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INVITED REVIEWS

Drug-associated ANCA-associated vasculitis: Overview based on Chapel Hill Conference Consensus 2012 and a case report

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Definition

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of small vessel vasculitides characterized by necrotizing inflammation with few or no immune complexes and classifed as primary or secondary based on underlying causes (various drugs, infections or malignancy vs). Drug-associated AAV is the one of most common cause of secondary form and characterized by use of spesific drugs [anti-thyroid drugs (propylthiouracil, carbimazole, methimazole), antibiotics (cefotaxime, minocycline, nitrofurantoin), TNF-inhibitors, sulfasalazine, allopurinol, D-penicillamine, isoniazid] that strongly related to vasculary inflammation while other etiologies are excluded [1]. The 2012 International Chapel Hill Consensus Conference classified drug-associated AAV as vasculitis associated with probable etiology [2].

Clinical Features

Drug-associated AAV presents with variable clinical findings and often mimics primary systemic vasculitis with manifestation of the cutaneous, renal and/or pulmonary involvement. Although it is difficult to distinguish of the drug-associated AAV from primary AAV by clinical and laboratory markers, some differences have been reported such as having a better prognosis, less severe disease, and less renal and major organ involvement [3].

Anti-thyroid drugs, especially propylthiouracil, is the most common cause of drug-associated AAV and considering the epidemyology of hyperthroidism, usually effect young and female population with mild symptoms [4]. Skin involvoment is the most common manifestations with petechiae, purpura, ulcer and necrosis. Renal involvement may be seen with mild severity.Pulmonary, gastrointestinal, nervous system involvement and constitutional symptoms are less frequent in drug-associated AAV compared to primary vasculitis [5,6].

There are no unique clinicopathological or laboratory markers that can distinguish drug-associated AAV from primary AAV. Similar to primary AAV, anemia, urinary abnormalities, increased creatinineurinary protein, and acute phase reactants levels may be present. Most patients with drug-associated AAV have a positive MPO-ANCA rather than PR3-ANCA. In addition ANCAs may recognize many target neutrophil antigens in this groups and both MPO-ANCA and PR3-ANCA positivity could be seen in the same patient. The other antibodies such as ANA, anti histone, anticardiolipine and anti b2-glycoprotein could be detected in drug-associated AAV and the presence of these autoantibodies can help differantiate from primary AAV [3].

Diagnosis

The diagnosis of drug-induced vasculitis is complicated due to variable clinical presentations and similar clinical and laboratory features with primary AAV. The pathological assesment such as tissue biopsy from skin lesions, renal and lung usually provide a diagnosis of vascular inflammation

to exclude other etiologies. Currently, there is no clear definition or a diagnostic criteria for drug-induced AAV. However, some papers reported some criteria that can be used for diagnosis. In an article, it is recommended that drug-induced AAV can be considered in the presence of the following conditions, after the other etiologies (infections, malignancies and other types of vasculitis) are excluded: (a) meeting the 2012 Chapel Hill Consensus Conference definition for AAV (b) positive serum ANCA (c) the clinical symptoms of vasculitis are induced with using the suspicious drug and regressed with discontinuation [7].

The main and most important principle of the treatment is withdrawal of the drug though to be responsible for vasculitis. In most cases, improvement is observed after discontinuation of the drug [1]. Immunosuppressive drugs should be reserved only severe and sustained clinical manifestations.

CASE PRESENTATION

A 63-year-old male patient was admitted to the rheumatology outpatient clinic in March 2017 due to the spread of rash around his ankles and calfs, which started 20 days ago. He had weakness, fatigue, and pain in his ankles and wrists for the last 3 days. He denied any recent infection, fever, cough, dyspnea, sinusitis symptoms, neuropathic complaints, and abdominal pain. He had a history of diabetes mellitus, hypothyroidism, hyperlipidemia, hypertension, coronary artery disease and atrial fibrillation. He was being treated with metformin 850mg/day, gliclazide 60 mg/day, propylthiouracil 150 mg/day, acetylsalicylic acid 150 mg/day, atorvastatin 20 mg/day, metoprolol 50 mg/day and warfarine 5 mg. In admission to the hospital, diffuse hemorrhagic bullae and erosions, necrotic ulcerations, and palpable purpura on bilateral lower extremities were seen. In laboratory evaluation, leukocytosis (13200 mm^3/uL), anemia (10.2 g/dl), thrombocytosis (535000 mm^3/uL), high level of creatinine (4.2 mg/dl) and acute phase reactants [CRP (38 mg/L), sedimentation (63 mm/h)], abnormality of coagulation test (INR:13) and hematuria (RBC 3 positive) were found. Echocardiography, chest X-ray, thoracic and abdominal CT scans were unremarkable.

