Peripheral Arterial Disease in Non-Diabetics: Don’t miss Vasculopathy of Specific Etiology – Non Atherosclerotic (VSE-NA) in young patients

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Abstract

Aim: To find out the proportion of non-diabetic peripheral arterial disease (PAD) attributable to systemic connective tissue diseases (CTD) or thrombophilic states as etiology and to identify clinical and laboratory features that would point towards systemic disease other than atherosclerosis.

Materials and Methods: We studied the etiology of PAD in 45 non-diabetic patients in a tertiary health care center in Mumbai prospectively from January 2004- December ’07.

History, clinical examination haemogram, routine biochemistry, lipid profile, serological tests for connective tissue diseases and vasculitis, tests for prothrombotic state, vascular Doppler and 2D echo were performed in all cases. Angiography, CT scan and biopsy were done wherever necessary.

We classified etiology of PAD as Gr I] Possibly Atherosclerosis OR Idiopathic, Gr II] Vasculopathy of specific etiology – Non Atherosclerotic (VSE-NA) : this included patients with CTD and thrombophilic states. We tried to identify clinical and laboratory features, that would differentiate VSE-NA (Gr II) from the other group (Gr I).

Results: There were 24 females, 21 males, age 18 to 70 years (average 45). Sixteen patients presented with UE (upper extremity) gangrene, 22 with LE (lower extremity) gangrene and 7 with both UE and LE gangrene. VSE-NA was detected in 44.4% of patients, 28.9% were possibly due to atherosclerosis and 26.6% were idiopathic. In VSE-NA group, 28.9% were due to CTD and vasculitis and 15.6% due to thrombophillias (2 APLA, 4 hyperhomocysteinaemia, 1 hyperviscosity due to multiple myeloma). In the CTD and vasculitis group (N=13), 9 (20%) were due to vasculitis (5 ANCA-associated vasculitis and 4 ANCA negative vasculitis. Out of 31 surgical referrals, 38.7% were VSE-NA whereas 57.14% of 14 medical patients were attributed to VSE-NA.

Younger age of onset (< 41 yr), fever, weight loss, multiple limb involvement, anemia, high ESR, abnormal urine routine- proteinuria and RBCs all point towards a systemic connective tissue disorder.

Conclusions: High index of suspicion, detailed investigations to detect VSE-NA in non-diabetic patients with PAD is important, as all these conditions have specific treatment.

Introduction

PAD is a clinical term that denotes an occlusive disease rising from narrowing of arteries distal to the arch of aorta. Etiology of PAD is attributed to atherosclerosis, diabetic vascular disease, smoking and Buerger’s disease. The past 20 years have unveiled a gamut of etiologies of vasculopathies including inflammatory or prothrombotic conditions. In 1969 Homocysteine and thrombosis correlation was considered but its importance in thrombophilic conditions is realized only in the recent decade. Other important milestones in the vasculopathies are in 1982: ANCA and vasculitis and in 1983: APLA syndrome. These laboratory tests are available in the metros in India 1995 onwards. Research on etiology of vascular diseases is concentrated on common and potentially lethal diseases like CAD and CVA. PAD has been definitely ignored. There are certain practical issues with the diagnosis of these conditions especially vasculitis, as serologic test like ANCA is not yet included in the diagnostic criteria of any vasculitis. Also there are ANCA negative vasculitis. Hence for confirmatory diagnosis of vasculitis biopsy or angiography is necessary. Regarding biopsy diagnosis the yield is poor (<40%) from most sites but for open lung biopsy (yield 90%), which is practically difficult. Investigations for prothrombotic conditions are expensive hence deferred.

Moreover gangrene is often admitted in surgical ward for emergency intervention where the focus is on immediate relief and less on etiology. Diabetic gangrene is a well established condition, therefore we decided to investigate etiology of PAD in non-diabetic patients. We also aimed to identify clinical and laboratory features that would suggest underlying systemic disease other than atherosclerosis.

Material and Methods

We studied the etiology of PAD in 45 non-diabetic patients in a tertiary health care center in Mumbai in the Medicine and Surgery departments prospectively from January 2004- December ’07.

Inclusion criteria: Adult patients with PAD (gangrene or pre gangrenous changes in limbs)

Exclusion criteria: 1) Diabetic patients with PAD 2) Venous gangrene 3) Patients with trauma or obvious compression as a cause of PAD 4) Patients with a confirmed diagnosis of a CTD presenting with PAD
Early age of onset (< 41 years), multiple limb involvement, presence of fever, mucocutaneous lesions, ESR > 70 mm/hr, Anaemia (Hb < 12 for males and < 10 for females), rBCs in the urine in a patient of PAD has statistically significant chance of PAD being due to VSE-NA. (Table 2). Upper limb involvement was more common in the VSE-NA group but the difference was not statistically significant. Lower limb involvement alone was found to be less likely to be due to VSE-NA (p 0.001). There was no sexual predisposition towards any group observed in this study. Only 6 patients gave history of smoking therefore no statistical inference could be derived. None of our patients were obese (study was conducted in a Municipal General Hospital). Twenty nine percent patients had abnormal lipid profile (average age- 59 years, 8 males, 4 smokers), their PAD was attributed to atherosclerosis.

