



Specific skin changes induced by chemotherapy

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Abstract: Cancer remains the leading cause to death among Chinese populations, with increasing incidence and mortality every year. As we know, chemotherapy is the main systemic therapy for cancer patients, which frequently causes skin toxicity. Since this side effect is non-life threatening, the impact of its occurrence is often being neglected. However, skin toxicity does influence the quality of life of the patient and often leads to the decrease in dosage or even suspension of treatment, and therefore significantly altered the therapeutic outcome. Hereby, we first report four specific skin changes induced by chemotherapy which are observed in patients treated in our department (from March to October in 2015). To further establish our current observation, we reviewed pertinent publications regarding skin toxicity due to chemotherapy and summarized common skin toxicity induced by chemotherapy. Herein, by summarizing both common and rare skin adverse reactions induced by chemotherapeutic drugs, we hope to increase awareness in this area and possibly to come up with therapeutic interventions that could curb these side effects.

Keywords: Chemotherapy; skin; side effect; Muehrcke's lines

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Introduction

The latest statistics showed that the year of 2015 witnessed 4,292,000 new cancer patients arise and 2,814,000 patients would eventually succumb to the disease. Cancer has been the leading cause of death in China and is one of the key issues threatening public health due to its increasing incidence and mortality (1). Apart from being used to treat cancer, chemotherapy also plays a pivotal role in treating blood disorders and some autoimmune diseases. Despite the considerable development of targeted therapy which substantially prolongs the survival of patients, chemotherapy in oncology is nonetheless essential, especially in adjuvant

and neoadjuvant therapy (2-4). However, one of the common adverse reactions caused by chemotherapy is skin toxicity though it does not attract sufficient attention as it does not lead to fatal outcomes. These adverse reactions generally display complex and diverse features on the skin of immunocompromised patients, and have a negative impact on these cancer patients, both mentally and physically. The physical presentation of these symptom could reduce the patients' treatment compliance and living quality (5). Hereby, four case reports regarding the side effects of chemotherapy on skin are presented and the relevant articles are reviewed and discussed.



Figure 1 Muehrcke's lines are white lines paralleling lunula and traversing the whole nail. These lines existed on her (case 1) each of the nails after 6 cycles of chemotherapy consisted of doxorubicin and would fade with digital compression.



Figure 2 The patient (case 2) with breast cancer was also found with Muehrcke's lines on her nails after 4 cycles of chemotherapy with epirubicin.

Case presentation

Case 1

A 43-year-old female presented to our department with one-month ulceration of right lower gingiva in March of year 2015. She had a resection of neoplasm from right lower gingiva on March 30th 2015 and the pathological diagnosis was extra-nodal NK-T cell lymphoma. The positron emission tomography-computed tomography (PET-CT) has revealed diffusive lymphoma with lung infiltration. She has received etoposide, doxorubicin, vincristine, cyclophosphamide and prednisone (EPOCH) chemotherapy for 8 cycles from April 14th to October 18th in 2015. The treatment evaluation after 4 cycles of EPOCH was partial response (PR, the evaluations were done according to the RECIST guidelines, namely

Response Evaluation Criteria in Solid Tumors) whereas after 8 cycles was complete response (CR). After completion of 6 cycles of chemotherapy, Muehrcke's lines emerged on all of the patient's nails (*Figure 1*). When she returned to our department for follow-up after 3 months from the last chemotherapy, the Muehrcke's lines had disappeared.

Case 2

Female patient, 44 years old, had undergone left modified radical mastectomy with left axillary sentinel lymph node biopsy successfully on June 16th 2015 because of a left breast mass. Grossly, the excised mass was approximately 2.2 cm × 1.8 cm × 1.7 cm. The histopathological analysis of the mass showed that it was invasive ductal carcinoma of the left breast (stage III) and is strongly positive for human epidermal growth factor receptor-2 (HER-2) but negative for estrogen receptor (ER) or progesterone receptor (PgR) with high expression of Ki-67 (80%). A few vessels with cancer embolism were observed while none of the nine resected nodes was found with carcinoma metastasis. She had 4 cycles of epirubicin and cyclophosphamide (EC) followed by 4 cycles of paclitaxel liposome and trastuzumab (TH) as adjuvant chemotherapy from June 26th to August 31st 2015. She showed good tolerance during the EC followed by TH chemotherapy after the operation. Muehrcke's lines were also observed on her nails after 4 cycles of chemotherapy (*Figure 2*). Three months after chemotherapy, Muehrcke's lines vanished without intervention.

