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【 CASE REPORT 】

Unexpected Acute Necrotizing Ulcerative Gingivitis in a Well-controlled HIV-infected Case

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Abstract:
We herein report the case of a 41-year-old Japanese man with well-controlled HIV who presented with diagnostically difficult acute necrotizing ulcerative gingivitis (ANUG). After diet-induced weight loss, he developed oral pain and disturbance of mouth opening, and was admitted to our hospital. Based on preconceptions of HIV-associated diseases, fluconazole was initiated for candidiasis. However, no improvement was seen and ANUG was finally diagnosed. This case suggests that physicians should consider ANUG in HIV-infected individuals when several risk factors are present, even if CD4+ T-lymphocyte counts have remained stable owing to long-term anti-retroviral therapy.

Key words: acute necrotizing ulcerative gingivitis (ANUG), periodontal disease, spirochete, candidiasis, HIV

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Introduction

Acute necrotizing ulcerative gingivitis (ANUG) is a periodontal disease, the main features of which are infection and inflammation of the periodontal tissues. ANUG is characterized by marginal gingival necrosis, gingival bleeding and painful ulceration of the gingival surface (1, 2). ANUG is caused by periodontopathic bacteria, mainly spirochetes and oral anaerobes (2, 3). As ANUG progresses, extensive bone loss can develop, so this is a serious and notable disease.

In human immunodeficiency virus and acquired immune deficiency syndrome (HIV/AIDS) patients, oral lesions are important because they are easily observed with the naked eye and can represent the first clinical signs of diseases. The prevalence of necrotizing gingivitis varies, but previous studies have suggested rates from 0% to 6.3% in HIV/AIDS patients (4, 5). Although ANUG is not particularly rare, it occurs less frequently than other oral diseases. Furthermore, ANUG has been correlated with CD4+ T-lymphocyte counts below 200 cells/μL (6). This indicates that physicians can speculate on CD4+ T-lymphocyte counts from the presence of ANUG, and vice versa. Thus, it is important for physicians to look for oral lesions including ANUG in HIV/AIDS patients.

We encountered a HIV-infected patient who presented with severe ANUG despite showing stable CD4+ T-lymphocyte counts above 500 cells/μL over the preceding years of good adherence with anti-retroviral therapy (ART). We herein report on the lessons learned from this case.

Case Report

A 41-year-old HIV-infected Japanese man had been receiving ART [abacavir/lamivudine, lopinavir/ritonavir] for 10 years. Compliance with anti-HIV drugs had been good and CD4+ T-lymphocyte counts had remained above 500 cells/μL, suggesting that his HIV status was stable. Two months prior to admission, he had started to go on a low-calorie diet and had thereby lost 10 kg. After 1 month of dieting, he visited an outpatient clinic complaining of a sore throat and oral pain, but no abnormal findings were evident. However, the pain gradually worsened to the point where he could not eat or drink. The day before his admission, he developed fever and general debilitation in addition to disturbance of mouth opening caused by harsh oral pain. He therefore visited our hospital the next day and was admitted. His medical history included no dental diseases and only cytomegalovi-

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Table. Laboratory Findings on Admission.

Hematology		Biochemistry		Infection/Immunology	
WBC	10,100 /μL	ALB	4.7 g/dL	HBs-Ag	(-)
Neu	72.9 %	BUN	13 mg/dL	HBs-Ab	(-)
Lym	18.3 %	Cr	0.8 mg/dL	HBc-Ab	(-)
Hb	15.7 g/dL	T.bil	0.9 mg/dL	HCV-Ab	(-)
Ht	45.4 %	AST	15 IU/L	HSV-IgM	(-)
Plt	21.6×10^4 /μL	ALT	12 IU/L	HSV-IgG	(+)
		LDH	151 IU/L	TPLA	0.0 T.U.
		Na	143 mEq/L	RPR	0.0 R.U.
		K	3.7 mEq/L	CD4 cell count	549 /μL
		Cl	105 mEq/L	HIV-RNA	Undetectable cp/mL
		Glu	97 mg/dL		
		CRP	7.94 mg/dL		

