Journal of Medical Case Reports

CASE REPORT

Open Access

Treatment-related hemophagocytic lymphohistiocytosis due to atezolizumab: a case report and review of the literature

Jaime Rubio-Perez[1*†], Ángel Ricardo Rodríguez-Perez[1*†], María Díaz-Blázquez[2], Victor Moreno-García[1,3] and Manuel Dómine-Gómez[1]

Abstract

Background: Immune checkpoint inhibitors avoid inhibition of T-cell responses, upregulating antitumor immune response. Moreover, a dysregulation with hyperactive immune response can be caused, some of them underdiagnosed. Hemophagocytic lymphohistiocytosis is a rare and often fatal syndrome of uncontrolled and ineffective hyperinflammatory response that triggers an inflammatory cascade that can lead in many cases to death.

Case presentation: We report the case of a 67-year-old Caucasian man with stage IV lung adenocarcinoma who developed hemophagocytic lymphohistiocytosis after initiation of atezolizumab, an antagonist of programmed death-ligand 1. Even with early diagnosis and proper treatment, death occurs in approximately half of all cases reported.

Conclusion: Key markers are needed to better identify patients at risk of developing severe immune-related adverse events. In addition to key markers, a higher degree of suspicion and early intervention are needed to improve outcomes in acquired hemophagocytic lymphohistiocytosis, especially with the increasingly and expanding use of immune activation.

Keywords: HLH, IrAE, Pharmacovigiliance, ICI

Background

It is now being seen, with the increasing number of tumor-related cases, that the use of immunotherapy is becoming more popular. An increase in the number of unknown immune-related adverse events (IrAEs) has been observed too, with secondary hemophagocytic lymphohistiocytosis (sHLH) being one of the most underrecognized and underreported of them all [1]. Immune checkpoint inhibitor (ICI) therapies exert their therapeutic effects by invigorating and stimulating an antitumor effect by CD8 T-cells. Off-target CD8 T-cell activation can trigger organ-limited damage or multiorgan failure as IrAE. Although the rate is low, in some cases this can be a life-threatening situation [2]. Besides, HLH syndrome is a hyperinflammatory reaction caused by uncontrolled activation of immune cells which results in a "cytokine storm" with progressive tissue injury and multiorgan dysfunction that, without treatment, causes death [3]. Depending on the etiology, it is classified as primary (due to genetic errors causing cytotoxic function defects) or secondary/acquired [1]. The different causes described in literature are immune dysregulation triggered by (mostly hematological) malignancies, different infections including novel severe acute respiratory syndrome coronavirus

†Jaime Rubio-Perez and Ángel Ricardo Rodríguez-Perez contributed equally to this work.

*Correspondence: jaime.rubiop@quironsalud.es; angel.rodriguezp@fjd.es

[1] Medical Oncology Department, University Hospital Fundacion Jimenez Diaz, Instituto de investigación sanitaria FJD, Madrid, Spain
Full list of author information is available at the end of the article

2 (SARS-CoV-2), or autoimmune diseases. Furthermore, it is also called macrophage activation syndrome (MAS). Some cases are induced by drug reactions (including chemotherapy), while in others it is caused by a combination of the aforementioned factors [1, 3]. sHLH is well documented in a small number of case reports [4–25], and a cohort of individual safety reports in patients treated with immune checkpoint inhibitors [26].

Different clinical criteria have been described to identify HLH. In 1991, the International Histiocyte Society established the first criteria, which they prospectively validated from 1994 to 2004 but only for the pediatric population, thus these criteria were designed for primary HLH [27]. Since then, it has been assumed by consensus that these criteria can be applied to diagnose adult patients, too. When meeting five out of the eight criteria, the clinical diagnosis is highly probable. In 2014, a probability score based on a previous web-based, international Delphi study was described and retrospectively validated in adults, being named the H-score. This scale includes several clinical and analytical variables scored according to the value presented, giving a final score and associated probability of the syndrome [28]. Determining the H-score may be a preferable approach, and it can be easily obtained using an online calculator [29]. Potential cutoffs range between 138 and 169, the latter accurately classifying 90% of patients.

