Relationship Between ANCA-Associated Vasculitis and Infection: A Review

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Abstract: ANCA-associated vasculitis (AAV) is an autoimmune disease with multiorgan involvement of the entire body. And infection has been paid more and more attention in the course of treatment. As far as the current research is concerned, infection participates in the pathogenesis of AAV, interferes with the treatment of AAV, and affects the prognosis of AAV. This paper focuses on the role of pathogen infections in AAV pathogenesis. This review also elaborates on the types and prognosis of secondary infections in AAV patients. According to the current study, maintaining an appropriate BMI and vaccination is beneficial to the prevention of infection and the prognosis of AAV patients.

Keywords: ANCA; Infection; Pathogenesis; Complications.

Introduction

Antineutrophil Cytoplasmic Antibody (ANCA) associated vasculitis (AAV) is characterized by inflammation of small vessels. It is an autoimmune disease that can affect a number of different systems of the body. The ANCA serotypes are PR3-ANCA, MPO-ANCA, and ANCA-negative. According to pathological classification, it is divided into Microscopic polyangiitis (MPA), Granulomatosis with polyangiitis (GPA), and Eosinophilic granulomatosis with polyangiitis (EGPA).[1] Although AAV is rare, the occurrence rate of AAV has been increasing over time.[2] And infection is involved in all stages of AAV. This review aims to illustrate the relationship between AAV and infection.

1. Pathogenesis

ANCA is an autoantibody that is in the neutrophils and monocytes. A case in 2009 reported that MPO-ANCA from a mother with MPA passed through the placenta into a preterm infant. Subsequently, the infant developed pulmonary hemorrhage and renal damage in a few days.[3] This report provides direct evidence that ANCA is pathogenic in humans. The main ANCA target antigens are Proteinase 3 (PR3) and Myeloperox-idase (MPO). Neutrophils and monocytes can be activated by MPO-ANCA and PR3-ANCA. Activated neutrophils undergo respiratory bursts and degranulation.[4] Similar responses were also observed in monocytes. [5] And then a series of inflammatory reactions happen and finally lead to vasculitis.

There are currently two hypotheses:

1) Molecular mimicry hypothesis: In a study, anti-human Lysosome-associated membrane protein 2 (LAMP-2) autoantibodies have also been found to participate in the pathogenesis of ANCA. There is 100% homology between bacterial adhesins FimH and LAMP-2, so FimH is considered to trigger autoimmunity to LAMP-2.[6]

2) Autoantigen complementation hypothesis: A study found antibodies against the complementary peptide of PR3 (cPR3) in some PR3-ANCA-positive patients.[7] Therefore, the initial immune response in AAV patients is not against the

self-antigen, but against the peptide complementary to the self-antigen epitope. In recent years, it has been found that neutrophils, Neutrophilextracellular traps (NETs), complement, and Lymphocytes all play a big part in AAV pathogenesis.

2. Infection induces AAV

According to the above two hypotheses, infectious factors are involved. The first hypothesis suggests that FimH is present in some Gram-negative bacteria. When humans are infected with FimH-bearing pathogens, it may lead to AAV. From the second hypothesis, pathogens with constitutive analogues of cPR3, such as Staphylococcus aureus and Ross River virus, could presumably act as exogenously introduced cPR3 to cause ANCA formation.

2.1 Staphylococcus aureus

In Stegeman's study, nasal S. aureus was present in 63% of patients with GPA in the experimental group. It was 25% in the control group. Meanwhile, there was a remarkably increased risk of GPA recurrence in the experimental one. [8] A 2017 study similarly confirmed that GPA patients with active nasal disease at admission were more likely to recur.[9] It has been demonstrated that superantigens, peptidoglycans, and fungal β-glucans derived from Staphylococcus aureus can induce the expansion of Th17 cells. [10] Th17 cells are considered central parts of the autoimmune response. [11] In addition, Staphylococcus aureus can induce NETs formation.[12] NETs destroy vascular endothelial cells. And they activate Lymphocytes to promote autoimmune responses.[13]

2.2 Viruses

It has been proposed that cytomegalovirus, HBV, HCV, etc., participate in the pathogenesis of autoimmune diseases.[14] Many studies have confirmed that SARS-CoV-2 can cause autoimmune diseases. The mechanism by which COVID-19 induces AAV is not clear. A theory suggests that COVID-19 could lead to an increase in proinflammatory cytokines and cytokine storm.[15] Another hypothesis is that COVID-19 causes transient immunosuppression and inappropriate immune reconstitution, causing the development of autoantibodies and the inability to correctly recognize self-antigens.[16]

3. Secondary infection

Immunosuppressive therapy can effectively improve the survival time and quality of life of AAV patients. But increased infection morbidity and mortality were found in AAV patients during immunosuppressive therapy. In a recent study, the cumulative rate of infection in AAV patients at 1 and 5 years was almost 50% and 65%. Serious infections were almost 20% and 25%. Respiratory tract infections were the most common. And Staphylococcus aureus was the highest proportion of pathogen cultures (41%).[17]

Another study found that the highest incidence of serious infection in AAV patients at 1 and 5 years was almost 20% and 10%, both lower than the rates in those studies. The study attributes this reduction to better long-term care, controlled long-term use of CYC, and limited initial prednisone use.[18] The 2021 KDIGO guidelines state that initial therapy for de novo AAV can be induction therapy with CYC or RTX plus glucocorticoids.[19] The happening of serious infections was found to be more in patients receiving CYC (20%) than RTX (11%) during the total induction treatment. The respiratory tract infections were 45%, followed by 24% herpes zoster.[18]

A Chinese study also found that lung infection was the most common type of infection (72%). Pathogens found during infection include bacteria, fungi, and viruses. the most common infections were bacterial (65%), particularly Acinetobacter baumannii and Staphylococcus aureus, followed by fungal (25%) and viral (10%) infections. These include cytomegalovirus and Pneumocystis.[20]

4. Prevention and prognosis

One study found that 14% of AAV patients who were infected during treatment died of severe pneumonia after immunosuppressive therapy.[18] In a large sample study in China, the cumulative survival rates at 1 and 5 years were almost 80% and 60%. Secondary infections were the major cause of death in the first year after diagnosis (40%).[21]

Kinds of literature has suggested that we should pay attention to the dose of immunosuppressive agents and the speed of dose reduction to avoid infection. For AAV patients treated with CTX or RTX ,trimethoprim-sulfamethoxazole is advised for the prophylaxis of Pneumocystis infection.[22] Guidelines recommend that most AAV patients receive vaccines, such as the influenza vaccine, pneumonia vaccine, and others.[23] A Japanese study found that malnutrition in patients at the time of AAV diagnosis may increase vulnerability to infection during immunosuppressive therapy.[24] Therefore, it is necessary to maintain an appropriate BMI in dealing with infection.

This review preliminarily elucidates the role of infection in the pathogenesis, progress, and prognosis of AAV. Now there are still no clear guidelines and norms for the treatment of AAV complicated with infection. There are still contradictions between immunosuppressive therapy and anti-infection therapy. Doctors can only make corresponding judgments according to the patient's individual condition and give the patient appropriate treatment measures.

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