Case Report

Docetaxel-Induced Supravenous Serpentine Dermatitis: A Case Report and Literature Review

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The author reported a rare case of 66-year-old man presenting with cutaneous lesion with a red line spreading along the venous path three days after the first cycle of docetaxel in advanced stage lung cancer. The examination revealed unilateral well-defined linear, non- blanchable erythematous to violaceous plaques along the superficial venous network of the right foot and then progressed to the right leg and extended above the right knee. A lesional skin biopsy was done and histopathological findings showed superficial interface dermatitis consistent with supravenous serpentine dermatitis. He was treated with topical betamethasone valerate (0.1%) cream twice daily for one week. The skin lesion improved but he still had residual hyperpigmented skin along the superficial venous network. However, there were some limitations of other chemotherapeutic agents, including pemetrexate and targeted therapy, such as the cost, the second cycle of docetaxel was used with more dilution, the extended time of intravenous transfusion, and the saline infusion before and after chemotherapy. This cutaneous side effect did not occur again. The present case report showed the interruption of docetaxel is not indicted when this reaction happens because it is self-limited. Prevention of this eruption can be achieved by extending the time of drug transfusion, and increasing the dilution of chemotherapy and saline infusion before and after chemotherapy.

Keywords: Docetaxel, Supravenous serpentine dermatitis, Lung cancer, Superficial interface dermatitis

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Docetaxel is a chemotherapeutic drug used to treat malignancy including breast, prostate, non-small cell lung cancer, stomach, and head and neck cancers[1]. Paclitaxel and docetaxel belong to the taxane class of cytotoxic agents. Paclitaxel is a natural extract derived from the bark of the specific yew tree (*Taxus brevifolia*). It became commercially available in 1992. On the other hand, docetaxel is a semisynthetic analogue of paclitaxel synthesized from the needles of the European yew tree (*Taxus baccata*)[2]. Docetaxel, a semisynthetic taxane, acts by altering the tubulin dissociation rate constants at both ends of microtubule causing microtubular disruption, thus disrupting mitosis and normal cell division, and eventually leading to cell death[3,4]. Common side effects include hair loss, neutropenia, numbness, shortness of breath, vomiting, and muscle pain. Other severe side effects include allergic reaction and future cancers. These side effects are common in people with liver problems[5]. Cutaneous side effects are frequent, with an estimated incidence of 65%. Cutaneous reported toxicities include hypersensitivity reaction, pigmentation, onycholysis, palmar-plantar erythrodysesthesia, cutaneous lupus, and toxic epidermal necrolysis[6]. Supravenous serpentine dermatitis is rare cutaneous side effect, characterized by increase pigmentation of the skin immediately overlying the venous network. It begins as red streaks commonly over the injected veins, followed by hyperpigmentation. This condition is benign and self-limiting[7]. Other terms of this condition include persistent supravenous erythematous eruption [PSEE], persistent serpentine supravenous hyperpigmented eruption [PSSHE], and persistent serpentine supravenous hyperpigmentation. At Vachira Phuket Hospital, between May 2016 and April 2017, twenty-two patients received docetaxel with sixty-nine docetaxel doses. The most cases were diagnosed with advanced stage lung cancer. Seventeen patients had advanced stage non-small cell lung cancer, three patients had prostate cancer, one patient had hypopharyngeal cancer and one patient had leiomyosarcoma. The most common side effects were hair loss, peripheral neuropathy, neutropenia, and nausea with vomiting. Only one patient had cutaneous side effect. The author reported and described a patient who developed linear serpentine erythematous eruption, a relatively rare condition, after treatment with intravenous docetaxel for non-small cell lung cancer.

