Non-specific oral ulceration associated with idiopathic CD4+ lymphocytopenia

ABSTRACT
Idiopathic CD4+ lymphocytopenia, which is a rare condition, was first defined in 1992 by the Centers for Disease Control and Prevention. This report is of a 38-year-old man who presented with a swelling on the upper left side of his face and pain in the upper posterior region for 10 days. He had a history of toothbrush trauma 2 days prior to the onset of symptoms. Intraoral examination revealed a large ulcer with necrotic slough extending from the first premolar to the second molar vestibular region on the left side. Blood investigations revealed a decrease in CD4+ cell count, although Western blot test for human immunodeficiency virus–1 and –2 showed negative results. The diagnosis of idiopathic CD4+ lymphocytopenia was made by exclusion. Clinicians should be aware of this rare immunologic disorder and that a decrease in CD4+ cell count is not a hallmark for human immunodeficiency virus infection, but could be due to other idiopathic causes.

Key words: Autoimmune diseases; CD4 lymphocyte count; HIV; Lymphopenia

Introduction
Resistance of the body against pathogenic agents is known as immunity, which is the ability of the body to resist entry of different types of foreign bodies such as bacteria, viruses, and toxic substances. Cellular immunity is provided by the activation of T lymphocytes, which destroy any organisms entering the body. Low CD4+ cell counts are associated with a variety of conditions, including viral, bacterial, fungal, and parasitic infections, sepsis, burns, trauma, intravenous injection of foreign proteins, malnutrition, over-exercising, pregnancy, normal daily variations, psychological stress, and idiopathic CD4+ lymphocytopenia (ICL).

The CD4+ cell, also known as the ‘T4 cell’ or ‘helper T cell’, is the primary target of the human immunodeficiency virus (HIV). The CD4+ plays a major role in the immune response such as signaling other cells in the immune system to perform their specific functions. Human immunodeficiency virus, an etiological agent of acquired immunodeficiency syndrome (AIDS), infects and depletes CD4+ lymphocytes. Patients with profound CD4+ lymphocytopenia but without any evidence of HIV infection were described, a condition now termed as ICL.

Idiopathic CD4+ lymphocytopenia was first defined in 1992 by the Centers for Disease Control and Prevention.
Disease Control and Prevention (CDC) as a documented absolute CD4+ lymphocyte count of <300 cells/µL or <20% of total T cells on more than one occasion, no evidence of infection on HIV testing, and the absence of any defined immunodeficiency or therapy associated with depressed levels of CD4+ cells. It is widely accepted that ICL is a rare heterogeneous syndrome that is not caused by HIV-1, HIV-2, human T-cell lymphotropic virus type I (HTLV-I), and HTLV type II (HTLV-II), and does not appear to be caused by any transmissible agent. The clinical course, immunologic characteristics, CD4+ cell kinetics, long-term outcome, and prognosis of this syndrome remain poorly defined. Hence, this report discusses the current knowledge of the poorly understood syndrome of ICL.

Case report

A 38-year-old man presented to the Pacific Dental College and Hospital (PDCH), Udaipur, India, with swelling on the upper left side of his face and pain in the left upper back teeth for 10 days. He had a history of toothbrush trauma 2 days prior to the onset of symptoms and had consulted a physician, who prescribed Tab Ordent b.i.d. (ofloxacin 200 mg + ornidazole 500 mg) for 5 days and Tab Ebility t.i.d. (diclofenac sodium 50 mg + paracetamol 500 mg + serratiopeptidase 10 mg) for 4 days and referred him to the PCDH. The patient had a habit of gutka chewing approximately 4 to 5 times per day for the previous 10 years.

General physical examination revealed pedal edema. Extraoral examination revealed a diffuse tender swelling 5 x 5 cm in the upper left cheek region with ill-defined margins, with slight induration evident (Fig 1a). Mild trismus was noted. At intraoral examination, a large ulcer was evident in the left upper vestibule extending from tooth 24 to 27 (Fig 1b). The margins were erythematous, indurated, and tender with the floor showing areas of necrosis extending onto the palatal region but not crossing the midline (Fig 2). The root stump was present in tooth 25 with decayed 26 and a removable prostheses on 11, 12, and 21. Oral hygiene was poor with severe attrition and generalized marginal gingivitis.

The intraoral periapical radiograph and orthopantomograph revealed the root stump of 25 and proximally carious 26 and 27 with mild generalized horizontal bone loss (Fig 3). Paranasal sinus view revealed no significant changes. A provisional diagnosis of chronic non-healing ulcer of the mucogingival sulcus and palate was made, and the differential diagnoses of squamous cell carcinoma, necrotizing sialometaplasia, and non-specific ulceration associated with systemic conditions such as tuberculosis or HIV infection were considered.

Investigations included routine laboratory tests, exfoliative cytology, incisional biopsy, microbiological tests, and immunological assays. Laboratory investigations included complete blood count and CD4+ and CD8+ counts, which revealed a low CD4+ count of 88 cells/µL (reference range, 500-1300 cells/µL) and CD4+:CD8+ ratio of 0.43 (Table). The blood results gave an impression of macrocytic anemia with a marked rise in erythrocyte sedimentation rate and reduced CD4+ count. Mantoux test was positive, but immunoassay for tuberculosis immunoglobulin G and enzyme-linked immunosorbent assay (ELISA) for tuberculosis immunoglobulin M was negative. The biochemical investigation for hepatitis B surface antigen was negative. The ELISA and Western blot test results for HIV-1 and HIV-2 were negative. The patient was referred to a general physician for management of anemia, and he was given intramuscular injection of vitamin B12 500 µg/mL daily for 5 days followed by one injection every month until the anemia was corrected, along with oral folic acid (Folvite Wyeth Limited, Mumbai, India) 5 mg once daily.