Case presentation

We report the case of a 67-year-old Caucasian man who was reported to be an active smoker. His oncological history included immune thrombocytopenic purpura (ITP) as a paraneoplastic syndrome with 7000 platelets/mcL, associated with a 4.6-cm lung carcinoma as an incidental diagnosis. Diagnostic testing was performed, ruling out syphilis, hepatitis, and human immunodeficiency virus (HIV) infection, without gamma alteration in serum protein electrophoresis or any blood smear findings. No further autoantibody tests were performed. Corticosteroids were administered during 1 week at 1 mg/kg of methylprednisolone doses together with intravenous immunoglobulins during 5 days, with complete resolution of ITP.

After surgery, stage IIB (pT2aN1), moderately differentiated nonkeratinizing squamous cell carcinoma was confirmed. Surgical margins were affected, thus treatment was completed with concurrent weekly docetaxel with radiotherapy with good tolerance. Six months after initial presentation, early progression was evidenced with pleural thickening and pleural effusion. The pathological study was completed with no targeted mutations found and with programmed death-ligand 1 (PD-L1) <1% in tumor cells and 25% in stroma cells by 22C3 immunohistochemistry assay. First-line chemotherapy with carboplatin and paclitaxel was started, with partial response after receiving six cycles. Eighteen months after finishing first-line chemotherapy, with maintained response, new pleural progression was evidenced, as confirmed by positron emission tomography (PET) scan. It was thus decided to start a second line with atezolizumab (an anti-PD-L1 antibody).

Two weeks after receiving immunotherapy, he presented to the emergency room with severe dyspnea accompanied by intense asthenia, myalgia, and fever of 39 °C. He denied contact with people suffering coronavirus disease 2019 (COVID19) infection. Upon presentation, he was conscious and alert with all neurological functions preserved, hemodynamically stable, tachypneic, with 93% oxygen saturation in room air. He looked pale and had bruises on both arms on physical examination. Painless hepatomegaly and splenomegaly stood out, and auscultation revealed an abolition of left lung sounds. A blood test confirmed moderate pancytopenia, glomerular filtration rate of 50 ml/minute (previously normal), an increase in acute-phase reactants (C-reactive protein and ferritin), and elevated levels of D-dimer >20 times normal value (Table 1). A computerized angiotomography was performed with no signs of pulmonary thromboembolism, neither lung infiltrates nor pleural effusion.

During the next 24 hours, he started vomiting with an altered level of consciousness with drowsiness. He had miotic pupils, without other signs of neurological dysfunction. On examination, he had developed progressive jaundice with abdominal pain in the right flank. A few hours later, he suffered a tonic–clonic seizure.

Initially, COVID-19 was rejected, and blood tests were repeated at 24 hours, revealing pancytopenia, hyperbilirrubinemia, and hypertransaminitis. Head computed tomography (CT) was performed with no alterations, and a blood smear showed anisocytosis with some elliptocytes. The patient was admitted to the intensive care unit (ICU) and intubated due to neurological deterioration with a score of 8 on the Glasgow scale. After assessing the risks and benefits, no lumbar puncture was done. Empirical broad-spectrum antibiotic treatment was started, but the possibility that it was a hemophagocytic syndrome was raised and a differential diagnosis was started. Serologies were negative for HSV1-2, CMV, EBV, HIV, HBV, HCV, and HLTV-1 viruses. Elevated IL-6 (19.4 pg/mL) and CD25 (6516 U/m) were found with normal angiotensin-converting enzyme levels. He had 110 CD4 and 620 CD8 lymphocytes with very low CD4/CD8 ratio of 0.18. H-score for hemophagocytic syndrome was 256 points (> 99% probability). Given the high suspicion, treatment with high-dose corticosteroids was initiated using 20 mg dexamethasone bolus as 1 mg/kg equivalent of methylprednisolone since day 1. Finally, bone marrow

biopsy was performed, showing reactive hypercellularity, hemophagocytosis, and dysplastic signs in megakaryocytic and erythroid reactive lines, thus confirming hemophagocytic syndrome (Fig. 1A).

