May 2016 Pulmonary Case of the Month

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History of Present Illness

A 24-year-old woman was diagnosed with pneumonia while on her honeymoon in Europe. She received an unknown treatment as an outpatient. When she returned a repeat chest x-ray showed persistent lung infiltrates. At that time she was asymptomatic. She was referred to pulmonary for further evaluation.

Past Medical History, Family History, Social History

- Idiopathic thrombocytopenic purpura at age 8
- Recurrent “bronchitis” since childhood
- Lifelong non-smoker, occasional ETOH, no illicit drugs
- No significant family history, other than hypertension in her father

Physical Examination

She had bibasilar fine crackles (fine) otherwise her physical examination was unremarkable.

Radiography

A chest x-ray was performed and interpreted as showing bilateral basilar interstitial infiltrates (Figure 1).

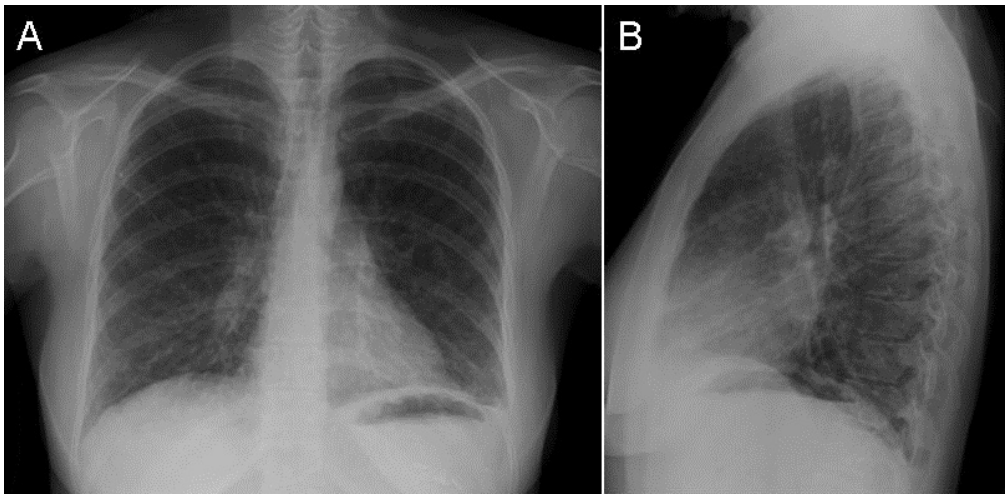

Figure 1. Chest x-ray showing bibasilar interstitial infiltrates.

To better define the abnormalities on chest x-ray a thoracic CT scan was performed (Figure 2).

