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

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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 hyper-inflammatory 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, Pharmacovigilance, ICI
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 Histiocytosis 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 targetted 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 mictotic 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, hyperbilirubinemia, 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) 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/m².

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.

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**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
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-γ), 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 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 milliliter, ALT alanine transaminase, mg/dL milligrams per deciliter, CRP C reactive protein, ng/mL nanograms per milliliter, sIL-2R soluble interleukin-2 receptor, CD25 cluster of differentiation protein 25, IL-6 interleukin 6, pg/ml picograms per milliliter
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/m² 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. VM 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 Jiménez 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.adreports.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.

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Received: 3 August 2021   Accepted: 21 August 2022

Published online: 04 October 2022

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