Case report

ANCA Associated vasculitis - A case of microscopic polyangiitis with proliferative glomerulonephritis

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ABSTRACT

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are a collection of diseases, characterised by destruction and inflammation of small and medium vessels. Microscopic Polyangiitis (MPA) is part of an ANCA-associated vasculitis (AAV).The clinical signs diverge and disturb a number of organs such as the kidneys, lungs, stomach and intestine. Skin manifestations such as purpuric, urticarial, nodular, ulcerative, livedoid and necrotic skin lesions were common as in other vaso-occlusive disorder. Morphology and added features aid the diagnostic approach. Here, we report a diagnostically challenging case of microscopic polyangiitis with progressive glomerulonephritis.

Keywords: Microscopic polyangiitis; leukocytoclastic vasculitis; ANCA.

INTRODUCTION

Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) are categorised by systemic inflammation of small to medium sized blood vessels (1). The unambiguous feature of AAV is the existence of ANCA (2). The AAV encompass granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, earlier known as Churg-Strauss syndrome). They are united by their link with antibodies focused against proteinase 3 (PR3) and myeloperoxidase (MPO). PR3 and MPO are proteins that function as antigens inside the azurophilic granules in the cytoplasm of a neutrophil. Both MPA and GPA are analogous in presentation. The chief difference being the lack of granulomatous inflammation in MPA.

Case report

73-year-old women presented with multiple discrete palpable purpuric lesions, few coalescing over bilateral lower limb for 10 days. Later in some areas, it turned dusky red giving rise to a blister which broke open into an ulcer on left dorsum of foot. Following these skin lesions, she developed bilateral leg swelling. She had fever in due course which was intermittent and high grade, subsided with medication and without any associated systemic complaints. She is a hypertensive for 10 years on T. Envas 5mg T. Aspirin 75mg. There are no similar complaints in the family. Systemic examination was normal.

Dermatological examination

Multiple well defined dusky red palpable, non-blanching purpuric lesion with bullae and necrotic ulcer present over B/L lower limb. B/L lower limb oedema + oral and genital mucosa – normal. Hair - normal, scalp – normal, nail- normal. No similar lesion elsewhere in the body (**Fig. 1).**

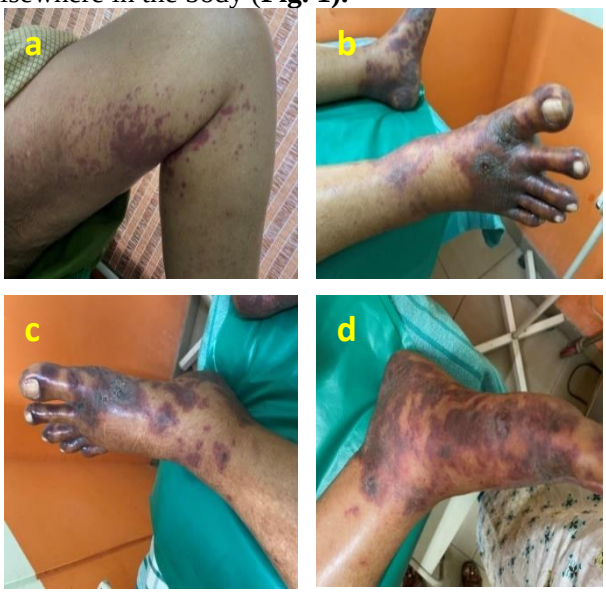

Fig. 1: Multiple palpable purpuras noted over the inner aspect of both thighs and bilateral foot (a, d) Few necrotic ulcer noted over the dorsum of foot (b, c)

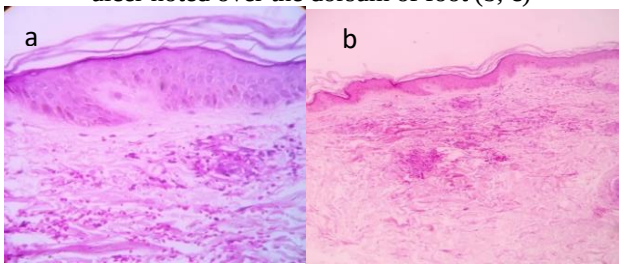

Fig. 2: Section shows skin with unremarkable epidermis, the dermis shows perivascular neutrophilic infiltration (a) some of which are seen infiltrating the vessel wall lined by plump endothelial cells with extravasation of RBCs are also noted (b). Biopsy of the skin was performed reports were suggestive of leucocytoclastic vasculitis.

