CASE REPORT

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Nivolumab associated DRESS syndrome: A case report

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ABSTRACT

Nivolumab is an IgG 4 antibody against PD-1 approved for treatment of metastatic lung cancer. We report a case of Drug rash with eosinophilia and systemic symptoms (DRESS) associated with Nivolumab therapy for lung carcinoma with metastasis to vertebra in a 55 -year-old male who presented with sudden onset of erythema involving more than 80% body surface area for 3 days after a week of treatment with Nivolumab. A diagnosis of DRESS was made based on temporal association of injection Nivolumab and appearance of skin lesion, and presence of eosinophils in dermis. The patient was started on prednisolone 70 mg per day based on the body weight along with other supportive measures. The case is being reported beca[illegible] Nivolumab in the literature and is first case report from[illegible] by Nivolumab is also done.

Key words: *Nivolumab; DRESS; Steroid.*

INTRODUCTION

DRESS (Drug reaction with eosinophilia and systemic symptoms) is potentially severe cutaneous adverse reaction characterized by an exanthem, fever, and hematologic and visceral organ involvement, which is associated with several common drugs, but less often related to biological treatment.[1]

In recent years, immune checkpoint inhibitors (ICIs) such as PD-1/PD-L1 inhibitors and CTLA-4 inhibitors have become the most used treatment in metastatic cancers besides the targeted treatments.[2] ICIs have been shown to improve survival in many types of cancers including melanoma, non-small cell lung carcinoma, renal cell carcinoma, breast, and cervical cancers.[3] Alongside the benefits of ICIs comes a set of immune related adverse effects affecting any organ systems. Dermatological adverse reactions associated with ICIs can range from mild maculopapular rash to more severe cutaneous manifestations like fixed drug eruption (FDE), acute generalized exanthematic pustulosis (AGEP), Stevens–Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS).[2]

Nivolumab is a fully human IgG 4 antibody, directed against PD-1, and is the first ICI treatment approved for metastatic lung cancer.[4] It is well tolerated by patients, but sometimes immune-related adverse effects affecting any organ systems including skin reactions may occur.[5]

We report a case of DRESS associated with Nivolumab therapy for lung carcinoma with metastasis to vertebra. The diagnosis was made based on clinical manifestations and histopathological findings.

CASE

A 55 -year-old male presented with sudden onset of erythema involving more than 80% body surface area for 3 days (Figure 1). It started as erythema on trunk 1 week back which had gradually increased to involve trunk, neck and all the extremities and was associated with severe pruritus. There was no history of fever, facial swelling, arthritis, or history of allergies. He was diagnosed as a case carcinoma of lungs with metastasis to vertebra (L3, L5, S1) while investigating for chronic paresthesia of upper and lower limb two and half months back and had received multiple medicines namely intravenous immunoglobulins, paracetamol, gabapentin, pregabalin and duloxetine, linagliptin-Metformin, a blend of PEA, genistein and daidzein, melatonin tablets, pramipexole and Zolpidem tartrate for a period of two weeks. The patient was recently started on injection Nivolumab 40 mg a week before the onset of present illness.

