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IgG4-Related Disease

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A 43-year-old man presented to the clinic for evaluation of fevers, night sweats, and weight loss.

History. He was originally from Singapore and had emigrated to the United States approximately 2 years prior to this visit. He was a doctoral student in psychology. He stated that he had enjoyed good health until approximately 1 month prior, when he first had developed fevers. He stated that he had 5 days of "attacks of fever" with a maximum fever of about 39°C. During this time, he also experienced rigors and night sweats, but he had no other obvious symptoms.

He denied having vomiting, diarrhea, upper respiratory tract symptoms, or rashes. His fevers had resolved after approximately 5 days, but he continued to have some fatigue and night sweats. He also had noticed a 4.5-kg weight loss in the 4 weeks prior to his visit. He had not traveled internationally since emigrating to the United States. He had no known tuberculosis (TB) exposure, and he denied having any recent illnesses or taking antibiotics. He had no known medical history, and he was not taking any medications or over-the-counter supplements outside of a daily multivitamin.

His family history was significant for hypertension and hyperlipidemia in his father. He had no allergies. He was a lifetime nonsmoker. He drank alcohol socially but not daily and not to excess. He denied any illicit drug use.

Physical examination. Physical examination revealed a 167-cm tall man with a weight of 69 kg and a body mass index of 24.4 kg/m^2. Blood pressure was 108/70 mm Hg, pulse was 90 beats/min, respiratory rate was 16 breaths/min, and temperature was 36.7°C taken orally. Oxygen saturation was normal at 98%.

Physical examination findings, including of the head, eyes, ears, nose, throat, neck, chest, cardiovascular system, gastrointestinal system, genitourinary system, skin, neurological system, and musculoskeletal system, were all within normal limits. He had no obvious lymphadenopathy.

Diagnostic tests. Results of an initial workup revealed an elevated C-reactive protein level of 42 mg/L and an elevated erythrocyte sedimentation rate of 32 mm/h. Results of a complete blood cell count revealed a normocytic anemia, with a hemoglobin level of 11.8 g/dL and a hematocrit of 35.1%. His white blood cell count was normal at 10,600/μL, and his platelet count was mildly elevated at 482 × 10^3/μL. Results of a comprehensive metabolic panel were unremarkable except for a significant elevation in alkaline phosphatase at 237 U/L. A purified protein derivative test was nonreactive for TB.

A chest radiograph revealed a subcentimeter nodular opacity of the left upper lobe (**Figure 1**), and computed tomography (CT) of the chest was recommended for further evaluation. Chest CT scans revealed that the finding on chest radiograph was artefactual. However, CT did reveal "multiple partially visualized liver lesions with differential considerations including multiple metastatic lesions, lymphoma, or hepatic abscesses," according to the radiologist's report. A dedicated CT scan of the liver was therefore recommended for further evaluation, and findings revealed 2 dominant liver lesions with target appearance and 2 additional smaller liver lesions (**Figures 2-5**). These findings were concerning for neoplasm such as metastatic disease with central necrosis.

