Letters

RESEARCH LETTER

Topical Timolol for Paronychia and Pseudopyogenic Granuloma in Patients Treated With Epidermal Growth Factor Receptor Inhibitors and Capecitabine

Paronychia and pseudopyogenic granuloma (pseudo-PG) are relatively common and difficult-to-manage adverse effects in patients undergoing treatment with epidermal growth factor receptor inhibitors and capecitabine.[1] Recently, Piraccini et al[2] reported the successful treatment of chemotherapy-induced fingernail PGs with topical propranolol, 1%, cream. The aim of this study was to evaluate the efficacy and tolerability of topical timolol, 0.5%, gel as a treatment of paronychia and pseudo-PG induced by antineoplastic agents.

Methods | We included 10 patients who were referred to our department with paronychia and/or periungual pseudo-PG as an adverse effect of epidermal growth factor receptor inhibitor or capecitabine from September 1, 2016, to May 31, 2017. The protocol was submitted to and approved by the institutional review board of Hospital de la Santa Creu i Sant Pau, and patients gave their oral informed consent to participate in the study. All data were deidentified.

Patients' demographic characteristics, lesion localization (fingernails, toenails, or both), number of lesions, duration of antineoplastic treatment before the appearance of lesions, and other skin manifestations were also recorded. All lesions were treated with topical timolol, 0.5%, gel (Timogel) twice daily under occlusion for 1 month. Response to treatment was assessed by clinical examination and photographic control at baseline and after 1 month of treatment and classified as complete response (disappearance of the lesion, absent pain, and/or bleeding), partial response (improvement in at least 1 of these 3 items), or lack of response.

Results | Of the 10 patients in the study, 5 were women and 5 were men (mean [SD] age, 66.4 [10.1] years; age range, 51-78 years). The baseline characteristics of the patients are summarized in the **Table**. The mean (SD) antineoplastic treatment duration was 3.8 (3.2) months (range, 1-12 months). Four patients were treated with panitumumab, 4 with cetuximab, 1 with erlotinib, and 1 with capecitabine. Seven patients were also treated with other antineoplastic agents.

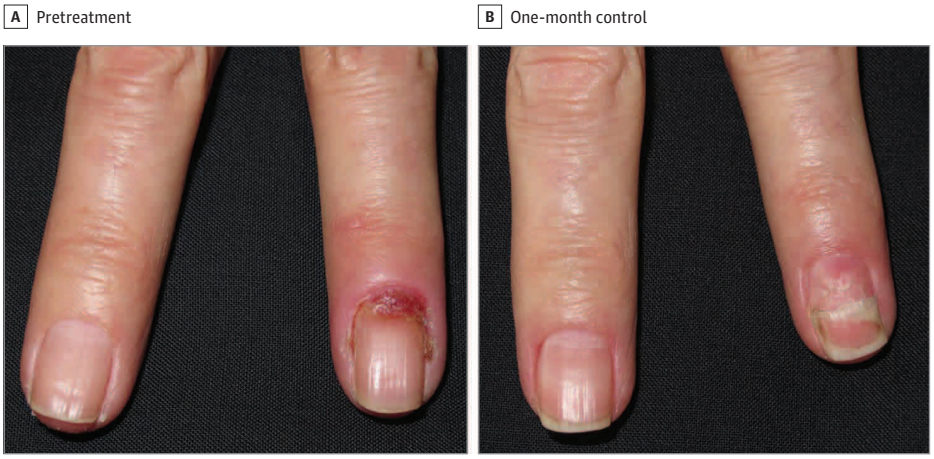
All patients clinically improved with timolol treatment at the 1-month evaluation: complete response in 9 patients (**Figure**) and partial response in 1 patient, who was receiving