HB: hepatitis B, HCV: hepatitis C virus, RPR: rapid plasma reagin test, TPLA: *Treponema pallidum* latex agglutination, ag: antigen, ab: antibody, cp/mL: copies/mL, T.U.: Timer Units, R.U.: RPR Units

rus and *Chlamydia* infections. He was not on any other significant medications. He had smoked cigarettes at 1 pack/day for 28 years. He had no history of ethanol abuse or illicit drug use. His sexual orientation was homosexual; last reported sexual contact was several years prior. On admission, his consciousness was clear. Body temperature was 38.2℃ and other vital signs were stable. Physical examination revealed redness from the oral cavity to the throat, accompanied by severe halitosis. Detailed intraoral observations were not possible because of the disturbance of mouth opening. In addition, some ulceration of the oral mucosa and pseudomembrane were found. No vesicles or skin manifestations were evident around the mouth. Neck and submandibular lymph nodes were not palpable. Results of other physical examinations were normal. The peripheral white blood cell count was 10,100 cells/μL and C-reactive protein was 7.94 mg/dL (Table).

Oral syphilis or oral herpes were initially suspected, but his serum was negative for syphilis and antibodies for herpes showed a pattern of past infection. Taking the prozone phenomenon of syphilis into consideration, the serum test was later re-checked; however, serum was again negative. Dentists were consulted, leading to an initial tentative diagnosis of oral candidiasis, including tongue candidiasis and candidiasis stomatitis, based on the ulcers of the oral mucosa and pseudomembrane, so intravenous fluconazole was initiated. Despite treatment for several days, the symptoms persisted and the dentists were again consulted. The severe inflammation had spread widely from the throat to the soft palate, with multiple ulcers over the mucosa and severe gingivitis of both upper and lower gingiva (Fig. 1), leading the dentists to diagnose ANUG. Gram staining of a specimen collected from the tongue swab showed numerous spiral bacteria, presumably representing spirochetes, supporting the diagnosis of ANUG. Accordingly, intravenous clindamycin was initiated for fusiform spirochetes, in addition to the fluconazole. Intravenous fentanyl was administered to control the severe oral pain and oral care was implemented. Immediately after these treatments, fever subsided and oral pain gradually improved. Fluconazole was continued because the comorbidity of oral candidiasis was not completely ruled out. Several days later, oral pain was sufficiently controlled that fentanyl was suspended and oral intake was resumed. Since the patient received clindamycin and fluconazole for a total of 10 days without side effects and oral manifestations improved (Fig. 2), he was discharged. As blood and intraoral cultures yielded negative results, causative pathogens remained unknown.

Discussion

We encountered a case of unexpected ANUG in a patient with well-controlled HIV. ANUG occurs most frequently in HIV-infected individuals and severely malnourished children (5, 7). Among HIV-infected individuals, ANUG has been reported to occur frequently in cases with CD4+ T-lymphocyte counts below 200 cells/μL (8). We therefore did not initially suspect ANUG because of the well-controlled status of HIV. Instead we suspected such pathologies as oral syphilis or herpes, which can arise in HIV-infected patients even when HIV status is stable. However, laboratory findings revealed that those diseases were unlikely. After no improvements were seen despite treatment initiated under a provisional diagnosis of oral candidiasis, the patient was referred to dentists, leading to an appropriate diagnosis of ANUG.

Irrespective of the presence of HIV infection, ANUG is caused by periodontopathic bacteria, mainly in the form of spirochetes and *Fusobacteria*, *Prevotella*, and *Peptostreptococcus* species (1-3, 9). For the coverage of these bacteria, commonly used antibiotics are penicillin or metronidazole. However, in this case, intravenous clindamycin was prescribed because the patient had difficulty opening his mouth and swallowing, and intravenous metronidazole was not approved for use in Japan at that time (10). Gram staining is generally very useful in diagnosing ANUG, because cultur-

