

Etiological and clinicopathological study of secondary small vessel vasculitis in elderly: A case series of 12 patients

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ABSTRACT

Background: Inflammation involving the postcapillary venular wall is defined as small vessel vasculitis. Small vessel vasculitis has various clinical manifestations. Etiologically, it can be primary or secondary. Literature regarding secondary vasculitis in elderly is scanty. **Aim and Objectives:** In this case series, we aimed to assess the clinical features and etiologies of biopsy-proven secondary small vessel vasculitis in the elderly. **Methodology:** Twelve elderly patients with biopsy-proven small vessel vasculitis were included in this study. All patients were thoroughly evaluated to assess the etiology and presence of major organ involvement. **Results:** Secondary small vessel vasculitis involved both the sexes equally. Constitutional symptoms including fever and weight loss were noticed by most of the (70%) patients. Neurological deficits were present in 83% of the study population. The most common finding in an electromyographic examination was an asymmetric sensory motor distal predominant polyradiculopathy. Fifty percent of the patients did fulfill the criteria for a definite autoimmune disease. More than 30% of the vasculitis was secondary to malignancies. **Conclusions:** Neurological manifestations are the most common systemic involvement in elderly patients with secondary vasculitis. Meticulous search for underlying malignancies is mandatory in elderly patients with secondary small vessel vasculitis.

Keywords: Elderly, malignancy, neuropathy, secondary, vasculitis

Introduction

Vasculitis refers to transmural inflammation of blood vessels. Although most forms do not respect vessel size, vasculitic syndromes have been classified based on predominant size or type of vessels involved. Small vessel vasculitis refers to the preferential involvement of capillaries, venules or arterioles, and intraparenchymal arteries. These have diverse clinical manifestations and can occur as a primary disorder or secondary to other medical conditions. Till date, most of the literature regarding vasculitis in elderly has been mostly on antineutrophil

cytoplasmic antibody (ANCA) positive vasculitis.^[1] We report the clinical features, laboratory parameters, and etiologies of biopsy-proven secondary small vessel vasculitis in a subgroup of 12 elderly patients.

Methodology

In this retrospective observational case series, we included all elderly patients (age >55 years) presenting to our tertiary care health center in South India with a diagnosis of small vessel vasculitis, between January 2009 and December 2010. The diagnosis of small vessel vasculitis was based on biopsy. Details of demography, clinical profile, electrophysiological findings,

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and laboratory investigations were obtained retrospectively, from the outpatient medical records database of our institution. All the patients had undergone a detailed evaluation for ruling out primary vasculitis and mimics of small vessel vasculitis.^[2] All patients included were assessed for the presence of major organ involvement. Entry and analysis of data were done using Microsoft Excel version 2010.

Results

The baseline characteristics of 12 patients have been shown in Table 1. In this group of patients, incidence of small vessel vasculitis was equal in both males and females ($n = 6$ each, 50%). The mean age of presentation for women was 63 years (59–70) and mean age of presentation for men was 65 years (55–74). At the time of diagnosis, 8 (67%) were between the age group of 60–69 and two patients were in their seventh decade of life. The common associated comorbidities present in this subgroup of patients were diabetes mellitus in 41% (5), essential hypertension in 41% (5), hypothyroidism in 41% (5), and reactive airway disease in 33% (3). Constitutional symptoms of fever, loss of appetite, and weight were present in 70% (9) of patients. Neurological deficits were present in 10 (83%) patients at the time of presentation. Most common neurological deficit reported was distal predominant motor weakness involving lower limbs more than upper limbs (10/83%), followed by positive and negative sensory symptoms on extremities in 4 (32%). Lower motor neuron type bulbar weakness in the form of dysphagia to liquids, nasal regurgitation, and nasal tone of voice was seen in 3 (25%) of the patients. Electromyography (EMG) including nerve conduction studies revealed asymmetric axonal, demyelinating motor sensory polyradiculoneuropathy in all the patients (100%) who underwent a nerve conduction velocity (NCV) study (10/10). Cutaneous involvement in the form of erythema, ulceration, and bullae, and joint symptoms such as inflammatory polyarthritis or polyarthralgia were seen in 5 (41%) patients each. Symptoms of respiratory and renal involvement were present in 3 (25%) patients each. On investigations, anemia, leukocytosis, leukocytopenia, thrombocytopenia were present in 6 (50%), 3 (25%), 2 (16%) each. Inflammatory markers such as erythrocyte

