Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome during treatment with the bivalent CD20xCD3 bispecific antibody glofitamab

Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) is a life-threatening clinical entity associated with T-cell redirecting treatments and first described after chimeric antigen receptor-T-cell infusions.[1] More recently, cases of IEC-HS have been reported following treatment with bispecific antibodies (BsAb), including epcoritamab, mosunetuzumab, and teclistamab.[2-4] A very recent study estimated the incidence rate of BsAb-associated IEC-HS to be 0.7%.[5]

Glofitamab is a BsAb with a unique 2:1 structure that binds bivalently to CD20 on B cells and monovalently to CD3 on T cells, offering enhanced avidity and potency compared to other formats.[6,7] Despite its extensive use in treating diffuse large B-cell lymphoma, real-world surveys and database studies have not reported any cases of IEC-HS associated with its administration.[2-4] Here, we present the first documented case of IEC-HS following treatment with glofitamab. Data were collected and the patient's informed consent was obtained according to LYMRO-22 protocol 20/22 OSS, approved by the Ethics Committee of the Istituto Pascale (07-27-2022).

A 62-year-old woman had primary refractory non-germinal center diffuse large B-cell lymphoma unresponsive to frontline treatment with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (6 cycles, October 2023 to February 2024; International Prognostic Index score: 2) and to salvage with rituximab plus bendamustine (4 cycles, August 2024 to November 2024). Polatuzumab was not administered upfront due to regulatory restrictions, nor as salvage therapy because of the risk of perforation from extensive gastric transmural lymphoma infiltration. Re-biopsy confirmed the diagnosis of diffuse large B-cell lymphoma, and the patient was ineligible for chimeric antigen receptor-T cells because of grade 3 portal vein thrombosis. Therefore, single-agent glofitamab was initiated in December 2024.

On cycle (C)1 day (D)1, she received obinutuzumab (1,000 mg) followed by glofitamab (2.5 mg, step-up dose 1) on C1D8. On C1D15, after glofitamab step-up dose 2 (10 mg), she developed grade 1 cytokine release syndrome (CRS) which resolved with antipyretics. On C2D1, within 24 h from a full dose of glofitamab (30 mg), she experienced fever and hypotension (grade 2 CRS), treated with antipyretics and dexamethasone (10 mg twice daily), along with an episode of CRS-related atrial fibrillation that resolved with steroids.

Within 24 h after C3D1, the patient developed fever and hypoxia requiring high-flow oxygen (grade 3 CRS). She received dexamethasone 10 mg (4 times daily) and two doses of tocilizumab (8 mg/kg), leading to resolution of the CRS in 5 days followed by steroid tapering. Concomitantly, she received ganciclovir (5 mg/kg twice daily) for cytomegalovirus (CMV) reactivation (viral DNA load: 570,001 IU/mL), and azithromycin plus meropenem for documented *Campylobacter jejuni* colitis, alongside *Escherichia coli* and *Haemophilus influenzae* isolated from bronchoalveolar lavage. These examinations were prompted by bilateral consolidative lesions with an interstitial lung pattern on high-resolution computed tomography. During steroid tapering (dexamethasone 10 mg twice daily), after the resolution of CRS, the patient developed progressive thrombocytopenia, neutropenia, hypofibrinogenemia, hyperferritinemia, hypertriglyceridemia, and new-onset fever (maximum temperature 39°C). On C3D16, her platelet count was $51x10^9$/L, absolute neutrophil count $0.3x10^9$/L, fibrinogen level 75 mg/dL, ferritin level 604 ng/dL, and triglyceride concentration 433 mg/dL. On the same day (C3D16), bone marrow biopsy was negative for lymphoma involvement, but showed macrophage activation, with large CD68/PGM1$^+$ cells with debris in their cytoplasm (Figure 1A-C). Reassessment for infections revealed evidence of resolution of the colitis and absence of CMV DNA in blood samples. However, due to the persistence of multiple consolidative and ground-glass areas with a diffuse interstitial-alveolar pattern, a further bronchoalveolar lavage was performed which was negative for infections, while flow cytometry identified an activated T-cell population (CD3$^+$/CD8$^+$/CD38^{high}/HLA-DR$^+$) both in bronchoalveolar lavage fluids and bone marrow, which accounted for 11.1% and 12.4% of T-lymphocytes, respectively (Figure 1D-G). High frequencies of T cells with this activation profile have been demonstrated to be a diagnostic biomarker for distinguishing patients with active hemophagocytic lymphohistiocytosis (HLH) from those experiencing sepsis.[8] Re-evaluation with concurrent positron-emission tomography and computed tomography (PET-CT) documented a partial metabolic response (not shown). Taken together, these findings led to the diagnosis of IEC-HS based on the guidelines.[1] In our case, however, creatinine, transaminase, and bilirubin levels were within normal limits.

