International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2018): 7.426

Rheumatoid Arthritis Rapidly Progressed to P-Anca Vasculitis Presented As Distal Limb Gangrene And Peripheral Neuropathy: A Less Recognised Overlap Syndrome

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Abstract: ***Anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis, is the most common primary systemic small-vessel vasculitis occurring in the adult population. Although the etiology is not well known always, the incidence of vasculitis is on increasing trend, with a variability in clinical expression. Renal and pulmonary manifestations are most common with all types of vasculitis. We are reporting a case of young male with un-specified small vessel vasculitis, presented initial as rheumatiod arthritis and later progressed very rapidly in the form of progressive vasculitic neuropathy and extensive limb gangrene and digital ischemia, with normal renal and pulmonary systems, which was diagnosed on the basis of clinical features and positive perinuclear anti neutrophil cytoplasmic antibodies (ANCA) P MPO done by Enzyme Linked Immunosorbent Assay (ELISA).***

Keywords: Acute vasculitis, anti neutrophil cytoplasmic antibodies P (MPO), Rheumatoid arthritis

1. Introduction

Anti-neutrophil cytoplasm antibody (ANCA) associated Vasculitis (AAV) comprises 3 different clinical entities: 1: GPA:granulomatosis with polyangiitis, formerly Wegener's granulomatosis, 2: MPA: microscopic polyangiitis and 3: EGPA: eosinophilic granulomatosis with polyangiitis , formerly Churg-Strauss syndrome. These clinical syndromes are frequently (but not always) characterized by ANCA reactive against one of two antigens namely, proteinase-3 (PR3) or myeloperoxidase (MPO), the former being more commonly associated with GPA and the later more frequently found in patients with MPA and EGPA [(1)]. The genetic basis of these clinical and immunological AAV subsets have recently been described through genome wide association studies and appear to be different between PR3- and MPO-AAV, with the most significant associations with HLA genes, implicated in other auto-immune diseases [(2)]. Clinically, AAV may be rarely associated with other immune mediated diseases, those that have been well recognized include antiglomerular basement membrane (GBM)[(3)], scleroderma[(4)], systemic lupus erythematosus[(5)], membranous glomerulonephritis[(6)], and rhematoid arthritis [(7)]. Association with rheumatoid arthritis was recent entity, where there is delay in presentation of vasculitis symptoms following rheumatoid arthritis. Knowledge of these overlap syndromes is very important in terms of early recognition of potential complications and thereby differences in clinical courses and management pathways.

2. Case Report

26 year old male patient, labourer by occupation, came with complaint of gradually progressive quadriparesis started with lower limbs and then involving both upper limbs, stocking and glove type of sensory loss in bilateral hand and feet since 3 months, gangrenous lesions on bilateral hands, legs and right hand fingers with nail bed since 1 week. Patient was apparently asymptomatic 5 months back when he developed sudden onset multiple joint aches involving both large and small joints. Patient was diagnosed to be having rheumatoid arthritis based on clinical features, positive RA factor, raised ESR and started on steroids and methotrexate. Later patient developed the complaints of weakness, sensory loss and gangrenous lesions as mentioned above. Patient had history of recurrent oral ulcerations in the past 3 years, also patient had past history of pulmonary kochs for which he took medications. On examination patient was severely emaciated but vitally stable. There was gross pallor, blackish discoloration of nails and skin over right index and ring finger and on dorsal aspect of both hands. There was dry gangrene on bilateral lower limbs over the lateral aspect of leg, (**Fig 1**). On examination of nervous system, loss of sensation to pain and touch in both hands and feet, weakness in all the limbs, reduced deep tendon reflexes. Patient was investigated and the following results were obtained as tabulated in **table 1**.

Hemogram suggested anaemia with Hemoglobin 7.1g%. Renal functions were within normal range, with creatinine of 0.9 mg/dl. Patient's ESR was 78 amd RA factor and CRP were positive.

Nerve Conduction Velocity studies were done in both upper limbs suggested of severe sensory motor axonal neuropathy. ANCA antibodies were tested by EIA method and found to be positive for ANCA P (MPO) antibodies.