Severe pancytopenia persisted despite transfusions, so it was decided to initiate tocilizumab at 8 mg/kg, without success, so we continued with anakinra without analytical or neurological improvement during day 2. Treatment with mycophenolate mofetil was added on day 3 for the next two days and finally, 5 days after admission, etoposide 100 mg/m^2.

Without any clinical improvement, magnetic resonance imaging (MRI) was performed, showing extensive white matter damage (Fig. 2). To study the degree of brain involvement, an electroencephalogram was done and revealed symmetrical background activity consisting of a 2–4 Hz, bilateral, irregular, low-voltage rhythm with no reactivity to eyelid closure–opening, corresponding to diffuse and severe degree brain involvement. Hence, it was decided to limit the therapeutic effort. Finally, the patient died 1 week after presentation.

Autopsy of the patient was performed, confirming the syndrome with hemophagocytic lymphohistiocytosis affecting the bone marrow, lymph nodes, liver, and spleen (Fig. 1B, C) as well as the central nervous system.

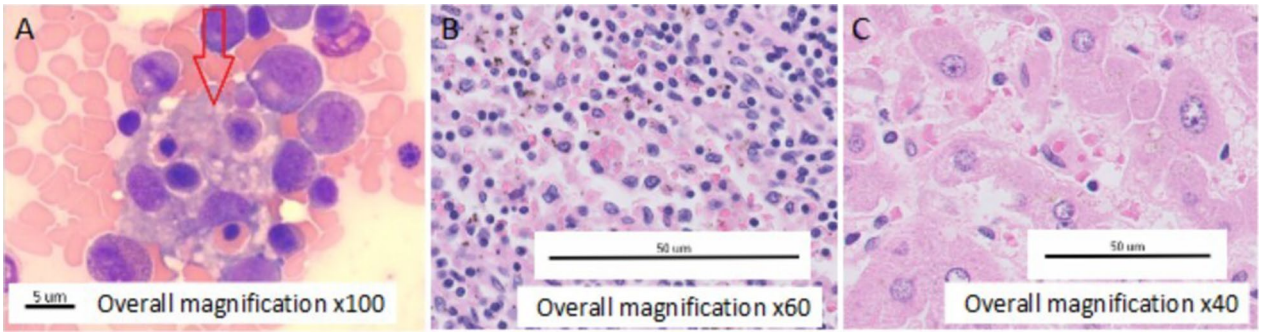

Fig. 1 **A** Bone marrow biopsy with reactive hypercellularity, hemophagocytosis (red arrow), and dysplastic signs in megakaryocytic and erythroid reactive lines, confirming hemophagocytic syndrome. **B**, **C** Hepatic and spleen tissue with hemophagocytosis

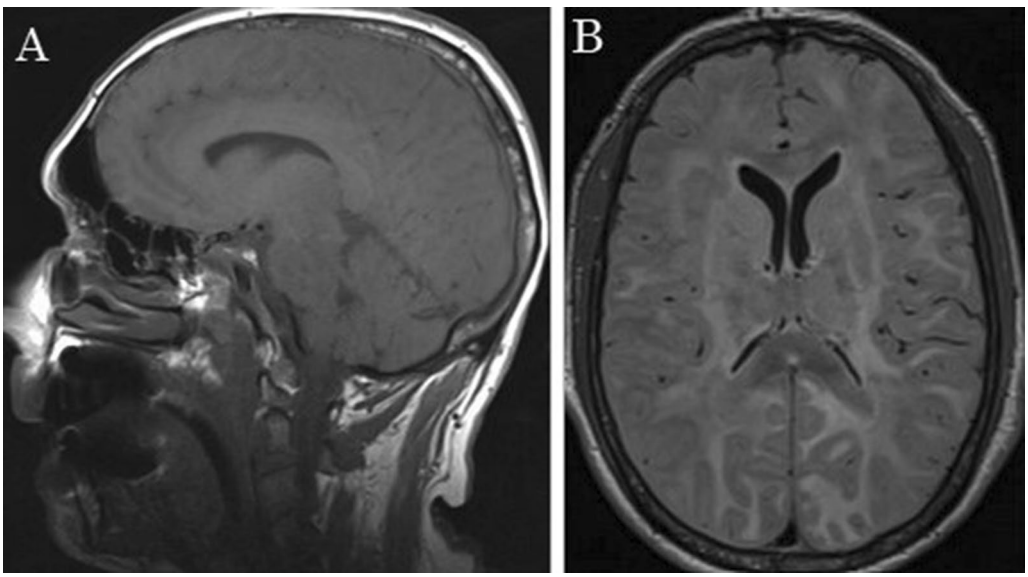

Fig. 2 MRI T1 and T2 sequences with extensive involvement of supra- and infratentorial white matter, with bilateral and asymmetric damage, deep and superficial, of corpus callosum and internal capsules. **A** sagittal plane. **B** axial plane

