Review Article

JRAD Journal of Research and Advancement in Dentistry

J Res Adv Dent 2017;6:2:83-89.

Idiopathic CD-4 Lymphocytopenia: A Review

Ashima Bali Behl[1*] Rajiv Bali[2] Vikram Bali[3] Roshani M Chawla[4] Ratnamala Gadge[5] Pranjan Mitra[6]

[1]Reader, Department of Oral Medicine, Diagnosis & Radiology, Baba Jaswant Singh (BJS) Dental College & Hospital. Ludhiana, Punjab, India.
[2]Professor and Head, Department of Conservative & Endodontics, BRS Dental College, Barwala, Panchkula, India.
[3]Reader, Department of Periodontology and Oral Implantology, BRS Dental College, Barwala, Panchkula, India.
[4]Senior Lecturer, Department of Public Health Dentistry, VYWS Dental College & Hospital, Amravati, Maharashtra, India.
[5]Tutor, Department of Public Health Dentistry, VYWS Dental College & Hospital, Amravati, Maharashtra, India.
[6]Senior Lecturer, Department of Public Health Dentistry, Institute of Dental Education and Advanced Studies, Gwalior, Madhya Pradesh, India.

ABSTRACT

Background: Idiopathic CD4+ T-cell lymphocytopenia (ICL) is a rare disorder of immune system with heterogeneous clinical manifestations and immunologic profile. This is a rare condition, which was first defined in 1992 by the Centers for Disease Control and Prevention. It is marked by a CD4_ count that is less than 300 cells/mm3 without human immunodeficiency virus infection. Its course differs from that of AIDS in that although patients with this disorder may develop opportunistic infections. Hence, the clinicians should be aware of this rare immunologic disorder and that a decrease in the CD4 count is not a hallmark for Human Immunodeficiency Virus infection, but could be due to other idiopathic causes as well.

Keywords: Idiopathic CD4+ lymphocytopenia, HIV negative CD4+ lymphocytopenia, CD 4 – T cell lymphocytopenia.

INTRODUCTION

Autoimmune manifestations have long been perceived as paradoxical in patients with Primary Immune Deficiencies (PID). More than one hundred cases of PID have been identified so far. Human immunodeficiency virus (HIV) infection is known to be typically characterized by a profound depression in CD4' lymphocyte numbers in peripheral blood [1 - 6]. It is now clear that infection with HIV I & II can result in depletion of CD4 T – helper lymphocytes & development of AIDS.

In the past 10-12 year, several groups have been described as HIV negative patients with CD4 lymphocyte depletion in conjunction with opportunistic infections or Kaposi sarcoma termed as Idiopathic CD4 T – Lymphocytopenia (ICL). According to Centers for Disease Control and Prevention (CDC) in 1992 [(1, 2)], ICL is a rare syndrome characterized by the depletion in the CD4 T – cells without evidence of HIV infection. The initial identification was based upon several cases of severe opportunistic infections and CD4 T lymphocytopenia in the absence of HIV infection. The clinical, immunologic, and epidemiologic features of this syndrome differ substantially from those of HIV infection. The suggested criteria for diagnosis:

(i) Absolute CD4 T lymphocyte count less than 300/ml or less than 20% of total T cells on more than 1 occasion.
(ii) No evidence of HIV infection.
(iii) Absence of any defined immune deficiency disease or therapy associated with depressed levels of $CD4^+$ T lymphocytes.

