

## **ANSWER TO FELLOW'S CHALLENGE (September-October Issue, 2004)**

Correct answers: 1) B or C

Diagnosis: Sarcoidosis or common variable immunodeficiency (CVID)

This PROJ challenge turned out to be more challenging and complex than anticipated when it was first published online in November 2004. The case of this 13 year old white male with non-caseating granulomas and hemolytic anemia has continued to evolve over time, and his diagnosis has changed/expanded during the past two months.

The patient's liver biopsy revealed non-caseating granulomas, and his chest CT showed scattered small lung nodules and adenopathy. These findings were suggestive of a diagnosis of sarcoidosis. However, he also had autoimmune hemolytic anemia which, although described, is extremely rare in sarcoidosis. It should be noted that autoimmune hemolytic anemia is reported more commonly in CVID (5-7% of patients) than in sarcoidosis. Granulomatous disease is also described in patients with CVID. Moreover, the patient had a history of recurrent respiratory tract infections (bronchitis, one pneumonia, as well as a few episodes of sinusitis, which was inadvertently omitted from the published history summary in the previous issue). This further raised concern of CVID. Initially, Wegener's granulomatosis was seriously considered in the differential diagnosis because of the pulmonary findings and the history of sinusitis, but the absence of any necrotizing granuloma on the liver biopsy decreased suspicion of this diagnosis.

The patient's pertinent laboratory results included a normal angiotensin converting enzyme level and negative anti-neutrophil cytoplasmic antibodies. His IgG and IgA levels were depressed. T-cell function studies were normal.

Only two weeks prior to the publication of this current PROJ issue, the patient presented again to his local hospital, this time with an enlarged cervical lymph node which was biopsied. Pathology studies showed non-Hodgkin's lymphoma. His previous liver and bone biopsies were reviewed at another medical center to look for evidence of malignancy, but were negative for this. Review of the liver biopsy also confirmed the presence of non-caseating granuloma. It is certainly possible that this patient's primary diagnosis is lymphoma. Hemolytic anemia is known to occur in patients with lymphoma, but the finding of non-caseating granuloma would not be expected.

Clinical complications reported in CVID include: recurrent infection (especially respiratory and gastrointestinal tracts); autoimmune disease (autoimmune cytopenia, inflammatory bowel disease, rheumatoid arthritis), granulomatous disease, malignancy (most commonly lymphomas and gastrointestinal adenocarcinomas). In addition to having decreased

quantitative immunoglobulins, this patient had several of the clinical problems associated with CVID (recurrent respiratory tract infections, autoimmune hemolytic anemia, granulomatous disease and lymphoma). However, there are some aspects of this case which are unexpected in CVID. Of note are the patient's normal T-cell function studies. Deficient lymphocyte proliferation to mitogens is frequently seen in CVID, particularly in patients with granulomatous disease. Furthermore, although lymphoma is not an uncommon complication (incidence of 6- 8%), it is reported much more commonly in women and older adults. Despite these inconsistencies, CVID is the diagnosis that best fits the course of this complex and unfortunate patient.

We would add a takeaway message. The differential diagnosis of a child with a granulomatous disease is fraught with pitfalls and challenges when he/she presents to a pediatric rheumatologist. In many countries tuberculosis is the first concern, but if it is not TB, sarcoid, CVID, and malignancies must be kept in mind.

Articles of interest:

1. Lee AH, Levinson AI, Schumacher HR Jr. Hypogammaglobulinemia and rheumatic disease. *Sem Arthritis Rheum.* 1993;22:252-64
2. Arkwright PD, Abinun M, Cant AJ. Autoimmunity in human primary immunodeficiency disease. *Blood* 2002;99:2694-2702
3. Mechanic LJ, Dikman S, Cunningham-Rimldes C. Granulomatous disease in common variable immunodeficiency. *Ann Int Med* 1997;127:613-617,

Regarding the fellows' responses, most selected sarcoidosis, and a few chose CVID. Given the changing and unclear course of this patient, no winner was selected for this month's challenge. Our apologies.