Chemotherapy-Related Reticulate Hyperpigmentation: A Case Series and Review of the Literature

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Introduction

Chemotherapy-induced pigmentary changes represent a well-recognized complication of cancer treatment [1–6]. They may involve the skin, hair or nails and a number of chemotherapeutic agents can predispose to the development of these lesions. Their clinical manifestations can vary from a progressive diffuse cutaneous hyperpigmentation (e.g. ‘busulfan tan’) to hyperpigmentation confined to the areas of skin trauma (under occlusion, on contact or pressure areas) or secondary hyperpigmentation following inflammatory dermatological lesions (e.g. after phototoxic reaction or hand-foot syndrome). Although available histopathological or ultrastructural studies remain scarce, the most frequent patterns suggest a direct toxic effect on melanocytes, inducing melanogenesis stimulation and a marked increase of epidermal melanin production, with a secondary accumulation in keratinocytes and the upper dermis or into melanophages. In addition, an increased number of melanosomes in keratinocytes, with a normal range of melanocytes [1, 5–10], has been identified.

More specific clinical presentations have been less frequently identified such as serpentine supravenous hyperpigmentation (mainly with 5-fluorouracil) [11–14] or bleomycin-induced flagellate hyperpigmentation [15–21].

However, reticulate hyperpigmentation has rarely been described in this context. Only 4 cases have been published until now [7, 22, 23]. We report here 5 new cases with similar aspects, comparing these features with currently available data from the literature.

Key Words
Reticulate hyperpigmentation · Chemotherapy · Flagellate hyperpigmentation · Pigmentary changes · Reflectance confocal microscopy · Cytarabine · Paclitaxel

Abstract

Background: Inherited or acquired reticulate hyperpigmentation represents a heterogeneous group of infrequent dermatological conditions. The development of reticulate hyperpigmentation has so far been rarely reported to be associated with chemotherapeutic agents, including fluorouracil, bleomycin or a combination of cytarabine and idarubicin. Case Reports: We describe 5 cases of chemotherapy-related reticulate hyperpigmentation in patients treated with different chemotherapeutic regimens, in particular paclitaxel or cytarabine. The lesions were similar in all cases, with reticulate and/or linear hyperpigmented streaks, which were mainly located to the back and buttocks. Histology showed increased melanogenesis, which suggests a direct toxic effect of chemotherapy on melanocytes. Reflectance confocal microscopy was performed in 2 patients showing a similar pattern, with an increased amount of melanin in basal keratinocytes. These features have been compared with the available data through a literature review. Conclusion: Reticulate hyperpigmentation is an underestimated but characteristic complication of chemotherapy. Neither specific management nor discontinuation of the chemotherapeutic regimen is required. © 2015 S. Karger AG, Basel
Case Reports

Patient 1
A 49-year-old Caucasian female patient with a history of metastatic breast cancer was treated with paclitaxel (80 mg/m² every week, 3 weeks per month). After six cycles, she developed an asymptomatic reticulate eruption with freckle-like hyperpigmented streaks on her back and the upper part of her thighs (fig. 1a). No other pigmentary changes were noted. There was no chronic heat exposure and no topical application preceding the development of the lesions. Skin biopsy with melanin staining showed a faint increase of basal keratinocyte pigmentation and mild melanin incontinence with the presence of melanophages in the upper dermis (fig. 1b, c). No symptomatic treatment was introduced. The lesions faded spontaneously within 3 months after discontinuation of the chemotherapy.

Patient 2
A 74-year-old Caucasian man with acute lymphoblastic leukemia was treated with conditioning regimen containing vincristine, idarubicin, dexamethasone, cyclophosphamide, and cytarabine. One month later, he developed a widespread reticulate hyperpigmented eruption associated with linear streaks on his back and shoulders (fig. 2a, b). A mild pruritus was present. Neither associated pigmentary changes on the nails and mucosae nor triggering factors were identified. A biopsy specimen revealed a melanin increase in basal keratinocytes with mild melanin incontinence and the presence of melanophages in the upper dermis (fig. 2c, d). In the absence of any therapeutic intervention, the lesions disappeared progressively within 6 months.

