Paronychia and Pyogenic Granuloma Induced by New Anticancer mTOR Inhibitors

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The mammalian target of rapamycin (mTOR) is a key regulatory protein in cancer. In particular, mTOR is involved in the control of cellular proliferation, survival (inhibition of apoptosis) and angiogenesis (1). This is the basis for the development of new drugs to inhibit this target in oncology. mTOR inhibitors act by selectively inhibiting the PI3K/AKT/mTOR intracellular signalling pathway in the tumour cell. The US Food and Drug Administration and the European Medicines Agency have recently approved temsirolimus (Torisel®, intravenous administration, 25 mg weekly) and everolimus (Afinitor®, oral administration, 10 mg daily) for use in metastatic renal cell carcinoma.

These drugs have good safety profiles, but are not free of adverse effects. Notably, during the development phases of everolimus and temsirolimus, dermatological toxicity emerged as the most frequent form of toxicity, affecting up to 70% of patients (2–5). For example, ungual toxicity was observed in 5–46% of patients, but no clinical description was provided in these studies (2–4).

We report here for the first time periungual toxicity associated with the use of anticancer mTOR inhibitors.

CASE REPORTS

In 7 patients treated with everolimus or temsirolimus (Table I) painful, progressive periungual inflammation, bilaterally affecting the big toes, occurred 2–6 months after initiation of treatment. Examination revealed oedema, erythema and tenderness in the paronychium of the affected toes, associated with crusted lesions along the nail folds (Fig. 1). A serous or suppurating discharge was noted in four patients with initially negative bacteriological samples. Two of these patients subsequently developed painful lateral nail-fold pyogenic granuloma-like lesions (Fig. 1b). None of the patients presented with concomitant neutropaenia or lymphopaenia, nor had they a past history of paronychiae of the same type prior to the introduction of mTOR inhibitors. Symptomatic treatment involved topical steroids under occlusion in two patients, silver nitrate in one patient, local antibiotic therapy in three patients with fusidic acid or mupirocin and systemic antibiotics such as pristinamycin in two patients and doxycycline in one patient. Nonetheless, a dose reduction was required in 3 patients and resulted in the regression of the lesions within a few weeks (Table I).

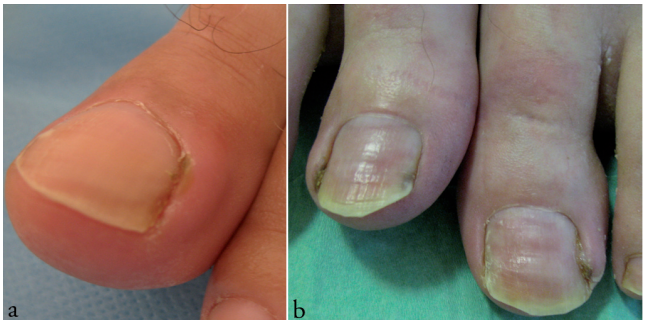

Fig. 1. Paronychia of the big toes (a). Pyogenic granuloma of the lateral nail-fold (b).

Table I. *Patients characteristics*

Age, years/ Sex	Diagnosis	Location of metastases	Treatment	Clinical presentation	Delay, months	Dose reduction	Other concomitant oncological treatments	Associated dermatological side-effects
71/M	RCC	Lung, mediastinum, pancreas	Everolimus	Paronychia	4	5 mg/day	No	Oral and lips ulcerations Rash Xerosis
52/M	RCC	Lung, mediastinum	Everolimus	Paronychia	6	No	No	Leg oedema Aphthous stomatitis
54/F	MAC	Liver	Everolimus	Paronychia	4	No	Paclitaxel Trastuzumab	No
36/M	RCC	Lung	Everolimus	Paronychia	2	No	Bevacizumab	Papulopustular rash
47/M	RCC	Lung	Temsirolimus	Paronychia with pyogenic granuloma	5	20 mg/week	Bevacizumab	Papulopustular rash Xerosis
65/M	RCC	Liver, lung	Temsirolimus	Paronychia with pyogenic granuloma	5	20 mg/week	No	Papulopustular rash Xerosis
58/M	RCC	Liver	Temsirolimus	Paronychia	6	No	No	Xerosis

RCC: renal cell carcinoma; MAC: mammary adenocarcinoma.

DISCUSSION

Even though it has not been reported previously, these periungual lesions may be related to everolimus and temsirolimus treatment, as all displayed identical clinical characteristics. In all cases, they appeared at the same time (several weeks after treatment initiation) and were similar to those reported with other mTOR inhibitor sirolimus (rapamycin, Rapamune®) or with epidermal growth factor (EGF) receptor inhibitors (gefitinib, erlotinib, panitumumab, cetuximab) (6, 7). Indeed, in 15% of cases, sirolimus induces paronychial damage, which is sometimes combined with a pyogenic granuloma (8). Similarly, EGF inhibitors also induce the same type of lesions in 10–15% of treated patients (9).

A relationship with combined chemotherapeutic treatments (bevacizumab, trastuzumab, paclitaxel) in the occurrence of paronychia in three of our patients seems unlikely, lesions of this type having only rarely been reported with these compounds (10). The absence of a clear-cut clinical improvement observed after treatment with antibiotics speaks against an infectious origin.

The pathogenesis of this paronychia-induced lesion is unknown. Some authors have suggested that EGF receptor inhibitors induce skin fragility, including thinning of the stratum corneum and reduced keratinocyte proliferation rates, with secondary penetration of nail-plate fragments into the periungual tissues (11). Moreover, the EGF cellular signalling pathway has been shown to be regulated through the mTOR signalling pathway (12).

The therapeutic management of these induced paronychiae does not differ from what has been proposed for EGF receptor inhibitors (13). A dosage reduction, even the cessation of treatment is also sometimes necessary.

Other adverse dermatological effects are also associated with anticancer mTOR inhibitors. The occurrence of a skin rash has been reported in approximately 25–61% of patients in the case of everolimus, and 43–76% for temsirolimus (2–5). This eruption usually takes an acne-like form, which is also similar to that observed with both sirolimus and EGF receptor inhibitors (7, 12).

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