Arterial Involvement in Behçet's Disease – the Search for New Treatment Strategies

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Behçet's disease is a chronic relapsing multisystemic disorder, traditionally described as a triad consisting of recurrent aphthous stomatitis, genital ulcerations and ocular disease. Since the first description of the disease in 1937 by the dermatologist Hulusi Behçet, various organ systems were found to be involved, including skin lesions, neurologic disease, vascular disease, gastrointestinal involvement, and arthritis. Although vascular lesions are not listed among the criteria for the diagnosis of Behçet syndrome, up to 25–35% of patients develop large vessel involvement during their disease course [1]. Vascular involvement may also be the presenting symptom of the disease.

The first description of arterial involvement in Behçet's disease, an abdominal aortic aneurysm in a 38 year old Japanese man, was reported in 1960 [2]. Thereafter, three forms of vascular involvement have been described: venous occlusion, arterial aneurysms, and arterial occlusion. The venous system is the major affected site, with subcutaneous thrombophlebitis and venous occlusion of the upper or lower extremities being the most common lesions. The next most common manifestations are superior and inferior vena cava occlusions, followed by arterial involvement. The artery most often affected is the aorta, followed by the pulmonary, femoral, popliteal, subclavian and common carotid arteries [1]. Virtually no large or medium-sized arteries are spared, including the coronary arteries. Acute myocardial infarction or Takayasu-like pulseless disease can occur as the result of vasculitis, but no coronary artery disease has been reported to date. Among the arterial lesions reported, about two-thirds were aneurysms, often multiple, the remainder being occlusive disease. Arterial involvement occurs in 3–5% of patients and, not infrequently, arterial and venous involvement coexists [2].

Arterial involvement may be dramatic and life threatening, and carries the poorest prognosis of Behçet manifestations. Rupture of large arterial aneurysms is the leading cause of death in these patients. In some cases, massive and fatal hemoptysis from ruptured pulmonary artery aneurysms may be an unsuspected manifestation of Behçet's disease [3].

The pathophysiologic mechanisms underlying the vascular complications in Behçet syndrome are not well understood. Vasculitis, affecting the vessel wall and perivascular tissues, has been proposed as the predominant cause [4]. Recently, endothelial vasomotor function has been reported to be impaired in patients with active Behçet's syndrome, though this phenomenon was not related to disease activity [5]. The endothelial dysfunction was reversed after intravenous administration of ascorbic acid, a potent antioxidant in human plasma. Thus, endothelial dysfunction may also be the result of increased oxidative stress. Pathologic studies of arterial lesions in Behçet's disease demonstrate inflammatory obliterative endarteritis of the vasa vasorum, most likely brought about by immune deposition, which causes destruction of the media and fibrosis and thus weakens the arterial wall, predisposes for aneurysm formation and eventually rupture. Behçet patients also have an increased tendency for thrombosis, including graft thrombosis after surgery [6]. Von Willebrand factor and tissue plasminogen activator are increased and thrombomodulin is decreased in these patients, leading some authors to recommend anticoagulant treatment, though it may increase the risk of pseudoaneurysm formation [7].

The involvement of large vessels in active Behçet's disease requires high dose corticosteroids, immunosuppressants, or both, and in some cases surgical intervention. There are limited data on the efficacy of medical therapy in patients with vascular, particularly arterial lesions. In a retrospective review of 25 patients with arterial disease, high dose corticosteroids did not ameliorate occlusive disease and may have contributed to one fatal infection. Aneurysms had a worse prognosis than occlusive disease, causing death in five patients. Surgical repair was necessary to prevent aneurysmal rupture, and immunosuppressive therapy postoperatively was necessary to prevent relapse. Steroids plus other immunosuppressants were more effective than steroids alone, and anticoagulation helped to prevent graft thrombosis postoperatively [8].

Existing aneurysms respond poorly to medical treatment, and large abdominal aortic aneurysms, which entail a high risk of rupture, are operated on to prevent this life-threatening complication. Surgery is performed on patients with large or growing aneurysms, acute bleeding, or acute ischemia. Surgery offers somewhat better results in treatment of aneurysmal or traumatic lesions, but the results of the occlusive disease are still poor. Surgical results are not satisfactory, mainly due to progression to graft thrombosis and formation of anastomotic aneurysms in up to 50% of patients [6]. Several reports demonstrate the rapid progression of the disease process following surgery, with a high rate of recurrence of true or false aneurysms at the anastomotic sites, disruption of grafts, and aneurysm formation in other vessels. A unique characteristic of Behçet's disease is the tendency to

develop aneurysms in the site of vessel trauma, such as surgery or arterial puncture for angiography or for blood gases. Recurrent aneurysms are common, as was demonstrated in a report by Bartlett et al. [9] of a patient requiring 7 operations for 14 arterial aneurysms developing over a period of 8 months. During acute exacerbation of the disease, in which there is a pronounced perivascular inflammatory involvement, surgery is difficult and postoperative complications are common, especially anastomotic disunion.

Since patients with Behçet's disease have a high complication rate with open surgical repair, less invasive endovascular techniques may offer a way to reduce morbidity and mortality. Endoluminal AAA repair uses minimally invasive techniques to exclude the aneurysmal sac from the arterial circulation by fixing a prosthetic graft within the aortic lumen. Patients with vascular Behçet are better candidates for endovascular repair technique than patients with atherosclerotic AAA. Behçet's disease patients are usually younger, have a shorter saccular aneurysmal sac, better renal function, and fewer co-morbidities. Due to the young age of most of the patients undergoing AAA repair, the stent is subjected to a long test, with the risk of various complications that have been described with endovascular repair, including migration of the stent, endoleaks, and a high percentage requiring re-interventions.

In this issue of *IMAJ*, Nitecki et al. [10] report their results of AAA treatment by surgery and by endovascular repair in Behçet patients. In the two patients who underwent endovascular repair, the in-hospital postoperative period was shorter and the early and intermediate term results were favorable, with shrinkage of the aneurysmal sac. During a 24 and 38 month follow-up, these patients did not have endoleaks or aneurysm formation. These results join several case reports of patients with Behçet's disease undergoing endovascular repair. In a series reported by Park et al. [11], percutaneous placement of stent-grafts was successful in six of nine patients with a variety of aneurysms (aorta, subclavian, common carotid, brachiocephalic, and iliac arteries). One patient had occlusion of the graft, and one had a recurrent aneurysm.

However, the small number of patients in these reports and the short follow-up period call for caution in embracing this procedure as the treatment of choice in Behçet's disease. Possible late complications include aneurysmal formation adjacent to the stent or in the femoral artery, stent migration, endoleaks, and a need for re-interventions. Nonetheless, the use of endovascular repair in Behçet patients is more appealing than in the general population, due to the unsatisfactory results following open surgery and the local inflammatory reaction caused by trauma to the blood vessels.

In summary, the initial experience with endovascular repair suggests that this procedure may be a safe and effective alternative to open surgery. However, further studies with long-term follow-up are needed to determine the optimal surgical strategy for arterial involvement in patients with Behçet's disease.

AAA = abdominal aortic aneurysm

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