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Early-Onset Autoimmune Hemolytic Anemia from Pembrolizumab in a Patient with Metastatic Lung Cancer: A Case Report

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

ABCDEF 1,2 Femi Williams Adeoye
ABCDEF 2 Sanggeeta Surandran
ADEF 1 Nida Jaffar
ABCDE 3 Shankari Serumadar
ABCDE 1,2 Gulshad Begum

1 Department of Oncology, Southend University Hospital, Southend-on-Sea, United Kingdom
2 Department of Internal Medicine, Basildon University Hospital, Basildon, United Kingdom
3 Department of Haematology, Basildon University Hospital, Basildon, United Kingdom

Corresponding Author: Femi Williams Adeoye, e-mail: Femi.Adeoye1@nhs.net
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Patient: Male, 69-year-old
Final Diagnosis: Pembrolizumab-induced autoimmune haemolytic anemia
Symptoms: Anaemia • dyspnea • jaundice
Clinical Procedure: —
Specialty: Oncology

Objective: Rare disease

Background: Immunotherapy is now a well-established systemic anticancer treatment in both curative and palliative settings in oncology. Immune-related adverse events associated with pembrolizumab, a novel humanized therapeutic monoclonal antibody, very rarely affect the hematologic system. While previous reports have noted autoimmune hemolytic anemia occurring after multiple cycles of immunotherapy, this article describes a case of a patient with advanced lung adenocarcinoma, who was diagnosed with autoimmune hemolytic anemia shortly after his first cycle.

Case Report: In this article, we report a rare case of autoimmune hemolytic anemia, occurring after 1 cycle of pembrolizumab, in a 69-year-old man with metastatic lung adenocarcinoma. He presented with new-onset severe anemia, jaundice, and dyspnea 14 days after his first cycle of pembrolizumab. The remarkable findings in the initial investigations included hyperbilirubinemia, severe anemia, markedly elevated serum lactate dehydrogenase levels, and positive direct and indirect antiglobulin (Coombs) test results. He had an urgent specialist review at presentation, and was promptly started on high-dose steroids, intravenous immunoglobins, blood transfusions, and other supportive treatments, with subsequent resolution of hemolysis over the next few days. He made a good clinical and hematological recovery and was discharged home after 5 days of hospitalization.

Conclusions: Autoimmune hemolytic anemia is a rare adverse effect of immunotherapy, which can be life-threatening without prompt recognition and appropriate management. This case also shows that this disease should be considered as a differential diagnosis of new-onset anemia or sudden-onset jaundice in patients on immunotherapy, regardless of the number of cycles received.

Keywords: Anemia, Hemolytic, Autoimmune • Immune Checkpoint Inhibitors • Immunotherapy

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/946630

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Introduction

The emergence of immune checkpoint inhibitors (ICIs) has revolutionized the management of various malignancies over the years [1]. The more widely used agents target the Cytotoxic T-Lymphocytes Associated protein 4 (CTLA-4) and Programmed Death 1/Programmed Death Ligand 1 (PD-1/PD-L1) checkpoint pathways [2]. Pembrolizumab is a novel humanized monoclonal antibody that binds to PD-1 on T-cell surfaces and blocks its interaction with its corresponding ligands (PD-L1) on cancer cells; by so doing, it prevents the downregulation of T-cell-mediated tumoricidal activities [3]. Pembrolizumab, since its initial approval for treatment of metastatic melanoma about a decade ago, has significantly altered the management of a growing number of cancer types, including non-small cell lung cancers (NSCLC) in both curative and palliative settings, recurrent and metastatic head and neck squamous cell carcinoma, and other cancers [3-5]. The Keynote-024 trial, for instance, showed that pembrolizumab monotherapy offered significantly improved overall survival benefits compared with platinum-based chemotherapy in patients with previously untreated metastatic NSCLC with PD-L1 Tumor Proportion Score (TPS) of 50% or greater [5].

Despite its well-established efficacy, pembrolizumab can cause a wide range of immune-related adverse events (irAEs) of varying severity in different organ systems. The commonly observed irAEs of pembrolizumab include pneumonitis, skin toxicities, colitis, hepatitis, nephritis; autoimmune endocrinopathies such as thyroiditis, adrenal dysfunction, and hypophysitis [3]. Rarely, irAEs involve the hematologic system, causing neutropenia, thrombocytopenia, or anemia due to pure red cell aplasia or autoimmune hemolysis [6]. Autoimmune hemolytic anemia (AIHA) due to pembrolizumab has been reported in a patient who had an acute exacerbation of pre-existing AIHA shortly after receiving his first dose, and in other patients with metastatic lung cancer who had no underlying predisposition [7-9]. In this article, we report a rare case of AIHA induced by immunotherapy to raise an awareness of this entity and contribute to a growing body of literature on rare irAEs and their management. This case, to our knowledge, also is one of the first case reports of this condition during the first cycle [7,8]. This report describes a 69-year-old man with advanced adenocarcinoma of the lung who was diagnosed with AIHA after his first cycle of pembrolizumab.