Table 1 Laboratory values along the clinical course, upon presentation, and after the different therapeutic strategies

	Presentation	Day 3 (48 hours after steroids)	Day 5 after MMF, anakinra, tocilizumab, and etoposide
White blood cells, k/cumm	2.58	3.08	1.92
Lymphocytes, k/cumm	1.2	2.3	0.7
Hemoglobin, g/dL	7.1	7.4	6.4
Reticulocytes (absolute)	0.0128		
Platelets, k/cumm	25	23	17
AST, U/mL	122		
ALT, U/mL	108	201	305
Creatinine, mg/dL	1.16	0.9	0.7
Total bilirubin, mg/dL	3.2	1.8	1.3
Indirect bilirubin, mg/dL	0.1	0.4	0.4
Triglycerides, mg/dL	151		
CRP, mg/dL	14.18	5.1	1.4
Ferritin, ng/dL	7035		
Fibrinogen, mg/dL	507	244	133
D-dimer	9042	8309	7357
sIL-2R (CD25), U/mL	6516		
IL-6, pg/dL	19.4		

K/cumm cells per microliter, *MMF* mycophenolate mofetil, *g/dL* grams per deciliter, *AST* aspartate aminotransferase, *U/mL* units per mililiter, *ALT* alaline transaminase, *mg/dL* miligrams per deciliter, *CRP* C reactive protein, *ng/mL* nanograms per mililiter, *sIL-2R* soluble interleukin-2 receptor, *CD25* cluster of differentiation protein 25, *IL-6* interleukin 6, *pg/ml* picograms per mililiter

Discussion

The major challenge in this case was the difficult differential diagnostic between HLH syndrome, an infection by different possible microorganisms including COVID-19 in the midst of the pandemic, together with ruling out other immune-related adverse events at the beginning of atezolizumab treatment. To the best of the authors' knowledge, this is the first case report describing this rare systemic toxicity with sole use of atezolizumab as cancer therapy. Another case has been described, with the use of combination chemotherapy with carboplatin and nab-paclitaxel with atezolizumab, and the addition of autoimmune hemolytic anemia to sHLH [22]. As in the previous case report, our case is alarming due to the fast development of this deadly complication, after a single infusion of atezolizumab. One limitation is that we did not study initial autoantibodies for the study of the paraneoplastic ITPI presentation of our case, which could have shed light on the possible correlation between preexisting autoantibodies as biomarkers for the risk of developing hematological or other immune-related toxicities [30, 31].

Survival in adult malignancy sHLH ranges from 20% to 88%, considering refractoriness, secondary infections due to heavy immunosuppression, and progression of the underlying cancer disease [32]. Nevertheless, in the context of therapy-related sHLH with ICI, good outcomes have been reported only with the use of high doses of steroids [9, 11], probably at an early phase of sHLH and because of their use for other immune toxicities (Table 2) [33]. Major contributors to fatal outcome appear to be delayed administration of treatment because of poor recognition of unspecific symptoms and the presence of neurological involvement [3].

By the time the HLH-2004 criteria are met, the patient may be beyond the point of optimal intervention. Furthermore, the H-score may be less specific for oncological patients, given baseline cytopenia and/or transaminitis due to previous therapy regimens, chemo-immunotherapy combination or metastasis, as could happen with organomegaly, too. Therefore, the trend among clinicians is to initiate therapy before traditional diagnostic criteria are met. Besides, the gradual introduction of new drugs based on clinical presentation and cytokine profile has resulted in the best adult survival rate reported in literature [34]

Activated immune effector cells and the local and systemic effects of inflammatory cytokines such interferon-gamma (IFN-g), tumor necrosis factor (TNF)-a, and interleukins (IL) 1b, 6, 8, 10, and 18 are responsible for the HLH pathogenesis [1]. Therefore, new strategies are under clinical development such as new targeted therapies such as ruxolitinib, a JAK 1-2 multicytokine receptor inhibitors [35] or drugs that block IL-1 (especially in the context of MAS [1, 33, 36]) or IL-6 [36].

