

Case Report

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?

von Bernuth H, Knöchel 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?

Pediatr Allergy Immunol 2002; 13: 381–384. © 2002 Blackwell Munksgaard

Idiopathic CD4⁺ T lymphocytopenia (ICL) has been defined as a cause of immunodeficiency with a variable clinical course and an unknown etiology. Here we describe a now 18-year-old boy with ICL, chronic mucocutaneous candidiasis (CMC), recurrent abscesses, and relapsing aphthous and ulcerous lesions. In addition to ICL the patient frequently showed a panlymphocytopenia. An increased percentage of $\gamma\delta^{+}$ T lymphocytes and IgD⁺ IgM⁺ B lymphocytes, and a decreased percentage of CD21⁺ B lymphocytes, were observed. *In vitro* assays showed normal T-cell responses to candidin and T-cell mitogens, but impaired B-cell responses to pokeweed mitogen (PWM). B-cell maturation after stimulation with *Staphylococcus aureus* Cowan I (SAC) and interleukin 2 (IL-2) was nearly normal. The clinical course of the patient improved substantially on administration of constant low-dose therapy with fluconazole.

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Key words: idiopathic CD4⁺ T lymphocytopenia; common variable immunodeficiency; chronic mucocutaneous candidiasis

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Accepted 25 January 2002

Primary immunodeficiencies as a result of defects in lymphocytes represent a large heterogeneous group of conditions with highly variable clinical courses. Although many immunodeficiencies can be defined by distinct molecular defects (1), disorders such as common variable immunodeficiency (CVID) (2), chronic mucocutaneous candidiasis (CMC) (3), and idiopathic CD4⁺ T lymphocytopenia (ICL) (4) still represent heterogeneous conditions with an unknown etiology. Here we describe a now 18-year-old patient with ICL, relapsing CMC, abscess formation, aphthous and ulcerous lesions, and recurrent

panlymphocytopenia. To our knowledge relapsing sterile aphthous and ulcerous lesions have not been reported in ICL to date.

Case report

Our patient has suffered since birth from recurrent mucocutaneous candidiasis, mainly of the oral cavity but also of the nails and the genitourinary tract. The candidiasis was controlled with ketoconazole and fluconazole but relapsed as soon as the antimycotic therapy was

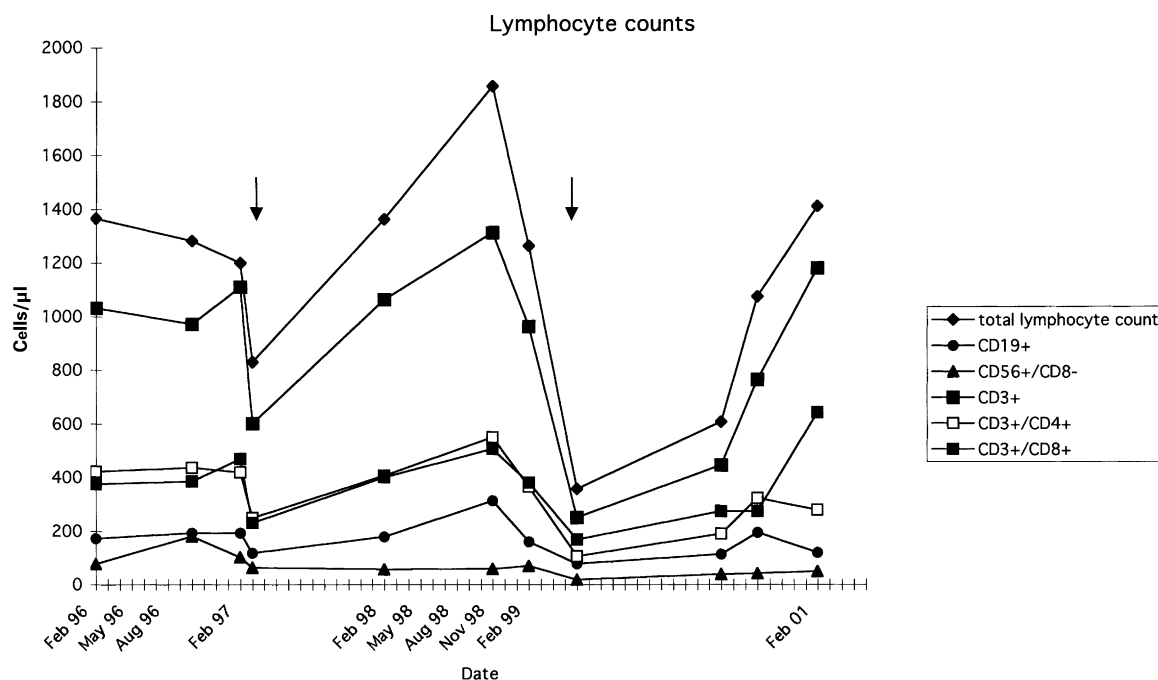


Fig. 1. Lymphocyte counts in peripheral blood from February 1996 to February 2001.