Skin biopsy was taken from the lesion and histo-pathological examination was done, which showed, diffuse neutrophilic infiltration in dermis, parakeratosis and ulceration in epidermis, and inflammatory infiltrates in subcutaneous tissue (**Fig 2**).

A primary diagnosis of progressive vasculitic neuropathy with Rheumatoid arthritis was done. Patient was started on corticosteriods, one gram methylprednisolone 24 hourly for 2 days followed by oral steroids. Skin debridement was done for the extensive gangrene. Patient was given three cycles of cyclophosphomide therapy. Patient made a stable recovery in terms of improvement in weakness and sensory loss. Patient was discharged with oral steroids and plan for giving 3 more cycles of cyclophosphamide. Patient lost for follow up after 3 cycles of cyclophosphamide.

3. Discussion

Vasculitis is a clinicopathologic process characterized by inflammation of and damage to blood vessels. The vessel lumen is usually compromised leading to ischemia of tissue supplied by involved vessel. According to the size of the vessel affected, vasculitis can be classified into[8]

1) Large vessel: Polymyalgia rheumatica, Takayasu's arteritis, temporal arteritis
2) Medium vessel: Buerger's disease, cutaneous vasculitis, Kawasaki disease, polyarteritis nodosa
3) Small vessel: Behçet's syndrome, Churg Strauss syndrome, cutaneous vasculitis, Henoch Schönlein purpura, microscopic polyangiitis, Wegener's granulomatosis.

ANCA are antibodies directed against certain proteins in the cytoplasmic granules of neutrophil and monocytes. These autoantibodies are present in high percentage of patients with Wegener's granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome. They share the presence of ANCA and small vessel vasculitis, so collectively known as ANCA associated vasculitis[9]

The diagnosis of ANCA associated vasculitis is made on the basis of clinical findings, biopsy of involved organs, and presence of ANCA. Testing for ANCA includes indirect immunofluorescence and antigen specific enzyme linked immunosorbent assay, which provides 99% sensitivity and 70% specificity [9].

Association of AAV and rheumatoid arthritis is a rare overlap syndrome that was recently identified. In the few cases reported till now **(table 2)**, the diagnosis of RA preceded the AAV and also there is a median delay of 10.5 years in between them [7]. Possible reasons for the association between systemic ANCA associated vasculitis and RA may be the common genetic predispositions to autoimmunity which involve the HLA region or genes such as PTPN22, reported in series of both RA and AAV [12, 13]. In our case the rheumatoid arthritis however progressed very rapidly to vasculitis in less than 3 months. There was significant renal involvement in all the cases reported till now, but in our case there is no renal and pulmonary involvement.

Case reported above had clinical spectrum with skin involvement as gangrene, nervous system involvement as peripheral neuropathy and proximal myopathy. Although our case had no renal and pulmonary involvement, skin lesions and skin biopsy with positive ANCA P(MPO) were diagnostic for small vessel vasculitis.

4. Conclusion

Recognition of overlap syndromes could lead to timely antibody screening of patients with the relevant clinical scenario and a more rapid initiation of appropriate management. One should always think about possibility of vasculitis in a patient who was diagnosed with rheumatoid arthritis and later presented with neuropathy as in our case, as timely intervention may prevent multiple system involvement and thereby leading to good outcomes of treatment.

5. Tables and Figures

Table 1: Investigations

Investigations	
Hemoglobin (gm%)	7.1
WBC count (per cu.mm)	13500
Platelet count (lakh/ cu.mm)	1.0
ESR	88
RA factor	Positive
CRP	Positive
Blood Urea (mg%)	19
Serum Creatinine (mg%)	0.9
Serum Bilirubin (mg%)	1.1
SGPT (IU/ L)	22
PT/ INR	2
HIV (ELISA)	Negative
RBS (mg/dl)	98
ANA	No specific pattern
HPLC	Normal
CHEST X Ray	No abnormality detected
ECG	Within normal limit
ULTRSONOGRAPHY	No abnormality detected
Arterial + Venous Doppler	No evidence of thrombosis
ANCA antibodies (EIA method)	ANCA P (MPO) : 63.3 u/ml, Positive ANCA C(CR3) :1.26 u/ml, Negative
NCV Studies	Severe sensory motor axonal neuropathy
Skin Biopsy	Non Specific vasculitis