Table 3 depicts the distribution of causes within CTD and vasculitis group presenting as PAD. Nine patients had primary vasculitis (5 ANCA positive and 4 ANCA negative) where as in 4 patients a CTD was diagnosed as a cause of PAD.

**Discussion**

We studied 45 patients presenting with PAD prospectively in a tertiary care center. We deliberately excluded diabetic patients as diabetes is a well established cause of microangiopathy, atherosclerosis and gangrene. Also we thought presence of infections in diabetics (urinary, foot ulcers) and diabetic nephropathy could interfere with our aim to identify clinical
In The VSE-NA group there were 9 patients (28.9%) of primary vasculitis, five (11.1%) of them were ANCA positive vasculitis (4 Wegener's and 1 Microscopic polyangiitis). Two patients of Wegener's granulomatosis were admitted in surgery wards. One of them M/ 45, presented with left hand gangrene, 5 days later developed pulmonary haemorrhage (Fig. 1. A, B, C), creatinine 2.5mg/dl, microscopic haematuria (Pulmonary renal syndrome). He was found to be c-ANCA positive. Biopsy of purpuric rash on his thigh revealed leucocytoclastic vasculitis. The second patient M/55, had undergone endoscopic sinus surgery in a private hospital. He was transferred to surgery ward in our hospital for multiple digital gangrene and severe exophthalmos 2 days following the surgery. (Fig. 2 A, B, C, D) His investigations revealed: ESR of 117mm/hr, Proteinuria and haematuria, normal X-ray chest but granuloma in the left lung lower zone on HRCT chest, c-ANCA positive. The other two patients of WG had presented to medicine, F/35 with right digital gangrene, hypertension and microscopic haematuria, ESR 127 mm/hr, c-ANCA positive and M/50 with bluish discolouration of fingers of left hand and toes, past history of sinus surgery 6 months back (biopsy from sinus mucosa- nonspecific sinusitis), right 1st metacarpophalangeal joint pain and oral and scrotal ulcer 1 month back, had ESR 80mm/hr, RBCs in the urine, skin biopsy from purpuric rash on leg revealed leucocytoclastic vasculitis and c-ANCA positive. All 4 were treated with steroids and cyclophosphamide. On review of literature we could find occasional case reports on limb ischemia in WG.

The 5th patient of ANCA positive vasculitis was a M/19, with multiple finger and toe gangrene and left foot drop (Fig. 3 A, B) his left sural nerve biopsy revealed vasculitis of vasa nervosum, other investigations were ESR 89, urine- proteins and RBCs, p-ANCA +ve and antibodies to myeloperoxidase (mpo)- was diagnosed as microscopic polyangiitis.

In one patient we suspected ‘probable Churg Strauss syndrome’. She was F/ 52, presented with left upper limb ischaemia (finger gangrene), a history of late onset asthma at age 46 years, investigations revealed ESR 77mm/hr, Urine –Normal, ANA and ANCA negative, CT scan of chest revealed patchy parenchymal opacities and peribronchial thickening, x-ray paranasal sinuses- opacification of both maxillary sinuses, but peripheral blood eosinophilia could not be documented and no biopsy was performed. Thus she satisfied 3 ACR criteria. Timely diagnosis of CSS becomes difficult as individual manifestations of the syndrome occur in isolation. The clinical elements occur in 3 sequential phases: Prodromal phase- allergic rhinitis and asthma in the third decade of life, Eosinophilic phase- peripheral blood eosinophilia and organ infiltration, Vasculitic phase-systemic vasculitis of medium and small vessel vasculitis in the 4th decade of life. Asthma is the cardinal feature of CSS (occurs in 95% patients) and usually precedes the vasculitis phase by 8-10 years when eosinophilia may be absent. Only 60-70% CSS are ANCA positive.

One patient (M/30) in whom we diagnosed Behcet’s disease as a cause of PAD presented with gangrene of right upper limb and left lower limb toes, he had fever, recurrent oral ulcers and genital ulcers on examination, skin rash which on biopsy revealed to be leucocytoclastic vasculitis. There are occasional reports of gangrene in Behcet’s disease.

One patient was categorized as ‘Unclassified systemic vasculitis’. She was F/40, who presented with blackening of
fingers and toes (Fig. 4A) and breathlessness. She was not on oral contraceptives. She had a scar of a healed leg ulcer. Her CT angiography revealed thrombus in the left pulmonary artery (Fig. 4B) with pulmonary hypertension. Her ESR, serology for CTD and work up for thrombophilia was negative. Her skin biopsy revealed leucocytoclastic vasculitis (Fig. 4C). She was treated with low molecular weight heparin, prednisolone 1mg/kg and pulse cyclophosphamide. Yet 1 month later she was admitted with breathlessness and investigations revealed recurrent pulmonary thromboembolism and increased gradient of pulmonary hypertension. Despite continued anticoagulation, steroids and pulse cyclophosphamide 2 months later she presented with pain in the right lower limb, investigations revealed thrombosis of the right superficial femoral and popliteal venous thrombosis.