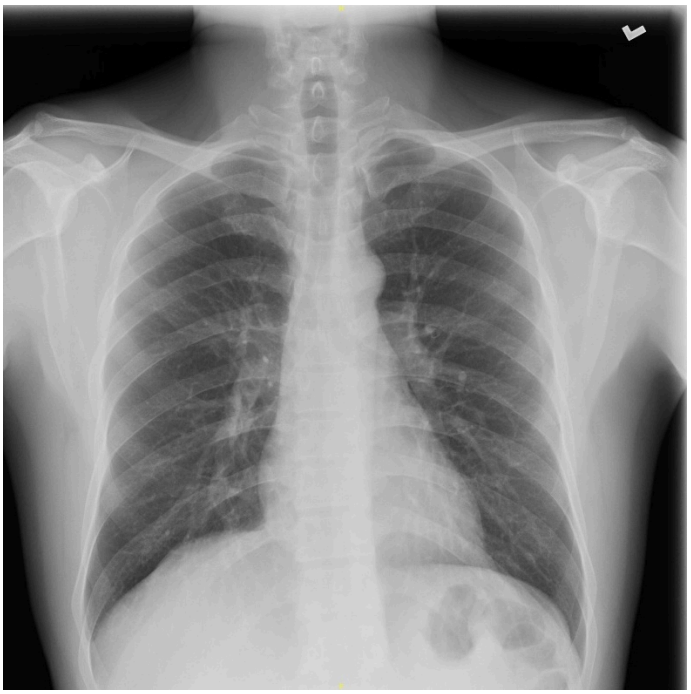
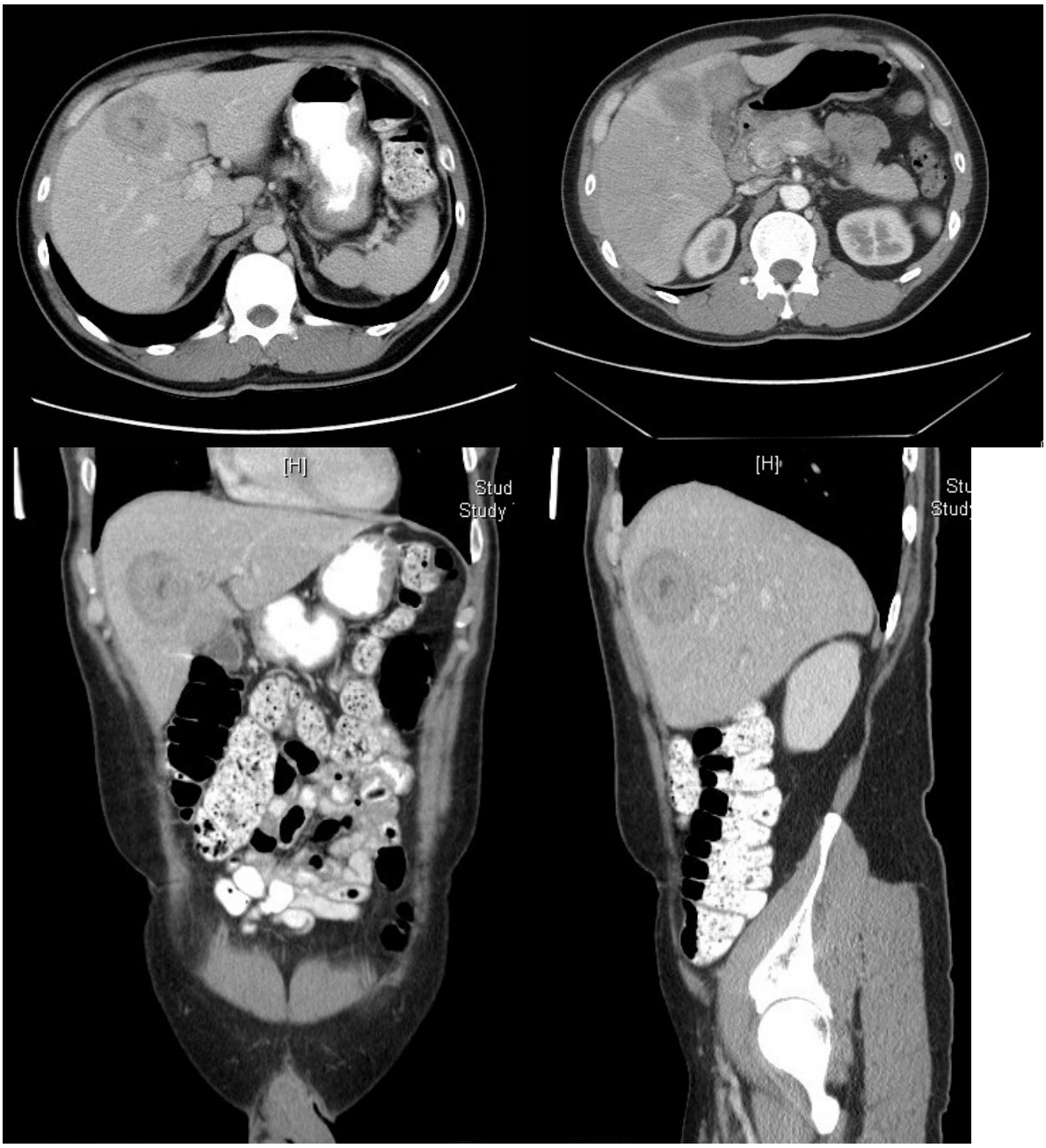


