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Hyperinflammatory differentiation syndrome with hemophagocytic lymphohistiocytosis-like features following menin inhibition in acute myeloid leukemia

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Artificial Intelligence

GitHub Copilot (version 0.67; GitHub/Microsoft; commercial software) was used for limited coding assistance in the preparation and formatting of data visualizations. The authors selected and designed the figures and determined the underlying data and analyses; AI assistance was limited to coding and formatting. All resulting figures were reviewed and verified by the authors.

Menin inhibitors (MENINi) are targeted therapies for acute leukemias with *HOX* gene dysregulation (e.g. *KMT2A*-rearranged, *NPM1*-mutated).¹ Differentiation agents like MENINi can cause differentiation syndrome (DS), marked by rapid malignant cell maturation, cytokine release, and inflammation.²

MENINi-associated DS (menin-DS) occurs in 10-20% of patients and is typically steroid-responsive.^{1,3,4} We report 3 cases of profound steroid-refractory inflammation during MENINi therapy with previously undescribed clinical features. Patients developed fevers, hypoxemia, hypotension, liver injury, and markedly elevated inflammatory markers such as ferritin, soluble IL-2 receptor α (sCD25), and CXCL9, reflecting a severe hyperinflammatory state with features overlapping with hemophagocytic lymphohistiocytosis (HLH).⁵⁻⁷ One patient additionally demonstrated hemophagocytosis in differentiated histiocytes of leukemic origin on bone marrow biopsy (BmBx).

We report a series of severe hyperinflammatory events during menin inhibitor-induced differentiation, underscoring the need for prompt inflammatory marker profiling and consideration of immunomodulatory therapy in patients with atypical or steroid-refractory menin-DS.

All 3 patients were identified from 60 patients treated with MENINi monotherapy at our center between January 2020 to June 2025. HLH-2024 criteria and HScore were used for inflammatory characterization, as descriptive frameworks given their limitations in active malignancy.⁸⁻¹⁰ Etiology was determined to be drug-associated after excluding alternative diagnoses such as disease progression, GVHD, and infection. CXCL9 and sCD25 were measured using clinically validated microfluidic ELISAs in a CLIA-certified laboratory. This project was approved by the institutional review board.

Patient 1 was a 40-year-old female with prior Burkitt lymphoma and therapy-related AML with t(11;19) *KMT2A::ELL* and *FLT3*-ITD who achieved complete remission (CR) with intensive

chemotherapy (IC) and then received allogeneic hematopoietic cell transplant (alloHCT). She relapsed 6 months later, and her AML was refractory to IC and gilteritinib. She had a history of skin and GI GVHD and was off tacrolimus and completing a prednisone taper at revumenib initiation (163mg Q12H, 12 months post-alloHCT). Her baseline marrow (12 days before revumenib) contained 98% abnormal myeloblasts. Her baseline CBC (Day 1 [D1] revumenib) showed WBC $6.8 \times 10^3/\mu\text{L}$, absolute neutrophil count (ANC) $0.1 \times 10^3/\mu\text{L}$, and 96% peripheral blasts (Figure 1). Her hemoglobin (Hgb) was 6.9 g/dL and her platelet count (PLT) was $33 \times 10^3/\mu\text{L}$.

On D16, she was hospitalized for fevers and progressive hypoxemia in the setting of myeloid differentiation. Leukocytosis reached $61 \times 10^3/\mu\text{L}$ (6% promyelocytes, 10% myelocytes, 3% metamyelocytes, 16% neutrophils, 15% monocytes, blasts to 3%). Revumenib was held. Chest CT revealed bilateral ground glass opacities. She received antimicrobials and was transferred to the ICU for mechanical ventilation. Infectious work-up was negative; hydroxyurea and dexamethasone 10 mg Q12H for suspected menin-DS led to clinical improvement, allowing extubation (D25) and transfer out of the ICU (D34). D37 BmBx showed trilineage maturing hematopoiesis without overtly increased blasts, and flow cytometry was indeterminate for measurable residual disease. D37 CBC showed WBC $0.4 \times 10^3/\mu\text{L}$, Hgb 7.0 g/dL, and PLT $32 \times 10^3/\mu\text{L}$.

