PRESENTATION OF CASE:

A 70-year-old man was evaluated in the rheumatology clinic of this hospital because of recurrent left sided pleural effusion.

Five years before this evaluation, pain developed in the bilateral shoulders, proximal arm muscles, and proximal leg muscles. The pain was described as aching, worse in the morning, and associated with fatigue. The pain was not associated with stiffness and would occur intermittently lasting for days at a time before resolving. The erythrocyte sedimentation rate (ESR) was mildly prolonged and the level of C reactive protein (CRP) was mildly elevated. Moderate dose prednisone was initiated for the possibility of polymyalgia rheumatica (PMR), with brisk improvement in symptoms. Over the next year, attempts to taper prednisone below 6 milligrams daily led to recurrent myalgias, prolonged ESR, and elevated CRP.

Three years before this evaluation, swelling, erythema, and pain developed in the cartilaginous parts of the left ear with sparing of the earlobe. There was no improvement after empiric antibiotics for presumed cellulitis. Prednisone was increased to a high dose and the ear symptoms improved, but recurred when prednisone was tapered. Biopsy of the left auricle showed perichondrial inflammation and decreased basophilia of the cartilage. High dose prednisone therapy led to resolution of ear symptoms, and weekly therapy with methotrexate was initiated for a presumed diagnosis of relapsing polychondritis. Over the next six months, attempts to taper from moderate to low doses of prednisone were associated with recurrence of PMR and chondritis symptoms typical for this patient, along with prolonged ESR and elevated CRP, which were as high as 89 mm per hour (reference range, 0 to 13) and 73.6 mg per L (reference range, <8.0), respectively.

Two years before this evaluation, monthly tocilizumab was added because of persistent fatigue, markedly elevated CRP and prolonged ESR despite moderate dose prednisone and continued methotrexate. PMR and relapsing chondritis symptoms improved, and prednisone was tapered to low dose. Two weeks after starting tocilizumab and upon further tapering of prednisone, pain and swelling developed in the right leg and ultrasound demonstrated distal deep venous thrombosis (DVT) in the right posterior tibial vein. Serial ultrasound of the leg two weeks later did not demonstrate propagation of the distal DVT, and pain and swelling resolved with the use of a compression stocking and elevation of the right leg. However, two months later, again upon further tapering of prednisone, PMR and relapsing chondritis symptoms recurred, and pain and swelling developed in the left leg. Ultrasound demonstrated DVTs in the left popliteal and calf veins and the right femoral vein, and rivaroxaban therapy was begun. The recurrent DVTs were attributed to his underlying inflammatory disease; prednisone was increased, and tocilizumab was replaced with infliximab. Methotrexate was continued to prevent immunogenicity of infliximab. However, over the next six months, PMR and relapsing chondritis symptoms repeatedly worsened when prednisone was tapered and only improved when prednisone was increased to moderate or high doses. Testing for anti-neutrophil cytoplasmic antibodies, rheumatoid factor, and anti-cyclic citrullinated peptide antibodies was negative. Fifteen months before this evaluation, treatment with rituximab was initiated and prednisone was decreased to moderate dose, but bilateral scleritis developed and prednisone was increased again to high dose with resolution of ocular pain and injection.

Over the next three months, attempts to taper prednisone resulted in recurrence of bilateral scleritis, as well as PMR and chondritis symptoms, but additional rituximab treatment was not pursued due to perceived lack of efficacy. One year before this evaluation, treatment

with low-dose cyclophosphamide was initiated but complicated by severe neutropenia, thereby preventing dose escalation. Nine months before this evaluation, treatment with cyclophosphamide was stopped, and intravenous tocilizumab was restarted given its prior efficacy in tapering prednisone. Tocilizumab also resulted in moderate but transient neutropenia following each infusion.

Seven months before this evaluation, pleuritic left lower chest pain developed, along with dyspnea on exertion and a dry cough. Chest radiography revealed a moderate left pleural effusion. Thoracentesis removed one liter of straw-colored pleural fluid; laboratory results are shown in Table 1. Pleural fluid gram stain showed abundant polymorphonuclear cells but no organisms; bacterial, fungal, and mycobacterial cultures revealed no growth. Cytology was without malignant cells. Computed tomography (CT) of the chest after pleural fluid drainage showed small left and trace right pleural effusions and bibasilar dependent atelectasis without consolidations, nodules, or lymphadenopathy. The pleural effusion was attributed to ongoing inflammatory disease, the dose of prednisone was increased with resolution of pleurisy and dyspnea, and five months before this evaluation, tocilizumab was changed to tofacitinib.

