CASE REPORT

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Adverse Cutaneous Drug Reaction Following Granulocyte Colony-Stimulating Factor Administration in Nasopharynx Cancer Patient with Febrile Neutropenia: A Case Report

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ABSTRACT

Introduction: Several side effects may occur during cancer treatment such as myelosuppression following systemic chemotherapy, which is mainly manifested as neutropenia and is associated with increased infection risk. Febrile neutropenia is associated with a worse prognosis. Granulocyte colony-stimulating factor (G-CSF) may be given prophylactically before chemotherapy in selected cases or as adjuvant therapy in febrile neutropenia. G-CSF administration may be associated with several side effects, including skin manifestation. More rarely, G-CSF administration may induce acute febrile neutrophilic dermatosis is which known as a Sweet syndrome.

Case Presentation: A 63-year-old man with nasopharyngeal cancer stage III on chemotherapy and radiotherapy came to our emergency department with a chief complaint of fever, coughing, and shortness of breath. He was diagnosed with community-acquired pneumonia and febrile neutropenia. His white blood cell (WBC) count was 200/mm^3. On the third day of hospitalization and G-CSF administration, he developed a rash and had skin desquamation mainly on his head including the scalp, face, lips, upper trunk, arms, and the surface of both hands. His follow-up laboratory result was WBC 8300/mm^3 with a neutrophil count of 87%. Presumable Sweet syndrome diagnosis with differential diagnosis of other drug eruption reactions was made. Systemic and topical were administered, and G-CSF was stopped. Significant improvement was observed.

Conclusions: G-CSF administration in febrile neutropenic cancer is generally safe; however, several adverse events may occur. Cutaneous adverse events following G-CSF administration should be recognized and treated accordingly. Sweet syndrome is rare but should be recognized as a possible G-CSF-induced drug skin complication.

INTRODUCTION

Comprehensive cancer management may require several combinations of therapeutic modalities, such as radiotherapy and chemotherapy. The aim of cancer management should be curative whenever possible; however, if the curative treatments are no longer feasible, the aim should be directed to palliative treatment and optimizing their quality of life [1]. Several side effects may occur during cancer treatment such as systemic chemotherapy; some may have already been recognized, and therefore can be anticipated. Side effects of chemotherapy may variably manifest in several organ systems and different magnitudes, which commonly depend on the drug type and dose. Several well-known side effects of chemotherapy are nausea and vomiting, alopecia, dry mouth, diarrhea, skin changes, myelosuppression, allergic reaction, and others.

The use of chemotherapy may induce neutropenia condition due to myelosuppression, which may lead to increased infection risk; this condition is called febrile neutropenia [2]. Febrile neutropenia is associated with a worse prognosis compared to the same infection which occurs in cancer patients with the non-neutropenic condition. Several measures have been done to prevent neutropenia conditions such as identification of high-risk cancer patients for neutropenia and giving granulocyte colony-stimulating factor (G-CSF) prophylactically before chemotherapy. Febrile neutropenia management involving prompt antibiotic administration and G-CSF may be given. G-CSF administration may be associated with several side effects such as dyspnea, chest pain, nausea, hypoxemia, diaphoresis, anaphylaxis, syncope, flushing, and several cutaneous manifestations [3]. More rarely, G-CSF administration may induce acute febrile neutrophilic dermatosis which is known as Sweet syndrome [4]. Here, we report a 63-year-old man with nasopharynx cancer and acute febrile neutropenia who had adverse cutaneous drug reaction presumably GCS-F induced Sweet syndrome.

CASE PRESENTATION

A 63-year-old man came to our emergency department with chief complaints of fever, coughing, and shortness of breath one day before admission. He was diagnosed with nasopharynx cancer stage III approximately 4 months ago. He had undergone 42 cycles of radiation therapy and two cycles of chemotherapy. His regiment of chemotherapy is docetaxel 129.5 mg and cisplatin 129.5 mg. No adverse effects were seen after each session of chemotherapy and radiation therapy, except the sign of alopecia and skin reaction over his neck following radiotherapy.