Patient 3
A 74-year-old Caucasian woman with stage IV serous ovarian cancer was treated with paclitaxel 175 mg/m² in combination with carboplatin every 3 weeks. The dose of carboplatin was calculated using a projected area under the concentration-time curve of 5 mg/ml/min (310–370 mg per perfusion). Six weeks after the introduction of this chemotherapeutic regimen, she developed an inflammatory and pruritic eruption of her entire back, with a reticulate distribution. The lesions progressively assumed the appearance of a reticulate hyperpigmentation (fig. 3a, b). Skin biopsy was refused by the patient. However, reflectance confocal microscopy by using MAVIG VivaScope 3000 was performed on the reticulate lesions and identified an increased content of melanin in basal keratinocytes (fig. 3c).

Patient 4
A 61-year-old Caucasian woman, with a relapse of acute myelogenous leukemia following allogenic hematopoietic stem cell
transplantation, was treated with a chemotherapeutic regimen containing cytarabine and a new topoisomerase II inhibitor under development. One month later, she developed a similar reticulate hyperpigmented eruption with linear streaks on her back, thighs and buttocks (fig. 4a, b). There were no associated symptoms. As in the previous cases, no other pigmentary changes were noted. Dermoscopy analysis of the lesions showed a hyperpigmented reticulate network (fig. 4c). Reflectance confocal microscopy (by using MAVIG VivaScope 1500) was also performed on the reticulate lesions, identifying a similar aspect to that observed in patient 3 with an increased amount of pigment in the basal layer of the epidermis (fig. 4d, e).

**Patient 5**  
A 64-year-old Caucasian man was treated with a first-line induction regimen containing cytarabine, idarubicin and lomustine for acute myelogenous leukemia. Three weeks later, an asymptomatic reticulate hyperpigmented eruption was discovered on his back and the upper part of his thighs (fig. 5).

### Table 1. Classification of reticulate pigmentary disorders [24–27]

<table>
<thead>
<tr>
<th>Inherited reticulate pigmentary disorders</th>
<th>Acquired reticulate pigmentary disorder</th>
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<tbody>
<tr>
<td>Dermatopathia pigmentosa reticularis</td>
<td>Reticulate papillomatosis of Gougerot and Carteaud</td>
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<tr>
<td>Dyskeratosis congenita</td>
<td>Ashy dermatosis</td>
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<tr>
<td>Fanconi anemia</td>
<td>‘Dirty neck’ sign in atopic dermatitis</td>
</tr>
<tr>
<td>Mitochondrial diseases</td>
<td>Prurigo pigmentosa</td>
</tr>
<tr>
<td>Certain forms of ectodermal dysplasia</td>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td>Naegeli-Franceschetti-Jadassohn syndrome</td>
<td>Riehl’s melanosis</td>
</tr>
<tr>
<td>Revesz syndrome</td>
<td>Erythema ab igne</td>
</tr>
<tr>
<td>X-linked reticulate pigmentary disorder</td>
<td>Lichen planus pigmentosus</td>
</tr>
<tr>
<td>Dowling-Degos disease</td>
<td>Occasional postinflammatory hyperpigmentation</td>
</tr>
<tr>
<td>Kitamura acropigmentation</td>
<td>Pigmented contact dermatitis</td>
</tr>
<tr>
<td>Galli-Galli disease</td>
<td>Drug-induced reticulate hyperpigmentation (diltiazem, Bier block, benzoyl peroxide, chemotherapeutic agents)</td>
</tr>
<tr>
<td>Incontinentia pigmenti</td>
<td></td>
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<tr>
<td>Dyschromatosis symmetrica or universalis hereditaria</td>
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### Discussion

Reticulate pigmentary disorders are uncommon dermatological conditions [24]. They represent a heterogeneous group of pigmentary disorders with overlapping phenotypic features, but controversy still exists regarding classification, with no clear consensus. Globally, the spectrum of reticulate hyperpigmentation includes inherited reticulate disorders with a freckle-like aspect and acquired disorders with a ‘reticulate’ or ‘reticular/net-like’ pattern of pigmentation (table 1) [24–26]. The patho-
genesis of reticulate hyperpigmentation is still poorly understood [27], and little is known about the mechanisms controlling this very specific anatomic distribution. The most commonly reported genetic defects in inherited reticular pigmentary disorders are localized in keratin 5 and keratin 14 genes, which play an important role in melanosomal transport [26, 28]. As a consequence, those gene mutations may affect pigment regulation in melanocytes, leading to pigmentary changes.

