Necrotizing Ulcerative Gingivitis in a Patient with Methimazole-Induced Agranulocytosis

YEE-HUANG KU¹, PING-CHIN CHANG¹, YUEH-FENG TSAI²

Agranulocytosis, which is often caused by drugs, is a rare but life-threatening disorder. A 38-year-old woman visited the emergency department with a sore throat and gum swelling for 3 days. Neutropenia was found via blood examination. She had been diagnosed with hyperthyroidism one month previously and had started methimazole 5 mg twice a day. The symptoms did not improve much with antibiotics (piperacillin/tazobactam 4.5g every 6 hours and amoxicillin/clavulanate 1.2g every 8 hour) and an antiseptic mouthwash (each bottle has 500 ml and contains sodium borate 30g, sodium bicarbonate 30, glycerin 66g, phenol 6 ml) even after the WBC count returned to normal. The symptoms dramatically improved after the use of intravenous hydrocortisone 100mg every 8 hours. Further clinical studies are indicated in determining the role of steroids in the treatment of necrotizing ulcerative gingivitis.

Key words: methimazole, necrotizing gingivitis, agranulocytosis

Introduction

Agranulocytosis is a rare hematological condition defined as a profound decrease in the circulating neutrophil count to less than $0.5 \times 10^9/L$ because of immunologic or cytotoxic mechanisms(1). Some drugs are well-documented causes of agranulocytosis, so discontinuation of treatment is crucial to avoid continued hazardous exposure(1,2). Necrotizing ulcerative gingivitis (NUG), also known as necrotizing gingivitis (NG), is an acute opportunistic infection of the gingivu(3,4). Here we reported an unusual case of necrotizing gingivitis which may have been secondary to agranulocytosis induced by methimazole.

Case Report

A 38-year-old housewife had been well until one month previously when she was diagnosed with hyperthyroidism. She had been taking anti-thyroid drugs, including methimazole 5mg twice a day, and oral propanolol 10mg three times a day, for more than one month. She presented in our emergency department with complaints of gum pain and a sore throat for 3 days. She had visited a local clinic, but her symptoms persisted and even progressed. There was no other associated discomfort, such as fever or chills, chest or abdominal discomfort, or skin manifestations. In the emergency department, her body temperature was $37^\circ C$, pulse rate 137 beats/min and respiratory rate 18 breaths/min. Her gums were swollen with ulcerative changes at the base of her teeth throughout her mouth. She had injected tonsils coated with pus bilaterally with ulcers. No other abnormalities were found. A complete blood count showed WBCs 800/mL, with segments 20%, lymphocytes 45%, monocytes
31%, and atypical lymphocytes 2%. The hemoglobin and platelet counts were 13.8g/dL and 217,000/mL, respectively. A blood chemistry test showed blood urea nitrogen 6mg/dL, creatinine 0.82mg/dL, sodium 137mmole/L, potassium 3.1mmol/L, aspartate aminotransferase 19IU/L, alanine transaminase 47IU/L, and C-reactive protein > 250mg/L. She was admitted to the infection ward. Initially, intravenous piperacillin/tazobactam 4.5g was given every 6 hours for the neutropenic necrotizing gingivitis. Her personal and medical history was reviewed thoroughly. She had taken only oral methimazole 5mg twice a day and propanolol 10mg three times a day for more than one month, and a non-steroidal inflammatory agent (NSAID) for the past 3 days for gum pain. The anti-thyroid drug was then discontinued after admission. She still had hyperthyroidism (TSH 0.03mIU/L, free T4 1.76ng/dL). A dentist performed a gingival biopsy. Pathologic findings included necrotic debris and many bacterial colonies. Blood cultures done in the emergency department revealed no growth. Serology examination for anti-nuclear antigen was negative, but the patient refused an anti-HIV examination. Her white blood cell count 2 days after admission was WBCs 6900/mL, with bands 1%, segments 49%, lymphocytes 27%, monocytes 15%, metamyelocytes 2%, and myelocytes 4%. Antibiotic therapy was then shifted to intravenous amoxicillin/clavulanate 1.2g every 8 hours. In addition, an antiseptic solution (each bottle has 500ml and contains sodium borate 30g, sodium bicarbonate 30, glycerin 66g and phenol 6ml) was prescribed as a mouth rinse. However, the symptoms did not improve much over the following 6 days. On the 6th hospital day her WBC count was 5600/mL, with bands 1%, segments 45%, lymphocytes 31%, monocytes 20%, metamyelocytes 2%, and myelocytes 1%. Hydrocortisone 100mg was started intravenously every 8 hours and an oral anti-histamine (cyproheptadine 4mg three times a day) were started on the 7th hospital day. The antibiotic regimen was changed to oral ofloxacin 400mg twice a day and clindamycin 600mg intravenously every 8 hours to avoid any further allergic drug reaction. The gum swelling and gum necrosis dramatically improved. The patient was discharged home on the 11th hospital day. Six days after discharge, she had recovered from the gum necrosis and had only mild gum pain. Further treatment with I$_{131}$ was recommended by an endocrinologist but the patient was lost to follow-up.