On D40, fevers recurred with hypoxemia and hypotension; infectious work-up remained negative. Revumenib was resumed on D46 (113mg Q12H) but held on D51 due to Grade 3 transaminase and direct bilirubin elevations. Persistent fevers and progressive organ dysfunction prompted revumenib reinitiation at 163mg Q12H in case symptoms were disease-driven and additional biomarker profiling on D59.

D59 labs showed WBC $0.1 \times 10^3/\mu\text{L}$, Hgb 8.6 g/dL, PLT $36 \times 10^3/\mu\text{L}$, ferritin 80,867 ng/mL, triglycerides 569 mg/dL, fibrinogen 434 mg/dL, and sCD25 of 3,482 U/mL (Figure 1).

Additionally, serum IFN γ and CXCL9 were elevated at 2,069 pg/mL (normal ≤ 1.4) and 49,778 pg/mL (normal ≤ 669 pg/mL), respectively.

Due to concern for HLH, she was treated with dexamethasone (D61, 10mg Q12H), anakinra (D62, 100mg Q6H), and emapalumab (D64, 3mg/kg Q72H). Fevers improved and inflammatory markers downtrended (Figure 1). Revumenib was discontinued due to concern that it drove the hyperinflammatory state (D63).

Additionally, D64 BmBx showed increased histiocytes with intracytoplasmic hemosiderin and debris consistent with hemophagocytosis and 12% blasts. FISH testing using *KMT2A* break-apart probes in combination with CD163 immunophenotyping showed most CD163+ histiocytes carried *KMT2A*r, confirming leukemic origin of hemophagocytic histiocytes (Figure 2). She met 6-of-7 HLH-2024 diagnostic criteria with HScore of 299.

The patient was continued on dexamethasone, anakinra, and emapalumab. Despite antibacterial and antifungal prophylaxis, she developed *Fusarium* fungemia and *E. coli* bacteremia (D68). Emapalumab was discontinued and dexamethasone was tapered while she received antimicrobial therapy.

Revumenib was re-initiated on D75 due to rising peripheral blasts. This was followed by fevers, hypoxemia, and inflammatory marker elevation. On D90, she suffered an intracranial hemorrhage and later transitioned to hospice.

Patient 2 was a 34-year-old man with history of Ewing's Sarcoma had relapsed therapy-related AML with t(9;11) *KMT2A::MLLT3* after IC and alloHCT. He had no GVHD history and was not on immunosuppression when he initiated revumenib (163mg Q12H, 6 months post-alloHCT). His baseline marrow (20 days before revumenib) showed 82% blasts. His D1 CBC showed WBC $9.1 \times 10^3/\mu\text{L}$, ANC $0.3 \times 10^3/\mu\text{L}$, 89% blasts, HgB 7.8 g/dL, and PLT $13 \times 10^3/\mu\text{L}$.

On D12, he was admitted for severe bone pain (hips and shoulders). His CBC showed WBC $9.6 \times 10^3/\mu\text{L}$, 80% blasts, HgB 7.5 g/dL and PLT $60 \times 10^3/\mu\text{L}$. Imaging was unrevealing. Hydroxyurea was initiated. Recurring fevers began D14, followed by rapidly progressive

hypoxemic respiratory failure. Despite dexamethasone 10mg Q12H (D15 start) and revumenib hold (D16), he was transferred to the ICU and intubated (D16). Imaging revealed diffuse bilateral opacities; cultures were negative. By D16, WBC was $17 \times 10^3/\mu\text{L}$, ANC $0.2 \times 10^3/\mu\text{L}$, peripheral blasts were 24% and monocytes had increased from 4% (D12) to 38%. HgB was 7.1 g/dL, and PLT $37 \times 10^3/\mu\text{L}$. D17 inflammatory markers showed ferritin 20,033 $\mu\text{g/L}$, sCD25 849 pg/mL, meeting 4 of 7 HLH-2024 criteria (Table 1). HScore was 218.