Table 2: Case reports published describing an overlap between ANCA associated vasculitis and rheumatoid arthritis

Year / Cases	Diagnosis	Age RA	Age VAS	Vasculitic symptoms	+VE auto antibodies	Therapy	Follow up
1974 / 1 [13]	RA/GPA	40	59	ENT	RhF, ANA	Gold, tuberculin injections, NSAID	D
1976 / 2 [14]	RA/GPA	45	45	ENT	RhF	HCQ, aspirin	I
	RA/GPA	73	75	ENT, Eyes, Lungs	RhF	Gold, NSAID	I
1992 / 1 [15]	RA/GPA	33	38	ENT	RhF	NSAID, Gold	I
1995 / 1 [16]	RA/MPA	49	62	Renal, lungs	RhF, ANA, p-ANCA	NSAID, Gold, SFZ	I
1997 / 10 [17]	RA/MPA	31-62	NA	5: Kidneys 1: Kidney, lungs, eye 3: Kidney, skin 1: Kidney, bowel, skin	4: p-ANCA 9: RhF 6: ANA	6: NSAID 1: NSAID, Penicillamine HCQ 1: Prednisone, SFZ, Gold 1: HCQ 1: HCQ, SFZ	4: D 2:HD 4: I
1999 / 1 [18]	RA/MPA	22	24	Kidney	RhF, ANA, MPO-ANCA	NSAID	I
2002 / 2 [19]	RA/GPA	32	32	ENT, Lungs, Kidney	p-ANCA	Prednisolone, NSAID, CYC	I
	RA/GPA	41	26	Lungs	p-ANCA		I
2003 / 2 [20]	RA/GPA	36	37	Oral, Lung, Kidney	RhF , PR3-ANCA	Prednisolone, MTX, NSAID	I
	RA/GPA	35	55	Lungs	RhF , PR3-ANCA	NSAID, MTX	I
2005 / 1 [21]	RA/MPA	44	48	Oral, Eyes, Kidney	RhF , MPO-ANCA ANA	MTX, Penicillamine, Gold, prednisolone	I
2008 / 1 [22]	RA/GPA	57	60	Lungs	RhF , PR3-ANCA, AntiCCP	Prednisolone, MTX, NSAID	I
2012 / 4 [23]	RA/GPA	40	70	Lung, Kidney	RhF , PR3-ANCA, AntiCCP	Prednisolone	I
	RA/MPA	49	44	Lung, Kidney	RhF , MPO-ANCA	Adalimumab, RTX	I
	RA/MPA	28	34	Lung, Kidney	RhF , MPO-ANCA	Prednisone, SFZ, MTX	I
	RA/EGPA	52	54	Skin	RhF , MPO-ANCA	MTX, Cyclosporine	I
2012 / 1 [24]	RA/GPA	36	37	Lung	RhF, c-ANCA		D
2013 / 1 [25]	RA/GPA	45	58	Kidney	RhF , PR3-ANCA	MTX, Etanercept	HD
2014 / 1 [26]	RA/GPA	65	67	Skin, Lung, ENT, Eye	RhF, c-ANCA	MTX, Prednisone, etanercept	I
2015 / 6 [7]	5 RA/MPA 1 RA/GPA	24-63	63-69	5: Kidney, Lung 1: Lung	3:RhF 1:Anti CCP 1:PR3- ANCA 3: MPO-ANCA	1:MTX, prednisone 1: SFZ 1: HCQ, MTX, leflunomide 1: Infliximab, MTX, SFZ 1: Etanercept, MTX, SFZ, AZA 1: Prednisolone	5: I 1: HD 1: D

RA: Rheumatoid Arthritis, **VAS:** Vasculitis associated symptoms, **GPA**: Granulomatosis with polyangiitis, **MPA**: Microscopic polyangiitis, **EGPA** (Churg-Strauss Syndrome), **ENT**: ear, nose and throat; **HCQ**: hydroxychloroquine, **NSAID**: non-steroidal anti-inflammatory drug, **CP**: cyclophophamide; **AZA**: Azathioprine, **SFZ**: sulfasalazine, **MTX**: methotrexate, **D**: dead, **I**: AAV improved, **HD**: Hemodialysis