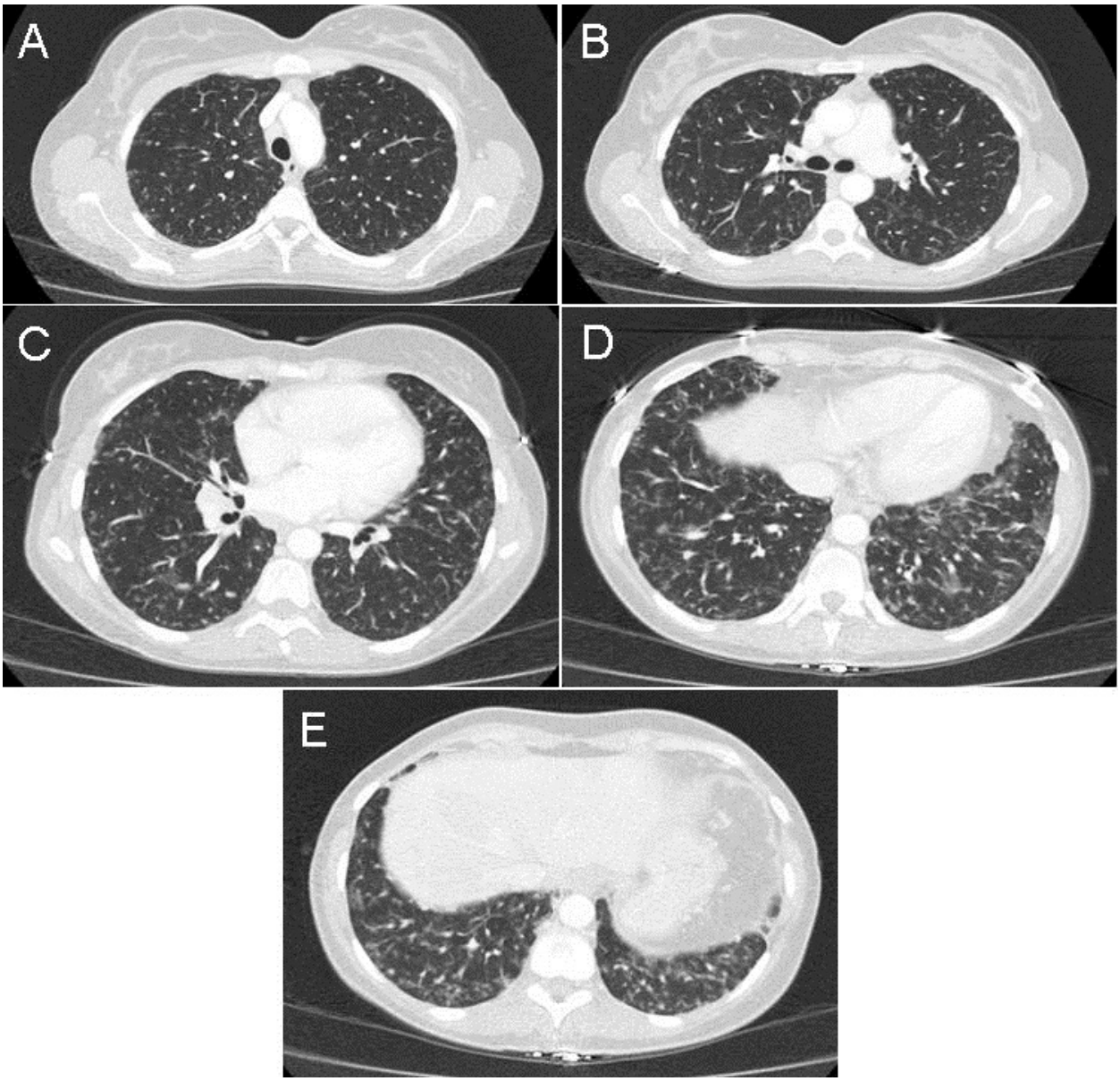

Figure 2. Representative images from the thoracic CT scan in lung windows.

Based on the CT scan, which of the following diagnosis is ***least likely***?

1. Hematogenous metastasis
2. Hypersensitivity pneumonitis
3. Lymphangitic metastasis
4. Miliary tuberculosis
5. Sarcoidosis

Correct!
2. Hypersensitivity pneumonitis

The thoracic CT scan shows small nodules that touch the pleura (Figure 3).