Case Report

We present the case of a 69-year-old man with background of gastritis, hyperlipidemia, and previous cholecystectomy. He was an ex-smoker with a baseline Eastern Cooperative Oncology Group (ECOG) Performance Status of 1. In late February 2024, he was diagnosed with de novo advanced lung adenocarcinoma with left adrenal and subdiaphragmatic metastases. Further molecular analyses were significant for high PD-L1 TPS of 70% on immunohistochemistry. A few weeks later, he was started on intravenous pembrolizumab monotherapy at a dose of 400 mg in 6-week cycles, with palliative intent.

Fourteen days after receiving his first dose of pembrolizumab, he presented via the Emergency Department with a 4-day history of progressive jaundice and dark stools with associated lethargy and light-headedness. He reported no bleeding, fever, cough, or abdominal pain. On examination at presentation, he was afebrile, pale, and deeply icteric. His vital signs revealed heart rate of 92 beats per minute, respiratory rate of 20 cycles per minute, and systolic blood pressure of 115 mmHg. His initial laboratory investigations (**Table 1**) showed severe anemia with hemoglobin 45 g/l (baseline level of 123 g/l) in the absence of any obvious bleeding. There was elevated serum lactate (4.2 mmol/l) and unconjugated hyperbilirubinemia. In view of the findings of severe anemia and unconjugated hyperbilirubinemia on initial blood tests, there was suspicion of an ongoing hemolytic process. Further laboratory investigations revealed profoundly low haptoglobin levels (<0.3 g/l), and markedly elevated ferritin (2441 ng/ml) and lactate dehydrogenase (LDH) 1214 u/l. A peripheral blood film showed marked reticulocytosis, spherocytosis, and reactive neutrophilia (**Figure 1A, 1B**). An urgent direct antiglobulin test (DAT) showed a moderately positive immunoglobulin G (IgG) antibody (2+), and strongly positive (5+) complement C3d reactivity. The DAT findings of IgG (2+) and C3d (5+) were consistent with an immune-mediated hemolytic process. Reactions of no specificity were detected by direct agglutination at 30°C. Pan-reactive autoantibody was detected by indirect antiglobulin test (IAT) and enzyme IAT, with no underlying allo-antibodies detected by IAT. Triple-phase computed tomography (CT) examination of the abdomen and pelvis was also performed, which showed no evidence of hemorrhage or intra-abdominal collection. Overall, the clinical and laboratory features were in keeping with acute autoimmune hemolytic anemia, presumably induced by pembrolizumab.

On the first day of admission, his case was promptly reviewed by the on-call Hematology team and started on intravenous immunoglobin (IVIG) 1 g/kg. He received IVIG in divided daily doses over the first 3 days in combination with steroid pulse therapy (methylprednisolone 500 mg/day) for the first 4 days. Also, during the first 72 hours, he was cautiously transfused with multiple units of red blood cells. There was prompt resolution of hemolysis (**Table 1**) and clinical improvement.

On day 4, his hyperbilirubinemia had declined remarkably (26 umol/l) and hemoglobin was stable at 86 g/l. He was ultimately discharged home after 5 days of hospitalization on a weaning course of prednisolone over a period of 6 weeks with

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Table 1. Trend of selected laboratory test results during hospitalization and 2 weeks after discharge.

Laboratory parameters	Day 1	Day 2	Day 4	Day 5	2 weeks after discharge	Normal range	SI unit
Lactate	4.2	(–)	(–)	(–)	(–)	0.4-2.2	mmol/l
Hemoglobin	45	67	86	93	114	130-180	g/l
LDH	1214	(–)	(–)	1128	860	240-480	u/l
Bilirubin (total)	61 (unconjugated 72%)	54	26	16	9	0-21	umol/l
INR	1.4	1.3	1.1	(–)	1.1	0.8-1.2	
Haptoglobin	<0.3	<0.3	(–)	(–)	(–)	0.3-2.0	g/l
Reticulocyte count	261.7 (23.7%)	(–)	(–)	(–)	(–)	50-100	10^9/l
Serum ferritin	2441	(–)	(–)	(–)	(–)	15-300	ng/ml
IgA	6.5	(–)	6.3	(–)	(–)	0.8-4.0	g/l
IgG	17.8	(–)	18.4	(–)	(–)	6-16.0	
IgM	0.6	(–)	0.6	(–)	(–)	0.5-2.0	
Complements	C3 1.0	(–)	(–)	(–)	(–)	0.9-1.80	g/l
	C4 0.12	(–)	(–)	(–)	(–)	0.14-0.54	

INR – international normalized ratio; LDH – lactate dehydrogenase; Ig – immunoglobulin; (–) – not tested.