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Case Report

A 66-year-old man was referred to Vachira Phuket Hospital with complaints of chronic cough and progressive dyspnea for one month. The chest computed tomography [CT] scan showed irregular heterogenous enhancing mass in left lung with massive left pleural effusion. This patient was diagnosed as advanced stage lung cancer by closed pleural biopsy. Palliative chemotherapy was initiated with combination of paclitaxel and carboplatin. After 3-cycle of paclitaxel and carboplatin, repeated chest CT scan showed increase in size of the ill-defined heterogenous enhancing mass in left lung and progression of liver metastasis. Subsequently, second line chemotherapy was initiated with docetaxel 75 mg/m^2 intravenously every three weeks. Docetaxel was diluted in 5% D/W 250 ml and infused intravenously within two hours. The patient had pre-medication with ondansetron 8 mg IV and dexamethasone 20 mg IV and continued dexamethasone 4 mg orally twice daily post-chemotherapy for two days. Docetaxel was administered via superficial vein at the dorsum of the right foot. The patient reported that three days after the first session of chemotherapy, he noticed a red line spreading along the path of infusion of the drug with mild itching but no pain sensation. Over the next few days, the red line spread further proximally. There were no constitutional symptoms, such as fever, anorexia, and weight loss in this situation. Examination revealed unilateral well-defined linear, non-blanchable erythematous to violaceous plaques along the superficial venous network of the right foot and progressed to the right leg and extended to above the right knee (Figure 1). There were no other mucocutaneous lesions or regional lymphadenopathy. The veins underlying the pigmented streaks were neither tender nor thrombosed.

Laboratory evaluation showed hemoglobin of 8 g/dl, total white blood cell counts 2.32×10^9/l, with 46% neutrophils, 38% lymphocytes with platelet of 156,000 cells/ml^3. The routine biochemistries were normal.

A lesional skin biopsy was performed on the third day of the appearance of the skin lesions. Histopathological examination revealed scattered necrotic keratinocytes and vacuolar alteration of basal cell layer in associated with perivascular inflammatory-cell infiltrate of lymphocytes, and numerous extravasated erythrocytes in the upper dermis. The underlying veins of the lesion were normal (Figure 2). This histopathological finding showed superficial interface dermatitis, correlated with clinical setting. The diagnosis was consistent with supravenous serpentine dermatitis.

The patient was prescribed betamethasone valerate (0.1%) cream applied twice daily for one week. The skin lesion improved within one week. He had residual hyperpigmented skin along the superficial venous network.

Because the chemotherapeutic treatment options, both targeted therapy and others chemotherapeutic agents, such as pemetrexate, were expensive, the patient could not afford them, thus limited the options of the treatment. The second cycle of docetaxel was tried at other location of venous site with more dilution and extended time of intravenous transfusion. Docetaxel 100 mg (75 mg/m^2) was diluted in 5% D/W 500 ml and infused intravenously within three hours with saline infusion before and after chemotherapy. The same pre-medications as the first cycle were introduced before chemotherapy. No cutaneous side effects occurred within three weeks after docetaxel infusion.

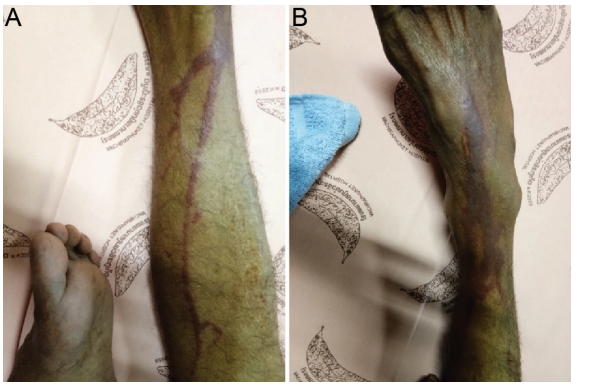

Figure 1. (A) Linear streak of hyperpigmentation along superficial vein of right leg. (B) Linear streak of hyperpigmentation along superficial vein of right foot.