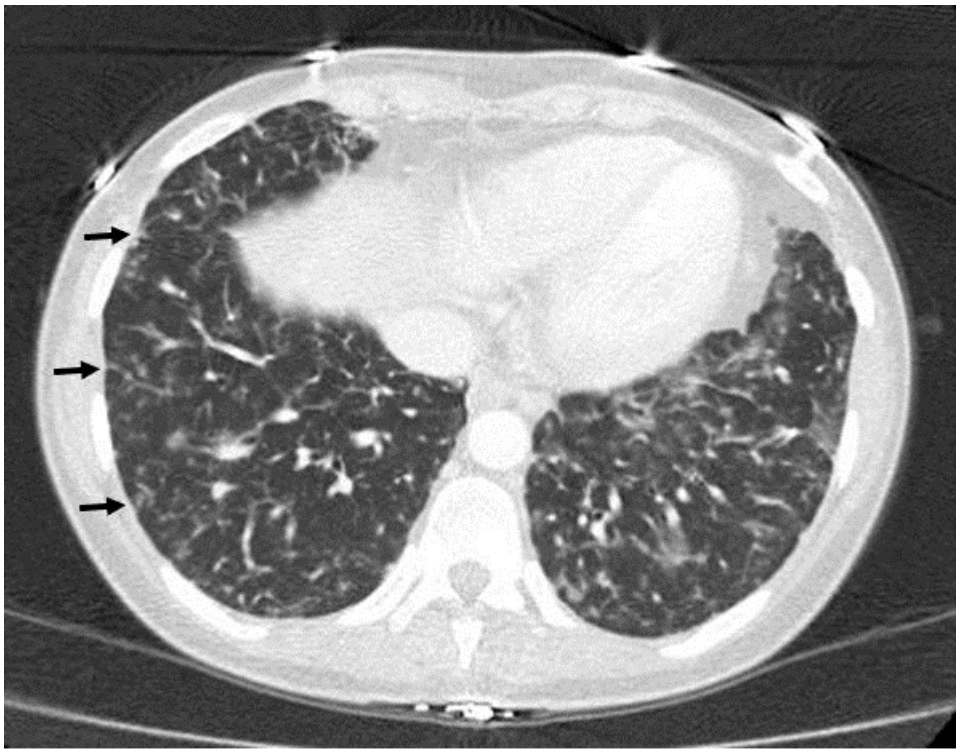

Figure 3. Small nodules are present that touch the pleura (arrows). There are also scattered areas of ground glass opacification.

Small nodules can be classified on CT scan as random, perilymphatic or centrilobular. Of these, centrilobular nodules do not touch the pleura unlike random and perilymphatic nodules. The most common cause of centrilobular nodules is hypersensitivity pneumonitis. Hematogenous metastasis and miliary tuberculosis usually present with random nodules while sarcoidosis and lymphangitic metastasis present with perilymphatic nodules.

The patient underwent bronchoscopy with transbronchial biopsy which was nondiagnostic.

What is the ***next step*** in the patient's work up?

1. CT/PET scan
2. Mediastinoscopy
3. Needle biopsy of the lung
4. Serum angiotensin converting enzyme (ACE)
5. Video-assisted thorascopic biopsy (VATS)

Correct!
5. Video-assisted thorascopic biopsy (VATS)

The next step which will likely result in a diagnosis is video-assisted thorascopic biopsy (VATS). The nodules most likely are random nodules. CT/PET scan could be performed but whether it is positive or negative a biopsy needs to performed. Mediastinoscopy is usually performed for enlarged mediastinal lymph nodes but there are no abnormal appearing nodes on the CT scan. Needle biopsy is usually performed for a pulmonary masses (> 2 cm). Serum angiotensin converting enzyme (ACE) is often elevated in sarcoidosis which seems unlikely from the clinical presentation.

The biopsy showed nodules consisting of diffuse infiltration of mature lymphocytes, plasma cells and histiocytes. There were no malignant cells apparent (Figure 4).

