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Gemcitabine, a rare cause of chemotherapy-related reticulate hyperpigmentation

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Abstract

Reticulate pigmentary disorders can be classified into inherited or acquired and cutaneous drug-induced reticulate hyperpigmentation belongs to this last group. The list of the drugs involved is constantly increasing and chemotherapy agents are frequently implicated. We report a new case of chemotherapy-related reticulate hyperpigmentation to gemcitabine, even though a previous chemotherapy with nanoparticle, albumin-bound (Nab®) paclitaxel and gemcitabine may have promoted the onset of the disease. Reassurance of the patients is important in these cases, in order to continue the chemotherapy, and gradual fading of the hyperpigmentation is usually observed, as in our case.

Introduction

Hyperpigmentation is probably one of the most frequent cutaneous adverse events of chemotherapy, even though it is probably underestimated due to its benign nature and the lack of symptoms. It may affect the skin, the mucous membranes and the nails (1). We recently had the opportunity to observe a case of a reticulate hyperpigmentation due to the chemotherapy agent gemcitabine.

Reticulate pigmentary disorders can be classified, according to the age of onset, into inherited or acquired and cutaneous drug-induced reticulate hyperpigmentation belongs to this last group (2). The list of the drugs involved is constantly increasing and chemotherapy agents are frequently implicated (3, 4).

Case report

A 40-year-old man affected by a pancreas cancer with lung metastases was referred to us for the onset of asymptomatic patches of reticulate hyperpigmentation located on the lumbosacral area and on the upper and lower limbs. Affected skin was xerotic and smooth (figure 1). A previous lacy erythema with dry skin in the same areas was referred. The patient had been treated with first line chemotherapy with nanoparticle, albumin-bound (Nab®) paclitaxel and Gemcitabine for 6 months, achieving a partial response. A therapeutic break of 3 months followed, then, two weeks before the onset of the rash, the patient started a maintenance treatment with gemcitabine as a single agent. Dermoscopy showed intersecting brown lines surrounding normally pigmented holes and the brown lines had a uniform reticular pattern (figure 2). These dermoscopic features were similar to the one reported by Masson Regnault *et al* in 2015 (2). Histology was unspecific, with mild hyperpigmentation of the basal layer of the epidermis. A diagnosis of chemotherapy-related reticulate hyperpigmentation (CRRH) due to gemcitabine was made, the patient was reassured about the benign nature of the rash,

topical emollients were prescribed and chemotherapy was continued, with clinical improvement after 3 months.

Discussion

Many different chemotherapy drugs had been associated with CRRH and the list is reported in table 1. To our knowledge, there is only one patient that developed CRRH under treatment with gemcitabine and carboplatin, but none with gemcitabine alone (2, 5-8).

The disease has no association with a specific malignancy and can occur both in solid and in hematologic cancers. CRRH is characterized clinically and dermoscopically by a net-like macular brown pigmentation, without scaling, located in different body areas including the back, the upper and lower limbs, the abdomen, the shoulders, the buttocks. The eruption can be preceded by an erythematous phase, with erythema involving in the same areas of the hyperpigmentation and can be associated with pruritus (9, 10). The course is usually self-limiting, with gradual fading of the hyperpigmentation over many weeks, up to a partial or complete resolution. Histology shows an increase of the melanin in the basal and suprabasal layers of the epidermis, with melanophages and pigmentary incontinence in the upper dermis, a histologic pattern considered typical of chemotherapy-induced cutaneous pigmentary disorders (2, 5). No increase of the number of the melanocytes is observed. Differential diagnoses mainly include erythema ab igne, prurigo pigmentosa, Dowling Degos disease, confluent and reticulated papillomatosis of Gougerot Carteaud. Personal history, clinical and dermoscopic features and, when necessary, histology, allow a correct diagnosis. The pathogenesis of CRRH is unclear, the disease seems to be related to a direct toxic effect of the chemotherapy agents towards the melanocytes, with an increase in melanogenesis (11). The frequent occurrence in the lumbosacral area and on the buttocks suggests that pressure may be a triggering factor, as hyperpigmentation frequently occur in areas of trauma (2).

Moreover, the preceding itchy erythematous phase, that was referred by our patient and had already been reported in other cases of the Literature, led us to hypothesize that CRRH could be linked to areas of asteatotic eczema that convert into areas of hyperpigmentation. It is well known that chemotherapy can induce skin changes, including skin dryness, pruritus and also asteatotic eczema (12, 13). The areas of asteatotic eczema could be a locus minoris resistentiae where the hyperpigmentation due to the chemotherapy agent develop, a sort of post-inflammatory hyperpigmentation that would explain the lacy appearance of this specific cutaneous adverse event.

Conclusions

In conclusion, we report a new case of CRRH due to gemcitabine, even though the previous chemotherapy with nanoparticle, albumin-bound (Nab®) paclitaxel and Gemcitabine may have promoted the onset of the disease. Clinicians should be aware of this specific cutaneous adverse event in order to reassure the patients. The chemotherapy can be continued without dose reduction or suspension of the treatment and the gradual fading of the hyperpigmentation over a period of weeks or months is usually observed, as in our case.

