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Atypical Case of Cold Agglutinins Disease (CAD), Hemophagocytic Lymphohistiocytosis (HLH), Narcolepsy, and Polymyalgia Rheumatica (PMR): Case Report & Management Discussion

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Abstract

Cold agglutinins disease (CAD) is a rare type of autoimmune hemolytic anemia. Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disease eventually caused or reactivated by a viral infection which can lead to the production of cold agglutinins. Narcolepsy is a sleep disorder caused by a lack of a brain chemical called hypocretin (orexin) secondary to immune attack related to Human Leukocyte Antigen DQB1 (HLA-DQB1). Polymyalgia rheumatica (PMR) is an inflammatory disorder that can be hard to diagnose and usually occurs with another serious condition called giant cell arteritis. We report a case of a 78-years-old male patient with an atypical presentation of possible associated to past Epstein Bar Virus (EBV) or Cytomegalovirus (CMV) and/or HLA. The purpose of this case is defining the first association within all four conditions as well as its biological and clinical manifestations plus the management with glutathione (GSH) as part of integrative therapeutically approach.

Keywords: ***Cold agglutinins disease; Hemophagocytic lymphohistiocytosis; Narcolepsy; Polymyalgia rheumatica; Atypical case***

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1. Introduction

Cold agglutinin disease (CAD) is a type of autoimmune hemolytic anemia defined by the presence of cold autoantibodies (autoantibodies which are active at temperatures below 30°C). Primary CAD has a prevalence of 16 cases per million inhabitants with an incidence of 1 per million per year, a median age of 67 years, and the male to female ratio was 0.55, but others report 16-32% of Autoimmune Hemolytic Anemias (AIHA), whose annual incidence is estimated to be between 1/35,000-1/80,000 in North America and Western Europe [1,2]. Autoimmune diseases other than CAD were reported in 8% of patients. Monoclonal IgM was detected in 90%; IgG and IgA in 3.5% each; with kappa light chains in 94% and an abnormal kappa/lambda ratio in bone marrow was found in 90%, lymphoma in 76%, and lymphoplasmacytic lymphoma in 50% [1].

Hemophagocytic lymphohistiocytosis (HLH) is a condition in which the body makes too many activated macrophages and lymphocytes. People with HLH usually develop symptoms within the first months or years of life. Symptoms may include fever, enlarged liver or spleen, cytopenia (decreased number of blood cells), and neurological abnormalities. HLH may be inherited in an autosomal recessive manner or it can have non-genetic causes in which case it is called acquired HLH [3-6].

Narcolepsy is a neurological disorder characterized by excessive daytime sleepiness, cataplexy, hypnagonic hallucinations, sleep paralysis, and disturbed nocturnal sleep patterns, caused by loss of orexin-producing neurons in the lateral hypothalamus. It usually starts in the second or third decade of life and affects both sexes equally. Although late-onset after the age of 40 is rare, these patients may receive treatment only in adulthood due to delayed diagnosis [7]. The association of narcolepsy with HLA DQB1*06:02 allele suggests an autoimmune process selectively targeting orexin-producing neurons [7].

Polymyalgia rheumatica (PMR) is considered a benign disease by some, while others consider it a more serious illness requiring a similar treatment approach as to giant cell arteritis (GCA). The diagnosis of polymyalgia rheumatica is usually based on clinical presentation and an increase of non-specific inflammatory markers. There are no pathognomonic findings that can confirm the diagnosis. PMR usually affects adults over the age of 50, and with an average of 70 years old. Women are twice as likely to get PMR as men and are more common among Caucasians. It is more likely to affect people of Northern European origin; Scandinavians are especially vulnerable [8,9].

To our knowledge, there is no published case report of concurrent CAD, HLH, narcolepsy, and PMR. In this report, we are making the first correlation or coexistence of these four diseases in an atypical presentation and our diagnostic and therapeutic approach.

