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Pattern of Primary Vasculitis with Peripheral Ischemic Manifestations: Report of a Case Series and Role of Vascular Surgery

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Abstract: Aim of the work: The aim of the present work was to study the role of vascular surgery in the management of primary vasculitis patients with peripheral ischemic manifestations. Patients and methods: Ten primary vasculitis patients with peripheral ischemic manifestations were studied and reviewed for the diagnosis, clinical manifestations, investigations, treatment options and role of vascular surgery. The Birmingham Vasculitis Activity Score (BVAS) was recorded. Results: Giant cell arteritis was present in one patient; granulomatosis with polyangiitis in 5, essential cryoglobulinemic vasculitis in 3 and 1 (child) had Henoch–Schönlein purpura. They showed the following peripheral vascular manifestations: intermittent claudications, Raynauds, deep venous thrombosis and thrombophelebitis in 10% each; digital ulceration and trophic changes in 20% while acrocyanosis and dry gangrene were present in 30%. Renal involvement was present in 60% of patients. The mean BVAS was 11.5±6.57 at initial presentation. The disease activity remarkably improved over the disease course in all patients to be at their last visit (2.6±2.22) (p=0.002). Regarding the vascular surgery role in their management, in addition to their medical treatment, 40% required an additional surgical intervention. Two had a minor amputation of the toes; one performed thoracoscopic cervical sympathectomy and another needed tibial angioplasty. Conclusion: Primary vasculitis patients presenting with peripheral ischemic manifestations require surgical attention. Their management is essentially medical and individualized to the diagnosis and presenting symptoms. Endovascular treatment may offer a safe and less invasive approach in high surgical risk patients. Sympathectomy is of high therapeutic potential in those with severe pain and trophic changes.

Keywords: Peripheral ischemia, vasculitis, vascular surgical procedures.

INTRODUCTION

Vasculitis is inflammation of the vessel wall that leads to its compromise or destruction with subsequent hemorrhage and ischemia. Vasculitis is either primary or secondary to a rheumatic or connective tissue disease (CTD). Cutaneous vasculitis may present as an important manifestation of rheumatoid vasculitis or anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitic syndromes and mostly manifests as palpable purpura denoting dermal superficial, small-vessel vasculitis (SVV), and less commonly as deep ulcers or digital gangrene indicating deep dermal or subcutaneous, muscular-vessel vasculitis [1].

Primary systemic vasculitides (PSV) include a heterogeneous set of complex clinical entities with a common substrate: inflammation and necrosis of blood vessels. The inflammatory process involves vessels of any caliber. The location and the different size of the affected vessels, the severity of vascular damage and the different histopathological patterns which may predominate are the basic characteristics that define the different vasculitic syndromes and enable individualization [2]. In patients with large or medium vessel vasculitis with no accessible tissue for histopathology, angiogram should then be well thought-out [3]. Advances in knowledge of primary vasculitides have evolved considerably in recent decades, allowing for a better resolution of the complex problems placed by these patients [2].

For treatment of cutaneous vasculitis, colchicine and dapsone are preferable. Severe cases may be managed by corticosteroids, azathioprine, methotrexate or cyclophosphamide. Combining steroids and cyclophosphamide is the treatment of choice for systemic vasculitis. In refractory cases, plasmapheresis and intravenous immunoglobulin are considered. Biologic agents as anti-tumor necrosis factor-alpha (TNF-α) and anti-B-cells show benefit in ANCA-associated vasculitis [1].

The wide spectrum of clinical manifestations and affected target vessels leads to the presentation of vasculitides to various clinicians including dermatologists, rheumatologists and vascular surgeons [4]. The real expertise of the rheumatologist or vascular surgeon depends on the accurate diagnosis of the underlying disease which manifests as peripheral limb ischemia. The use of clinical history, likelihood ratios and appropriate investigations asked in the right clinical scenario greatly enhance the accuracy of diagnosis [5]. The vascular surgeon attends to the sequelae of vasculitic injury. Thrombosis, aneurysm formation, hemorrhage or arterial occlusion may all follow or accompany transmural

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damage created by inflammatory reactions on the vascular wall [6]. The vast majority of disorders that present with peripheral limb ischemia generally have limited therapeutic options in the form of antiplatelet therapy, anticoagulation, surgical bypass grafts and thrombectomy. These therapeutic modalities reduced not only the mortality but also the morbidity in the form of amputations [5]. Even though primary vasculitic syndromes are rare diseases, vascular surgeons should be aware of their classification criteria, different treatment options and special considerations when managing or operating these patients [7].

