Adult-Onset Still's Disease and Macrophage-Activating Syndrome Progressing to Lymphoma

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Clinical Presentation

A 66-year-old man with adult-onset Still's disease (AOSD) and macrophage-activation syndrome (MAS) presented with four weeks of progressive fatigue and weakness. Past history was notable for gout and a deep vein thrombosis provoked after a long flight, and there was no family history of autoimmune conditions or malignancy. Two and a half years

prior, he developed anemia, thrombocytopenia, hypoalbuminemia, and hyperferritinemia, followed by fatigue, weight loss, fever, and night sweats. He had no rash, arthritis, arthralgias, or pleuritic chest pain.

On physical examination, he had splenomegaly with mild lymphadenopathy. The patient underwent an extensive workup including malignancy screening, in which cross-sectional imaging confirmed splenomegaly and scattered lymphadenopathy. Bone marrow biopsy was hypercellular, with normal cell lines and no hemophagocytosis. Left inguinal lymph node biopsy showed reactive hyperplasia, suggestive of Castleman's disease-like features (Fig. 1a). Several months later he developed arthralgias, mild arthritis, and rash, along with continued fever, fatigue, cytopenia, and hyperferritinemia. A diagnosis of MAS in the setting of AOSD was made. He was treated with methylprednisolone 100 mg daily and anakinra 100 mg daily with rapid resolution of symptoms. Over the next six months, steroids and anakinra were tapered off completely.

Three months after discontinuation of anakinra and one month prior to his in-hospital presentation, the patient developed recurrent fatigue and weight loss, without fever, rash, or localizing symptoms. Physical examination was again notable for lymphadenopathy; laboratory tests revealed recurrent anemia, thrombocytopenia, hypoalbuminemia, and hyperferritinemia. He was restarted on anakinra and prednisone 100 mg daily for treatment of presumed relapse of MAS/AOSD but without improvement. The patient was re-hospitalized for further evaluation and management.

He was noted to have diffuse lymphadenopathy and hepatosplenomegaly on cross-sectional imaging, and interleukin (IL)-6 and tumor necrosis factor (TNF)- α levels were elevated. Laboratory findings were notable for leukopenia, profound anemia and thrombocytopenia, hypoalbuminemia,

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hyperferritinemia, and elevated creatinine level (Table 1). Blood and urine cultures were negative, as were HIV and viral hepatitis serologies. Serum cytomegalovirus viral load was negative; however, serum Epstein–Barr virus (EBV) viral load was positive, at 8880 copies/mL. Bone marrow biopsy was not diagnostic for MAS flare or malignancy. He received red blood cells, platelets, and antibiotics, as well as pulse steroids followed by dexamethasone 40 mg daily, intravenous immunoglobulin, cyclosporine, and tocilizumab for a presumed MAS flare, given the lack of other definitive diagnosis. Nonetheless, he had refractory anemia, thrombocytopenia, and hypoalbuminemia with anasarca. Right axillary lymph node biopsy was performed.

Pathologic Discussion

Right axillary lymph node biopsy showed a large cell lymphoma with plasmablastic features. The lymph node had an effaced architecture with large anaplastic, pleomorphic lymphoid cells, many with eccentric, prominent nucleoli, Golgi hof, amphophilic cytoplasm, karyorrhexis, and apoptosis (Fig. 1b). The malignant cells expressed CD79a with aberrant CD3 positivity and co-expression of EBV RNA1 by in situ hybridization and human herpesvirus 8 (HHV-8). Other

T cell markers (including CD2, CD4, CD7, and CD25) and natural killer (NK) cell markers (including CD56 and TIA-1) were all negative, as was CD138. Immunoglobulin heavy chain (IgH) and T cell receptor (TCR) gene rearrangements were also negative (Fig. 1b–d).

Bone marrow biopsy showed a hypercellular marrow for the patient's age (70% cellularity) and trilineage hematopoiesis, with an increase in all elements but no evidence of lymphoma or hemophagocytosis. Microclusters of CD138 plasma cells, EBV-encoded RNA1 (EBER1+) cells, and a rare single HHV-8 cell were noted (Fig. 1e). Immunohistochemistry for CD163 or CD68 was not performed on the bone marrow. Aspirate smears were not available for review.

