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Management of paronychia with pseudopyogenic granulomas secondary to epidermal growth factor receptor inhibitors: An assessment of topical timolol and the need for multiple medical and procedural therapies

To the Editor: Paronychia and pseudopyogenic granulomas (PGs) occur in 10% to 30% of patients receiving epidermal growth factor receptor (EGFR) inhibitor therapy and frequently affect patients' quality of life.[1] Recently in case series, topical beta-blockers have been explored as a noninvasive strategy to treat this nail toxicity.[1-4] However, their rate of efficacy varies widely across studies when used as monotherapy.

To assess our experience of topical timolol for this indication, we conducted a retrospective review of patients with EGFR inhibitor–related paronychia with PGs who were referred to the Oncodermatology Clinic at the Yale Cancer Center from 2018 to 2020. Patients treated with topical timolol (0.5% twice daily under occlusion) monotherapy were included. Timolol treatment response was recorded as either complete, partial, or no response at 4 weeks. Those who did not respond were treated according to recommendations for the management of EGFR inhibitor–associated paronychia.[5] In addition, patient characteristics; cancer treatment; lesion number and location; additional medical, physical, or surgical therapy; and impact on cancer therapy were recorded. All patients tolerated dermatologic treatment without significant adverse effects.

Table I summarizes patient characteristics and treatment response. There were 10 patients, including 5 men and 5 women (mean age, 60 years; range, 49-78 years) with lung (n = 7) and head and neck (n = 3) cancer treated with topical timolol. Associated EGFR inhibitors included afatinib monotherapy (n = 2), afatinib followed by osimertinib (n = 2), combination afatinib/cetuximab (n = 2), erlotinib monotherapy (n = 1), combination erlotinib/nivolumab (n = 1), and poziotinib monotherapy (n = 1).

The median time receiving EGFR inhibitor(s) before development of paronychia with PGs was 146 days. There were, on average, 2.3 PGs per patient, and 7 of 10 patients had both fingernail and toenail involvement. Topical timolol monotherapy resulted in complete response in 2 patients at 4 weeks (patient 8 and patient 10), of whom 1 experienced recurrent PGs that partially responded. Nine of 10 patients required additional therapy because of insufficient (partial or no) response. Adjunct medical treatment included topical antibiotics/antiseptics (n = 9), topical steroids (n = 5), and oral antibiotics after bacterial culture (n = 5). Adjunct procedural intervention included silver nitrate cauterization (n = 5), cryotherapy (n = 1), and partial or full nail plate avulsion (n = 3) by podiatry for recalcitrant cases. Overall, all patients showed a clinical response (n = 4 complete, n = 6 partial) to dermatologic therapy (Fig 1), and no patients required interruption of oncologic therapy. Concurrent cutaneous toxicities included acneiform

Table I. Patient characteristics and response to dermatologic treatment

Patient number/ sex/ age, y	Primary neoplasm (grade)	EGFR inhibitor(s)	Time from start of EGFR inhibitor to nail toxicity, d	Number of PG lesions	Location of PGs (fingernails, toenails, or both)	Adjunct therapy required after topical timolol	Treatment response
1/F/57	Lung (stage 4)	Afatinib	291	2	Both	Topical steroid Topical antibiotic/ antiseptic* Oral antibiotic† Nail avulsion	Partial response
2/M/78	Lung (stage 4)	Afatinib	191	2	Both	Topical antibiotic/ antiseptic* Oral antibiotic† Silver nitrate	Partial response
3/F/58	Lung (stage 4)	Afatinib followed by osimertinib	187	1	Both	Topical steroid Topical antibiotic/ antiseptic* Silver nitrate Nail avulsion	Complete response
4/F/60	Head and neck SCC (stage 4)	Afatinib and cetuximab	105	2	Both	Topical antibiotic/ antiseptic*	Partial response
5/M/52	Lung (stage 4)	Poziotinib	71	5	Fingernails	Topical antibiotic/ antiseptic* Silver nitrate	Partial response
6/F/70	Lung (stage 4)	Afatinib followed by osimertinib	101	2	Toenails	Topical antibiotic/ antiseptic* Oral antibiotic† Silver nitrate	Complete response
7/M/49	Head and neck SCC (stage 3)	Cetuximab	274	2	Both	Topical steroid Topical antibiotic/ antiseptic* Cryotherapy	Partial response
8/F/68	Lung (stage 4)	Erlotinib‡	456	2	Toenails	—	Complete response with timolol monotherapy
9/M/62	Lung (stage 4)	Erlotinib	105	2	Both	Topical steroid Topical antibiotic/ antiseptic* Oral antibiotic† Nail avulsion	Complete response
10/M/58	Head and neck SCC (stage 4)	Afatinib and cetuximab	73	6	Both	Topical steroid Topical antibiotic/ antiseptic* Oral antibiotic† Silver nitrate	Complete response with timolol monotherapy, then recurrence with partial response

