

Case Report

The Tale of Unexplained pancytopenia: The Unusual Instance of Cemiplimab-Associated Non-Hodgkin's Lymphoma

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Abstract

Cemiplimab is a human immunoglobulin G4 monoclonal antibody directed against programmed cell death protein 1 (PD1). It is the treatment of choice in locally advanced or metastatic cutaneous squamous cell carcinoma (mCSCC). This popular and lifesaving drug also has many known adverse events, most of which are immune mediated. The most common adverse events include hepatotoxicity, rash, colitis, pneumonitis, and infusion related reactions. Although minimally hematotoxic, anemia is common and deranged coagulation cascades can be seen, albeit rare with Cemiplimab therapy [LD1]. We present a highly unusual case of an 84-year-old gentleman who

developed an unexplained pancytopenia and was found to have novel Non-Hodgkin's Lymphoma after receiving Cemiplimab therapy for mCSCC. Although the exact mechanism is unknown, it is likely that immune checkpoint inhibitor therapy led to stimulation of B cells and uncontrolled proliferation leading to development of low-grade B cell lymphoma. We aim to highlight this rare yet significant manifestation of this new therapy, and the need for further research to better understand the exact pathogenesis of this unique outcome

Keywords: Hemato-oncology; Non-Hodgkin's Lymphoma; Anti PD-L1; Immunotherapy; Cancer

Immunotherapy; Squamous cell carcinoma (SCC);
Cemiplimab

1. Introduction

Cutaneous Squamous Cell Carcinoma (CSCC) is now almost equivalent in incidence to Basal Cell Carcinoma with nearly 1.5 million cases per year and increasing through the years [1, 2]. Chronic sun exposure, advanced age and immunosuppression are risk factors for developing CSCC [3-6]. Lesions are generally seen in the areas that are exposed to sun the most, like face, neck, trunk and extremities [7, 8]. The current treatment of choice is to do surgical resection of the skin lesion using Mohs micrographic procedure, which is possible in around 95% patients who are diagnosed in early stages of cancer [9-11]. Advanced CSCC is generally defined as either metastatic disease (mCSCC), especially with distant metastases to nodes, (usually recurrent despite radiation therapy and lymphadenectomy; or locally advanced disease not amenable for surgical or radiation therapy [12, 13]. Due to chronic skin exposure to Ultraviolet light, the cancers are usually hypermutated [14, 15]. Patients with high tumor burden, have been found to have clinical benefit from immunotherapy agents, especially PD1 inhibiting agents [16, 17].

Cemiplimab is a high affinity, potent, human immunoglobulin G4 monoclonal antibody directed against programmed cell death protein 1 (PD1) [18]. Cemiplimab showed substantial antitumor activity in a Phase I trial (NCT02383212) and produced objective response rate of around 47% in 75 mCSCC patients in phase 2 trial (NCT02760498). Based on these studies, Cemiplimab became the first therapy to be approved by US Food and Drug Association for

advanced CSCC including mCSCC [19]. Its safety profile was studied in both the studies, with most serious adverse events being immune mediated reactions (like pneumonitis, colitis, hepatitis, hypo/hyperthyroidism, diabetes mellitus and nephritis), anemia and most common being fatigue, rash and diarrhea [19]. There have been no reports about Cemiplimab causing lymphoma/leukemia like event post therapy so far.

2. Case Presentation

An 84 years old male with essential hypertension and chronic kidney disease stage II presented to our oncology clinic after he underwent Computed Tomography of abdomen and pelvis for some other reason and incidentally was found to have inguinal lymphadenopathy. He underwent ultrasound guided biopsy of the node, which revealed metastatic keratinizing squamous cell carcinoma (SCC). On further evaluation, the primary lesion was found to be SCC of the left leg, for which he underwent surgical excision followed by graft placement. For his mCSCC, he was started on Cemiplimab as palliative systemic immunotherapy. A follow up Positron Emission Tomography (PET) CT a month later showed decreased fluorodeoxyglucose (FDG) uptake at inguinal nodes compared to PET/CT before the commencement of the therapy. During the course of treatment, he developed anemia, for which he required recurrent packed red blood cell transfusions. No history of gastrointestinal bleeding was found, and iron studies along with B12 and folic acid levels were found to be normal. There was no evidence of hemolysis given a normal haptoglobin and a negative Coomb's test. Eventually, he also developed thrombocytopenia and leukopenia.