Clinical Discussion

A 66-year-old man with a known diagnosis of AOSD/MAS, who had been successfully treated with steroids and anakinra, subsequently developed recurrent symptoms refractory to therapy in the setting of a new diagnosis of atypical large-cell lymphoma with EBV and HHV-8 positivity. This case raises several questions about the relationship between MAS and malignancy, particularly in the setting of immunosuppression and viral infection.

Fig. 1. **a** Inset (upper left panel): showing low power of initial left inguinal lymph node biopsy (two years prior to presentation); at higher power ($\times 40$ objective): showing reactive hyperplasia with focal regressed follicles (indicated by arrow) and “lollipop sign” (hyalinized blood vessels penetrating the follicles with concentric rimming of mantle zone lymphocytes), suggestive of Castleman’s disease-like features. **b** Right axillary lymph node biopsy showing sheets of discohesive large anaplastic, pleomorphic, lymphoid cells, many with eccentric, prominent nucleoli, Golgi hof, amphophilic cytoplasm, karyorrhexis, and apoptosis; at high power ($\times 40$ objective). **c** Right axillary lymph node biopsy by immunohistochemical staining: CD3 (large neoplastic lymphoid cells, diffusely positive), CD79a (focally positive neoplastic lymphoid cells), Epstein–Barr virus-encoded RNA1 (EBER1) in situ hybridization (large neoplastic cells positive), HHV-8 latency-associated nuclear antigen (LANA) (large neoplastic cells, diffusely positive) all at high power ($\times 40$ objective). **d** Right axillary lymph node biopsy by immunohistochemical staining: CD2, CD4, CD7, TIA-1, CD25, and CD56, showing that neoplastic large lymphoid cells are negative, with few internal reactive lymphoid cells positive, all at $\times 40$ objective. **e** Bone marrow biopsy: inset (upper left panel) with low-power, $\times 2$ objective and high power at $\times 40$ objective showing hypercellular marrow, trilineage hematopoiesis without evidence of lymphoma or hemophagocytosis, focal microcluster of CD138-positive plasma cells, noted positive microcluster of small cells by EBER1 in situ hybridization, and HHV-8 LANA single rare positive cell, all at $\times 40$ objective.

Fig. 1. (continued).

MAS is a subtype of hemophagocytic lymphohistiocytosis (HLH) associated with autoimmune disease, most typically AOSD or systemic juvenile idiopathic arthritis (sJIA). HLH is classified as either primary or secondary to triggering factors [2, 52, 55]. Primary HLH occurs in the setting of genetic disorders [43, 73]. Secondary HLH is associated with viral infections (29%), other infections (20%), malignancies (27%), rheumatologic disorders (referred to as MAS) (7%), and immunodeficiency syndromes (6%) [14]. Viral infections include EBV, cytomegalovirus, parvovirus B19, HIV, and human herpesvirus-6. Malignancies associated with secondary HLH are mainly lymphomas (lymphoma-associated hemophagocytic syndrome) [16, 32].

The syndrome of MAS/HLH is characterized by acute fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, and elevated levels of serum ferritin, triglycerides, CD25 (sIL2-receptor), and liver enzymes, as well as a paradoxically low erythrocyte sedimentation rate (ESR). The diagnosis of MAS/HLH is often challenging; patients are acutely ill, with multiple organs involved, and teasing out sepsis can be difficult. Since the definitive genetic expression profiles of peripheral blood mononuclear cells in HLH may take many days, several attempts have been made to establish strict clinical criteria [12, 62]. The most widely used diagnostic criteria are HLH-2004 guidelines [27] (Table 2).

