

Serum IL-12 and soluble IL-2 receptor levels as possible biomarkers of granulomatous and lymphocytic interstitial lung disease in common variable immunodeficiency: A case report

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Clinical Implications

- No previously published reports exist describing biomarkers for granulomatous disease in common variable immunodeficiency. Serum IL-12 and soluble IL-2 receptor may hold promise as clinically useful biomarkers of disease activity and/or response to treatment in granulomatous and lymphocytic interstitial lung disease.

TO THE EDITOR:

Complications of common variable immunodeficiency (CVID) can be characterized as infectious and noninfectious. Infectious complications of CVID can be dramatically diminished by making a timely diagnosis and initiating gamma globulin replacement therapy. Nevertheless, there remains significant morbidity and mortality from noninfectious complications. One such example is granulomatous and lymphocytic interstitial lung disease (GLILD), which occurs in 10% to 15% of the patients with CVID in the United States.¹ GLILD is a multisystem disorder that typically affects the lungs, spleen, liver, and lymph nodes. In addition, occasional reports describe involvement of the brain and retina.²⁻⁵ The underlying pathogenesis of GLILD is unknown. The ideal approach to treatment and monitoring disease activity is also unknown. We present the case of a 21-year-old man with CVID, GLILD, and neuroophthalmologic symptoms who gradually responded to therapy when azathioprine and rituximab were added to prednisone. At the time of presentation, serum levels of IL-12 and soluble IL-2 receptor (sIL-2R) were elevated and these normalized in parallel with clinical improvement.

At age 14 years, the patient was diagnosed with Evan syndrome, which was successfully treated with azathioprine and rituximab. The following year CVID was diagnosed on the basis of decreased serum IgG level of 253 (normal, 600-1606), decreased IgA level of 18 (normal, 46-287), and poor antibody responses to protein and polysaccharide antigens (antitetanus <0.01, antidiphtheria 0.04, anti-*Haemophilus influenzae* type b <0.18, *Streptococcus pneumoniae* decreased in 14 of 14 measured serotypes). In addition, he had absent memory B cells and decreased *in vitro* lymphoproliferative responses to antigen stimulation. He had normal expression of CD40L and inducible T cell costimulator and normal CD40L and CD40 gene analysis.

At age 17 years, he had a prolonged hospitalization for severe disseminated zoster with visceral involvement, from which he

fully recovered. He remained in good health on monthly intravenous immunoglobulin (530 mg/kg/month), until he presented with a dull headache and diplopia secondary to a new-onset right sixth cranial nerve palsy. He denied associated constitutional or respiratory symptoms, but later recalled a 6-week illness, occurring 5 months before presentation, characterized by cough, laryngitis, night sweats, and fevers.

Neuroophthalmologic evaluation was notable for retinal inflammation. A brain magnetic resonance imaging with and without intravenous gadolinium revealed multifocal areas of FLAIR signal abnormality in the bilateral temporal and occipital lobes, mass-like enhancements in the temporal horn of the left lateral ventricle and inferolateral aspect of the right cavernous sinus, and abnormal pachymeningeal enhancement of the cerebellar tentorium (Figure 1). A chest radiograph revealed reticular and nodular opacities (Figure 2). A computed tomography scan (Figure 3) of the chest, abdomen, and pelvis revealed diffuse pulmonary nodular and ground-glass opacities with septal line thickening, mediastinal and hilar lymphadenopathy, and marked splenomegaly. Spirometry evaluation revealed interval development of a restrictive pattern (Table I).

Extensive laboratory evaluations of blood and cerebral spinal fluid (CSF) were negative for infectious etiologies, including tick-borne illnesses and viral, mycobacterial, and fungal diseases. Varicella zoster PCRs performed on serum and CSF and serologies performed on CSF were all negative, excluding recurrence of herpes zoster. Serum protein electrophoresis and immunofixation were normal with no evidence of clonality. Remarkable findings included an elevated erythrocyte sedimentation rate, an elevated serum angiotensin-converting enzyme (ACE) level with a normal ACE level in the CSF, pleocytosis of the CSF (90% lymphocytes) with normal cytology, and elevated CSF protein (Table I).

