathy or cavitation. A small pleural effusion is apparent on the left.

Table 2. Microbiological and Hematological Investigations

Test	Result
Hematologic	
Erythrocyte sedimentation rate (mm/h)	20 (normal 0–20)
Mean corpuscular volume (fL)	72.8 (normal 90 ± 9)
Mean corpuscular hemoglobin (pg)	24.5 (normal 30 ± 3)
Reticulocyte production index (%)	0.8 (< 2 marrow maturation disorder)
Serum iron concentration (μg/L)	26 (normal 50–150)
Transferrin saturation (%)	10 (normal 25–50)
Serum ferritin (μg/dL)	50 (normal adult female 30–100)
Peripheral smear	Microcytes, hypochromia with moderate aniso-poikilocytosis
Sputum	
Bacterial culture and sensitivity	Sterile
Acid-fast bacilli × 3	Negative
Tuberculin skin testing (7×5 mm)	Negative
Blood cultures	Sterile
Bronchoalveolar lavage fluid	
Acid-fast bacilli	Negative
Cytology	Lymphocytic inflammation predominantly
Malignant cytology	Negative
Fungal smear and culture	Negative
Serology	
Human immunodeficiency virus serology (ELISA)	Negative
Rheumatoid factor, anti-nuclear antibody, anti-nuclear cytoplasmic antibody	Negative
Lactate dehydrogenase (U/L)	468 (normal 240–480)
C-reactive protein (semi-quantitative)	Elevated
Schirmer's test	Normal

ELISA = enzyme-linked immunosorbent assay

to's thyroiditis, Sjögren's syndrome, and multiple sclerosis. Low-grade lymphomas account for 58–87% of all primary pulmonary lymphoma (B-cell).[7] Most affected patients are 50–60 years of age, with no predilection for either sex. Most patients are asymptomatic at onset. The classic radiologic finding is that of alveolar opacity with air bronchograms. The differential diagnosis of a chronic alveolar opacity is wide (see Table 2) and can be narrowed by good history and examination. The presence of distended bronchi in the lesions may help point to this diagnosis.[8]

Once the diagnosis is established, pretreatment disease evaluation is essential. Contrast-enhanced CT of the chest and abdomen and bone marrow biopsy are required to stage the disease, and the latter may be positive in 20–25%.[9] Systematic screening of other extra-nodal sites, including stomach, ear, nose, and throat, is required by clinical evaluation and endoscopy. Serum electrophoresis shows a monoclonal gammopathy in 20–60%. β_2-microglobulin elevation denotes advanced disease and is an independent predictor of survival.[10] Therapy is controversial. Mucosal-associated lymphoid-tissue type primary pulmonary lymphoma has a good prognosis, with 5-year survival > 80% and median survival of 10 years. In univariate analysis, age > 60 years, elevated β_2-microglobulin, failure to enter remission after one cycle of chemotherapy, and intra-tumoral amyloid deposition indicate poor prognosis, while lympho-epithelial lesion is associated with good prognosis. The presentation, bilaterality, and mode of therapy have not been shown to alter prognosis.[11] Our patient was treated with cyclophosphamide, vincristine, and prednisolone for 6 cycles. Her course was complicated by one episode of febrile neutropenia, which resolved with broad-spectrum antibiotics. She tolerated chemotherapy with granulocyte-colony stimulating factor support subsequently and improved symptomatically. Repeat chest radiograph and high-resolution CT done at the end of therapy revealed substantial improvement of infiltrates (Fig. 4). She received another 2 cycles of chemotherapy and is being followed up at 3-month intervals with repeat radiology. She has no evidence of relapse at 2 years of follow-up.

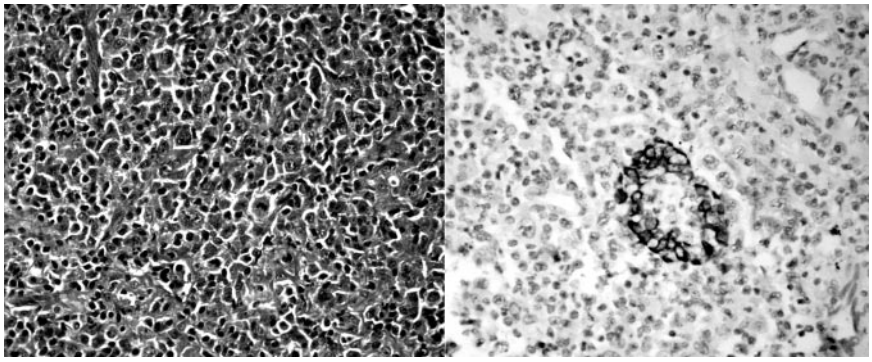

Fig. 3. Left: Photomicrograph showing sheets of neoplastic lymphoid cells having vesicular nuclei with prominent nucleoli (hematoxylin and eosin ×200). Right: Immuno-histochemistry with membranous positivity of neoplastic lymphoid cells, using CD20, a B-cell marker (CD20 immunostain ×200)

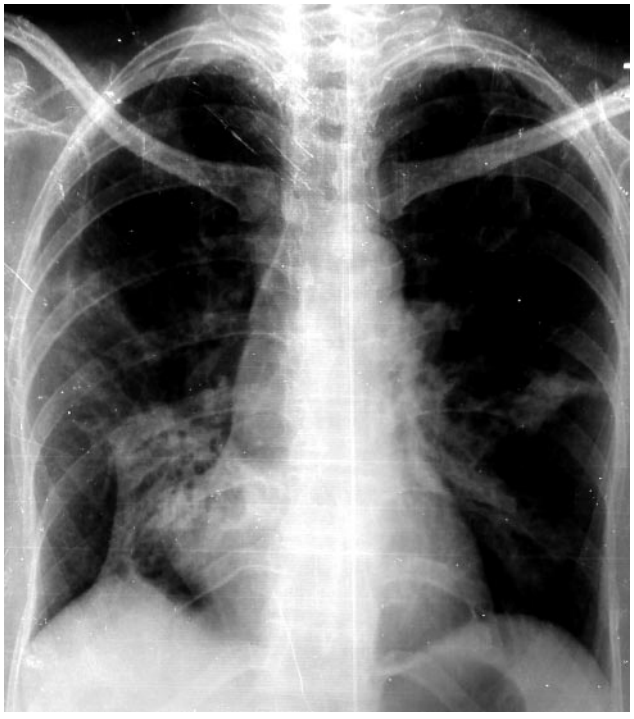

Fig. 4. Chest radiograph after chemotherapy, showing substantial improvement. The corresponding gallium scans showed no uptake in the areas of residual fibrosis.

Teaching Points

1. Non-resolving pneumonia must be distinguished from "progressive" and "non-responding" pneumonia.

2. Subacute infectious processes and non-infectious diseases masquerading as pneumonia must be considered in all patients with non-resolving pneumonia who have been adequately treated.

3. Primary pulmonary lymphoma is a clonal lymphoid proliferation affecting one or both lungs, with no detectable extra-pulmonary involvement at diagnosis or during the subsequent 3 months.

4. Treatment of these rare tumors needs to be individualized, but advanced age, extensive consolidation, or elevated lactate dehydrogenase and β_2-microglobulin levels may suggest the need for chemotherapy.

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