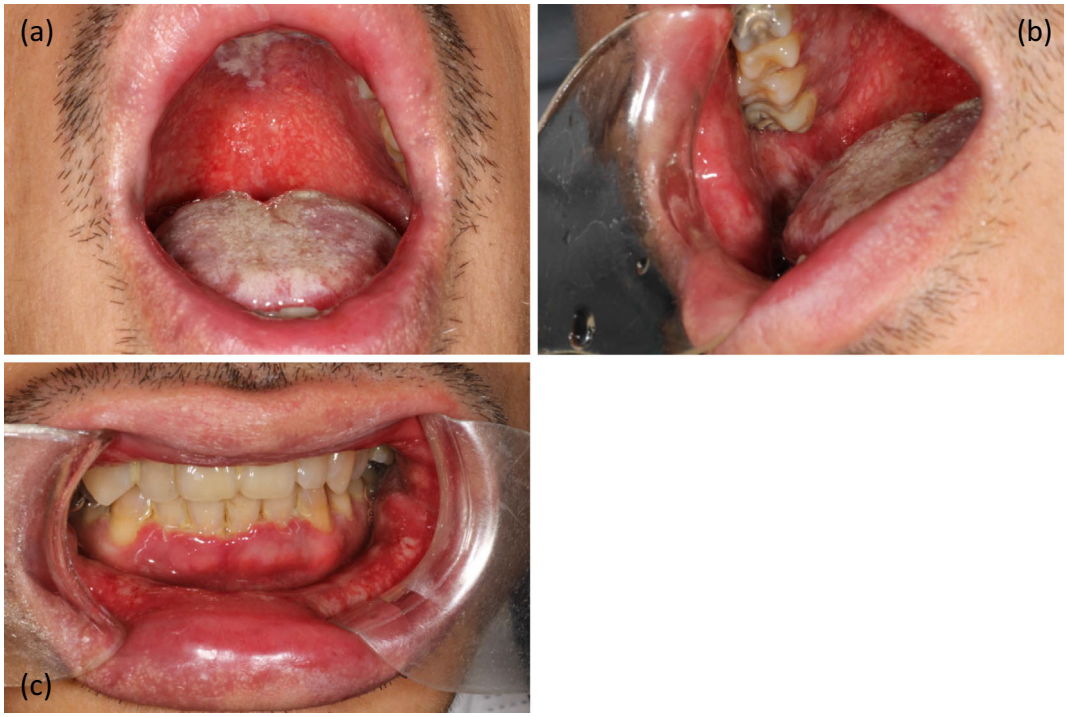

Figure 1. **Oral findings on admission. a: Frontal view with open mouth shows redness from the soft palate to the throat, accompanied by pseudomembrane and white plaque. b: Oblique view shows several ulcers in the buccal mucosa. c: Frontal view with closed mouth shows inflammation and necrosis of the lower gingiva.**