Episodic oral erythematous candidiasis and persistent angular cheilitis are an indication of opportunistic infection - which may be expected in a reduced state of immunocompetence. The rate at

Received: Jan. 22, 2017: **Accepted**: Mar. 11, 2017
***Correspondence Dr. Ashima Bali Behl.**
Department of Oral Medicine, Diagnosis & Radiology, Baba Jaswant Singh (BJS) Dental College & Hospital. Ludhiana, Punjab, India.
Email: ashimabali2@yahoo.co.in

pISSN 2278-0076
eISSN 2321-9270

which such CD4 lymphocytopenia occurs varies substantially between individuals [7, 8, 9]. Since risk of acquired immunodeficiency syndrome (AIDS) is small until the CD4 lymphocyte count is low [9, 10, 11], this variation accounts in large part for the extensive differences between individuals in the time taken for AIDS to develop after infection with HIV [7, 11]. In addition to inter-individual variation in the rate of $CD4^+$ lymphocyte depletion, patients also vary in the $CD4^+$ lymphocyte count at which AIDS develops [12 - 16].

Etiology

Idiopathic CD4 lymphocytopenia is a rare immunodeficiency of unknown cause that clinically closely resembles HIV infection, but the absence of this and related viruses by means of all serologic and molecular methods of detection is a crucial element of the case definition [17]. Patients have persistently low CD4 T-cell counts (<300 cells/mm3) and experience opportunistic infections, autoimmune disease, and hematologic malignancies. The etiology of ICL is not clear [18, 19]. In some cases, low CD4 T lymphocyte counts may reflect transient responses to infections or other conditions or even normal clinical status in asymptomatic patients. In other patients, low CD8 T lymphocyte counts and low immunoglobulin levels (especially IgG) cause suspicion of possible generalized immunodeficiency disorders. ICL may be found in some patients with diseases associated with immunosuppression (Kaposi's sarcoma) [20, 21] and lymphoma [22, 23] . There is no evidence for a transmissible agent or an environmental cause of the disease [24, 25]. Sexual and household contacts are not affected and persons who donated blood to the affected patients showed normal CD4 T lymphocyte counts. There is no geographic clustering of affected patients.

Heterogeneous immunologic profiles have been reported so far in ICL patients. Interleukin-2 (IL-2) has been reported to increase CD4 T-lymphocyte count and improve the outcome in a few ICL patients. Mechanistic studies of T-cell function in ICL remain scarce. Decreased T-cell responses as well as increased T-cell activation have been reported (26, 27) .CD8 T-cell counts remain in the normal range or are often decreased in ICL (28). Functional investigations have revealed an increased propensity of ICL T cells to undergo apoptosis, a process partially dependent on FAS expression(18, 20). Markers for activation and turnover are increased in CD4 T cells but not in CD8 T cells, pointing at a specific alteration of the CD4 T-cell compartment(28). Another factor that may contribute to the CD4 T-cell defect is a decreased clonogenic capacity of the bone marrow (BM) in ICL patients(29). A frequent alteration observed in ICL consists is increased levels of IL-7 in peripheral blood, consistent with the triggering of a homeostatic response to restore normal CD4 T-cell counts(30, 31). The literature indicates that neither human retroviruses (HIV-1, HIV-2, HTLV-I, or HTLV-II) nor other transmissible agents play a role in the pathogenesis of ICL (1, 2, 6). Patients with ICL are registered worldwide (34)

The underlying pathophysiology of this unusual disorder is yet to be ascertained conclusively. Infectious etiology have been ruled out. Some researchers have considered ICL to be an extreme of the spectrum of common variable immunodeficiency(29). The recent views on potential mechanism for CD4 depletion include FAS/FAS ligand over expression leading to apoptosis (30) defective cytokine (tumor necrosis factor and interferon-gamma) production, regenerative failure of haematopoietic stem/progenitor cells(31), impaired thymic T-cell maturation(32), autoantibody against CD4 cells(33). The molecular basis of ICL is still unknown. It has been hypothesized that expression or function of CXCR4 could be altered in ICL CD4_ T cells.