Case 3

A 64-year-old female came to our department with a mass on her left breast. After systemic examination, she underwent a modified radical mastectomy with left axillary sentinel lymph node biopsy of the left breast was done on June 25th 2010. The microscopic observation revealed mucinous carcinoma of the breast, 5.0 cm × 5.0 cm × 3.5 cm in size, with immunohistochemistry of ER(++), negative expression for both PgR and HER-2 and low expression of Ki-67 (10%) and no tumor metastasis found on the nine resected nodes. Six cycles of the adjuvant chemotherapy with cyclophosphamide and docetaxel (DC) were then performed. During the follow-up on October 12th for reexamination, the CT detected multiple carcinomas in hilar and mediastinal lymph nodes of both lungs. She then received chemotherapy of gemcitabine, endocrine therapy

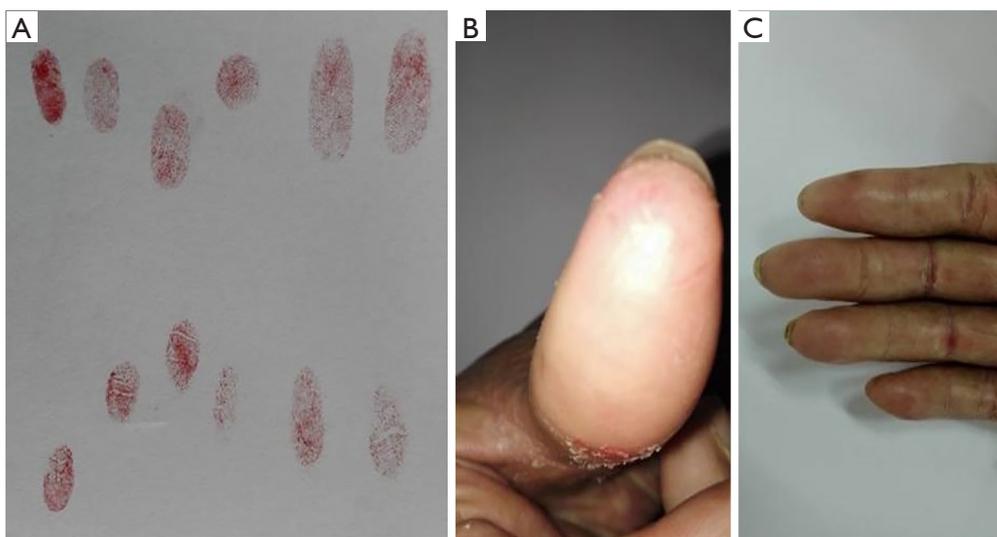


Figure 3 Loss of fingerprints and hand-foot syndrome of the patient in case 3. (A) The breast cancer patient (case 3) experienced loss of fingerprints after 40 cycles of capecitabine (upper) compared with the normal fingerprints of her husband at the meantime (below); (B) loss of fingerprints at a close range; (C) the hand-foot syndrome can be concomitantly noted.



Figure 4 Band-like or diffusive black pigmentations appear on the nails of the patient (case 4) with breast cancer after the chemotherapy of epirubicin.

of sequentially anastrozole, exemestane and toremifene from October 2010 to April 2014, all of which were failed eventually. The CT in the follow-up on May 22nd 2013 showed new bone and bilateral adrenal glands metastasis. Forty cycles of capecitabine in total were administered from May 2013 to August 2015. All of her treatment evaluations of the subsequent follow-ups for the capecitabine regime were stable disease (SD). Notably, she experienced slight finger stiffness and loss of fingerprints in most of her fingers in August 2015 when returned for review (*Figure 3*).

She was advised to increase vegetables and fruits intake to obtain sufficient natural vitamins instead of administrating more pills. In the following 5 months, she continued the treatment of capecitabine until disease progression. When she returned to our clinic after capecitabine was terminated for 2 months, physical examination showed that the symptom of finger stiffness has improved while her fingerprints were recovered.

Case 4

A 57-year-old female presented to our department in October 2015. After a needle biopsy of the right breast mass and relevant radiological examinations, she was clinically diagnosed with right breast invasive ductal carcinoma (T2N0M0) according to the TNM classification, with the molecular classification of luminal B and HER-2 positive. From October 13th to December 15th 2015, she received EC for 4 cycles as neoadjuvant therapy. The right breast mass of the 4th patient has shrunk from 2.6 cm × 1.5 cm to 2.4 cm × 1.3 cm in gross measurement according to ultrasound imaging. The post-treatment evaluation for the neoadjuvant chemotherapy of EC was SD. During treatment, the patient was found to have multiple black pigmentation throughout her body, of which there were band-like or diffusive black pigmentation on her nails (*Figure 4*).

