CASE REPORT

Treatment of Skin Reaction Induced by Nivolumab Combined with Radiotherapy in Non-small Cell Lung Cancer: A Case Report

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Abstract Skin reaction or dermatological toxicities induced by immunotherapy is common. It usually manifests skin rash or erythema and can be cured by skin lotion or steroid. Nivolumab, a human IgG4 programmed cell death protein 1 (PD-1) inhibitor, blocks T cells activation preventing signal and allows the immune system to clear cancer cells. Nivolumab was approved in the second-line therapy in squamous cell lung cancer by FDA, with less than 10% unusual skin reaction, like sensory neuropathy, peeling skin, erythema multiforme, vitiligo, and psoriasis. Radiotherapy could aggravate this skin reaction through inflammatory response and promotion of immunity. The combined treatment of anti-PD-1 and radiotherapy represented a new promising therapeutic approach in many studies, but the risk of side effects may be high. We reported a patient with advanced squamous cell lung cancer who suffered from serious skin immune-related adverse events when he was treated with nivolumab and radiotherapy. The immune overreaction of the treatment of anti-PD-1 treatment and radiotherapy might cause these serious skin adverse events. Our report warranted careful workup to reduce the risk of side effects by combinative therapy with anti-PD-1 and radiotherapy.

IMMUNE checkpoint inhibitors have led to considerable therapy improvement in cancer patients.¹ Nivolumab (Opdivo, Bristol-Myers Squibb), a fully human IgG4 programmed cell death pro-

tein 1 (PD-1) inhibitor, blocks PD-1 and promotes antitumor immunity. Nivolumab was first approved for immunotherapy in March 2015 by FDA for the 2nd line treatment of metastatic squamous cell lung cancer, based on the results of the CheckMate 017 (CM017) clinical trial.² Therefore, an increasing number of patients will be treated with nivolumab and there will be more chances of developing toxicities from this treatment. The activated T-cells can cause immune-related adverse events (irAEs), such as skin rash, colitis, hepatitis, or pneumonitis. It was reported that irAE of nivolumab was 58% in treated patients, and 7% of them were grade 3 and 4.² Skin irAEs are the most

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frequent irAEs and are reported in approximate 34% of the patients treated with nivolumab.³ In non-small cell lung cancer (NSCLC) patients treated with nivolumab, skin irAEs are reported approximately 10% or more.^{2, 4-6} Skin irAEs usually happen early in the course of treatment; most of them appear in the first few weeks after initiation. However, serious skin irAEs are rare and dose reductions or treatment discontinuation is not needed. Grading of toxicity is commonly classified according to Common Terminology Criteria for Adverse Events (CTCAE version 4.0).⁷ Managements of skin irAEs include symptomatic treatment with antihistamines and topical steroids, or systemic immunosuppression may be applied in severe cases.⁸

Radiotherapy (RT) has been widely used to treat various forms of cancers. It is estimated that RT is required in the treatment of over 50% of all patients with cancer.⁹⁻¹⁰ Radiodermatitis could be very common; about 95% patients receiving RT would develop some form of radiodermatitis.¹¹⁻¹² The most common and early form of skin reaction of RT is erythema, occurring in more than 90% of patients, then followed by moist desquamation in more than 30% of patients. The varying severities of radiation-induced skin reactions in cancers are commonly associated with dose. Erythema, dry desquamation and moist desquamation develop dose of 20-40 Gy, ≥ 30 Gy and ≥ 40 Gy respectively. In recent years, emerging evidence suggests that the promotion of immunity may also play an important role in the adverse events of RT.

Notably, the synergistic effects of RT and anti-PD-1 treatment have become the hot issue in the immunotherapy era. However, excessive immune activation and inflammatory response induced by RT may develop; the potential risk of side effects by the combinative therapy is worthy of being investigated. In this report, we described the clinical manifestation, management and outcome of a patient who developed serious skin irAEs while receiving anti-PD-1 and RT combined treatment.

