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Oral Lesion like Mucous Membrane Pemphigoid under Carboplatin-induced Hemolytic Anemia and Pancytopenia as Hypersensitive Reactions in a case with Maxillary Sinus Cancer: A Case Report

Yuki Hokita, DH[1], Kazuyo Mori, DH[1], Taihei Yamaguchi, DDS[2]*, Takahiko Oho, DDS[2]

[1]Section of Oral Hygiene, Kagoshima University Hospital, Kagoshima, Japan

[2]Department of Preventive Dentistry, Research Field in Dentistry, Medical and Dental Sciences Area, Kagoshima University, Kagoshima, Japan

ABSTRACT

Here we report the first case of fatal carboplatin induced immune hemolytic anemia in a patient with head and neck malignant neoplasms followed by onset of multi-organ failure. While carboplatin is an effective agent used to treat many kinds of malignant tumorigenic lesion, a number of reports about allergic side effects are present. A 64-year-old male patient diagnosed as maxillary sinus cancer was treated by radiation therapy associated with weekly intravenous infusions of carboplatin. After five times of carboplatin infusion, white blood cell and platelet counts and hemoglobin value gradually decreased, and reached to almost bottom level. Both direct and indirect coombs tests were negative. Reticulocyte count and the value of platelet-associated IgG were high level, and oral lesion-like mucous membrane pemphigoid appeared on tongue and hard plate. Recognition of the particular oral abnormality in the early stage could allow for correct diagnosis and a potentially effective therapy.

Keywords: hypersensitivity, carboplatin, pemphigoid, maxillary sinus cancer, chemotherapy

***Correspondence to Author:**
Taihei Yamaguchi
Department of Preventive Dentistry, Research Field in Dentistry, Medical and Dental Sciences Area, Kagoshima University, Kagoshima, 8908544, Japan

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Introduction:

Among malignant neoplasms in the head and neck region, maxillary sinus cancer is in the majority with 60-70% occupation and approximately 80% is histopathologically diagnosed as squamous cell carcinomas in Japan [1]. The standard protocols for the treatment include surgical resection with adjuvant radiotherapy with or without chemotherapy. Regimens, including a combination of platinum, 5-fluorouracil, and cetuximab, are mainly administrated [2]. For the patients with complications, especially reduced kidney function and/or the elderly, weekly administration of carboplatin has been applied instead of cisplatin. Carboplatin is frequently used for the treatment of malignant neoplasms by gynecologists [3] and pulmonologists [4] expecting good prognosis in spite of the possibility of drug-induced hypersensitivity.

In this report, we present the case of a patient who was diagnosed with maxillary sinus cancer and had a severe episode of hemolytic anemia and pancytopenia after the course of concomitant chemoradiotherapy with carboplatin followed by multiple organ failure. At an early stage of this case, an oral symptom like mucous membrane pemphigoid appeared prior to other symptoms.

Case presentation:

A 64-year-old male patient presented with pain in the nasal region. The history of the present illness revealed that the patient had noticed the pain during the last month. He had a habit of smoking 12 cigarettes per day for 20 years which he quit 25 years ago. Five years ago, he underwent an operation for the removal of prostatic carcinoma, and had been followed up by medical examination every six months with no symptoms of relapse. He never exhibited an allergic reaction for any foods and medicines.

The clinical examination revealed inflammatory features in both maxillary sinus and bone defect in the anterior wall of the right maxillary sinus by computed tomography and magnetic resonance imaging. A biopsy was performed, and the lesion was pathologically diagnosed as squamous cell carcinoma. The T-stage was in grade 2. He had received radiation therapy associated with chemotherapy by weekly administration of 130 mg carboplatin six times. Carboplatin, instead of cisplatin, was administrated for this case to avoid neurotoxicity and nephrotoxicity because of renal dysfunction. Radiation therapy was five days a week using a single daily fraction of 2.0 Gray for 35 times in total. The patient had been employed under the management of the dental staff members for mainly oral hygiene during the period of the concomitant chemoradiotherapy without significant problems in the oral area.