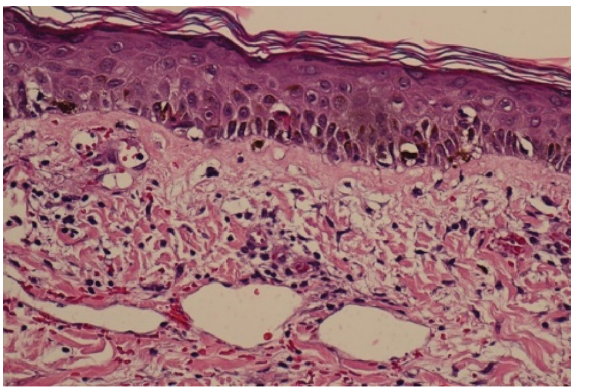

Figure 2. H and E; ×400.

Discussion

Docetaxel is a chemotherapeutic agent from taxane group and has been used as a second-line treatment of non-small cell lung cancer. Major systemic side effects of docetaxel include bone marrow suppression, hypersensitivity reactions, fluid retention, neurotoxicity, myositis, and cardiovascular side effect[5]. Hematologic adverse effects include neutropenia, anemia, febrile neutropenia, and thrombocytopenia. Hypersensitivity reaction can range from minor rash to severe anaphylaxis. Skin reactions include maculopapular rash, supravenous discoloration, mucosal ulcers, alopecia, and nail hyperpigmentation and destruction[6]. Supravenous serpentine dermatitis is one of cutaneous side effect, which is relatively rare. The present case is the first case report of docetaxal-induced supravenous serpentine dermatitis in our institute. This rare case was found in the patient with non-small cell lung cancer.

Schrijvers et al[8] first reported supravenous discoloration of the skin due to docetaxel. Their patient developed reddish discoloration of the skin above the veins at the injection site. Aydogan et al[9] reported one case of squamous cell carcinoma of the lung with failure to treatment with cisplatin and gemcitabine followed by radiation therapy. Their patient received second-line therapy with intravenous infusion of docetaxel and developed linear, erythematous eruption at the site of the docetaxel injection on his right forearm. At the end of six months, the eruption had cleared completely. No details were noted about the prevention of this cutaneous side effect.

Umemura et al[10] reported a 54-year-old man with non-small cell lung cancer, receiving the first course of docetaxel plus cisplatin. On the tenth day after the first infusion from the left cephalic vein, the patient noticed a mildly pruritic, erythematous, bullous eruption around the injection site with painless linear erythematous eruption following the route of the superficial venous network of the distal portion of the left forearm and spread up to the anterior aspect of the distal portion of the upper arm, which looked like the patient in the present case, but the onset of symptoms was longer. Ghosh et al[7] reported a 45-year-old woman with recurrent breast carcinoma scheduled for chemotherapy with docetaxel. She developed supravenous serpentine dermatitis on the next day after received docetaxel. Fernandes and Felix[11] reported two cases with breast carcinoma that developed skin reaction due to docetaxel. Both cases were diagnosed as supravenous erythematous eruption that occurred within a few days after docetaxel infusion. In the first case, skin lesion progressed with residual hyperpigmentation but the second cases showed complete remission of skin lesion within three months after the end of chemotherapy. Therefore, the onset of symptoms is quite variable. They may be acute or delay onset after docetaxel was transfused. Some patients developed residual hyperpigmentation, but some patients got complete remission. The pigment aberrations may persist for more than one year after chemotherapy.

Supravenous serpentine dermatitis is a rare sequel of many chemotherapeutic agents[9,12-15], such as nitrogen mustard, notrosoureas, cyclophosphamide, fotemustine, actinomycin, doxorubicin, vinca alkaloids, vinorelbine, taxanes, proteasome inhibitors, and bortezomib. Although the exact mechanism is unknown but it has been postulated that these cytotoxic drugs cause a direct effect on the vascular endothelium then loss of integrity and lead to leakage of the drug from the vessel to the overlying epidermis, leading to hyperpigmentation[14]. Some postulated mechanisms for PSSHE is showed in Table 1[9]. Based on the morphology of the lesion, the clinical differential diagnosis should include thrombophlebitis, cutis marmorata, livedo reticularis, and lichen planus[13]. Unlike tender, clot-forming thrombophlebitis, the underlying vessels of serpentine supravenous hyper-pigmentation remain patent. Each of these diagnoses can be readily excluded from the history and clinical examination[7].

