CLINICAL VIGNETTE

New-Onset Graves' Disease as a Possible Trigger for Hemophagocytic Lymphohistiocytosis

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Introduction

Hemophagocytic Lymphohistiocytosis (HLH) is a systemic, life-threatening hyperinflammatory syndrome that is due to severe autoimmune system dysregulation. HLH can be primary or secondary in etiology, though the distinction is now less definitive. Classically, primary HLH occurs due to genetic mutations in childhood, with high mortality, being uniformly fatal within a median of 1-2 months without treatment.[1] Secondary HLH occurs in adulthood and is triggered by an underlying condition, including infection, malignancy, rheumatologic condition, or autoimmune disease, with reported mortality of 8-24% of patients.[2] To our knowledge, endocrine triggers for HLH are extremely rare. At least three prior instances of autoimmune thyroid diseases as possible secondary triggers have been listed, but details of the cases were not included.[3,4] Our case is the first that described Graves' disease as a potential trigger or exacerbating precipitant for secondary HLH.

Case Report

Our patient is a 47-year-old previously healthy female who was hospitalized multiple times with recurrent high fevers, tachycardia, fatigue, night sweats, neuropathy, arthralgias, synovitis, lymphadenopathy, and weight loss with hospital course complicated by deep vein thrombosis. Evaluation revealed hepatosplenomegaly and lymphadenopathy, including enlarged cervical, inguinal and iliac chain lymph nodes. Labs showed an unremarkable comprehensive metabolic panel and anemia with hemoglobin 8.4 g/dL (11.6-15.2 g/dL). It also revealed overt thyrotoxicosis with TSH <0.02 mcIU/mL (0.3-4.7 mcIU/mL), free T3 1030 pg/dL (222-383 pg/dL), free T4 4.6 ng/dL (0.8-1.7 ng/dL), and elevated TRAb 2.35 IU/L (<=1.75 IU/L), consistent with recently diagnosed Graves' disease. On review, the patient had labs 8 months prior showing TSH 0.03 mcIU/mL, free T3 473 pg/dL, and free T4 1.5 ng/dL, after which the patient was lost to follow up. The patient was initially started on methimazole 20mg twice daily and propranolol. A few days after initiation of methimazole, the dosage was decreased to 5-10mg daily due to development of leukopenia to nadir WBC of 3.2 $x10^3$/mL (4.16-9.95 x 10^3/mL), which improved with the lower methimazole dose.

This period of thyrotoxicosis was followed by rapid onset of HLH within 2-3 weeks of initiation of methimazole therapy. Oncological evaluation was pursued during recurrent hospitalizations for persistent symptoms. HLH is diagnosed by the presence of five out of eight criteria: fever, extremely high ferritin levels >500 ng/mL, peripheral blood cytopenia, splenomegaly, hypertriglyceridemia, low NK cell activity, elevated soluble CD25 (soluble IL-2 receptor alpha or sIL-2R) >2400 unit/mL, and hemophagocytosis in the bone marrow, lymph node, spleen, or liver.[1,2] Development of HLH in our patient was demonstrated via an increase in ferritin levels from 452 ng/mL (8-180 ng/mL) to >20,000 ng/mL after three weeks of methimazole therapy, during which time the free thyroid hormone levels normalized (Figure 1). Labs also showed triglyceride level of 279 mg/dL (<150 mg/dL), elevated sIL-2R of 3410 unit/mL (45-1105 unit/mL), and elevated lactate dehydrogenase level of 778 U/L (125-256 U/L). Further testing on one of the bone marrow aspirates, including a comprehensive hematologic malignancy sequencing panel, FISH, karyotyping, and flow cytometry, returned negative. Testing for infectious etiologies for HLH were negative, including blood cultures and testing for Epstein-Barr virus, cytomegalovirus, rickettsia, human immunodeficiency virus, and hepatitis A, B, and C.

The patient's bone marrow biopsies after methimazole therapy documented the evolution of HLH, in parallel with the marked rise in ferritin levels. The initial bone marrow biopsy 18 days after starting methimazole showed a mildly hypercellular bone marrow with a reactive process (Figure 2A). Eight days later, repeat bone marrow biopsy revealed a hypercellular bone marrow with abnormal histiocytes and phagocytosis, consistent with HLH (Figure 2B). Around the time of diagnosis, hematology-oncology consult raised concern that the patient's Graves' disease may have triggered the patient's HLH. Per rheumatology consult, the patient – who had an elevated ANA of 1:320 titer with a negative reflux panel – did not meet criteria for a clear rheumatological diagnosis, and the patient's synovitis was attributed to thyrotoxicosis.

