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Hemophagocytic Lymphohistiocytosis in a Patient with Goodpasture's Syndrome: A Rare Clinical Association

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Patient: Female, 31
Final Diagnosis: Hemophagocytic lymphohistiocytosis (LHL)
Symptoms: Hemophthisis
Medication: —
Clinical Procedure: —
Specialty: Oncology

Objective: Rare disease

Background: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening clinical syndrome. HLH can occur in the setting of an autoimmune disease, chronic immunosuppression, malignancy, and infection. We discuss a rare case of a young woman who was diagnosed with Goodpasture's syndrome that was most likely complicated by HLH. To the best of our knowledge, this is the first report of HLH in the setting of this rare autoimmune disease.

Case Report: A 31-year-old woman who was diagnosed with Goodpasture's syndrome 7 years prior presented with febrile neutropenia. She was initially receiving treatment with azathioprine and prednisone, which was subsequently switched to hydroxychloroquine. Over time, she had developed polyarthritis and was later diagnosed with MPO-ANCA-positive vasculitides. On this admission, her clinical status deteriorated from persistent pancytopenia. This was initially attributed to the immunosuppressive effect of hydroxychloroquine. A bone marrow biopsy was performed and revealed hypercellular bone marrow without any cytogenetic abnormalities. Due to a prolonged pancytopenia thought to be of autoimmune etiology, treatment with high-dose steroids was initiated. With the persistent febrile episodes, hepatosplenomegaly on examination, and laboratory workup that revealed hyperferritinemia and pancytopenia, HLH syndrome was suspected. A repeat bone marrow biopsy confirmed this diagnosis with the presence of hemophagocytosis, demonstrated by the presence of histiocytes engulfing erythroid cells. She also met 5 of 8 diagnostic criteria, which confirmed the diagnosis of HLH. The patient eventually died despite aggressive treatment with high-dose steroid therapy for her autoimmune disorder, as well intravenous antibiotics and supportive care for her underlying infections.

Conclusions: HLH is a syndrome marked by a hyper-inflammatory state aggravated by specific triggers. To make the diagnosis of HLH, at least 5 of the 8 criteria must be met. Treatment involves suppression of the overwhelming inflammatory response by the use of immunomodulators. The mortality rate can range from 50–90% due to delayed recognition and onset of treatment. Here, we present a rare case of Goodpasture's syndrome with overlap and pauci-immune vasculitis, which may have triggered the HLH. This correlation has not been described before in the literature.

MeSH Keywords: Anti-Glomerular Basement Membrane Disease • Cytokines • Lymphohistiocytosis, Hemophagocytic


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Background

Hemophagocytic lymphohistiocytosis (HLH) is not an independent disease but rather a life-threatening clinical syndrome that occurs in many underlying conditions and in all age groups [1]. It is the consequence of a severe uncontrolled hyper-inflammatory reaction, in most cases is triggered by an infectious agent [1,2]. Two variants exist within this clinical spectrum of disease – familial and acquired [1,2]. Acquired HLH occurs in the setting of an autoimmune disease, chronic immunosuppression, and in malignancies [1–3]. This can also be seen in otherwise healthy patients with severe infections.

HLH that occurs in patients with autoinflammatory or autoimmune diseases is believed to be secondary to macrophage activation syndrome [4,5]. HLH is suspected to be secondary to defective natural killer (NK) cell removal of antigen, which in turn causes persistent T cell activation [4].

This syndrome has been described in patients with systemic juvenile idiopathic arthritis (sJIA) and its adult-onset form, Still's disease. This entity has also been documented in SLE and other rheumatic diseases, specifically rheumatoid arthritis, dermatomyositis, Kawasaki disease, systemic sclerosis, Behçet's disease, polyarteritis nodosa, ankylosing spondylitis, sarcoidosis, mixed connective tissue disorder, Sjögren's syndrome, and Wegner's granulomatosis [6].