Predominant considerations in the differential diagnosis included malignancy (ie, lymphoma) and infectious (ie, fungal, tuberculosis, and viral) and granulomatous (ie, sarcoid) diseases. Bronchoscopic evaluation included a bronchoalveolar lavage and transbronchial biopsy. Cultures for bacteria, mycobacteria, fungi, and respiratory viruses were negative. The bronchoalveolar lavage revealed a predominance of macrophages and lymphocytes with rare neutrophils. Flow cytometry performed on the bronchoalveolar lavage showed mostly T cells, most of which were CD8⁺ cells (CD3⁺ 82%, CD4⁺ 15%, CD8⁺ 69%, CD19⁺ 4%). The transbronchial biopsy showed chronic interstitial lymphocytic inflammation (Figure 4). The clinical and histopathologic features were consistent with GLILD. Serum levels of IL-12 and sIL-2R were markedly elevated (Table I). HIV and hepatitis C had been evaluated in the past, and the patient was negative for these.

Treatment with high-dose systemic corticosteroids was of no immediate clinical benefit. Thus, additional immunosuppressive therapy was cautiously considered after the above-described efforts to exclude infection in the central nervous system and lungs. Because of the severity of impairment and absence of identifiable infection, the patient was started on the same combination chemotherapy protocol as outlined by Chase et al,¹ with intravenous rituximab (375 mg/M²) infused intravenously once weekly for 4 weeks and then repeated every 6 months for a total of 3 courses and oral azathioprine (1.7 mg/kg/d) to complete a total of

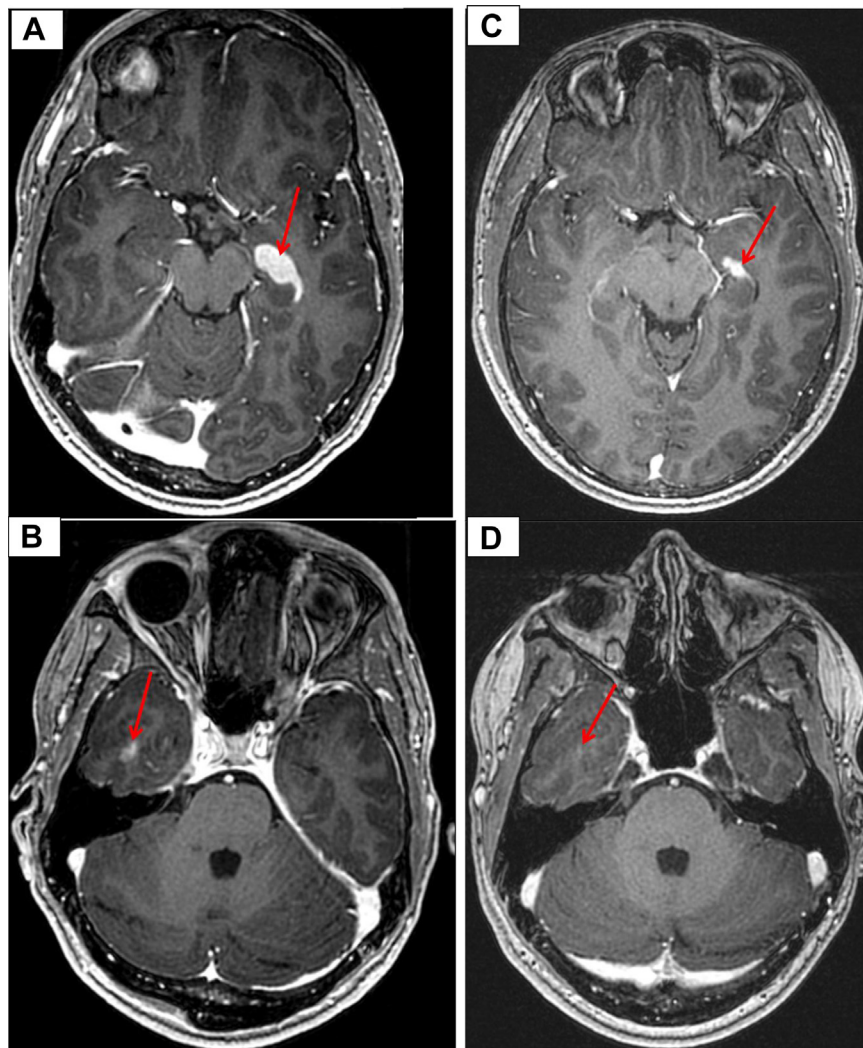


FIGURE 1. Before treatment, there is a mass-like enhancement and thickening effect of the left choroid plexus in the temporal horn of the left lateral ventricle (A) and contrast enhancement in the anterior/inferior right temporal lobe (B). After treatment, there is marked reduction of the mass-like enhancement and thickening effect of the left choroid plexus in the temporal horn of the left lateral ventricle (C) and the contrast enhancement in the anterior/inferior right temporal lobe has resolved (D).