More recently, sporadic cases of drug-induced reticulate hyperpigmentation have been reported with diltiazem [29] and topical benzoyl peroxide [30] or after regional anesthesia with a Bier’s block [31]. Reticulate hyperpigmentation has also rarely been

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**Fig. 4.** a, b Reticulate hyperpigmentation with visible linear streaks on the back and buttocks. c–e Dermoscopic and reflectance confocal microscopy aspects showing an increased melanin content in basal keratinocytes. Reflectance confocal microscopy (MAVIG VivaScope 1500; 0.5 mm for each square).
<table>
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<tr>
<th>Reported cases</th>
<th>Patient characteristics</th>
<th>Underlying malignancies</th>
<th>Lesions</th>
<th>Time to development</th>
<th>Associated symptoms</th>
<th>Histopathological aspects or reflectance confocal microscopic aspects</th>
<th>Antineoplastic regimen</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright et al. [7], 1990</td>
<td>M, 55 years old</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Widespread lesions on the trunk and limbs</td>
<td>6 weeks</td>
<td>None</td>
<td>Increased melanin production located in basal and suprabasal keratinocytes; presence of melanophages in the papillary dermis; increased number of melanosomes in keratinocytes; normal number of melanocytes</td>
<td>Bleomycin, cyclophosphamide, vincristine, Adriamycin, methotrexate</td>
<td>Regression</td>
</tr>
<tr>
<td>Allen et al. [22], 1995</td>
<td>M, 61 years old, Caucasian</td>
<td>Metastatic gastrointestinal carcinoma</td>
<td>Widespread lesions predominantly located on the trunk</td>
<td>3 days</td>
<td>Preexisting asymptomatic erythema</td>
<td>NR</td>
<td>5-Fluorouracil</td>
<td>Regression</td>
</tr>
<tr>
<td>Jogi et al. [23], 2005</td>
<td>F, 63 years old</td>
<td>Mucoid epidermoid carcinoma of the parotid gland</td>
<td>Back and thighs</td>
<td>3 days</td>
<td>Preexisting asymptomatic erythema</td>
<td>NR</td>
<td>5-Fluorouracil, carboplatin</td>
<td>Gradual fading</td>
</tr>
<tr>
<td>Jogi et al. [23], 2005</td>
<td>F, 51 years old</td>
<td>Acute myelogenous leukemia</td>
<td>Lower back</td>
<td>4 weeks</td>
<td>None</td>
<td>NR</td>
<td>Idarubicin, cytarabine</td>
<td>NR</td>
</tr>
<tr>
<td>Patient 1</td>
<td>F, 49 years old, Caucasian</td>
<td>Metastatic breast cancer</td>
<td>Thighs and back</td>
<td>18 weeks</td>
<td>None</td>
<td>Increased melanin amount in basal keratinocytes; associated pigmented incontinence and melanophages in the papillary dermis</td>
<td>Paclitaxel</td>
<td>Regression</td>
</tr>
<tr>
<td>Patient 2</td>
<td>M, 74 years old, Caucasian</td>
<td>Acute lymphoblastic leukemia</td>
<td>Back and shoulder</td>
<td>4 weeks</td>
<td>Mild pruritus</td>
<td>Increased melanin amount in basal keratinocytes with melanophages in the papillary dermis</td>
<td>Vincristine, idarubicin, dexamethasone, cyclophosphamide, cytarabine</td>
<td>Regression</td>
</tr>
<tr>
<td>Patient 3</td>
<td>F, 74 years old, Caucasian</td>
<td>Metastatic ovarian cancer</td>
<td>Back</td>
<td>6 weeks</td>
<td>Preexisting erythema and pruritus</td>
<td>Reflectance confocal microscopy: increased melanin amount in basal keratinocytes</td>
<td>Carboplatin, paclitaxel</td>
<td>Slight regression</td>
</tr>
<tr>
<td>Patient 4</td>
<td>F, 61 years old, Caucasian</td>
<td>Acute myelogenous leukemia</td>
<td>Back, buttocks and thighs</td>
<td>4 weeks</td>
<td>None</td>
<td>Reflectance confocal microscopy: increased melanin amount in basal keratinocytes</td>
<td>Cytarabine, topoisomerase II inhibitor</td>
<td>Unknown</td>
</tr>
<tr>
<td>Patient 5</td>
<td>M, 64 years old, Caucasian</td>
<td>Acute myelogenous leukemia</td>
<td>Back and buttocks</td>
<td>3 weeks</td>
<td>None</td>
<td>NR</td>
<td>Cytarabine, idarubicin and lomustine</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