Table 2 List of case reports of hemophagocytic lymphohistiocytosis in oncological patients with immune checkpoint inhibitors

Ref.	Immunotherapy	Primary tumor	Bone marrow biopsy	Neurology symptoms	Treatment	Clinical outcomes
[4]	Nivolumab	NSCLC	+	No	Steroids	Improvement
[5]	Nivolumab/ Ipilimumab/ Avelumab (3 cases, monotherapy)	Melanoma/ Merkel cell carcinoma	+/−	Unknown	Steroids	Death/ improvement
[6]	Pembrolizumab	Bladder carcinoma	+	Unknown	Steroids and etoposide	Unknown
[7]	Ipilimumab and nivolumab	Melanoma	Not done	No	Steroids and mycophenolate mofetil	Improvement
[8]	Pembrolizumab	Melanoma	Not done	No	Steroids	Improvement
[9]	Ipilimumab and nivolumab	Melanoma	+	No	Steroids	Improvement
[10]	BRAF inhibitors sequential after pembrolizumab	Melanoma	Not done	No	Steroids	Improvement
[11]	Ipilimumab sequential after pembrolizumab	Melanoma	+	No	Steroids and etoposide	Death
[12]	Pembrolizumab	NSCLC	+	No	Steroids	Improvement
[13]	Nivolumab	NSCLC	Not done	No	Steroids and mycophenolate mofetil	Improvement
[14]	Pembrolizumab	Thymic cancer	+	Yes	Steroids, IVIG, anakinra	Death
[15]	Pembrolizumab	Prostate cancer	+	No	Steroids+ plasmapheresis + etoposide + tacrolimus	Improvement
[16]	Pembrolizumab	Breast cancer	Not done	No	Steroids	Improvement
[17]	Nivolumab and anti-IDO	Glioblastoma	+	Yes	Steroids	Death
[18]	Pembrolizumab	Head and neck	+	No	Steroids and etoposide	Improvement
[19]	Pembrolizumab	NSCLC	+	No	Steroids	Improvement
[20]	Ipilimumab and nivolumab	Melanoma	+	No	Steroids, tocilizumab	Improvement[
[21]	Pembrolizumab	Pulmonary sarcomatoid carcinoma	Not done	No	Steroids	Death
[21]	Ipilimumab + nivolumab	Melanoma	Not done	No	Steroids + etoposide + IVIG + tocilizumab	Improvement
[21]	Ipilimumab + nivolumab	Melanoma	+	No	Steroids + etoposide	Death
[21]	Ipilimumab + nivolumab	Melanoma	−	No	Steroids	Improvement
[21]	Ipilimumab + nivolumab	Melanoma	+	No	Steroids	Improvement
[22]	Atezolizumab + chemotherapy	NSCLC	+	No	Steroids	Improvement
[23]	Pembrolizumab	NSCLC	+	No	Steroids	Improvement
[24]	Pembrolizumab	NSCLC	+	No	Steroids	Improvement
[24]	Pembrolizumab	NSCLC	Not done	No	Steroids	Improvement
[25]	Pembrolizumab	NSCLC	+	No	Steroids + etoposide	Improvement

NSCLC non-small cell lung cancer, *antiIDO* anti Indoleamine 2,3-Dioxygenase, *IVIG* intravenousimmunoglobulins

Immune-activating therapies for cancer may induce a systemic IrAE named "cytokine release syndrome" (CRS), caused by overactivation of T-cells upon recognition of its target. The average time to CRS is the first week after administration of immunotherapy. This syndrome is characterized by the presence of pyrexia, tachycardia, hypotension, tachypnea, myalgia, transient confusion, delirium, aphasia, and seizures, among other symptoms mimicking sHLH in our case, and it is secondary to high amounts of TNF-a and IL-6 being released [37]. This differences in the cytokine profile between CRS and sHLH may be owing to differences in the immune cell subtypes stimulated and the different cytokines produced. Accordingly, new therapies focused against T-cells are being evaluated in this context, such as alemtuzumab, an antibody directed to CD-52 [38], or CD25.