18 months.¹ Symptom improvement was noted after approximately 3 months, and his right cranial nerve palsy resolved at 4 months. In addition, there was resolution of all previously enhancing intracranial lesions (Figure 1), interval decrease in the scattered pulmonary nodular and interstitial opacities (Figure 2), and improved spirometry. The serum IL-12, sIL-2R, ACE, and erythrocyte sedimentation rate levels normalized (Table I).

There appears to be a propensity for GLILD to develop in patients with CVID complicated by autoimmunity, particularly the autoimmune cytopenias. Patients with CVID with granulomatous and/or autoimmune complications are often found to have a deficiency of switched memory B cells, suggesting that aberrant B-cell maturation may play a role in the development of granulomas.^{2,4} Another previously well-described yet poorly understood phenomenon seen in patients with CVID complicated by GLILD is skewing of T lymphocytes toward the memory phenotype.¹ Our patient had an increased percentage of CD4⁺CD45RO⁺ T cells (Table I). An additional potential

contributor to the development of GLILD is HHV-8 infection. HHV-8 infection might explain the concomitant appearance of GLILD and neuroophthalmologic manifestations. However, HHV-8 was not assessed in this patient.^{4,6} Notably, previously described sarcoidosis in patients with CVID may actually have been GLILD.^{2,5,7,8} This is an important distinction to make because therapy differs for the 2 entities and misdiagnosis could lead to a delay in optimal management.

The use of biomarkers to follow disease progression and/or response to treatment in sarcoidosis is limited because ACE levels are controversial and serum sIL-2R is nonspecific. In fact, sIL-2R is an established and reliable biomarker for a number of inflammatory conditions, including autoimmune diseases (ie, systemic lupus erythematosus and rheumatoid arthritis) and certain malignancies (ie, hepatocellular carcinoma, esophageal squamous cell carcinoma, adult T-cell leukemia/lymphoma, and hemophagocytic lymphohistiocytosis). However, serum IL-12 is not commonly used as a biomarker of inflammatory diseases, but it

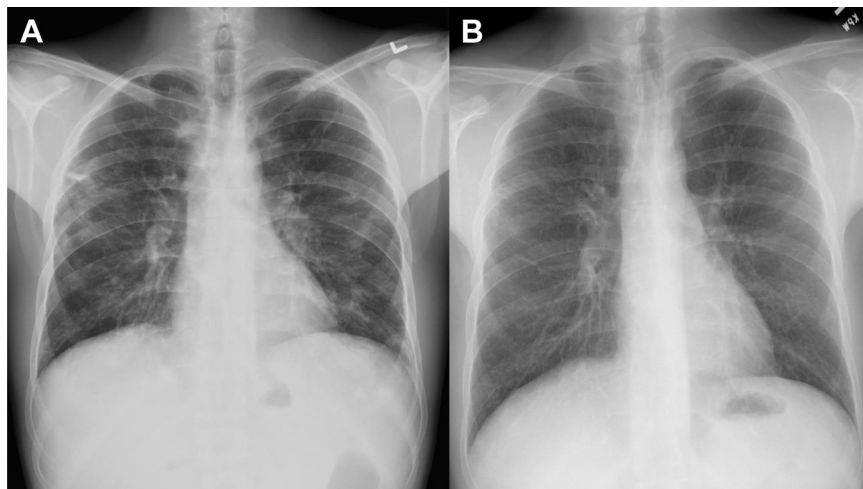


FIGURE 2. Posterioranterior radiographs of the chest demonstrating reticulonodular opacities (A) before therapy and 6 months later (B) after therapy with rituximab showing interval improvement.