Figure 1. *A chest radiograph revealed a subcentimeter nodular opacity of the left upper lobe which was later found to be artefactual on CT scans.*



Figures 2-5. *CT scans of the liver revealed 2 dominant liver lesions with target appearance, and 2 additional smaller liver lesions.*

After a discussion with the patient, we decided to pursue tissue pathology testing to confirm a suspected diagnosis of lymphoma as opposed to metastatic liver lesions. He was referred to an interventional radiologist, and a biopsy of the larger liver lesion was performed. Surprisingly, the pathology report revealed an inflammatory myofibroblastic tumor consistent with IgG4-related disease (IgG4-RD).

Treatment. The patient was referred to a rheumatologist for treatment and, because he was asymptomatic at the time of his consultation, continual observation was elected. The patient was also referred for a colonoscopy, since IgG4-RD can affect multiple organ systems and can cause autoimmune enteritis.

Outcome of the case. Approximately 1 year after the initial diagnosis of IgG4-RD, the patient's symptoms returned, with 3 days of fevers, headaches, and severe malaise requiring hospitalization. He was ultimately started on prednisone and azathioprine. He had been doing very well on azathioprine monotherapy after discharge.

Discussion. IgG4-RD is an immune-mediated[1] fibroinflammatory condition characterized by tumefactive lesions, a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, and, often, elevated serum IgG4 concentrations.[2] The key histopathologic characteristics are lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis.[1]

IgG4-RD has only recently been recognized in 2003 as a systemic condition,[2] and has been shown to affect every organ system and often mimics malignant, infectious, and inflammatory disorders.[1,3] It has been shown to be present in patients with a variety of diseases, including Mikulicz disease, autoimmune pancreatitis, hypophysitis, Riedel thyroiditis, interstitial pneumonitis, interstitial nephritis, prostatitis, lymphadenopathy, retroperitoneal fibrosis, inflammatory aortic aneurysm, and inflammatory pseudotumor.[4]

Clinically, IgG4-RD most commonly affects middle-aged men, except in the case of head and neck disease in which the occurrence rate between the sexes is approximately equal.[5] IgG4-RD often presents with tumor development (often subacute) in one or multiple organs, but only 10% to 20% of patients have solitary-organ involvement.[6]

Lymphadenopathy is common[7]; however, lymph node biopsy (which likely often occurs, given that IgG4-RD often mimics lymphoma) can complicate the diagnosis, since the affected lymph nodes commonly lack the storiform fibrosis classically seen with IgG4-RD, and since lymph nodes containing IgG4-postive plasma-rich cells are present in multiple disease processes.[8] Serum IgG4 levels are elevated in IgG4-RD in as many as 80% to 90% of patients; however, sample sizes are often small, the sensitivity and specificity of this biomarker often vary significantly among studies, and utilizing the ratio of serum IgG4 to total IgG does not increase diagnostic yield of serum IgG4 levels.[8] The diagnosis commonly relies on the histopathologic findings described above.

Glucocorticoids are the first-line treatment for this disorder, with retreatment indicated for relapses after remission, and with azathioprine and mycophenolate mofetil serving as suitable second-line agents.[8]

IgG4-RD is a great masquerader and can affect nearly every organ system with such disorders as cutaneous pseudolymphoma, diseases of the salivary and lacrimal glands leading to orbital pseudotumor and a Sjögren-like picture, chronic autoimmune pancreatitis, prostatitis, and aortitis with potential aneurysm formation.[8,9] Having a broad differential diagnosis is paramount,

especially in cases of diagnostic uncertainty. For example, in 1 study, up to 40% of patients with IgG4-related pancreatitis also had salivary or lacrimal involvement.[8]

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