Table 1: Laboratory values and reference values

Laboratory parameters	Patient's value	Reference value
Total leucocyte count	20400 cells/cu mm	4000-10000 cells/cu mm
Blood RBC	4.38 millions/cu mm	3.8-4.8 millions/cu mm
Differential leucocyte count – Neutrophils	95.8%	40-80%
Lymphocytes	2.9%	20-40%
Monocytes	1%	2-10%
Eosinophils	0.1%	1-6%
Basophils	0.2%	<1-2%
Hemoglobin	**10.5g/dl**	12-15g/dl
Platelet	**5.45 lakhs/cu mm**	1.5-4 lakhs/cu mm
ESR	**80 mm/hr**	0-10 mm/hr
RBS	**144 mg/dl**	<140 mg/dl
Urea	**67 mg/dl**	19-40 mg/dl
Creatinine	**2 mg/dl**	0.6-1.2 mg/dl
T. Bilirubin	1.0 mg/dl	0.2-1.3 mg/dl
D. Bilirubin	0.4 mg/dl	0.1-0.4 mg/dl
SGOT	47 IU/L	17-59 IU/L
SGPT	32 IU/L	5-50 IU/L
ALP	82 IU/L	38-126 IU/L
Total Protein	6.8 g/dl	6-8 g/dl
Total Albumin	3.2 g/dl	3.5-5 g/dl
Sodium	**130 meq/L**	137-145 meq/L
Potassium	5 meq/L	3.5-5.1 meq/L
Chloride	99 meq/L	98-107 meq/L
Bicarbonate	20 meq/L	22-28 meq/L
Calcium	7.9 mg/dl	8.1-10.2 mg/dl
Phosphorus	4.8 mg/dl	2.5-4.5 mg/dl
Uric Acid	7.2 mg/dl	3.5-8.5 mg/dl
Urine PCR (protein creatinine ratio)	**3.1 mg/mg**	<0.2 mg/mg
Urine Routine – Protein	**++**	Absent
RBC	**25-30**	Absent
Blood	**Present**	Absent
Cast	**RBC Cast**	Absent
ANA	**3+ (1:100)**	Negative
ANCA MPO	**2+ Positive**	Negative
ANCA PR3	**Positive**	Negative
C3	**0.85 g/L**	0.9-1.80 g/L
C4	**0.04 g/L**	0.1-0.40 g/L
Serology	**Negative**	Negative

Peripheral smear

RBC – Microcytic hypochromic with anisocoikilocytosis
WBC – Neutrophilic leucocytosis
Platelets – Increased in number

In view of elevated urine PCR (protein creatinine ratio), Renal function test, Nephrologist opinion was obtained and they suggested to perform a renal biopsy.

Renal biopsy

Endocapillary focal proliferation with mild C3 deposits observed on immunofluorescence and these features suggestive of progressive glomerulonephritis.

DISCUSSION

We here by discuss a rare case of ANCA associated vasculitis microscopic polyangiitis, patient presented with palpable purpuric lesions on both legs for 10 days. Upon evaluation, her ANCA MPO, PR3 is positive, total count, ESR were elevated. Renal function test was deranged. Urine routine showed RBC cast and proteinuria, urine protein creatinine ratio was increased, skin and renal biopsy revealed features of leucocytoclastic vasculitis and progressive glomerulonephritis respectively. Correlating the clinical manifestation and investigation details obtained, we diagnosed it as Microscopic polyangiitis (MPA). It is important to differentiate from other ANCA associated vasculitis. Absence of granuloma excludes the diagnosis of granulomatosis with polyangiitis. Absence of peripheral eosinophilia and other cardinal features rules out eosinophilic granulomatosis with polyangiitis.

The ANCA-associated vasculitis (AAV) remains as an infrequent multisystem autoimmune disease, more shared in population aged over 65 years old. Microscopic polyangiitis (MPA) is a necrotizing vasculitis frequently affecting small vessels (i.e., capillaries, venules, or arterioles) with hardly any or no immune deposit. Necrotizing glomerulonephritis is

not uncommon and pulmonary capillaritis frequently happens. Granulomatous inflammation lacks in microscopic polyangiitis. Previously, MPA was compiled with polyarteritis nodosa, then, it was defined and classified as a separate condition in 1994 at the first Chapel Hill consensus conference and were revised in 2012 (3).

