



Case Report

Metastatic squamous non-small cell lung cancer: Complete response following desmocollin-3 targeting immunotherapy as a monotherapy: A case report

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ABSTRACT

Non-small cell lung cancer (NSCLC) constitutes the majority of lung cancer cases. Among them, about one-third of the cases are of the squamous cell subtype and are associated with a poor prognosis compared to non-squamous NSCLC. Immunotherapy in the form of checkpoint inhibitors targeting the cell surface receptor PD-1, i.e. pembrolizumab plays a pivotal role in the treatment of advanced squamous NSCLC in the absence of the driver mutation and has become one of the first-line therapies. However, in patients with negative expression of PD-L1 and poor performance status, no optimal therapeutic strategy has been defined. A heat-killed Mycobacterium w (Mw) is a potent Toll-like receptor-2 (TLR-2) agonist, which induces a cell-mediated immune response targeting cancer cells expressing Desmocollin-3 (DSC3). Mw has been approved in India for the treatment of advanced NSCLC along with chemotherapy. Mw has shown maximum benefit in patients with squamous NSCLC without any added systemic toxicity. We present the case of a 65-year-old patient with PD-L1 negative and DSC3 positive metastatic Squamous NSCLC achieving a durable and complete response after monotherapy with heat-killed Mw.

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1. Introduction

Immunotherapy such as checkpoint inhibitors like pembrolizumab, a type of targeted therapy, has become one of the first-line therapies for the treatment of non-small cell lung carcinoma (NSCLC). It provides a durable response in patients expressing programmed cell death ligand 1 (PD-L1). Although a survival benefit has been observed with pembrolizumab, a complete response is observed in only 1.5% of patients.¹ Squamous NSCLC is associated with shorter survival than non-squamous NSCLC.² Checkpoint inhibitors alone have shown limited role in patients with negative PD-L1 squamous NSCLC (SNSCLC).

Here we report a case of a 65-year-old patient with PD-L1 negative and desmocollin-3 (DSC3) positive metastatic

SNSCLC that achieved a durable and complete response with heat-killed Mycobacterium w (Mw) as monotherapy. Mw has been approved in India by the Drugs Controller General of India (DCGI) for the treatment of advanced NSCLC along with chemotherapy. It induces DSC3 expression on immune cells and induces Th1 type of immune response through TLR2 agonist activity.³⁻⁷ It preferentially kills DSC3 expressing tumor.^{3,4} The killing of cancer cells is mainly through CD8+T cells secreting IFN-gamma.⁷

2. Case Report

A 65-year-old man with a history of smoking 50 packs per year and suffering from hypertension and chronic obstructive pulmonary disorder (COPD) presented with complaints of bloody cough, breathlessness, limited

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mobility, and severe fatigue over the past two months. A contrast-enhanced computed tomography (CECT) scan in May 2020 revealed a 6.9 x 4.5 cm tumor in the left upper lobe (Figure 1 A), along with some enlarged left hilar and prevascular lymph nodes. In Section VII of the liver parenchyma, a 10 x 9 mm lesion was revealed (Figure 1 B). Bilateral adrenal glands were hyperplastic, with a 9 x 6 mm nodule in the left adrenal. A CT-guided lung biopsy showed poorly differentiated SNSCLC. Desmocollin-3 (DSC3) expression was observed in 27% of tumor cells (Figure 2) with absent PD-L1 expression. He had an Eastern Cooperative Oncology Group performance status (ECOG) of 2. He was diagnosed with SNSCLC (T3N1M1c; Stage IVb) with metastasis to the liver and left adrenal gland.

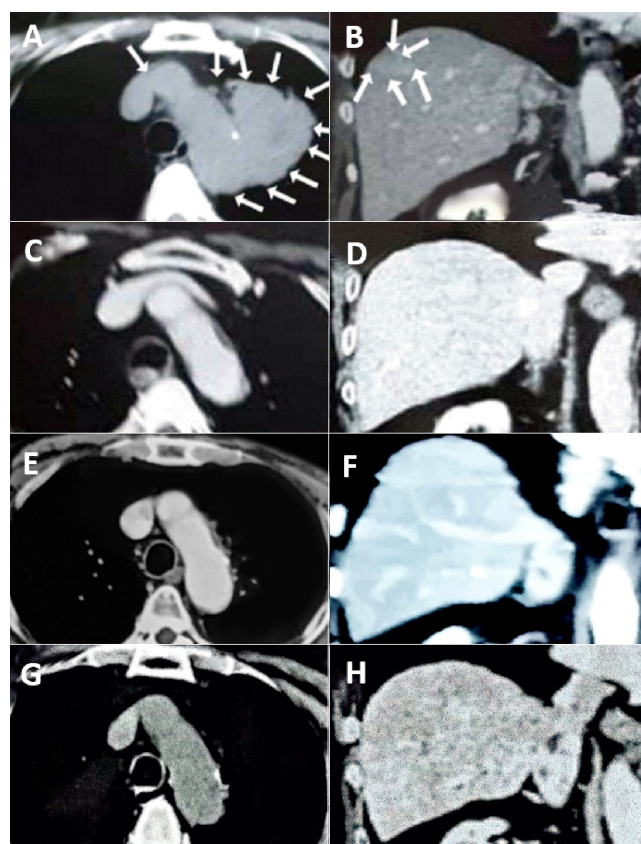


Figure 1: Contrast-Enhanced Computed Tomography (CECT) images of lung and liver at diagnosis (May 2020, A, B) and following treatment (March 2021, C, D; December 2021 E, F; July 2022, G, H): **A):** Tumor in the left upper lobe of lung measuring 6.9 x 4.5cms on May 2020; **B):** Lesion in segment VII of liver measuring 10x9 mm on May 2020; **C):** Lesion in left upper lobe of lung replaced by fibrous band (March 2021); **D):** Absence of any evidence of lesion in Liver lesion in segment VII (March 2021); **E), F):** Maintained response in lung and liver on December 2021; **G, H):** Maintained response in lung and liver on July 2022

