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LETTER TO THE EDITOR

Dermatitis after suspected imatinib–levothyroxine interaction in a patient with gastrointestinal stromal tumor

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Dear Editor,

Imatinib is an accepted therapeutic option for gastrointestinal stromal tumors (GIST). Imatinib is metabolized by CYP3A4, which is the predominant cytochrome P450 expressed in human liver [1].

A 73-year-old man was admitted to our Department with pruritic dermatitis and low grade fever of 7 days duration. He has suffered from GIST, which had been diagnosed and treated surgically 18 months prior to his admission. The patient had experienced recurrence of the tumor and was being treated with imatinib (Gleevec®) 400 mg/day for the last 9 months. The patient was free from any other medical problems, except from primary hypothyroidism, which had been diagnosed 2 months ago and was being treated with levothyroxine 0.1 mg/day. On admission, the clinical examination revealed generalized dermatitis with superficial desquamation (Fig. 1a, b). Laboratory findings included: Hematocrit: 30.5%, Creatinine: 151 μmol/l, C-reactive protein: 6.2 mg/l, TSH: 0.02 μIU/l (0.49–4.67 μIU/l), FT_4: 1.95 pmol/l (0.71–1.85 pmol/l). Imatinib and levothyroxine were discontinued and corticosteroids (methylprednizolone 40 mg tid intravenously) with antihistamine (cetirizine 10 mg for 7 days) were received.

On the following days, the patient's clinical condition rapidly improved and he had an uncomplicated recovery. Skin biopsy was not performed, because the patient refused to undergo to this procedure and his skin lesions lasted only for 3 days. He was discharged after 5 days in a good condition with steroids on a tapering dose and his thyroid function tests gradually returned to normal. Imatinib was re-started after 3 months at the same dose and 6 months later the patient remains without any recurrence of dermatitis.

Imatinib is a potent protein tyrosine kinase inhibitor and is considered the treatment of choice for advanced or metastatic GISTs [1]. Imatinib is a well-tolerated drug; dermatological reactions to imatinib are the most common side effects and are usually mild, such as maculopapular eruptions and periorbital edema. Imatinib can also induce severe and generalized skin lesions (DRESS, exanthematous pustlosis, Sweet's syndrome, toxic epidermal necrolysis and Stevens Johnson syndrome). All these cutaneous reactions seem to be more frequent in higher doses of imatinib or when the latter is co-administered with other drugs, such as ketoconazole and lansoprazole [2], which are metabolized by the same liver enzyme (CYP3A4) leading to elevation in the plasma concentration of imatinib.

There are increasing evidences that protein tyrosine kinase inhibitors (sunitinib, imatinib) frequently cause hypothyroidism [3, 4]. Similarly to the previous reports [3, 4], our patient developed primary hypothyroidism 7 months after initiation of imatinib. What is new here is that our patient was being treated with imatinib 400 mg/day for several months without any adverse effects and the cutaneous reaction occurred when the patient started taking levothyroxine therapy.

Recent studies have tried to elucidate the possible interaction between imatinib and thyroid hormones. In the study by de Groot JW et al. [5], 11 patients received imatinib: 8 had undergone thyroidectomy and used levothyroxine, and 3 had the thyroid gland in situ. Interestingly, all the former

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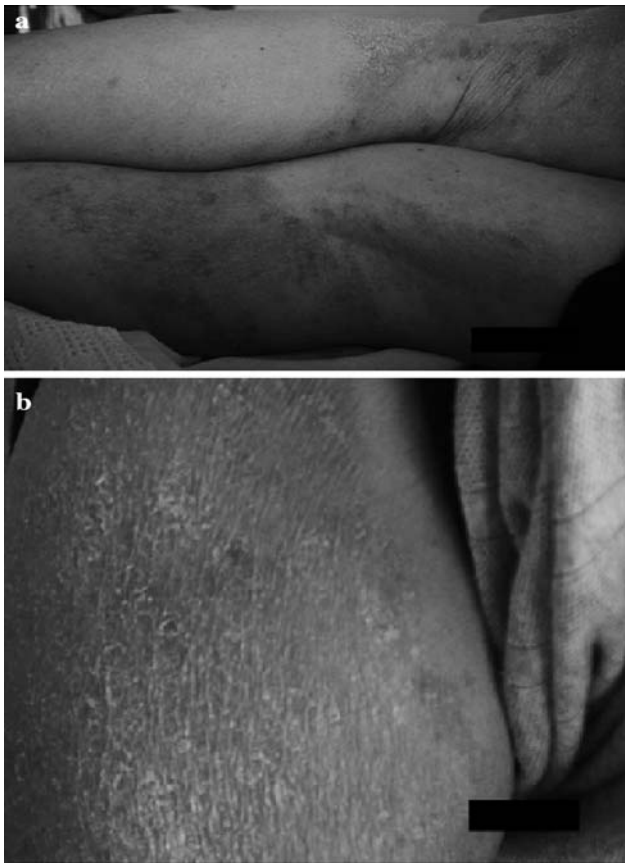

Fig. 1 Clinical pictures of our patient at the time of admission, showing desquamation dermatitis over his feet (**a**) and right arm (**b**)

patients developed symptoms of hypothyroidism possibly due to the effect of imatinib on uridine diphosphate-glucuronosyltransferases enzymes. However, the authors did not evaluate the effect of levothyroxine on imatinib metabolism. The latter was evaluated in another study, which suggested that iodothyronines can directly affect on human hepatocytes leading to a marked reduction of CYP3A4 activity [6]. Thus, it is possible that a down regulation of CYP3A4 might have occurred due to levothyroxine therapy, leading to an increase of imatinib concentration in the plasma and appearance of skin reaction. Use of the Naranjo ADR Probability Scale [7] indicated that dermatitis was possibly due to imatinib–levothyroxine interaction. Finally, although our patient had a low glomerular filtration rate (Cr: 151 μmol/l), pharmacokinetics of imatinib are not affected by renal dysfunction [8].

In conclusion, although the exact role of imatinib on metabolism of levothyroxine and visa versa needs further elucidation, close monitoring and caution is advised in imatinib and levothyroxine co-administration, considering the widespread use of the latter in the older adult population.

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