One patient, F/45, presented with bluish discolouration of the left hand (Fig. 5A), her arch aortogram (Fig. 5B) revealed narrowing of the left subclavian artery, ESR 65mm/hr, urine - normal, lipid profile and thrombophilia profile were normal, ANA and ANCA were negative and she was diagnosed as aortoarteritis.

One F/35, who presented with left 3rd, 4th finger tip gangrene, 8 months later developed skin rash (which was diagnosed by dermatologists as DLE rash) was negative for all serological tests as well as thrombophilia workup. Patients with Raynaud’s phenomenon or digital ischaemia should be followed up for 2 years for development of a CTD.

One F/30, presented with bilateral upper limb finger tip gangrene, there were no systemic constitutional signs or symptoms like fever or rash, the skin was not tight, her ANA was 1:40 (2+), Anti-Scl-70 and anticientromere antibodies were negative. Her skin biopsy revealed oedema stage of scleroderma.

A F/40, presented with bluish black discoloration of fingers of both hands (index and middle finger) of 1 week duration. She had fever on and off, rash, alopecia for 6 months prior to current visit. She was ANA +ve 1: 320, Urine protein ++ and RBCs 20/ hpf, Low compliments, Anticardiolipin antibodies IgG 45 U, IgM 36 U. She was diagnosed as SLE with APLA syndrome. In this patient diagnosis of lupus was evident at the time of presentation. She presented late to doctors due to financial reasons.

M/50, was referred to us after left below knee amputation. In his past history 10 years back he had rabbit like red pinna. But there was no biopsy proven relapsing polychondritis. Considering his age his left leg gangrene could be due to atherosclerosis or vasculitis due to relapsing polychondritis. At present admission, there was no inflammation or deformity of the ear. Therefore, to document chondritis, a CT scan of the tracheobronchial tree was done, which showed erosions in the thyroid cartilage (Fig. 6). He was treated with corticosteroids and cyclophosphamide.

Seven patients (12%) of PAD had prothrombotic conditions. Two patients had Antiphospholipid antibody syndrome (Fig. 7 A, B, C, D) where as four patients had PAD due to Hyperhomocysteinaemia and one hypercoagulable state due to multiple myeloma. In a prospective study from Dept of vascular surgery, St George Hospital, London on ‘Prevalence of thrombophilia in patients with symptomatic peripheral vascular disease’, a quarter patients with PVD had evidence of thrombophilia and a third had hyperhomocysteinaemia. 4% patients had APLA. In this study peripheral venous disease patients were also included and extensive thrombophilia work up inclusive of protein S, protein C, factor V Leiden mutation was also studied. These tests were not performed in our study for financial reasons and secondly we did not include patients with venous gangrene or occlusion in our study. British Committee for Standards in Haematology (BCSH) has recommended thrombophilia screening in patients with arterial thrombosis before age 30. In a study from Greece, the prevalence of APLA ranged from 1.7- 6% in patients of PVD. Clarke et al reported hyperhomocysteinaemia in 28% patients of premature vascular disease.

One patient, F/43 presented with severe pain in feet for 18 months, macular rash on legs for 1 year, 5kg weight loss in 5 months, fever for 6 weeks. All her toes were blue and tender. As per old records her haemoglobin decreased from 11 to 7.8 gm%, ESR was 135mm/hr, urine was normal, ANA and ANCA were negative, skin biopsy from macular rash on leg was unyielding, serum protein were 11.5 gm/dl, gamma globulins 9gm/dl,
serum protein electrophoresis revealed ‘M’ band in serum with 30% myeloma cells in the bone marrow. She was diagnosed as multiple myeloma with hyperviscosity syndrome and painful sensory neuropathy.

We detected VSE-NA in many young patients presenting with PAD. Yet there were limitations of this study as complete work up for prothrombotic state like Protein C, protein S, antithrombin III, factor V Leiden mutation were not done due to financial constraints. The sample size was small considering varied etiology. Possibility of referral bias due to rheumatology specialty of the unit can not be ruled out.

**Conclusion**

PAD may be the first presentation of a systemic CTD or thrombophilic state. Younger age of onset (<41yr), fever, weight loss, multiple limb involvement, anemia, high ESR, abnormal urine routine-proteinuria and RBCs all point towards a systemic connective tissue disorder with a p value of <0.01. Upper limb PAD was more common in VSE-NA group but the difference was not statistically significant. Whereas lower limb PAD alone was statistically uncommon in VSE-NA group (p < 0.003). Laboratory tests for a systemic CTD and thrombophilia work up should be done in all non diabetic PAD patients. Timely treatment of underlying cause will prevent damage to vital organs like the kidney in CTD patients and to the heart or brain in patients with hyperhomocysteinaemia and antiphospholipid antibody syndrome.

**References**