

# Common variable immunodeficiency mimicking rheumatoid arthritis with Sjögren's syndrome

Li-Hsin Lin, Chih-Neng Tsai, Ming-Fei Liu, Chrong-Reen Wang

*Section of Rheumatology and Section of Allergy and Immunology, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan*

Received: August 20, 2004 Revised: December 25, 2004 Accepted: March 25, 2005

Several autoimmune diseases have been reported to be associated with common variable immunodeficiency disease (CVID), including rheumatoid arthritis and Sjögren's syndrome. On the other hand, approximately 20-30% of patients with rheumatoid arthritis develop secondary Sjögren's syndrome. A 26-year-old woman had a 6-year history of chronic symmetric polyarthritis and 3-year history of sicca syndrome prior to admission for pneumonia. Rheumatoid arthritis with secondary Sjögren's syndrome had been diagnosed 1 year before. The patient had experienced 3 episodes of pneumonia during the previous 3 years. Markedly depressed serum immunoglobulin levels prompted a suspicion of common variable immunodeficiency, and the impression was confirmed after a series of examinations. Monthly administration of intravenous immunoglobulin (IVIG) alleviated the polyarthritis and improved the sicca syndrome. IVIG replacement therapy was ultimately successful in curing recurrent bacterial infections, chronic polyarthritis, and improving the severity of sicca syndrome.

**Key words:** Common variable immunodeficiency, intravenous immunoglobulins, rheumatoid arthritis, Sjögren's syndrome

Common variable immunodeficiency (CVID) is characterized by markedly decreased serum immunoglobulin concentrations, normal or nearly normal numbers of circulating immunoglobulin-bearing mature B cells, impaired antibody response and recurrent bacterial infections of the sinopulmonary tract often associated with chronic progressive bronchiectasis. A delay of several years between the initial onset of recurrent infections and the establishment of the diagnosis of CVID is not unusual. In addition, patients exhibit increased susceptibility to autoimmune, gastrointestinal, neoplastic, and inflammatory disorders [1]. We describe a young woman with delayed diagnosis of CVID and the co-existence of rheumatoid arthritis and Sjögren's syndrome.

## Case Report

A 26-year-old woman was brought to our emergency room because of productive cough with high fever for 1 week. Chest roentgenogram revealed a pneumonia

patch with pleural effusion in the lower left lung. She was admitted to our medical ward for further management. Her medical history revealed 2 previous bouts of pneumonia and frequent episodes of upper respiratory tract infection within the previous 3 years, with the first bout of pneumonia occurring at the age of 23. Otitis media occurred twice during this period. Chronic paranasal sinusitis had also been diagnosed.

She had a 6-year history of chronic progressive symmetric polyarthritis in the bilateral temporomandibular, wrist, metacarpophalangeal (MCP), proximal interphalangeal (PIP), hip, and knee joints. There were no deformities associated with the arthritis. However, intolerable joint pain with prolonged (more than 1 h) morning stiffness had made routine work impossible. Arthrocentesis on her left knee and hip had been performed several times, and revealed inflamed synovial fluid. Treatment for the inflammatory arthritis included the intra-articular injection of corticosteroids, and prescription of non-steroidal anti-inflammatory drugs (NSAIDs).

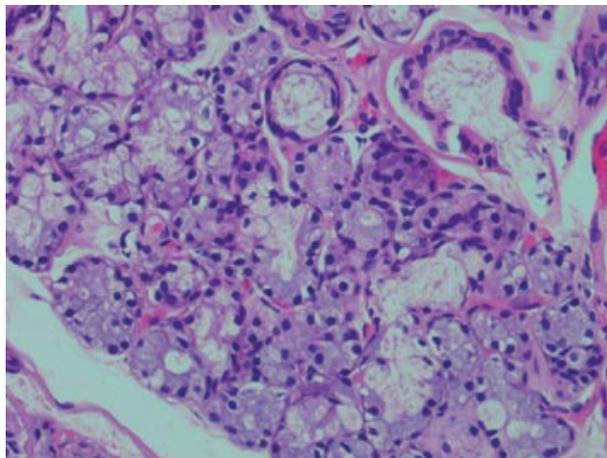
During the previous 5 years, the patient had experienced chronic diarrhea with more than 5 defecations of loose to watery feces every day, but she had not sought medical help for this problem. In addition, she had developed progressive sicca syndrome 3 years

---

*Corresponding author: Dr. Li-Hsin Lin, Section of Rheumatology and Section of Allergy and Immunology, Department of Internal Medicine, National Cheng Kung University Hospital, No. 138 Sheng-Li Road, Tainan 704, Taiwan.  
E-mail: lihsin@info.hosp.ncku.edu.tw*

prior to the current hospitalization. Xerophthalmia had been diagnosed by an ophthalmologist 1 year prior to this hospitalization, with the prescription of artificial tears at least 6 times every day and the frequent consumption of water because of xerostomia. Follow-up examinations had been conducted for the following 7 months at the rheumatology outpatient department of a local hospital. Rheumatoid arthritis with secondary Sjögren's syndrome was diagnosed, and sulfasalazine (2 g/day) and NSAIDs were prescribed, but the polyarthritis persisted.

