BRIEF ARTICLES

Minocycline-Induced Agranulocytosis Presenting as Ecthyma Gangrenosum

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ABSTRACT

A 51-year-old female with a history of rheumatoid arthritis was admitted for progressive fevers, chills and malaise. Five weeks prior, she started minocycline for an RA exacerbation. Two weeks after starting minocycline she developed an abscess on her right ankle that was treated at an urgent care facility with ceftriaxone and trimethoprim-sulfamethoxazole. She had minimal improvement so was switched to clindamycin. She developed additional abscesses on her right ankle and right axilla and spiking fevers so she was treated with incision and drainage under general anesthesia. Routine blood work obtained prior to surgery revealed severe neutropenia (0.74 103/ul) and the patient was urgently referred to the emergency department. Skin biopsy was obtained on admission and revealed ulceration, necrosis, acute and chronic inflammation, vasculitis with vascular thrombosis and rod-shaped bacteria in blood vessel walls and lumina consistent with ecthyma gangrenosum. The following day tissue and blood cultures confirmed the growth of Pseudomonas aureginosa.

Bone-marrow biopsy showed decreased granulopoiesis and hematopoiesis, and a diagnosis of minocycline-induced agranulocytosis presenting as ecthyma gangrenosum was made. The patient had dramatic improvement with appropriate antibiotic therapy, discontinuation of minocycline and initiation of filgrastrim. She has remained healthy without recurrence for 17 months.

CASE REPORT

A 51-year-old woman with a history of rheumatoid factor negative rheumatoid arthritis was admitted for tender abscesses, intermittent spiking fevers, chills, night sweats, malaise, shortness of breath and non-productive cough. She was diagnosed with rheumatoid arthritis 16 years prior to

presentation. Her rheumatoid arthritis was successfully treated with minocycline 100 mg daily for 6 months and subsequently her disease went into remission.

Five weeks prior to admission she developed worsening joint pain and swelling. Given her prior treatment success with minocycline, her rheumatologist prescribed minocycline 100 mg daily. Three weeks prior to admission she developed a tender violaceous papule with surrounding erythema on the right lateral leg. Over the following 3 weeks the patient was treated at an urgent care center four times. She was diagnosed with an abscess and treated with intramuscular ceftriaxone, trimethoprim-sulfamethoxazole DS twice a day, clindamycin 300 mg three times a day. She developed additional abscesses at distant sites and ultimately was treated with incision and drainage of the abscesses under general anesthesia because of the progression of symptoms despite oral antibiotics. The following day, the patient was notified that blood work drawn prior to surgery revealed an abnormally low white blood cell count. She was referred to the emergency department for further evaluation and admission for intravenous antibiotics. At the time of admission, review of systems was positive for intermittent spiking fevers, chills, night sweats, malaise, shortness of breath and non-productive cough. She denied unintentional weight loss. The patient had a complete blood count 3 months prior, which was normal.

On admission the patient had temperature of 98.2F, heart rate 77, respiratory rate 20, blood pressure 113/77. She was initially treated with vancomycin but continued to develop intermittent episodes of fever (Tmax 103.2F) a blood pressure of 79/50 so meropenem was added.

Pertinent laboratory analyses included decreased white blood cell count of 0.74 10^3/ul, hemoglobin 11.2 g/dL, hematocrit 33.5% (mean cell volume 87.5 fL) and absolute neutrophil count of 0.16 10^3/ul but increased platelet count 514 10^3/ul, ESR 72 mm/hr, CRP 153 mg/L and lactic acid 3 mmol/L.

Chest x-ray showed peripheral prominent patchy airspace opacities more confluent in the bilateral upper lung fields and bilateral lower lung fields, blunting of the costophrenic angles consistent with multifocal pneumonia and small bilateral pleural effusions.

Dermatology was consulted and a skin biopsy was obtained for tissue culture and histology. Histopathologic analysis of the edge of the right lateral leg ulcer showed ulceration, necrosis, acute and chronic inflammation, vasculitis with vascular thrombosis, and rod-shaped bacteria in blood vessel walls, lumina and the dermis. With this result, vancomycin and meropenem were discontinued, piperacillin-tazobactam, ciprofloxacin and filgrastrim were initiated. The following day, tissue culture and blood cultures grew *Pseudomonas aureginosa*.

Peripheral blood flow cytometry failed to reveal a monoclonal B-cell proliferation or an aberrant T-cell immunophenotype and there was no evidence of a discrete blast population. Bone marrow biopsy showed decreased granulopoiesis and hematopoiesis with adequate iron stores and without evidence of fibrosis, necrosis, granulomatous inflammation, lymphoma, leukemia, or cells extrinsic to the marrow. Based on these findings, a diagnosis of minocycline-induced agranulocytosis presenting as ecthyma gangrenosum was made.

Minocycline had been discontinued upon admission to the hospital. The patient had a dramatic improvement after piperacillin-tazobactam, ciprofloxacin and filgrastrim were initiated; vital signs and white blood cell count normalized and repeat blood cultures were negative for growth of *P. aeruginosa*.