The patient's symptoms initially improved on antithyroidal medications and dexamethasone for HLH treatment. Five

months after the diagnosis of HLH, the patient developed a new, evanescent rash in the setting of recurrent high fevers and polyinflammatory arthritis. The patient then met criteria for diagnosis of Adult-onset Still's disease (AOSD), raising incipient AOSD as another possible etiology for the patient's HLH. The patient was started on anakinra for several days, then placed on methotrexate in combination with high dose prednisone.

Discussion

Given that AOSD has classically been associated with secondary HLH,[2] it is possible that incipient AOSD triggered the patient's HLH. However, the patient's clinical presentation and sequence of events – initially with new-onset Graves' thyrotoxicosis that was untreated for at least 8 months, with subsequent development of HLH, followed 5 months later by a new diagnosis AOSD – raise the possibility that a prolonged period of untreated Graves' Disease triggered an inflammatory cascade. The other possibility is that an underlying severe inflammatory predisposition led to development of an unusual constellation of autoimmune diseases. The close proximity of the onset of HLH with initiation of methimazole also raises the question of whether effects on the bone marrow from anti-thyroid drug (ATD) therapy contributed towards precipitating HLH.

Though the pathophysiology that is often highlighted in Graves' disease is the production of thyrotropin receptor antibodies, this patient highlights the immune dysregulation and inflammation that occur in Graves' disease. A central component of HLH is thought to involve dysfunctional cytotoxic T lymphocytes and NK cells that fail to mount proper responses against target cells affected by the secondary trigger, leading to uncontrolled, sustained lymphocytic proliferation, cytokine storm, and deregulated macrophage hyperactivation.[5] Graves' disease, in turn, involves breakdown of central and peripheral tolerance,[6,7] leading to aberrant B and T cell lymphocytes and cytokine release, the latter of which contributes to thyroid-associated ophthalmopathy.[8] Peripheral blood from patients with Graves' disease shows higher levels of activated T lymphocytes and transitional and pre-naive mature B lymphocytes.[9] Graves' disease can also affect hematopoietic lineages, causing cytopenias that reverse with treatment of thyrotoxicosis.[10] Studies on bone marrow transplant patients have shown transfer of Graves' disease from donor to recipient,[6] highlighting the presence of immune dysregulation at the level of the bone marrow. We hypothesize that Graves' disease may have contributed to HLH by causing lymphocytic and cytokine dysregulation and formation of inflammatory target antigens[6,7] in a patient with genetic susceptibility for immune dysfunction and autoimmunity.

Conclusion

We present a patient with new-onset Graves' disease who developed HLH after a prolonged period of undiagnosed thyrotoxicosis, well documented by serial bone marrow biopsies, with subsequent development of AOSD. Though AOSD is a known trigger for secondary HLH, the sequence of events in our patient raises the possibility that Graves' disease precipitated secondary HLH in a patient with underlying severe inflammatory predisposition. Though Graves' disease is primarily thought to be driven by thyrotropin receptor antibodies, the case highlights that Graves' represents a systemic autoimmune process that can trigger severe inflammation.

Disclosure

The authors have no multiplicity of interest to disclose.