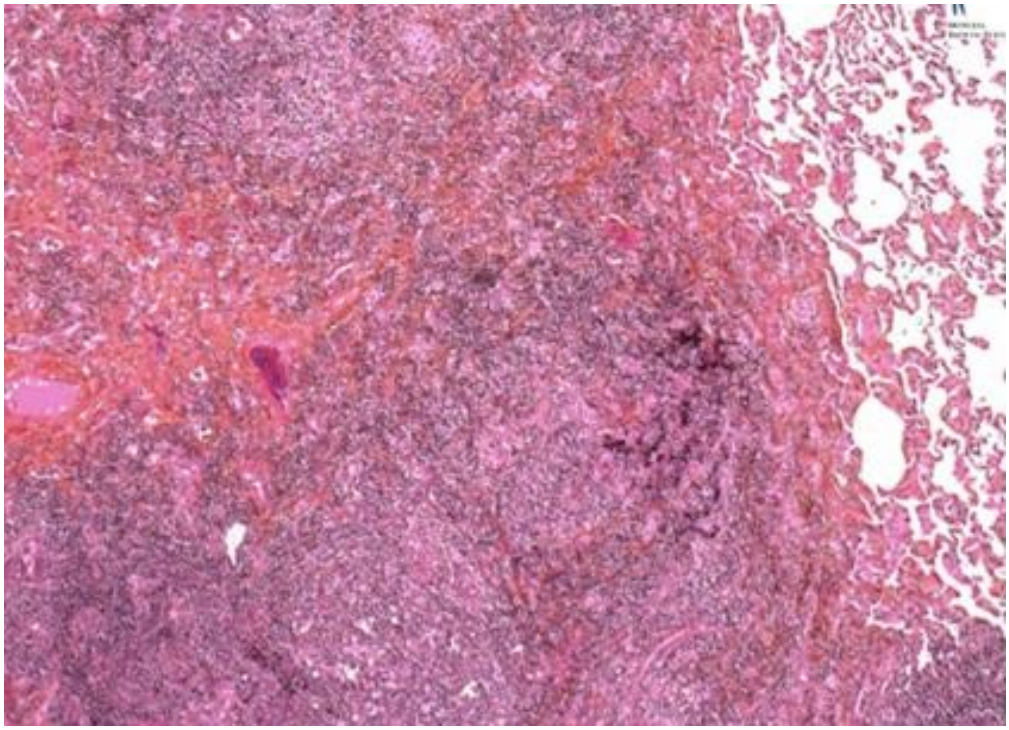

Figure 4. H & E stained lung biopsy showing nodule with a diffuse infiltration of mature lymphocytes, plasma cells and histiocytes. Normal lung is shown in the upper right.

A diagnosis of lymphocytic interstitial pneumonia (LIP) was made (1,2).

Which of the following diagnosis has been ***associated with LIP***?

1. Acquired immunodeficiency syndrome (AIDS)
2. Hypogammaglobulinemia
3. Sjogren's syndrome
4. Systemic lupus erythematosus (SLE)
5. All of the above

Correct!
5. All of the above

LIP may be associated with autoimmune and lymphoproliferative disorders, including rheumatoid arthritis, Hashimoto thyroiditis, myasthenia gravis, pernicious anemia, autoerythrocyte sensitization syndrome, chronic active hepatitis, common variable immunodeficiency, Sjögren syndrome, allogeneic bone marrow transplantation, lupus, and lymphoma. LIP has also associated with infection via human immunodeficiency virus (HIV), Epstein-Barr virus, and human T-cell leukemia virus (HTLV).

The major principle is to treat the underlying disease. LIP patients who are asymptomatic and physiologically unaffected patients may not require treatment. Symptomatic patients may require supportive care and immunosuppressives, chiefly corticosteroids. Occasionally, cytotoxic therapy has been used.

Our patient was found to have hypogammaglobulinemia and started on weekly intravenous immunoglobulin (IVIG).

She had frequent infections including a diagnosis of *Mycobacterium avium-intracellulare* over the next 2 years despite the immunoglobulin therapy. She underwent splenectomy for ITP. Biopsies of the spleen, omentum and liver revealed reactive follicular lymphoid hyperplasia with non-necrotizing granulomas.

Which of the ***following diseases associated with LIP*** is likely in our patient?

1. ADA deficiency
2. Common variable immunodeficiency
3. Severe combined immunodeficiency (SCID)
4. Wiskott-Aldrich syndrome (WAS)
5. X-linked agammaglobulinemia (Bruton disease; XLA)

Correct!
2. Common variable immunodeficiency

Wiskott-Aldrich is seen only in males. X-linked agammaglobulinemia (Bruton disease; XLA) is seen predominately in males although a similar disease has been seen in some females. Severe combined immunodeficiency, SCID, is also known as the bubble baby disease or bubble boy disease because its victims are extremely vulnerable to infectious diseases. Our patient's course is not compatible with SCID. Most individuals with ADA deficiency are diagnosed with severe combined immunodeficiency in the first 6 months of life. Without treatment, these babies usually do not survive past age 2.

CVID affects 1:20,000 to 1:50,000 live births (3). The mean onset of symptoms is in the third decade, but diagnosis is often delayed until 7-10 years after symptoms. CVID should be considered in a patient with recurrent sino-pulmonary infections. Joint, bone and gastrointestinal infections may also occur. Diagnosis requires low IgG, low IgA or IgM, and impaired capacity to make specific antibodies in response to immunization or infection. Patients often have T-cell abnormalities as well.

A form of LIP, known as granulomatous and lymphocytic interstitial lung disease (GLILD) seen in patients with CVID. It occurs in ~ 15% of pt with CVID. The etiology is unknown, but it has been suggested that certain viruses may play a role (human Herpes virus 8, EBV, and HIV).

References

1. Saukkonen JJ. Lymphocytic interstitial pneumonia. Medscape. 2015 Dec. Available at: http://emedicine.medscape.com/article/299643-overview (accessed 4/19/16).
2. Fagan KA and King TE. Lymphoid interstitial pneumonia in adults. UpToDate 2016 Mar. Available at: http://www.uptodate.com/contents/lymphoid-interstitial-pneumonia-in-adults (requires subscription).
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