The aim of the present work was to retrospectively study the role of vascular surgery in the management of primary vasculitis patients with peripheral ischemia.

PATIENTS AND METHODS

Ten patients with established primary vasculitis syndromes and peripheral ischemic manifestations were included; their files were retrospectively thoroughly investigated to detect their management outcomes and role of vascular surgery in their treatment disciplines. Patients with a primary vasculitic syndrome were included when they had peripheral ischemic manifestations in the form of peripheral gangrene, ischemic limb ulcers and intermittent claudications. Any patients with diabetes, atherosclerosis, age > 50 years or any underlying cause of secondary vasculitis were excluded.

The patients' files were reviewed for the diagnosis (type of vasculitic syndrome), clinical manifestations, system and organ involvement, distribution of vessels affected, treatment options and the role of vascular surgery after being consulted. The Birmingham Vasculitis Activity Score (BVAS) [8] was recorded at the initial establishment of the diagnosis as well as the last visit.

The patients' files data were reviewed regarding detailed history including the smoking status, history of hypertension and dyslipidemia with emphasis on the vascular symptoms such as ulcers, cyanosis, intermittent claudications and gangrene. The general examination of the patients was recorded as well local vascular examination including distal pulses, color changes, trophic changes and tissue loss (ulcer or gangrene).

The following investigations were revised: Erythrocyte sedimentation rate (ESR), creatinine, urine analysis and anti-neutrophil cytoplasmic antibody (ANCA). Renal biopsy result was recorded in indicated cases. Abdominal ultrasound was considered. Duplex ultrasonography of the affected limb was noted for specified cases. The medical treatment of the patients was reviewed regarding the primary vasculitic syndrome and the vascular affection. Surgical treatment of vascular lesions was considered with special consideration to the role of amputation, sympathectomy and angioplasty.

Statistical analysis: Data were presented as number (percentage) and mean±SD when suitable. The comparison of the BVAS was performed by student t test and significantly different at $p<0.05$. Results were analysed and interpreted.

RESULTS

Ten primary vasculitic syndrome patients with peripheral ischemic manifestations were selected from the Rheumatology department, Faculty of Medicine, Cairo University (Kasr Al Ainy) hospitals. They were 8 females and 2 males. One patient was juvenile (6 years old) with a disease duration of 1 year. The mean age of the other patients was 44± 4 years. The disease duration in the adult patients was 3.5±1.72 years. Only one male used to smoke and stopped a year following disease onset.

The diagnosis according to the size of vessel involvement was large-vessel vasculitis; Giant cell arteritis (GCA) in one patient and the other nine presented with small-vessel vasculitis (SVV); Granulomatosis with polyangiitis (GPA) (formerly Wegeners granulomatosus) was present in 5, essential cryoglobulinemic vasculitis (ECV) in 3 cases and 1 (child) had Henoch–Schönlein purpura (HSP). Regarding the peripheral vascular manifestations of the studied patients they are presented in Table **1**.

Table 1. Peripheral vascular manifestations in the selected patients with primary vasculitis.

Peripheral vascular Feature Number (%)	Primary vasculitis patients (n=10)
Intermittent claudications	1 (10)
Acrocyanosis	3 (30)
Digital dry gangrene	3 (30)
Digital ulcerations	2 (20)
Trophic changes of the digits	2 (20)
Raynauds disease	1 (10)
Deep Venous Thrombosis	1 (10)
Thrombophlebitis	1 (10)

Other non-vascular system involvement of the patients included: Renal affection in 6 patients (60%) which was early in the disease course as evidenced by an increased cortical echogenecity by ultrasound. Findings of renal involvement varied from granular casts in urine (1 patient), proteinuria (2 patients), and elevated creatinine was detected in 5. The patient with GCA had an end stage renal disease (ESRD) and was on regular peritoneal dialysis. Four of the 5 GPA patients had renal involvement and one of them dialyzed once followed by an improvement of the kidney function. Renal biopsy was performed in 4 patients and the histopathology revealed renal vasculitis in 3 cases with glomerulonephritis (GN); focal GN, membranous GN and glomerulosclerosis with crescent formation. Pulmonary involvement was present in 3 patients giving a history of hemoptysis and radiological chest findings in the form of opacities or nodules. Four patients presented with nasal affection in the form of epistaxis, deviated septum, sinusitis, nasal polyps and depressed nasal bridge. Peripheral neuritis (numbness and

parasthesias) were present in 40% of the cases. Arthritis was present in 4 patients, jaw claudication in the GCA patient and 2 had oral ulcers.