Table 1 Laboratory results at presentation

	Result	Normal value
White blood cell count	3.5	4.0–10.0 × 10 ⁹ /L
Hemoglobin	6.3	12–16 g/dL
Hematocrit	19.7	35–45%
Platelets	13	150–350 × 10 ⁹ /L
Blood urea nitrogen	95	5–25 mg/dL
Creatinine	1.3	0.4–1.2 mg/dL
Aspartate aminotransferase (AST)	9	15–41 U/L
Alanine aminotransferase (ALT)	8	14–54 U/L
Alkaline phosphatase	59	30–110 U/L
Total bilirubin	5	0.3–1.2 mg/dL
Albumin	2.6	3.5–4.8 g/dL
Lactate dehydrogenase	203	105–333 U/L
Haptoglobin	120	36–195 mg/dL
Fibrinogen	163	180–440 mg/dL
Ferritin	3685	22–275 ng/mL

Abnormal results are in italics

While there are no established definitive diagnostic criteria for MAS, a preliminary diagnostic guideline for MAS complicating sJIA based on retrospective laboratory and clinical criteria has been published [52] (Table 3). These guidelines are limited by the non-specific nature of some of the laboratory criteria in autoimmune diseases. They also omit biopsy-proven hemophagocytosis in the extra-marrow sites, where it is frequently demonstrated at early stages. These criteria require further validation.

MAS is a serious and sometimes catastrophic complication in autoimmune diseases such as AOSD and in children with sJIA [12, 38, 68]. Although MAS is a rare condition, it is not uncommon in AOSD (up to 10% in some cohorts) [44]. MAS can be deadly, with mortality rates between 10 and 22% [15, 39, 66]. It is unclear why patients with AOSD have an increased risk of MAS, but some theorize that the

Table 2 Hemophagocytic lymphohistiocytosis (HLH) diagnostic criteria

The diagnosis of HLH may be established by^a

1. A molecular diagnosis consistent with HLH

Example: pathologic gene mutations of *PRF1*, *UNC13D*, or *STX11* are identified

OR

2. Fulfillment of 5 of 8 criteria listed below:

- Fever
- Splenomegaly
- Cytopenias (affecting at least 2 of 3 lineages in peripheral blood):
 - Hemoglobin < 9 g/100 mL (in infants < 4 weeks old: hemoglobin < 10 g/100 mL)
 - Platelets < 100 × 10⁹/L
 - Neutrophils < 1 × 10⁹/L
- Hypertriglyceridemia (fasting, ≥ 265 mg/100 mL) and/or hypofibrinogenemia (≤ 150 mg/100 mL)
- Hemophagocytosis in bone marrow, spleen, or lymph nodes
- Low or absent NK cell activity
- Ferritin ≥ 500 ng/mL
- Soluble CD25 (that is, soluble IL-2 receptor) > 2400 U/mL

Adapted from Henter et al. [27]

^a In addition, in the case of familial HLH, no evidence of malignancy should be apparent

Table 3 Preliminary diagnostic guidelines for macrophage activation system complicating systemic juvenile idiopathic arthritis

Laboratory criteria

1. Decreased platelet count (≤ 262 × 10⁹/L)
2. Elevated levels of aspartate aminotransferase (> 59 U/L)
3. Decreased white blood cell count (≤ 4.0 × 10⁹/L)
4. Hypofibrinogenemia (≤ 2.5 g/L)

Clinical criteria

1. Central nervous system dysfunction (irritability, disorientation, lethargy, headache, seizures, coma)
2. Hemorrhages (purpura, easy bruising, mucosal bleeding)
3. Hepatomegaly (≥ 3 cm below the costal arch)

Histopathological criterion

Evidence of macrophage hemophagocytosis in the bone marrow aspirate

Diagnostic rule

The diagnosis of MAS requires the presence of any 2 or more laboratory criteria or of any 2 or 3 or more clinical and/or laboratory criteria. A bone marrow aspirate for the demonstration of hemophagocytosis may be required only in doubtful cases.

Adapted from Ravelli et al. [52]

immunodeficiency state induced by AOSD treatment may reactivate latent viruses, such as EBV, which could lead to MAS [71]. Others suggest that therapeutic agents, such as sulfasalazine, are capable of provoking MAS [59].

