CASE REPORTS

A CASE OF C-ANCA ASSOCIATED VASCULITIS PRESENTING WITH LOCALISED SKIN THICKENING

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Abstract

ANCA vasculitis, caused by antibodies named ANCA (anti-neutrophilic cytoplasmic autoantibodies), is an autoimmune disorder affecting small blood vessels of the body. Among p-ANCA and c-ANCA, c-ANCA (cytoplasmic ANCA) usually targets proteinase three inside neutrophils, causing inflammation of blood vessels. Herein, we report a case of a 56-year-old female patient with c-ANCA-associated vasculitis. The patient presented with a localized skin thickening on the medial aspect of the left thigh and an oral ulcer. Skin biopsy shows erythema induratum (nodular vasculitis). After several investigations, we found c-ANCA positive and concluded the diagnosis as c-ANCA-associated vasculitis. We treat the patient with injectable methylprednisolone, injectable cyclophosphamide, and Mesna. Then we gave oral mycophenolate mofetil and prednisolone.

Keywords: *Vasculitis, ANCA-associated vasculitis, Response to treatment.*

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Introduction

Vasculitis is inflammation and necrosis of large, medium, or small blood vessel walls, which can also cause damage to the skin, kidney, lung, heart, brain, and gastrointestinal tract. Patients with systemic vasculitis present with fever, weight loss, fatigue, rash, raised inflammatory markers, and abnormal urinalysis.[1,2] It is ANCA-associated vasculitis when there is inflammatory infiltration of small blood vessels, fibrinoid necrosis, and circulating antibodies to antineutrophil cytoplasmic antibody (ANCA). Two antibodies are involved in ANCA vasculitis: P-ANCA (perinuclear ANCA) and c-ANCA (cytoplasmic ANCA). c-ANCA usually attaches to proteinase three inside the neutrophils.[1,3,4] ANCA-associated vasculitis typically occurs in older patients, usually between 60 and 70 years old.[1]. The patient presents with fever, polyarthralgia, polymyalgia, rash, headache, malaise, anorexia, unintended weight loss, cutaneous vasculitis, and tender skin nodules. ANCA-associated vasculitis is currently treated with high-dose glucocorticoid and high-dose cyclophosphamide for 3 to 6 months and maintaining remission with azathioprine or methotrexate, which has proved to be shown dramatic response in the treatment.[1,2]

Case Presentation

A 56-year-old, hypertensive, non-diabetic, non-asthmatic female was admitted to DMCH with complaints of thickening and blackening of the skin of the medial aspect of her left thigh for the last year & oral ulcer for the previous month (fig 1 and fig 2). During 1.5 years, she had occasional fever and headaches. Then she suddenly noticed multiple patchy, reddened skin lesions over the left thigh's medial aspect, which was hot, itchy, and painful. She had no history of trauma or insect bite. The lesion was initially discrete and became confluent later on.

She consulted a dermatologist and was treated for focal cellulitis in the left thigh

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Then she gradually developed thickening and blackening of her medial thigh skin over the last year, the margin of which was well-defined, palpable & raised (fig 3 and fig 4). She also complained of an oral ulcer for the last month, which was painful and not associated with any genital/other site ulcer. Her bowel-bladder habit was regular. On query, she complained of joint pain for the last 22 days involving both ankle joints, knee joints, metacarpophalangeal joints, and interphalangeal joints of both hands, wrist, and elbow joints which were gradual in onset. Joint swelling and redness involved the ankle joints only. The pain increased during movement and was associated with morning stiffness for about 30-40 minutes. This joint pain was accompanied by multiple erythematous and purpuric rashes over both legs, occasional fever, headache, nasal discharge, and crusting. The fever was low-grade in nature with an evening rise of temperature and night sweats (the highest recorded temperature was 101°F), not associated with any chills or rigors, and responded poorly to antipyretics. She gave no history of skin lesions on other sites, weight loss, contact with any tuberculosis patient, cough, hemoptysis, shortness of breath, dyspnoea, alopecia, photosensitivity, and malar rash. She suffered from Chikungunya back in 2019. All the family members are in good health, and no such illness in the family. Her medication history revealed that she received treatment for panniculitis, focal cellulitis, suspected morphea, oral steroids for suspected vasculitis, and even a trial of anti-tubercular medication. But none of them seemed to improve her condition.

A general examination revealed the patient was ill-looking, mildly anemic, with an average body build. There was no jaundice, cyanosis, clubbing, koilonychia, leukonychia, lymphadenopathy, bony tenderness, edema, or dehydration; other parameters are normal. Vitals were absolutely within normal range. The skin over the medial aspect of the left thigh was indurated and hyperpigmented, measuring about 10cm x 8cm in size and hard in consistency; the overlying hair follicle is normal. Also, multiple tender erythematous and palpable purpuric lesions are present on both legs. The examination of the musculoskeletal system revealed that both ankle joints are swollen and tender with restricted movement due to severe pain, and both knee joints, metacarpophalangeal and interphalangeal joints of both hands, wrist and elbow joints -all are tender with slightly restricted movement but not swollen. Examination of other systems revealed no abnormality.