Studies have reported the occurrence of CD4 – lymphocytopenia in children also (3,4,5). Only few pedriatic cases with this type have been reported from India. The definition of idiopathic CD4+ T-lymphocytopenia among children as given by the CDC includes the following criteria (6) :

1. A CD4+ T-cell count of less than 1000 cells per cubic millimeter in children 0 to 23 months of age and of less than 300 cells per cubic millimeter in children 2 to 12 years of age, or a CD4+ T-lymphocyte count that is less than 20 % of total lymphocytes, on at least two separate measurements;

2. No serologic evidence of infection on HIV testing (even if the child's mother is HIV-seropositive);

3. Absence of any defined immunodeficiency or therapy associated with T-cell depletion.

Clinical features

ICL was initially considered to be an extremely rare syndrome [34, 35]. There are numerous reports of ICL associated with different diseases and clinical conditions [36, 37, 38]. Opportunistic infections, mostly seen in HIV patients, are the most common among them [39-44]. Patients have persistently low CD4 T-cell counts (<300 cells/mms3) and experience opportunistic infections, autoimmune disease, and hematologic malignancies.Clinically ICL may present with a spectrum ranging from asymptomatic to serious infections. Opportunistic infections like candida, cytomegalovirus, Mycobacterium tuberculosis have been described in adult patients with ICL [34]. Reports have suggested that around 50% of these patients demonstrate at least one skin manifestation ranging from infections to atopic dermatitis to basal cell carcinoma [45].

The repertoire of lymphocyte abnormalities in ICL is distinct from that found in HIV. In ICL generally there is lymphopenia, as unlike HIV infection, the CD8+ counts do not rise [39]. As compared to HIV infected, these patients have decreased counts of CD8+ cells & more lymphopenia [24, 46] ICTL has been associated with various cutaneous disorders including psoriasis[47], cutaneous T-cell lymphoma [48], atopic dermatitis [49], skin carcinomas including squamous cell carcinoma in situ and basal cell carcinoma[46], chronic pruritic papules[50] and cutaneous infections such as papillomavirus, herpes zoster, molluscum contagiosum, and tinea corporis[45, 51].

Manifestations of proven or suspected autoimmune mechanism associated with common variable immunodeficiency

Haematological
• Autoimmune cytopenias
○ Autoimmune haemolytic anemia
○ Idiopathic thrombocytopenic purpura
○ Autoimmune neutropenia
• Gastro-intestinal
○ Pernicious anemia
○ Atrophic gastritis
○ Celiac disease
○ Primary biliary cirrhosis
○ Inflammatory bowel disease
• Rheumatological
○ Sjögren syndrome
○ Systemic lupus erythematosus
○ Rheumatoid arthritis
○ Chronic juvenile arthritis
○ Vasculitis
• Endocrinological
○ Hashimoto's thyroiditis
○ Type 1 diabetes mellitus
• Dermatological
○ Vitiligo
○ Alopecia
• Neurological
○ Guillain-Barré syndrome

Aside from the low CD4 lymphocyte counts, immunologic findings in these patients are distinct from abnormalities found in HIV infection [24]. In general, immunologic evaluation might only reveal reduction in the number or activity of NK cells (CD3 2 and CD161 or CD56), with the preservation of T cells and B cells. A very small percentage of patients with ICL have hypergammaglobulinemia that is typically seen in HIV infected patients. Almost all of them have normal or slightly low levels of immunoglobulins [24, 52]. As compared to HIV-infected, these patients have lower counts of CD8 cells and more lymphopenia. CD4 CT cells counts are relatively stable, without progression over time [24, 46]. In these patients, care should be taken to exclude other immunodeficiencies known to be associated with defects of NK cell number or function, such as SCID [53], Chediak-Higashi syndrome, X-linked lymphoproliferative disorder, CD40 ligand deficiency, Wiskott-Aldrich syndrome, X-linked agammaglobulinemia and nuclear factor (NF) kB essential modulator (NEMO) deficiency [54].

Treatment

The optimal treatment for this disorder has not been determined. Until the date, the treatment of ICL is mainly symptomatic, with emphasis on

prevention and treatment of opportunistic infections. Some novel approaches like allogenic bone marrow transplantation [55], IL-2 administration [56] have been tried in adult patients and may prove beneficial in the future. The natural history of ICL is variable. Though most reports suggest that these patients have a stable course unlike HIV/AIDS but mortality remains a high probability due to the recurrent serious opportunistic infections.

