Nivolumab induced cutaneous reactions in a patient with lung cancer – A case study

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Abstract
Nivolumab, a PDL1 antagonist is an immunotherapeutic agent that is effectively used for the second-line treatment of advanced or metastatic lung carcinoma. Although Nivolumab improved the overall survival of patients with non-small cell lung cancers in the setting, it is known to result in adverse events called immune-related adverse events (irAEs) like colitis, pneumonitis, skin disorders, and myasthenia gravis. The majority of cutaneous reactions associated with Nivolumab therapy are Grade 1 or Grade 2 but Grade 3 skin reactions are very rare. The grade 3 skin reactions are macules or papules covering >30% of body surface area with moderate or severe symptoms (pruritis, burning, tightness) often impacting the patient’s quality of life. This is a case of a 78-year-old man with Stage 4 metastatic squamous cell lung carcinoma (SqCC), treated with Nivolumab following disease progression after 4 cycles of Paclitaxel / Carboplatin chemotherapy. The patient developed mild hyperpigmentation over the upper and lower limbs after eight cycles of Nivolumab, which progressed to Grade 3 skin reaction with intense pruritis after the eleventh cycle. He was treated with systemic steroids and Nivolumab was discontinued after which the patient’s condition improved. Health care professionals should be aware of the immunological side effect profile of Nivolumab. Close monitoring, periodic dermatological evaluation, and appropriate clinical management is recommended in patients on immunotherapy.

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INTRODUCTION
Immune checkpoint inhibitors have emerged as one of the most promising modalities in the treatment of many metastatic cancers, especially lung cancer. The standard therapy for the advanced as well as relapsed lung cancers currently used includes the anti-programmed cell death 1 antibodies like nivolumab, pembrolizumab, or the anti-programmed cell death ligand 1 (PD-L1) antibodies such as atezolizumab and durvalumab. Compared to conventional chemotherapy, immunotherapy is much less toxic and select groups of patients derive dramatic survival benefits. However, immunotherapy may cause a distinctive set of immune reactions known as immune-related adverse events (irAEs). Skin disorders, thyroiditis, pruritis, fatigue, colitis, diabetes mellitus, interstitial pneumonitis are the common immune-related adverse events seen in clinics. Though immune checkpoint inhibitors...
frequently develop mild cutaneous toxicities, high grade and potentially life-threatening skin reactions are very rare. Here we present a case of grade 3 cutaneous reaction following the administration of Nivolumab.

CASE REPORT

Mr X, a 78 year old gentleman, was evaluated for complaints of cough and back pain radiating to the right hypochondrium. CT of the chest revealed a right lung mass with multiple lung nodules and multiple vertebral metastasis. An image guided trucut biopsy revealed squamous cell carcinoma (SqCC). He was started on palliative chemotherapy with Paclitaxel / Carboplatin after pain palliative radiation for the bone metastasis. He received 4 cycles, without any major issues. He was on follow up and 6 months down the line, a PET (Positron emission tomography) scan done showed disease progression. He was subsequently planned for nextline Nivolumab. He was started on Injection Nivolumab 240mg every 2 weeks. There were no adverse events till cycle 8, when he developed mild skin reaction with erythema over the upper and lower limbs. The therapy was continued with supportive care as he had symptomatic relief. The skin reaction worsened to Grade 3 after cycle 11 (Figure 1). Immunotherapy was stopped and intervenous steroids were administered. The symptoms persisted for more than 4 weeks and Nivolumab was discontinued.

DISCUSSION

Presented here is a rare case of grade 3 skin reaction induced by Nivolumab in a 78-year-old male with metastatic squamous cell lung carcinoma. Detection and clinical care of severe adverse events due to checkpoint inhibitors assumes significance as the use of these agents are on the rise. Lung cancer is a deadly disease that is the leading cause of death due to cancer worldover. Lung cancers are broadly divided into small-cell lung cancer (SCLC) and non- small-cell lung cancer (NSCLC); NSCLC accounts for approximately 85% of all cases of lung cancer (Sher et al., 2008). The most common types of NSCLC are adenocarcinoma(40%), squamous cell carcinoma (25-30%) and large cell carcinoma (10-15%). Almost 70 % of these patients have advanced/metastatic disease at presentation (Molina et al., 2008). The most common site of metastasis is the bone (30-40%) (Rosen et al., 2004; D'Antonio et al., 2014). Metastatic squamous cell carcinomas are usually treated with platinum based doublet chemotherapy, the commonly used regimens with great efficiency and have response rates of close to 50% (Herbst et al., 1998).

