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Pembrolizumab-Induced Cold Agglutinin Disease

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

DEFG 1 Osman Atiq
EF 2 Saad O. Atiq
E 3 Zainab O. Atiq
B 4 Vijay Patel
E 5 Mohammad O. Atiq
BDE 6 Omar T. Atiq

1 Department of Internal Medicine, Unity Health, Searcy, AR, U.S.A.
2 Department of Internal Medicine, Duke University, Durham, NC, U.S.A.
3 College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, U.S.A.
4 Department of Pathology, University of Arkansas for Medical Sciences, Little Rock, AR, U.S.A.
5 Department of Hematology and Oncology, Baylor University, Houston, TX, U.S.A.
6 Department of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, U.S.A.

Corresponding Author: Osman Atiq, e-mail: Osman.atiq@unity-health.org
Conflict of interest: None declared

Patient: Female, 58-year-old
Final Diagnosis: Cold agglutinin disease • lung adenocarcinoma
Symptoms: Anemia • fatigue • GI bleeding • neck mass • thrombocytopenia
Medication: —
Clinical Procedure: —
Specialty: Hematology • General and Internal Medicine • Oncology

Objective: Unusual clinical course

Background: The introduction of immunotherapy in the management of metastatic lung cancer appears to be changing their natural history. Most patients tolerate immunotherapy without any significant adverse events. Nevertheless, a significant number of patients still experience adverse effects. Autoimmune hemolytic anemia has been described as mostly related to warm autoantibodies. The following case report describes cold agglutinin disease with hemolysis secondary to Pembrolizumab therapy for the treatment of metastatic lung cancer.

Case Report: A 58-year-old woman noted a left neck mass 4 months prior to her presentation. A biopsy confirmed the presence of metastatic adenocarcinoma, consistent with primary lung cancer. Further evaluation revealed the tumor to be PDL-1-positive. She was started on Pembrolizumab, Pemetrexed, and carboplatin chemotherapy regimen. Her CBC was within normal limits when she started therapy, but within 4 weeks hemoglobin dropped to 4.3 g/dL. Further evaluation showed high cryoglobulin levels and a high cold agglutinin titer. Complement C3 DAT was positive. A peripheral smear showed clumps of red cells and the serum IgM was elevated. The diagnosis of CAD was made. She was then started on Rituximab. Imaging showed a significant response, with decreased disease burden.

Conclusions: Our case shows a unique presentation of CAD, initially presumed to be myelosuppression secondary to chemotherapy. Instead, a peripheral smear revealed Pembrolizumab to be the cause of cold agglutinin disease. Due to the relatively unknown association between these 2 entities, patient care was delayed. Finally, after initiation of Rituximab therapy, the patient's CBC began to recover.

MeSH Keywords: Anemia, Hemolytic, Autoimmune • Immunotherapy • Lung Neoplasms

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/924283

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Background

Cold agglutinin disease (CAD) is the second most common cause of autoimmune hemolytic anemia. However, the average time to diagnose a patient with CAD is 37.4 months [1]. CAD is mostly associated with infections, autoimmune disease, and malignancies. While it has been described in patients with various cancers, the association was believed to be incidental rather than secondary to malignancy [1].

The recent introduction of immunotherapy has revolutionized the treatment of cancer. Tumors use PD-L1 receptors as a means of hiding from the body's own defense mechanisms – the T cells. Pembrolizumab, a humanized monoclonal antibody, allows the T cells to overcome this defense mechanism by binding to the PD-1 receptor, thereby inhibiting the deactivation of T cells and allowing for the destruction of the tumor cells by T cells. Common adverse effects of immunotherapy include fatigue, pruritis, lymphocytopenia, hyperglycemia, and hypothyroidism. CAD alone had not yet been directly associated with Pembrolizumab therapy.

We present a unique case of symptomatic hemolytic anemia caused by CAD after undergoing treatment with Pembrolizumab, leading to cessation of treatment; a follow-up PET scan showed complete remission.

