Left Pleural Effusion and Fever of Unknown Origin—A Clue to Thoracic Arterial Pathology

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The subset of patients who have both fever of unknown origin (FUO) and a nondiagnostic pleural effusion on presentation has not been previously investigated. A retrospective search of all patients classified as 'classic' FUO one week after admission to a department of general internal medicine identified 71 patients over 15 years. Seven were found to have associated pleural effusion(s) on admission (9.8%). In three patients thoracic large vessel pathology was diagnosed (chronic aortic dissection, giant cell arteritis and Takayasu arteritis). In these patients, the pleural effusion was predominantly left-sided, small to moderate in amount and nondiagnostic on thoracentesis. The effusions resolved spontaneously or with appropriate treatment. Thus, in patients with prolonged fever and systemic symptoms, a 'bland' left-sided pleural effusion may be a diagnostic clue to underlying inflammation of large thoracic arteries. Pleural irritation due to its anatomical proximity to the large arteries on the left side of the thorax may underlie the pathogenesis. Recognition of this sign may lead to a more timely diagnosis of occult thoracic large vessel pathology.

KEY WORDS: fever of unknown origin; pleural effusion; giant cell arteritis; Takayasu arteritis; aortic dissection.

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INTRODUCTION

Despite advances in medicine, fever of unknown origin (FUO)—defined as a temperature greater than 38.3°C on several occasions over a period of at least 3 weeks and without definitive diagnosis after one week of in-hospital study¹—remains a diagnostic dilemma for clinicians. A recent series found that the cause of FUO was not identified in 51% of patients; among patients with a definitive diagnosis, noninfectious inflammatory diseases were the most common culprits of FUO (22%).² A subset of patients

with FUO present with an associated pleural effusion, which may be ultimately diagnostic for a malignancy or infection.³ However, in other patients with FUO and a pleural effusion, an evaluation of the pleural fluid may not reveal specific findings and the effusion may be deemed noncontributory or nondiagnostic. To identify the significance of a pleural effusion in the diagnosis of FUO, a retrospective analysis of all patients who presented with a nondiagnostic pleural effusion on admission was conducted at a university hospital.

PATIENTS AND METHODS

Kaplan Medical Center is a large university-affiliated teaching hospital in central Israel that serves as the primary referral center for a mixed urban and rural population of 300,000 with four internal medicine wards. A retrospective search of one department's database using ICD-9 codes identified all patients between 1995 and 2009 who were not immunocompromised and were classified as FUO after one week of in-hospital workup, meeting accepted criteria.¹ Their charts and imaging were reviewed and those who had a pleural effusion on the day of their admission constituted the study population. None of the other patients developed an effusion later in the admission.

RESULTS

Over 15 years, 71 'classic' FUO patients were identified, with seven of these patients presenting with a pleural effusion on admission (9.8%). Diagnostic thoracentesis was performed in all patients revealing an exudative effusion with normal cytology and bacteriological stains. Two patients had an associated pericardial effusion and were finally diagnosed as idiopathic pleuropericarditis. Both recovered with anti-inflammatory treatment. One patient was diagnosed with tuberculosis and responded to treatment and another patient's symptoms and pleural effusion resolved spontaneously without a definitive diagnosis. Three of the patients were found to have a common denominator and are reported below.

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Case 1: Chronic Aortic Dissection

A 66-year-old patient with hypertension presented with 2 months of low-grade fever, profuse night sweats, weight loss and left sided back pain. An ambulatory workup revealed anemia and a small left pleural effusion. Examination was noncontributory except for fever (38.3°C) and signs of a small left pleural effusion confirmed by CXR. Thoracentesis revealed an exudate with normal cytology and negative stains and cultures. Additional labs included Hb 10 g/dL (normocytic), normal WBC and platelets, serum albumin 3.4 g/dL, globulins 4.2 g/dL, ESR 120 mm/hr and CRP 300 mg/dL (normal <6). Autoantibody screen was negative as were extensive cultures and serologic tests. Staining and cultures for acid fast bacilli in the effusion and bone marrow were negative. Chest CT and MRI revealed widening of the ascending aorta and aortic arch and a long intramural thrombus from the origin of the innominate artery to the renal arteries within a false lumen. Chronic aortic dissection was diagnosed. The patient declined any intervention and was discharged on warfarin and anti-hypertensive medications. The effusion, fever, and acute-phase reactants slowly and spontaneously resolved, as has been previously reported in survivors of chronic aortic dissection.⁴