According to the report by Wilhelm in 2001, several different phases of an immunologic disorder have responded to IL-2 therapy.

- In the first phase, idiopathic CD4 T lymphocytopenia was asymptomatic and discovered only by accident.
- The second phase was characterized by monoclonal immunoglobulin increases and associated renal failure manifested by increased levels of creatinine, plus anemia, wasting, and failure to respond to conventional therapies for multiple myeloma.
- A third phase, involved IL-2 therapy with alleviation of the major disease manifestations. CD4 T cells increased, and the monoclonal gammopathies and creatinine levels decreased.

CONCLUSION

Autoimmune manifestations are frequent and often multiple in patients with PID. The diagnosis of PID should be made early in disease evolution since it may influence the therapeutic strategy. ICL although a rare entity, should be included in the differential diagnosis of unexplained opportunistic infections and suspected T-cell disorder.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Update: CD41 T-lymphocytopenia in persons without evident HIV infection—United States. MMWR 41, 578–579, 1992.

2. Centers for Disease Control, Update: CD41 T-lymphocytopenia in persons without evident HIV infection—United States. JAMA 268, 1252, 1992.

3. Kanno H, Sasaki M, Kumagai H et al. Epstein-Barr viruspositive malignant lymphoma of salivary gland developing in an infant with selective depletion of CD4-positive lymphocytes. Leuk Lymphoma 2007; 48: 183-186.

4. Tanaka S, Teraguchi M, Hasui M, Taniuchi S, Ikemoto Y, Kobayashi Y. Idiopathic CD4+ T-lymphocytopenia in a boy with Down syndrome. Report of a patient and a review of the literature. Eur J Pediatr 2004; 163: 122-123.

5. Pasic S, Minic P, Dzudovic S, Minic A, Slavkovic B. Idiopathic CD4+ lymphocytopenia and juvenile laryngeal papillomatosis. Pediatr Pulmonol 2005; 39: 281-283

6. Smith DK, Neal JJ, Holmberg SD, Centers for Disease Control. Idiopathic CD4+ T-Lymphocytopenia Task Force. Unexplained opportunistic infections and CD4+ Tlymphocytopenia without HIV infection- an investigation of cases in the United States. N Engl J Med 1993; 328: 373-379.

7. Phillips AN, Lee CA, Elford J, et al. Serial CD4' lymphocyte counts and the development of AIDS. Lancet 1991; 337: 389-392.

8. Veugelers PJ, Schecter MT, Tindall B, et al. Differences in time from HIV seroconversion tu CD4' lymphocyte end-points and AIDS in cohorts of homosexual men. AIDS 1993; 7: 1325-1329.

9. Munoz A, Schrager LK, Bacellar H, et al. Trends m the incidence of outcomes defining acquired immunodeficiency syndrome (AIDS) in the Multicenter AIDS Cohort Study: 1985-1991. Am J Epidemiol 1993; 137: 423-438.

10. Masur H, Ognihene FP, Yarchoan R, et al. CD4' counts as predictors of opportunistic pneumonias in human immunodeticiency virus (HIV) infection. Ann Intern Med 1989; 111: 223-231.

11. Phillips AN, Pezzotti P, Cozzi Lepri A, Rezza G, Italian Seroconversion Study. The CD4' lymphocyte count as determinant of the time from HIV seroconversion to AIDS and death from AIDS: Evidence from the Italian Seroconversmn Study. AIDS 1994; 8: 1299-305

12. Crow SM, Carlin JB, Stewart KI, Lucas CR, Hoy JF. Predictive value of CD4+ lymphocyte numbers for the development of opportunistic infections and malignancies in HIV-infected persons. J Acquir Immune Defic Syndr 1991; 4: 770-776.