Finally, we followed the latest guidelines regarding sHLH management [1, 27], which suggests that patients with severe active disease or neurological involvement, despite steroids, cyclosporine, or mycophenolate mofetil, and/or anakinra, may benefit from a reduced

dose of etoposide (50–100 mg/m^2 once weekly), to remove activated T cells and suppress inflammatory cytokine production [39]. We tried this, and added tocilizumab also, although it does not cross the blood–brain barrier, given the ICI trigger and the elevation of IL-6 found, but without any success. This may be due to the late diagnosis and the rapid worsening with extensive neurological involvement.

Conclusion

With the increasing use of novel agents such as checkpoint inhibitors, the toxicity profile of drugs has changed and uncommon syndromes are more frequent nowadays, being more common in patients with comorbidity or treated using drug combinations. Recently, sHLH has been described in patients receiving ICI therapy more frequently. It is considered a rare adverse event, but may be underdiagnosed. It can develop from the first few weeks to months after treatment initiation and can occur at any time, even after discontinuation. Finding hemophagocytosis is neither pathognomonic nor required for diagnosis, and it is often not detected at initial presentation. Early intervention is critical to prevent progression and improve the patient's condition, so premature steroid initiation generally carries a favorable prognosis. In cases where there is no improvement with steroids, aggressive supportive management is necessary with intensification of therapy, following multi-immune suppressive drug protocols and adding interleukin-targeted therapies, with previous poor results reported. While the potential impact of such procedures is recognized, an optimal regimen sequence still has to be found, and the development of specific protocols for these patients is necessary.

Abbreviations

ICI: Immune checkpoint inhibitors; HLH: Hemophagocytic lymphohistiocytosis; PD-L1: Programmed death-ligand 1; IrAE: Immune-related adverse events; sHLH: Secondary hemophagocytic lymphohistiocytosis; MAS: Macrophage activation syndrome; ITP: Immune thrombocytopenic purpura; IFN-g: Interferon-gamma; TNF-a: Tumor necrosis factor; IL: Interleukin.

Acknowledgements

We thank Dr. Emilia Rosas Carvajal for intensive care unit admission and care and Ms Brittney Lockhart for proofreading.

Author contributions

J.R and A.R writing—original draft preparation. M.B. conceptualization and image acquisition. V.M and M.D writing—review and editing. M.D. funding acquisition. All authors read and approved the final manuscript.

Funding

No funds were needed to manage this patient care neither for manuscript realization. Publishing fees will be financed by our institution health research institute: Instituto de Investigación Sanitaria Fundación Jímenez Díaz (IIS-FJD)

Availability of data and materials

Information was obtained from the patient´s medical history records, images were from authorized investigations. Published reports were accessed from medical journals, and safety signals gathered from public access pharmacovigilance databases: Eudra (https://www.adrreports.eu/en/search.html), Vigibase (http://www.vigiaccess.org).

Declarations

Ethics approval and consent to participate

We obtained informed consent from the patient's guardian. As a case report, ethical clearance was not requested.

Consent of publication

Written informed consent was obtained from the patient's next of kin for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare no conflicts of interest.

Author details

[1]Medical Oncology Department, University Hospital Fundacion Jimenez Diaz, Instituto de investigación sanitaria FJD, Madrid, Spain. [2]Anatomic Pathology Unit Department, University Hospital Fundacion Jimenez Diaz, Madrid, Spain. [3]START Madrid-FJD, University Hospital Fundacion Jimenez Diaz, Madrid, Spain.