sedimentation rate (ESR) and C-reactive protein (CRP) were elevated in 6 of the 12 (50%) patients. Out of the four patients who were diagnosed to have hematological malignancy, three had normal levels of inflammatory markers. Abnormal urinalysis in the form of proteinuria and hematuria was present in 6 (50%) of the patients. Diagnosis of small vessel vasculitis was confirmed with combined nerve, muscle, and skin biopsy in 9 (75%) among which peroneal nerve was biopsied in 8 and sural nerve was biopsied in 1. In the remaining three, diagnoses were confirmed with combined muscle and skin biopsy and only skin biopsy in one and two patients, respectively. On etiological evaluation, 6 (50%), 4 (34%), and 2 (16%) of the patients were found to have small vessel vasculitis secondary to underlying autoimmune diseases [Table 1], hematological malignancies, and non-ANCA small vessel vasculitis, respectively. Most of the patients underwent blood culture, hepatitis B and C serology, HIV, venereal diseases research laboratory test, mycobacterial and fungal cultures, SS-A, SS-B, lupus anticoagulant, Jo1, SCL 70, ENA, anti-RNP, serum electrophoresis, and bone marrow examination to rule out mimics of small vessel vasculitis. Nine (75%) of these patients were treated with 1 mg/kg of steroid and six (50%) had received second-line agent either cyclophosphamide or mycophenolate mofetil [Table 1]. In the remaining three, treatment with immunosuppression was withheld as requested by the patient or caregiver. Response to treatment and long-term outcome was not evaluated for this subset of patients.

Discussion

The term vasculitis implies inflammation of walls of blood vessels which can occur in a heterogeneous group of diseases resulting in various organ involvements.^[2] Systemic vasculitis has been classified either based on the size and type of vessel (large, medium, and small) or based on the histopathological (leukocytoclastic, granulomatous) features.^[1,2] Small vessel vasculitis refers to preferential involvement of capillaries, venules, or arterioles involving any organ and can present with varied clinical manifestations. The two pathological features involved in vasculitis are inflammation of vessel wall and resultant ischemia of the tissue.^[3] The mechanism behind

Table 1: The details of demography, diagnosis, and treatment of patients with vasculitis

Number	Age/sex	Diagnosis	Treatment
1	60/female	Mixed connective tissue disorder	Cyclophosphamide+prednisolone
2	70/female	Polymyositis	Prednisolone
3	74/male	Anaplastic large cell lymphoma	Denied
4	69/male	Chronic lymphoid leukemia	MMF + prednisolone
5	60/female	Mixed connective tissue disorder	Cyclophosphamide + prednisolone
6	65/male	Idiopathic small vessel vasculitis	Cyclophosphamide + prednisolone
7	61/male	Non-Hodgkin's lymphoma	Denied
8	69/male	Urticarial cutaneous vasculitis	Prednisolone
9	64/female	Rheumatoid arthritis	Denied
10	59/female	Idiopathic small vessel vasculitis	Methyl prednisolone
11	54/male	Angioblastic T-cell lymphoma	MMF+prednisolone
12	64/female	Sjogren's syndrome	MMF+prednisolone

MMF: Mycophenolate mofetil

the involvement of vessel wall can be antibody-mediated angitis, immune complex-mediated vasculitis, or allergic induced.^[3,4] These small vessel vasculitis can be primary or secondary. The presence of a vasculitis in the setting of a specific disease or precipitating etiology it is called a secondary vasculitis. The various systemic diseases known to cause vasculitis are rheumatoid arthritis, lupus, sarcoidosis, relapsing polychondritis, etc. The various etiologies causing vasculitis include drugs, infections, malignancies, and serum sickness. When there is no associated specific disease or cause, it is classified as a primary vasculitis.^[1,3] Incidence of primary systemic vasculitis has been found to be 19.8/million with a peak of up to 60.1/million in elderly (65–74 years). While the literature on small vessel vasculitis is limited in elderly, most of the work on epidemiology, clinical profile, management, and outcome of vasculitis has been on ANCA-positive patients with renal involvement.^[5,6] The above phenomenon is mostly due to a reported trend of increase in primary systemic vasculitis with advancing age.^[1,5] The mean and median age of elderly population presenting with primary systemic vasculitis has been reported to be 60–65 years, which is similar to our patients.^[5] Constitutional symptoms of fever, fatigue, loss of appetite, and weight can be seen in any of the systemic vasculitis and were present in the majority of the patients (70%).^[2,4] Involvement of central nervous system (CNS) and peripheral nervous system (PNS) is common in systemic vasculitis. It has also been reported that involvement of nervous system is more common in secondary vasculitis as compared to primary vasculitis, which is in keeping with our study with the presence of neurological deficits in majority of the patients (83%).^[7] The PNS involvement in vasculitis is uniform, manifesting as sensory axonal polyneuropathy or mononeuritis multiplex. CNS involvement though lesser than PNS involvement can be diverse and can manifest as angitis of hemispheres or spinal cord, aneurysms, thrombosis, granulomatous meningitis, or stenosis. In our cohort, 83% of patients presented with asymmetric motor weakness, positive and negative sensory symptoms, and diminished reflexes in the involved limb suggesting of peripheral neuropathy which is in keeping with the previous reports.^[7,8] The cutaneous presentation of vasculitis depends on the size of the vessel involved. Small vessel vasculitis most commonly presents as petechiae and palpable purpura. In event of blood vessel involvement throughout the dermis, overlying tissue necrosis can lead to presentation with vesicles and hemorrhagic bullae which can then become superficial erosions. Rarely, wheals (in urticarial vasculitis) and erythema multiforme-like lesions (in secondary vasculitis caused by drugs, infection, and connective tissue diseases) can be seen. Medium vessel vasculitis usually presents as digital gangrene, deep ulcers, subcutaneous nodules, and livedo reticularis. Skin biopsy done from a recent lesion shows transmural inflammation by inflammatory cells, fibrinoid necrosis, and extravasation of red blood cells with nuclear debris. A direct immunofluorescence needs to be done to rule out an immune complex-mediated vasculitis.

