Multifocal periungual granulation tissue related to ibrutinib therapy

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INTRODUCTION

Ibrutinib is a Bruton tyrosine kinase inhibitor that affects not only malignant B-cell proliferation but is also used for the treatment of chronic lymphocytic leukemia, previously treated mantle cell lymphoma, Waldenström macroglobulinemia, and graft-versus-host disease (GVHD).[1] As the indications for ibrutinib therapy and the number of treated patients have grown, so too has the knowledge of ibrutinib's adverse effect profile. The literature has shown that roughly 2% to 27% of patients receiving ibrutinib therapy will develop cutaneous adverse reactions.[2] Although a handful of case reports and small retrospective cohorts have cataloged manifestations such as rash, petechiae, and bruising, there is a paucity of literature describing the cutaneous adverse effect profile of ibrutinib. There is much variation in the spectrum of ibrutinib-induced cutaneous adverse reactions. Iberri et al[1] reported on a small case series of 14 patients who developed ibrutinib-associated rashes and determined that there were 2 characteristic presentations: (1) a nonpalpable, petechial eruption or (2) a palpable purpuric rash.[1] On the other hand, a case report published by Ghasoub et al[3] described a more nefarious ibrutinib-associated rash resulting in severe skin toxicity. In that case report, a 68-year-old man developed multiple hyperpigmented lesions that progressed to pustules and cellulitis. The pustules and cellulitis were likely related to immunosuppression and *Staphylococcus* infection rather than to skin toxicity of ibrutinib.

Given the spectrum of adverse reactions for ibrutinib, it is important for providers to be aware of the potentially severe adverse effects. In our case report, we highlight a unique manifestation of multifocal periungual granulation tissue related to ibrutinib therapy. We hope that this critical review will add to the literature, help providers inform patients about this potential risk, and aid with targeted clinical management of periungual granulation tissue.

Abbreviation used:

GVHD: graft-versus-host disease

CASE REPORT

A 64-year-old man with a history of bone marrow transplant for T-cell lymphoma complicated by sclerodermoid GVHD was referred to the dermatology department. He was treated with ultraviolet A-1 light therapy, ibrutinib, prednisone, and cyclosporine. His GVHD was well controlled with this regimen. Six months after starting cyclosporine (300-350 mg a day) and 3 months after starting ibrutinib (420 mg a day), he developed painful nodules on the third fingers bilaterally with excess granulation tissue around the nail bed (Fig 1). In the clinic, the lesions were debulked, tissue was sent for pathologic assessment, and intralesional Kenalog (5 mg/ml) (Bristol-Myers Squibb, Princeton, NJ) was administered at the base of each lesion. The pathologic assessment showed large, polypoid acral skin fragments with edema, an increased number of thin-walled vessels, and a mixed inflammatory infiltrate concerning for granulation tissue (Fig 2). The patient was instructed to soak his affected fingers with acetic acid solution, cover the lesions with petroleum jelly and bandages, and apply clobetasol 0.05% cream

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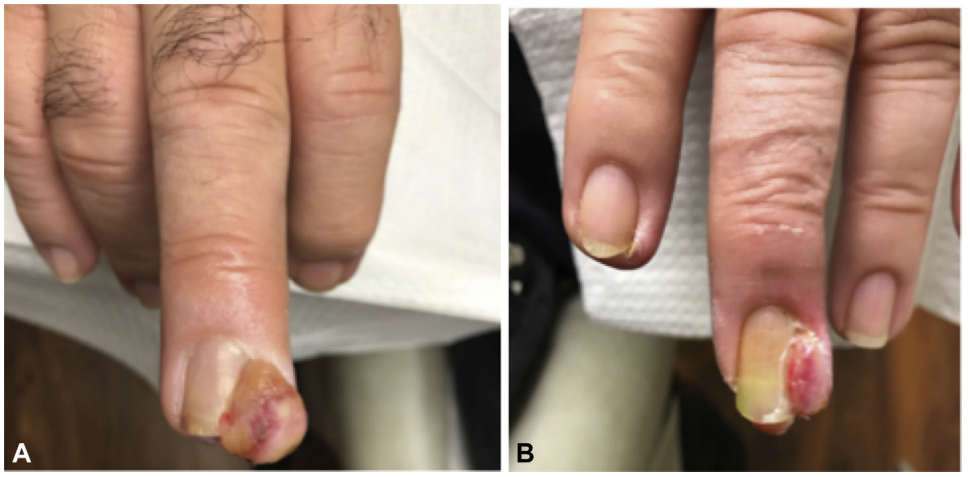

Fig 1. Excess granulation tissue on the right and left third fingers. **A**, The right third finger and (**B**) left third finger show erythematous nodules consisting of excess tissue growth around the edge of the nail bed. Pathologic assessment confirmed excess granulation tissue.