Goodpasture's syndrome is a rare auto-antibody – mediated disorder that typically presents as rapidly progressive glomerulonephritis (RPGN), which may be accompanied by pulmonary hemorrhage. This syndrome is mediated by an auto-antibody against the glomerular basement membrane and is also referred to as anti-GBM disease. The diagnosis is usually made by demonstration of anti-GBM antibodies in the serum using a direct enzyme-linked immunoassay (ELISA) or a histopathology finding of anti-GBM disease in the renal biopsy [7]. Serum anti-GBM can have false-negative rate as high as 40%, depending on the kit used [8]. Thus, a renal biopsy demonstrating a linear deposition of IgG antibodies along the glomerular basement membrane is considered the standard diagnostic of choice. At the time of diagnosis, 10–38% of patients with anti-GBM antibody disease also test positive for anti-neutrophil cytoplasmic antibodies (ANCA), usually anti-myeloperoxidase (MPO) antibody [9]. This was described in the case we presented here.

The incidence of Goodpasture's syndrome is 0.5–1 case per million population. It can present in children older than 10 years and in adults of all ages, but most commonly 30–60 years of age. Younger adults tend to present with acute glomerulonephritis and pulmonary hemorrhage, whereas older adults tend to present with only glomerulonephritis [10]. The prevalence

is higher in whites than in blacks, and is also common in the Maori people of New Zealand. Immunosuppressive therapy or plasmapheresis is the mainstay of treatment for this process. Goodpasture's syndrome is fatal if untreated, since it results in a progressive impairment of kidney function.

In this case report, we discuss a rare case of a woman who was diagnosed and was being treated for Goodpasture's syndrome using immunosuppressive agents. We suggest that her autoimmune disorder may have caused HLH syndrome, most possibly triggered by a septic process, which eventually may have led to her death. A literature review showing reports of an association between HLH and Goodpasture's syndrome has yet to be described.

Case Report

We present the case of a 31-year-old woman who was well known to our institution for the last 7 years. She originally had a medical history that was significant for hypertension. Within months of her original diagnosis of hypertension, she was admitted to the hospital with complaints of hemoptysis. Chest X-ray done at that time revealed extensive bilateral perihilar consolidations. Sputum culture had been performed, which stained negative for acid-fast bacilli (AFB). Upon further laboratory evaluation, she was found to be in acute renal failure. Due to the complaints of hemoptysis seen in the setting of renal failure, a renal biopsy had been performed. Immunofluorescence microscopy had demonstrated a diffuse, necrotizing, crescentic, pauci-immune type glomerulonephritis. A linear deposition of IgG along the glomerular basement membrane, suggestive of anti-GBM nephritis, was seen (Figures 1 and 2), but serum anti-GBM antibodies were negative. With this significant biopsy result, coupled with the presentation of hemoptysis from pulmonary hemorrhage, the diagnosis of Goodpasture's syndrome was made.

Over the course of the next 7 years, she eventually developed end-stage renal disease and became dialysis-dependant. She also developed worsening polyarthritis, involving multiple small and large joints. At that time, she was also found to have antibodies to cyclic citrullinated peptide (anti-CCP) >250 units, rheumatoid factor (RF) with a titer of 1: 32, and MPO-ANCA >100. Laboratory work-up further revealed an anti-proteinase 3 (anti-PR3) level of less than 6, a negative anti-double stranded DNA (dsDNA), and a negative anti-nuclear antibody (ANA). These results essentially ruled out Wegener's granulomatosis and SLE, respectively, which also can present with lung, kidney, and joint involvement. With the diagnosis of an overlap syndrome involving a pauci-immune vasculitides with Goodpasture's syndrome, she was initially placed on azathioprine and prednisone therapy. The response of her disease

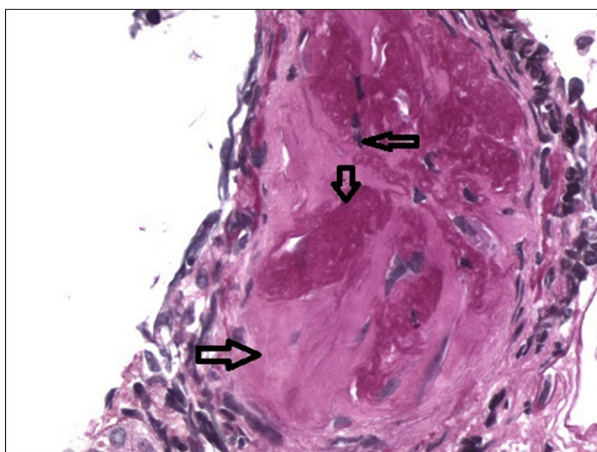


Figure 1. Demonstrating diffuse necrotizing and crescentic glomerulonephritis (left arrow) with widespread destruction of the glomerular tufts (down arrow) in renal biopsy. Mesangial cells demonstrated by long arrow.