EGFR, Epidermal growth factor receptor; *F,* female; *M,* male; *PG,* Pseudopyogenic granuloma; *SCC,* squamous cell carcinoma.
*Topical antibiotics/antiseptics included mupirocin, clindamycin, and/or gentamicin/vinegar soaks, dilute hydrogen peroxide soaks, dilute sodium hypochlorite soaks, or iodine.
†Oral antibiotics included doxycycline, trimethoprim-sulfamethoxazole, or cephalexin.
‡Cotreatment with nivolumab.

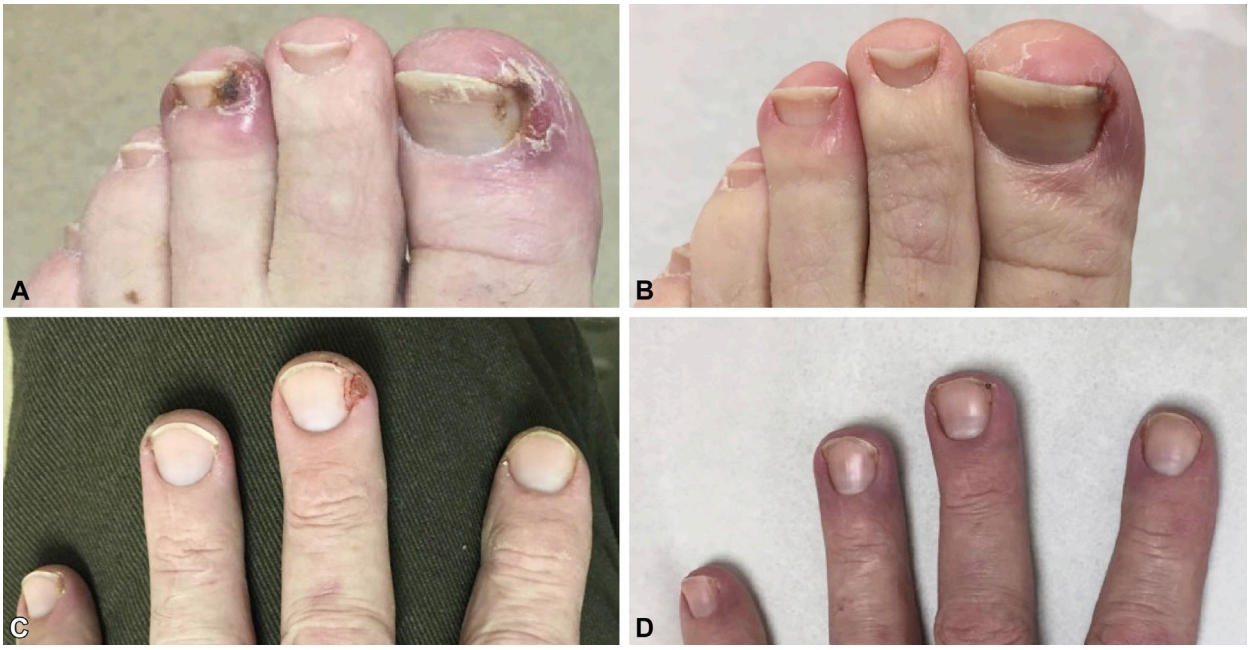

Fig 1. Before and after 0.5% topical timolol on the (**A** and **B**) fingernails and (**C** and **D**) toenails to treat paronychia with PGs from EGFR inhibitor therapy (patient 10).

rash (n = 10), alopecia (n = 3), nasal vestibulitis (n = 3), and trichomegaly (n = 1).

Paronychia with PGs typically presents months into EGFR inhibitor therapy and commonly requires dermatologic evaluation. The results of our study suggest that although topical timolol is well tolerated, its utility as monotherapy may be limited, and therefore, it should be considered as an adjunct to medical, physical, and surgical therapy. Patient adherence, the size of the PGs, superinfection, and the severity of the paronychia may affect its efficacy. Further prospective studies are needed to identify the optimal use of topical beta-blockers for EGFR inhibitor–associated paronychia with PGs. Although this study is limited by its retrospective nature, our experience highlights the need for combination medical, physical, and/or surgical therapy for the management of this important dermatologic toxicity from targeted therapy.

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