13. Schwartlander B, Horshurgh CR, Hamouda 0, Skrahis H, Koch MA. Changes in the spectrum of AIDS-defining conditions and decrease in CD4' lymphocyte counts at AIDS manifestation in Germany from 1986 to 1991. AIDS 1992; 6: 413-420.

14. Van Leeuwen R, van den Hurk PHJ, Mulder JW, et al.. Opportunistic infections as measure of immunodeficiency in human immunodeficiency virus (HIV) infection. In Janossy G, Autran B, Miedema F, Eds. Immunodeficiency in HIV-1 Infections and AIDS. EC/FERS/MRC Workshop tm Immunodeficiency in HIV-1 Infections, Windsor, Surrey, 1991. Basel: Karger; 1992.

15. Pedersen C, Gerstoft J, Tauns I', Lundgren JD, Gtitzsche PC, Buhl M, Salim Y, Schmidt K. Opportunistic infections and malignancies in 231 Danish AIDS patients. AIDS 1990; 4: 233-238.

16. Miro JM, Buira E, Gallart T, et al. CD4' lymphocytes and oppertunistic infections and neoplasms in patients with the human immunodeficiency virus. Med Clin (Barc) 1994; 102: 556-570.

17. Tanaka S, Teraguchi M, Hasui M, Taniuchi S, Ikemoto Y, Kobayashi Y. Idiopathic CD41 T-lymphocytopenia in a boy with Down syndrome. Report of a patient and a review of the literature. Eur J Pediatr 2004;163:122-3

18. Laurence J, Mitra D, Steiner M, Lynch DH, Siegal FP, Staiano-Coico L. Apoptotic depletion of CD4_ T cells in idiopathic CD4_ T lymphocytopenia. J Clin Invest. 1996; 97(3):672-680..

19. Roger PM, Bernard-Pomier G, Counillon E, Breittmayer JP, Bernard A, Dellamonica P. Overexpression of Fas/CD95 and Fas-induced apoptosis in a patient with idiopathic CD4_ T lymphocytopenia. Clin Infect Dis. 1999; 28(5):1012-1016.

20. Garcia-Silva, J., Almagro, M., Pena, C., Lopez Calvo, S., Castro, A., Soriano, V., and Fonseca, E., CD41 T-lymphocytopenia, Kaposi's sarcoma, HHV-8 infection, severe seborrheic dermatitis, and onychomycosis in a homosexual man without HIV infection. Int. J. Dermatol. 38, 231–233, 1999.

21. Hernandez, D. E., Fernandez, L., Azuaje, C., and Tassinari, P., Idiopathic CD41 T-cell lymphocytopenia syndrome associated with immunodeficiency diseases. Sangre (Barcelona). 44, 392– 393, 1999.

22. Longo, F., Hebuterne, X., Michiels, J. F., Maniere, A., Caroli- Bosc, F. X., and Rampal, P., Multifocal MALT lymphoma and acute cytomegalovirus gastritis revealing CD4 lymphopenia without HIV infection. Gastroenterol. Clin. Biol. 23, 132–136, 1999.

23. Quiles, I., Anaut, P., Cibrian, F., Gainzarain, J., Vega, L., and Andia, A., Idiopathic CD41 T-lymphocytopenia with opportunistic infection and non-Hodgkin's lymphoma. J. Intern. Med. 238, 183–184, 1995.

24. Spira, T. J., Jones, B. M., Nicholson, J. K., Lal, R. B., Rowe, T., Mawle, A. C., Lauter, C. B., Shulman, J. A., and Monson, R. A., Idiopathic CD41 T-lymphocytopenia—an analysis of five patients with unexplained opportunistic infections. N. Engl. J. Med. 328, 386–392, 1993.

25. Smith DK, Neal JJ, Holmberg SD, The Centers for Disease Control Idiopathic CD4CT-Lymphocytopenia Task Force. Idiopathic Cd4C T-lymphocytopenia e17 Unexplained Opportunistic infections and CD4CT-lymphocytopenia without HIV infection—an investigation of cases in the United States. N Engl J Med 1993; 328:373–9.