We advised many investigations. CBC and renal function tests are described in Table-I and Table II, respectively.

Table-I

Complete Blood Count and ESR

CBC	Hb : 12.7g/dl
07/06/20	WBC: 7340/Cmm (Neutrophil-53%, Lymphocyte- 41%) Platelet: 301000/Cmm
CBC	Hb% -12.4 g/dl
21/04/2021	WBC-7090/Cmm, Eosinophil -11% ↑ Platelet-404000/Cmm
CBC26/08/2021	Hb -13.7 g/dl WBC- 10.2 X 10^9/L
Follow-up	Neutrophil- 82% ↑ Lymphocyte- 16% ↓ Eosinophil- 00 % Platelet 220x 10 ^{9}/L
ESR	57 mm in 1st hour ↑↑ 07/06/20 73mm in 1st hour ↑↑ (21/04/2021) 09 mm in 1st hour (26/08/2021)

Table-II

Renal function tests

07/06/20	Urine Routine Examination Epithelial cell : 4-5/HPF Pus cell: 3-5/HPF RBC- nil	Serum Creatinine 0.7 mg/dl
21/04/2021	Urine Routine Examination Ca oxalate (++++) ↑↑↑ Epithelial cell : 3-4/HPF Pus cell: 1-2/HPF RBC: 4-5/HPF	Serum Creatinine 0.8 mg/dl
23/06/2021	Pus cell : 6-10/HPF ↑ Epithelial cells : Plenty Hyaline cast : (++) RBC: 5-6/HPF Ascorbic acid: 40mg/dl (++)	Serum Creatinine 0.8 mg/dl

Chest X-ray P/A view revealed Cardiomegaly. ECG showed left axis deviation but was otherwise normal. Doppler study of the left thigh revealed focal cellulitis. CRP was 37.7 mg/L. Anti-histone Ab (Ig G) was Positive (21.80 U/ml). c-ANCA was found positive on multiple occasions with high titers (done by ELISA method). But due to the economic constraints of the patient, PR3 couldn't be done. ANA and anti-ds DNA both came out negative. ENA profile was also negative. Quanti Feron-TB Gold plus ELISA Test(for the detection of interferon-^{3} specific for Mycobacterium tuberculosis infection) also came out negative. Skin biopsy revealed inflammation of small vessels.

Our final diagnosis was c-ANCA-associated vasculitis. We started the treatment with injection methylprednisolone (1 gm), injection omeprazole 40 mg and tablet mycophenolate mofetil 500 mg daily. As the patient's condition didn't improve, we started injection of cyclophosphamide (500mg) and mesna (400 mg/ 4 ml). Then the patient's condition improved and we continued tablet mycophenolate mofetil 500 mg and tablet prednisolone 20mg daily for six months. The patient continued on her regular anti-hypertensive medication (amlodipine+ olmesartan combination) throughout the journey.

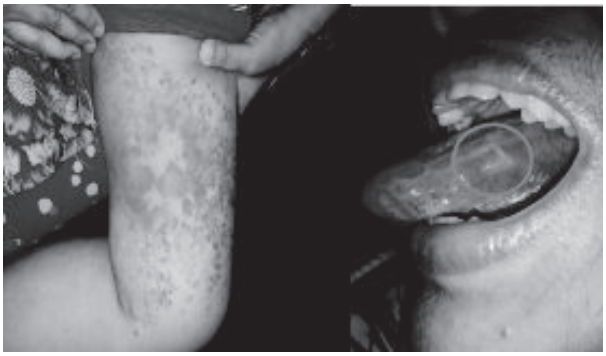

Fig.-1: *Skin thickening and pigmentarian in leg arm*

Fig.-2: Oral ulcer

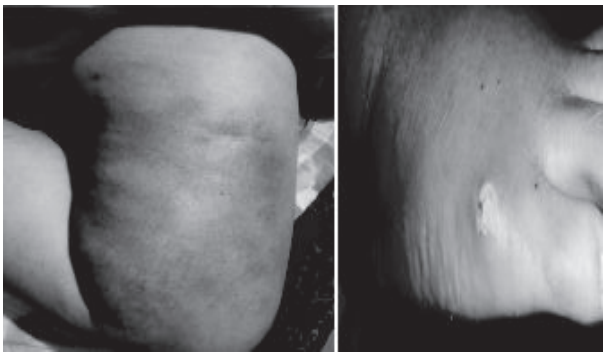

Fig.-3: *Skin changes over thigh*

Fig.-4:

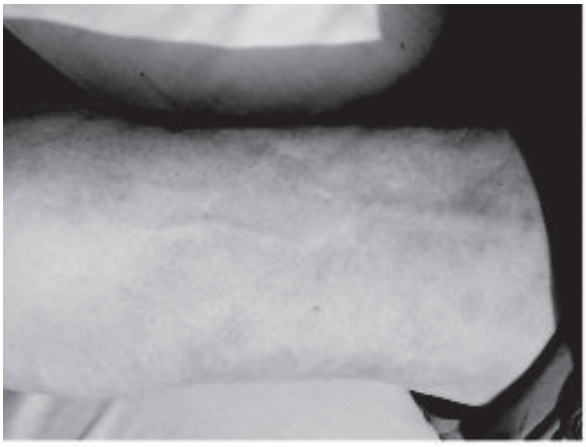

Fig.-5: *Skin changes in ankle*

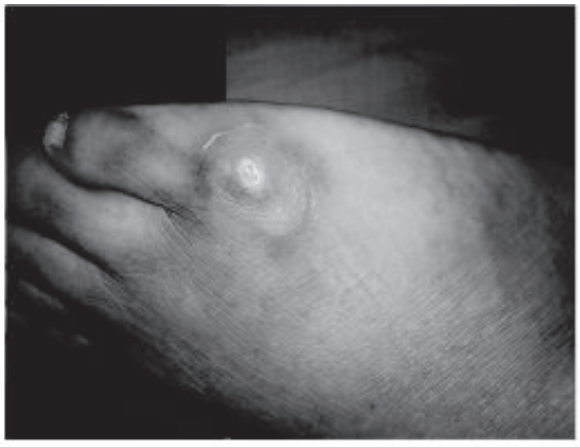

Fig.-6: *Skin changes in the foot*

Discussion

Systemic vasculitis is inflammation of the vessel wall classified as large, medium, or small-vessel vasculitis. They are also associated with p-ANCA (antibody against myeloperoxidase) and c-ANCA vasculitis (antibody against proteinase 3). Ours was a case of c-ANCA vasculitis, though we could not go for PR3 association due to the economic constraint of the patient. Disease onset usually occurs at 65-74 years, and prevalence is higher in men of European and Asian ancestry.[1,2] Our patient, in this case, is also approaching the similar age group of the previous studies and is of Asian origin.

The patient presents with "flu-like symptoms" from weeks to months. The presentation may vary between fever, polymyalgia, polyarthralgia, headache, malaise, anorexia, and weight loss. There are overlapping features between several ANCA-associated vasculitides, but some specific features are for some particular diseases. E.g., hearing loss, rhinorrhea, otalgia, otorrhoea, sinusitis, and recurrent otitis media occur in 90% of patients with granulomatosis with polyangiitis. Rash and tender nodules in the skin occur in 50% of patients.[1] Our patient also had symptoms of occasional fever, headache, nasal symptoms, and joint pain. Two techniques for detecting ANCA are indirect immuno-fluorescence (IF) and ELISA.[1,2] We detected the c-ANCA positivity in this patient using by ELISA method.

The pathogenesis of ANCA-associated vasculitis is based on the hypothesis that genetic factors produce antibodies that activate neutrophils and monocytes, which causes endothelial damage, cytokine production, and activation of alternate complement pathways.[1,2,5]

Some viruses, bacteria, and drugs such as Hydralazine, Allopurinol, Propylthiouracil, and Methimazole sometimes trigger ANCA-associated vasculitis.[2-4] In the case of Antithyroid medications, 10% of patients develop ANCA-associated vasculitis in the first eight months of drug use, and the prevalence is 27% after chronic use.[2]. In our mentioned case, neither did we find any association with any drug nor any evidence of bacterial or viral infection related to this presentation.

Clinical manifestation of drug-induced vasculitis is similar to primary vasculitis, such as skin rash, fever, arthralgia, and myalgia. However, renal involvement with haematuria, proteinuria, and elevated serum creatinine is more common.[5] Although some RBC was found in our patient's routine urine examination, her renal function was normal. But no causative drug history was found in our patient, which might lead to these features.

Standard treatment of ANCA-associated vasculitis includes high-dose glucocorticoid and high-dose pulse cyclophosphamide for 3 to 6 months and maintenance therapy with azathioprine or methotrexate with withdrawal from glucocorticoid. In a large randomized, unblinded trial, the remission rate is 75% in patients treated with cyclophosphamide and prednisolone.[1,4] Besides trying with high-dose

steroids and cyclophosphamide , we treated the patient with Mycophenolate mofetil. Ultimately patient responded very well to this treatment regimen. So further large-scale studies are required to focus on mycophenolate mofetil in the treatment protocol for this sort of patients with small vessel vasculitis.

Modern treatment improved the life-threatening condition of ANCA-associated vasculitis, but the disease course became prone to relapse. According to an observational study of 107 patients, it is found that 50% of treated patients experience one or more relapses within five years 1. Though our patient hasn't faced relapse yet, it's a matter of regular follow-up, keeping the findings of previous studies in mind.

Patient Consent

Written consent about the presentation of the case is obtained from the patient herself.

Conflict Of Interest

The authors declare that the research was conducted without any commercial or financial relationship that can be constructed as a potential conflict of interest.

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