Table. Clinical Characteristics and Treatment of the Patients Observed

Patient No./ Sex/Age, y	Primary Neoplasia	Lesion Localization (No. of Lesions)	Neoplasia Treatment	Co-treatment	Antineoplastic Treatment Duration Before Lesions, mo	Other Toxic Effects	Timolol Response Evaluation
1/M/60s	Pyriform sinus carcinoma, stage IV	Fingernail (1 PR and 1 PG)	Cetuximab	Cyclobutane dicarboxylic acid or carboplatin with fluorouracil	4	PPE	Complete
2/M/50s	Colon ADK, stage IV	Toenail (2 PR and 2 PG)	Panitumumab	Folinic acid, fluorouracil, and irinotecan	4	PPE, trichomegaly	Complete
3/F/70s	Colon sigma ADK, stage IV	Fingernail (2 PG)	Panitumumab	Folinic acid, fluorouracil, and irinotecan	2	PPE, trichomegaly, hirsutism, seborrheic dermatitis	Complete
4/M/50s	Rectum ADK, stage IV	Toenail (2 PR)	Panitumumab	Folinic acid, fluorouracil, and oxaliplatin	4	PPE	Partial
5/M/70s	Tonsillar SCC, stage IV	Both (2 PG and 2 PR)	Cetuximab	NA	1	PPE	Complete
6/F/70s	Sigma ADK, stage IV	Fingernail (3 PG)	Panitumumab	Folinic acid, fluorouracil, and oxaliplatin	12	PPE, severe xerosis cutis, palmoplantar fissures, seborrheic dermatitis	Complete
7/F/70s	Lung ADK, s tage IV	Fingernail (2 PG)	Erlotinib	NA	1	Acute pancreatitis, palmoplantar fissures	Complete
8/F/70s	Colon ADK, stage IV	Toenail (2 PG)	Capecitabine	NA	5	Hand-foot syndrome	Complete
9/M/50s	Colon ADK, stage IV	Toenail (2 PG)	Cetuximab	Folinic acid, fluorouracil, and oxaliplatin	3	PPE	Complete
10/F/60s	Tonsillar SCC, stage IV	Fingernail (5 PR and 1 PG)	Cetuximab	Paclitaxel	2	PPE, mucositis, onycholysis	Complete

Abbreviations: ADK, adenocarcinoma; NA, not applicable; PG, pyogenic granuloma; PPE, papulopustular eruption; PR, paronychia; SCC, squamous cell carcinoma.

Figure. Fingernail Pseudopyogenic Granuloma



Note that the secondary onychomadesis is attributable to the initial nail matrix affectation.

treatment with panitumumab for 2 toenails with pseudo-PG. Regardless of the degree of response, all patients reported a high degree of satisfaction and tolerance to treatment. No adverse events were reported within 1-month to 8-month follow-up.

Discussion | Epidermal growth factor receptor inhibitors are increasingly used for the treatment of advanced solid malignant tumors. Paronychia and pseudo-PG occur in 10% to 30% of cases, and their appearance is dose dependent, requiring at least 4 to 8 weeks of continued therapy.[1] Their etiopathogenesis remains unknown. Some authors[1,3] suggest that initial desquamation and thinning of the periungual epidermis, induced by the antineoplastic drugs, would cause onychocryptosis and periungual inflammation, leading to granulomatous tissue outgrowth. Pain secondary to paronychia seriously impairs self-care and daily activities and thus the quality of life of these patients. Management of this condition is usually difficult, with poor response to multiple treatments (eg, surgery, topical antiseptics, antibiotics, corticosteroids), and dose reduction or withdrawal of the antineoplastic agent may be required.[1,4]

Topical timolol has emerged as a promising treatment for infantile hemangiomas and idiopathic PG.[5] In a recently published series of 10 patients with periungual PG,[2] topical treatment with propranolol cream, 1%, under occlusion has been reported to cure fingernail lesions regardless of the cause, with no response or even worsening in toenail PG. In our series, timolol, 0.5%, gel under occlusion was associated with good response, regardless of the localization. A potential explanation might be the superior activity,[6] increased penetration, or better excipient of timolol gel compared with propranolol cream.

Our open study provides initial evidence of the efficacy, safety, and tolerance of timolol, 0.5%, gel under occlusion for the treatment of paronychia and pseudo-PG associated with antineoplastic treatment. Future randomized clinical trials are required to confirm our findings and provide information regarding the optimal dose and duration of treatment.

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Study concept and design: Cubiro, Planas-Ciudad, Garcia-Muret.
Acquisition, analysis, or interpretation of data: All authors.
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