On physical examination, he looked anemic, severely ill, and fully alert. His blood pressure was 110/60 mmHg, heart rate 110 bpm, respiration rate 28 times/minute, and oxygen saturation 95% at room temperature. He has anemic conjunctiva. No visible neck was seen. A lung examination revealed a crackles sound on the right lung. There were no significant findings on the heart and abdominal examination. He had warm extremities, and no skin lesions were observed.

Laboratory examination revealed hemoglobin 10.3 g/dL, hematocrit 28.1%, platelet 193,000/mm^3, white blood cell 200/mm^3, ureum 55 mg/dL, creatinine 1.4 mg/dL, natrium 126 mEq/L, potassium 4.29 mEq/L, random blood glucose 175 mg/dL, AST 49 U/L, ALT 60 U/L, negative for anti-HIV and hepatitis marker. Chest X-ray showed infiltrate predominantly on the right lung.

Based on those findings, he was diagnosed for having community-acquired pneumonia, febrile neutropenia, nasopharynx cancer stage III, anemia, and hyponatremia. His Multinational Association of Supportive Care in Cancer (MASCC) score was 19 indicating a high risk for poor outcomes. He was admitted to the intermediate care ward and given Cefepime, G-CSF, and supportive treatment. The laboratory result on the second day showed Hb 8.8 g/dL, WBC 400/mm^3, and platelet 194,000/mm^3. On the third day of hospitalization and G-CSF administration, he developed a rash and skin desquamation mainly on his head including the scalp, face, lips, upper trunk, arms, and the surface of both hands. His follow-up laboratory results were Hb 8.6 g/dL, WBC 8300/mm^3 with differential count of eosinophile 1%, basophile 0%, band neutrophile 47%, segment neutrophile 40%, lymphocyte 8%, monocyte 4%, and platelet 169000/mm^3. We suspected that he had G-CSF-induced acute febrile neutrophilic dermatosis (Sweet syndrome). Consultation with the dermatology department was made. Skin lesion was described as multiple erythematous papules with diffuse border, notable nodules, and squamous distributed at his head involving the scalp, face, both upper arms, anterior and posterior trunk, and the surface of both hands' palms (**Figure 1**). The lesions were non-itchy, but he complained that he was painful due to skin lesions, especially on palpation. He also felt a headache, and lethargy, and was still on fever with a temperature of 38.8 °C. He was clinically diagnosed with the presumable Sweet syndrome with a differential diagnosis of other drug eruption reactions. He was prescribed desoximetasone 0.25% cream, emollient cream, and oral methyl-prednisolone 48 mg per day. A skin biopsy was planned; however, the patient refused the procedure. Serum IgE level and CRP were obtained before steroid administration and showed the IgE value of 103.9 IU/mL (normal value: 0-100 IU/mL), and his CRP was 24.0 mg/L (normal value < 6.0 mg/L). The G-CSF administration was stopped, and cefepime was continued. On the fifth day of hospitalization, he showed improvement in his pneumonia and skin lesions. He was discharged on the tenth day with no complaints, his Hb was 9.9 g/dL, WBC 7,400/mm^3, platelet 159,000/mm^3, and steroid was tapered off. On the follow-up visit, he had no complaints and had an improvement in his skin lesion (**Figure 2**).

DISCUSSION

Febrile neutropenia is an oncologic emergency defined as the clinical presentation of fever (one temperature ≥ 38.3 °C or sustained temperature of greater than 38 °C for ≥ 1 hour) in a patient with an absolute neutrophil count of fewer than 500 cells/µL or expected to decrease to < 500 cells/µL [5]. Neutropenia is often associated with the use of cytotoxic chemotherapy agents which lead to bone marrow suppression [6]. Febrile neutropenia may lead to a fatal outcome and be associated with increased morbidity, organ failure, and a higher mortality risk especially if the neutrophile count is < 500/µL [7]. Therefore, prompt diagnosis and treatment