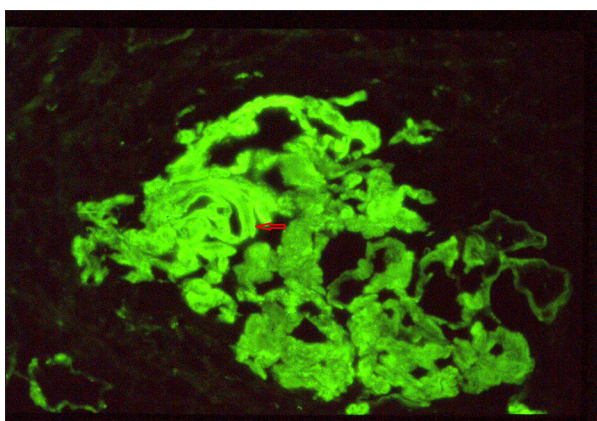


Figure 2. Immunofluorescence demonstrating diffuse, linear staining (red arrow) of glomerular basement membrane for IgG and C3, suggesting anti-GBM antibody deposition in renal biopsy.

control was followed by serial measurements of MPO-ANCA levels, which had decreased during the course of her treatment. Her symptoms of hemoptysis had resolved upon starting therapy. Azathioprine was eventually replaced by hydroxychloroquine.

Approximately 2 months after initiating therapy with hydroxychloroquine, she had presented to the hospital with new-onset fevers. She was found to be neutropenic with pancytopenia and was started on broad-spectrum antibiotics. She continued to have persistent pancytopenia, despite treatment for her underlying sepsis. Her source of sepsis was pneumonia, and her respiratory cultures had grown *Pseudomonas aeruginosa*. She was aggressively treated with culture sensitive antibiotics during this time. Her pancytopenia was initially attributed to the immunosuppressive effects of hydroxychloroquine. As

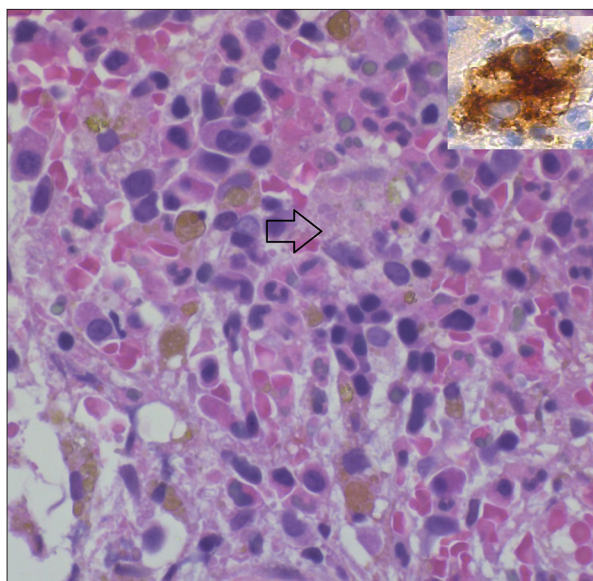


Figure 3. H/E stain of bone marrow, demonstrating histiocytes with hemophagocytosis (engulfing erythrocytes indicated by the arrow) and with CD-68 staining positive cells in the insert. (Image courtesy of Dr. Heidi Fish).

her pancytopenia persisted, a bone marrow biopsy was performed. The biopsy revealed a normocellular marrow, with normal cytogenetics, and a flow cytometry specimen that lacked a clonal population. She had subsequently developed ventilator-dependent respiratory failure (VDRF) with persistent pulmonary infiltrates. A lung biopsy was performed, which showed signs of dense alveolar hemosiderin deposits and proliferation of alveolar epithelial cells with pulmonary hemorrhage. This finding was consistent with her original diagnosis of Goodpasture's syndrome. During this time, a repeat MPO-ANCA was performed and was found to be 318 mg/dl, which was a significant increase from prior results. This suggested a possible flare-up of disease. The lung tissue culture for viruses such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV), as well as *Aspergillus* and *histoplasma* were all found to be negative, similar to results from a bronchoalveolar lavage (BAL) done previously. BAL cytology and lung biopsy did not demonstrate malignant cells.