Despite broad spectrum antibiotics, corticosteroids, and hydroxyurea, his hypoxemia worsened and he was palliatively extubated on D33.

Patient 3 was a 53-year-old man had *FLT3*-ITD and *NPM1*-mutated AML treated with IC and alloHCT. He relapsed 6 months post-alloHCT and was treated with gilteritinib (9-month CR) then quizartinib. He had no GVHD history and was not receiving immunosuppression when he initiated revumenib (276mg Q12H, 23 months post-alloHCT). His baseline marrow (7 days before revumenib) showed 4% blasts. His D1 CBC showed WBC $10.3 \times 10^3/\mu\text{L}$, ANC $2.8 \times 10^3/\mu\text{L}$, 31% blasts, HgB 7.3 g/dL, PLT $19 \times 10^3/\mu\text{L}$. He was hospitalized on D15 (WBC $10.1 \times 10^3/\mu\text{L}$, ANC $0.2 \times 10^3/\mu\text{L}$, 28% blasts, HgB 8.6, PLT $12 \times 10^3/\mu\text{L}$) for severe bone pain (chest) and revumenib was held. CT showed new splenomegaly. He developed fever, tachycardia, and rapidly progressive hypoxemia on D16. Dexamethasone 10mg Q12H, hydroxyurea, and antibiotics were started. Repeat CT chest showed bilateral infiltrates. D18 studies showed WBC $19.4 \times 10^3/\mu\text{L}$, ANC $0.8 \times 10^3/\mu\text{L}$, 34% blasts, HgB 7.8 g/dL, PLT $13 \times 10^3/\mu\text{L}$, ferritin 183,447 $\mu\text{g/L}$, sCD25 3,905 U/mL, and CXCL9 5,267 pg/mL. He met 5 of 7 HLH-2024 criteria with HScore 221.

Despite antibiotics, corticosteroids, and respiratory support, his clinical status declined. He became anuric and was transferred to the ICU, where he transitioned to comfort care on D19.

This case series demonstrates a severe hyperinflammatory phenotype during MENINI-associated differentiation beyond classical DS. This hyperinflammatory presentation appears

rare but severe, distinct from classical DS by its steroid-refractory and aggressive presentation. Consistent with malignancy-associated HLH-spectrum disease broadly, formal criteria fulfillment varied across patients, reflecting the known limitations of HLH diagnostic tools in active malignancy.¹⁰

Hyperinflammatory DS fits within the spectrum of hyperinflammatory toxicities linked to oncologic therapies. Like classic DS, cytokine release syndrome, and immune effector cell-associated HS, it reflects excessive immune activation leading to cytokine storm.^{11–13} It appears particularly potent, possibly because MENINi preferentially promotes monocytic and histiocytic differentiation, triggering a marrow-centered inflammatory cascade driven by differentiated myeloid cells." In patient 1, hemophagocytic histiocytes bore the *KMT2A* translocation, providing direct evidence that malignant cells differentiated into effector cells capable of propagating the inflammatory cascade. This is consistent with proposed mechanisms of leukemia-driven macrophage activation in malignancy-associated HLH. The marked elevation of IFN- γ and CXCL9 across cases suggests a predominantly interferon-driven inflammatory axis, consistent with macrophage activation biology.⁷

Our cohort consisted of young adults with refractory AML. Two had therapy-related AML, 2 had *FLT3*-ITD co-mutation, and all 3 underwent alloHCT. Active malignancy and immunocompromise are risk factors for hyperinflammatory conditions. At MENINi initiation, 2 patients had $\geq 80\%$ marrow blasts and all had $\geq 30\%$ peripheral blasts, suggesting that high disease burden may amplify differentiation-driven inflammation.

Clinically, all patients experienced refractory fevers and pulmonary infiltrates without alternative explanation; two had intractable bone pain. All were refractory to corticosteroids and hydroxyurea. Inflammatory markers were profoundly elevated and hemophagocytosis was confirmed in Patient 1; whether similar marker elevations occur in all menin-DS is unknown and warrants further study.