The mainstay of treatment for MAS/HLH is the control of hyperinflammation and its elimination if the trigger is known [33]. Steroids, chemotherapeutic agents, and targeted biologics have all been successfully used, and many consider pulse steroids to be the most important immediate treatment for MAS/HLH. Chemotherapeutic regimens include cyclosporine A (CSA), etoposide, intravenous immunoglobulins, and anti-thymocyte globulin (ATG). CSA inhibits calcineurin, which normally activates interleukin IL-2 transcription; CSA also likely inhibits the cytokine storm of MAS/HLH. A pulse of high-dose corticosteroids with or without CSA is effective in most patients. Etoposide causes DNA strands to break by unwinding and preventing re-ligation of DNA strands through the formation of a ternary complex between DNA and the topoisomerase II enzyme. Etoposide appears to interfere with EBV-induced lymphocyte transformation and suppresses the formation of EBV nuclear antigen. Etoposide is used in serious or resistant cases of EBV-associated HLH and improves survival [30, 31]. Determining the number of EBV genome copies in peripheral blood may be useful in predicting prognosis and the effectiveness of therapy [53, 60]. In patients with severe kidney and liver disease, ATG may be a safer alternative to etoposide [11, 40]. ATG is effective via depletion of CD4+ and CD8+ T cells through complement-dependent cell lysis, though it is associated with infusion reactions [57].

Biologics are preferred in patients with underlying autoimmune conditions, and they include IL-1 and IL-1β inhibitors, rituximab, anti-TNF agents, and anti-CD52 antibodies. Anakinra blocks the biologic activity of naturally occurring IL-1 by competitively inhibiting the binding of IL-1 to the IL-1 receptor, which is expressed in many tissues and organs. Anakinra has dramatically benefitted patients with MAS [9, 37]. Canakinumab is a human monoclonal antibody targeted at IL-1β; theoretically, patients responding to anakinra should respond to canakinumab.

However, several reports suggest poor response in practice, so canakinumab has not been used as standard therapy [13]. Anti-TNF agents have shown promise when used in early stages of disease in some cases [1, 49], although there are also many case reports of new or worsening MAS in patients on TNF inhibitors [3, 50, 61]. As a result, anti-TNFs are no longer recommended. Rituximab, an anti-CD20 antibody that depletes B lymphocytes, has been used successfully in EBV-induced lymphoproliferative disease and could be considered in EBV-driven MAS/HLH [4, 8]. Alemtuzumab, an anti-CD52 antibody that is present not only on T cells but also on histiocytes, has been shown to be beneficial in patients with refractory HLH [41]. Plasma exchange, a long-standing treatment for removal of antibodies, may be of use to patients who do not respond to standard treatment or to buy time until other therapies reach therapeutic effect [42, 51]. Finally, definitive treatment of MAS/HLH with bone marrow transplantation has been proposed [34].

Immunologic Discussion

On a cellular level, HLH/MAS is characterized by defective cytotoxic cell function coupled with uninhibited macrophage activation and cytokine secretion, which cause cellular and organ damage. Several pro-inflammatory cytokines including interferon γ (INF- γ), IL-6, IL-8, IL-10, IL-12, IL-18, TNF- α , and macrophage inflammatory protein (MIP 1- α) are elevated in HLH/MAS [17, 26, 32, 46, 56, 63, 65]. Also central in the pathogenesis of HLH/MAS are NK cells, which directly destroy damaged or infected cells [21]. Thus, both a cytokine storm and hemophagocytosis function in a self-perpetuating, feed-forward inflammatory cycle [6, 64]. It is important to note that studies demonstrate that the amount of hemophagocytosis in the bone marrow of suspected HLH patients does not correlate with disease severity [23, 24, 28]. Consequently, some consider hyperinflammation, rather than hemophagocytosis, as the cellular pathology of HLH/MAS [69].