stopped. The patient also suffered from recurrent perianal abscesses caused by *Staphylococcus aureus* and *Actinomyces* spp., which required surgical intervention and subsequent antibiotic therapy. In addition to opportunistic infections, the patient suffered from recurrent, obviously sterile, aphthous and sometimes even deep ulcerous mucocutaneous lesions. During the most pronounced episode the patient developed disseminated aphthae and ulcers reaching from the oral cavity to the duodenum (Figs 1 and 2), which caused such severe pain that nutrition was seriously impaired and the patient lost 10 kg in weight. On one occasion the patient presented with ≈ 30 disseminated *Mollusca contagiosa*. In infancy an infection with varicella zoster virus and a herpes zoster infection took an uncomplicated course. Growth and mental development of our patient have been normal. His family history was remarkable, for his now 25-year-old brother recently developed an acute lymphatic T-cell leukemia with a translocation 11 $\rightarrow$ 22 and a deletion in the 9q34 locus. No such translocation or deletion was detected in our patient.

The levels of total immunoglobulin G (IgG) (6.2–6.8 g/l, normal range: 7–16 g/l) and total immunoglobulin M (IgM) (0.2–0.48 g/l, normal range: 0.4–2.1 g/l), were decreased on several occasions; the levels of IgG₁ (4.44 g/l, normal range: 5.15–9.2 g/l), IgG₂ (0.68 g/l, normal range: 1.5–4.9 g/l) and IgG₄ (<0.04 g/l, normal range: 0.08–1.51 g/l) have been decreased on follow-up of the patient at our clinic since the age of 12

(February 96). Immunoglobulin A (IgA), immunoglobulin D (IgD), immunoglobulin E (IgE), and IgG₃ levels were normal. Antibody titers against candida, varicella zoster, herpes simplex, Epstein–Barr virus, and cytomegalovirus were all negative. Although the patient had been vaccinated, his antibody titers against diphtheria and tetanus toxoid were low and increased only weakly after several boosters. Antibody titers against *Streptococcus pneumoniae* were normal.

We observed a constant CD4⁺ T lymphocytopenia (104–404 CD4⁺ cells/ μ l), and, to date, two episodes of panlymphocytopenia (CD3⁺ T cells: 249–762/ μ l; CD3⁺ CD8⁺ T cells: 100–272/ μ l; CD56⁺ CD8⁺ natural killer (NK) cells: 17–62/ μ l, and once CD19⁺ B cells: 76/ μ l). These

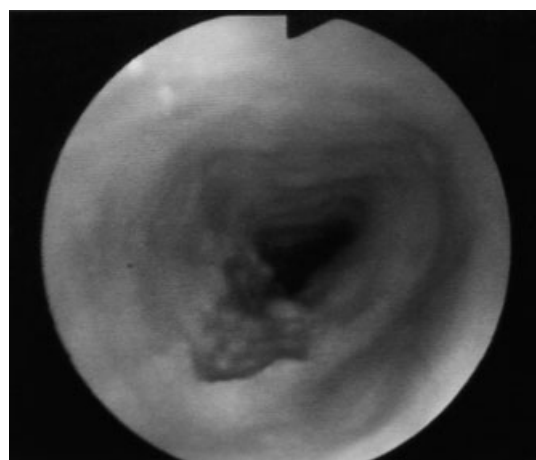


Fig. 2. Esophagoscopy in June 1999. Deep ulcer in the middle third of the esophagus.

episodes were accompanied by a severe candida-esophagitis and by the most severe manifestation of aphthae and ulcers in the upper gastrointestinal tract (Figs 1 and 2). The number of granulocytes and platelets was always normal. Adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP) deficiency were excluded.