In MENINi-treated patients with fevers unresponsive to conventional therapy, particularly when clinical features are disproportionate to typical DS, we recommend prompt evaluation of inflammatory markers (e.g. fibrinogen, triglycerides, ferritin, sCD25) and marrow assessment to reduce diagnostic uncertainty and guide therapy. Additional immune profiling (e.g. IFN- γ , CXCL9) may guide immunomodulatory treatments. Patient 1 showed clinical and cytokine improvement with corticosteroids, anakinra (IL-1 receptor antagonist) and emapalumab (anti-IFN- γ antibody), established HLH therapies.^{14,15} However, infectious complications limited treatment.

In summary, MENINi can be associated with a severe hyperinflammatory phenotype with features overlapping HLH, a rare but potentially fatal complication. As their use expands, prospective efforts are needed to define its incidence, risk factors, diagnostic criteria, and optimal management.

References

1. Issa GC, Aldoss I, DiPersio J, et al. The menin inhibitor revumenib in KMT2A-rearranged or NPM1-mutant leukaemia. *Nature*. 2023;615(7954):920-924.
2. Issa GC, Stein EM, DiNardo CD. How I treat acute myeloid leukemia with differentiation therapy. *Blood*. 2025;145(12):1251-1259.
3. Wang ES, Issa GC, Erba HP, et al. Ziftomenib in relapsed or refractory acute myeloid leukaemia (KOMET-001): a multicentre, open-label, multi-cohort, phase 1 trial. *Lancet Oncol*. 2024;25(10):1310-1324.
4. Issa GC, Aldoss I, Thirman MJ, et al. Menin inhibition with revumenib for KMT2A-rearranged relapsed or refractory acute leukemia (AUGMENT-101). *J Clin Oncol*. 2024;43(1):75-84.
5. De Benedetti F, Prencipe G, Bracaglia C, Marasco E, Grom AA. Targeting interferon- γ in hyperinflammation: opportunities and challenges. *Nat Rev Rheumatol*. 2021;17(11):678-691.
6. Humblet-Baron S, Franckaert D, Dooley J, et al. IFN- γ and CD25 drive distinct pathologic features during hemophagocytic lymphohistiocytosis. *J Allergy Clin Immunol*. 2019;143(6):2215-2226.e7.
7. Rocco JM, Oved JH, Patel RJ, et al. CXCL9 as a novel prognostic marker to identify high-risk adults with hemophagocytic lymphohistiocytosis. *Blood*. 2026;147(9):960-972.
8. Henter J-I, Sieni E, Eriksson J, et al. Diagnostic guidelines for familial hemophagocytic lymphohistiocytosis revisited. *Blood*. 2024;144(22):2308-2318.
9. Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol*. 2014;66(9):2613-2620.
10. Setiadi A, Zoref-Lorenz A, Lee CY, Jordan MB, Chen LYC. Malignancy-associated haemophagocytic lymphohistiocytosis. *Lancet Haematol*. 2022;9(3):e217-e227.
11. Hines MR, Knight TE, McNerney KO, et al. Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome. *Transplant Cell Ther*. 2023;29(7):438.e1-438.e16.
12. Fajgenbaum DC, June CH. Cytokine Storm. *N Engl J Med*. 2020;383(23):2255-2273.
13. Radtke KK, Bender BC, Li Z, et al. Clinical pharmacology of cytokine release syndrome with T-cell-engaging bispecific antibodies: current insights and drug development strategies. *Clin Cancer Res*. 2025;31(2):245-257.
14. Locatelli F, Jordan MB, Allen C, et al. Emapalumab in children with primary hemophagocytic lymphohistiocytosis. *N Engl J Med*. 2020;382(19):1811-1822.
15. Naymagon L. Anakinra for the treatment of adult secondary HLH: a retrospective experience. *Int J Hematol*. 2022;116(6):947-955.

Table 1. Baseline Patient Characteristics and Features of Hyperinflammatory Differentiation Syndrome.