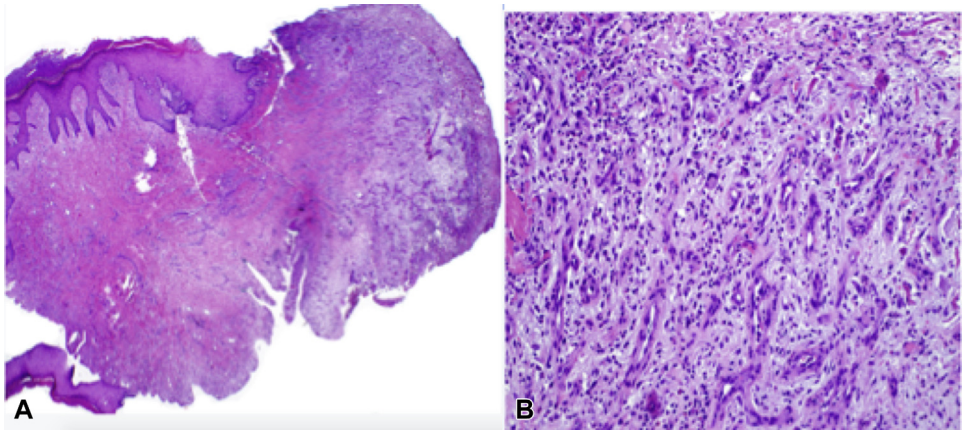

Fig 2. Histology. **A**, The gross tissue specimen and (**B**) a zoomed-in view of granulation tissue showed large, polypoid acral skin fragments with edema, an increased number of thin-walled vessels, and a mixed inflammatory infiltrate.

twice daily for 2 weeks. After 5 months of conservative therapy, ibrutinib was suspected as a causative agent and discontinued; subsequently, the lesions began to resolve. The patient continued to take cyclosporine 250 to 300 mg a day, but the periungual granulation tissue has continued to improve.

DISCUSSION

This case report is essential because it highlights an important, yet relatively unknown, adverse reaction of ibrutinib therapy. Mohandas et al[4] published an abstract describing 2 patients who developed severe paronychia and excessive granulation tissue within 3 months of the initiation of ibrutinib therapy. One patient had mantle cell lymphoma, and the other had chronic lymphocytic leukemia. Although one patient was lost to follow-up, the second patient endured an excessive treatment regimen including azithromycin, nail avulsion, linezolid, itraconazole, and oral and topical acyclovir with no improvement. Results of a subsequent biopsy were negative for infection on organism stains and tissue culture but showed perivascular lymphohistiocytic inflammation with neutrophils. The researchers concluded that the granulation tissue must represent inflammatory sequelae rather than infection and began acetic acid soaks and clobetasol ointment twice daily. There was some improvement with this revised treatment regimen. Although this provides some insight, more research is required to determine the mechanism of periungual granulation tissue development.

Periungual granulation tissue is not a phenomenon exclusive to ibrutinib therapy. Both gefitinib, an

epidermal growth factor receptor inhibitor, and indinavir, a protease inhibitor used in highly active retroviral therapy for HIV, have been implicated in the development of periungual granulation tissue, typically within the first month of treatment.[5] A large series published in 1988 on adverse reactions to isotretinoin therapy showed 4 cases of paronychia and periungual granulation tissue development.[6] Similarly, Figueiras et al[7] reported on a case of excess granulation tissue in the nail furrows in a 19-year-old man treated with isotretinoin for acne. Periungual granulation tissue has also been noted when retinoids have been used to treat other disease processes. Campbell et al[8] reported on a series of 6 patients who developed periungual granulation tissue during therapy with etretinate for psoriasis. The literature has shown that retinoids are associated with periungual granulation tissue between 3 and 12 weeks of initiating therapy. Periungual granulation tissue has been associated with cyclosporine treatment as well. Higgins et al[9] published a case report of a 24-year-old man who was receiving cyclosporine for his history of renal transplant and subsequently developed periungual granulation tissue within 6 months. Our patient's lesions were more temporally associated with the initiation of ibrutinib than cyclosporine and began resolving after cessation of ibrutinib but continuation of cyclosporine, supporting ibrutinib as the most likely causative agent in this case. Despite the temporal relationship, there is still the possibility that the periungual granulation tissue was related to the higher doses of cyclosporine and that reducing the dosage of cyclosporine had some therapeutic effect. Finally, we must also consider the possibility that the combination of ibrutinib and cyclosporine creates a risk of granulation tissue formation.

CONCLUSION

Because a growing number of patients will be treated with ibrutinib, it is important for treating physicians to be aware of severe and unusual adverse events. We hope that this report will add to the growing body of information regarding ibrutinib's adverse effect profile and, ultimately, aid in patient care. Periungual granulation tissue is not a new phenomenon, and it is a documented adverse effect of retinoid therapy and cyclosporine as well as epidermal growth factor inhibitor and antiretroviral therapy. For those using ibrutinib, periungual granulation tissue may result from downstream changes in nuclear factor-κB–mediated pathways and therefore likely represents sequelae from an inflammatory rather than an infectious etiology. A previous report by Mohandas et al[4] has corroborated this notion, given their patient's response to steroidal agents rather than to antimicrobial agents. Although the pathophysiology and definitive treatment of periungual granulation tissue may require further elucidation, awareness of ibrutinib-associated sequelae is vital when planning the treatment trajectory to avoid aggressive and ineffective treatments. This awareness will improve patient care, decrease health care costs, and reduce morbidity for patients.

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