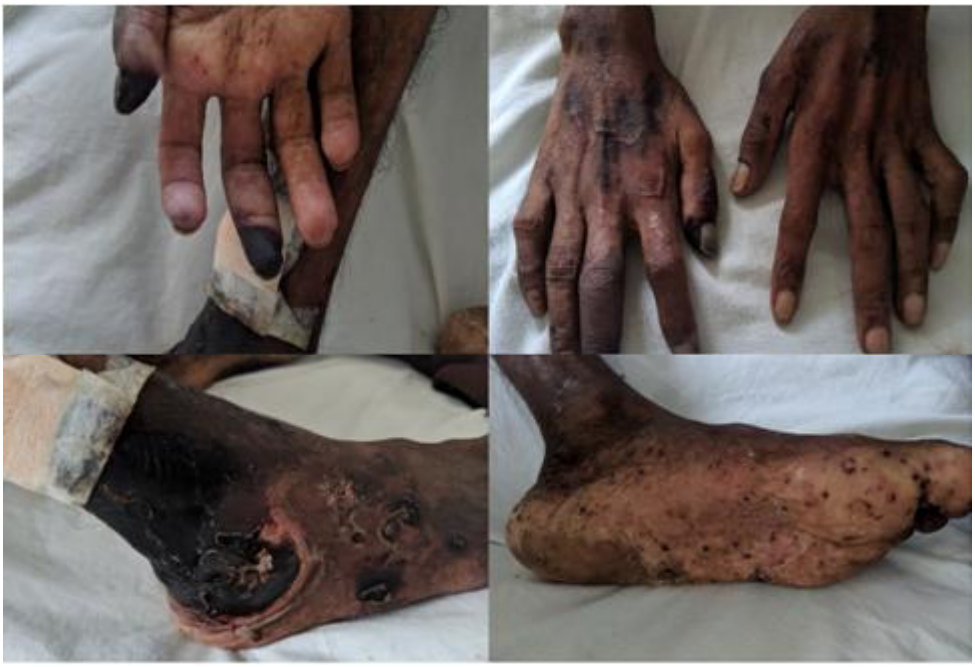

Figure 1: Gangrenous lesions at presentation

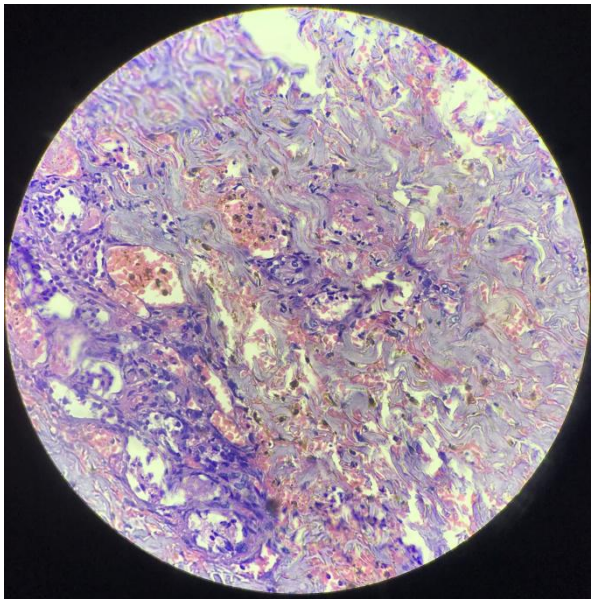

Figure 2: HPE of skin biopsy specimen: showing subcutaneous inflammation of fat cells with inflammatory infiltrates. Dermis shows diffuse neutrophilic infiltrates and few lymphocytes, dilated blood vessels

6. Ethical Guidelines

Funding information: This project was not funded by any sources.

Conflict of interest: There was no conflict of interest to any of the authors.

Informed Consent: A written informed consent for publishing the case report and relevant photographs, was taken from the patient and patient relatives after preparing the manuscript.

Ethical statement: This case report is being send for publication after taking approval and no objection from the institutional ethics committee.

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