Immunotherapy has remodelled the therapeutic approach to chemotherapy-resistant and metastatic cancers. It has resulted in a paradigm shift in therapy with improved survival, response rates, and much less toxicity. Nivolumab improved the expected five-year survival rate compared to conventional chemotherapy from 6% to 15.6% in NSCLC (Topalian et al., 2019). Nivolumab is a fully human IgG4 monoclonal antibody that particularly inhibits the PD1 receptor, thereby preventing the binding of its ligands PDL1 and PDL2. The drug finally intercepts the negative signal that regulates T-cell activation and proliferation, which plays a major role in tumor evasion from host immunity, resulting in a potent antineoplastic activity. The overall incidence of serious adverse events associated with Nivolumab was found to be 11.25% with an incidence rate of 0.3% of fatal adverse events (Zhao et al., 2018). The risk of any type of adverse events due to Nivolumab was found to be much lower than conventional chemotherapy. The most common adverse events are fatigue, rash, pruritus, diarrhoea, nausea, and asthenia. The rashes are predominantly grade 1-2 and may be variable, self-limiting but may worsen if left untreated (Viladolid and Amin, 2015). The incidence of severe diarrhoea, nausea and decreased appetite were found to be similar to chemotherapy and occurs at the rate of 1.4%, 0.7% and 0.6% respectively (Tie et al., 2017). Incidence of all grade (3.2%) and high-grade pneumonitis (1.1%) were found to be higher with Nivolumab (Zhang et al., 2017). The principal cause of death associated was due to pulmonary toxicity. Early detection, intense management and close monitoring are needed to prevent the development of very severe adverse events like pneumonitis, colitis and hepatotoxicity in patients on Nivolumab.

Following the eighth cycle of immunotherapy, our patient developed faint self-limiting erythema and moderate swelling over his forelimbs and hind limbs, and the erythematic lesions extended over

Figure 1: Nivolumab induced Grade 3 skin reaction in our patient
the trunk in the subsequent cycles. The condition worsened to Grade 3 after the eleventh cycle, where the patient had complaints of severe itching with moist desquamation all over the body requiring hospitalization. The exact mechanism of such an adverse reaction is not known, but there is a presumption of possible autoimmune etiology. In several reports of patients with immune-related adverse events, increased T cell activation is involved in the progression of adverse events (Johnson et al., 2019). Immune-related skin reactions associated with Nivolumab accounts for 10% or more in many series (Borghaei et al., 2015), though Nivolumab induced Grade 3 skin reaction is very rare (Remon et al., 2018) and seldom discussed. Grade 1 skin reactions involve mild erythema or desquamation covering < 10% of the body surface area (BSA). Grade 2 rashes involve macules or papules that covers up to 10-30% of the BSA. Both Grade 1 and 2 reactions either resolve by its own or can be managed using topical emollients, mild steroids, and or oral antihistamines without any treatment discontinuation (Lacouture, 2014). Reactions are referred to as Grade 3 when it affects more than 30% of the body surface area. Grade 4 skin reactions involve papulopustular rashes along with life-threatening infections or Steven-Johnson syndrome. Immuno-therapy should be discontinued for moderate to severe grade 3-4 rashes. Our patient was administered prednisone 1mg/kg/day along with the cessation of immunotherapy. Then the dose of steroid was tapered and stopped as the condition improved. Several reports suggest that retreatment with anti-PD-1 therapy resulted in the recurrence of irAEs in 52% of patients with non-small-cell lung cancer (Santini et al., 2018) necessitating discontinuation.

CONCLUSIONS

Although very rare, it is important to recognise and institute early treatment for grade 3/4 adverse skin reaction to immunotherapy. It severely hampers quality of life and may affect prognosis since discontinuation of therapy is often needed. Here we report a rare occurrence of grade 3 rash due to immunotherapy that led to discontinuation of treatment. Although dermatological adverse reactions induced by immunotherapy are usually self-limiting, rarely they may turn severe and require discontinuation of therapy.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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