After the infusion of carboplatin for five times, white blood cell, platelet counts, and the value of hemoglobin decreased gradually and reached to almost bottom level after about 1 month of the last infusion instead of the adoption of granulocyte-colony stimulating factor (Figure 1). The symptoms of anemia, including head ache, fatigue, and cardiac disease, simultaneously appeared in association with pancytopenia. Both direct and indirect Coombs tests were negative on the 19th day after the last

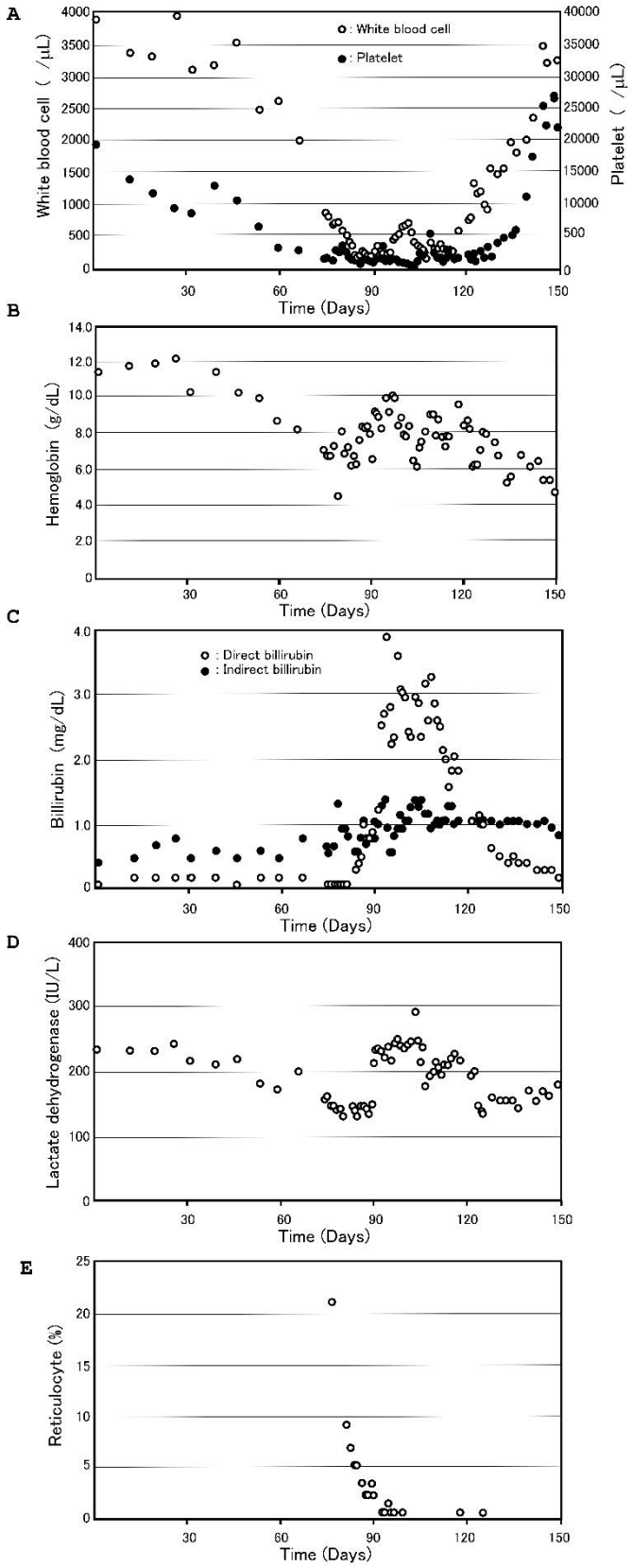

Figure 1. Timeline of the patient's course. Graphs indicate the number of white blood cells and platelets (A), the concentration of hemoglobin (B), the concentration of direct and indirect bilirubin (C), the unit value of lactate dehydrogenase (D), and rate of reticulocyte in peripheral blood examined (E). Carboplatin alone (130 mg) was administrated six times on days 21, 28, 35, 42, 49, and 56. Day 1 is defined as three weeks before the day of the first infusion of carboplatin.