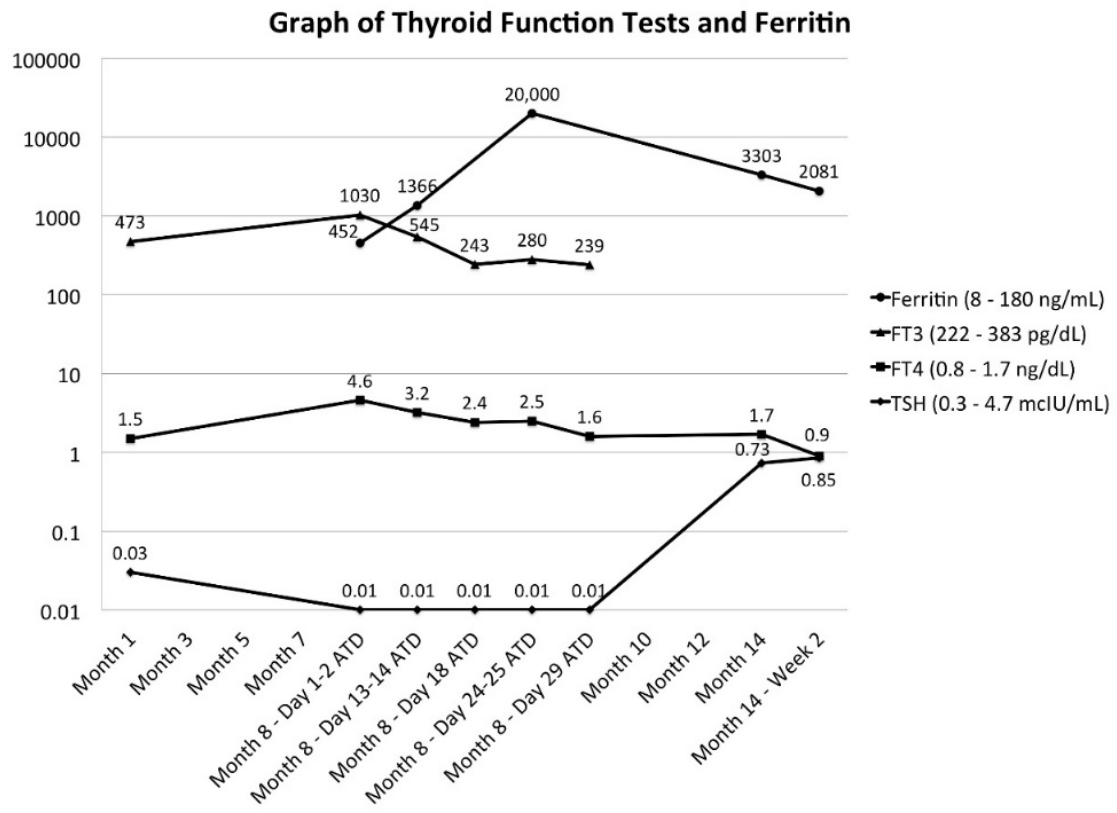

Figure 1. Graph of the patient's thyroid function tests and ferritin levels. The patient's labs revealed a previously undiagnosed and untreated history of thyrotoxicosis (month 1), with elevated thyroid function tests since at least 8 months prior to the diagnosis of hemophagocytic lymphohistiocytosis (HLH) (month 8). The patient presented to the emergency room with worsening thyrotoxicosis, with elevated TRAb levels diagnostic of Graves' disease, and started on antithyroidal drug (ATD) therapy with methimazole (month 8 – day 1 ATD). The patient was recurrently hospitalized for persistent fevers in setting of cytopenia, lymphadenopathy, hepatosplenomegaly, and deep vein thrombosis. Further labs documented a rise in ferritin levels, meeting HLH criteria of >500 ng/mL, with a rise from 452 ng/mL (month 8 – day 2 ATD) to >20,000 ng/mL (month 8 – day 24 ATD). Other labs were consistent with HLH, including elevated soluble IL-2 receptor alpha (siL-2R) and triglyceride levels. The rise in ferritin levels also reflected changes in bone marrow pathology from a reactive process to findings consistent with HLH (Figure 2).