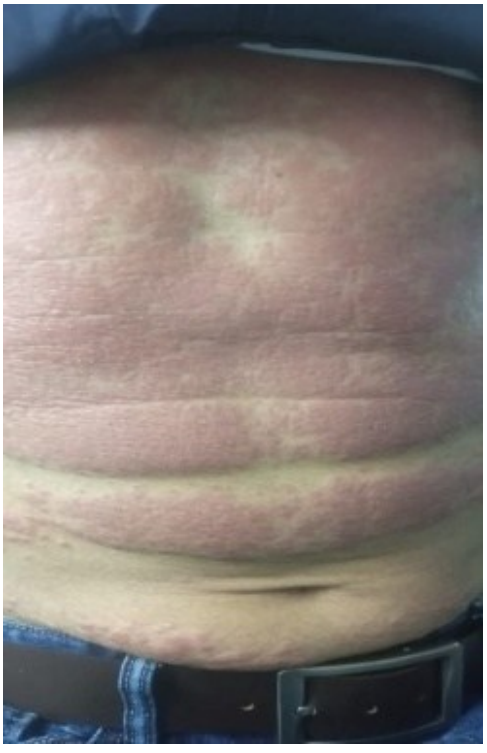

Figure 1. Diffuse infiltrative plaque on abdomen

On examination, there was non- tender diffuse ill-defined infiltrative coalescing plaques involving trunk, extremities, and neck with mild erythema of face involving more than 80% body surface area. The folds on the abdomen were relatively spared. There was no lymphadenopathy or organomegaly. Mucosal examination, hair and nails were normal. On investigation, his complete blood count, ANA profile, renal function test, blood sugar, electrolytes, urine routine were normal except for raised alkaline phosphatase, transaminases and raised CRP. A skin biopsy was done which showed focal spongiosis, exocytosis of lymphocytes, patchy basal layer degeneration, and interface inflammation. Superficial dermis showed moderate perivascular lymphocytic infiltration with eosinophils and neutrophils (Figures 2 and 3).

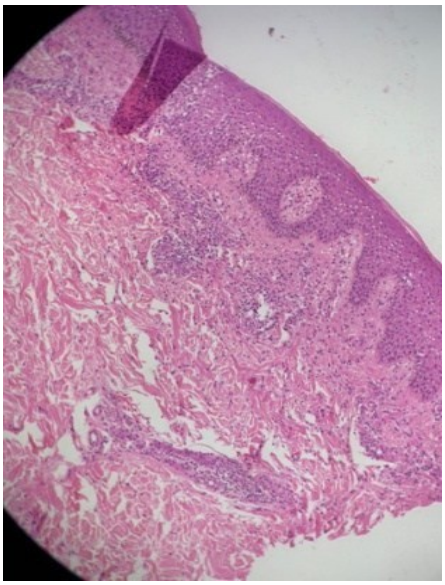

Figure 2. Inflammatory infiltrate with interface dermatitis(10X)

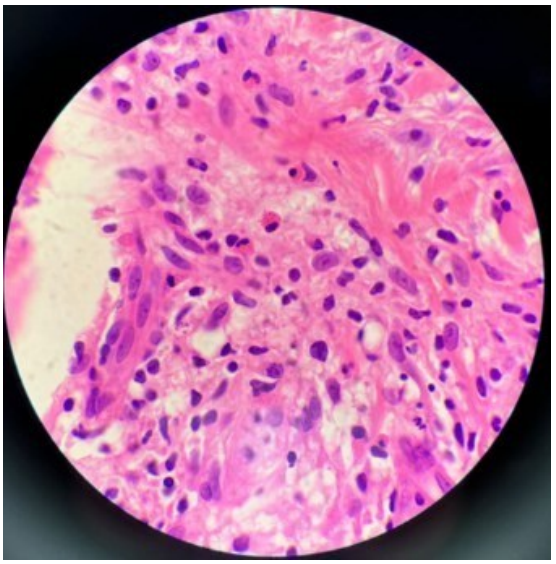

Figure 3. Moderate perivascular infiltrate with eosinophils(40X)

A diagnosis of Drug rash with eosinophilia and systemic symptoms (DRESS) was made based on temporal association of injection Nivolumab and appearance of skin lesion, and presence of eosinophils in dermis. The RegiSCAR for DRESS was 2, meaning possible case of DRESS. The patient was prescribed prednisolone 70 mg per day based on the body weight along with other supportive measures. Injection Nivolumab was advised to be discontinued. There was gradual improvement of skin lesion at last follow-up at one week (Figure 4).