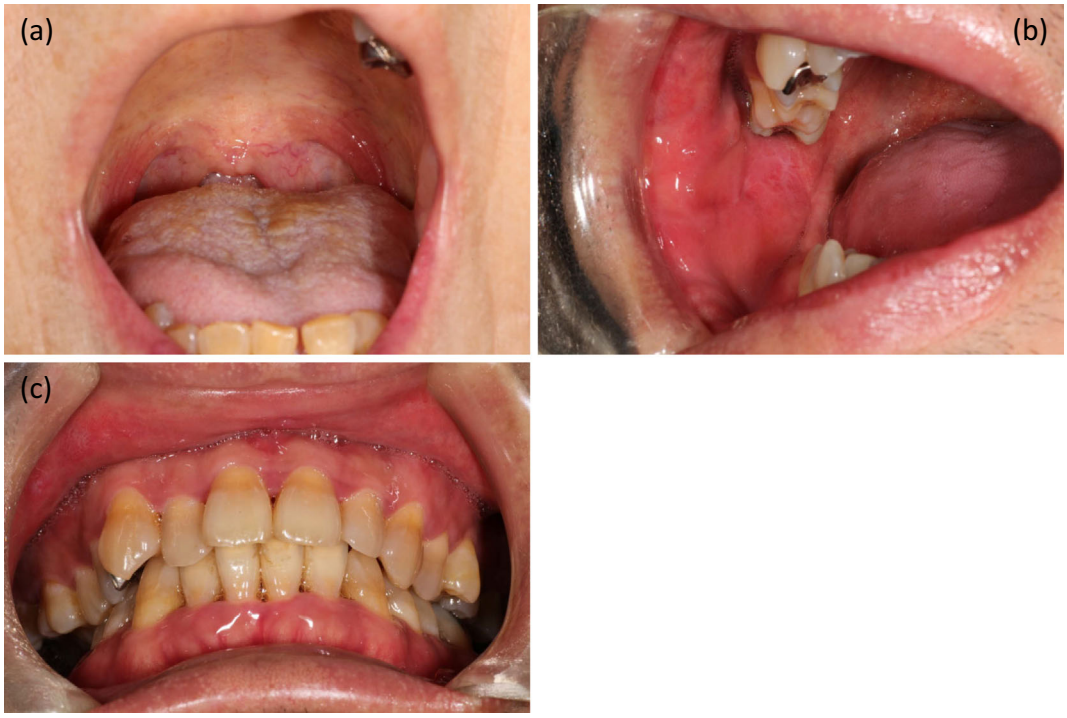

Figure 2. **Oral findings on discharge. a-c: Oral manifestations have completely resolved, but gingiva shows recession.**

ing these bacteria is difficult in common clinical settings in Japan. A previous study reported that all sampled cases showed moderate to high numbers of fusiform bacilli and spirochetes were visible on Gram staining (9). In the present case, spirillum observed on Gram staining of oral samples may have implied spirochetes. In addition, halitosis in the present case indicated possible involvement of oral anaerobes, although cultures yielded negative results. This case

emphasized the importance of these basic signs and examinations in the diagnosis of ANUG.

In addition to bacteria such as spirochetes and *Fusobacteria*, *Prevotella*, and *Peptostreptococcus* species, ANUG in HIV-infected individuals has been associated with the presence of *Candida* species in the oral cavity (9). In the present case, the comorbidity of oral candidiasis was not completely ruled out because of the presence of white plaque in his oral cavity, although intraoral cultures yielded negative results. Decreased immunity, such as that caused by malnutrition, might have contributed to oral candidiasis, in addition to ANUG, in the present case. Decreased host responses due to lower CD4+ T-lymphocyte counts or functions cause local immunological deficiencies around the periodontal pockets and soft tissues, thus facilitating the invasion of bacteria and fungi (1, 11). In addition, *Candida* species themselves can evoke proinflammatory cytokines (12). These factors might contribute to periodontal tissue necrosis and recession. Empiric broad-spectrum antibiotics for suspected pathogenic bacteria should be prescribed carefully, owing to the risk of overgrowth of *Candida* species (13-15).

Lower CD4+ T-lymphocyte counts are a risk factor for HIV-associated necrotizing periodontal disease (1). ART can improve the clinical periodontal features of HIV-infected individuals, leading to reductions in the incidence and prevalence of both periodontitis and periodontal pathogens among the subgingival microbiota of these individuals (1, 16). Along with lower CD4+ T-lymphocyte counts, other risk factors in the development of necrotizing periodontal diseases include smoking, presence of *Candida* species or herpesviruses, malnutrition and lack of oral hygiene (17-19). In the present case, severe ANUG occurred despite stable CD4+ T-lymphocyte counts over the preceding years. Presumably, the presence of multiple risk factors such as smoking, lack of nutrition due to excessive dieting, and poor oral health care contributed to the occurrence of ANUG, rather than the immunological status associated with HIV. Interestingly, one study found that a long-term ART group showed a greater risk of developing oral lesions than a short-term ART group, due to salivary impairment as an adverse effect (16). Another recent report suggested that the level and extent of periodontal disease were high, despite most patients being treated with ART (20). In Japan, the number of HIV-infected individuals treated with long-term ART in the post-ART era is expected to increase. Accordingly, not only HIV-related diseases, but also non-HIV-related diseases (e.g. lifestyle diseases, vascular disorders, bone diseases and metabolic diseases) should be considered in the treatment of HIV/AIDS patients. Also, it is possible that the number of ANUG patients associated with long-term ART will increase. Importantly, in HIV-infected individuals presenting with oral pain of unknown origin, physicians should consider ANUG due to long-term ART as a differential diagnosis and refer to dentists when other risk factors exist, even if CD4+ T-lymphocyte counts are stable.

In summary, we herein reported a case of unexpected ANUG in a patient with well-controlled HIV. In the post-ART era, physicians should take detailed histories and perform physical examinations, and should be aware of ANUG when several risk factors are present, even if the CD4+ T-lymphocyte counts remain stable under long-term ART.

The authors state that they have no Conflict of Interest (COI).

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