Table 1 Cutaneous adverse reactions caused by chemotherapy

Skin lesions	Cutaneous adverse reactions	Chemotherapeutic agents
Skin barrier lesion	Maculopapules	Taxane, docetaxel, gemcitabine
	Nettle rashes	Oxaliplatin, bleomycin
	Erythematous bulla, sclerodermoid lesion and flagellate erythema	Bleomycin
	Hyperpigmentation	5-FU, cyclophosphamide, methotrexate, busulfan, epirubicin, adriamycin
	Hand-foot syndrome	5-FU, capecitabine, docetaxel, liposomal doxorubicin, cytarabine
	Radiation recall	Adriamycin, paclitaxel, gemcitabine, bleomycin, pemetrexed
	Skin necrosis and ulceration	Adriamycin, vinca alkaloids, large dose of methotrexate
Skin appendage lesions	Alopecia	Paclitaxel, docetaxel, adriamycin, vinca alkaloids
	Onycholysis	Paclitaxel and docetaxel
	Subungual or splinter hemorrhage	Paclitaxel
	Beau's lines	Paclitaxel
	Mees' lines	Paclitaxel, cyclophosphamide, vincristine and Adriamycin

We tried but failed to contact the patient during the follow-up.

Discussion

The case reports above are unique and rare skin changes caused by chemotherapy, which are rarely reported in oncology cases. Alkylating agent, including vinblastine and vincristine, one of the widely-used anti-tumor drugs, is likely to induce multiple side effects on skin and mucosa, with diverse and complex symptoms including alopecia, paronychia, dry skin, pigmentation, and skin rashes (5). The occurrence of these symptom not only increase pain to the patients, but also tend to decrease their compliance for the treatment. Until now, the presentation of specific skin changes induced by chemotherapy has been side-tracked and their relevant systemic reviews are rare. Herein we present a thorough review concerning two major classes of common skin toxicity caused by chemotherapy on the basis of the reported cases and previous literatures. We reviewed pertinent publications retrieved by a selective search in PubMed from 1950 to 2017 regarding skin toxicity due to chemotherapy with the inclusion of the following key terms (including “skin”, “cutaneous”, “toxicity”, “reaction” or “change”). After careful scrutinization, we identified common

skin toxicity induced by chemotherapy. *Table 1* lists the adverse dermatological effects caused by chemotherapy and we summarize the incidence of the adverse dermatological effects caused by chemotherapy on *Table 2*.

Skin barrier lesions

Skin rash

Skin rash is a common manifestation of skin allergy on chemotherapy. For example, taxanes are widely utilized in the treatment for solid tumor. Both paclitaxel and docetaxel can lead to maculopapules on faces, limbs and butts, and might cause secondary infection of pustular rash (23,24). Gemcitabine, an anti-metabolism chemical drug, also causes skin rashes associated with allergy and itching (25). Other anti-cancer drugs such as oxaliplatin and bleomycin may present patient with either typical nettle-rashes or non-specific ones. One retrospective study shows that over 15% of the patients experience hypersensitivity during the treatment with oxaliplatin (26). The analysis points out that being a male and an increase in eosinophils of the peripheral blood are two indicators to be susceptible to oxaliplatin-related hypersensitivity reactions. Bleomycin, used mainly for Hodgkin's lymphoma, germinoma and malignant pleural