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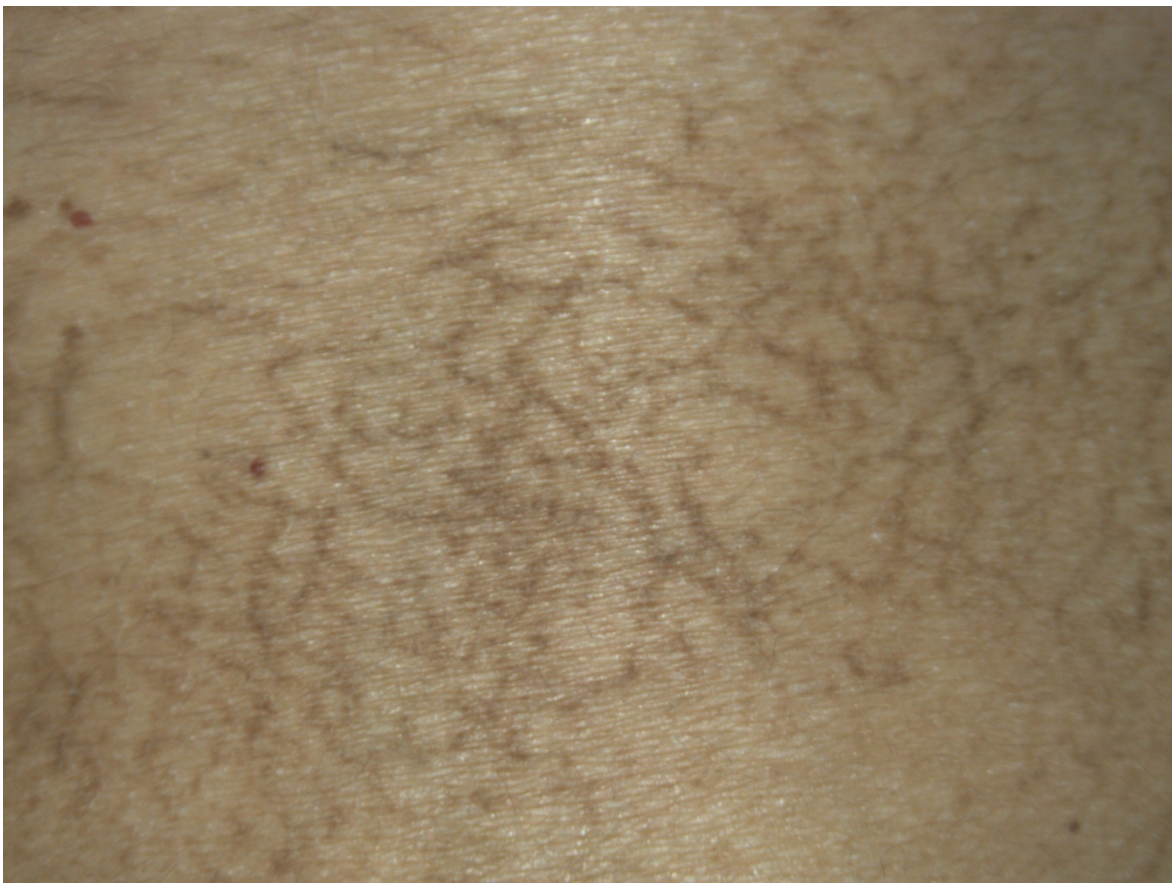

Figure 1. The reticulate hyperpigmentation located on the lumbosacral area.

Figure 2. Intersecting brown lines surrounding normally pigmented holes; the brown lines show a uniform reticular pattern.

Table 1. List of chemotherapy drugs associated with CDIRH.

Reference	Chemotherapy agent
- Wright AL *et al*. Dermatologica. 1990; 180 (4): 255-7.	Association of bleomycin, cyclophosphamide, vincristine, adriamycin, methotrexate
- Allen BJ *et al*. Int J Dermatol 1995; 34 (3): 219-20. - Sanz- Sanchez T *et al*. Actas Dermosifiliogr. 2008; 99 (7): 573-4.	5-fluorouracil
- Jogi R *et al*. J Drugs Dermatol. 2005; 4 (5): 652-6	5-fluorouracil plus carboplatin
- Jogi R *et al*. J Drugs Dermatol .2005; 4 (5): 652-6	Idarubicin plus cytarabine
- Youssef M *et al*. Int J Clin Pharm. 2013; 35 (3) 309-12.	Cyclophosphamide
- Youssef M *et al*. Int J Clin Pharm. 2013; 35 (3) 309-12.	Cyclophosphamide, doxorubicin, vincristine and prednisone
- Necessary CA *et al*. J Am Acad Dermatol. 2014; 71 (1): e23-24.	Association of doxorubicin, cisplatin, methotrexate, ifosfamide, etoposide
- Masson Regnault M *et al*. Dermatology. 2015; 231 (4): 312-8.	Association of vincristine, idarubicin, dexamethasone, cyclophosphamide, cytarabine
- Masson Regnault M *et al*. Dermatology. 2015; 231 (4): 312-8.	Carboplatin plus paclitaxel
- Masson Regnault M *et al*. Dermatology. 2015; 231 (4): 312-8.	Cytarabine plus topoisomerase II inhibitor
- Masson Regnault M *et al*. Dermatology. 2015; 231 (4): 312-8.	Association of cytarabine, idarubicin and lomustine
- Kumar S *et al*. Indian J Dermatol Venereol Leprol. 2021; 87 (3): 386-388.	Association of rituximab, methotrexate and cytarabine
- Kumar S *et al*. Indian J Dermatol Venereol Leprol. 2021; 87 (3): 386-388.	Association of methotrexate, cyclophosphamide, cytarabine, vincristine and asparaginase
- Kumar S *et al*. Indian J Dermatol Venereol Leprol. 2021; 87 (3): 386-388.	Association of carboplatin and gemcitabine