2. Case Report

2.1 History and physical exam

A 78-years-old white Latino male from Colombia living in Puerto Rico for around 40 years, was referred to the hematology/oncology service due to suspected underlying malignancy. His symptoms included mostly nocturnal fever

for the last 3 months associated with 15 pounds weight loss, weakness, fatigue, cold sensitivity, and polyarthralgias with morning stiffness. Prior workup for infectious diseases to account for fever was negative. His pertinent past medical history consisted of benign prostatic hyperplasia, spinal radiculopathy from degenerative disc disease with spinal surgery during the 1970s requiring blood transfusion, and more recently early dementia and narcolepsy. Narcolepsy without cataplexy was diagnosed 5 years before, confirmed by polysomnography and multiple sleep latency testing, and with HLADQB1*6:02 alleles positive status. He has been taking donepezil 10 mg/day and methylphenidate 5mg in the mornings and had known allergy to iodine. His family history was positive for unknown malignancies in one brother and 2 sisters, plus chronic kidney disease in his father and one brother. He had no toxic habits. At the physical exam, he was afebrile but chronically ill, tachypneic, anxious, with bilateral axillary nonfixed lymphadenopathy, palpable liver edge at the right upper quadrant, and arthritic joint changes. No skin or mucosal lesions or bleeding signs were observed.

2.2 Investigations

His initial laboratories revealed a total white blood cell count of 20,300 per microliter with a normal differential, hemoglobin of 13.5 gm/dL, platelets of 417,000 per microliter, blood urine nitrogen of 25mg/dL with a serum creatinine of 0.85 mg/dL, normal electrolytes, normal liver function tests, normal creatine phosphokinase (CPK) levels but elevated serum aldolase of 17.9 U/L, positive C-reactive protein (CRP) titers of 1:16, erythrocyte sedimentation rate (ESR) of 67 mm/hr. (maximal value of 108 mm/hr later in clinical course), positive Direct Antiglobulin Test (DAT), normal urinalysis, negative urine, and blood cultures, and normal chest x-ray and echocardiogram. Further evaluation demonstrated an abnormal serum protein and immune electrophoresis with low albumin of 2.8 gm/dL, elevated alpha1 globulin of 0.5 gm/dL, and a polyclonal IgM pattern. He had elevated free kappa light chains of 60.76 mg/L, but normal serum B2-microglobulin of 0.25 mg/dL and lactic acid dehydrogenase of 145 U/L. The leukocyte alkaline phosphatase score was high at 231 with positive cold agglutinin's (CA) titers at 1:4 dilutions. All the antibodies for autoimmune disease workup were negative including ANA, Rheumatoid factor, anti-ds-DNA, anti-SS-A, anti-SS-B, anti-centromere, and anti-SCL70 antibodies. Regarding viral serologic tests, he had non-reactive Hepatitis B core IgG and IgM antibodies and Hepatitis B surface antigen, as well as his Hepatitis B surface antibody, was negative with <3.5mIU/mL. The Herpes Simplex virus (HSV) type II IgG antibody was negative with <0.2 antibody index (AI), but his HSV type I IgG antibody was positive with 6.9 AI indicative of past infection or exposure. The HSV IgM I/II combination was negative with <0.91 ratio. HIV testing was negative. Epstein Bar virus (EBV) serology revealed VCA IgM negative with 0.2 AI but EBV VCA IgG positive with >8.0 AI also indicative of past infection or exposure. Cytomegalovirus (CMV) serology was similar to EBV with negative IgM (<0.2 AI), but IgG positive (>8.0 AI).

A body PET-CT scan from the base of the skull to mid-thighs using fluorodeoxyglucose (FDG) was done and no evidence of malignant process was found, but increased diffuse uptake in the vertebral column suggested anemia (Fig. 1-A & 1-B). Bone marrow aspiration and biopsy with flow cytometry demonstrated a normal-to-mildly hypercellular bone marrow with trilineage hematopoiesis, granulocytic left shift, a mild increase of hemophagocytic histiocytes, and mildly increased iron stores (Fig. 2). No evidence of lymphoproliferative or plasma cell neoplasia was observed.

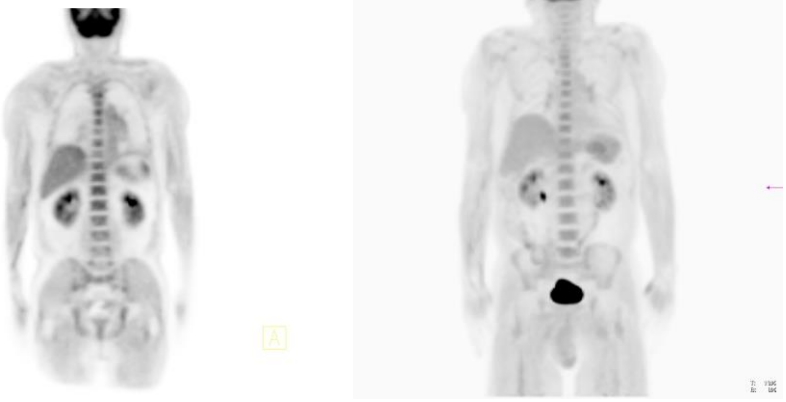

Fig. 1-A: PET CT coronal images Fig. 1-B: PET MIB images

Fig. 1. Fluorodeoxyglucose (FDG) PET CT scan revealed no evidence of hypermetabolic adenopathy, although increased uptake was seen diffusely in the vertebral column most suggestive of bone marrow activation such a in anemia

