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Tuberculosis Cutis Orificialis in Adalimumab Related Immunosupressive Patient

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Dear Editor:

Tuberculosis cutis orificialis (TCO) is a periorifical mucocutaneous disorder usually evolves secondary to active tuberculosis (TB) infection of gastrointestinal, respiratory and genitaurinary system. Orifical TB infection develops due to autoinoculation of bacilli from primary active tuberculous source. TCO has a poor prognosis. It is a sign of advanced TB infections[1]. TCO is a secondary TB infection. However, primary TCO suggesting cases also reported in the literature[2]. Here, TCO in adalimumab (ADMB) related immunosupressive patient will be presented.

Forty-eight years old male patient referred to dermatology department with gingival ulceration for a year. Patient received ADMB therapy for five year due to existing ankylosing spondylitis. Before ADMB initiation, isoniazid prophilaxy therapy was started for nine month due to latent TBC which was proved by positive 11 mm purified protein derivative (PPD) test and negative interferon-gamma release assays (IGRAs) test. Chest x-ray was clear at that time. On dermatological evaluation, ulceration on upper left gingiva was found (Fig. 1A). Physical examination revealed intermittent nocturnal fever up to 38°C. Pulmonary symptoms such as cough, hemoptysis was absent and patient's general health was fine. Cervical lymph node ultrasonography (USG) showed pathologic lymphadenomegalies (LAM), while visceral USG examination revealed hepatosplenomegaly (HSM). On routine blood test, liver enzymes, acute phase reactants elevation was found. Histopathologic and immunofluorescence examination of the tissue samples taken from ulceration demonstrated nonspecific features. PPD skin test was 16 mm and IGRAs was positive. Pulmonary high resolution computer tomography test (HRCT) examination, demonstrated disseminated miliar nodules and mediastinal calcified LAMs (Fig. 2). Histopathologic examination of the cervical LAM revealed caseating granulomas (Fig. 3). Mycobacterium TB

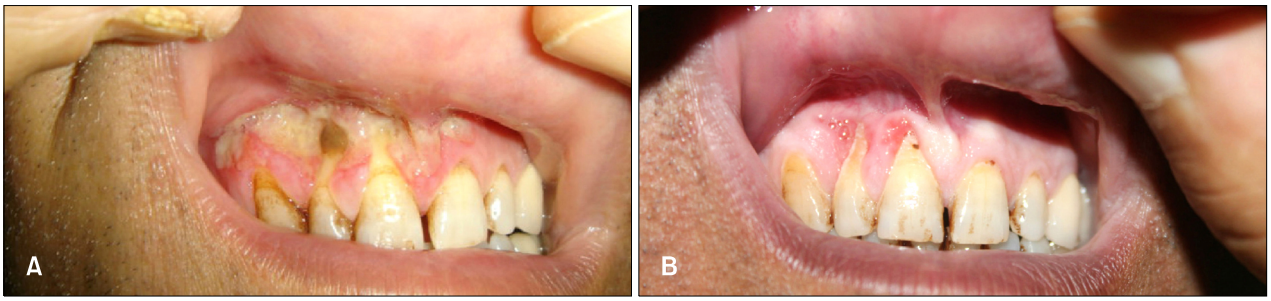

Fig. 1. (A) Irregular, well-demarcated ulceration with pseudomembranous base on upper gingival mucosa. (B) Healed gingival ulceration following the nine month of antituberculous therapy.

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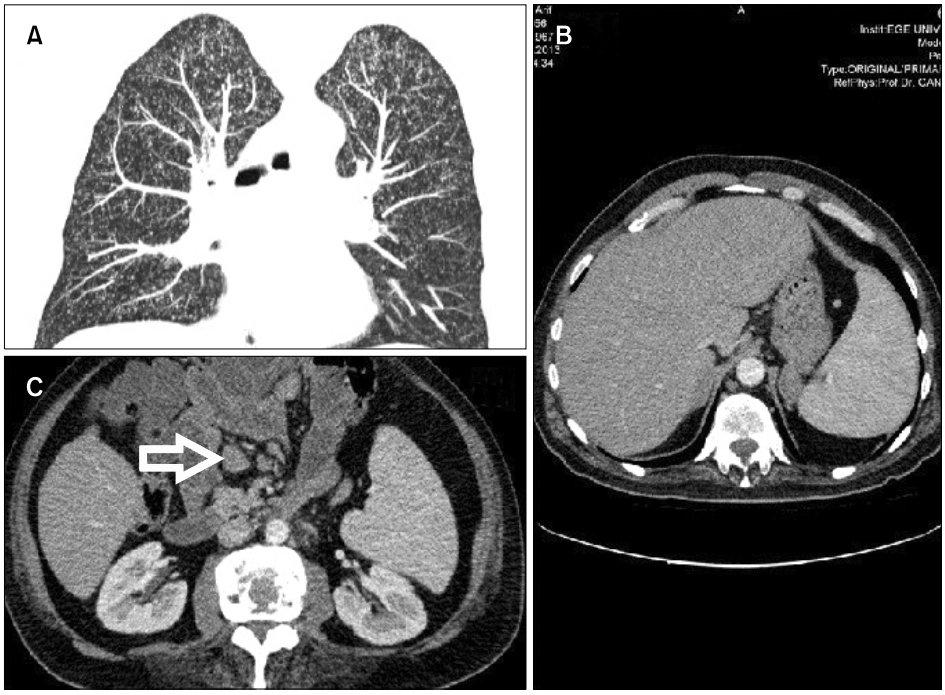

