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Minocycline is effective in treating bullous pemphigoid in a patient with advanced cancer

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Abstract

Although oral steroid therapy is commonly used to treat pemphigoid, complications associated with steroids often cause several problems in patient with advanced cancer. Although the effectiveness of tetracycline antibiotics against pemphigoid has been recently demonstrated, there is still room for debate. We encountered a case in which minocycline was effective for bullous pemphigoid in a patient with advanced lung cancer who had developed oral candidiasis during steroid treatment and was unable to continue steroid therapy.

Case: An 80-year-old male. While receiving treatment for advanced lung cancer, he developed multiple blisters in his mouth, and was diagnosed as bullous pemphigoid, although he was treated by prednisolone, oral candidiasis developed soon after initiation of the treatment, making it difficult to continue oral steroid; therefore, oral minocycline was added. The bullous pemphigoid improved, and the patient was able to gradually reduce and withdraw from prednisolone. Minocycline is believed to have fewer side effects than steroids and is considered effective and safe for the treatment of bullous pemphigoid in patients with advanced cancer.

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Introduction

Pemphigoid is an autoimmune bullous disease that causes subepidermal blisters owing to autoantibodies (IgG) against epidermal basement membrane antigens. In Japan, the incidence of a combination of pemphigoid and malignant tumors is as high as 5.8% [1], and screening for malignant tumors is required for pemphigoid [2]. Immune-related Adverse Events (irAEs) associated with immune checkpoint inhibitors may occur in cancer patients [3]. Although the general treatment is oral steroid therapy, complications associated with oral steroid therapy cause problems in patients with advanced cancer. Although tetracycline antibiotics have been shown to be effective in recent years as an alternative to oral steroid therapy for pemphigoid with fewer side effects, there is still room for debate. Its main pharmacological effects are thought to be due to anti-inflammatory effects, based on inhibition of neutrophil migration [4] and the suppression of the production of active oxygen [5-9], which suppress blister formation through a mechanism different from that of steroids and immunosuppressants. Here, we report a case in which pemphigoid was improved with a combination of steroids and oral minocycline, and steroids were gradually tapered and withdrawn.

Case: An 80-year-old male.

Diagnosis: Right lung squamous cell carcinoma Stage IV.

Medical history: Diabetes.

Life history: Lived alone.

Family history: His wife had died seven years ago. His son and daughter lived outside the prefecture.

History of present illness

In the year X-1, during his visit to a dermatologist for bullous pemphigoid, a chest CT scan performed for cancer screening revealed a mass shadow in the right S6, enlarged lymph nodes at the bronchial bifurcation, and suspected invasion to the mediastinum. A lymph node biopsy revealed squamous cell carcinoma of the lung, and further examination and treatment were suggested; however, he did not wish to do so and was referred to a palliative care department for the purpose of alleviating his symptoms. Although he received home-visit medical care for treatment at home, he was hospitalized in November 2016 because of a poor appetite and decreased ADL.

Current symptoms at admission

No communication problems were encountered. blood pressure was 136/69 mmHg, pulse was 78 beats/min, normal, body temperature was 36.8°C, SpO_2 was 97% (room air, respiratory rate 12 breaths/min), and Performance Status was 3.

Blood tests showed an elevated white blood cell count and an inflammatory response. There were no abnormalities in liver function, renal function, or electrolyte levels, and anemia was not observed. Serum albumin was 2.7 g/dl, HbA1c was 6.3%.

Multiple tension blisters were observed on the hard and soft palates of the oral cavity. Erosion and ulceration were observed on the dorsum of the tongue, left and right buccal mucosa, and inner surfaces of the upper and lower lips (Figure 1).

The chief complaints were pain in the oral cavity, loss of appetite, and unsteadiness while walking.

Immunohistological findings

Direct fluorescent antibody staining demonstrated linear deposition of IgG and complement C3 on the basement membrane.

Progress after hospitalization

At the time of admission, the patient had experienced pain in his oral cavity and had numerous blisters, erosions, and ulcers. Based on the clinical findings, we suspected herpes zoster, and intravenous acyclovir was administered; however, the symptoms did not improve. A culture test of the swab from the affected area revealed Candida 2+, and although the patient was treated with amphotericin B gargle for oral candidiasis, there was little improvement. Suspecting recurrence of pemphigoid, the patient was consulted by a dermatologist. Tissue biopsies from blisters on the hard palate and ulcers on the dorsum of the tongue revealed linear deposition of IgG and complement C3 on the basement membrane using direct fluorescent antibody methods. Blood tests were negative for anti-BP180 antibodies but positive for anti-BP230 antibodies, and he was diagnosed as having bullous pemphigoid. He had been taking betamethasone 2 mg/day for approximately two months ago, to treat loss of appetite and general malaise due to cachexia. However, when the patient was switched to oral prednisolone 20 mg/day, a decrease in oral blisters, an improvement in erosion, and the epithelialization of ulcers were observed on the 5th day of oral administration. However, on the 14th day of oral administration, white moss appeared on the tongue, which was suspected to be oral candidiasis. As the cause was thought to be a weakened immune system due to long-term oral steroid use, we decided to add minocycline (200 mg/day) as an alternative treatment to gradually reduce prednisolone. From day 3 of oral minocycline administration, oral blisters decreased, erosion improved, ulcer epithelialization progressed, and oral pain decreased. Subsequently, prednisolone was tapered off and discontinued; however, the symptoms did not worsen. The white coating on the tongue improved with the combined use of amphotericin B gargling. On the 15th day of oral minocycline administration, it became difficult to administer due to a decline in the general condition, and oral minocycline was discontinued after cessation of the treatment erosion in the oral cavity worsened. Four days after discontinuing oral administration, the patient died due to a decline in his general condition caused by lung cancer.