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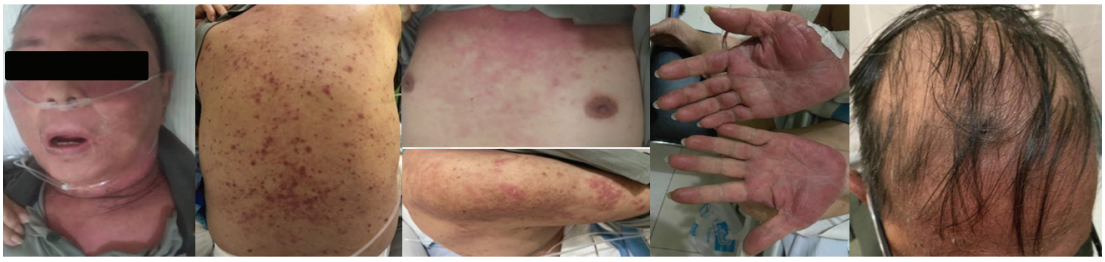

Figure 1. Skin lesions of the patient on day 2

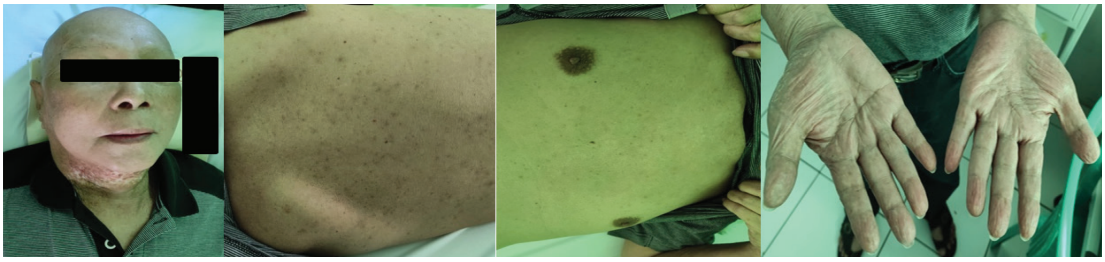

Figure 2. The patient's skin condition on the follow-up visit

Table 1. Drug-Induced Sweet's Syndrome Diagnostic Criteria [13]

Abrupt onset of painful erythematous plaques or nodules
Histopathological findings of dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis
Pyrexia >380C
Temporal relationship between drug ingestion and clinical presentation, or temporally related recurrence after intake
Temporally related resolution of lesions after discontinuation or treatment with systemic corticosteroid

All criteria are required to establish the diagnosis

should be employed. The main core of febrile neutropenia management consists of adequate empirical antibiotics administration for the duration of neutropenia [5]. The administration of G-CSF for febrile neutropenic patients is still debatable. In 2015, the American Society of Clinical Oncology (ASCO) issued practical guidelines regarding the use of G-CSF. ASCO stated that there is no evidence of benefit in the administration of G-CSF for febrile neutropenic patients; however, it can still be administered in the clinical setting of high risk for infection-associated complications or having prognostic factors predictive of poor clinical outcomes [8].

Administration of G-CSF is generally well tolerated; however, several side effects still may occur, such as headache, local and generalized musculoskeletal pain, dyspnea, chest pain, diaphoresis, flushing, syncope, and severe allergic reaction such as anaphylaxis [3]. Rare and potentially fatal adverse events also have been reported regarding the use of G-CSF such as aortitis, capillary leak syndrome, glomerulonephritis, acute respiratory distress syndrome, alveolar hemorrhage, severe sickle cell crisis, and splenic rupture [9]. Various skin complications also have been reported due to G-CSF administration. The adverse cutaneous drug complications may be manifested as localized skin reactions, folliculitis, vasculitis, pyoderma gangrenosum, or generalized allergic rash with or without anaphylaxis [10,11]. Therefore, the magnitude of skin drug reactions can be ranging from mild and self-limiting to severe conditions. Bustillo et al. [10] reported the occurrence of facial rash which was described as pruritic and non-painful maculopapular rash after the administration of pegfilgrastim in patients with advanced pancreatic cancer. They stopped the G-CSF administration and diphenhydramine with dexamethasone. The skin lesion gradually improved. Mori et al. [12] described a case of erythema exsudativum multiforme induced by G-CSF administration in an allogeneic peripheral blood stem cell donor. A 40-year-old man that underwent bone marrow harvest for the donor was administered G-CSF (lenograstim) subcutaneously with a dose of 5 μg/kg every 12 hours for 5 days. After the third day of administration, he started complaining of fever and itchy skin eruptions. Erythema exsudativum multiforme was clinically diagnosed. G-CSF administration was continued, and topical corticosteroids were given. The skin eruptions were resolved within one week. They did not biopsy the erupted skin. The pathogenesis of G-CSF-induced erythema exsudativum multiforme remained unclear; however, allergic reaction was generally thought to be the underlying mechanism.