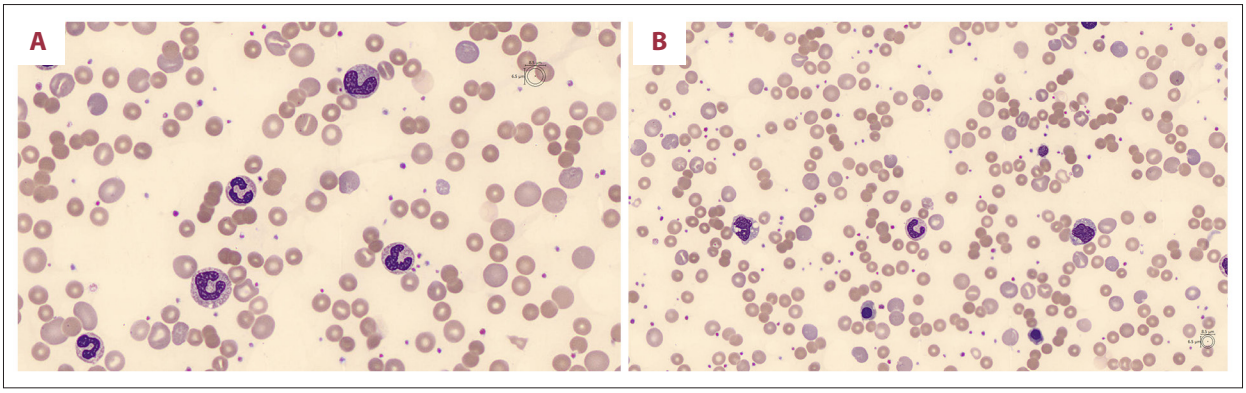

Figure 1. (**A, B**) Photomicrographs of peripheral blood film showing spherocytes, nucleated red blood cells, and polychromasia, consistent with a hemolytic process.

outpatient follow-up by Hematology and Oncology teams. Two weeks after discharge from the hospital, his hemoglobin, bilirubin, and LDH levels were 114 g/l, 9 umol/l, and 860 u/l, respectively. Given the severity of his irAE, immunotherapy was permanently discontinued.

Discussion

This patient with advanced lung cancer presented with clinico-pathologic features of immunotherapy-induced AIHA, a rare irAE, about 2 weeks after his first dose of pembrolizumab. He made a remarkable clinical and biochemical recovery after prompt initiation of immunosuppressant, IVIG, and other supportive measures. This case highlights the fact that, despite the benefits of immunotherapy in a growing number of cancer types, the risks of common and rare immune-related adverse events like AIHA remain a real clinical challenge. The exact incidence of immunotherapy-induced AIHA is uncertain, possibly due to underdiagnosis, heterogenous clinical and pathologic patterns, and increasing use of ICIs [10]. Previous studies have shown hematological irAEs to be extremely rare (0.5%), with

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immunotherapy-induced AIHA comprising 16-26% of these, yet with fatality rates up to 16.7% [11-13].

While the pathogenesis of this entity remains unclear, ICI-induced immunologic dysregulation leading to autoantibody formation, blunting of regulatory T-cell activity, and activation of nascent T-cell clones has been theorized [10]. These autoantibodies directed against own red blood cells, cause clinical and laboratory features of hemolysis as evidenced by anemia, low serum haptoglobin levels, unconjugated hyperbilirubinemia, elevated LDH, reticulocytosis, and, commonly, positive direct antiglobulin test [10]. It is important to bear in mind that, although our patient had positive IgG and complement C3d, this is not always the case. For instance, a literature review by Tanios et al suggests that out of 12 published cases of ICI-induced AIHA, complements and IgG were only detected on the red cell surface in 3 and 9 cases, respectively [13].