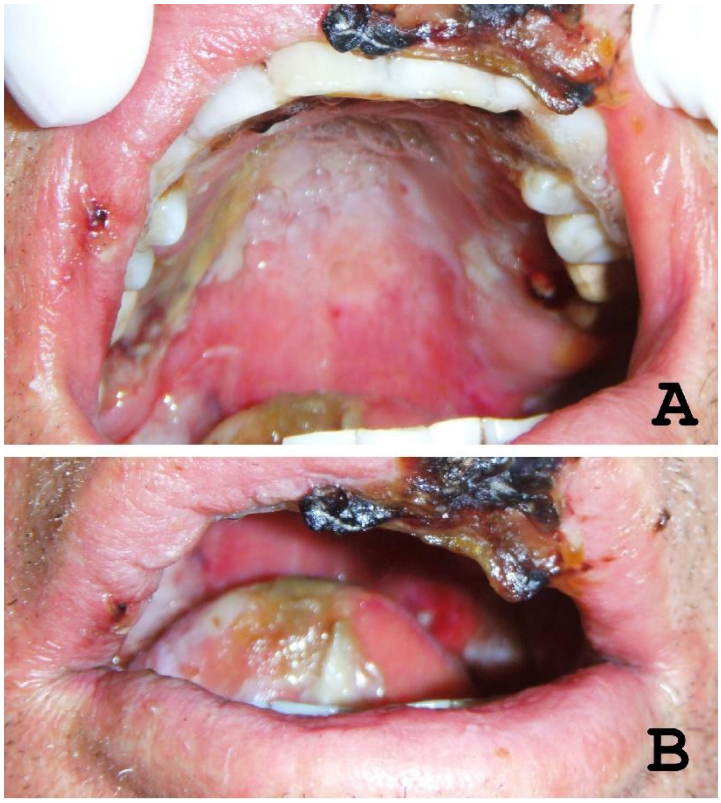

Figure 2. Oral lesion on day 110, which is day 54 after the 6th infusion of carboplatin.

infusion, and the indirect test was negative on the 26th day. During the follow-up, lactate dehydrogenase and indirect bilirubin were maintained in high concentration. Reticulocyte count was 21.0% on day 21 after the last infusion, and the examination of bone marrow ruled out the hemophagocytic syndrome. On day 31 after the last infusion, a clinical view like bullous pemphigoid emerged with pain and ulcers in oral plate and tongue, which continued over two months (Figure 2).

Thereafter methicillin-resistant *Staphylococcus aureus* was infected under febrile neutropenia and severe pneumonia occurred followed by severe renal failure and hepatitis. Direct bilirubin and lactate dehydrogenase increased dramatically due to the dysfunction of the liver. The value of platelet-associated IgG was 168 ng. All symptoms were gradually resolved after about three months of the last infusion of carboplatin by the adoption of antibiotics, including vancomycin, and respiratory management, and the blood counts recovered to almost normal level. The patient was discharged from our hospital on the day 121 after the last infusion of carboplatin.

Discussion:

Platinum-based compounds have been approved for the treatment of many solid tumors as the frontline efficacious therapy. On the other hand, these drugs cause cytopenias as adverse effects through not only marrow suppression but immune-mediated allergic mechanisms [5]. Allergic hypersensitive reactions caused by platinum-based compounds have been widely reported. While the incidence was reported in approximately 44% of patients receiving two or more

carboplatin regimens, the cumulative episodes increase considerably either in a dose-dependent manner or as per the number of cycles administered [6]. The symptoms of most cases are consistent with the type I reaction by the repeated exposure to the antigen, and generally, appear within a few hours or one to two days after drug administration [7]. A part has been suggested to be associated with type IV mechanism. This reaction develops hours or even days after infusion as a delayed inflammatory reaction [6].

The allergic events by platinum-based components through type II mechanism are relatively rare. While there are some reports about oxaliplatin-induced immune cytopenias [8], only a few events on carboplatin have been described [9, 10]. The symptoms, including hemolytic anemia, thrombocytopenia, or neutropenia, were dependent on each case. Drug-induced immune hemolytic anemia is a rare case with an incidence of one per million patients including approximately 15% by anti-neoplastic agents [11]. In this patient, pancytopenia in association with hemolytic anemia was identified. The systemic conditions and blood examination gradually turned worse for over one week after the last infusion of carboplatin, and subsequently, systemic inflammatory responses led to acute multi organ failure. These clinical characteristics and laboratory evaluation suggested the pathophysiologic mechanism of drug-dependent immune hemolytic anemia. The symptom in the mouth was detected prior to multiple organ failure and was suggested as pemphigoid. Since there was no erythematous skin associated with blisters whole body [12], this case suggested mucous membrane pemphigoid. Unfortunately the serological examination for differential diagnosis was not performed. The intervention of oral practitioner could play an important role in the detection of similar episodes at an early stage, certainly resulting in an accurate diagnosis.

Conflict of interest: The authors declare that they have no competing interest.

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