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Granulomatosis with Polyangiitis Occurring Concurrently With Human Monocytic Ehrlichiosis, a Causative Relationship or Coincidence

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Abstract The relationship between some infections and vasculitides especially antineutrophil cytoplasmic antibodies (ANCA) mediated disease is well established. However, the mechanisms by which infection triggers ANCA formation are not fully understood. We report a case of granulomatosis with polyangiitis (GPA) occurring concurrently with human monocytic ehrlichiosis (HME) and discuss the possible relation between the two disease processes. A 49 year old Caucasian female presented with septic shock with multiple organ dysfunction syndrome that was attributed to HME. The patient was noted to have a small crusted lesion on the left nasolabial fold. Over the course of her hospitalization, it gradually expanded and eroded into the nasal cavity. After appropriate workup, she was diagnosed with GPA. HME hasn't been clearly linked to any type of vasculitis. Review of the literature revealed scarce evidence limited to case reports and retrospective studies describing the association between GPA and HME. We highlight in this case a possible link between HME and GPA, however, the exact relationship between HME and GPA remains unclear and warrants further study.

Keywords: *granulomatosis with polyangiitis, human monocytic ehrlichiosis, vasculitis*

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1. Introduction

The causative relationship between some infections and vasculitides especially antineutrophil cytoplasmic antibodies (ANCA) mediated disease is well established. Epidemiological studies have suggested that infection may trigger ANCA formation and exacerbation of ANCAmediated disease. The mechanisms by which infection triggers ANCA formation are not fully understood. The infection may directly invade vessel walls or trigger immune complex deposition within the vessels [1].

We report a case of granulomatosis with polyangiitis (GPA) which is an ANCA mediated disease occurring concurrently with human monocytic ehrlichiosis (HME). To the best of our knowledge, there is only one case report in literature that describes a patient with history of GPA who was later diagnosed with HME [2].

2. Case Report

A 49 year old Caucasian female presented to our emergency department in the summer of 2013 with seizures, hypotension, and hypoxic respiratory failure requiring intubation.

The patient lived on a farm in rural Illinois and had a history of tick bite. She had no other past medical history. Aside from hypotension and hypoxic respiratory failure, her physical exam was only remarkable for a small crusted lesion on the left nasolabial fold.

Admission laboratory tests were remarkable for WBC count of 16.3 10^3/uL, hemoglobin of 10.7 g/dl, platelets of 98 10^3/uL, alanine aminotransferase of 682 units/L, aspartate aminotransferase of 2296 units/L, total bilirubin of 6.2 mg/dl, blood urea nitrogen of 70 mg/dl, creatinine of 5.1 mg/dl, and lactic acid of 8.2 mmol/L. Urinalysis was remarkable for 27 red blood cells and 6 white blood cells/HPF. Chest radiograph revealed bibasilar infiltrates.

The patient was admitted to the medical intensive care unit (ICU) and was treated for septic shock with multiorgan failure. She was started on broad spectrum antibiotics with Vancomycin and Aztreonam. Unfortunately, her shock persisted. Bacterial cultures from blood, sputum and urine remained negative. Serology for Ehrlichia chaffeensis revealed IgG antibodies >1:1024 and IgM antibodies> 1:128. Serologies for other infectious

agents remained negative. Doxycycline was added to her antibiotics regimen. Her shock gradually improved. Her shock and multiorgan failure were attributed to HME. The patient had also developed acute kidney injury briefly requiring renal replacement therapy (RRT).

As mentioned above, the patient was noted to have a small crusted lesion on the left nasolabial fold. Over the course of her hospitalization, it gradually expanded and eroded into the nasal cavity (Figure 1). Two weeks into admission, the lesion was described as 5 cm nontender, pinkpurple, indurated nodule with erosion of inferior left ala.

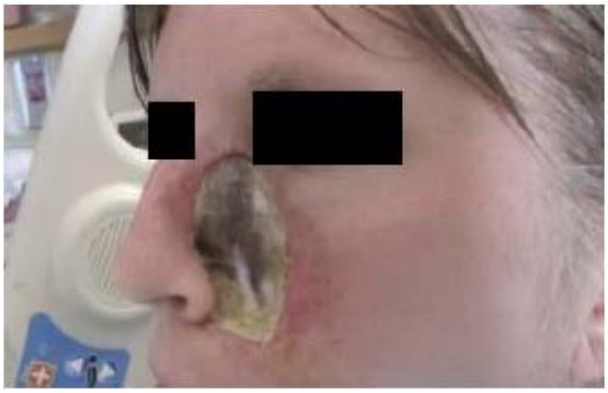

Figure 1.

CT scan of facial bones showed a lytic lesion on the floor of maxillary sinus, as well as periorbital soft tissue swelling (Figure 2). Punch biopsy revealed acute and chronic inflammation with perivascular involvement. Autoimmune workup was remarkable for positive C-ANCA 1:320, PR3 of 4.1, and undetectable P-ANCA. She was diagnosed with granulomatosis with polyangiitis. Kidney biopsy did not revealed vasculitis, necrosis or crescents and Immunofluorescent stains were negative. She was started on intravenous methylprednisolone and Rituximab. She eventually she was discharged to rehabilitation facility.