Fig. 2. (A) Millet seeds appearance of the lungs due to miliary tuberculous (TB) infection. (B) Hepatosplenomegaly as a manifestation of disseminated TB infection. (C) Enlarged lymph node (arrow) due to TB lymphadenitis.

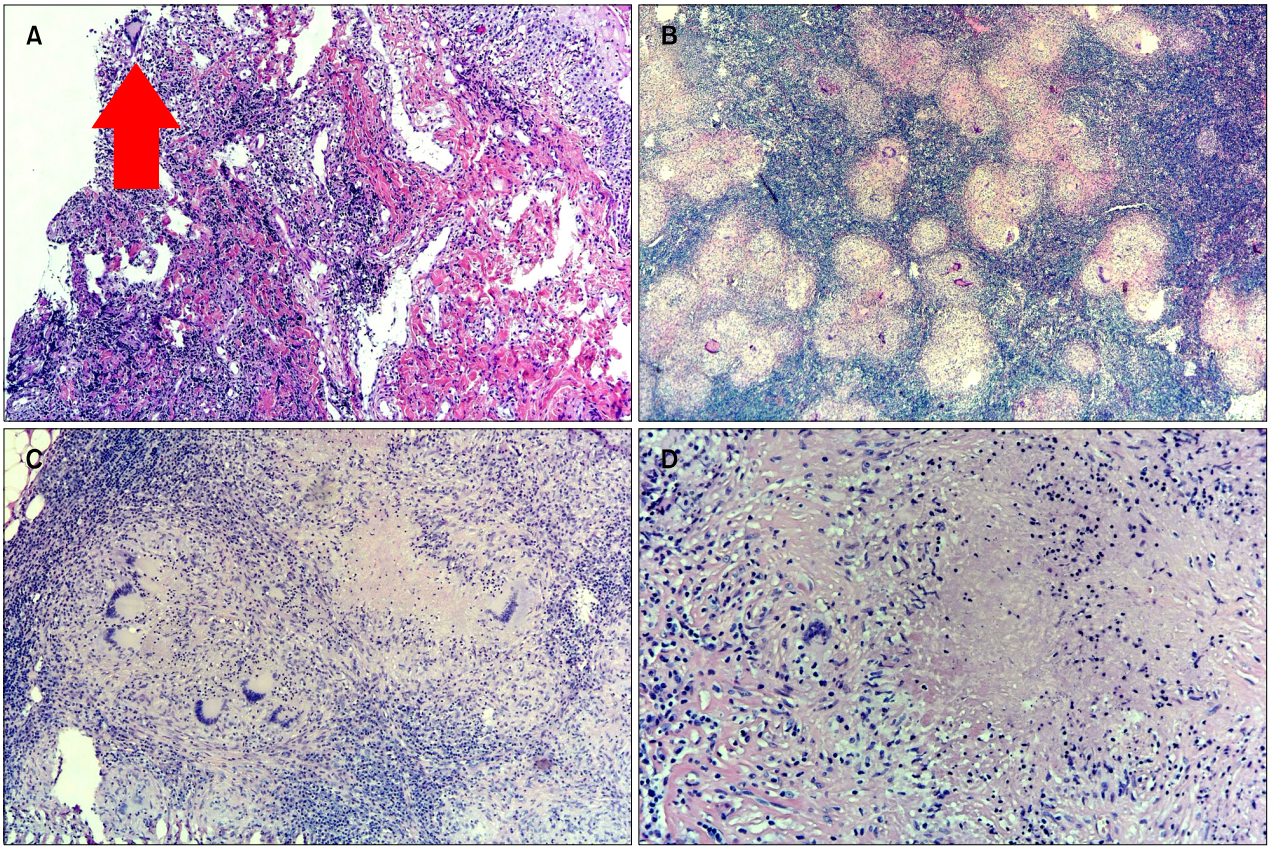

Fig. 3. (A) Single multinuclear Langhans type giant cell without granulomatous inflammation in tissue sample taken from gingiva (H&E, ×40). (B) Granulomatous inflammation in the excised lymph node (LN) (H&E, ×40). (C) Multinuclear Langhans type giant cells around granular formations in excised posterior triangle LN (H&E, ×10). (D) Giant cells and histiocytes around caseous necrosis (H&E, ×200).

complex was isolated from samples taken from bronchoscopic aspiration, broncoalveolar lavage, sputum and gingival ulceration. At the end of ninth month of antituberculous therapy gingival ulceration almost completely healed (Fig. 1B).

