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Refractory Ulcerative Lupus Vulgaris Associated with CD4 Lymphocytopenia, Inversion of Chromosome 14, Primary Amenorrhoea and Mental Retardation

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A case of ulcerative lupus vulgaris, confirmed by polymerase chain reaction (PCR) is reported. The initial lesion of our case was a papule on the nose, which progressed during antituberculous treatment and caused cartilage destruction and ectropion. Immunological analysis revealed CD4 lymphocytopenia, and the possibility of idiopathic CD4 lymphocyte deficiency was considered. In addition, the patient had primary amenorrhoea, mental retardation and inversion of chromosome 14. CD4 lymphocytopenia and chromosomal abnormality are the possible causes of antituberculous treatment failure. ***Key words: tuberculosis; immunodeficiency; chromosomal abnormality.***

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Lupus vulgaris is a chronic and progressive form of skin tuberculosis. The incidence of tuberculosis is increased in immunosuppressed patients in comparison with the normal population (1). The exact immune mechanism against tuberculosis is still under investigation and needs to be defined. However, the T-cell-dependent immune function plays an important role in the pathogenesis (1).

Our case of lupus vulgaris, with dominating destructive features, was resistant to treatment, probably due to CD4 lymphocytopenia. The patient had primary amenorrhoea and mental retardation, with a probable association with inversion of chromosome 14.

CASE REPORT

In 1989, an 18-year-old female patient presented with an erythematous, indurated plaque on her nose (Fig. 1a). She had no history of blood transfusions, operations or opportunistic infections. Her parents were first-degree relatives. Physical examination was normal, except for the absence of secondary sexual characteristics. She was mentally retarded. Clinical examination of ophthalmologic and ear-nose-throat systems was normal. The following laboratory tests were within normal range: complete blood count, erythrocyte sedimentation rate, biochemical tests (glucose, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, urea, creatinine, electrolytes, protein electrophoresis), rheumatoid factor, anti-neutrophilic cytoplasmic antibody, *Borrelia burgdorferi* IgM, IgG. Antibodies against HIV were negative at repeated tests (ELISA). Purified protein derivative test (5 IU) for *Mycobacterium tuberculosis* (PPD) showed anergy. IgA and IgE levels were normal; IgG was decreased (300 mg/dl; normal range 700–1700 mg/dl) and IgM was increased (376 mg/dl; normal range 50–300 mg/dl). A biopsy specimen from the lesion showed lymphomonocytic infiltration consisting of histiocytes with indefinite granuloma formation. No special features were found with Ehrlich-Ziehl-Neelsen, PAS, Warthin-Silver-Starry and elastic stains. Microbiological analysis of the sputum, purulent secretion and tissue from the lesion showed no acid-resistant bacilli, *leishmania* or fungi. Polymerase chain reaction (PCR) for *leishmania* was also negative. No abnormalities were found in the chest, paranasal sinus and cranial X-rays. Abdominal ultrasonography revealed uterine hypoplasia only.

In July 1989, the patient received therapy for presumed lupus vulgaris. She was given isoniazid (300 mg daily), rifampicin (450 mg daily) and streptomycin (1 g daily for 40 days). The patient did not comply with the protocol after 6 months. In February 1990, she returned with remarkable progression of the lesions, which had expanded, ulcerated and caused destruction of the cartilage of the nose. Skin biopsy and all other laboratory investigations, including microbiological analysis of tissue and purulent secretion, were performed again but no changes were noted. Because histopathological examination revealed granulomatous changes, methylprednisolone (40 mg daily) was started. After 6 weeks, there was a flare in the lesion and corticosteroid therapy was terminated.

Drug therapy with isoniazid, ethambutol, rifampicin and pyrazinamide (2 g daily) was initiated, but it was discontinued after 12 months due to elevation of liver enzymes. For the next 18 months, the patient was followed up without systemic treatment. In December 1992, further immunological tests were performed. T-cell responses to *Candida* and *Trichophyton* antigen were negative, spontaneous rosette formation was 4% (normal range >40%). Kweim test was negative. Complement activation tests were normal. Lymphocyte subset analysis repeatedly showed lymphocytopenia (<200 cells/mm^3) and CD4-T-lymphocytopenia. CD4:CD8 ratio was always less than 1.0. Cytogenetic investigations showed paracentric inversion of chromosome 14 (46 xx, 14 q11- q32) and multiple chromosomal deletions. Karyotypic analysis of her parents was normal. In January 1993, a combination of quadruple anti-tuberculous drugs (isoniazid, ethambutol, pyrazinamide and rifampicin (600 mg daily) with immunoglobulin (Sandoglobulin, 6 g i.v. every 3 weeks) and ciprofloxacin (500 mg bid for 2 months) was initiated and continued for 12 months. The lesions showed no change during this period. From January 1994 to May 1995, she was treated with immunoglobulin (15 g every 3 weeks) plus clarithromycine (500 mg bid). Facial edema, ectropion (Fig. 1b) and a new lesion on the leg apperead in May 1995 and anti-tuberculous drugs were initiated again. In October 1995, PCR was performed for *Mycobacterium tuberculosis* complex from the paraffin-embedded tissue, and it was found to be positive for *Mycobacterium tuberculosis* complex DNA.

DISCUSSION

The patient with lupus vulgaris confirmed by PCR showed cellular immune deficiency in immunological analysis. The CD4 lymphocyte count was low and the CD4:CD8 ratio was less than 1.0. Acquired causes of CD4 lymphocyte deficiency are HIV and other chronic infections, collagen diseases, drugs and splenectomy. CD4 lymphocyte count also varies with age and diurnal rhythm (2, 3). "Idiopathic CD4 Lymphocyte Deficiency" (ICLD) has been described as a clinical entity, not associated with HIV infection (4). Cutaneous manifestations of ICLD are infections including thrush, herpes virus, warts, molluscum, cryptococcosis, toxoplasmosis and Kaposi's sarcoma (5).