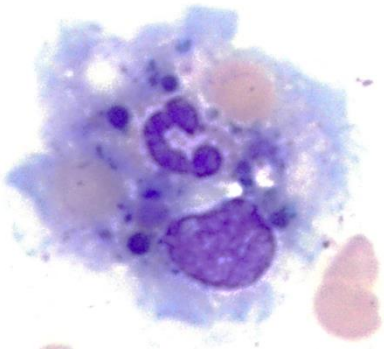

Fig. 2. The bone marrow aspirate showed the presence of increased histiocytes, including hemophagocytes containing engulfed granulocytes, erythrocytes, lymphocytes, and hemosiderosis debris. These were present throughout the marrow and occasionally in small groups.

2.3 Differential diagnosis

The diagnostic criteria for CAD are chronic hemolysis, positive DAT with multiple specificities, a single antigen DAT antibody strongly positive for C3d, CA titer ≥64 at 4°C, and no evidence of malignancy by clinical examination [9]. The CA titer is usually highest than the minimum titer required for diagnosis and, as noted anteriorly, the single antigen DAT antibody may be weakly positive for IgG in up to 20% of patients. Additional testing for determination of the thermal amplitude (TA) can be considered but is time-consuming and in most cases is not required for diagnosis. However, TA determination may be useful in some situations, particularly to exclude normally occurring CA's as a cause of false-positive findings in cases with relatively low titers.

Serum electrophoresis with immunofixation, Ig class quantification, flow cytometry in bone marrow aspirate, and examination of a bone marrow biopsy should always be done to detect and distinguish the clonal lymphoproliferative disease (LPD). Negative results do not forbid primary CAD, however, because this may be a matter of sensitivity. For serum immunoglobulin analyses and CA titration, it is important that blood specimens are kept between 37 to 38°C from sampling until the serum has been removed from the clot [9].

The clinical presentation in CAD often provides an crucial key to the differential diagnosis, making a focused history and clinical examination even more informative than in warm AHIA. Ninety percent of patients have cold-induced circulatory symptoms, which can range from slight acrocyanosis to disabling Raynaud phenomena. Approximately 70% of them experienced an exacerbation of anemia during febrile infections, as described previously. In Scandinavia, the median hemoglobin (Hb) level in CAD is 9.0 g/dL and the lower tertile 8.0 g/dL. About half of the patients not treated are considered transfusion-dependent for shorter or longer periods [10].

The standard definition of HLH, according to the HLH-2004 study group, requires that at least five of the following clinical criteria are met: fever, splenomegaly, peripheral cytopenia's of 2 or 3 lineages, hypertriglyceridemia, hypofibrinogenemia, no evidence of malignancy, elevated ferritin (>500 µg/L), elevated sCD25 (interleukin-2 (IL-2) receptor ≥2400 U/mL), low or absent NK cell activity and histological evidence of hemophagocytosis in bone marrow, lymph nodes or spleen [11]. A molecular diagnosis consistent with HLH may also be enough for the diagnosis [6]. Atypical forms of HLH may have an indolent course and the diagnosis must be considered in the presence of prolonged fever, cytopenias, and liver failure [10].

According to ACR and EULAR [12], the diagnostic criteria for PMR includes patients more than 50 years old presenting with new bilateral shoulder pain and elevated CRP/ESR in the presence of morning stiffness more than 45 minutes, and new hip involvement in the absence of peripheral synovitis or positive RA serology.

Our patient completed two criteria for CAD (positive DAT and CA), only one defined criteria (fever) for HLH except for bone marrow histology and three PMR diagnostic criteria (age more than 50 years old presenting with pain, and elevated CRP and ESR).

Defining the type of HLH can be difficult, despite the advances in molecular diagnosis. In this case, autoimmune disease, malignancies, and infectious conditions were excluded during the investigation, except for EBV and CMV titers suggesting that he had previous infections.