The treatment plan was decided as weekly nab-paclitaxel 100 mg/m² and two weekly carboplatin AUC from June 15, 2020. On the 15th day after starting chemotherapy, the patient developed severe acute neuropathy and ECOG deteriorated to 3. After discussing various options with the patient in view of his deterioration in performance status, no further chemotherapy was administered, and he was changed to Mw 0.1 ml on 14 August 2020, intradermally every week for two months, as it is known to have no systemic side effects. Mw was well tolerated with some symptomatic relief. The frequency of Mw administration was reduced from 0.1 ml intradermally per week to 0.1 ml intradermally per two weeks for the next two months. This was further reduced to 0.1 ml by intradermal route every month after four months. In January 2022, the route of administration of Mw was changed from intradermal to inhalation by nebulizer after dissolving Mw in 10 ml of normal saline.

The patient did not experience any systemic side effects. Only local injection site reactions, i.e. scab and minor ulcerations, were observed after Mw treatment. The patient continued to experience gradual improvement in symptoms that was also associated with gradual improvement in performance status. After five months of initiation of treatment, he was symptom-free. In March 2021 his performance status improved to an ECOG score of 0. CT imaging performed in March 2021 revealed a fibrous band that replaced the lesion in the left upper lobe (Figure 1 C) with no evidence of the liver segment VII lesion (Figure 1 D), and a nodule in the left adrenal. There was no evidence of any new development of the lesion. Repeat CT scan in December 2021 (Figure 1 E, F) and July 2022 (Figure 1 G, H) did not reveal any change compared to March 2021. The patient is symptom-free, and disease-free with ECOG status 1 till the last follow-up in July 2024.

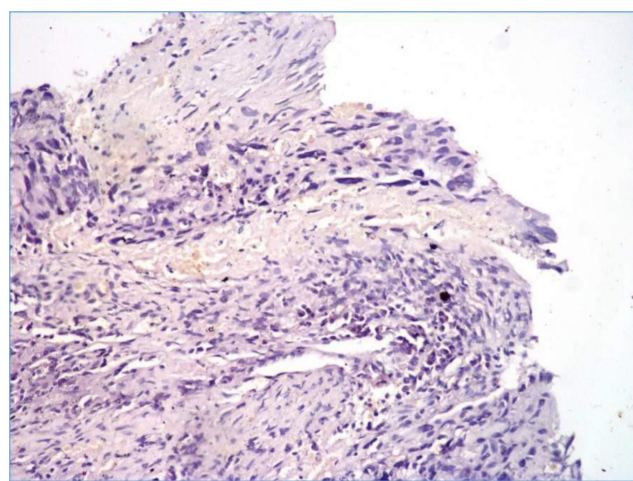


Figure 2: Microphotograph of biopsy demonstrating expression of Desmocollin-3 using immunohistochemistry. (200X)

3. Discussion

In this report, we present the complete response (CR) in a patient with negative PD-L1 - DSC3 expressing advanced SNSCLC (stage IVb) with poor ECOG after monotherapy with Mw. CR is seen in 1.5% of patients receiving checkpoint inhibitors, while 3% of patients receiving Mw with chemotherapy.^{1,3} CR with Mw monotherapy is described for melanoma but not for SNSCLC.⁸ Mw is known to preferentially kill DSC3 expressing tumor.^{3,4} It is also known to change the tumor immune microenvironment. Its efficacy is associated with an increase in immunostimulant tumor-infiltrating lymphocytes (TIL) consisting IFN-gamma secreting cells of adaptive (CD4+T cells, CD8+T cells) innate immune system (NK cells, NKT cells, and macrophages) immune system,^{5–7} decreased immunosuppressive TIL consisting of Treg, CTLA-4, PD-1, M2 macrophages^{5,6,8,9} and cytokines such as IL-6 and IL-10⁷ with a net result of increased intratumoral Teff/Treg ratio with change in macrophage profile from M2 to M1.^{6,9}

The findings of this case demonstrate the safety of Mw monotherapy in a patient with a poor performance status and its efficacy in patients with advanced SNSCLC patients positive for DSC3 and negative for PD-L1 which needs to be confirmed in a larger study.

4. Conclusion

About half of the Squamous NSCLC patients have negative PD-L1 expression and no optimal therapeutic strategy has been defined for this group of patients. Mw has an effective immunomodulatory role in the management of squamous NSCLC. This report describes a durable and complete response in a patient with a DSC3 positive and PD-L1 negative advanced squamous NSCLC patient with Mw monotherapy. It also highlighted the role of Mw in improving quality of life.

5. Source of Funding

None.

6. Conflict of Interest


Co-author Dr. Rudri Modi is an employee of Cadila Pharmaceuticals Limited.

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