CASE DESCRIPTION

In June 2017, a 60-year-old male was admitted to Qingdao Central Hospital for worsening cough and shortness of breath for two weeks. He was diagnosed with metastatic squamous cell lung cancer, cT4N3M1a, stage IV A. His disease progressed after four cycles of platinum-based chemotherapy, and then therapeutic

regimen was changed to intravenous infusion of second-line nivolumab monotherapy at a dose of 3 mg/kg every two weeks. After two doses of nivolumab, the patient suffered from grade 2 skin irAE. Skin toxicities were evaluated and recorded according to CTCAE version 4.0. The macules/papules on the upper limbs and back covered 20% body surface area with pruritus, burning and limited instrumental activities of daily living (Fig. 1A). Symptomatic treatment with topical emollients, oral antihistamines and topical steroids was administered until the skin irAE reverted to grade 1 (Fig. 1B). However, the bilateral neck and supraclavicular metastatic lymph nodes were progressed. He then underwent external beam RT. The total dose of 60 Gy in 30 fractions was administered to gross lung tumor and metastatic mediastinal lymph nodes. He also received the third cycle of nivolumab concurrently. However, grade 4 skin adverse events (rash and moist desquamation) developed after 3 days of nivolumab treatment. At that time, the dose of radiation was 36 Gy/18f (Fig. 2A). The anti-PD-1 treatment and RT were interrupted. Intravenous methylprednisolone 1 mg/kg with tapering when the toxicity resolves to normal was initiated. In addition of routine daily care, the patient got infrared-ray therapy by photon therapeutic apparatus, twice a day, and 10 minutes per time. The rash and moist desquamation had significantly improved after 10 days (Fig. 2B).

DISCUSSION

Immunotherapy with checkpoints inhibitors has become standard of care for an increasing number of cancers.¹³⁻¹⁵ PD-1, an inhibitory receptor expressed on activated T cells, can reverse immune suppression and release T cell activation. Side effects of PD-1 inhibitors may be attributed to a persistently stimulated immune system, and are thus termed irAEs. Rash and pruritus are frequent skin irAEs during immunotherapy.

The precise mechanisms underlying the development of irAEs are not fully understood, but are postulated to be largely T cell mediated.¹⁶ Hasan Ali *et al*¹⁷ reported that the histological analysis of the rashes on the patients with metastatic NSCLC displayed distinct skin inflammatory infiltrates consisting mainly of cytotoxic CD8⁺ T-cells. Civatte bodies (damaged basal keratinocytes) suggested that these lymphocytes induced keratinocyte death. Based on this report, we deduced that the skin of these patients harbored auto-immune

Figure 1. Grade 2 skin adverse events after 2 doses of nivolumab treatment. Red macules/papules covered 20% body surface area with pruritus; limiting instrumental activities of daily living (A). After the symptomatic treatment, skin adverse events have reverted to grade 1. Red macules/papules covered < 10% body surface area without pruritus (B).

Figure 2. Grade 4 skin adverse events (rash and moist desquamation) were developed on the irradiated area when the patient received nivolumab treatment combined with radiotherapy (A). The moist desquamation was improved and the rash disappeared. Holistic treatment that cured the grade 4 skin toxicity induced by combined therapy, and the irradiated area was hyperpigmented (B).

T-cells which could be activated and attack healthy keratinocytes. It is further possible that tumor-specific T-cells, activated by anti-PD1 treatment, migrated to the skin. Since T-cells can migrate and scan antigens presented by MHC-I molecules on all body cells, they can recognize the same antigen at any tissue. It is possible that keratinocytes express antigens which are identical or very similar to those of the tumor, known as antigen sharing.¹⁸