Tumour necrosis factor alpha (TNF-alpha) plays a major role in granuloma formation and antituberculous immunity. Medication againt TNF-alpha cytokine increase the risk of TB infection. Risk of TB infection is higher in patients who receives infliximab and ADMB. The TB incidence in patient with etanercept a little bit lower[3].

Incidence of extrapulmonary and miliary TB (MTB) infection is higher in patient who receives TNF-alpha blockers compare to usual TB infection. Pulmonary symptoms usually not present in those patients. Therefore, diagnosis of TB infection could be delied[4]. Moreover, TB infection in TNF-alpha blocker related immuncompromised patients, usually evolves due to reacitvation of latent mycobactery bacilli. However, in some mathematical modeling studies demostrated that patient with TNF-alpha blockers may reinfected with a new type of mycobacteries which treatment could be complicated[5]. Some studies showes that, developement of TB infection sooner after initiation of TNF-alpha blocker therapy, probably due to reactivation of latent TB, whereas those that occur later may be because of reinfection of new TB[3]. In the prospective of above mentioned knowledges, we can speculate that, in this case, gingival ulceration probably was a primary source of disseminated TB reinfection. Primary Ghom complexes or cavitary lesions in the upper lobes of the lung as a sign of pulmonary TB (PTB) reacitvation was absent in HRCT examination. Furthermore, patient's general health was quite normal, without active upper and lower respiratory symptoms. Therefore, MTB developed probably secondarily to primary TCO at the background of long-lasting and uncontrolled ADMB treatment in this patient. However, the exact differentiation of reinfection and reactivation of TB should be done by DNA fingerprinting of isolated bacilli. Unfortunately, we were unable to implement this kind of test.

In this patient TB infection rapidly confirmed by lymph node (LN) histopathology examination (Fig. 3). Several tissue samples taken from gingival mucosa was unhelpful for diagnosis TBC infection. However, in one sample, giant langhans cells was found similarly to giant cells in LN pathology (Fig. 3). Nevertheless, the nature of gingival ulceration confirmed by isolation mycobacterium in tissue culture. In the differential diagnosis of gingival ulceration, neoplastic diseases, cronic herpes simplex, Behçet's diseases, autoimmune bullous diseases, inflammatory diseases and other infectious diseases considered in this patient and ruled out. Secondarily TCO due to active PTB was thought in this patient. However, abscence of cavitary lesions in the lung and active pulmonary symptoms made us to think about primary TCO. Probably, gingival ulceration was a primary inoculation side of bacilli as a reinfection phenomenon of TB. MTB evolved in this patient presumably secondarily to gingival ulceration. In MTB, lungs, LN, liver and spleen most common involved organs. Hepatomegaly in 37% cases, splenomegaly in 32% cases could be sign of MTB (Fig. 2)[6]. In this case, HSM was considered as part of MTB infection.

In conclusion, by this case we are trying once more emphasize that patients with monoclonal antibody treatment should be closely monitored since they are more vulnerable to TB recurrences wheather by reactivation or reinfection. In this patient, exact differention of reactivation and reinfection of TB infection was not obtained, however by clinical course and radiological examination we thought about primary TCO reinfection due to five year continious ADMB administration. Patients under the treatment of TNF-alpha blockers can show unusual TB presentation with an extrapulmonary predominance like in this case. Therefore, before approvement of TNF-alpha blockers especially monoclonal antibodies, mucocutanoues examination should be performed carefully, since some TB related lesions could be asymptomatic like in this patient.

REFERENCES

1. Bravo FG, Gotuzzo E. Cutaneous tuberculosis. Clin Dermatol 2007;25:173-180.
2. Turkmen M, Turk BG, Kandıloglu G, Dereli T. Tuberculosis cutis orificialis in an immunocompetent patient. Cutis 2015; 95:E4-E6.
3. Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, Ustianowski A, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis 2010;69:522-528.
4. Mohan AK, Coté TR, Block JA, Manadan AM, Siegel JN, Braun MM. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. Clin Infect Dis 2004;39:295-299.
5. Wallis RS. Mathematical modeling of the cause of tuberculosis during tumor necrosis factor blockade. Arthritis Rheum 2008;58:947-952.
6. Mert A, Bilir M, Tabak F, Ozaras R, Ozturk R, Senturk H, et al. Miliary tuberculosis: clinical manifestations, diagnosis and outcome in 38 adults. Respirology 2001;6:217-224.