The patient, therefore, started treatment with the interleukin-1 receptor antagonist anakinra (100 mg twice daily) along with intravenous immunoglobulins. A week later, the fever resolved, and cytopenias and coagulopathy improved (absolute neutrophil count >$1.0x10^9$/L; platelet count >$50x10^9$/L; unsupplemented fibrinogen >100 mg/dL). The patient received granulocyte colony-stimulating factor for grade 4 neutropenia, which resolved only after anakinra improved all other laboratory parameters.

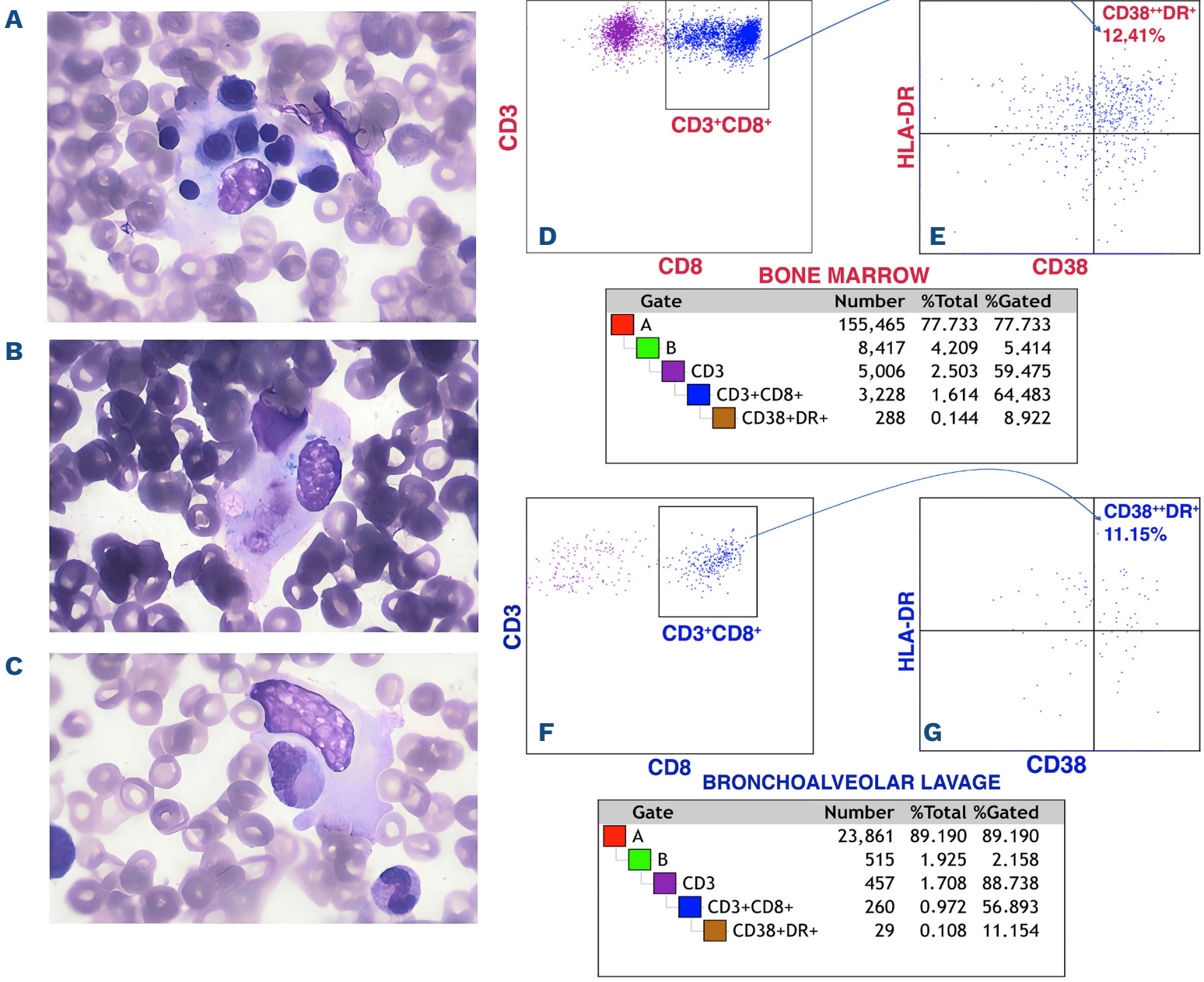

Figure 1. Macrophage activation and hemophagocytosis in bone marrow aspirate, and flow cytometric analysis of CD3⁺CD8⁺ T cells and activation markers in bone marrow and bronchoalveolar lavage. In the bone marrow aspirate, there is evidence of macrophage activation with erythrophagocytosis (A), macrophages with cellular debris (B), and initial hemophagocytosis (C) on hematoxylin and eosin stained preparations (x1,000 magnification). (D-G) In the flow cytometric analysis, total lymphocytes were initially selected based on forward scatter and side scatter characteristics and CD45 expression. From this gate, cells were plotted for CD3 *versus* CD8 to identify the CD3⁺CD8⁺ T-cell subset both in the bone marrow (D, blue population) and bronchoalveolar lavage (F, blue population). Within the CD3⁺CD8⁺ populations defined in (D) and (F), expression of activation markers CD38 and HLA-DR was assessed. The CD38⁺⁺HLA-DR⁺ activated subset is gated in the upper right quadrant both for the bone marrow (E) and the bronchoalveolar lavage fluid (G). A subset of CD38⁺⁺HLA-DR⁺ cells exceeding 7% was considered indicative of pathological T-cell activation, as reported in hemophagocytic lymphohistiocytosis.