Variable	Patient 1	Patient 2	Patient 3
Patient Characteristics			
Age — yr	40	34	53
<i>KMT2A</i> translocation or gene Mutation	t(11;19) <i>KMT2A::ELL</i>	t(9;11) <i>KMT2A::MLLT3</i>	<i>NPM1c</i>
Line of treatment — no.	4	2	4
Prior AlloHCT	Yes (12 months prior)	Yes (6 months prior)	Yes (23 months prior)
ECOG performance status	1	1	1
HLH symptom onset — menin inhibitor day	40	14	15
Presenting symptoms	Fever, hypoxemia, hypotension	Fever, bone pain, hypoxemia, hypotension	Fever, bone pain, hypoxemia, altered mental status
HLH-2024 Diagnostic Features			
Fever $\geq 38.5^{\circ}\text{C}$	Yes	Yes	Yes
Splenomegaly*	No	No	Yes
Cytopenia (≥ 2 lineages)	Yes	Yes	Yes
Hemoglobin < 9 g/dL	Yes	Yes	Yes
Platelets $< 100 \times 10^9/\text{L}$	Yes	Yes	Yes
Neutrophils $< 1.0 \times 10^9/\text{L}$	Yes	Yes	Yes
Hypofibrinogenemia (≤ 150 mg/dL)	Yes (74)	No	No
Hypertriglyceridemia (≥ 265.7 mg/dL)	Yes (1422)	Yes (932)	No
Hyperferritinemia (≥ 500 $\mu\text{g/L}$)	Yes (283,381)	Yes (20,033)	Yes (218,147)
Hemophagocytosis	Yes	Unknown	Unknown
Elevated sCD25 (> 2400 U/mL)**	Yes (4,373)	No (849)	Yes (3,905)
HLH-2024 criteria met	6 of 7	4 of 7	5 of 7
H-Score (probability of HLH)	299 (>99%)	218 (93–96%)	221 (96–98%)
Additional Findings			
Hepatomegaly	No	No	No
Elevated aminotransferases	Yes	Yes	Yes
Elevated bilirubin	Yes	Yes	Yes
Elevated LDH	Yes	Yes	Yes
Elevated D-dimer	Yes	Yes	Yes
CSF cell or protein abnormalities	Unknown	Unknown	Unknown
Known immunosuppression***	Yes	No	No

AlloHCT: Allogeneic Hematopoietic Stem Cell Transplantation, ECOG: Eastern Cooperative Oncology Group; **Maximum values are shown in red.***Splenomegaly determined based on exam or imaging; **A conversion factor of 4.3 was applied to convert sCD25 pg/mL to U/mL. ***Defined as use of immunosuppressive medications