Received: 3 August 2021 Accepted: 21 August 2022
Published online: 04 October 2022

References

1. Griffin G, Shenoi S, Hughes GC. Hemophagocytic lymphohistiocytosis: an update on pathogenesis, diagnosis, and therapy. Best Pract Res Clin Rheumatol. 2020;34: 101515.
2. Ramos-Casals M, Brahmer JR, Callahan MK, *et al*. Immune-related adverse events of checkpoint inhibitors. Nat Rev Dis Primers. 2020;6:38.
3. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, *et al*. Adult haemophagocytic syndrome. Lancet. 2014;383:1503–16.
4. Takeshita M, Anai S, Mishima S, *et al*. Coincidence of immunotherapy-associated hemophagocytic syndrome and rapid tumor regression. Ann Oncol. 2017;28:186–9.
5. Malissen N, Lacotte J, Du-Thanh A, *et al*. Macrophage activation syndrome: a new complication of checkpoint inhibitors. Eur J Cancer. 2017;77:88–9.
6. Shah D, Shrestha R, Ramlal R, Hatton J, Saeed H. Pembrolizumab associated hemophagocytic lymphohistiocytosis. Ann Oncol. 2017;28:1403.
7. Satzger I, Ivanyi P, Länger F, *et al*. Treatment-related hemophagocytic lymphohistiocytosis secondary to checkpoint inhibition with nivolumab plus ipilimumab. Eur J Cancer. 2018;93:150–3.
8. Sadaat M, Jang S. Hemophagocytic lymphohistiocytosis with immunotherapy: brief review and case report. J Immunotherapy Cancer. 2018;6:49.
9. Hantel A, Gabster B, Cheng JX, *et al*. Severe hemophagocytic lymphohistiocytosis in a melanoma patient treated with ipilimumab + nivolumab. J Immunotherapy Cancer. 2018;6:73.
10. Sasaki K, Uehara J, Iinuma S, *et al*. Hemophagocytic lymphohistiocytosis associated with dabrafenib and trametinib combination therapy following pembrolizumab administration for advanced melanoma. Ann Oncol. 2018;29:1602–3.
11. Michot J-M, Pruvost R, Mateus C, *et al*. Fever reaction and haemophagocytic syndrome induced by immune checkpoint inhibitors. Ann Oncol. 2018;29:518–20.
12. Okawa S, Kayatani H, Fujiwara K, *et al*. Pembrolizumab-induced autoimmune hemolytic anemia and hemophagocytic lymphohistiocytosis in non-small cell lung cancer. Intern Med. 2019;58(5):699–702.
13. Honjo O, Kubo T, Sugaya F, *et al*. Severe cytokine release syndrome resulting in purpura fulminans despite successful response to nivolumab