After 2 days without further improvements, the dose of anakinra was increased to 100 mg four times daily. At best response (after 2 weeks of treatment), we observed a clinical, radiological (Figure 2) and laboratory improvement (hemoglobin 10.5 g/dL, platelet count $63x10^9$/L, absolute neutrophil count $10.5x10^9$/L, ferritin 630 ng/dL, triglycerides 185 mg/dL, fibrinogen 364 mg/dL). Three weeks after the initiation of anakinra, the patient developed a systemic infection from multidrug-resistant *Pseudomonas aeruginosa*. Despite empirical broad-spectrum antibiotics (meropenem, vancomycin) followed by targeted antimicrobials (ceftolozane/tazobactam), and anakinra dose reductions, the clinical condition rapidly worsened, requiring admission to the Intensive Care Unit, and the patient succumbed to septic shock. The clinical timeline of our patient, her laboratory parameters and treatments are summarized in Figure 3.

To the best of our knowledge, this is the first documented case of IEC-HS linked to administration of glofitamab. Secondary HLH after BsAb, while infrequent, presents several diagnostic and therapeutic challenges.

First, this potentially fatal T-cell-mediated hyperinflammatory response, eventually leading to uncontrolled macrophage transactivation, may be triggered by other conditions that frequently coexist in patients receiving BsAb, such as infections, metabolic disturbances, and the malignancy itself.[1,9] Second, during the initial phases of IEC-HS, clinical and