Acute febrile neutrophilic dermatosis or sweet syndrome is a rare inflammatory skin reaction that may

be idiopathic, malignancy-associated, and drug-associated. Hematological malignancy, especially acute myeloid leukemia, is the most common malignancy associated with Sweet syndrome [13]. Several autoimmune diseases and infectious agents such as rheumatoid arthritis, systemic lupus erythematous, Cytomegalovirus, and Human Immunodeficiency Virus were also associated with Sweet syndrome [14]. G-CSF is the most reported drug associated with Sweet syndrome occurrence. The mechanisms of G-CSF-induced Sweet syndrome are possibly explained because G-CSF in stimulating stem cell proliferation, neutrophils differentiation, maturation, and activation, leading to the localization of neutrophils to the skin which is accumulated. Elevated G-CSF levels have been observed in various Sweet syndrome cases [4,15]. The clinical manifestation of Sweet syndrome is typically fever that may precede several days to weeks before skin eruptions, lethargy, arthralgia, headache, and myalgia. Skin lesions are typically described as red or purple-red painful papules or nodules, plaques that are commonly asymmetrically distributed may present as single or multiple lesions. Vesicles, bullae, and pustules occurrences also have been reported. The most frequently affected regions are the upper extremities, face, and neck. Atypical skin distribution manifestation of Sweet syndrome also has been reported. Sweet syndrome may also involve extracutaneous organs such as bones, central nervous system, ears, kidneys, eyes, and many others [4,16,17].

The typical laboratory result for Sweet syndrome is peripheral leukocytosis with neutrophilia [17]. Skin lesion biopsy is needed to confirm the clinically suspected Sweet syndrome which reveals neutrophilic dermatosis or panniculitis. Histopathological examinations may reveal edema in the superficial dermis with dense neutrophil infiltrate in the dermis and upper epidermis [4,16]. Differential diagnosis of Sweet syndrome consists of erythema nodosum, erythema multiforme, erythema elevatum diutinum, leukocytoclastic vasculitis, leukemia cutis, pyoderma gangrenosum, panniculitis, and other drug eruptions [17]. Diagnostic criteria of the drug-associated Sweet syndrome can be seen in **Table 1**. Management of drug-induced Sweet syndrome is to stop the associated medication. Systemic corticosteroids may be given due to the nature of the inflammatory properties of Sweet syndrome. Prednisone can be initiated at 1 mg/kg/day and tapered off accordingly. Other drugs such as potassium iodide and colchicine may also be helpful for Sweet syndrome treatment [13].

Our case was clinically diagnosed as possible Sweet syndrome due to the matching clinical characteristics of Sweet syndrome diagnostic criteria. However, a histopathological examination was not made in this case. The IgE level commonly elevated in typical drug allergy reactions is also not elevated in our case [18]. Our patient also developed symptoms after G-CSF administration, and the neutrophil was drastically increased after G-CSF administration. Therefore, the patient was predisposed to the drug-induced Sweet syndrome. He also well responded with systemic corticosteroid administration and G-CSF cessation.

CONCLUSIONS

G-CSF administration in febrile neutropenic cancer patients may induce several adverse events from mild to severe degrees. Cutaneous adverse events following G-CSF administration should be recognized and treated accordingly. Consultation with the dermatology department is needed. Sweet syndrome is rare but should be recognized as a possible G-CSF-induced drug skin complication.

DECLARATIONS

Competing of Interest

The authors declare no competing interest in this study.

Acknowledgment

Not applicable

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