Case Report

A 59-year-old woman with a history of alcohol and tobacco abuse presented with a left neck mass. A CT scan showed a right upper-lung mass with right hilar, right mediastinal, and left supraclavicular lymphadenopathy. Fine-needle aspiration confirmed the presence of metastatic adenocarcinoma. PET-CT and MRI of the brain showed no other metastases. The tumor was negative for EGFR, ALK, ROS1, BRAF, MET, and ERBB2. KRAS-G12A mutation was present. Microsatellite status was stable, and the tumor mutational burden could not be determined. PD-L1 immunohistochemistry showed a Tumor Proportion Score (TPS) of 90%. The patient was started on a regimen of Pembrolizumab, Pemetrexed, and Carboplatin, and was also started on vitamin B12 and folic acid supplementation, per protocol. Baseline CBC, CMP, and TSH were within normal limits, except for a WBC 16.46×10^3 cells/dL (neutrophils 92.2%, lymphocytes 5.4%, monocytes 1.0%, basophils 0.4%, eosinophils 0.0%), an elevated total bilirubin (3.7 mg/dL) with a direct bilirubin of 0.4 mg/dL, and alkaline phosphatase of 170 IU/L. She tolerated the first cycle of chemotherapy without any reported issues. At the time of her second cycle, 3 weeks later, her hemoglobin (Hgb) had dropped to 8 g/dL, with an MCV of 100.4 and an elevated RDW of 18.8. The WBC remained elevated at 13.2 and platelets remained normal at 401 k. LDH had increased from 187 to 262, while total bilirubin decreased to 1.7 mg/dL. She received her second cycle of treatment as planned. Ten days later, the WBC decreased to 2.8, platelets decreased to 36 k, Hgb was 7.6, and total bilirubin normalized to 1.2, while LDH and MCV decreased to 229 and 87.6, respectively. RDW remained elevated. At the time of the third cycle of therapy, WBC and platelets were normal and Hgb was stable. A week later, she developed melena and Hgb dropped to 6.4 mg/dL, WBC to 2.5, and PLT to 136. She was admitted to the hospital and given PRBCs for symptomatic anemia. EGD showed a Mallory Weiss tear, with oozing of blood and chronic active gastritis/peptic ulcer disease. She was continued on a PPI and discharged. At the time of her fourth and last cycle of therapy, total bilirubin, MCV, WBC, and PLT were normal. LDH and RDW were elevated, with a stable Hgb. PET-CT showed no evidence of disease, except for a right upper-lobe lung lesion measuring 1.7×1.2 cm, with an SUV of 1.4. Three weeks later, her Hgb was 9.6, while her MCV and total bilirubin were normal. She was started on maintenance Pembrolizumab and Pemetrexed. Laboratory values continued to fluctuate as above. She periodically required PRBCs for symptomatic anemia, but there was no evidence of ongoing GI bleeding. Bone marrow evaluation was normal except for being mildly hypocellular. After the fifth cycle of maintenance therapy, she was admitted to the hospital with chest tightness and increased dyspnea. The evaluation was unremarkable and she was discharged upon resolution of symptoms. Treatment was held to allow her to recuperate. A month later, she still required PRBCs almost every 2 weeks, so further hematologic evaluation was undertaken. A peripheral blood smear showed marked red cell agglutination and polychromasia. The retic count was 6.19%, haptoglobin was low-normal at 32 mg/dL, while DAT-poly-specific, IgG, and C3 were positive. Serum protein electrophoresis, ANA antibody panel, PNH panel, and hepatitis profile were normal. Serum IgM was elevated at 259, with normal IgG and IgA. Mycoplasma IgM was negative, but IgG was positive at 0.35U/L. Cryoglobulins were detected at 48 h. Immunofixation showed type II cryoglobulin with monoclonal IgM kappa and polyclonal IgG. Serum IgM cryoprecipitate was elevated at 1 mg/dL, with normal IgG and IgA. The cold agglutinin titer was elevated at 1: 128 and was as high as 1: 512.

A diagnosis of secondary cold agglutinin disease was made. The patient was given steroids, with stabilization of Hgb lasting a couple of weeks, and then the steroids were tapered off. Rituximab was then administered at 375 mg/m^2 weekly for 4 weeks, with stabilization and gradual improvement of Hgb over the following several weeks. The patient did not require any further PRBC transfusions. Serum cryoglobulins became undetectable, and the cold agglutinin titer decreased to 1: 64. A follow-up PET-CT showed essentially complete metabolic resolution of lung cancer (Figure 1).