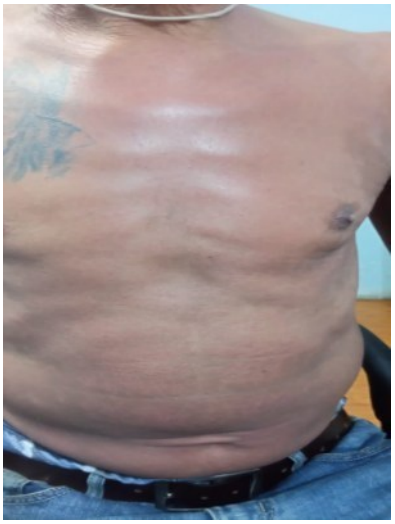

Figure 4. Post treatment after one week

DISCUSSION

DRESS is a delayed hypersensitivity reaction mostly caused by drugs and is characterised by exanthem, fever, and hematologic and visceral organ involvement, typically presents with exanthematous eruption 2-6 weeks after drug exposure, and is usually associated with significant morbidity, mortality, and risk of relapse.[1] DRESS results from a complex interaction between medication exposure, genetic predisposition and reactivation of latent viruses, particularly the Herpesviridae. [6] Though rare, mortality rate as high as 10 % has been reported in the literature.[7]

More than 60 medications have been reported to be associated with DRESS.[6] This number may increase with the advent of newer therapeutic options developing with time.

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that block key mediators of tumor-mediated immune evasion. The frequency of its use has increased rapidly and has extended to numerous cancers. The hypersensitivity reactions to Nivolumab, a fully human IgG 4 antibody, directed against PD-1, are reported to be very rare, between 1% and 3%.[7] The hypersensitivity reactions may be immediate (occurring < 1hour; like pruritus, urticaria, anaphylaxis) or delayed (occurring > 1hour; like FDE, SJS, TEN, AGEP, DRESS).[2] Eighty-nine cases of DRESS associated with Nivolumab have been reported till 2022, with identification of DRESS risk allele HLA- A*31:01, which is also a predictor of carbamazepine associated DRESS, in one case.[3,7]

DRESS with classic presentation is rare to ICIs and patients usually present with generalized maculopapular rash, fever, and concurrent extracutaneous manifestations like transaminitis, azotemia, and colitis, mimicking classic DRESS hence a diagnostic challenge.[3]

The RegiSCAR group has suggested inclusion criteria for hospitalized patients suspected to have DRESS, consisting of at least 3 of the following systemic features developing weeks to months after drug initiation: acute skin rash, fever greater than 38 ^{0}C, lymphadenopathy, internal organ involvement, and hematologic abnormalities, including atypical lymphocytosis, eosinophilia, and thrombocytopenia.[8]

Based on suggestive cutaneous rash, biopsy suggesting DRESS, and internal organ involvement, our patient scored as a possible case of DRESS per the RegiSCAR criteria. Nivolumab was the only new medication added a week back. Though nivolumab is reported to cause adverse cutaneous reactions later in treatment, our case developed the reaction a week after first dose.[9] The skin rash and organ dysfunction is supposed to gradually improve with discontinuation of suspected medications, with an average recovery period of 6 to 9 weeks; however, disease is known to persist for several months with relapses in more than 20% of cases.[10] The recommended treatment for adverse reactions due to ICIs is rapid discontinuation of the suspected drug followed by administration of systemic steroids. In our case, Nivolumab was discontinued and Prednisolone 1mg per kg per day was added. The patient responded well to prednisolone.

CONCLUSIONS

Growing access to novel oncological therapies like the ICIs has resulted in improved patient prognosis. Though rare, these drugs come with unexpected, life-threatening adverse effects like DRESS. The early onset of symptoms should not misguide the diagnosis, and

suspected drug should be instantly discontinued. Multi-disciplinary approach along with initiation of systemic steroids is highly recommended. HLA genotyping and genetic markers may be helpful in identifying individuals at risk for hypersensitivity.

CONFLICT OF INTEREST

None

SOURCES OF FUNDING

None

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