NR = Not reported. 1 Suspected chemotherapeutic agent.
described in association with chemotherapy. To our knowledge, only 4 cases have been reported until now (table 2). Patients were treated with a chemotherapeutic regimen containing bleomycin, fluorouracil (twice) or a combination of idarubicin and cytarabine, respectively [7, 22, 23]. Wright et al. [7] first reported 1 patient developing widespread reticulate hyperpigmentation after cancer treatment with a chemotherapeutic regimen containing bleomycin. The lesions were mainly located on the trunk and limbs and were strictly similar to those observed in our patients. In the same way, skin biopsy also showed an identical histopathological pattern, including active melanogenesis with an increase in melanin amount in basal and suprabasal keratinocytes, pigmentary incontinence and dermal melanophages. The number of melanocytes appeared to remain within the normal range. Electron microscopic analysis confirmed an increased number of melanosomes in basal keratinocytes associated with mitochondrial damage, suggesting a local toxic effect. In fact, as in our 2 biopsied patients, the histopathological changes were similar to those chiefly observed in other chemotherapy-related pigmentary changes and evoking increased melanogenesis in response to direct damage to epidermal cells [1, 2, 5, 6, 8–10]. The 3 other remaining case reports were also clinically similar to our patients, but skin biopsies were not performed in any of the latter cases. We report here 5 additional cases of chemotherapy-related reticulate hyperpigmentation with a pattern of pigmentation identical to that previously published. One patient presented a preexisting erythematous phase before developing pigmentary changes, as already described [22, 23] (table 2). Three of our patients developed lesions after treatment with cytarabine alone or in combination with idarubicin, like 1 of the patients reported by Jogi et al. [23]. It is probably not anecdotic and patients treated with these antineoplastic drugs are potentially more susceptible to develop this characteristic skin toxicity. In addition, we report the first 2 cases induced by paclitaxel. The exact mechanism of chemotherapy-related reticulate hyperpigmentation remains speculative. These reticular lesions do not respect Blaschko’s lines and are not suggestive of a mosaicism. It has been hypothesized that this distribution especially in contact areas (e.g. back and buttocks) could be partially explained by local changes in blood flow in susceptible individuals. It may lead to a direct toxic effect of chemotherapy on melanocytes, with a secondary increase in melanogenesis [7, 22].

Above all, reticulate hyperpigmentation should be differentiated from the well-identified chemotherapy-induced flagellate hyperpigmentation. Although the latter has very rarely been reported with docetaxel [32], flagellate hyperpigmentation should be considered as a specific reaction to bleomycin therapy. We should stress that none of our patients presenting reticulate hyperpigmentation were treated with bleomycin. Moreover, whip-like striped lesions observed with bleomycin usually develop in a well-demarcated linear configuration and are most often papular and larger [17, 18, 20]. Flagellate dermatitis also mainly involves the back and pressure areas, but the lesions are generally more self-limiting and preceding pruritic erythematous linear streaks, sometimes severe, are much more frequently noted in comparison with reticulate hyperpigmentation [15, 17–19]. Histopathological findings can also include a localized increase in melanogenesis with melanin incontinence, as well as the presence of melanophages in the papillary dermis. However, histopathological changes are not uniform and a broad spectrum of histological features has been reported, including perivascular or perisudoral lymphohesinophilic cell infiltration, hyperkeratosis with focal parakeratosis and spongiosis [15–17]. Pathophysiological mechanisms leading to flagellate hyperpigmentation are still unknown, but a local toxic effect after drug leakage within the skin or a reduced epidermal turnover with prolonged contact between melanocytes and keratinocytes have been postulated [15, 17, 20]. Finally, it has been hypothesized that bleomycin may persist longer in the skin due to a lower level of bleomycin hydrolase [15, 16].

Finally, we performed reflectance confocal microscopy imaging in 2 patients, which had never been performed so far in the context of chemotherapy-induced pigmentary changes. Imaging features were consistent with histopathological findings previously described [1–6], i.e. suggestive of a stimulation of melanogenesis with an increased content of melanin in basal keratinocytes.

Conclusion

Chemotherapy-related reticulate hyperpigmentation has so far been only rarely reported in the literature. However, our single-center experience with the description of 5 additional cases suggests that this very characteristic dermatological toxicity is probably underestimated. Dermatologists should be aware of this poorly recognized but specific enough adverse event of chemotherapy, which does not require specific management, dose reduction or discontinuation of cancer therapy. By contrast, reassurance of the treated patients is crucial.

Disclosure Statement

The authors report no conflicts of interest related to this work.

References