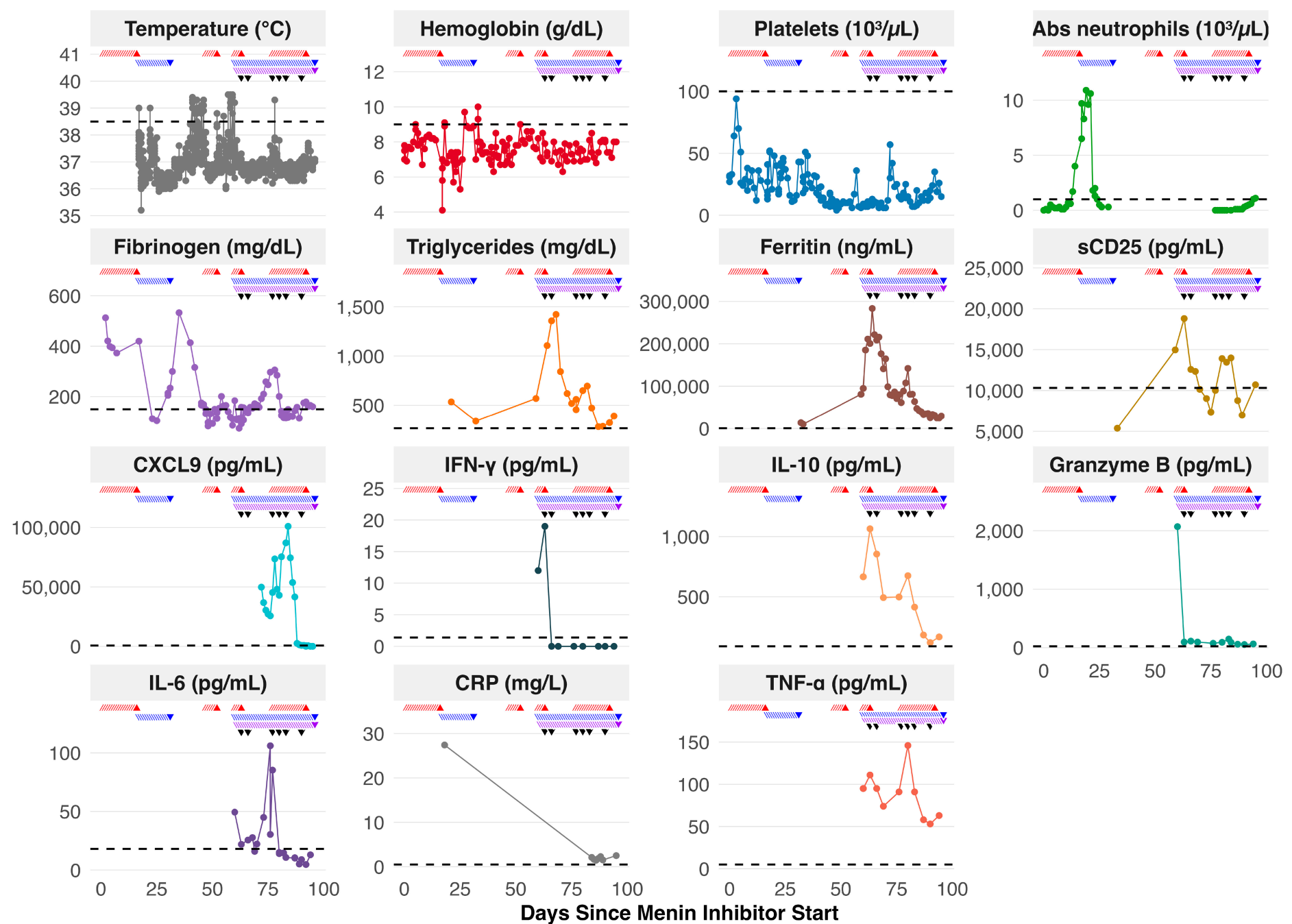
Figure 1. Hematologic and inflammatory laboratory Values and temperature trend for Patient 1.

Serial hematologic, inflammatory, and cytokine laboratory measurements and temperature are shown by days since menin inhibitor initiation. Medication exposures are indicated above each panel. ANC: Absolute Neutrophils; sCD25: soluble IL-2 receptor α ; CXCL9: C-X-C motif chemokine ligand 9; IFN- γ : interferon-gamma; IL-10: Interleukin-10, IL-6: Interleukin-6; CRP: C-Reactive Protein; TNF- α : tumor necrosis factor-alpha

The figure was selected and designed by the authors. AI-assisted coding (GitHub Copilot) was used for limited formatting of the data visualization.

Figure 2. Morphologic, immunophenotypic and genetic evidence of hemophagocytosis in leukemia derived histiocytes.

- A.** H&E section (x600) of bone marrow biopsy shows an increase in histiocytes including hemophagocytic histiocytes (inset).
- B.** Immunohistochemical staining for CD163 (brown, x400) highlights an increase in histiocytes on the bone marrow biopsy with strong membranous and cytoplasmic staining.
- C.** Combined immunophenotyping using CD163 (aqua), and FISH testing using *KMT2A* break-apart probes (5'MLL in green and 3' MLL in orange, Abbott Molecular, Des Plaines, IL). Most CD163 positive cells are positive for *KMT2A* translocation, i.e., t(11;19).
- D.** A CD163 positive cells show *KMT2A* split signal pattern, with evidence of hemophagocytic feature, i.e., two red blood cells (white arrows) in the cytoplasm. Two CD163 negative cells (green arrows) are also positive for *KMT2A* translocation.



Medication ▼ Anakinra ▼ Corticosteroids ▼ Emapalumab ▲ Revumenib