Figure 1 (a) Unilateral extraoral diffuse swelling on the upper left cheek region with ill-defined margins, and (b) intraoral view showing an ulcer in the upper posterior vestibule with erythematous margins and floor covered with necrotic slough
The exfoliative cytology showed no evidence of fungal hyphae or spores. Incisional biopsy revealed areas of granulation tissue with acute inflammation suggestive of a granulomatous condition. The patient was advised to continue taking the medication prescribed by his physician (Tab Ordent b.i.d. for 5 days and Tab Ebility t.i.d. for 4 days). The patient was requested to attend after 1 week for follow-up. At follow-up, intraoral examination revealed areas of denudation and necrotic slough with exposure of the underlying alveolar bone in the ulcerated region of 25 to 27 (Fig 4). Local debridement of the ulcerated lesion along with extraction of the 25 root stump was done. The patient was advised to undergo scaling and oral prophylactic measures, and restoration of 26 and 27. Complete blood count and CD4+ and CD8+ counts were repeated, and showed an increase from the previous reports, with a CD4+ count of 241 cells/µL and CD4+:CD8+ ratio being 0.80 (Table). The blood results gave an impression of normochromic macrocytic megaloblastic anemia.

At the patient’s third visit, his CD4+ count had increased to 741 cells/µL, his CD4+:CD8+ ratio was 2.76, and his blood count was normal (Table). Intraoral examination was clinically unremarkable except for apparent healing in the region where the local debridement was done. The patient was recalled after 2 weeks for further follow-up, but he failed to attend. The laboratory reports, non-specific clinical findings, and absence of an alternative explanation for CD4+ lymphocytopenia caused by other possibilities led to a final diagnosis of ICL.
Discussion

A severe decrease of CD4+ cells predisposes humans to opportunistic infections. In adults, HIV is the most common cause of CD4+ lymphocytopenia, but other causes such as infections, autoimmune diseases, immunosuppressive therapy, lymphoma, and idiopathic disease need to be considered 8.

The ICL syndrome is extremely rare. No explanation of the possible origin of this syndrome has yet been found. The mandatory criteria for the diagnosis of ICL are: (1) low number of CD4+ cells on two or more measurements, including a CD4+ cell count of <300 cells/µL or <20% of T lymphocytes are CD4+ cells; (2) lack of laboratory evidence of HIV infection; and (3) absence of an alternative explanation for CD4+ lymphocytopenia 9.

Laurence et al. 10 demonstrated that an increased spontaneous and activation-induced apoptosis was associated with symptomatic ICL and this might represent one of the pathophysiological mechanisms of the disease. Roger et al. 11 demonstrated monoclonal antibodies to CD95 that dramatically increased apoptosis of CD4+ cells exclusively, which correlated with an overexpression of Fas, a cell surface protein that belongs to the tumor necrosis factor (TNF) family, together with spontaneous and Fas-induced apoptosis. However, defective T-cell protein p56 (tyrosine kinase) activity in an adult patient with ICL confirms the critical role of this p56 (Lck) kinase in the maintenance of the peripheral CD4+ cell subpopulation 12.

Netea et al. 13 postulated that decreased production of TNF-α and interferon-γ might be the mechanism responsible for the immune defect in HIV-seronegative patients with CD4+ lymphocytopenia.

Documentation of oral manifestations in patients with ICL in the literature is sparse and appears to consist of a variety of opportunistic infections. Reichart et al. 14 described a 56-year-old patient with ICL who presented with oral manifestations, including episodic erythematous candidiasis, persistent angular cheilitis, lingua areta exfoliativa, and telangiectasia of the facial skin and buccal mucosa. Hochauf et al. 15 reported a 25-year-old man with fatal progression of primary varicella zoster virus infection who was given a postmortem diagnosis of ICL. The patient had clinical signs of oral thrush that had been diagnosed accidentally 2 years previously during clinical examination.

Idiopathic CD4+ lymphocytopenia differs from HIV infection in its immunologic characteristics and apparent lack of progression over time. Nothing about the immunologic or viral culture studies performed in these patients or about their family members or blood donors suggests that a transmissible agent causes this condition. In contrast to the CD4+ cell depletion caused by HIV, patients with ICL generally have a good prognosis 16. The decline in CD4+ cells in patients with ICL is generally slower than that seen in HIV-infected patients 17.

The optimal treatment for patients with ICL remains to be defined. Cunningham-Rundles et al. 18 reported that low-
dose interleukin-2 therapy for 5 years resulted in marked long-term immunologic improvement with normalized T-cell functions and increased CD4+ cell numbers.

The major risk to people with ICL is an unexpected infection, including cryptococcosis, atypical mycobacteria, and *Pneumocystis jiroveci* pneumonia. The condition may resolve on its own. However, ICL sometimes progresses and may be the first sign of several blood cancers. Patients with ICL have developed primary effusion lymphoma, primary leptomeningeal lymphoma, diffuse large-cell lymphoma, mucosa-associated lymphoid tissue lymphoma, and Burkitt’s lymphoma among others. Idiopathic CD4+ lymphocytopenia may indirectly trigger an autoimmune disease such as Sjögren’s syndrome. Since all the reported autoimmune diseases and lymphomas involve B cells, one hypothesis proposes that ICL’s narrow T-cell repertoire predisposes the immune system to B-cell disorders. CD4+ cell counts provide an effective surrogate marker for clinical disease progression in HIV-infected patients. It is unclear whether similar principles apply to patients with ICL. It is evident from this patient that ICL should be included in the differential diagnosis of unexplained infections manifesting as non-specular ulcers appearing in the oral cavity.

References