2.4 Management

Due to a diagnosis impression of cold agglutinin's disease plus polymyalgia rheumatica, he has placed on prednisone 20 mg plus 1 mg of folate oral daily empirically but in view of no significant improvement after one month and increasing ESR, he was admitted for pulse steroid intravenous therapy followed by moderate improvement. He went home on oral prednisone 1 mg/kg per day shortly followed by recurrence of signs and symptoms. Oral azathioprine was added at 50 mg daily with an orthomolecular glutathione dose of 1000 mg intravenously every three weeks. His last ESR is 22

mm/hr. with CRP titer of 1:4. This approach resulted in good performance status and excellent response. Currently, he is the process of weaning off azathioprine.

3. Discussion

This is the first report describing atypical HLH in an adult with CAD, narcolepsy, and PMR without any other laboratory and studies suggestive of malignancy or recent infection. The diagnosis of this case was challenging, and it took a few weeks to confirm the PMR presentation and the associated diagnoses.

After reviewing the medical literature, we found one paper from Colombia describing four pediatric cases with HLH where only one patient fulfilled the diagnostic criteria for 2 months of age, three patients exhibited the disease manifestations later in their childhood, and all four cases were confirmed to have the genetics of Familial HLH [13]. Niece et al [14] performed a retrospective chart review of local oncology and pathology databases and identified 70 patients with HLH from 1992 to 2007 with a median age of 1.8 years (range 0.1-16.5 years) and 43% were Latino. Primary HLH is common in children and associated with family history and/or a homozygous mutation in the Perforin, Syntaxin-11 or Munc 13-4 genes, although secondary HLH is usually present at any age and related to a variety of infections [14]. Our case is particular or atypical due to the late adulthood presentation without a family history of HLH. However, this patient is originally from Colombia, corresponding with most Latin Americans presented in the above study. Regarding his clinical picture, he only had a fever with histologic findings on his bone marrow.

Regarding our patient's concurrent narcolepsy diagnosis with HLADQB1*6:02 allele positivity, and literature reports of a possible association of narcolepsy to various HLA class II encoded HLA-DRB1-DQA1-DQB1 haplotypes and other autoimmune diseases including Graves's disease, rheumatoid arthritis, and type 1 diabetes [7], no association of narcolepsy to PMR has been described. In fact, PMR has been associated with HLA alleles DR4 and DRB1*04, the later also associated with rheumatoid arthritis [15]. Despite narcolepsy and PMR respective HLA DRB1 associations in common to rheumatoid arthritis, our patient did not fulfill clinical criteria and did not have positive rheumatoid arthritis antibodies, which makes concurrent narcolepsy and PMR disorders a very rare occurrence.

We found that CAD and PMR seem to be rare in Hispanics and Gonzalez et al [16] found a relative occurrence and pattern of demographic involvement of PMR in the Gulf Coast region of the United States and most of them are of the white race. This also makes our case exclusive and atypical.

Another interesting issue, in this case, is the response to a combination of oral immunosuppressive therapy (azathioprine) plus a parenteral natural antioxidant (glutathione). Barcellini [17] wrote an excellent review of current therapeutic management of autoimmune hemolytic anemia including CAD using systemic corticosteroids as standard treatment and rituximab also recommended as first-line treatment. Azathioprine is another CAD treatment option. Regarding PMR, azathioprine has been a treatment option known since 1977 [17] but glucocorticoids remain the cornerstone treatment for polymyalgia rheumatica. Often PMR patients react swiftly to this approach but in 29-45% of cases the efficacy is delayed for 3 to 4 weeks [18]. The typical PMR treatment course lasts from 1 to 3 years. Other

steroid-sparing treatment alternatives include methotrexate, leflunomide, and tocilizumab, an IL-6 receptor inhibitor [18,19].

There is one reported case using azathioprine after steroids in Systemic Lupus Erythematosus with Hemophagocytic Lymphohistiocytosis in a Male [20]. Various immunomodulatory and immunosuppressive agents [21], as well as T-cell and cytokine antibodies, have been used in this setting including corticosteroids, cyclosporine A, intravenous immunoglobulin, etoposide, cyclophosphamide, anti-TNF alpha, methotrexate, G-CSF (granulocyte colony-stimulating factor), and in some rare cases, plasmapheresis [20]. Currently, corticosteroids are the first-line treatment. Intravenous cyclophosphamide has been found to be more beneficial than intravenous cyclosporine or immunoglobulin Biologic agents such as etanercept, alemtuzumab, rituximab, and interferon γ, have also shown promising results [19].