Table 2 Incidence of cutaneous adverse reactions by chemotherapeutic agents

Cutaneous adverse reactions	Agents	Dosage	Incidences (all grades)
Maculopapules	Taxane	Weekly 80 mg/m ² , iv	13.3% (6)
	Docetaxel	100 mg/ m ² , iv, on day 1 of each 21-day cycle	56.6%*
		75 mg/m ² , iv, on day 1 of each 21-day cycle	15.7%*
Nettle rashes	Gemcitabine	1,000 mg/m ² , iv, on day 1 of each 21-day cycle	25%*
	Oxaliplatin	85 mg/m ² , iv, on day 1 of each 14-day cycle	1–10%*
Erythematous bulla, sclerodermoid lesion and flagellate erythema	Bleomycin	30 mg, im, days 2, 9, 16	CR (7)
		30 mg, im, days 2, 9, 16	CR (7)
Hyperpigmentation	5-FU	1,500 mg–2,500 mg/m ² , civ	2–5% (8)
	Methotrexate	50 mg, im, on days 1, 3, 5 and 7	CR (9)
	Cyclophosphamide	500 mg/m ² , iv	CR (10)
	Busulfan, epirubicin, adriamycin	NR	CR (11)
	Bleomycin	15 mg/m ²	CR (12)
Radiation recall	Gemcitabine	1,000 mg/m ² , iv, on day 1 of each 21-day cycle	CR (13)
	Paclitaxel, adriamycin	NR	CR (14)
	Bleomycin	NR	CR (15)
	Pemetrexed	500 mg/m ² , iv	CR (16)
Skin necrosis and ulceration	Adriamycin	NR	CR (11)
	Vinca alkaloids	NR	CR (17)
	Methotrexate	50 mg/m ² , iv for 5 days	CR (18)
Alopecia	Docetaxel	100 mg/m ²	79%*
	Docetaxel	75 mg/m ²	38%*
	Paclitaxel	135–175 mg/m ² , iv	87%*
HFS	Docetaxel	100 mg/m ² , iv	6–58% (19)
	Continuous infusion of 5-FU	1,500 mg–2,500 mg/m ² , civ	34% (19)
	Capecitabine	1,250 mg/m ² , twice, daily	50–60% (19)
	Pegylated liposomal doxorubicin	40–50 mg/m ² , iv	40–50% (19)
	Cytarabine	1,000 mg/m ² , iv	14–33% (19)
Nails change**	Docetaxel	100 mg/m ² , iv	27.9%*
		75 mg/m ² , iv	9.9%*
Beau's lines	Paclitaxel	NR	CR (20)
Mees's lines	Paclitaxel, cyclophosphamide, vincristine and adriamycin	NR	CR (21,22)

*, incidence of the agent is referred to the manufacture's instruction; **, nails change incorporates hyperpigmentation or hypopigmentation on nails, subungual or splinter hemorrhage and onycholysis. iv, intravenous; im, intramuscular; civ, continuously intravenous; NR, not reported in the study; CR, only reported in a case or cases; HFS, hand-foot syndrome; 5-FU, 5-fluorouracil.

effusion, results in various skin rashes such as eczematous change, erythematous bulla, sclerodermoid lesion and infrequent flagellate erythema (7).

Hyperpigmentation

Hyperpigmentation refers to the abnormal increase of melanin, which can be subdivided into diffuse and local hyperpigmentation according to its region. The former has been reported to appear after the prescription of 5-fluorouracil (5-FU), cyclophosphamide, methotrexate and busulfan (9,10), and the latter occurred in patients who received adriamycin, 5-FU, cyclophosphamide and busulfan, which may have local hyperpigmentation in their mouths. Bleomycin may cause pigmentation on the body induced by exogenous sources of pressure, as seen our case presentation 4 patient whose nails was presented with diffuse or band-like pigmentation after 4 cycles of epirubicin (12). The occurrence of the band-like shape might be the discontinuation of adriamycin drugs and the recovery in the growth of the nail matrix, thus changing the color of nails (19).

Hand-foot syndrome (HFS)

HFS frequently happens on compression zones, such as palms and plantars. The clinical manifestations are numbness, paresthesia, skin swelling, erythema, desquamation and severe pain. This is especially common for patients who receive 5-FU or capecitabine. After oral administration of capecitabine, more than half of the patients suffered from HFS (19). A retrospective study indicates that for the gastroenteric cancer patients, the occurrence of side effects after the usage of the combination of capecitabine with oxaliplatin was similar to that of pumping 5-FU intravenously (13). An analysis based on a randomized trial shows that HFS induced by capecitabine might be the independent predictor in prolonging the overall survival (OS) of colon cancer patients (27). Other chemotherapeutic drugs that have been reported to induce HFS include docetaxel, liposomal doxorubicin, cytarabine among others (24,28). Incidence of HFS may be reduced by local cooling, using urea ointment and vitamin B6 (19). Nevertheless, these methods are still short of clinical evidences. The 4th patient presented received capecitabine for 40 cycles, and grade II HFS developed with the loss of fingerprints. Likewise, Chavarri-Guerra *et al.* in 2015 reported a breast cancer patient who was denied by a bank to authorize a financial transaction due to her loss of fingerprints. The author explained that the phenomena of

fading fingerprints may be an outcome of HFS induced by capecitabine (29).