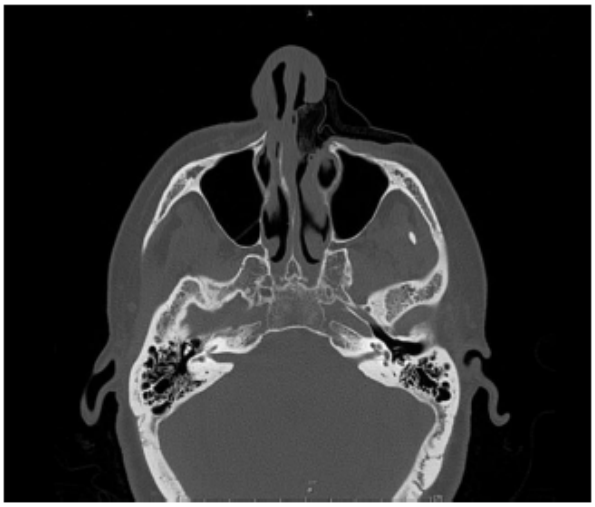

Figure 2.

3. Discussion

HME is caused by E. chaffeensis, a rickettsialike obligate intracellular bacteria. These bacteria infect the human monocytes [2,3]. HME is highly endemic in the Midwestern United States as well as in the southeast, south-central, and mid-Atlantic regions of the United States where the white-tailed deer (Odocoileus virginianus), the reservoir, and the Lone star (Amblyomma americanum) tick, the vector, are abundant. The spectrum of disease is broad, ranging from a mild febrile illness to fulminant, multi-system organ failure resulting in death. The diagnosis of HME begins with a careful detailed history to include travel history to endemic areas and exposure to ticks. As the symptoms and signs are nonspecific, the diagnosis relies primarily on clinical suspicion and laboratory tests. The diagnosis is suggested by a febrile illness with history of tick bite or exposure, thrombocytopenia and leukopenia. Elevated transaminases are frequently seen in the more severe cases of HME. Examination of peripheral blood with Giemsa stain occasionally reveals characteristic intra-leukocytic vacuoles (morulae). Detection of the IgG antibody of a titer of at least 1:256 in the blood or CSF is considered diagnostic [4]. Doxycycline is the drug of choice based upon in vitro studies, empirical data, and expert consensus. No controlled prospective studies have been conducted. Given increased morbidity and mortality with delayed treatment, empiric therapy with doxycycline should be started as soon as possible whenever there is clinical suspicion of the disease. Treatment should be continued for at least 10 days or until 3 days of defervescence. Persistence of fever for more than 48 hours following treatment suggests a different diagnosis. Rifampin is an effective alternative in pregnant women and children.

GPA is an ANCA-mediated systemic vasculitis that affects both small- and medium-sized vessels, it mostly affects older adults although it can be seen in younger age. Patients with GPA usually present with chronic constitutional symptoms such as fatigue, malaise, weight loss and arthralgias. GPA is commonly presented as a combination of renal failure and upper airway involvement. The diagnosis is usually confirmed by biopsy of a site of active disease which shows leukocytoclastic vasculitis with evidence of necrotic changes and granulomatous formation [5].

Although associations between infections and vasculitis are well established in some instances, HME hasn't been clearly linked to any type of vasculitis. Bacterial as well as viral infections are associated with GPA but no association with ehrlichioses was described [6,7,8]. Several mechanisms by which infection triggers ANCA formation have been described; One important concept is *Autoantigen complementarity*, which suggest that the initial immune response in patients with ANCA mediated disease is not directed toward the autoantigen but rather to a peptide complementary to the original autoantigen leading to inflammatory response triggered by microbial exogenous peptides that mimic the complementary peptide and cross-react with the original protein [9]. Another proposed theory is the *Neutrophil extracellular traps (NETs)* which are a mechanism that controls bacterial infections. NETs formation is characterized by production and recruitment of neutrophils to a meshwork of chromatin fibers that trap and kill microbial pathogens [10]. NETs can induce an autoimmune response by exposing autoantigens, inducing IFN-α production, complement system activation, and granulomatous formation [11].

Review of the literature revealed a case report of a patient with GPA who was later diagnosed with HME. Additionally, a retrospective study of fifty-five patients with various types of vasculitis revealed that 5.5% of the patients had titers of 1:128 or higher against E. chaffeensis [12] . Rickettsiae are known to invade the endothelial cells in blood vessels and induce a vasculitic state, however, this is not seen with HME which can induce a granulomatous response similar to that seen in GPA [13] . This granulomatous formation found in HME may suggest a unique immunologic response explained by mechanisms similar to the ones mentioned earlier and leads to GPA or other vasculitides.

4. Conclusion

There is a relationship between certain infections and vasculitis. This case report highlights a possible link between HME and GPA. The exact relationship between HME and GPA remains unclear and warrants further study.

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