# Zoledronic Acid–Induced Interface Dermatitis

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**Abstract:** Zoledronic acid (ZA) is a bisphosphonate given intravenously, most commonly for the treatment of postmenopausal osteoporosis. Increase in usage of ZA because it was FDA-approved has resulted in increasing reports of side effects. For the most part, these are systemic. Cutaneous side effects associated with ZA are infrequent and limited to 2 reports of dermatomyositis to date. In both, patients presented with clinical and laboratory stigmata of dermatomyositis soon after initiation of therapy. In this report, we describe a 62-year-old woman who presented with diffuse, erythematous scaly plaques over the right thigh after 12 hours of infusion of ZA. Histopathologic examination of a skin biopsy from the right thigh revealed patchy scale crust containing neutrophils and inspissated serum, interface change with scattered individually necrotic keratinocytes, and a mild, superficial perivascular lymphocytic infiltrate with scattered eosinophils and pigment incontinence—findings consistent with an interface dermatitis. Given that the patient had no other systemic manifestations or laboratory abnormalities, to the best of our knowledge, ours is the first report of interface dermatitis secondary to ZA with the caveat that longer follow-up is required to definitively exclude the development of drug-induced connective tissue disease.

**Key Words:** zoledronic acid, interface dermatitis

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## INTRODUCTION

Zoledronic acid (ZA) (Reclast, Zometa), first FDA-approved in 2001, is a bisphosphonate most commonly used for the treatment and prevention of postmenopausal osteoporosis, along with metastatic disease to the bone, hypercalcemia associated with malignancy, Paget disease, and multiple myeloma. ZA inhibits osteoclast proliferation and induces osteoclast apoptosis, thus slowing down bone resorption, allowing the bone-forming cells time to rebuild normal bone and allowing bone remodeling.[1]

The increase in usage of bisphosphonates has resulted in increasing reports of side effects. Common systemic side effects include upper gastrointestinal tract adverse events such as nausea and dyspepsia, ocular side effects such as nonspecific conjunctivitis, and more serious systemic side effects that include renal toxicity, atrial fibrillation, and osteonecrosis of the jaw.[2] However, cutaneous side effects associated with bisphosphonate usage are extremely uncommon and include lichen planus,[3] figurate erythema,[4] spongiotic dermatitis,[5] and vasculitis.[6]

## CASE REPORT

We describe a 62-year-old woman who presented with diffuse erythematous scaly plaques over the right thigh after 12 hours of infusion of ZA for osteoporosis. She was not on any other medication, and her medical history was otherwise unremarkable. Histopathologic examination of the skin biopsy taken from the right thigh revealed patchy scale crust containing neutrophils and inspissated serum, interface change with scattered individually necrotic keratinocytes, and a mild, superficial perivascular lymphocytic infiltrate with scattered eosinophils and pigment incontinence —findings consistent with an interface dermatitis (Fig. 1). To note, however, there was no increase in dermal mucin and PAS stain did not indicate basement membrane zone thickening. Given that the patient had no systemic manifestations of connective tissue disease and negative blood work (CBC, ANA, ESR, and CRP), the patient was diagnosed with isolated interface dermatitis secondary to ZA. As per the referring physician, the patient had clearance of her lesions after discontinuation of ZA.

## DISCUSSION

Cutaneous side effects associated with ZA are extremely limited and, to date, only 4 cases have been reported in the literature. In terms of histopathologic reaction

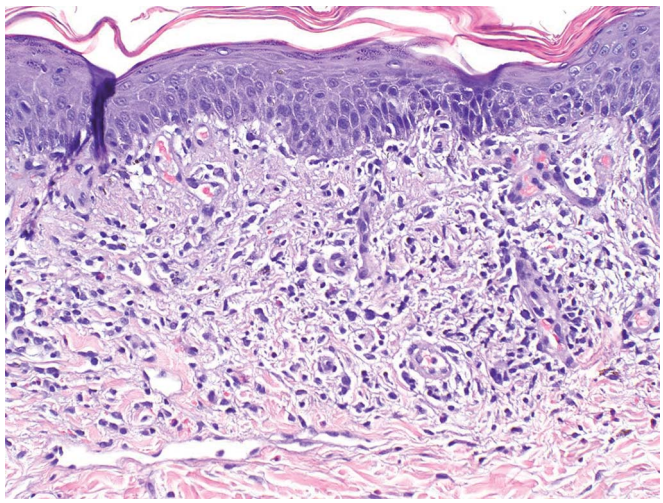

**FIGURE 1.** H&E (×10): patchy scale crust containing neutrophils and inspissated serum, interface change with scattered individually necrotic keratinocytes, and a mild, superficial perivascular lymphocytic infiltrate with scattered eosinophils and pigment incontinence.