The latest episode of pneumonia led to the patient's admission to the medical ward of our hospital. Overt active polyarthritis was evident over bilateral PIP, MCP, wrist, and knee joints. Sublingual saliva production was minimal. No lymphadenopathy, tonsillary enlargement, or splenomegaly were found. Thymus was not detectable on chest roentgenogram. Laboratory analyses revealed very low levels of serum immunoglobulin A (IgA) <6.67 mg/dL (normal range, 90-450 mg/dL), IgG <33.3 mg/dL (normal range, 810-1690 mg/dL), and IgM 5.15 mg/dL (normal range, 60-280 mg/dL). Serial counts of absolute lymphocytes, and circulating T and B cells were within normal limits. Analysis of circulating lymphocytes revealed the percentage of cells expressing CD3 as 90% (reference value, 50-82%), CD19 4% (4-24%), CD4 51% (25-49%), and CD8 33% (9-41%). The CD4<sup>+</sup>/CD8<sup>+</sup> T lymphocyte ratio was 1.55 (1.1-2.5), and the absolute CD4<sup>+</sup> T lymphocyte count was 1267/mm<sup>3</sup> (reference value, >430/mm<sup>3</sup>). Serum complement levels were also normal (C3 101 mg/dL, C4 27 mg/dL). Serum protein electrophoresis revealed no monoclonal gammopathy. Screening was negative for anti-nuclear antibodies, anti-extractable nuclear antigens antibodies, antibodies to double-stranded DNA, anti-cardiolipin antibodies, rheumatoid factor, serum and plasma cryoprotein, and anti-human immunodeficiency virus antibodies. Repeated stool analyses and stool cultures were negative. Bilateral X-rays of the hands were unremarkable, with no evidence of marginal bony erosions or juxta-articular osteoporosis. Ophthalmology examination revealed a positive Schirmer's test, leading to a diagnosis of xerophthalmia. Salivary scintigraphy showed moderate xerostomia in class II/IV. A minor salivary gland biopsy obtained from the lower lip demonstrated mild inflammatory change with a lymphocyte count of less than 50/4 mm<sup>3</sup> (Fig. 1). Sputum culture during the episode of pneumonia was positive for *Haemophilus influenzae*. Common variable immunodeficiency was



**Fig. 1.** Minor salivary gland biopsy from lower lip showed mild inflammatory change with some lymphocyte infiltration (hematoxylin and eosin stain,  $\times 200$ ).

diagnosed, and 0.5 g/kg/month intravenous immunoglobulin (IVIG) was prescribed.

The patient was discharged after the pneumonia symptoms improved. Subsequent regular follow-up at the outpatient department was performed. She received regular IVIG replacement therapy (0.5 g/kg/month), which successfully controlled the chronic paranasal sinusitis and pyogenic infections. Complete remission of polyarthritis occurred in the absence of disease-modifying antirheumatic drugs and NSAIDs. Some relief in chronic diarrhea was achieved, with less than 3 defecations per day, and sicca syndrome also improved during the follow-up.

## Discussion

CVID can occur at any age. Typically, the disease does not become clinically apparent until the second or third decade of life, and a delay of several years between the initial onset of recurrent infections and the establishment of the diagnosis is not unusual [2]. The clinical hallmark of CVID is recurrent bacterial infection, most commonly sinusitis, otitis media, bronchitis and pneumonia, which are caused by encapsulated bacteria, particularly *Streptococcus pneumoniae*, *H. influenzae*, and *Staphylococcus aureus* [3]. This patient had recurrent episodes of pneumonia, sinusitis, and otitis media, which led to suspicion of immunodeficiency. The results of immunologic laboratory studies were characteristic of patients with CVID, including markedly depressed serum immunoglobulin levels, and normal T and B lymphocyte counts.