ICI-induced AIHA may also pose a diagnostic challenge in an acute medical setting for different reasons. Apart from its rarity and heterogenous clinical and laboratory findings, anemia in cancer patients may be due to a myriad of other etiologies [10]. In this patient, although other differential diagnoses, including acute upper-gastrointestinal bleeding, cancer-related anemia, acute viremia, disease progression, and disseminated intravascular coagulopathy, were considered, the clinical and laboratory features were more in keeping with a hemolytic process. Furthermore, the onset time of AIHA from start of immunotherapy appears variable. A recent review of literature showed a median onset time of 10 weeks (range, 2-78 weeks) [13]. AIHA occurring 17 days after the first cycle of pembrolizumab was reported in an 86-year-old Japanese man with a pre-existing AIHA [7]. However, unlike our case, the patient had an underlying AIHA exacerbated by ICI therapy. Another case of early-onset AIHA was reported in a 70-year-old man with metastatic lung cancer who developed progressive dyspnea and hyperbilirubinemia 2 weeks after starting pembrolizumab, who was also receiving concurrent doublet cytotoxic chemotherapy with cisplatin and pemetrexed, unlike our patient, who received pembrolizumab monotherapy [8]. Johnstone et al also reported a case of pembrolizumab-induced AIHA in a patient who presented with hemoglobin 74 g/l (from his baseline of 110 g/l) after 13 cycles [9]. Our patient's symptoms began less than 2 weeks after his first cycle of immunotherapy, representing an early-onset presentation of AIHA. Clinicians must therefore be aware of the diverse clinical presentations and variable onset times of this disorder. New-onset severe anemia and jaundice in cancer patients receiving ICIs like pembrolizumab should prompt physicians to consider a diagnosis of ICI-induced AIHA regardless of the duration of treatment, as this could be potentially fatal if not recognized early and managed appropriately.

The management of this irAE may be challenging for clinicians, as it is a rare entity. The European Society for Medical Oncology therefore recommends early consultation with a hematologist to guide investigation and management [14]. According to the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group, the general recommendation for management of irAEs entails steroid therapy with slow taper as a first-line approach, and use of immunomodulatory medications in refractory cases [15]. Immunotherapy should be discontinued in patients with life-threatening presentations or in severe cases without prompt resolution of hemolysis [15]. This guideline, however, makes no firm recommendation of steroid dose specifically in ICI-induced AIHA, to allow for individualized treatment. Systemic corticosteroids with prednisolone 0.5-2 mg/kg, or methylprednisolone equivalent dose, has been recommended as a first-line approach, with consideration of IVIG as an adjunctive therapy in severe cases of warm AIHA [10,14]. Due to the severity of our patient's presentation, there was early involvement of a specialist hematology team, prompt initiation of immunosuppression with high-dose steroid therapy (methylprednisolone 500 mg/day), and IVIG. There was rapid resolution of hemolysis, as evidenced by decline in LDH and bilirubin levels, and symptomatic improvement after a few days. Upon discharge, steroid dose was tapered slowly under careful monitoring in the outpatient clinic.

In steroid-refractory cases, we observed some variability in practice in the literature. For instance, in the case reported by Baek and Chae, there was no resolution of hemolysis despite administering first-line high-dose steroid (prednisolone 1 mg/kg/day) for over a week [8]. This steroid-refractory pembrolizumab-induced AIHA required steroid dose escalation and plasmapheresis 5 times on alternate days for 2 weeks, with good outcome [8]. Another patient who had AIHA relapse following immunotherapy rechallenge was refractory to a repeat course of high-dose steroid, but ultimately had resolution of hemolysis with addition of weekly rituximab over 4 weeks [16]. Similarly, Hasanov et al reported a case of cold agglutinin AIHA syndrome secondary to nivolumab in a metastatic urothelial cancer patient after the seventh cycle of immunotherapy, which initially did not respond to steroids but was then treated successfully with rituximab [17]. The evidence for use of other agents, including azathioprine, mycophenolate mofetil, and cyclophosphamide, in this setting currently remains weak and requires more investigations [10]. The observed variability in practice in second-line treatment shows the need for more studies in this area to determine the optimal treatment approach.

The decision to rechallenge patients with immune checkpoint inhibitors after recovering from AIHA should be carefully made in consideration of the risks and benefits, as reinitiation of

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immunotherapy comes with a significant risk of exacerbation of symptoms [14]. Our patient was not rechallenged with immunotherapy given the severity of his adverse effect.