**Discussion**

Thyroid disease, as well as its treatment, is well known to affect the hematopoietic system$^{(5)}$. Antithyroid drugs are associated with a variety of minor side effects, as well as lethal events. Transient mild leukopenia is rather a benign adverse drug effect that had been reported with an incidence rate of 12% in treated patients$^{(6)}$. It is often noticed only if there is routine monitoring of the WBC count. However, this practice is still controversial$^{(5,7)}$.

Agranulocytosis (an absolute granulocyte count < 500/mL) is the most feared side effect of antithyroid-drug therapy and mostly occurs within the first 90 days of treatment. Antithyroid drug-induced agranulocytosis has been estimated to occur in approximately 0.37% of patients receiving propylthiouracil and 0.35% of patients receiving methimazole. In addition, the side effects of methimazole are clearly dose-related whereas with propylthiouracil they are not$^{(5)}$. Nevertheless, our reported patient had taken only a low dose of methimazole (10mg daily) for more than one month although the baseline WBC differential count was unremarkable. Discontinuing possible associated antithyroid drugs is essential. In addition, studies also recommend the administration of granulocyte colony-stimulating factor (G-CSF) or even steroids,
so that the WBC count can promptly recover\(^{(1,5,6)}\). However, the WBC count in our patient recovered spontaneously and promptly without any intervention except for discontinuation of the antithyroid agent.

Necrotizing ulcerative gingivitis (NUG) has a unique presentation among periodontal diseases. It is characterized by interdental gingival necrosis, intense pain and spontaneous bleeding. No doubt, NUG is considered an opportunistic infection of the gingiva. Reduction of the microbial population in the gingival plaque by systemic antibiotic therapy and/or mechanical debridement results in a dramatic resolution of symptoms and signs\(^{(4,8)}\). However, NUG is associated with several predisposing factors such as psychological stress, malnutrition, smoking and immunosuppression. Studies show that a compromised immune status plays a predominant role in the development of NUG\(^{(4,8)}\). Our patient had received intravenous broad-spectrum antibiotic therapy from the beginning of the hospital course, but her clinical condition failed to respond, even after recovery of the WBC count, until steroid therapy was started. This may give us a clue that NUG is not only an infectious disease, but also a consequence of inflammation. More clinical experience is needed to further define the role of steroids.

In conclusion, NUG is classically considered as an opportunistic infection and even a consequence of a modified immune status. Treatment should include antibiotics and mechanical debridement. More clinical experience is indicated in determining the role of steroids in the treatment of NUG.

References

壞死性牙齦炎發生於一位因服用抗甲狀腺素(甲硫嘧啶)引發顆粒性白血球缺乏症的病人

丘憶芬¹ 張炳欽¹ 蔡岳峰²

顆粒性白血球缺乏症常由藥物引起，發生率低但致命性高。一位38歲女性因3天的喉嚨痛及牙齦腫痛而到急診就診。抽血檢查發現白血球數低下。這位女性過去健康狀態良好，約一個多月前因被診斷甲狀腺機能亢進而開始服用抗甲狀腺素(methimazole 5mg一天兩次)。縱然白血球數有回昇，可是給予抗生素(pepiracillin/tazobactam 4.5g每8小時及後來的amoxicillin/clavulanate 1.2g每8小時)治療及抗菌液漱口(每500ml含sodium borate 30g, sodium bicarbonate 30, glycerin 66g, phenol 6ml)時，成效不彰。直到類固醇(Hydrocortisone 100mg每8小時)的使用，症狀才有明顯的改善。而類固醇的使用在治療壞死性牙齦炎上所扮演的角色為何，則需更多的臨床研究來證實。

關鍵詞：甲硫嘧啶，壞死性牙齦炎，顆粒性白血球缺乏症