As many as 60% of untreated CVID patients will develop a variety of infectious and non-infectious

gastrointestinal diseases. *Giardia lamblia* is the most common infectious cause [4]. Although this patient had no evidence of infectious diarrhea or inflammatory bowel disease, chronic diarrhea improved after IVIG replacement therapy. Thus, CVID-related gastrointestinal perturbations may have well occurred in this patient. After IVIG replacement therapy, chronic paranasal sinusitis abated. No further bacterial infections had developed during the subsequent one and a half years of follow-up.

Approximately 20% of patients with CVID develop one or more autoimmune diseases, indicating that CVID is a disease of abnormal immune regulation as well as immunodeficiency [5]. Autoimmune diseases associated with CVID include autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, pernicious anemia, autoimmune thyroid disease, rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, and Sjögren's syndrome [6]. Patients with CVID are unable to mount an antibody response to infecting microorganisms but retain the ability to produce autoantibodies against erythrocytes, platelets, granulocytes, and other autoantigens. CVID is associated with particular major histocompatibility complex haplotypes that are also associated with autoimmune states. In addition, lack of a normal mucosal IgA response may fail to exclude entry of environmental proteins at mucosal surfaces. This can lead to immunization by environmental antigens that crossreact with self-antigens and thus the induction of immune elements that mediate autoimmunity [7]. Septic arthritis, particularly *Mycoplasma* infection, is not uncommon in CVID patients, but this patient had no evidence of septic arthritis. CVID is also associated with an aseptic polyarthritis that resembles RA. This inflammatory arthritis is usually chronic, non-erosive, oligoarticular, or polyarticular and most commonly affects the knees, wrists, ankles, and fingers. In most patients, the arthritis responds rapidly to IVIG therapy. The pathogenesis of this form of arthritis is poorly understood [8]. Sjögren's syndrome is rarely associated with CVID, but severe sicca syndrome was apparent in this patient.

In this patient, rheumatoid arthritis and Sjögren's syndrome were diagnosed according to the classification criteria of the American College of Rheumatology prior to the diagnosis of CVID. IVIG replacement therapy dramatically and rapidly alleviated the arthritis symptoms. CVID is a life-long disease that, with only rare and poorly understood exceptions, does not spontaneously remit [9]. Standard therapy

of CVID consists of IVIG, which is less painful and more effective at preventing infections than the intramuscular administration of immunoglobulin [10]. Adequate IVIG replacement therapy reduces the frequency of infections and, if started early enough, is also thought to reduce the occurrence of pulmonary complications [11].

In conclusion, recurrent bacterial infections in youth should always lead to suspicion of CVID, especially in patients with some autoimmune manifestations. In this case, rheumatoid arthritis with secondary Sjögren's syndrome was diagnosed with poor response to medical management. IVIG replacement therapy was ultimately successful in curing the chronic paranasal sinusitis and rheumatoid arthritis, lessening the frequency of the chronic diarrhea, and improving the severity of sicca syndrome.

## References

1. Sicherer SH, Winkelstein JA. Primary immunodeficiency diseases in adults. *JAMA* 1998;279:58-61.
2. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol* 1999;92:34-48.
3. Cunningham-Rundles C. Clinical and immunological analyses of 103 patients with common variable immunodeficiency. *J Clin Immunol* 1989;9:22-33.
4. Sneller MC. Common variable immunodeficiency. *Am J Med Sci* 2001;321:42-8.
5. Hermans P, Diaz-Brujo JA, Stobo JD. Idiopathic late-onset immunoglobulin deficiency. Clinical observations in 50 patients. *Am J Med* 1976;61:221-37.
6. Conley ME, Park CL, Douglas SD. Childhood common variable immunodeficiency with autoimmune disease. *J Pediatr* 1986;108:915-22.
7. Sneller MC, Strober W, Eisenstein E, Jaffe JS, Cunningham-Rundles C. NIH conference. New insights into common variable immunodeficiency. *Ann Intern Med* 1993;118:720-30.
8. Lee AH, Levinson AI, Schumacher HR Jr. Hypogammaglobulinemia and rheumatic disease. *Semin Arthritis Rheum* 1993;22:253-64.
9. Strober W, Chua K. Common variable immunodeficiency. *Clin Rev Allergy Immunol* 2000;19:157-81.
10. NIH consensus conference. Intravenous immunoglobulin. Prevention and treatment of disease. *JAMA* 1990;264:3189-93.
11. Kainulainen L, Nikoskelainen J, Ruuskanen O. Diagnostic findings in 95 Finnish patients with common variable immunodeficiency. *J Clin Immunol* 2001;21:145-9.