Effect of Topical Rapamycin 1% on Multiple Trichoepitheliomas
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Trichoepitheliomas are benign adnexal neoplasms with follicular differentiation that can occur as isolated sporadic lesions or as part of multiple familial trichoepithelioma (MFT) syndrome, a phenotypic variant of Brooke-Spiegler syndrome associated with autosomal dominant mutations of the tumour suppressor gene CYLD (16q12.1) (1, 2). In the MFT setting, trichoepitheliomas appear during childhood as multiple skin-coloured papules or small nodules, usually present with a symmetrical distribution and localized on the scalp, neck and face (with predominance on the nose, cheeks, forehead, nasolabial folds and inner aspects of the eyebrows). Trichoepitheliomas progressively increase in number and size over years and usually result in significant aesthetic disfiguring. Brinkhuizen et al. (3) recently demonstrated that, similarly to tuberous sclerosis (4), the pathogenesis of trichoepitheliomas involves an activation of the mammalian target of rapamycin (mTOR) signalling pathway. We report here the effect of topical rapamycin 1%, an efficient topical treatment of cutaneous angiofibroma, in patients with tuberous sclerosis, on trichoepitheliomas of 5 patients with MFT.

CASE REPORTS

The patients’ characteristics are summarized in Table SI1. All trichoepitheliomas were histologically confirmed, showing basaloid lobules with keratocysts and infundibular keratinization without epidermal continuity, and with cellular fibroblastic stroma (Fig. 1). All patients were female, with a median age of 45 years (range 26–54 years). Lesions first appeared at the median age of 15 years (range 4–23 years) and were located exclusively on the face (front, nose, nasolabial folds). The number of lesions was between 20 and 500, and their diameter ranged from 2 to 5 mm. Molecular analysis was conducted in one patient showing a heterozygous mutation of side-effects. Among the 4 patients who had an improvement in their trichoepitheliomas, 2 are currently under treatment (patients 2 and 4). Patient 3 stopped the treatment and was then treated with CO2 laser. Ten months after stopping topical rapamycin, patient 1 has new lesions, but the size of treated lesions did not change.

DISCUSSION

A number of therapeutic options have been proposed previously in MFT-related trichoepitheliomas, including surgery, dermabrasion, ablative CO2 laser and cryotherapy. However, these invasive procedures have a limited efficacy and may be complicated by permanent scarring, hypopigmentation and atrophy. There is also a high risk of relapse (5, 6). Topical imiquimod also proved effective in 2 patients with solitary desmoplastic trichoepithelioma but the lesions relapsed after treatment discontinuation (7). More recently, the effect of topical mTOR inhibitors on MFT-related skin lesions was reported by Tu & Teng (2) in 2 siblings aged 6 and 8 years. A formulation of 1% rapamycin cream was applied on numerous, but small
by the fact that other pathways, such as the hedgehog, might play a more relevant role in the pathogenesis of trichoepitheliomas than the m-Tor pathway (8). Baur et al. (8) recently showed a significant regression of the highly differentiated TE upon vismodegib, that could be explained by the upregulation of Gli1 (glioma-associated oncogene) mRNA in these tumours, indirectly upregulated by CYLD mutation. Contrasting with the limited clinical impact reported by the physicians, patients self-reported a higher efficacy that may reflect their high level of request for an effective therapy for these disfiguring lesions. Tolerance appears good overall. The occurrence of headaches, a side-effect reported for oral sirolimus may suggest a systemic diffusion of the drug (9). It is notable that this side-effect was not previously reported with the topical formulation, either in tuberous sclerosis (10) or in MFT-related trichoepitheliomas (2).

In conclusion, topical rapamycin, although off-label and expensive, may be considered in MFT-related facial trichoepitheliomas. Concomitant therapy, such as prior ablative laser, may be considered in order to optimize the efficacy of the drug.

REFERENCES