The patient presented to the rheumatology clinic for evaluation after sudden onset left-sided back pain prompted CT of the chest and abdomen which revealed a punctate stone in the lower pole of the left kidney without hydronephrosis and a left pleural effusion increased in size compared to the prior CT of the chest six month before. There was no dyspnea, cough, or fever, and the patient remained without ocular pain, visual changes, joint pain, stiffness, ear or nose pain or swelling, rashes, or focal weakness. On examination, the temperature was 36.7°C, the heart rate 64 beats per minute, the blood pressure 145/75 mmHg, the respiratory rate 18 breaths per minute, the oxygen saturation 99% while the patient was breathing ambient air, and the body

mass index (BMI; the weight in kilograms divided by the square of the height in meters) 29.2. The heart sounds were regular with no murmur. Breath sounds were decreased at the base of the left lung. There was no leg edema. There was no scleral injection or ear helix erythema. There was no joint swelling or tenderness, purpura, petechiae, or motor deficits.

There was a history of mucinous adenocarcinoma of the cecum treated with laparoscopic right sided colectomy and oxaliplatin therapy without evidence of recurrence. Other history included peripheral neuropathy attributed to oxaliplatin, hypothyroidism, and monoclonal gammopathy of unknown significance. A macrocytic anemia had been present for three years before this evaluation, with normal blood levels of cobalamin and folate. There was also a history of intermittent leukopenia and neutropenia over the 10 years before this evaluation, but most marked following treatment with cyclophosphamide and tocilizumab. Medications included alendronate, atorvastatin, cholecalciferol, folic acid, levothyroxine, methotrexate, omeprazole, prednisone, rivaroxaban, sulfamethoxazole-trimethoprim, and tofacitinib. Prednisone had recently been decreased by 1 milligram. He drank alcohol occasionally; he did not smoke tobacco or use illicit drugs. The patient lived in New England and was retired. There was no family history of autoimmune disease.

The blood levels of electrolytes, glucose, folate, cobalamin, thyroid stimulating hormone were normal, as were tests of liver- and kidney-function. Other laboratory tests results are shown in Table 1.

A diagnostic test was performed and management decisions were made.

Table 1. Laboratory Data

Variable	Reference Range, Adults* (MGH)	Six months before evaluation	This evaluation
Hemoglobin (g/dl)	13.7-17.5	12.4	11.1
Hematocrit (%)	41.0 -53.0	37.1	33.7
Mean corpuscular volume (fL)	80-100	108.5	112.7
White-cell count (per μl)	4500 – 11,000	5,700	3,030
Differential			
Neutrophils (%)	40 – 70	80.4	49.6
Lymphocytes (%)	22 - 44	7.7	32.3
Monocytes (%)	4-11	6.5	12.5
Eosinophils (%)	0 - 8	1.2	2
Basophils (%)	0 – 3	0.7	1
Platelets (per uL)	150,000-400,000	165,000	246,000
Erythrocyte sedimentation rate (mm/hr)	0-13	55	107
C-reactive protein (mg/L)	<8	88.7	205.8
Lactate dehydrogenase (U/L)	110-210	192	N/A
Total protein (g/dL)	6.0-8.3	7.2	7.4
Pleural Fluid			
Lactate dehydrogenase (U/L)	N/A	195	N/A
Total protein (g/dL)	N/A	4.8	N/A
Albumin	N/A	3.3	N/A
Glucose	N/A	111	N/A
Red Blood Cells (per uL)	N/A	55,000	N/A
Nucleated Cells (per uL)	N/A	2,742	N/A
Differential			
Neutrophils (%)	0	30	N/A
Lymphocytes (%)	0	51	N/A
Macrophages (%)	0	11	N/A
Monocytes	0	2	N/A
Eosinophils	0	3	N/A
Basophils	0	1	N/A
Unclassified cells	0	2	N/A

* Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at the MGH are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.