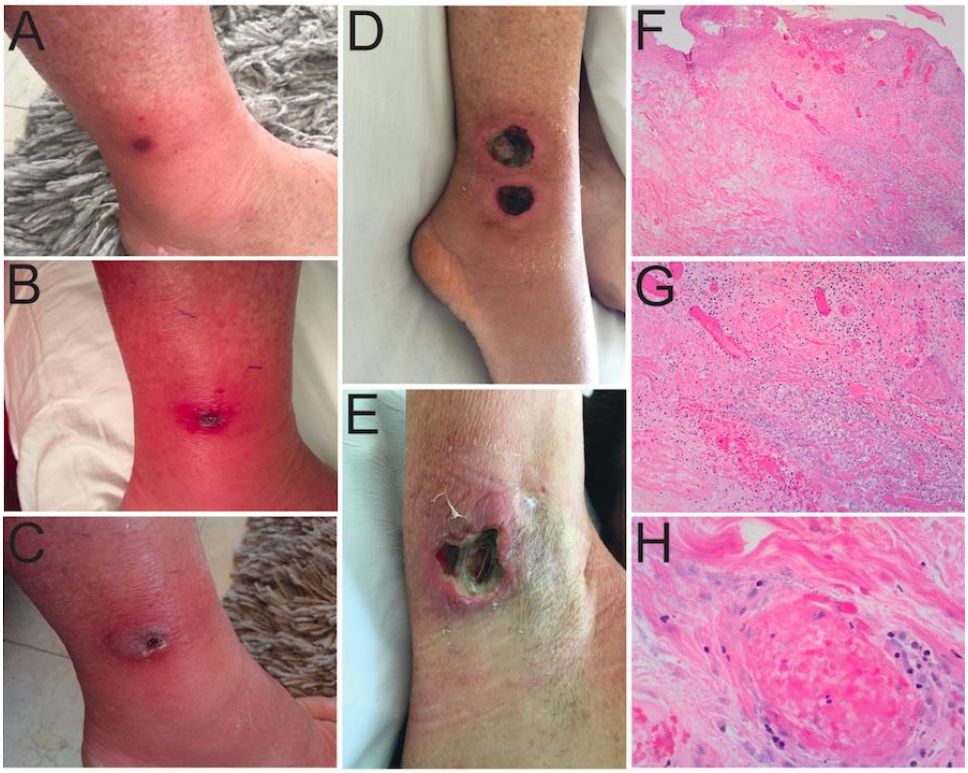

Figure 1. Clinical and histopathological images of ecthyma gangrenosum that developed in a patient treated with minocycline for rheumatoid arthritis. Clinical progression of the initial lesion on the right ankle from a dusky, violaceous and tender papule to a necrotic ulcer in the weeks prior to hospitalization, images were taken by the patient (A-C). Appearance of the lesions on the day of presentation to the hospital (D-E). Histopathology revealed ulceration, necrosis and mixed acute and chronic inflammation (F-G) and vessels with vasculitis and rod shaped bacteria within the lumen and wall (H).

DISCUSSION

Minocycline is a semisynthetic tetracycline derivative antibiotic commonly used for the treatment of aerobic and anerobic gram positive and negative bacterial as well as fungal infections. Interestingly, minocyline is involved with a wide variety of biological actions other than anti-microbial activity. For example, this drug decreases the production of substances causing inflammation, such as prostaglandins, metalloproteinases and leukotrienes and therefore is used to treat the inflammation associated with acne vulgaris as well as that inherent to autoimmune diseases such as rheumatoid arthritis.

Although minocycline has been used as a successful treatment for many diseases, serious but rare adverse events such as neutropenia associated autoimmune hepatitis and minocycline-induced lupus with neutropenia have been reported.[1-2] Drug-induced agranulocytosis occurs with a

variety of classes of medications including dipyrone, diclofenac, ticlopidine, antithyroid drugs such as methimazole, carbamazepine, clozapine, and trimethoprim-sulfamethoxazole. A rapid decrease in agranulocytes often occurs within hours 1 to 2 days after administration of the drug. The recovery of the neutrophil count can take an average of 9 days to return to within normal limits (range: 9-24 days).[3] Treatment of neutropenia usually consists of supportive care, including broad-spectrum antibiotics for febrile patients.[4] Delivery of granulocyte colony stimulating factors such as G-CSF and GM-CSF, has been shown to contribute to rapid healing by partial recovery of neutrophil production and function.[4]

The neutropenia caused by minocycline therapy is thought to be immunologic in origin. Although the mechanism(s) are unclear, it is thought that the unique metabolism of minocycline may be responsible for the increase in serious adverse events compared to other tetracycline antibiotics. Minocycline reactive metabolites may bind tissue macromolecules causing direct cell damage or these metabolites may act as haptens and elicit immune responses in a secondary manner.[5]

In conclusion, we present a rare case of minocycline-induced agranulocytosis presenting as ecthyma grangrenosum in a previously healthy patient with rapid resolution upon immediate discontinuation of minocycline and subsequent treatment with piperacillin-tazobactam, ciprofloxacin and filgrastrin. Seventeen months after this illness, she remains in excellent health without any recurrences. Although neutropenia due to minocycline appears to be a rare adverse event, it is important to draw attention to these known severe sequelae given the frequently with which minocycline is used. Immediate discontinuation of the offending medication, initiation of broad-spectrum antibiotics and consideration of the use of granulocyte colony-stimulating factors may help improve outcomes in similar cases.

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