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Toxic epidermal necrolysis after dactinomycin and vincristine combination chemotherapy for nephroblastoma*

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In this study, we describe a 2-year-old boy patient with nephroblastoma who has developed toxic epidermal necrolysis (TEN) associated with the combination chemotherapy administration of dactinomycin and vincristine. A skin biopsy confirmed the diagnosis of TEN, and with methylprednisolone pulse therapy, intravenous immunoglobulin (IVIG), and supportive care, the patient improved significantly.

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a rare, acute, and life-threatening mucocutaneous spectrum disease characterized by extensive, full-thickness epidermal necrosis and sloughing of the skin and the mucosal surface of the oral cavity, gut, kidney, eye, genitalia, and/or lung. According to the severity and extent of widespread epidermal detachment, SJS/TEN is classified as SJS, SJS/TEN overlap, and TEN with less than 10%, 10%–30%, and 30% of body surface area, respectively. The majority of cases of SJS/TEN are the results of a hypersensitive reaction to a drug, and the drugs most commonly associated with the diseases are anticonvulsants, sulfa preparations, antibiotics, nonsteroidal anti-inflammatory drugs, allopurinol and antiretroviral drugs, etc. (Chung *et al*., 2016). In addition to drugs, other precipitating factors include the infection-, malignancy-, collagen-, and vascular-related factors. The study of Hockett (2004) is very nonspecific regarding the types of malignancies connected with SJS and TEN, but this association may be related to the drugs used to treat specific malignancies or their side effects. In addition, there remain approximately 20% of SJS/TEN cases without an identified cause (Schwartz *et al*., 2013; Chung *et al*., 2016).

A 2-year-old boy was admitted to the Department of Urological Surgery, Beijing Children's Hospital, Capital Medical University, Beijing, China, with an abdominal mass that ultrasound and computed tomography examination revealed as a left kidney nephroblastoma (size 15.8 cm×14.5 cm×12.4 cm) with pulmonary and osseous metastases, and the patient received combination chemotherapy with dactinomycin (Cosmegen; 15 μg/(kg·d) intravenously in the first 5 d) and vincristine (1.5 mg/(m^2·d) intravenously once per week). After one week, he developed multiple morbilliform rashes initially over limbs, then chest, with high fever, and his rash quickly progressed into a widespread confluent erythematous and necrosis eruption with blistering (Figs. 1a and 2b), painful oral erosions and conjunctivitis (Fig. 1c).

The patient was clinically diagnosed as TEN by a dermatology consultation. A skin biopsy showed loss of epidermis secondary to full thickness necrosis, with mild chronic inflammation noted in the dermo-epidermal junction and upper dermis (Fig. 2). These findings were consistent with TEN. Dactinomycin and vincristine were immediately discontinued and the patient was started on IVIG 1.0 g/kg body weight per day infused and methylprednisolone pulse therapy (20 mg/kg body weight) for 3 successive days. The other supportive cares included wound care, fluid and electrolyte management, nutritional support, ocular

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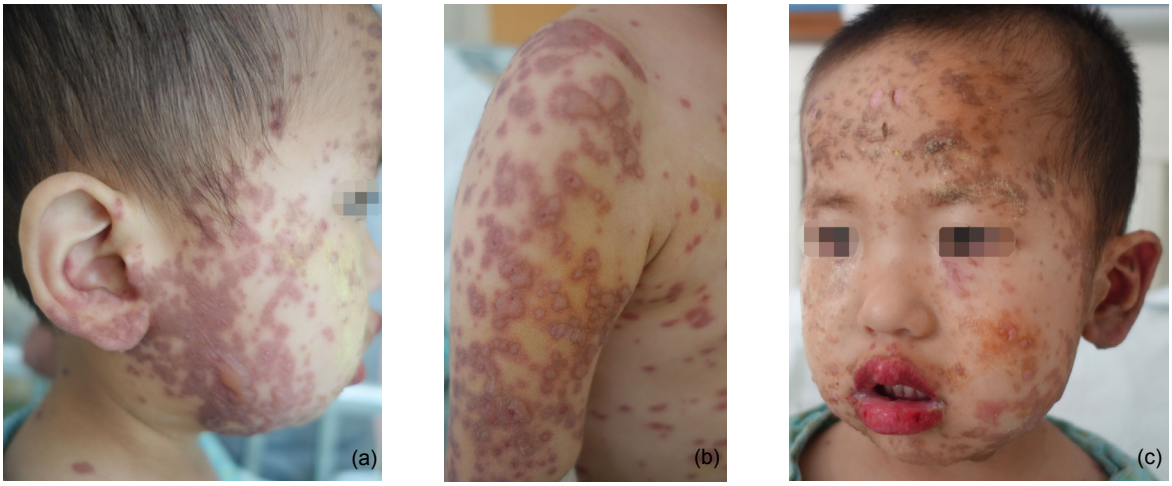

Fig. 1 Clinical presentations of TEN after dactinomycin and vincristine administration
(a) Coalescing violaceous macules with flaccid bullae developed on face; (b) Right arm showing bullae on the original erythematous dusky red macules; (c) Erosions with hemorrahagic crusts on lips and conjunctivitis