26. Walker UA, Warnatz K. Idiopathic CD4 lymphocytopenia.Curr Opin Rheumatol. 2006; 18(4):389- 395.

27. Netea MG, Brouwer AE, Hoogendoorn EH, et al. Two patients with cryptococcal meningitis and idiopathic CD4 lymphopenia: defective cytokine production and reversal by recombinant interferon- gamma therapy. Clin Infect Dis. 2004; 39(9): e83-87.

28. Zonios DI, Falloon J, Bennett JE, et al. Idiopathic CD4_ lymphocytopenia: natural history and prognostic factors. Blood. 2008; 112(2):287-294.

29. Lebranchu Y, Thibault G, Degenne D et al. Abnormalities in CD4+ T lymphocyte subsets in patients with common variable immunodeficiency. Clin Immunol Immunopathol 1991; 61: 83-92.

30. Roger PM, Bernard-Pomier G, Counillon E et al. Overexpression of Fas/CD95 and Fas-induced apoptosis ina patient with idiopathic CD4+ T lymphocytopenia. Clin Infect Dis 1999; 28: 1012-1016.

31. Isgro A, Sirianni MC, Gramiccioni C et al. Idiopathic CD4+ lymphocytopenia may be due to decreased bone marrow clonogenic capability. International Arch Allergy Immunol 2005; 136: 379-384.

32. Fru¨wirth M, Clodi K, Heitger A et al. Lymphocyte diversity in a 9-year-old boy with idiopathic CD4+ T-cell lymphocytopenia. International Arch Allergy Immunol 2001; 125: 80-85.

33. Salit RB, Hankey KG, Yi R et al. Detection of CD4+ T-cell antibodies in a patient with idiopathic CD4+ T lymphocytopenia and cryptococcal meningitis. Br J Haematol 2007; 139: 133-137.

34. Smith DK, Neal JJ, Holmberg SD, The Centers for Disease Control Idiopathic CD4CT-Lymphocytopenia Task Force. Idiopathic Cd4C T-lymphocytopenia e17 Unexplained Opportunistic infections and CD4CT-lymphocytopenia without HIV infection—an investigation of cases in the United States. N Engl J Med 1993; 328:373–9.

35. Fauci AS. CD4CT-lymphocytopenia without HIV infection— no lights, no camera, just facts. N Engl J Med 1993;328: 429–31.

36. Sheppard H, Winkelstein W, Lang W, Charlebois E, Heymann DL, Belsey E, Esparza JG, Laurence J, Corboy JR, Stevens SR, Griffiths TW, Cooper KD, Smith DK, Neal JJ, Holmberg SD. CD4CT-lymphocytopenia without HIV infection. N Engl J Med 1993;328:1847–50.

37. Aldrich J, Gross R, Adler M, et al. The effect of acute severe illness on CD4C lymphocyte counts in nonimmunocompromised patients. Arch Intern Med 2000;160:715–6.

38. Busse PJ, Cunningham-Rundles C. Primary leptomeningeal lymphoma in patient with concomitant CD4Clymphocytopenia. Ann Allergy Asthma Immunol 2002;88:339–42.

39. Spira TJ, Jones BM, Nicholson J, Lal RB, Rowe T, Mawle AC, Lauter CB, Shulman JA, Monson RA. Idiopathic CD4CTlymphocytopenia— an analysis of five patients with unexplained opportunistic infections. N Engl J Med 1993;328: 386–92.

40. Nakahira M, Matsumoto S, Mukushita N, Nakatani H. Primary aspergillosis of the larynx associated with, CD4(C) T lymphocytopenia. J Laryngol Otol 2002;116:304–6.

41. Stetson CL, Rapini RP, Tyring SK, Kimbrough RC. CD4CT lymphocytopenia with disseminated HPV. J Cutaneous Pathol 2002;29:502–5.