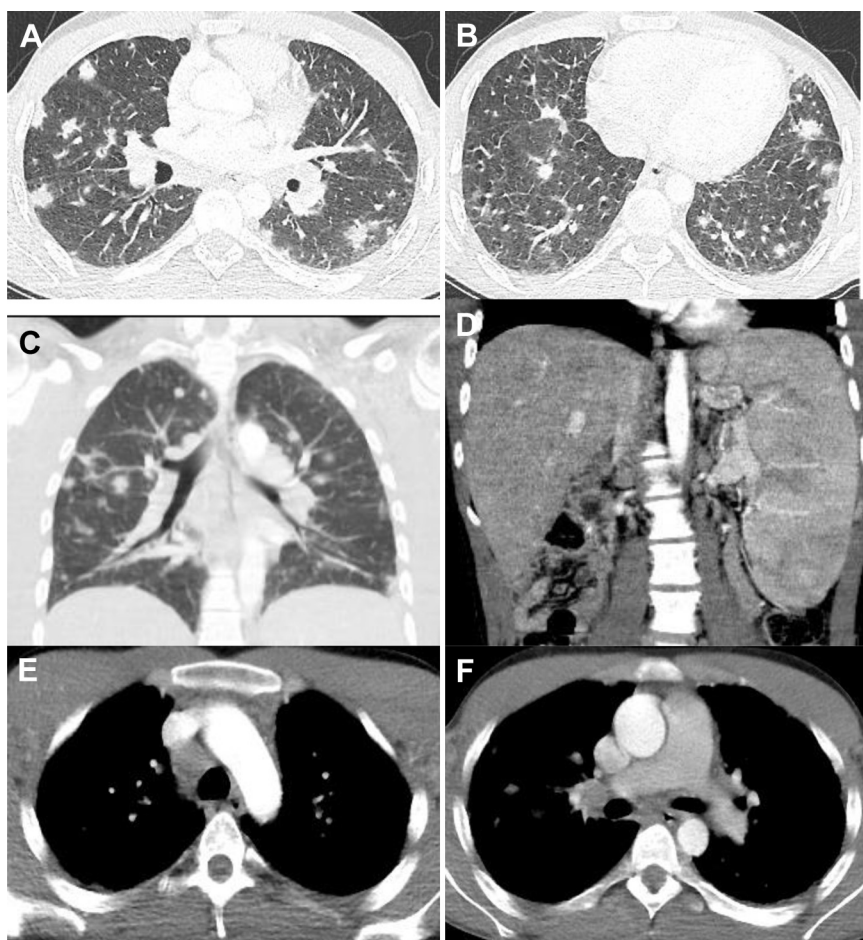
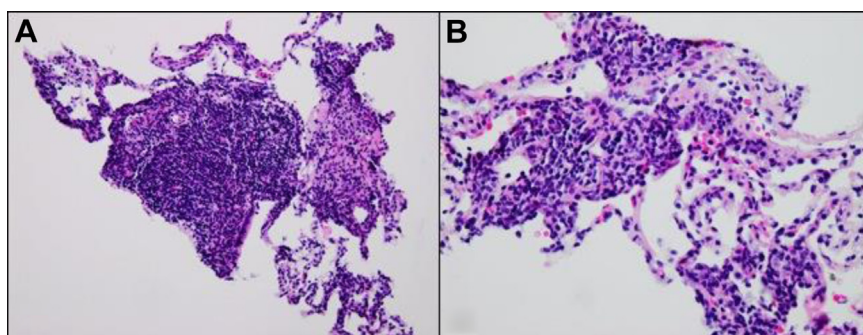


FIGURE 3. Axial computed tomography (CT) images with lung windows (A and B) and coronal CT image with lung windows (C) demonstrate ground-glass and nodular opacities with septal line thickening. Coronal CT image of the abdomen (D) demonstrates marked splenomegaly. Axial CT images in bone windows (E and F) demonstrate mediastinal and right hilar lymphadenopathy.

TABLE I. Laboratory studies pre- and posttreatment with prednisone, azathioprine, and rituximab

Parameter	Pretreatment	Posttreatment	Normal range
ESR (mm/h)	75	5	0-15
Serum ACE (U/L)	78	16	9-67
CSF ACE (U/L)	1.9	-	0-2.5
CSF Protein (mg/dL)	108	-	15-40
IL-2R (pg/mL)	1527	906	0-1033
IL-12 (pg/mL)	198	14	0-6
Pulmonary function tests			
FVC (L)	2.99	3.61	
FEV ₁ (L)	2.52	2.98	
Memory CD4 ⁺ /CD45RO ⁺ T cells (%)	93	93	18-38
Memory CD19 ⁺ CD27 ⁺ B cells (%)	0	0	25-40

CSF, cerebral spinal fluid; ESR, erythrocyte sedimentation rate; IL-2R, interleukin-2 receptor; IL-12, interleukin-12; FVC, forced vital capacity.

**FIGURE 4.** Histopathological findings, transbronchial biopsy. Microscopic examination of the transbronchial lung biopsy revealed peribronchial lymphocytic infiltration (A, H&E 200 $\times$). Other areas showed interstitial lymphocytic infiltrates (B, H&E 400 $\times$).

was recently identified as a novel biomarker for the polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes syndrome.⁹

Our case highlights an uncommon presentation of GLILD in CVID that responded nicely to treatment with combined azathioprine and rituximab. It also underscores that serum IL-12 and sIL-2R may hold some promise as clinically useful biomarkers of disease activity and/or response to treatment in GLILD. Further evaluation is warranted to determine the full potential value of serum IL-12 and sIL-2R levels in these patients. Moreover, phenotyping of B-cell subpopulations to identify patients with CVID at increased risk of developing lymphoproliferative and autoimmune complications is an important concept that should continue to be pursued.¹⁰

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