Two patients with ECV had a positive hepatitis C-virus (HCV) test. Nine patients had an elevated ESR throughout the disease course (range: 45-110 mm/1st hour). There was a remarkable decrease in the ESR in three patients with medical treatment. The c-ANCA was positive in 2 GPA patients. The mean BVAS was 11.5±6.57 (range: 3-26) at initial presentation. The disease activity remarkably improved over the course of the disease in all patients to be at their last visit (2.6±2.22; range 0-6) (p=0.002).

Duplex ultrasonography of the vessels of the upper and lower limbs in the patients with primary vasculitis revealed a normal study (and fully felt distal pulses) in 3 patients. The patient with GCA had brachial artery occlusion. Three GPA patients showed evidence of medium-sized vessel disease involving ulnar, radial and tibial arteries. Small vessel vasculitis was evidenced on biopsy from those patients with essential cryoglobulinemic vasculitis and the one with Henoch–Schönlein purpura.

On analyzing the lines of treatment, patients received medications for the primary vasculitis in the form of corticosteroids of varying doses (8 patients) and immunosuppressives in the form of cyclophosphamide (4 cases), methotrexate (2 cases) while azathioprine and colchicine were provided to one patient each. Throughout the disease course patients were treated by more than one drug combination. For management of the vascular manifestations, patients received anticoagulants (enoxaparin LMWH and warfarin) in 3 cases and low dose aspirin in 4 patients. Vasodilators were used in 5 patients; calcium channel blocker 'nifedipine' was used by 4, a prostacyclin analogue 'alprostadil' in 2 and pentoxaphylline in 4.

Regarding the vascular surgery role in the management of these patients, in addition to their medical treatment, four (40%) required an additional surgical intervention. The following procedures were undertaken: Two of the 3 ECV patients with dry gangrene had a minor amputation of the toes (one of them was an ex-smoker); one GPA patient performed a thoracoscopic cervical sympathectomy for severe upper limb distal pain with recurrent digital infection and ulceration not responding to medical treatment. Another GPA patient needed tibial angioplasty for anterior and posterior tibial arteries occlusion and stenosis (without stenting) inspite the prolonged use of immunosuppressives. None of the patients required a bypass surgery. These medical and surgical procedures had a good control on both the disease activity and vascular symptoms.

DISCUSSION

The present study included ten primary vasculitis patients with peripheral ischemic manifestations that required vascular surgery consultation. In the present study, 60% of the cases had renal involvement throughout the disease course especially the patient with GCA and 4 with GPA (of which 2 were c-ANCA positive). The patient with GCA and another with GPA had impaired renal function necessitating dialysis. Glomerulonephritis (GN) is a frequent manifestation of the ANCA -associated systemic vasculitides (AASV), including GPA. The intensity of renal involvement is vastly predicts mortality and should be evaluated early to maintain the kidney function. Renal vasculitis is common in patients with a severe disease and poorer prognoses [7]. Combined cyclophosphamide and steroid therapy for those with renal involvement in GPA may prevent progression to end stage renal disease (ESRD) [3]. In a previous study, it has been reported that although renal vasculitis is usually associated with ANCA, it is rarely studied in non-ANCA patients. Understanding the manifestations of systemic vasculitis allows for the precise selection of immunomodulatory agents [9]. It is important that the awareness of renal involvement is raised for vascular surgeons regarding the renal condition in these cases especially when indicated for angioplasty as all measures should be taken to avoid contrast induced nephropathy. Vascular complications are frequent in long-term dialysis patients [10]. Patients with diffuse vascular disease and ESRD are at increased risk for the development of finger gangrene due to distal atherosclerosis [11]. It should be stressed on the importance of periodic evaluation of the renal cortex echogenicity and renal artery hemodynamics in patients with primary vasculitis and peripheral ischemic manifestations. Renal vasculitis is an independent risk factor for cardiovascular events [9].