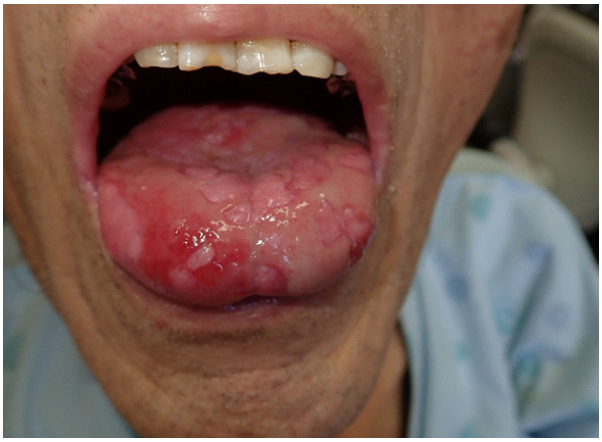

Figure 1: Clinical image.

Discussion

Pemphigoid varicella is a subtype of pemphigoid and the most common disease with anti-epidermal basement membrane antibodies. It is common in the elderly, with a male-to-female ratio of 1:1.7, and oral mucosal symptoms occur in 27.0%-39.4% of cases [10,11]. The target antigens of bullous pemphigoid are BP180 (type XVII collagen: COL17) and BP230.

Generally, the main treatment for pemphigoid is oral steroid therapy, in which prednisolone (mild cases: 0.2 to 0.3 mg/kg/day, moderate to severe cases: 0.5 to 1 mg/kg/day) is administered. In severe cases, concomitant immunosuppressants or pulse therapy with methylprednisolone was used [12]. Oral steroid therapy is the basic therapy, and complications caused by oral steroid therapy (such as infectious diseases, peptic ulcer disease, impaired glucose tolerance, and myopathy) will become a problem. Although it is known that steroids increase the risk of infection according to the dose and duration, especially by the increase of cumulative dose [13]. It has been reported that even short-term oral steroid use (within 30 days) increase the risk of sepsis [14]. It has also been reported that cancer patients have a significantly higher risk of developing sepsis and local candidiasis than non-cancer patients, and hypoalbuminemia in cancer patients has been considered one of the reasons for this [15]. As terminal cancer patients often have hypoalbuminemia, it is necessary to carefully consider the indications for administering steroids to terminal cancer patients and minimize their use. In this case, oral candidiasis developed on the 14th day of prednisolone administration. It is believed that the patient was susceptible to infection because he had been taking 2 mg of betamethasone for anorexia and general malaise for about 2 months, and he had hypoalbuminemia. We considered it dif-

ficult to continue administering prednisolone in this situation, because it was thought that the risk of sepsis would increase. Although there was concern that oral prednisolone might worsen the patient's blood sugar control, as the patient had a history of diabetes, blood sugar levels remained stable even after starting treatment.

In recent years, tetracycline antibiotics have been shown to be effective in treating pemphigoid as an alternative to oral steroid therapy, with fewer side effects [16]. Hashimoto believes that it would be appropriate to administer minocycline alone in mild cases, while combined oral administration of nicotinic acid amide at doses of 600-900 mg/day should be considered in severe cases [12]. With regard to concomitant use with oral steroids, Horiguchi reported that steroid dosage could be reduced by triple combination therapy with steroids, tetracycline antibiotics, and nicotinamide, or a combination therapy of steroids and tetracycline antibiotic [17]. Hashimoto believes that a combination of tetracycline antibiotics and steroids should be considered in severe cases [12]. This case also indicated that the combination of oral prednisolone with minocycline improved the symptoms, and the patient was able to gradually reduce and withdraw from prednisolone. Because the oral lesions in this case were severe [16], if tetracycline antibiotics had been used in combination from the beginning of treatment, the symptoms might have improved earlier, and the prednisone dosage could have been reduced.

With respect to the choice between minocycline and tetracycline, Hashimoto pointed out that minocycline is easier to use for the following reasons: (1) in cases with renal dysfunction, minocycline, which is metabolized by the liver, is considered to be safer than tetracycline, which is metabolized by the kidney; (2) gastrointestinal disorders are observed when administering 1500 mg/day of tetracycline; and (3) minocycline only needs to be taken 1-2 times/day, while tetracycline is taken 3 times/day [12]. Because the side effects of minocycline include dizziness, pigmentation, and interstitial pneumonia, these should be considered when selecting a drug for each case.

This case showed an effect on day 3 of oral minocycline administration. According to reports, it takes 2-14 days for the effect to appear, often within a week. Berk & Lorincz suggested, regarding the administration period of minocycline, that the dose should be reduced after 6 months of remission [6] while Thomas et al. maintained the same dose as maintenance therapy for 1 to 2 months after epithelialization was completed, and then gradually tapered off over 4 months [18]. A limitation of this case is that oral minocycline was discontinued on the 15th day of oral minocycline treatment due to a decline in general condition, and the long-term therapeutic effect could not be evaluated. Furthermore, the use of tetracycline antibiotics and nicotinic acid amide for bullous pemphigoid is not covered by insurance, and it is hoped that the therapeutic efficacy and safety evaluations will be accumulated through large-scale clinical trials in the future.

Conclusion

The combination of steroids and oral minocycline improved the symptoms in the treatment of bullous pemphigoid in a patient with advanced cancer, and steroids were gradually reduced and withdrawn. Minocycline therapy therefore appears to be a promising treatment option for bullous pemphigoid.

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