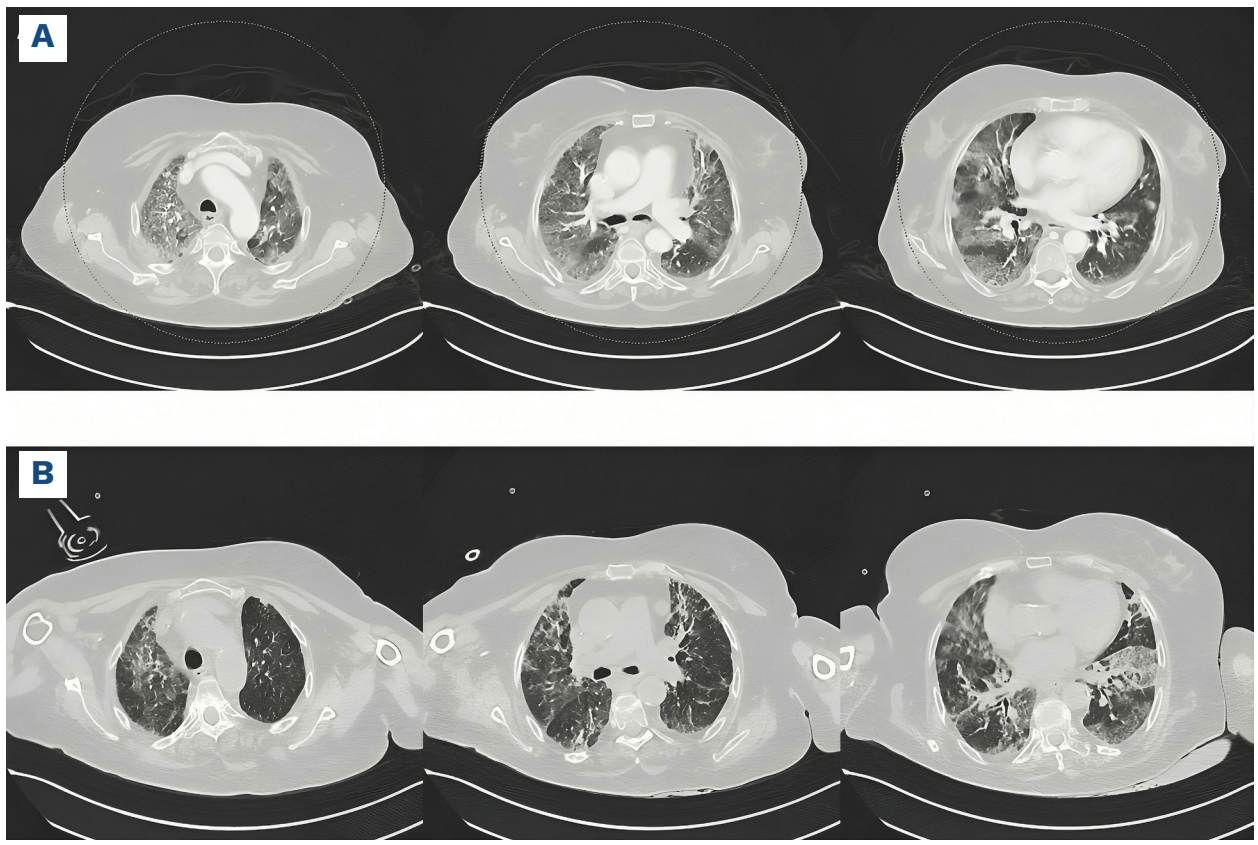

Figure 2. High-resolution computed tomography scans of immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome at diagnosis and after treatment. Bronchoalveolar lavage was performed after acquisition of the first computed tomography scan. (A, B) High-resolution computed tomography scans at diagnosis of immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (A) and after 3 weeks of treatment with anakinra (B).

laboratory features, including cytokine abnormalities, may exhibit overlapping characteristics with a severe CRS.[1]

A proposed model for IEC-HS suggests that T-cell activation and proliferation, triggered by tumor antigens, leads to the release of cytotoxic granules and tumor lysis, which in turn results in macrophage transactivation.[1] This process generates a positive feedback loop involving soluble factors such as IFN-γ, sIL-2R, IL-6, IL-10, IL-12, IL-18, IL-1β, TNF-α, IL-33, and ferritin, similarly to primary HLH.[10]

A diagnostic framework for identifying IEC-HS and grading its severity has recently been established.[1] In our patient, the co-occurrence within 72 h of cytopenias, hypofibrinogenemia, and hyperferritinemia prompted further investigations, revealing five of the six most common manifestations (hyperferritinemia, onset after CRS resolution, hypofibrinogenemia, hemophagocytosis in bone marrow and lungs, newly developed cytopenias) and four of nine accompanying manifestations (elevated lactate dehydrogenase, new fever, pulmonary infiltrates, hypertriglyceridemia) outlined in IEC-HS criteria.[1]