Case 2: Giant Cell Arteritis

A 75-year-old man presented with a 2-week history of fever (up to 39°C), profuse sweats and cough. His history included controlled hypothyroidism, hypertension and diabetes. Examination revealed only fever and dullness to percussion at the left lung base with rales. CXR showed a small left pleural effusion and small linear atelectasis. Labs included Hb 13.8 g/dL, WBC $14.6 \times 10^3/\mu\text{L}$, platelets $475 \times 10^3/\mu\text{L}$ and ESR 96 mm/hr. Urinalysis and other blood chemistries and TSH were normal, with the exception of an elevated serum ALP 199 IU/L (normal <130) and GGT 131 IU/L (normal <61). Chest CT showed moderate pleural effusion on the left and minimal fluid on the right. Thoracentesis revealed an exudate with normal adenosine deaminase, normal cytology and negative stains and cultures. Autoantibody screen was negative. Ceftriaxone and clarithromycin had no effect. Fever persisted, accompanied by fatigue, anorexia and weight loss. Tests showed further increases in ESR (140 mm/hr), CRP (324 mg/dL), WBC ($25.1 \times 10^3/\mu\text{L}$), platelets ($740 \times 10^3/\mu\text{L}$), ALP and GGT, while Hb and albumin decreased (11.3 g/dL and 2.0 g/dL, respectively). Cultures and extensive serological tests were negative, as were fundoscopy, echocardiography, abdominal CT, colonoscopy, endoscopy and gallium-67 scan. As a final diagnostic procedure after an extensive search, a temporal artery biopsy of a clinically-normal artery was conducted, revealing giant cell arteritis (temporal arteritis). The patient continued to deny headaches, vision changes, jaw claudication, or polymyalgia rheumatica symptoms.

Prednisone treatment (1 mg/Kg/d, slowly tapered to 5 mg/d over several months) led to complete recovery.

Case 3: Takayasu Arteritis

A healthy 35-year-old woman was admitted with five weeks of fever (maximal 38.9°C) associated with drenching night sweats, fatigue and marked weight loss. Examination revealed splenomegaly (span 15 cm), a 2/6 mitral systolic murmur, and retinal "cotton wool" exudates. CXR demonstrated a small left pleural effusion. Blood tests showed Hb 9.1 g/dL (MCV 75), WBC $10.2 \times 10^3/\mu\text{L}$ (neutrophils 8.1; lymphocytes 1.2; eosinophils $0.6 \times 10^3/\mu\text{L}$) (normal eosinophils $0-0.5 \times 10^3/\mu\text{L}$), platelets $456 \times 10^3/\mu\text{L}$, ESR 140 mm/hr, CRP 102 mg/dL, serum albumin 3.6 g/dL, globulins 4 g/dL (polyclonal) and normal kidney and liver function tests. Urinalysis revealed microscopic hematuria. Autoantibody screen was negative except for positive anti-smooth muscle antibodies. Echocardiography, chest and abdominal CT added no new information. Cultures and multiple serologic tests were negative. Thoracentesis showed an exudate with normal adenosine deaminase, normal cytology and negative stains and cultures. Gallium-67 scan and biopsies of the liver and bone marrow were noncontributory. After 6 weeks of hospitalization during which the Hb fell to 7.6 g/dL and globulins increased to 4.3 g/dL, fever gradually resolved but inflammatory markers persisted. At this time, a new carotid murmur appeared and MRA confirmed Takayasu arteritis involving the proximal aorta and right carotid artery. Prednisone 50 mg/d and methotrexate 7.5 mg/wk were tapered over months to just 5 mg/d prednisone and aspirin. She remains well 14 years later, with stable arterial imaging findings and normal laboratory markers.

DISCUSSION

Various infectious, neoplastic and inflammatory conditions can lead to the clinical picture of prolonged fever, prominent systemic symptoms and an associated pleural effusion^{1,2} (Table 1), which was seen in nearly 10% of our cohort patients. Usually, the majority of these patients have other symptoms, signs or laboratory features that lead to a definitive diagnosis.^{1,3}

The three patients reported in detail in this study presented a diagnostic dilemma. All had marked systemic symptoms including prolonged fever, sweats, fatigue, anorexia and weight loss that defied extensive investigations. Their blood tests were characterized by intense acute-phase activation with ESR >100 mm/hr, anemia of chronic disease, reactive thrombocytosis and hyperglobulinemia. These three patients also shared the presence of a pleural effusion on admission. The effusion was predominantly left-sided, relatively small,

Table 1. Conditions That May Present as Prolonged Undiagnosed Fever with Pleural Effusion***Inflammatory:**

Giant cell arteritis (temporal arteritis)
 Takayasu arteritis
 Behcet's disease
 Wegener's granulomatosis
 Churg-Strauss syndrome
 Polyarteritis nodosa
 Adult Still's disease
 Systemic lupus erythematosus (including drug-induced)
 Mixed connective tissue disease
 Rheumatoid arthritis
 Sjogren's syndrome
 Postpericardial injury syndrome
 Familial Mediterranean fever (FMF)

Infectious:

Tuberculosis
 Brucellosis
 Psittacosis
 Lyme disease
 Salmonellosis
 Whipple's disease
 Infective endocarditis
 Intra-abdominal abscess**
 Viral / idiopathic pleuropericarditis
 Herpesvirus infections (EBV, CMV)
 Human immunodeficiency virus (HIV)
 Fungal infections, pulmonary

Neoplastic:

Lymphoma, especially non-Hodgkin's***
 Castelman's disease, multicentric
 Rosai-Dorfman disease
 Hepatocellular carcinoma
 Pancreatic carcinoma
 Renal cell carcinoma
 Atrial myxoma

Miscellaneous:

Sarcoidosis
 Thromboembolic disease
 Chronic dissecting aneurysm of aorta
 Idiopathic retroperitoneal /mediastinal fibrosis

* Several of the associations are quite rare

** Subphrenic, perinephric, hepatic or splenic abscesses

*** Includes primary effusion lymphoma and intravascular lymphoma

asymptomatic and exudative, but without distinctive features of any kind.² Specifically, despite extensive in-hospital investigations (median, 4 weeks) no evidence of cancer, tuberculosis, or other infection was found. Eventually, in all three patients, the prolonged systemic illness and the pleural effusion were found to be due to chronic pathology of the large thoracic arteries— either different types of vasculitis (Cases 2, 3) or a chronic dissecting aortic aneurysm (Case 1). Thus, this association could be significant and may provide a new diagnostic clue.

Our observation—that patients presenting with both FUO and a bland, predominantly left-sided pleural effusion may have occult thoracic artery disease—is supported by the literature.⁴⁻²² In a review, 11 patients with chronic aortic dissection who presented as FUO were identified, and four of these (36%) had left pleural effusion, as in our Case 1.⁴ Additional reports confirming the association have been published⁵ but did not identify the FUO and left pleural effusion association as a clue to the diagnosis. Several types

of vasculitides may share this association, albeit, rarely. Giant cell arteritis (GCA) is a chronic vasculitis of large- and medium-sized vessels affecting patients over 50 years of age. GCA often presents as FUO,⁶ rarely as left effusion⁷⁻¹⁰ and may present as a combination of both as in case 2. Although aortic involvement in GCA is frequent, it usually does not cause symptoms. Seventy-three percent of patients with GCA may have inflammatory aortic thickening at diagnosis.¹¹ The pleural effusion seen in GCA may be a manifestation of silent aortitis or of rare involvement of other major thoracic arteries. Takayasu arteritis is another chronic vasculitis that primarily affects young women and involves the aorta and its major branches. It may present as FUO without signs of arterial obstruction, as in Case 3.¹² The presence of pleural effusions in Takayasu arteritis has been reported,^{13,14} possibly due to aortitis and frequent pulmonary artery involvement.^{15,16} Although not captured by our case series, Behcet's disease is another systemic vasculitis that may present with fever and pleural effusion.¹⁷ Behcet's disease is notable for its ability to involve small, medium or large vessels, either venous or arterial. Vascular disease occurring in one quarter of the patients may constitute the presenting sign either alone or together with other symptoms.¹⁸ Arterial complications of Behcet's disease have similar prevalence to the venous lesions.^{19,20} Inflammatory involvement of large thoracic arteries including the aorta, pulmonary and subclavian arteries often are found,¹⁹⁻²² and may be related to systemic symptoms and pleural effusions.

Pleural and mediastinal anatomy may explain the observed association of a predominantly left-sided effusion in the context of thoracic large artery pathology. The right pleura, is predominantly in contact with major veins. The left pleura, however, is in contact with the aortic arch, aorta, left common carotid and subclavian arteries, and the pulmonary artery.²³ An inflammatory reaction in the larger thoracic arteries may cause left-sided pleural irritation and an inflammatory reaction in the overlying parietal pleura that manifests itself as a barely symptomatic but detectable exudative left pleural effusion. Recognition of this association and its pathogenesis is useful. When pleural fluid examination and workup remain negative for other diseases such as cancer or infection, a persistent effusion in the setting of a prolonged systemic illness may indicate an unsuspected large vessel vasculitis or chronic aortic dissection. Recognition of this association may lead to a more timely, cost-effective, diagnostic workup.

In conclusion, while previous isolated case reports have noted the occurrence of pleural effusions in vasculitis or aortic dissection, our study, to our knowledge, is the first case series of patients with FUO and pleural effusion to note a potential association with underlying thoracic artery pathology. We also describe the characteristic profile of the pleural effusions in this presentation (left-sided predominance, asymptomatic, relatively small, exudative, nonspecific and associated with intense acute phase markers). Finally, we cite anatomical data to explain the phenomenon.

Our findings (Text Box 1), may be useful for generalists and specialists evaluating patients with FUO.

Textbox 1. Take-home Points about Pleural Effusions and FUO

- Patients with 'classic' FUO and systemic symptoms who have an associated pleural effusion on admission should be considered as a separate subgroup with a specific differential diagnosis.
- In patients with FUO, a left-sided pleural effusion that is relatively small, 'bland', and exudative in nature, should be evaluated for occult large-vessel thoracic vasculitis or aortic pathology.
- The left pleura is in contact with major thoracic arteries; thus, an inflammatory process may cause left-sided pleural irritation and effusion, explaining the association between thoracic artery disease and left-sided pleural effusions.

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