After five months of therapy, Cemiplimab was stopped secondary to development of pancytopenia and a rash. The rash was followed up with a biopsy, which showed possibility of recurrent CSCC and topical medications including corticosteroid ointment were started. For pancytopenia, he underwent bone marrow (BM) biopsy, which showed hypercellular marrow with 80% overall cellularity, out of which 60% were lymphocytes. On flow cytometry, B cell proliferation that was Kappa light chain restricted was discovered. Cluster of Differentiation (CD) analysis showed positive CD20 and CD19, while CD5, CD10, CD11c, CD23 and CD38 were found to be negative. These BM biopsy results supported a diagnosis of low-grade B cell Non-Hodgkin's Lymphoma (NHL), either marginal zone lymphoma or lymphoplasmacytic lymphoma. The absence of prior history of lymphoma or blood dyscrasias, new lymphadenopathy and organomegaly in conjunction with the timeline of sudden and rapidly worsening pancytopenia was highly suggestive of an adverse reaction secondary to the ongoing Cemiplimab therapy. The patient was subsequently scheduled for Rituximab therapy for the NHL, and was referred to a tertiary hematology/oncology center where he is currently being followed for these scheduled therapies.

3. Discussion

The development of Immune Checkpoint Inhibitors (ICI) with anti PD1/PDL1 monoclonal antibodies has led to a paradigm shift in cancer treatment. ICI therapy is either used to enhance or normalize the patient's immune system, which sometimes leads to development of tertiary lymphoid structures (TLS) or organized lymphoid aggregates in the tumor micro-environment [20-24]. Responders of ICI therapy have

shown to have enrichment of memory B-Cells in TLS with single sequence RNA studies showing clonal expansion of the same [25]. There have been instances especially in autoimmune diseases, chronic infections, and cancers where TLS formation is a marker of adaptive immune response [26]. TLS have a structure similar to a lymph node, with B cells and T cells being the main component [27, 28]. Patients treated with ICI therapy can exhibit similar response with chronic antigenic stimulation. Sweeney K et al. reported a case of a patient treated with Cemiplimab for recurrent SCC who developed marginal zone lymphoma in the surrounding skin lesion. They showed that TLS following ICI therapy exhibit a lymphocytic and plasma cell infiltrate in the perivascular area in the tumor bed, which resembles marginal zone lymphoma (MZL) [29].

In our case, the patient was treated with Cemiplimab for mCSCC with lymph node involvement. After the commencement of the treatment, he did have regression of the tumor with visible improvement as seen on repeat imaging. He later developed pancytopenia, which on further investigation with bone marrow biopsy was found to be from evolution of MZL. As seen in the study earlier by Sweeney K et al., the patient treated with Cemiplimab developed MZL in the tumor bed. Our patient was treated for mCSCC with metastasis to inguinal lymph nodes and hence the development of MZL was systemic and was seen in bone marrow as well. Therefore, we suspect that ICI therapy led to stimulation of B cells and uncontrolled proliferation leading to development of low-grade B cell lymphoma. With this case report, we aim to highlight this rare yet significant manifestation of these new modalities, and the need for further research and long term follow up of

patients receiving ICI therapy to understand the exact pathogenesis of the same.

4. Conclusions

Novel therapies such as Cemiplimab have shown great promise in skin and non-small cell lung cancers, but their long term and rare short term adverse events continue to surface. All physicians involved in care of cancer patients receiving novel therapies, i.e., primary care physicians, hospitalists, and hematologists/oncologists, should maintain a low threshold to suspect novel therapies in light of unexplained symptoms. A multi-disciplinary approach is the best way forward in identifying and managing these manifestations.

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Conflicts of Interest

None

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