Since secondary HLH can be associated with multiple conditions, the diagnosis of IEC-HS must include continuous reassessment for alternative etiologies.[1] Acquired immune dysfunction and viral infections commonly trigger HLH.[10] Our patient experienced both viral and bacterial infections prior to the diagnosis of IEC-HS. However, CMV reactivation resolved before HLH development, as did the pulmonary and gastrointestinal infections. Accordingly, the reported cases of CMV-related HLH developed during the active phase of infection but never after its resolution.[11] Additionally, HLH has been associated with infections caused by intracellular pathogens or during sepsis, neither of which was present in our patient at onset. Other infectious triggers of secondary HLH, such as human immunodeficiency virus and influenza, were absent in our patient, as was Epstein-Barr virus, which was consistently ruled out by serial DNA testing.[10]

While the clinical timeline indicates T-cell redirecting treatment as the main cause of HLH in our patient, we must also recognize the predisposing role of the inflammatory environment caused by preceding infections.[5] Similarly, 'malignancy-triggered HLH' usually arises in the context of active progressive disease, PET-CT indicates that our patient was responding to treatment before HLH developed.

Emerging evidence suggests that chronic anti-IL-6 treatment in rheumatologic patients may lead to HLH and that tocilizumab might be linked to chimeric antigen receptor-related HLH.[12] This intriguing hypothesis needs to be contextualized in the efficacy-toxicity tradeoff of a critical tool for CRS management such as tocilizumab.

The diagnosis of IEC-HS was supported by flow cytometry, which identified a distinct population of activated T cells with a typical $CD8^+/CD38^{high}/HLA\text{-}DR^+$ phenotype. The evidence of >7% $CD38^{high}/HLA\text{-}DR^+$ cells among $CD8^+$ T cells differentiated HLH from sepsis, with a positive predictive value of 96% and a negative predictive value of 100%, both in pediatric and adult populations.[7,8,13] This case is unique in documenting these T-cell findings, both in bone marrow and bronchoalveolar lavage fluid.

Our patient displayed atypical IEC-HS dynamics. There were no cytopenias in the preceding cycles, and previous episodes of mild (≤ grade 3) CRS (step-up dosing and first full dose) resolved with standard management, which did not contraindicate further delivery of glofitamab. This strengthens the connection between the risk of developing IEC-HS and the severity of the nearest CRS episode, rather than the order of cycle administration.