In his follow-up, he suffered bloody stool. Duodenal ulcer was found in endoscopic examination. Renal and skin biopsies were planned, but renal biopsy could not be performed due to warfarine overdose

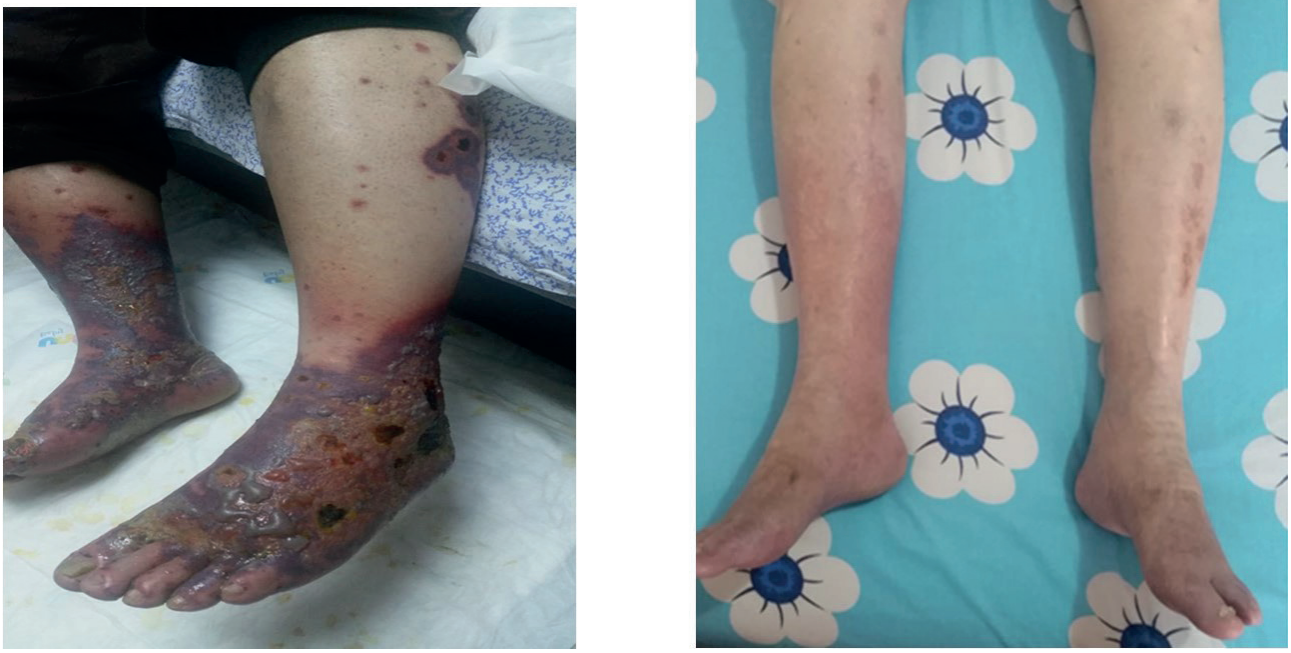

Figure 1. Before treatment (a) and after treatment (b).

and patient preference. Warfarin, statin, and PTU were discontinued because of the possibility of drug-related eruptions. His skin biopsy revealed leukocytoclastic vasculitis. Further evaluation revealed p-ANCA and anti MPO ELISA positivity. The patient was evaluated as "PTU-associated AAV" thus 1 mg/kg/day prednisone treatment was started. On the 7th day of treatment, creatinine (1mg/dl) and CRP (5 mg/l) levels were found normal and urinalysis was unremarkable. In the follow-up, the skin findings, joint complaints and constitutional symptoms improved. While the steroid dose was decreased, the lesions did not relapsed and no additional systemic involvement developed.

Key messages

- Propylthiouracil (PTU) is a commonly used antithyroid medication, can induce antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Compared with primary AAV, PTU-induced vasculitis generally has a mild disease severity with good prognosis.
- A standard treatment protocol is not clear for drug-induced AAV and should be based on disease activity and severity. While for patients who had mild symptoms, without organ involvement, cessation of drug might be sufficient to induce disease remission while active management is reserved for patients with more severe conditions.

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