In the present study, 60% of the patients were controlled well by the combined medications including steroids and immunosuppressives. The primary systemic vasculitic syndromes include a range of diseases distinctively known by their clinical, histopathologic and therapeutic features. They also differ in severity and could be life-threatening if timely treatment is not initiated. Immunosuppressives are used to treat many of these syndromes. However, the long-term course and organ damage are affected by the initial presentation, disease relapses and medication toxicity [12]. The prostanoid 'iloprost' is safe and effective for digital ischemia and ulcers. In combination with immunosuppressives, it has a potential role in preventing irreversible complications as digital gangrene and amputation [13].

Surgical intervention was encountered in 40% of cases with peripheral ischemic manifestations. Two had digit amputation; one patient performed a thoracoscopic cervical sympathectomy and another needed tibial angioplasty. None of the patients required a bypass surgery. Treatment of digital gangrene is multifactorial. For vasospasm, vasodilators and calcium channel blockers are used. For prevention and treatment of thrombosis, low-dose aspirin and heparin are required. Digital sympathectomy may be considered to preserve ischemic tissue. Once demarcation occurs a vascular surgeon may amputate gangrenous areas to reduce pain and improve cosmetic appearance [14]. Operative surgery is rarely indicated in the management of many vasculitides and is performed in selected cases. The more distal the occlusion, the less the development of collateral pathways and the more the possibility of critical ischemia that may progress to digital ulceration and even gangrene. The distal nature of most of the vasculitic syndromes makes the surgical options limited and with poor outcomes. Surgery is considered for in-

tractable pain, ulcers or gangrene. Surgical options include sympathectomy, bypass procedures and amputation [15] In various case reports, digit amputation was a terminal option in patients with vasculitic diseases and digital gangrene especially after failure of medical treatment [16-18]. Cutaneous ischemia is a rare manifestation of systemic necrotizing vasculitis but is associated with an increased risk of relapse and mortality [19].

Two of the patients with essential cryoglobulinemic vasculitis had a positive HCV test. HCV is mainly related to type II mixed cryoglobulinaemia. Chronic HCV infection in the presence of cryoglobulinaemia is usually a devastating multisystem disease. Digital ischemia (cryoglobulin-induced gangrene) managed by opiates, calcium channel blockers and prostacyclin revealed limited improvement [20].

The patient in the present study that underwent a thoracoscopic cervical sympathectomy had peripheral ischemic symptoms refractory to medical treatment and remarkably improved postoperatively. It has been described that sympathectomy has a role in relieving ischemic pain as symptoms improve in the early postoperative period in >70% of patients and in the remote period in >60% [21]. Thoracoscopic sympathectomy in those with severe upper limb ischemia allows symptomatic relief and optimum tissue salvage. As the procedure is minimally invasive, safe and associated with minumum complications, it could be attempted early in the disease [22].

In the present study, one patient performed tibial artery angioplasty with a favorable outcome. Angioplasty is a safe and effective limb salvage method in patients with critical limb ischaemia (CLI) as eventual loss of limb is the feared sequelae [23].

The patients in the present study had a controlled disease activity and ischemic vascular symptoms by the medical and surgical treatments. It has been reported that the minority of primary vasculitis patients require operation with occlusive symptoms being the most common indication. Operation was safe, with no operative mortality. Patients with active disease needing operation are likely to require revision or develop progress at another site and the survival rate is excellent [24]. This supports the need for continuous monitoring of vascular reconstruction in patients with primary vasculitis.

CONCLUSION

In conclusion, primary vasculitis presenting with peripheral ischemic manifestations is rare. Their management is essentially medical and individualized to the diagnosis and presenting symptoms. Open revascularization and bypass surgery may have a role in selected cases in spite of its known significant morbidity and mortality. Endovascular treatment may offer safer and a less invasive approach in high surgical risk patients. Sympathectomy is of high therapeutic potential in those patients with severe pain and trophic changes. It is further recommended that future studies are longitudinally conducted on a larger number of patients.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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