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***Cover Letter**

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Dear Sir,

We are submitting a manuscript entitled "*Pseudomonas aeruginosa Necrotizing* Fasciitis in a Patient with Methimazole-Induced Agranulocytosis" as a Brief Report for consideration for publication in your *Journal*. We present a rare case involving a 68-year-old woman with recurrent hyperthyroidism had methimazole-induced agranulocytosis and developed *Pseudomonas aeruginosa* necrotizing fasciitis after a hand injury. The manuscript and figures have not been previously published. The manuscript is not under consideration elsewhere. We hope that the manuscript is suitable for publication in your *Journal*.

Sincerely yours

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Pseudomonas aeruginosa Necrotizing Fasciitis in a Patient with Methimazole-Induced Agranulocytosis

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Agranulocytosis is a rare but feared side effect of methimazole treatment of hyperthyroidism. Life-threatening infection, including sepsis or septic shock, may develop among these patients. *Pseudomonas aeruginosa* is the most commonly associated organism. [1]

A 68-year-old woman was transferred to the emergency department (ED) because of pain and swelling in her left hand. She had a history of hyperthyroidism and received subtotal thyroidectomy eight years previously. She had been well until two months earlier, when she started medical treatment with methimazole (15 mg twice a day) and propranolol (10 mg per day). About two weeks before admission, she achieved euthyroid status, and the dose of methimazole was changed to 15 mg per day.

Nine days before admission, she injured her left hand in a fall, which resulted in an abrasion wound. Two days later, the hand became swollen and painful. By evening, she had chills and her temperature rose to 38.9℃. At another hospital, the white-cell count was 770 / mm3 (reference range, 3990 to 10390) with 3% neutrophils (40 to 74%) and 89% lymphocytes (19 to 48%). Her hand became even more mottled and swollen, and she received emergent fasciotomy. Parenteral antibiotics, piperacillin and tazobactam, were also initiated. However, because of the persistent febrile status with rapid progression of swelling and cyanosis, she was transferred to the ED of this hospital on postinjury day (PID) 8.

Her vital signs were: blood pressure, 96/64 mmHg; temperature, 36.5℃; pulse, 83 beats per minute; respiratory rate, 26 per minute; and oxygen saturation, 100% while breathing 3 liters of oxygen by nasal cannula. The skin of her left hand appeared cyanotic with scattered bullae; the swelling extended up to the forearm (Fig. 1). Laboratory tests revealed pancytopenia, hyperbilirubinemia, and azotemia. Intravenous cefepime (1 g every 12 hours) was initiated.

On the next day, another fasciotomy was done with the incision extended to her arm. Granulocyte-colony stimulating factor (G-CSF) was administered once daily for 3 days starting on day 3 of hospitalization. Moreover, because of acalculous cholecystitis, she received percutaneous transhepatic gallbladder drainage. Her left middle finger was amputated because of severe necrosis. The forearm and dorsal hand skin and soft tissue defect were reconstructed with skin-grafting and pedicle groin flap, respectively. The groin flap was divided three weeks later. After 50 days of hospitalization, the patient was discharged in stable condition.

The soft tissue and pus cultures from her left hand yielded solely *Pseudomonas aeruginosa*. Antibiotic-susceptibility patterns showed susceptibility to all antibiotics. No organisms were obtained from the blood cultures. Necrotizing fasciitis in the necrotic tissue from her left hand was proved the by pathology.

Agranulocytosis (absolute granulocyte count less than 500 per cubic millimeter) is the most serious and potentially fatal side effect of antithyroid therapy. Agranulocytosis occurs in 0.17% to 0.35% of patients receiving methimazole.[1] The mechanism of methimazole-induced agranulocytosis is thought to be a drug-induced immune-mediated process and is dose-related. Doses of methimazole greater than 30 mg/day and/or age over 40 years are risk factors for development of agranulocytosis, which usually occurs within the first 2 months of methimazole therapy.[2] Fever and sore throat are the most common presenting symptoms of agranulocytosis. If there is rapid onset of fever, chills, and prostration, agranulocytosis-related sepsis is highly likely. The patient should discontinue the use of methimazole, and intravenous broad-spectrum antibiotics covering *Pseudomonas aeruginosa* should be initiated.[1] Our patient developed a methimazole-induced agranulocytosis aggravated by a *Pseudomonas aeruginosa* necrotizing fasciitis. Although no organism was produced from blood cultures, we believe that the patient may have initially developed a *Pseudomonas aeruginosa*-related sepsis despite the negative results from blood culture, which may have been

caused by the previous treatment with piperacillin/tazobactam and amikacin.

Necrotizing fasciitis is an uncommon severe soft tissue infection, which has high mortality. The major pathogens causing necrotizing fasciitis include streptococci, staphylococci, and anaerobes. *Pseudomonas aeruginosa* may cause soft tissue infections with peri-vasculitis secondary to bacteremia, but it is rarely associated with necrotizing fasciitis unless the patient is immunocompromised. In our patient, necrotizing fasciitis of her left hand may have been due to bacteremia after the hand trauma.

The administration of G-CSF was shown to shorten the time to recovery and length of hospitalization in patients with methimazole-induced agranulocytosis. Although a prospective randomized controlled trial showed no significant difference in recovery times compared to no treatment,[3] most clinicians recommend using G-CSF for methimazole-induced agranulocytosis. In our patient, G-CSF was administered since PID 11 for 3 days. The absolute neutrophil count returned to the normal range on PID 19. The recovery period was similar to that in previously reported series. [4]

In conclusion, we report a rare case of *Pseudomonas aeruginosa* necrotizing fasciitis in a patient with methimazole-induced agranulocytosis. Clinicians should be vigilant for *Pseudomonas aeruginosa*-related soft tissue infection in such patients. Timely surgical intervention and adequate antibiotics play vital roles in the patient's recovery.

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Figure legends

Figure 1. Hemorrhagic bullae with skin necrosis of the wounded left hand and forearm on postinjury day 10.

Figure(s)

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