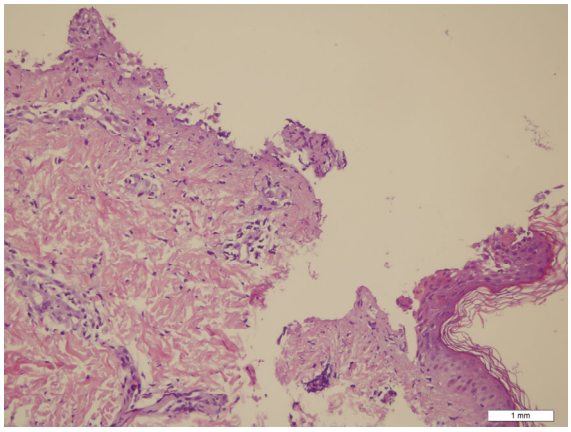

Fig. 2 Characteristics of pathology of TEN
Skin biopsy shows that completely necrotic epidermis is detached from underlying dermis, with mild chronic inflammation noted in the dermo-epidermal junction and upper dermis (hematoxylin and eosin staining). Bar=1 mm

care, temperature management, and pain control. By Day 11 his temperature was normal; by Day 13 the rash was not deteriorating and the dosage of methylprednisolone began to reduce gradually. On Day 20, there was quite a resolution of the rash, and almost healing of the oral mucous. All dermal and mucosal lesions have healed without scarring after 23 d. Then other regimen chemotherapy was initiated.

The results of laboratory tests including complete blood counts, electrolytes, kidney function, and liver function were nearly normal. The infectious workup including blood cultures, mycoplasma pneumoniae, herpes simplex virus, Epstein Barr virus, cytomegalovirus, and coxsackievirus was done, and the results were negative.

Identification and prompt removal of precipitating factors are the most pivotal and important steps for the lifesaving management of TEN. In our case, we believed that the patient problem was related to one of two chemotherapy drugs because no convincing alternative explanation such as other suspected drug or infection was proposed. In addition, the syndrome was not present before the initiation of chemotherapy, suggesting that it was not part of the presenting features of his nephroblastoma. In this case, dactinomycin was more suspected as the offending drug than vincristine, because SJS/TEN has been reported with dactinomycin use in postmarketing surveillance (http://www.rxlist.com/cosmegen-drug.htm), while vincristine is not commonly associated with skin reactions. Moreover, the patient was started on other regimen chemotherapy, which included vincristine, and this regimen did not cause any rashes. Although TEN occurs in a very small percentage of patients who use chemotherapy drugs, several reports have described SJS/TEN induced by other anticancer agents such as methotrexate, procarbazine, gemcitabine, cisplatin, and 5-FU (Yang *et al.*, 2000; Jones *et al.*, 2006; Yoshifuku *et al.*, 2015; Aznab and Khazaei, 2016).

Malignancy is known to be associated with an increased mortality rate in patients with TEN. Therefore, except for antineoplastic drugs, we should also consider the link between malignancies themselves and SJS/TEN. There were two case reports on SJS associated with Hodgkin's disease, which illustrated the rare association of SJS revealing Hodgkin's disease and postulated that the link between both diseases may be a paraneoplastic syndrome induced by granulysin secretion by tumor cells, a mediator responsible for damage to keratinocytes (Schoeffler *et al.*, 2014). Gravante *et al.* (2007) suggested that oncologic diseases were the most frequent comorbidities in their SJS/TEN case series; Wu *et al.* (2015) found that for specific cancer types (hepatocellular carcinoma and colorectal cancer), chemotherapy and malnutrition may contribute to poor prognosis in patients with malignancies developing SJS/TEN.

In conclusion, it is very critical but complicated to identify the offending agents when oncologic patients develop SJS/TEN during chemotherapy. Apart from identification of suspected culprit drugs including chemotherapy agents, concurrent multi-drug regimens such as anticonvulsants, antibiotics, antivirals, or nonsteroidal anti-inflammatory drugs, influences of malignancies on occurrence and prognosis of SJS/TEN should be considered. Early recognition and intervention can significantly alter the course of the disease and improve the outcome. This case has served as an alert that the oncologist must be aware in his/her clinical practice of this particular syndrome and should be able to observe patients closely for potentially dangerous cutaneous reaction and treat it as an oncologic emergency. Also the dermatologist must be alert to the possibility of the development of SJS/TEN in oncologic patients with chemotherapy. As soon as the first suspicious sign is observed, they need to make a correct diagnosis, discontinue culprit drugs immediately, and initiate aggressive medical management or refer to appropriate centers promptly.

Compliance with ethics guidelines

Yuan LIANG, Zhou YANG, Zi-gang XU, and Lin MA declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study. Additional informed consent was obtained from all patients for which identifying information is included in this article.

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中文概要

题　目：肾母细胞瘤更生霉素和长春新碱联合化疗并发中毒性表皮坏死松解症的报道

概　要：中毒性表皮坏死松解症是一类临床罕见但严重威胁患者生命的重症药疹，死亡率高达 30%~50%。儿童中最常见致敏药物为抗癫痫药、抗生素和解热镇痛药。化疗药物引发中毒性表皮坏死松解症报道少见。本文报道一例 2 岁肾母细胞瘤患儿经更生霉素联合长春新碱化疗 1 周后并发严重皮肤药物不良反应——中毒性表皮坏死松解症。本报道旨在提醒肿瘤科医生警惕肿瘤患者治疗过程中发生中毒性表皮坏死松解症这一高致死性重症药疹的可能，需要在临床中密切观察患儿皮肤表现，一旦出现相应症状须立即作为危重症处理；同时提示皮肤科医生警惕化疗药更生霉素有引发中毒性表皮坏死松解症的可能，发现此类病人用药时出现皮疹应重视。早期识别并停用可疑药物，联合积极支持治疗可显著改善患者预后，降低死亡率。

关键词：药疹；恶性肿瘤；中毒性表皮坏死松解症；化疗；肾母细胞瘤