Rising evidence states that ANCA have an essential portion in the pathogenesis of MPA. It might occur in two steps. At first neutrophils are primed by pro-inflammatory cytokines (4). The primed neutrophil exhibit myeloperoxidase on surface, these neutrophils attach to the endothelial surface of blood vessels or glomeruli. Secondly, neutrophils are triggered by contact with MPO-ANCA, either through binding of its substrate (5) or contact with neutrophil Fc receptors (6). ANCA can promote degranulation which can provoke respiratory burst leading to discharge of toxic oxygen radicals and intracytoplasmic enzymes giving rise to vascular inflammation.

Almost 40% of patients have palpable purpura on dependent skin sites upon presentation. They can also present with necrotic lesions on the fingers or toes, mouth ulcers, livedo reticularis and splinter hemorrhages. About 80% of patients will have renal manifestation. The presentation may be aggressive with rapidly progressive glomerulonephritis or pulmonary hemorrhage. Peripheral neuropathy is also common. Mononeuritis multiplex and even cranial nerve can also be involved.

Microscopic polyangiitis should be distinguished from other ANCA-associated vasculitis and polyarteritis nodosa. Significant peripheral eosinophilia, nasal or paranasal sinus involvement, endobronchial involvement, granulomas on a biopsy, fixed pulmonary infiltrates, cavitating nodules on a chest X-ray, asthma and mastoidal or retro-orbital disease are the cardinal features in EGPA and GPA. The absence of blood, red cell casts or protein in the urine rules out MPA.

Laboratory testing

Currently, there is no specific lab diagnosis for MPA. ANCA positivity is not confirmatory as ANCA can be detected only in 50-75% of MPA patients and a negative ANCA do not eliminate the diagnosis. ANCA associated with MPA mostly have a perinuclear staining pattern (P-ANCA) caused by antibodies against myeloperoxidase (MPO-ANCA), which can be detected using enzyme-linked immunoassays which has good specificity compared to immunofluorescence which has higher sensitivity. But none of the tests are specific for MPA, as these antibodies can be present in other ANCA-associated vasculitis in addition to other inflammatory diseases (7), such as drug-induced ANCA-associated vasculitis (8), cystic fibrosis (9), and various infections (10, 11). Nonspecific markers of inflammation are also detected in patients with MPA. The most common findings are an elevated erythrocyte sedimentation rate and C-reactive protein. Other findings include elevated white blood cell and platelet counts, and a normochromic, normocytic anemia (12).

Treatment

Immunosuppressive therapy is the main stay of treatment.

Remission induction

Pulsed IV Cyclophosphamide 15mg/kg every 2-3 weeks or oral cyclophosphamide 2mg/kg/day up to 6 months can be given. As an adjunct, oral prednisolone 1mg/kg/day can be added to cyclophosphamide, or even IV methylprednisolone can be added to speed up the induction. In view of cyclophosphamide cytotoxicity, Rituximab presents as an alternative (375mg/m2 IV weekly for 4 weeks). Many trials support rituximab strongly as an alternate to cyclophosphamide (13, 14). In patient with severe renal manifestations, plasmapheresis might save the kidney.

Remission maintenance

At the end of 6 pulses of IV cyclophosphamide or 6 months of oral cyclophosphamide patient might develop cumulative toxicity, in that condition azathioprine 2mg/kg/day is used to maintain remission. Patient who was on rituximab, suggest that it can be used at an interval of 4 to 6 months as a maintenance agent.

CONCLUSION

Microscopic polyangiitis is an uncommon systemic vasculitis. Current evidence supports the contribution of ANCA in the pathogenesis. The diagnosis can be perplexing and primarily depend on the physician gathering elements together of patient history, symptoms and diagnostic test like skin biopsy and autoantibody testing. Prognosis is great with the use of cyclophosphamide and steroids. Biologicals like rituximab has shown promising results with potentially less toxicity. In our case, patient received systemic steroids and patient showed good response.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

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