Moreover, the skin irAEs may be aggravated by RT. Radiodermatitis is a major side effect related to radiation exposure. The pathogenesis of radiodermatitis involves a subsequent inflammatory response and immune activation, influencing cellular elements in the epidermis, dermis, and vasculature. The keratinocytes, fibroblasts, and endothelial cells in the skin stimulate immune cells (i.e., mast cells, T cells) in the epidermal and dermal layers, prompt cytokines and chemokines releasing (interleukin 1- α , interleukin 6, tumor necrosis factor- α , etc.), which lead to inflammation cells accumulation in the irradiated skin area and skin fibrosis

finally.^{12, 19} The production of the matrix metalloproteases also contributes to degrade dermal components and the basal cell layer, and upregulate adhesion molecules intercellular adhesion molecule 1 (ICAM1), vascular cell adhesion molecule 1 (VCAM1), and E-selectin on vascular endothelial cells. These adhesion molecules are important in the transendothelial migration of immune cells circulating to irradiated skin.²⁰⁻²² So, the promotion of T-cells activation and migration induced by RT may contribute the aggravation of skin irAEs.

Many studies showed that immunotherapy combined RT had synergy effects in cancer treatments.²³⁻²⁴ However, the risk of side effects with combination therapy may increase and this issue is worthy of being investigated. Several cases had been reported RT combined immunotherapy could cause pneumonitis.²⁵ We reported skin reaction induced by nivolumab treatment might be aggravated by external beam radiation. The rash and moist desquamation developed after the 3rd cycle of nivolumab treatment while the irradiation dose was 20Gy at that time. Anti-PD-1-related severe skin

adverse events were considered and excessive immune response was suspected. In terms of treatment, topical and systemic glucocorticoids were administered. B cell activating factor (BAFF), a member of the tumor necrosis factor family, is an important factor in regulating B cells survival and proliferation as well as antibody production of T cells stimulation.²⁶⁻²⁷ Glucocorticoids treatment could reduce BAFF expression, thus inhibiting antigen presentation.²⁸⁻²⁹ Antibiotic might be applied for patients with grade 4 skin reaction which reduced the risk of skin bacterial infection.³⁰⁻³¹ In addition, the photon therapeutic apparatus in this report can significantly improve skin adverse events, reduce pain, shorten healing time and increase clinical efficacy.

Thus, greater care should be used upon combination of RT and anti-PD-1 treatment in patients with progressive disease. Keep irradiated area dry and clean, topical glucocorticoids use may prevent progressing of the skin reaction induced by nivolumab and radiotherapy combination. The management of serious skin adverse events in this report may help other clinicians in managing this rare but potentially serious toxic effect. Early diagnosis and close clinical monitoring are essential for successful prevention and management of skin adverse events.

Conflicts of interest statement

The authors declare that they have no competing interests.

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纳武单抗联合放疗治疗非小细胞肺癌引起严重皮肤反应 1 例报道

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关键词: 皮肤反应; 纳武单抗; 免疫治疗; 放射治疗; 非小细胞肺癌

摘要 P 免疫治疗引起的皮肤反应或皮肤毒性很常见, 通常表现为皮疹或红斑, 可以通过润肤露或类固醇治愈。纳武单抗是一种人 IgG4 程序性细胞死亡蛋白 1 (PD-1) 抑制剂, 可阻断抑制 T 细胞激活的细胞通路, 促进免疫系统清除癌细胞, FDA 批准用于鳞状细胞肺癌的二线治疗, 其皮肤反应发生率不到 10%, 多表现为感觉神经病变, 皮肤脱皮, 多形性红斑, 白癜风和牛皮癣。放射治疗可以通过增加炎症反应和调节免疫加剧皮肤反应。许多研究发现, 抗 PD-1 治疗联合放射治疗是一种新的有希望的肿瘤治疗方法, 但发生副作用的风险可能很高。我们报道了 1 例晚期鳞状细胞肺癌患者, 接受纳武单抗和放射治疗时发生严重的皮肤免疫相关不良事件。抗 PD-1 治疗可以引起皮肤过度免疫反应, 放疗加重皮肤反应, 二者联合可能是导致这种严重皮肤不良事件的原因。联合应用抗 PD-1 治疗和放射治疗时要严密防范此不良反应发生的风险。