There is a complex association among viral infections, MAS/HLH, medications, and malignancy. The connection between MAS/HLH and malignancy is poorly understood, and viral infection and immune system dysregulation likely

play a major role (Fig. 2). Our patient had both HHV-8 and EBV positivity in the setting of aggressive lymphoma, and it is unclear what role his prior AOSD/MAS and immunosuppression played in viral reactivation and malignant transformation. This is an unusual scenario, and only one similar case has been reported to our knowledge [58]. EBV, also called human herpesvirus 4 (HHV-4), has been the most consistently reported virus associated with HLH [7, 10, 20, 22, 29]. No single sub-strain of EBV is identified with HLH [36]. There are several reports that other infectious agents, such as HIV, parvovirus B19, varicella zoster, herpes simplex, cytomegalovirus, salmonella, mycobacteria, and leishmania, can be associated with HLH [47, 54]. It is well known that EBV can be reactivated in immunosuppressed states and that it has a causal association with malignancy [67]. HHV-8 is also associated with lymphomas [18, 35, 70]. Lastly, it is known that lymphomas (T cell and NK cell, most commonly) are associated with HLH [5, 25]. Immunosuppressive medications such as tocilizumab (an IL-6 receptor inhibitor) have been associated with MAS in patients with autoimmune diseases [71]. However, our patient received anakinra (an IL-1 receptor inhibitor). In the pediatric literature, there have been reports of anakinra paradoxically causing HLH, but this has not been reported in adults [45, 72]. Anakinra is not associated with increased risk of lymphoma or EBV reactivation [19]. These associations could be causal or simply due to the association of autoimmune diseases with HLH/MAS [48].

Hospital Course

The patient's treatment of lymphoma started with cyclophosphamide and etoposide, followed by two cycles of etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone (EPOCH) with gradual improvement. Dexamethasone was tapered without a flare in symptoms. He received supportive transfusions, romiplostim and intravenous immunoglobulin for refractory thrombocytopenia, and rasburicase for tumor lysis syndrome. His hospital course was otherwise complicated by candida esophagitis and mucositis, febrile neutropenia, supraventricular tachycardia, and a lower-extremity deep vein thrombosis for which an

Fig. 2. Complex relationships among autoimmunity, immunosuppression, infection, and malignancy in macrophage-activating syndrome/hemophagocytic lymphohistiocytosis.

inferior vena cava filter was placed. One month after the diagnosis of lymphoma, the patient was improving and was discharged home with a plan for additional chemotherapy. Unfortunately, however, over the next six months he developed resistant lymphoma and died.

Conclusion

Our patient with EBV and HHV-8-associated lymphoma had a preceding history of AOSD/MAS. Immunosuppression and reactivation of EBV and HHV-8, as well as genetic susceptibility, could be responsible for his transition to malignancy. While the exact pathogenesis of lymphoma in his case is unclear, it is likely that the patient's MAS and prior immunosuppression played some role. Monitoring these patients for this complication is thus critical. Once diagnosed, our patient received an etoposide-based regimen because it would treat MAS/HLH, EBV, and lymphoma.

Compliance with Ethical Standards

Conflict of Interest: Bella Mehta, MD, Shanthini Kasturi, MD, MS, Julie Teruya-Feldstein, MD, and Anne R. Bass, MD, declare that they have no conflicts of interest. Steven Horwitz, MD, reports receiving grants and personal fees from Celgene, Millennium/Takeda Oncology, Kyowa Hakko Kirin, Seattle Genetics, Forty Seven, and Infinity/Verastem; personal fees from HUYA Bioscience International, Bristol-Myers Squibb, and Mundipharma; and grants from Spectrum Pharmaceuticals, ADC Therapeutics, and Aileron Therapeutics, outside the submitted work. Doruk Erkan, MD, MPH, reports receiving grants from the Lupus Clinical Trial Consortium, the National Heart, Lung, and Blood Institute, HSS Medical Education Academy, EMD Serono, and Xencor; grants and personal fees from GlaxoSmithKline; and personal fees from Ablynx, outside the submitted work.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013.

Informed Consent: Informed consent was waived from all patients for being included in this study.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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