Despite normal bone marrow biopsy results, she continued to have pancytopenia. High-dose steroid treatment was initiated for possible chronic immunosuppression caused by her autoimmune condition. She was found to be anemic during this time and laboratory work-up had revealed an elevated ferritin level of 6275 ng/ml. As very few diseases cause an elevated ferritin level, HLH was suspected in the differential. For this, a fibrinogen level was measured and was found to be elevated at 426 mg/dl with a normal serum triglyceride of 153 mg/dl. Her elevated fibrinogen may have been in response to

Table 1. HLH 2004 Diagnostic criteria (modified from ref. [4,11]).

The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled:

1. A molecular diagnosis consistent with HLH.
2. Diagnostic criteria for HLH are fulfilled (five out of eight criteria below):
 - a. Fever
 - b. Splenomegaly
 - c. Cytopenias (affecting ≥ 2 lineages in the peripheral blood):
 - i. Hemoglobin $< 90\text{g/l}$ (in infants < 4 weeks: hemoglobin $< 100\text{g/l}$)
 - ii. Platelets $< 100,000/\text{ml}$
 - iii. Neutrophils $< 1000/\text{ml}$
 - d. Hypertriglyceridemia and/or hypofibrinogenemia:
 - i. Fasting triglycerides $\geq 265\text{mg/dl}$
 - ii. Fibrinogen $\leq 1.5\text{ g/L}$
 - e. Hemophagocytosis in bone marrow or spleen or lymphnodes
 - f. Low or absent NK-cell activity
 - g. Ferritin $\geq 500\text{microgram/l}$
 - h. Soluble CD25 $\geq 2400\text{U/l}$

Comments:

1. If hemophagocytic activity is not proven at the time of presentation, further search for hemophagocytic activity is encouraged. If the bone marrow specimen is not conclusive, material may be obtained from other organs. Serial marrow aspirates over time may also be helpful.
2. The following findings may provide strong supportive evidence for the diagnosis: (1) spinal fluid pleocytosis (mononuclear cells) and/or elevated spinal fluid protein, (2) histological picture in the liver resembling chronic persistent hepatitis (biopsy).
3. Other abnormal clinical and laboratory findings consistent with the diagnosis are: cerebromeningeal symptoms, lymph node enlargement, jaundice, edema, skin rash. Hepatic enzymes abnormalities, hypoproteinemia, hyponatremia, increased VLDL, decreased HDL.

her inflammatory state from her underlying infection. With the persistent febrile episodes, hepatosplenomegaly on examination, persistent pancytopenia, and a suspicion of a hemophagocytic syndrome (HLH), a repeat bone marrow biopsy was performed. Biopsy results now demonstrated normocellular marrow for her age, with increased number of histiocytes with hemophagocytosis identified. There was no evidence of overt myelodysplasia, increase in myeloblasts, plasma cell dyscrasia, or lymphoma. Histiocytes were also highlighted by immunohistochemical stain for CD68 and demonstrated to have been engulfing erythroid cells. Flow cytometry on the aspirate showed no abnormal myeloid maturation, increase in blasts, or clonal population. Cytogenetics was also found to be normal (Figure 3). With these findings, our patient met 5 out of 8 criteria required for the diagnosis of HLH. This included: persistent fevers, hepatosplenomegaly, hyperferritinemia, pancytopenia, and bone marrow demonstration of hemophagocytic cells. Subsequently, she was started on high-dose steroid therapy and she improved modestly. Within 1 week, she once again developed worsening pancytopenia. At this point, she was given intravenous cyclophosphamide for her diagnosed HLH. Her clinical condition continued to deteriorate despite these aggressive efforts and she could not tolerate any further therapy aside from high-dose steroid. She eventually died from hypoxic respiratory failure with worsening pneumonia, secondary to multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.

We have presented the case of a patient with a diagnosis of Goodpasture's syndrome with an overlap of MPO-ANCA-positive vasculitides, which was complicated by hemophagocytic lymphohistiocytic (HLH) syndrome. This syndrome may have been triggered secondary to infections that had developed from her poor autoimmune state.

Discussion

HLH is a condition marked by a severe hyperinflammatory response and is not an independent disease [1,2,4]. HLH can either be primary in nature, which involves genetic mutations, or it can be secondarily associated with malignancies, autoimmune diseases, organ transplant, acquired immune deficiency, or infections. The latter is also referred to as acquired HLH [1,2]. HLH might also be triggered by the immunosuppressive treatment used in autoimmune conditions, such as azathioprine, sulfasalazine, methotrexate, and monoclonal antibodies such as adalimumab, infliximab, and etanercept [2].

