Atypical ANCA-Associated Vasculitis with Rheumatoid Arthritis Literature Overview and Literature Review
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BACKGROUND

Our understanding of the vast world of vasculitis has dramatically improved over the past several decades. However, despite the tremendous progress, anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV) is one of the last remaining immune-mediated vascular diseases where diagnostic strategies can pose a challenge. As true for most autoimmune disease states, general serology and clinical findings do not always lead to predictable and reproducible outcomes, making it difficult for specialists to diagnose and subsequently manage. We present a case report of an atypical presentation of cutaneous vasculitis with abnormal ANCA and other serologies, and discuss other diagnostic strategies to consider when presented with atypical ANCA-associated vasculitis.

PATIENT PRESENTATION

A 76-year-old female presented to our dermatology office complaining of a rash on her lower extremities for several months. The patient stated that she initially noticed a purplish color change on her lower leg which she thought was related to her use of sunscreen. She does not recall any major trauma to the area. Her past medical history consisted of atrial fibrillation for which she was taking warfarin, and osteoporosis. Review of systems was negative for joint pain, vision, or other symptoms related to the vasculitis.

Physical examination revealed a 76-year-old female with mild diffuse erythema on her bilateral lower extremities. The patient also displayed mild edema of the bilateral lower extremities. She also mentioned that the rash was accompanied by a tingling sensation. On physical exam, she displayed generalized non-blanching red to brown palpable purpura on bilateral lower extremities. The patient also showed mild joint pain and stiffness in the hands and wrists which the patient states were chronic. On physical exam, she displayed generalized non-blanching red to brown palpable purpura on bilateral lower extremities. The patient also showed mild joint pain and stiffness in the hands and wrists which the patient states were chronic.

Two 4-mm punch biopsies were collected on the lower legs and the patient was given topical steroids for symptomatic relief. Laboratory studies were collected (Figure 1). Biopsy results showed an unremarkable epithelium with underlying dermal mononuclear inflammatory infiltrate around the superficial vascular plexus. After pathological and serological examination, the patient was diagnosed with an atypical ANCA-associated vasculitis with rheumatoid arthritis overlap. She was started on prednisone 40mg daily with vitamin D and calcium supplementation. She was also given coticosteroids 0.5mg twice daily and referred to rheumatology.

ANCA-ASSOCIATED VASCUITIS (AAV)

Vasculitis is a common condition involving inflammation of vessel walls which can lead to a disruption of blood supply to various tissues. Any blood vessel may be affected including arteries, arterioles, veins, venules, and capillaries (see figure 2). Vasculitis can typically be classified as either primary, in which case the cause of the vascular inflammation is idiopathic, or secondary in which the inflammation can be incited by other inflammatory autoimmune conditions, medications, infections or malignancies. The International Chapel Hill Consensus Conference (CHCC) has established a nomenclature for noninfectious vasculitides.

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What about diagnostic results indicating ANCA positivity but fails to detect antibodies against MPO and PR3? In cases of a positive ANCA on IF, but negative PRD or MPO ANCA serology, one must control the possibility of autoantibodies to a minor antigen. Atypical ANCA on IF is described as being a different pattern from either c-ANCA or p-ANCA and is seen when the autoantibodies are targeting minor antigens, or antigens other than PR3 or MPO. These autoantibodies are not detected by the current diagnostic tests, which are performed with a combination of the two tests together for diagnostic purposes.

Antineutrophil cytoplasmic antibodies or ANCA, describe a well-characterized molecule often targeted toward intracellular or other molecules that can have detrimental pathophysiological outcomes. C-ANCA or cytoplasmic antineutrophil cytoplasmic antibodies typically involves autoantibodies targeting antigens within the cytoplasm of neutrophils with proteinase 3 (PR3) being the suspected target. P-ANCA or perinuclear anti neutrophil cytoplasmic antibodies consist of autoantibodies targeting the protein myeloperoxidase (MPO) also within neutrophils. Detection of ANCA involves indirect immunofluorescence (IIF) in which patient sera against C-ANCA or P-ANCA respectively. An alternative method for screening ANCA is through the use of enzyme-linked immunosorbent assay (ELISA) to detect the specific antibodies targeting either the antigen MPO or PR3. Current guidelines recommend completing both the IF and the ELISA for screening ANCA.

There is significant variation in the reported sensitivities and specificities in both detection methods seen in the literature. Classification of the ANCA pattern on IF is based on objective visual inspection, and depends partly on the examiner’s skill, experience and previous training. There are also no standardized reference ranges and cut off markers for positive and negative values that vary among different laboratories. The ELISA testing suffers from similar pitfalls as there are also varying cutoff markers and different types of ELISA testing methods which may prove inconsistent when comparing one laboratory to the next. It, therefore, is not surprising to read of significant variation of the reported sensitivities and specificities of both testing methods in the literature.

In a large cross-sectional study of 850 patients, it was demonstrated that the IF had greater sensitivity than the ELISA. However, the ELISA had greater specificity and almost double the positive predictive value for AAV. The sensitivity of ANCA based on IF was 67% and the specificity was 33% for AAV, while the sensitivity of ANCA based on ELISA was only 55%, but the specificity was 99%. The combination of a positive IIF and ELISA lead to a much greater likelihood ratio than either test alone which illustrates the importance of using combination of the two tests together for diagnostic purposes.

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Vasculitis

Large Blood Vessel

Takayasu Arteritis

Temporal Arteritis

Medium Blood Vessel

Polyarteritis Nodosa

Vasculitis

ANCA-Associated

 Wegener’s Granulomatosis

Microscopic Polyangiitis

Churg-Strauss syndrome

Other Vasculitis

Minor Antigens Associated with ANCA Positivity

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