The percentage of $\gamma^+\delta^+$ T lymphocytes was increased (26%), as was the percentage of IgD⁺ IgM⁺ B lymphocytes (94% of all B lymphocytes, normal range: 45–90%). The percentage of CD21⁺ B lymphocytes was decreased (83% of all B lymphocytes, normal level > 88%). B lymphocytes were not activated by pokeweed mitogen (PWM), but proliferated and developed to immunoglobulin-secreting plasma cells after stimulation with *Staphylococcus aureus* Cowan I (SAC) and interleukin-2 (IL-2). Stimulation with candidin and T-cell mitogens led to a normal proliferative response.

The patient repeatedly had a negative human immunodeficiency virus (HIV) status. Basal thyroid-stimulating hormone (TSH), morning cortisol and Ca²⁺, as screening parameters for a polyendocrinopathy, as well as levels of auto-antibodies (anti-neutrophil cytoplasmic perinuclear antigens [pANCA]; anti-neutrophil cytoplasmic antigens [cANCA]; against exocrine pancreas [PAB]; against goblet cells [GAB]), were normal. In his 16th year of life the patient developed a mild splenomegaly.

Discussion

In CMC, T lymphocytes are considered to be selectively anergic against *Candida* spp. This is usually reflected by a poor *in vitro* response against candidin, which is contrasted by a rather strong humoral response against *Candida*. Inconsistent with this our patient exhibited no humoral, and a normal cellular, *in vitro* response to candidin. CMC was often reported to be associated with polyendocrinopathies, autoimmune diseases, and interstitial keratitis (3). None of these was observed in our patient. Further primary immunodeficiencies, which may also manifest with CMC, are the biotin-dependent carboxylase defect and the major histocompatibility complex (MHC) II defect. The first usually presents with dermatitis and alopecia; the second usually presents early in infancy with chronic diarrhea and severe viral infections. None of these clinical features was observed here.

A normal humoral response against polysaccharide antigens (*S. pneumoniae*) and an impaired response against protein antigens such as tetanus

and diphtheria toxoid, in combination with an impaired *in vitro* maturation of B lymphocytes after stimulation with PWM, but a normal maturation after stimulation with SAC and IL-2, suggest a normal T-cell-independent B-lymphocyte response and an impaired T-cell-dependent response. The increased percentage of IgD⁺ IgM⁺ B lymphocytes and the decreased percentage of CD21⁺ B lymphocytes reflect a grossly normal antigen-independent maturation but could fit to an altered antigen-dependent maturation of B lymphocytes. This block may lead to the lowered levels observed of IgG, IgG₁, IgG₂, and IgG₄. In conclusion, our patient's condition could reflect a variant of CVID, probably group C (2). However, CVID itself is an umbrella term that groups similar clinical and immunological features, but it does not describe distinct entities defined at the molecular level (2).

Frequent CD4⁺ T lymphocytopenia with counts of <300 CD4⁺ cells/ μ l, absence of HIV-1 and HIV-2 infection, a somewhat stable clinical course, and decreased immunoglobulin levels, are consistent with the diagnosis of ICL (4). An increase of $\gamma^+\delta^+$ T lymphocytes and panlymphocytopenia in ICL have been described previously (5–7). However, ICL with recurrent panlymphocytopenia (Fig. 1) and accompanying aphthous lesions has not previously been described. In our patient, CD4⁺ T lymphocytopenia was not accompanied by accelerated apoptosis of CD4⁺ T lymphocytes, as previously described (8). As late-onset forms of ADA and PNP deficiency have been reported (9,10), we also excluded these rare conditions. In a few patients ICL has been treated with interferon- γ , IL-2 (6) and even bone marrow transplantation (7). In our patient, low-dose fluconazole was able to prevent candidiasis. Other opportunistic infections were well controlled by limited courses of antibiotic therapy. The comparison between severe clinical courses of ICL described in the literature and our patient emphasizes the broad variability of this condition.

It is obviously not possible to group our patient to a molecularly defined immunodeficiency based solely on his clinical features and specific alterations in immune status. Our findings of elevated $\gamma^+\delta^+$ T-cell receptor (TCR) T cells and CD4⁺ lymphopenia are, however, suggestive of an impaired development to $\alpha^+\beta^+$ T cells. This defect could further lead to the impaired interaction of T and B lymphocytes. In addition, the molecule leading to the immunodeficiency described here may also play a common role for proliferation and maturation of $\alpha^+\beta^+$ TCR T

lymphocytes and for the integrity of epithelial tissue.

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