The established first-line treatment of IEC-HS is anakinra

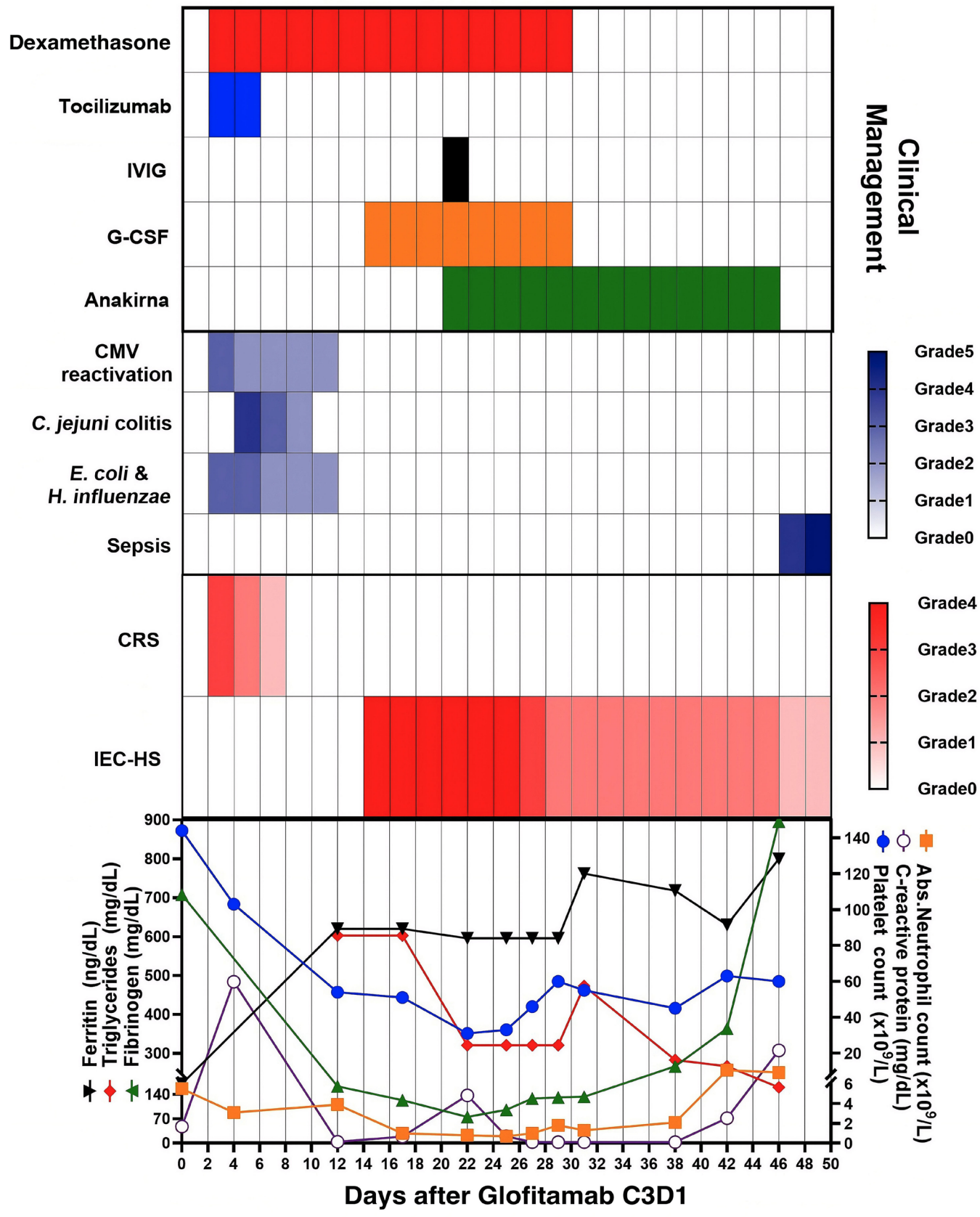

Figure 3. Trends of cytopenias, hypofibrinogenemia, hypertriglyceridemia and hyperferritinemia since glofitamab administration (C3D1), during the development and resolution of cytokine release syndrome, the onset of immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome and after the start of treatment with anakinra. IVIG: intravenous immunoglobulin; G-CSF: growth stimulating factor; CMV: cytomegalovirus; CRS: cytokine release syndrome; IEC-HS: immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome; C3D1: cycle 3 day 1; BAL: bronchoalveolar lavage; Abs.: absolute.

with or without corticosteroids.[1] Since our patient was tapering dexamethasone, we introduced anakinra (2-10 mg/kg per day) along with intravenous immunoglobulins. Although not explicitly recommended, intravenous immunoglobulins have demonstrated clinical benefits[14] and are suggested for managing secondary HLH due to their anti-inflammatory properties, ability to inhibit complement activation, blocking antibody Fc fragments and macrophage Fc receptors, and neutralize cytokines.[9] We increased the dosage of anakinra after the initial response, leading to further clinical and laboratory improvements; unfortunately, it did not prevent the fatal bloodstream infection.[1]

For refractory cases, alternatives such as ruxolitinib, emapalumab, and etoposide may be considered based on clinical and laboratory presentations.[1,15] The main 'primary' concern remains the risk of infection, necessitating ongoing monitoring and prompt intervention.[1] Despite therapeutic advancements,[1] IEC-HS mortality rates can reach 58%,[2-4] highlighting the need for further studies to improve screening, diagnosis, and management.

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Disclosures

No conflicts of interest to disclose.

Contributions

AF, AC and MB conceived and designed the study and managed the patient. DG, GF, FV, EM and SM procured data. SC, MR and MO elaborated and analyzed data. AF, RDF and AP drafted the manuscript. AF, RDF, AC and AP edited the manuscript and provided critical inputs to data interpretation. All authors reviewed and approved the final draft of the manuscript.

Data-sharing statement

Data supporting the findings of this study are available from the corresponding author, upon specific request.

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