Glutathione (GSH) is a major intracellular antioxidant capable of scavenging free radicals and detoxifying electrophiles from endogenous and exogenous sources via the free thiol group. Several studies have investigated GSH efficacy in immune diseases [22-26], but no studies have been published regarding its use in CAD, HLH, and PMR. We tested GSH combined with azathioprine in our case and the excellent clinical response allowed for weaning off the immunosuppressive drug. Thus, we postulate that adding complementary GSH as integrative medicine management deserves further investigation in PMR and possibly other autoimmune diseases with systemic inflammatory markers.
Kelkar et al [27] presented a similar case to ours of a 25 years-old female patient complicated by the development of the nephrotic syndrome and autoimmune hemolytic anemia (AIHA). Antinuclear antibody and ribonucleoprotein were positive, with concurrent physical examination findings, indicating underlying mixed connective tissue disease (MCTD). Ferritin was greater than 40,000 ng/dL. Viral studies, including hepatitis A, B, and C, cytomegalovirus (CMV), and Epstein-Barr virus (EBV) were negative. Based on her clinical presentation, a diagnosis of HLH secondary to MCTD was made and started on high-dose prednisone with excellent response followed then by azathioprine, hydroxychloroquine, prophylactic antibiotics, and a prednisone taper for long-term management. This is the only first case with an association of both AIHA and MCTD with HLH, providing support for a possible relationship between these 3 conditions like our case, but we are reporting an association of atypical CAD, HLH and PMR, although we recognize that some tests such as ferritin level were not done.

Another important aspect is the shared immunopathogenesis among these conditions. HLH involves inborn defects in lymphocytes (particularly in cytotoxic cells, such as natural killer [NK] cells, cytotoxic T cells, and T-regulatory cells), which normally mediate control of infectious and inflammatory conditions within the immune system and in other tissues. As per Usmani et al [28], HLH is a reactive process resulting from an uncontrolled immune response triggered by different stimuli based on an underlying inherited or acquired inability to regulate this trigger. Impaired NK-cell cytotoxicity is a hallmark HLH. Severe immune dysregulation occurs when perforin-mediated cytotoxicity is diminished or absent, compromising the homeostatic removal of target cells. The result is the excessive proliferation and persistent activation of antigen-presenting cells (histiocytes, macrophages, and CD8+ T cells) as well as excessive cytokine production, proliferation and ectopic migration of T cells [28]. Hemophagocytosis, the characteristic finding for which the disorder was named, is a hallmark of activated macrophages/histiocytes. Because of the clinical importance of hemophagocytosis for the diagnosis of HLH, macrophages have long been assumed to play an essential role in HLH.

Remarkably, no clinical or experimental data have distinguished whether these cells play a causal role in the development of HLH or are simply an epiphenomenon of systemic inflammation. Indeed, hemophagocytosis is not only seen in HLH but has also been reported in critically ill patients with a variety of infectious or inflammatory disorders.

CAD is frequently related to lymphoproliferative disorders; it commonly thought that autoimmunity is the result of the interaction of genetic predisposition and environmental factors; IgM is directed against I/I system, and the role of the complement system is important due to IgM cold autoantibody binding to C1 and therefore initiating the classical complement pathway [29].

Regarding narcolepsy, an autoimmune basis for the orexin cell loss has long been suspected due to its specific association to HLA DQB1*06:02 allele. HLA genes encode multiple subtypes of MHC class I and II molecules involved in presenting antigens to T cells during infections thereby triggering immune responses via T cell activation. In addition, there is an association between narcolepsy and other immune system gene polymorphisms, such as the T cell receptor alpha locus. It is suggested that this association confers an increased risk for molecular mimicry during antigen presentation to T cells. Support for this molecular mimicry mechanism includes the increased rates of narcoleptic onset in children following exposure to influenza A H1N1 infections and selected H1N1 vaccine preparations [7]. Thus, a population of T cells is be activated by H1N1 epitopes then leading to the destruction of orexin-producing neurons.

Inflammation in PMR patients occurs in the synovium and bursae of the shoulder and hip girdles where recognition of an unknown antigen by dendritic cells or macrophages occurs. This synovitis is characterized by vascular proliferation and leukocyte infiltration predominantly macrophages and T lymphocytes, probably activated through the innate immune response [30]. In addition, there is an increased production of IL-6 and IL-1 beta, but the role of other circulating cytokines remains unclear [29-31]. The scarce number of studies makes difficult to evaluate the exact contribution of cytokine polymorphisms to PMR pathogenesis.

4. Conclusion

In conclusion, our present case suggests the importance of the association of those atypical condition's CAD, HLH, narcolepsy, and PMR as well as its integrative medical management and may demonstrate the need for new approaches for PMR patients.

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