The pathophysiology of HLH involves defects in transport, processing, and functioning of cytotoxic granules found in natural killer cells and cytotoxic T lymphocytes [2]. Increase in levels of T-cell- and macrophage-derived cytokines — particularly TNF-alpha, interleukin (IL-1), IL-6, interferon gamma, soluble IL-2 receptors and soluble TNF receptors — are thought to result in this

clinical syndrome. This is thought to occur secondary to dysregulation of the macrophage-lymphocyte interaction system [1].

Atteritano et al. published a review of 421 patients with rheumatological disorders with an association with HLH, reporting an association with HLH in 94 patients with SLE, 37 patients with Still's disease, 25 patients with Kawasaki's disease, 13 patients with rheumatoid arthritis, 7 patients with dermatomyositis, and 6 patients with polyarteritis nodosa. Other disease entities mentioned with an association to HLH include sarcoidosis, systemic sclerosis, Sjögren's disease, ankylosing spondylitis, mixed connective tissue disease, Behçet's disease, and Wegener's granulomatosis [6]. Of note, this review article did not include any description of an association with Goodpasture's syndrome.

HLH is diagnosed using the clinical criteria developed by the study group of the Histiocyte Society. It includes a molecular diagnosis consistent with HLH or a fulfillment of 5 out of the following 8 diagnostic criteria (Table 1): fever; splenomegaly; cytopenias (affecting greater than or equal to 2 lineages in the peripheral blood); hypertriglyceridemia and/or hypofibrinogenemia; hemophagocytosis in bone marrow, spleen, or lymph nodes; low or absent NK-cell activity; hyperferritinemia; and increased soluble CD25 marker [4,11].

The management of HLH involves suppressing the hypercytokinemia that causes this disease process. It also entails eliminating activated and infected cells. Patients diagnosed with the genetic form of HLH can be cured through hematopoietic stem cell transplantation [6,12]. Acquired HLH, however, may not respond to this treatment. Because the underlying cause of the acquired form varies, treatment options have not yet been standardized [1,5,7,13]. To date, various agents have been used for the treatment of the underlying disease process causing HLH. Immunomodulatory and immunosuppressive agents, as well as T-cell and cytokine antibodies have been used in this setting. These agents include corticosteroids, cyclosporine A, intravenous immunoglobulin, etoposide, cyclophosphamide, anti-TNF alpha, methotrexate, G-CSF (granulocyte colony-stimulating factor), and in some rare cases, plasmapheresis. Currently, corticosteroids are the first-line treatment. Intravenous cyclophosphamide has been found to be more beneficial than intravenous cyclosporine or immunoglobulin [2]. Biologic agents

such as etanercept, alemtuzumab, rituximab, and interferon γ , have also shown promising results [1,14]. Supportive care for the aggravating event, such as infection, remains paramount in the treatment of this process. This contributes to the rapid reduction of the antigenic burden, which eventually helps control the disease activity. Once the diagnosis of HLH has been made, immediate treatment should ensue because the mortality rate can be as high as 50–90% [1,2,15]. In most cases, this is in part due to late recognition and delayed onset of treatment [12].

We have described a patient who had HLH associated with her rheumatological condition, Goodpasture's syndrome with an overlap, and ANCA-positive vasculitides. We feel that due to her complex and rare autoimmune condition, HLH was probably the ultimate cause of death.

Conclusions

HLH is a state of hyperinflammation characterized by nonspecific symptoms and laboratory findings. A high clinical suspicion of HLH must be considered patients with prolonged fever, cytopenias, and hyperferritinemia. The lack of a standardized treatment plan continues to be a challenge. With the reporting of this case, we hope to emphasize the known association of autoimmune conditions with HLH. Here, we considered a possible cause of secondary HLH to be that of Goodpasture's syndrome with pauci-immune vasculitides, a disease entity with a well known autoimmune pathophysiology. Severe infection, as discussed earlier, was most likely the triggering factor in the causation of HLH. Early recognition severe infection as a possible inciting factor for this disease state may lead to decreased morbidity and mortality in future cases through early treatment interventions.

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Conflict of interest disclosure

The authors declare no competing financial interests. Off-label drug use: None disclosed.

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