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**TABLE 1.** Biopsy-Proven Noninterface Dermatitis Side Effects to ZA

| | Patient 1[7] | Patient 2[8] |
|---|---|---|
| Age, years | 57 | 52 |
| Gender | Female | Female |
| Reason for administration of ZA | Metastatic breast cancer | Metastatic breast cancer |
| Morphology of lesions | Edematous papules and plaques over extremities | Necrotic ulcers on lip |
| Histopathologic findings | Reactive, nodular lymphoid hyperplasia | Nonspecific ulcerations and a mild, superficial perivascular inflammation |

**TABLE 2.** Biopsy-Proven Interface Dermatitis Associated With ZA Use

| | Patient 1[9] | Patient 2[10] | Our Patient |
|---|---|---|---|
| Age, years | 65 | 57 | 62 |
| Gender | Female | Female | Female |
| Reason for administration of ZA | Osteoporosis | Osteoporosis | Osteoporosis |
| Morphology of lesions | Erythematous scaly plaques on face, chest, and upper extremities | Erythematous atrophic macules over forehead | Erythematous scaly plaques over right thigh |
| Histopathologic findings | Basal cell layer vacuolization and a superficial, perivascular lymphocytic inflammation | Lichenoid lymphocytic inflammation with basal cell layer vacuolization, and increased dermal mucin | Patchy scale crust with neutrophils, mild basal cell layer vacuolization, individually necrotic keratinocytes, and a superficial, perivascular lymphocytic inflammation with scattered eosinophils and pigment incontinence |
| Associated systemic findings | Proximal muscle weakness, fatigue, weight loss | Proximal muscle weakness, weight loss | None |

patterns, cutaneous side effects fall into no definite categories. Briefly, in one, the histopathology was that of benign lymphoid hyperplasia, whereas in another it was that of an ulcer with nonspecific underlying inflammation. The first patient was a 57-year-old woman who was on ZA for metastatic breast cancer. She presented with a 1-month history of pruritic papules and plaques over extremities after 9 months of ZA administration.[7] The second patient was a 52-year-old woman who was on ZA for metastatic breast cancer as well, but her clinical presentation was that of painful erosions on the lip. Her symptoms started after 8 months of initiation of ZA[8] (Table 1). In the other two, histopathologic findings were those of an interface dermatitis with concomitant clinical manifestations of dermatomyositis. Briefly, the first patient was a 57-year-old woman who presented with a widespread erythematous rash associated with fatigue, proximal muscle weakness, and weight loss 3 days after a single infusion of ZA for osteoporosis. Her laboratories confirmed the diagnosis with an extremely elevated creatinine kinase, alanine transaminase, and alkaline phosphatase, along with a positive antinuclear antibody.[9] The second patient was a 65-year-old woman, also on ZA for osteoporosis, presented with widespread erythematous plaques along with proximal muscle weakness and weight loss 5 months after ZA administration. The patient had positive antinuclear and anit-Jo-1 antibodies, elevated AST, alanine transaminase, and creatinine kinase[10] (Table 2). Although the histopathologic reaction pattern in our case was also that of an interface dermatitis, the distinguishing feature in our case was the presence of scattered eosinophils (reportedly not present in the other 2 cases of interface dermatitis associated with ZA). The presence of eosinophils in the setting of an interface dermatitis is uncommon in connective tissue disease such as dermatomyositis or lupus erythematosus, and the presence of "even 1 eosinophil" reportedly argues in favor of a drug reaction and against the diagnosis of interface dermatitis secondary to connective tissue diseases.[11] Furthermore, our patient had no weight loss, fatigue, nor any proximal muscle weakness, and had a negative connective tissue disease workup (CBC, ANA, ESR, and CRP)—all of which argued against underlying/associated dermatomyositis.

Although long-term follow-up is required to definitively exclude the development of drug-induced connective tissue disease, given that systemic manifestations of the same typically develop *soon after* initiation of ZA therapy, to best of our knowledge, our patient is the first report of ZA-induced interface dermatitis without clinical stigmata of dermatomyositis.

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