42. Etienne M, Gueit I, Abboud P, Pons JL, Jacquet S, Caron F. Fusobacterium nucleatum hepatic abscess with pylephlebitis associated with idiopathic CD4(C) T lymphocytopenia. Clin Infect Dis 2001;32:326–7.

43. Matsuyama W, Tsurukawa T, Iwami F, Wakimoto J, Mizoguchi A, Kawabata M, Osame M. Two cases of idiopathic CD4(C) T-lymphocytopenia in elderly patients. Internal Med 1998;37:891–5.

44. Seligmann M, Autran B, Rabian C, Ferchal F, Olive D, Echard M, Oksenhendler E. Profound and possibly primary idiopathic CD4(C) T lymphocytopenia in a patient with fungal infections. Clin Immunol Immunopathol 1994;71: 203–7.

45. Ohashi DK, Crane JS, Spira TJ, Courrege ML. Idiopathic CD4+ T-cell lymphocytopenia with verrucae, basal cell carcinoma and chronic tinea corporis infection. J Am Acad Dermatol 1994; 38: 889-891.

46. Duncan RA, von Reyn CF, Alliegro GM, Toossi Z, Sugar AM, Levitz SM. Idiopathic CD4CT-lymphocytopenia—four patients with opportunistic infections and no evidence of HIV infection. N Engl J Med 1993; 328:393–8.

47. Hardman CM,Baker BS, Lortan J, Breuer J, Surentheran T,Powles A, et al. Active psoriasis and profound CD4+ lymphocytopenia. Br J Dermatol 1997; 136:930-2.

48. Grossman D, Lewis DE, Ballas ZK, Duvic M. Idiopathic CD4+ T lymphocytopenia in a patient with mycosis fungoides. J Am Acad Dermatol 1994; 31:275-6.

49. Goodrich AL,Tigelaar RE,Watsky KL, Heald PW. Idiopathic CD4+ lymphocyte deficiency: report of an unusual case associated with atopic dermatitis and allergic contact dermatitis and review of the literature. Arch Dermatol. 1993; 129:876-8.

50. Wakeel RA, Urbaniak SJ, Armstrong SS, Sewell HF, Herriot R, Kernohan N, et al. Idiopathic CD4+ lymphocytopenia associated with chronic pruritic papules. Br J Dermatol 1994;131:371-5.

51. Manchado Lopez P, Ruiz de Morales JM, Ruiz Gonzalez I, Rodriguez Prieto MA. Cutaneous infections by papillomavirus, herpes zoster and Candida albicans as the only manifestation of idiopathic CD4+ T lymphocytopenia. Int J Dermatol 1999; 38: 119-21.

52. Ho DD, Cao Y, Zhu T, Farthing C, Wang N, Gu G, Schooley RT, Daar ES. Idiopathic CD-4 CT-lymphocytopenia—immunodeficiency without evidence of HIV infection. N Engl J Med 1993; 328:380–5.

53. Vitale M., Zimmer J., Castriconi R., Hanau D., Donato L., Bottino C. Analysis of natural killer cells in TAP2-deficient patients: expression of functional triggering receptors and evidence for the existence of inhibitory receptor(s) that prevent lysis of normal autologous cells. Blood 2002; 99: 1723-9.

54. Orange JS. Human natural killer cell deficiencies and susceptibility to infection. Microbes Infect 2002; 4:1545-58.

55. Peterson EJ, Arska MR, Dekkar AW et al. Allogeneic bone marrow transplantation can restore CD4+ T-lymphocyte count and immune function in idiopathic CD4+ Tlymphocytopenia. Bone Marrow Transplant 1996; 18: 813- 815.

56. Cunningham-Rundles C, Murray HW, Smith JP. Treatment of idiopathic CD4 T lymphocytopenia with IL-2. Clin Exp Immunol 1999; 116: 322-325.