While the exact underlying factors predisposing certain groups of patients to this rare irAE remain uncertain, it is apparent that ICI-associated AIHA is observed more in patients with certain cancer types, with melanoma and lung cancers accounting for about two-thirds (41% and 26%, respectively) of all cases [13]. Furthermore, most cases of ICI-induced AIHA (63.2%) are related to nivolumab, and less frequently with pembrolizumab and anti-CTLA-4 agents [13]. Patients with underlying hematological disorders such as chronic lymphocytic leukemia are at higher risk of developing this irAE [7,18].

Overall, we postulate that the occurrence of AIHA in patients with different cancer types and in association with different ICIs could suggest that there may be inherent genetic or other acquired characteristics that increase certain individuals' risks of developing this condition. Further studies to establish these specific predisposing factors as clinically validated biomarkers are needed to identify higher-risk individuals.

Conclusions

This report describes a rare occurrence of AIHA shortly after a first dose of pembrolizumab, an immune checkpoint inhibitor. While ICI-induced AIHA is rare, it can be rapidly fatal if not recognized early and managed appropriately. With increasing use of ICIs globally for various indications, this entity is likely to be seen more frequently in acute-care settings. Therefore, it is important for physicians to be aware of this entity and consider it as a differential diagnosis of new-onset anemia and jaundice in patients on immunotherapy regardless of the number of cycles. Early specialist involvement and prompt initiation of immunosuppressants and other supportive care measures is vital to ensuring good outcomes.

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Institution Where Work Was Done

Basildon University Hospital, Nethermayne, Basildon, United Kingdom.

Consent Declaration

Written consent was obtained from next-of-kin (wife), as patient is now dead.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Darvin P, Toor SM, Sasidharan Nair V, Elkord E. Immune checkpoint inhibitors: Recent progress and potential biomarkers. Exp Mol Med. 2018;50(12):1-11
2. Schaub J, Tang SC. Beyond checkpoint inhibitors: The three generations of immunotherapy. Clin Exp Med. 2025;25(1):43
3. Flynn JP, Gerriets V. Pembrolizumab. [Updated 2023 Jun 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK546616/
4. Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): A randomised, placebo-controlled, double-blind, phase 3 clinical trial: Lancet, 2020; 396(10265);1817-28
5. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: Pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. J Clin Oncol. 2019;37(7):537-46
6. Leaf RK, Ferreri C, Rangachari D, et al. Clinical and laboratory features of autoimmune hemolytic anemia associated with immune checkpoint inhibitors. Am J Hematol. 2019;94(5):563-74
7. Ogawa K, Ito J, Fujimoto D, et al. Exacerbation of autoimmune hemolytic anemia induced by the first dose of programmed death-1 inhibitor pembrolizumab: A case report. Invest New Drugs. 2018;36(3):509-12
8. Baek DW, Chae YS. Pembrolizumab-related autoimmune hemolytic anemia in a patient with metastatic lung adenocarcinoma: A case report. Yeungnam Univ J Med. 2021;38(4):366-70
9. Johnstone P, Khan O. Pembrolizumab-associated autoimmune haemolytic anaemia. BMJ Case Rep. 2019;12(10):e229064
10. Hwang SR, Saliba AN, Wolanskyj-Spinner AP. Immunotherapy-associated autoimmune hemolytic anemia. Hematol Oncol Clin North Am. 2022;36(2):365-80
11. Delanoy N, Michot JM, Comont T, et al. Haematological immune-related adverse events induced by anti-PD-1 or anti-PD-L1 immunotherapy: A descriptive observational study. Lancet Haematol. 2019;6:e48-57
12. Michot JM, Lazarovici J, Tieu A, et al. Haematological immune-related adverse events with immune checkpoint inhibitors, how to manage? Eur J Cancer. 2019;122:72-90
13. Tanios GE, Doley PB, Munker R. Autoimmune hemolytic anemia associated with the use of immune checkpoint inhibitors for cancer: 68 cases from the Food and Drug Administration database and review. Eur J Haematol. 2019;102:157-62
14. Haanen J, Obeid M, Spain L. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(12):1217-38
15. Puzanov I, Diab A, Abdallah K, et al. Society for Immunotherapy of Cancer Toxicity Management Working Group. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017;5(1):95
16. Khan U, Ali F, Khurram MS, et al. Immunotherapy-associated autoimmune hemolytic anemia. J Immunother Cancer. 2017;5:15
17. Hasanov M, Konoplev SN, Hernandez CMR. Nivolumab-induced cold agglutinin syndrome successfully treated with rituximab. Blood Adv. 2018;2(15):1865-68
18. Smithy JW, Pianko MJ, Maher C, et al. Checkpoint blockade in melanoma patients with underlying chronic lymphocytic leukemia. J Immunother. 2021;44:9-15

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