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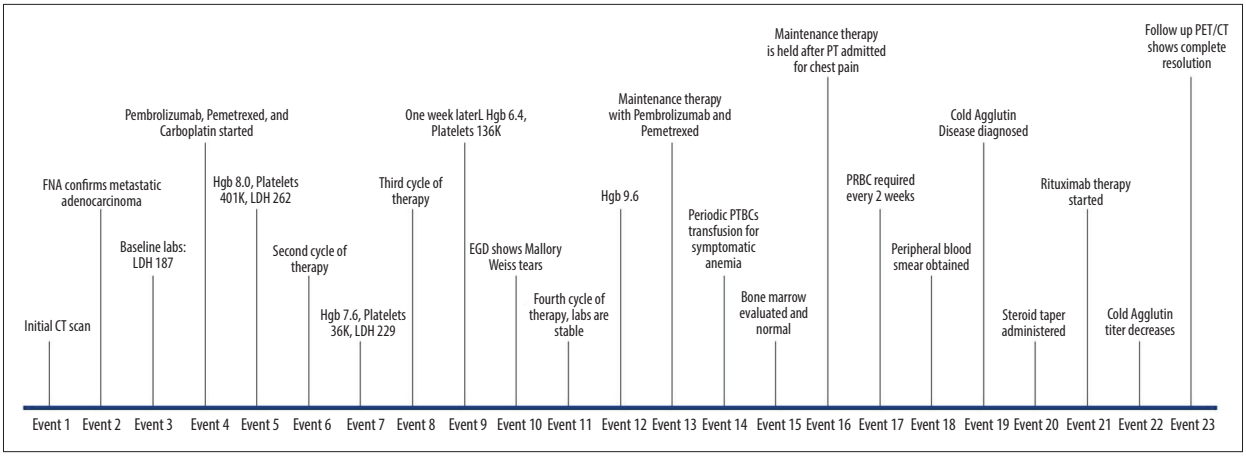

Figure 1. Timeline of events from initial contact until resolution.

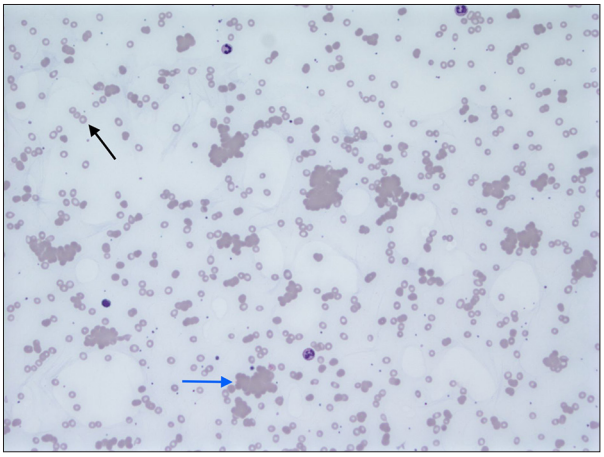

Figure 2. Peripheral smear showing agglutination and faint polychromasia. Stained with Wright-Giemsa. 200× magnification.

Discussion

We present a case of cold agglutinin disease, secondary to the use of Pembrolizumab, that remitted after treatment with Rituximab. Although there are some case reports describing the association between Nivolumab and CAD, our literature search showed only 1 other possible instance of Pembrolizumab-induced CAD, reported by Okawa et al. [2], which was complicated by the fact that the patient developed hemophagocytic lymphohistiocytosis. Our case is also unique in that there was no other associated autoimmune condition.

Upon review, our patient developed CAD after 2 cycles of treatment with Pembrolizumab. This follows a trend that was reported in treatment with Nivolumab, another PD-1 inhibitor [3]. When these checkpoint inhibitors are used, they typically cause AIHA within 2–8 weeks of therapy [4]. Checkpoint inhibitors, in general, have been associated with warm antibody AIHA rather than CAD [5].

Admittedly, our patient was not being treated solely with Pembrolizumab when she was diagnosed with CAD. A second drug, Pemetrexed, had been started and stopped alongside Pembrolizumab. However, Pemetrexed has been described in association with warm AIHA rather than CAD [6]. Severe hematologic toxicity has also been reported with Pemetrexed use. We were able to avoid this by supplementing the patient with vitamin B12 and folate, as shown in the early trials of Pemetrexed [6].

Our patient's ongoing alcoholism lead to an episode of acute gastritis and melena, requiring transfusions of PRBCs. The patient continued to require transfusions and her immuno-chemotherapy was held, with the intention to restart once the hemoglobin stabilized. However, she continued to require frequent transfusions despite cessation of GI bleeding. A review of her peripheral blood smear proved to be the needed catalyst that led to the diagnosis of Pembrolizumab-induced cold agglutinin disease and its successful management (Figure 2).

Conclusions

The case described shows a unique example of cold agglutinin disease secondary to the use of Pembrolizumab while treating metastatic lung cancer. Other possible causes were ruled out through laboratory testing and literature review. An early diagnosis may be possible by having a low threshold for review of peripheral blood smear at the earliest suspicion of hemolysis when using Pembrolizumab. As suggested by this case, steroids may be ineffective, and Rituximab should be started early after the diagnosis of CAD secondary to checkpoint blockade. Whether CAD is a marker of long-term remission of an otherwise fatal lung cancer following a few months of Pembrolizumab along with standard chemotherapy therapy is unknown but is an interesting question.

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