therapy in a patient with pleomorphic carcinoma of the lung: a case report. J Immunother Cancer. 2019;7(1):97.
14. Laderian B, Koehn K, Holman C, *et al*. Association of hemophagocytic lymphohistiocytosis and programmed death 1 checkpoint inhibitors. J Thorac Oncol. 2019;14:e77–8.
15. Lorenz G, Schul L, Bachmann Q, *et al*. Hemophagocytic lymphohistiocytosis secondary to pembrolizumab treatment with insufficient response to high-dose steroids. Rheumatology. 2019;58:1106–9.
16. Al-Samkari H, Snyder GD, Nikiforow S, *et al*. Haemophagocytic lymphohistiocytosis complicating pembrolizumab treatment for metastatic breast cancer in a patient with the *PRF1A91V* gene polymorphism. J Med Genet. 2019;56:39–42.
17. Thummalapalli R, Heumann T, Stein J, *et al*. Hemophagocytic lymphohistiocytosis secondary to PD-1 and IDO inhibition in a patient with refractory glioblastoma. Case Rep Oncol. 2020;13:508–14.
18. Kalmuk J, Puchalla J, Feng G, *et al*. Pembrolizumab-induced hemophagocytic lymphohistiocytosis: an immunotherapeutic challenge. Head Neck. 2020;5:3.
19. Takahashi H, Koiwa T, Fujita A, *et al*. A case of pembrolizumab-induced hemophagocytic lymphohistiocytosis successfully treated with pulse glucocorticoid therapy. Respir Med Case Rep. 2020;30: 101097.
20. Özdemir BC, Latifyan S, Perreau M, *et al*. Cytokine-directed therapy with tocilizumab for immune checkpoint inhibitor-related hemophagocytic lymphohistiocytosis. Ann Oncol. 2020;31(12):1775–8.
21. Dupré A, Michot J, Schoeffler A, *et al*. Haemophagocytic lymphohistiocytosis associated with immune checkpoint inhibitors: a descriptive case study and literature review. Br J Haematol. 2020;189:985–92.
22. Endo Y, Inoue Y, Karayama M, *et al*. Marked, lasting disease regression and concomitantly induced autoimmune hemolytic anemia and hemophagocytic lymphohistiocytosis in a patient with lung adenocarcinoma and autoantibodies receiving atezolizumab plus chemotherapy: a case report. JTO Clin Res Rep. 2021;3(1): 100263.
23. Okawa S, Kayatani H, Fujiwara K, *et al*. Pembrolizumab-induced autoimmune hemolytic anemia and hemophagocytic lymphohistiocytosis in non-small cell lung cancer. Intern Med. 2019;58(5):699–702.
24. Kurozumi A, Takahashi H, Watanabe T, *et al*. Two cases of lung cancer with hemophagocytic lymphohistiocytosis caused by immune checkpoint inhibitors. Thorac Cancer. 2021;12(10):1625–8.
25. Yu Akagi Y, Awano N, Inomata M, *et al*. Hemophagocytic lymphohistiocytosis in a patient with rheumatoid arthritis on pembrolizumab for lung adenocarcinoma. Intern Med. 2020;59:1075–80.
26. Noseda R, Bertoli R, Müller L, *et al*. Haemophagocytic lymphohistiocytosis in patients treated with immune checkpoint inhibitors: analysis of WHO global database of individual case safety reports. J Immunotherapy Cancer. 2019;7:117.
27. Henter J-I, Horne A, Aricó M, *et al*. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48:124–31.
28. Fardet L, Galicier L, Lambotte O, *et al*. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome: score for reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014;66:2613–20.
29. https://www.mdcalc.com/hscore-reactive-hemophagocytic-syndrome. December 2021.
30. Les I, Martínez M, Narro A, *et al*. Association of immune-related adverse events induced by nivolumab with a battery of autoantibodies. Ann Med. 2021;53:762–9.
31. Toi Y, Sugawara S, Sugisaka J, *et al*. Profiling preexisting antibodies in patients treated with anti–PD-1 therapy for advanced non-small cell lung cancer. JAMA Oncol. 2019;5(3):376–83.
32. Tamamyan GN, Kantarjian HM, Ning J, *et al*. Malignancy-associated hemophagocytic lymphohistiocytosis in adults: relation to hemophagocytosis, characteristics, and outcomes: secondary HLH in adults. Cancer. 2016;122:2857–66.
33. La Rosée P, Horne A, Hines M, *et al*. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood. 2019;133:2465–77.
34. Kumar B, Aleem S, Saleh H, *et al*. A personalized diagnostic and treatment approach for macrophage activation syndrome and secondary hemophagocytic lymphohistiocytosis in adults. J Clin Immunol. 2017;37:638–43.
35. Ahmed A, Merrill SA, Alsawah F, *et al*. Ruxolitinib in adult patients with secondary haemophagocytic lymphohistiocytosis: an open-label, single-centre, pilot trial. Lancet Haematol. 2019;6:e630–7.
36. Minoia F, Davì S, Horne A, *et al*. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients: macrophage activation syndrome in systemic JIA. Arthritis Rheumatol. 2014;66:3160–9.
37. Rodríguez Pérez Á, Campillo-Davo D, Van Tendeloo VFI, *et al*. Cellular immunotherapy: a clinical state-of-the-art of a new paradigm for cancer treatment. Clin Transl Oncol. 2020;22:1923–37.
38. Marsh RA, Allen CE, McClain KL, *et al*. Salvage therapy of refractory hemophagocytic lymphohistiocytosis with alemtuzumab: alemtuzumab for refractory HLH. Pediatr Blood Cancer. 2013;60:101–9.
39. Gavand P-E, Serio I, Arnaud L, *et al*. Clinical spectrum and therapeutic management of systemic lupus erythematosus-associated macrophage activation syndrome: a study of 103 episodes in 89 adult patients. Autoimmun Rev. 2017;16:743–9.

Publisher's Note