Abstract. Pemetrexed (Alimta™) is used frequently for the treatment of lung cancer and is associated with various types and grades of cutaneous side-effects. We report here one patient who presented with asymptomatic hyperpigmentation of the skin, localized on the palms of the hands and the soles of the feet after administration of pemetrexed for lung cancer despite receiving standard pre-medication. This type of skin toxicity was completely reversible after withdrawal of the drug (without pharmacologic intervention) and has to our knowledge not been reported before.

The novel multi-targeted antifolate pemetrexed (Alimta™) is used in clinical practice as a single agent or in combination with platinum analogs to treat inoperable or metastatic cancer of the respiratory tract (non-small cell lung cancer and mesothelioma) (1-3). The occurrence of pruriginous skin rash, also labelled as dermatitis, and haematological toxicity is frequent with this drug and in some cases severe. To avoid these adverse events, prophylactic pre-medication with folic acid, vitamin B12 and corticosteroids without loss of antitumour activity has been recommended (4). Here we report on one patient treated with pemetrexed for non-small cell lung cancer, fully supplemented with vitamins and corticosteroids in which an unusual hyperpigmentation of the palms of the hands and soles of the feet developed without additional symptoms in other parts of the skin. This hyperpigmentation was fully reversible upon withdrawal of the drug.

Case Report

A male Caucasian patient, 59 years old, was initially treated for stage IV adenocarcinoma of the left upper lung and one adrenal metastasis with six induction cycles of paclitaxel and carboplatin at standard dosage, with pre-medication based on antihistamines and corticosteroids. He achieved stable disease after the induction chemotherapy. Consolidation radiotherapy on the primary tumour and left adrenal metastasis was performed. This resulted again in stable disease. The patient experienced relapse of the primary tumour of the lung and developed liver metastases nine months after the end of the radiotherapy and received 3 cycles of single agent pemetrexed (500 mg/m²) as second-line chemotherapy, in association with standard pre-medication of dexamethasone 4 mg in the morning and the evening the day before, the day of and the day after chemotherapy, 1000 μg vitamin B12 intramuscularly and oral folic acid supplementation 0.4 mg total dose per day seven days before initiation of pemetrexed as recommended (4). A few days after administration of the second cycle, the patient presented a ‘brownish’ hyperpigmentation of both palms of the hands and soles of the feet without effect on other parts of the skin, mucosa or nails. The skin felt dry and ‘raspy’ but the effect occurred in the absence of accompanying symptoms such as itching, pain or ridging. The hyperpigmentation was not preceded by an inflammatory reaction of the skin and disappeared progressively and completely within three weeks after discontinuation of pemetrexed. The drug was discontinued because of rapid development of extensive brain metastases and peripheral progressive disease. The patient received palliative radiotherapy to the whole brain, was not rechallenged with pemetrexed and died at home in a palliative setting one month later.

Discussion

In several clinical trials and in routine clinical practice, treatment with pemetrexed has been shown to be accompanied by haematological and non-haematological (e.g. dermatological) toxicity (1-3). The skin toxicities are most often benign in nature and consist of a diffuse inflammatory rash, also referred to as dermatitis, localised on different parts of the body. The skin toxicity grading is most often less than grade 2 using the common terminology criteria for adverse events (CTCAE) scale (5) and may be accompanied with symptoms such as itching or pain at the location of the skin lesions. Treatment of this rash largely
depends on its severity and is mainly based on the oral administration of antihistamines and corticosteroids, and, when deemed necessary, also antibiotics. However, on rare occasions, the clinical presentation may be more dramatic and even life-threatening e.g. due to the development of a toxic epidermal necrolysis syndrome (Steven-Johnson’s syndrome) (6, 7). To prevent the occurrence of adverse events following pemetrexed use, a pre-medication regimen consisting of dexamethasone, folic acid and vitamin B12, as used here, has been developed and recommended for clinical use. This strategy does not influence the cytotoxic efficacy of the drug but reduces its toxicity (4).

To our knowledge, hyperpigmentation of the skin, such as described for our patient, without accompanying local inflammatory or systemic symptoms after the administration of pemetrexed has not been reported in the literature yet. A review of the database of Eli Lilly referring to spontaneous reports of side-effects of pemetrexed up to February 2010, using the terms ‘pigmentation disorder’, ‘skin hyperpigmentation’ and ‘skin discoloration’ found this phenomenon in fewer than 0.01% of the adverse event reports. This side-effect was therefore labelled as ‘very rarely reported’ (Eli Lilly, Belgium, personal communication). In contrast, at our institution, of over a hundred patients treated with the drug at the same dose level and with the same pre-medication, this adverse event was observed in one case (around 1%). This patient did not have any obvious particular clinical characteristics that would differentiate him from the overall treated population. The observed toxicity did not parallel disease progression, but was clearly chronologically related to pemetrexed administration and discontinuation. In the current published literature, only one black male patient was previously shown to have developed a complex pattern of nail toxicity referred to as melanonychia and onycholysis after treatment with pemetrexed for lung cancer (8).

The physiopathological mechanism behind the hyperpigmentation remains unclear and one can only be speculative about its aetiology. A normal thyroid profile and no signs of endocrine dysfunction were found during the medical evaluation and no hirsutism, hair and nail, or mucosal abnormalities were present. Other medications received by the patient e.g. the drugs in the pre-medication
regimen have not been associated with hyperpigmentation. Moreover the patient had been pre-treated with dexamethasone used as an anti-anaphylactic drug before treatment with paclitaxel and carobplatin and did not show hyperpigmentation of palms and soles during the first-line chemotherapy. Because the skin abnormalities were without accompanying symptoms and the treatment with pemetrexed was discontinued rapidly (due to development of massive brain and peripheral metastasis), no skin biopsies were performed in order to analyse any possible underlying histological and molecular modifications, nor were specific endocrine tests of the blood e.g. in the secretion of melanocyte-stimulating hormone, carried out.

Hyperpigmentation of the skin has been reported previously in relation to the use of imatinib for the treatment of chronic myeloid leukaemia and gastrointestinal stromal tumours. In these malignant diseases, the hyperpigmentation of the skin was tentatively linked to alterations in the c-KIT signalling pathway of the skin, which plays an important role in melanogenesis and is inhibited by imatinib (9). Pemetrexed does, to our knowledge, not interfere with the c-KIT transduction pathway. Therefore it seems unlikely that this mechanism would be pivotal in the process underlying the hyperpigmentation of the skin in the case of pemetrexed. The parental antifolate drug methotrexate, with a somewhat similar intracellular mode of action, has not been shown to produce similar cutaneous hyperpigmentation. In the same class of drugs, the presently described cutaneous side-effect described seems to be related to pemetrexed only.

In summary, in view of the temporal relationship of the appearance of the skin hyperpigmentation and the administration of pemetrexed, we suggest that the patient reported in this article suffered from an unusual side-effect of pemetrexed use. A paraneoplastic cutaneous syndrome cannot be completely excluded but seems unlikely because of the absence of any accompanying symptoms and the temporal relationship with the administration and withdrawal of the drug. The pathophysiological basis of this ‘cosmetic’, not harmful, side-effect is unclear but stimulation of melanogenesis by pemetrexed (or one of its constituents) through an as yet unknown mechanism is possible. In addition it is not clear why specific parts of the skin are more affected than others (hands, feet and nails versus other parts of the body), suggesting the presence of an unidentified predisposing factor. The hyperpigmentation seems benign and reversible upon withdrawal of the drug. Further research is needed to investigate this unpleasant apparently mainly cosmetic toxicity.

References