Radiation recall

Radiation recall refers to inflammation led by chemotherapeutic drugs in previously irradiated tissues, such as: skin, mucosa, lung, esophagus, intestine and heart with unknown mechanisms. Different from radiation damage, radiation recall develops several months to years after termination of radiotherapy. It has been reported that patients who have received adriamycin and paclitaxel bear more risk of radiation recall. Besides that, gemcitabine, bleomycin and pemetrexed were reported as well (14-16,30).

Skin appendage lesions

Alopecia

About 65% of the patients who receive chemotherapy may suffer from alopecia (31). Most chemotherapeutic drugs like paclitaxel, adriamycin, vinca alkaloids can lead to alopecia, which is hair loss and even short hair loss, including eyebrow, eyelashes and armpit hair, etc. However, hair will regenerate within 3–6 months from the discontinuation of chemotherapeutic drugs generally, while only very few patients will develop permanent hair loss (32,33). It might be useful to prevent hair loss by wearing ice cap or using tourniquet during chemotherapy to constrict local vessels and reduce the intake of chemotherapeutic drugs. However, the side effects of this method is the possibility of metastasis to the scalp (34,35).

Nail change

Both paclitaxel and docetaxel can lead to onycholysis. Other changes caused by paclitaxel, including subungual hemorrhage, splinter hemorrhage, Beau's lines, and Mees' lines (20,21). Beau's lines are a series of traversing depressed lines through the nail, which indicates the inhibition or pause of nail matrix mitosis (36). The depth of the depressions reflects the duration and severity of these lesions. Cyclophosphamide, Vincristine and Adriamycin may lead to Mees' lines-white lines paralleling lunula, as an outcome of impaired keratinization of the nail matrix (22). Both of the lines will move forward to the tip as nail grows.

Similarly, Muehrcke's lines are white lines lie parallel to lunula and extend across the nail. In fact, these are the signs of loss of pigmentation, as a consequence of nail bed rather than the influence to the nail itself. Therefore, the lines will not alter as the nails grow. It was reported that the formation

Table 3 Identification of Beau's lines, Mees' lines and Muehrcke's lines

Classification	Manifestation	Part affected	Move as nail grows	Change with digital compression	Pathogenic factors
Beau's lines	Depressed lines paralleling lunula and traversing the whole nail	Nail matrix (its mitosis is restrained or stopped)	Yes	Dents can be touched	Infection, surgery, trauma, Reynold's disease, chemotherapy, etc.
Mees' lines	White lines paralleling lunula and traversing the whole nail	Nail matrix (unable to keratinize and mitosis unaffected)	Yes	No change	Arsenic poisoning, Hodgkin lymphoma, benign tumor, chemotherapy, etc.
Muehrcke's lines	White lines paralleling lunula and traversing the whole nail	Nail bed (the vessel blocked and pigmentation fades)	Yes	White lines fade	Liver disease, kidney disease, malnutrition, chemotherapy, etc.

of Muehrcke's lines may be attributed to hypoalbuminemia. Various diseases accompanied by hypoalbuminemia, such as glomerular diseases, infections and so on, might also cause Muehrcke's lines, while replenishing albumins can possibly makes the lines fade (20,37). As seen in our cases, the first patient's serum albumin has decreased to as low as 35 g/L, while the second patient did not have hypoalbuminemia during her treatment. It still warrants further study to explore the association between Muehrcke's lines and hypoalbuminemia. The methods to identify each of the lines are listed below (*Table 3*).

Other skin changes caused by chemotherapy were dry skin and desquamation. Strong irritating chemotherapeutic drugs like adriamycin and vinca alkaloids can lead to skin necrosis and ulceration if exuding out of vessels. Large dose of methotrexate would possibly result in vesiculation and ulceration of the skin even if rescued by calcium folinate (38).

Prospective

Skin changes induced by chemotherapy are extremely common and are often neglected. Not only should clinicians focus on the therapeutic results, more attentions should be paid to the skin toxicity of chemotherapy. It is crucial to prevent and treat skin changes as early as possible during the treatment, for it is highly related to the quality of patient's life and compliance to the treatment. Studies show that from the beginning of chemotherapy, skin care managements like proper skin cleaning and application of certain dermatological products were deemed to be effective in reducing the incidence of skin side effects (21). For most of the skin changes, perhaps physical therapy treatment like topical cooling weigh more advantages in treatment than utilizing certain chemical products. Further studies are

warranted to investigate the ideal methods to prevent and cope with skin changes induced by chemotherapy.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2018.05.17>). The authors have no conflicts of interest to declare.

Ethical statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the

Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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