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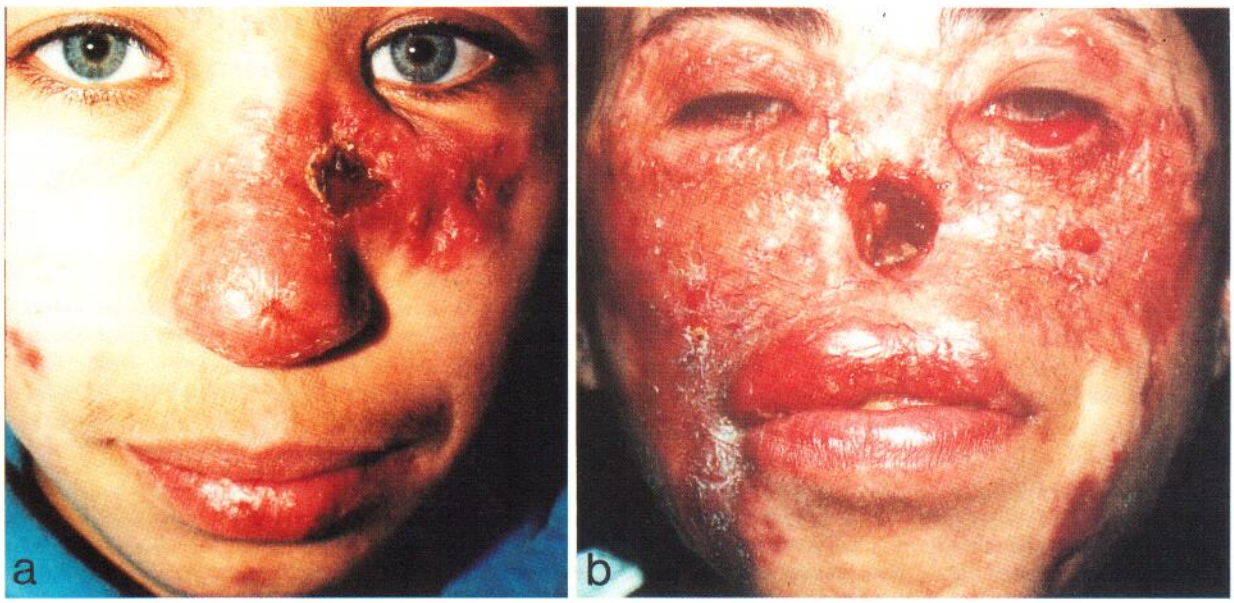

Fig. 1. (*a*) Erythematous, indurated plaque beginning from the nose (in 1989). (*b*) Lesion in 1992. Note the ectropion and the complete destruction of cartilage.

The associations between CD4 lymphocytopenia and infections caused by mycobacteria, *Pneumocystis carinii*, fungi and parasites have not been clearly understood (3). CD4 lymphocytopenia caused by infections or drugs resolves with the treatment of infections or withdrawal of drugs; in this population the CD4:CD8 ratio is greater than 1.0 (3). In our case, the CD4/CD8 ratio was less than 1.0 and CD4 lymphocytopenia persisted during the drug-free interval; these findings reject drugs and infection as etiologic factors. Common variable immunodeficiency causes CD4 lympocytopenia in adult life and is very important in the differential diagnosis of ICLD. Common variable immunodeficiency is caused by a B-cell maturation defect, and CD4:CD8 ratios of less than 1.0 are unusual (3). In ataxia-telangiectasia syndrome, there is both cellular and humoral immune deficiency. Cases of cutaneous granulomatous lesions and sarcoidosis associated with ataxia-telangiectasia syndrome have been reported. Unfortunately, in these patients, infectious agents which can lead to granulomatous histopathology have not been identified (6, 7). Recently, PCR facilitated differential diagnosis of granulomatous lesions of the skin. In our case, there was neither oculocutaneous telangiectasia nor cerebellar ataxia, which are the characteristics of this syndrome.

Our patient meets all of the criteria for ICLD proposed by the Center for Disease Control (CDC) (4). She also had paracentric inversion of chromosome 14, which carries the genes for T-cell receptors α and δ, which are thought to be responsible for the cellular immune function. Some of the cases in the literature reported as ICLD might turn out to be due to chromosomal abnormality, if evaluated by cytogenetic analysis. Response to treatment in skin tuberculosis depends on the disease stage and immune status of the patient. T-cell-dependent immunity plays an important role in resistance. Interferon-γ (IFN-γ) has a major function in the immune response to *Mycobacterium tuberculosis*. In AIDS patients with CD4 lymphocytopenia, IFN-γ secretion is decreased. However, the role of exogenously administered IFN-γ has not been clearly defined (1). A patient with avian tuberculosis and lupus vulgaris and anergy to *Mycobacterium avium* was reported to show a clinical positive response to a transfer factor preparation, which could have contained interferons (8).

Despite early treatment, the lesions in our patient showed progression. Resistance to treatment was probably associated with immune deficiency and chromosomal defect. None of the case reports reported in English language literature as ICLD has been associated with chromosomal abnormality. This patient with chromosomal abnormality associated with CD4 lymphocytopenia is an original case, and her resistance to therapy is probably due to immune deficiency. In the confirmation of the diagnosis of ICLD, cytogenetic analysis must be considered.

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