

Letter to the Editor

Editor,

We read with interest the case report published by von Bernuth et al. (1). We are following a patient whose clinical presentation is quite similar to that of the patient described by them.

Our patient, now a 20-year-old young man, started suffering from recurrent oral aphthous ulcers at the age of 16 years. At the age of 17, he also developed oral candidiasis and an endoscopy revealed *Candida* esophagitis and esophageal ulcers. Treatment with fluconazole was initiated and maintained due to frequent relapses of the oral candidiasis. Nevertheless, this treatment did not eliminate the frequent appearance of the major oral aphthous ulcers. Due to several episodes of rectal bleeding, he also underwent a colonoscopy with biopsy which did not reveal any pathological findings. Slit lamp examination of the eyes was normal. A patch test was negative. Laboratory work up revealed normal white blood cell counts and normal percentages and numbers of peripheral B and total T (CD_3^+) lymphocytes but low numbers of CD_4^+ lymphocytes ($200\text{--}400/\text{mm}^3$) with a reversed CD_4^+/CD_8^+ ratio. The percentage of $\gamma^+\delta^+$ T lymphocytes was 7.6%. HIV status was negative. Serum immunoglobulin levels were normal to high with protective levels of antibodies against tetanus and diphtheria toxoids, poliovirus, and measles, mumps and rubella viruses. A delayed-type hypersensitivity skin test with *Candida* antigen was positive. *In vitro* lymphocyte responses to mitogens (ConA, PHA and PWM) were mildly reduced and *in vitro* lymphocyte response to *Candida* antigen was normal.

ADA and PNP deficiencies were excluded. Neutrophil function tests (chemotaxis, bactericidal activity and superoxide generation) were normal. No autoantibodies were found and serum levels of FT₄, TSH, cortisol and PTH were all normal.

Our patient resembles the patient described by von Bernuth et al. (1) as both patients have a combination of idiopathic CD_4^+ lymphocytopenia,

recurrent aphthous ulcers, persistent oral candidiasis and candida esophagitis with ulcers. One differential diagnosis which was not mentioned by von Bernuth et al. (1) is Behçet's disease (BD). Recurrent major aphthous ulcers are common in patients with BD and are associated with a more severe, repeated and prolonged oral disease compared with recurrent minor aphthous ulcers (2). It was also found that the first manifestations of BD in children are almost exclusively in the form of oral ulcers (3). We could not make the diagnosis of BD in our patient as no other required criteria for diagnosis of the disease were observed throughout the follow-up period. He also tested negative for HLA-B51, which is associated with BD in Israel (4, 5).

One case of idiopathic CD_4^+ T lymphocytopenia associated with Behçet's-like syndrome was published recently. The adult patient described had recurrent oral and genital ulcers, oral and esophageal candidiasis, pansinusitis, and tested positive for HLA-B51 (6).

Of interest are the findings of increased numbers of peripheral T cells bearing the $\gamma^+\delta^+$ T-cell receptor in the patient described by von Bernuth et al. (1). Increased numbers of $\gamma^+\delta^+$ T cells have been demonstrated in patients with BD (7–9). Some of these cells were sensitized to the 65 kDa heat shock proteins (8). In BD patients, it was found that the $\gamma^+\delta^+$ T cells were in an activated stage whereas the $\alpha^+\beta^+$ T cells were not activated compared with controls (9).

Gamma-delta T cells play major roles in mucosal immunity acting as the first line of defense (10). Gamma-delta T cells can also modulate epithelial cell growth (11) and recognize structures presented by microorganisms as well as by stressed cells but not normal cells (12). Whether this is the immunological link that plays a direct role in the pathogenesis of a new syndrome of 'idiopathic CD_4^+ lymphocytopenia with recurrent aphthous ulcers and oral and esophageal candidiasis', or just the result

of the inflammatory process, has yet to be determined.

Y. Levy¹, M. Mukamel² and Y.L. Danon¹

¹Kipper Institute of Immunology and ²Rheumatology Unit, Schneider Children's Medical Center of Israel, Petah Tikva and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

References

1. VON BERNUTH H, KNOCHEL B, WINKLER U, ROESLER J, SCHLESIER M, GAHR M. Immunodeficiency with recurrent panlymphocytopenia, impaired maturation of B lymphocytes, impaired interaction of T and B lymphocytes, and impaired integrity of epithelial tissue: a variant of idiopathic CD₄⁺ T lymphocytopenia? *Pediatric Allergy Immunol* 2002; 13: 381–4.
2. KRAUSE I, ROSEN Y, KAPLAN I, et al. Recurrent aphthous stomatitis in Behcet disease: clinical features and correlation with systemic disease expression and severity. *J Oral Pathol Med* 1999; 28: 193–6.
3. KRAUSE I, UZIEL Y, GUEDJ D, et al. Mode of presentation and multisystem involvement in Behcet's disease: the influence of sex and age of disease onset. *J Rheumatol* 1998; 26: 1566–9.
4. BRAUTBAR C, CHAJEK T, BEN-TUVIA S, LAMM L, COHEN T. A genetic study of Behcet disease in Israel. *Tissue Antigens* 1978; 11: 113–20.
5. PAUL M, KLEIN T, KRAUSE I, MOLAD Y, NARINSKY R, WEINBERGER A. Allelic distribution of HLA B₅ in HLA B₅ positive Israeli patients with Behcet's disease. *Tissue Antigens* 2001; 58: 185–6.
6. VENZOR J, HUA Q, BRESSLER RB, MITANDA CH, HUSTON DP. Behcet's-like syndrome associated with idiopathic CD₄⁺ T lymphocytopenia, opportunistic infections and a large population of TCR $\alpha\beta$ CD₄⁺CD₈⁺ T cells. *Am J Med Sci* 1997; 313: 236–8.
7. FORTUNE F, WALKER J, LEHNER T. The expression of $\gamma\delta$ + cell receptor and the prevalence of primed activated and IgA-bound T cells in Behcet disease. *Clin Exp Immunol* 1990; 82: 326–32.
8. HASAN A, FORTUNE F, WILSON A, et al. Role of $\gamma\delta$ T cells in pathogenesis and diagnosis of Behcet's disease. *Lancet* 1996; 347: 789–94.
9. FREYSDOTTIR I, LAN S, FORTUNE F. Gamma delta T cells in Behcet disease (BD) and recurrent aphthous stomatitis (RAS). *Clin Exp Immunol* 1999; 118: 451–7.
10. JANEWAY CA Jr, JONES B, HAYDAY A. Specificity and function of T cells bearing $\gamma\delta$ receptors. *Immunol Today* 1988; 9: 73–6.
11. KOMANO H, FUJIURA Y, KAWAGUCHI M, et al. Homeostatic regulation of intestinal epithelia by intraepithelial $\gamma\delta$ T cells. *Proc Natl Acad Sci USA* 1995; 92: 6147–51.
12. TANAKA Y, MORITA CT, TANAKA Y, et al. Natural and synthetic non-peptide antigens recognized by human $\gamma\delta$ T cells. *Nature* 1995; 375: 155–8.