Anemia of chronic disease, leukocytosis, elevated ESR, and CRP, which are reported to be seen in most systemic vasculitis, were seen in 50% of our patients.^[2] Renal involvement progressing to

end-stage renal disease is common in primary vasculitis. It is an uncommon entity in secondary vasculitis with very few reports in literature.^[2,5,9,10] While renal involvement in primary systemic vasculitis can present as renovascular hypertension, subnephrotic range proteinuria, interstitial nephritis, and rapidly progressive glomerulonephritis, renal involvement in secondary vasculitis has not been reported to predict disease severity or disease outcome.^[9,10] In keeping with the same, in our set of patients, only 50% had urinary abnormality, and of these, one patient had high creatinine (2.3 g/dl). Vasculitic neuropathy secondary to inflammation of vasa nervorum of epineural arteries of nerve is diagnosed with neurophysiological or histopathological evaluation. EMG classically shows multifocal axonal neuropathy with reduced compound motor action potential suggesting asymmetric sensory motor polyneuropathy and was present in all the patients who underwent the study.^[8,11] Nerve biopsy is done only if the evidence of systemic vasculitis is not established with autoantibodies. Superficial peroneal nerve with peroneus brevis muscle and sural nerve biopsy has been used to establish diagnosis of vasculitis. As reported by Agadi *et al.*, in our group of patients, superficial peroneal nerve with peroneus brevis muscle biopsy was the most yielding biopsy site.^[12]

Literature on secondary causes, management, and outcome for systemic vasculitis in elderly is scanty with one study reporting only six patients and high mortality.^[13] The various etiological factors are categorized into drugs, infections, connective tissue diseases, malignancies, and paraneoplastic small vessel vasculitis.^[2,4,13-16] While certain type of vasculitis can have a concurrent association of malignancies, certain malignancies can also present as vasculitis.^[17] In a previous case series of 12 patients who were diagnosed to have vasculitis and cancer within a duration span of 12 months out of 15 million patients presenting to Cleveland Clinic, 6 had solid organ tumors, 4 had lymphoma, and the other 2 had leukemia and multiple myeloma.^[18] The mean age of the patients in the above study was 65 years, like in our study. However, in our study, one-third (33.5%) of the vasculitis was secondary to malignancy, and all of them were secondary to hematopoietic malignancies [Table 1]. There are various mechanisms postulated for the development of vasculitis in patients with malignancy, prime among them being impaired clearance of immune complexes, sharing of homology between cancer and vascular antigen, alteration of vessel wall antigen, and chemotherapy-related vasculitis.^[4,17,18]

Advanced age is known to be an indicator of poor prognosis in patients with ANCA-associated vasculitis (AAV).^[19] In a study including patients above 75 years of age with both primary and secondary vasculitis, rapid deterioration, severe functional impairment, and death were seen in more than 80% of patients.^[13] Other adverse indicators that have been identified in elderly patients with AAV were advanced renal dysfunction and noninitiation of immunosuppressive agent.^[6,20] Role of immunosuppressive agent in secondary vasculitis is unclear; however, the role of glucocorticoids, cyclophosphamide, and mycophenolate mofetil in elderly patients with AAV and

renal involvement is clear.^[5,6,19,20] Among our patients, 25% did not consent for any treatment and the remaining 75% were treated with prednisolone and only 50% received a second-line immunosuppressant. In view of the retrospective nature of the study, follow-up details of the above patients were not available. However, advanced age, presence of malignancy, refusal to treatment, and risk of increased complications following immunosuppressive therapy can contribute to poor outcome in this group of patients as mentioned earlier.

Conclusions

Meticulous search for underlying malignancies is mandatory in all elderly patients with ANCA-negative small vessel vasculitis. A thorough clinical examination for neurological deficits and EMG with NCV is essential in the evaluation of vasculitis in the elderly.

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Conflicts of interest

There are no conflicts of interest.

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