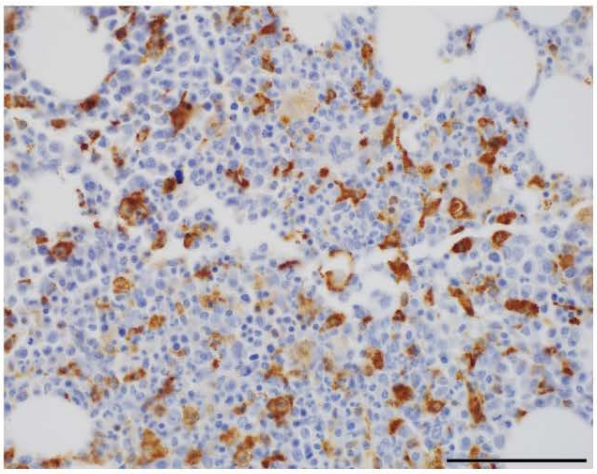

Fig. 2A

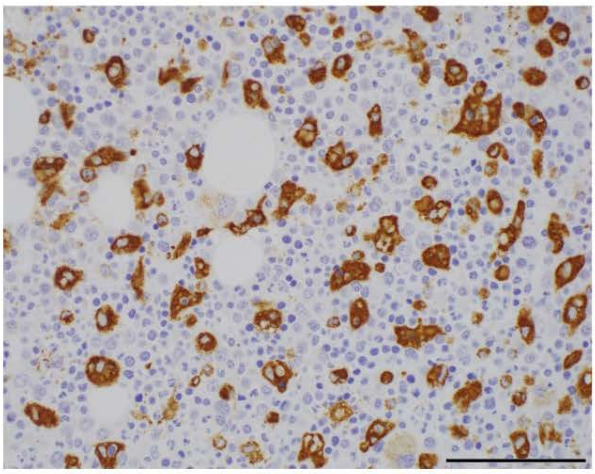

Fig. 2B

Figure 2. Bone Marrow Biopsies – CD68 IHC, hematoxylin counterstain, 400x magnification, scale bar 100mm. The histiocyte antigen, CD68, shows positive staining in both cases. In the earlier bone marrow biopsy (Fig. 2A), performed 17 days after initiation of methimazole (month 8 – Day 18 ATD on Figure 1), there were increased histiocytes, but the proportion of histiocytes with ingested cellular debris was fairly low. The pathology was consistent with a mildly hypercellular bone marrow with a reactive process. In the latter bone marrow biopsy (Fig. 2B), obtained 8 days after the initial bone marrow biopsy (month 8 – Day 26 ATD on Figure 1), the majority of the cells that were staining were enlarged in size, and showed numerous fragmented cells and nuclei. In fact, there were hardly any normal histiocytes. The latter bone marrow biopsy was diagnostic of hemophagocytic lymphohistiocytosis (HLH). The changes in the bone marrow reflected the biochemical increase in ferritin levels during a similar time period (Figure 1).

REFERENCES

1. **Rosado FG, Kim AS**. Hemophagocytic lymphohistiocytosis: an update on diagnosis and pathogenesis. *Am J Clin Pathol*. 2013 Jun;139(6):713-27. doi: 10.1309/AJCP4ZDKJ4ICOUAT. PMID: 23690113.
2. **Kleynberg RL, Schiller GJ**. Secondary hemophagocytic lymphohistiocytosis in adults: an update on diagnosis and therapy. *Clin Adv Hematol Oncol*. 2012 Nov;10(11):726-32. PMID: 23271259.
3. **Yoon JH, Park SS, Jeon YW, Lee SE, Cho BS, Eom KS, Kim YJ, Kim HJ, Lee S, Min CK, Cho SG, Lee JW**. Treatment outcomes and prognostic factors in adult patients with secondary hemophagocytic lymphohistiocytosis not associated with malignancy. *Haematologica*. 2019 Feb;104(2):269-276. doi: 10.3324/haematol.2018.198655. Epub 2018 Sep 13. PMID: 30213834; PMCID: PMC6355492.
4. **Schram AM, Comstock P, Campo M, Gorovets D, Mullally A, Bodio K, Arnason J, Berliner N**. Haemophagocytic lymphohistiocytosis in adults: a multicentre case series over 7 years. *Br J Haematol*. 2016 Feb;172(3):412-9. doi: 10.1111/bjh.13837. Epub 2015 Nov 5. PMID: 26537747.
5. **Canna SW, Behrens EM**. Making sense of the cytokine storm: a conceptual framework for understanding, diagnosing, and treating hemophagocytic syndromes. *Pediatr Clin North Am*. 2012 Apr;59(2):329-44. doi: 10.1016/j.pcl.2012.03.002. PMID: 22560573; PMCID: PMC3368378.
6. **McLachlan SM, Rapoport B**. Breaking tolerance to thyroid antigens: changing concepts in thyroid autoimmunity. *Endocr Rev*. 2014 Feb;35(1):59-105. doi: 10.1210/er.2013-1055. Epub 2013 Dec 4. PMID: 24091783; PMCID: PMC3895862.
7. **Morshed SA, Latif R, Davies TF**. Delineating the autoimmune mechanisms in Graves' disease. *Immunol Res*. 2012 Dec;54(1-3):191-203. doi: 10.1007/s12026-012-8312-8. PMID: 22434518; PMCID: PMC4504182.
8. **Gianoukakis AG, Khadavi N, Smith TJ**. Cytokines, Graves' disease, and thyroid- associated ophthalmopathy. *Thyroid*. 2008 Sep;18(9):953-8. doi: 10.1089/thy.2007.0405. PMID: 18713026; PMCID: PMC2879490.
9. **Van der Weerd K, Van Hagen PM, Schrijver B, Kwekkeboom DJ, De Herder WW, Ten Broek MR, Postema PT, Van Dongen JJ, Staal FJ, Dik WA**. The peripheral blood compartment in patients with Graves' disease: activated T lymphocytes and increased transitional and pre-naive mature B lymphocytes. *Clin Exp Immunol*. 2013 Nov;174(2):256-64. doi: 10.1111/cei.12183. PMID: 23901889; PMCID: PMC3828829.
10. **Naji P, Kumar G, Dewani S, Diedrich WA, Gupta A**. Graves' disease causing pancytopenia and autoimmune hemolytic anemia at different time intervals: a case report and a review of the literature. *Case Rep Med*. 2013;2013:194542. doi: 10.1155/2013/194542. Epub 2013 Nov 11. PMID: 24319463; PMCID: PMC3844236.