The histopathological findings of this reaction

Table 1. Possible mechanisms of PSSHE and other drug-induced hyperpigmentation

1.	Post-inflammatory hyperpigmentation secondary to subclinical phlebitis
2.	Increased blood flow to certain areas leading to drug deposition with subsequent increase in pigmentation
3.	Direct skin toxicity caused by secretion of the drug in sweat with subsequent accumulation of the drug on the skin
4.	Endocrinological abnormalities with increased adreno-corticotrophic hormone and melanocyte-stimulating hormone causing hyperpigmentation as a result of suppressed adrenal function
5.	Depletion of tyrosinase inhibitors, resulting in increased hyper-pigmentation
6.	Direct toxic effect on epidermal melanocytes
7.	Erythema multiforme-like drug reaction due to spongiosis and occasional dyskeratotic cells in the epidermis with subsequent pigment incontinence

PSSHE = persistent serpentine supravenous hyperpigmented eruption

are non-specific. The condition may show vacuolar interface dermatitis with isolated necrotic keratinocytes, papillary dermal edema, and superficial perivascular inflammatory infiltrates[13]. The presence of spongiosis and occasional dyskeratotic cells have been reported[11]. The features of interface dermatitis and necrotic keratinocyte were observed in the present patient. Some authors had described this eruption histologically as an erythema multiforme-like drug reaction in the earlier onset of this adverse reaction[17].

In the present case, the patient previously received paclitaxel, which was in the same group as docetaxel, but this patient had no cutaneous side effect from paclitaxel, thus, the previous use of paclitaxel could not predict docetaxel side effect. Physicians should be aware of this distinctive cutaneous side effect of chemotherapeutic agents in the treatment of malignancy. However, although this side effect occurred, it does not stop the use docetaxel in the next cycle. An increased incidence of cutaneous toxicity has been reported when docetaxel is infused rapidly[16]. More dilution of chemotherapeutic agent and slower transfusion rate are necessary. In the other hand, this eruption may occur after insufficiently venous washing. Therefore, saline infusion before and after chemotherapy should be considered. It was found that this patient was able to continue docetaxel in the second cycle without cutaneous side effect after these strategies were applied.

Conclusion

Docetaxel may cause a variety of side effects such as alopecia, hypersensitivity reaction, onycholysis, palmar plantar erythrodysesthesia, cutaneous lupus, and toxic epidermal necrolysis. Supravenous serpentine dermatitis is a rare side effect, presenting with well-defined linear, erythematous to violaceous plaques along the affected superficial venous network. It is self-limited. The topical corticosteroid has been found to be beneficial. Physicians should be aware of this side effect from cytotoxic agents due to their widespread use in the treatment of malignancies.

What is already known on this topic?

Docetaxel-induced supravenous serpentine dermatitis is rare condition, characterized by increase pigmentation of the skin overlying the venous network. It begins as red streaks commonly over the injected veins, followed by hyperpigmentation. It is benign and self-limiting. Topical application of corticosteroid has been found to be beneficial.

What this study adds?

Although paclitaxel is a drug in the same group as docetaxel, the absence of cutaneous side effects of paclitaxel does not predict docetaxel cutaneous side effects. It does not constrain the use of docetaxel in the next chemotherapy cycle. Prevention of this eruption can be achieved by extending the time of drug transfusion, diluting further the chemotherapeutic concentration, and increasing the saline infusion before and after chemotherapy.

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Potential conflicts of interest

The author declares no conflict of interest.

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