



Surgical Treatment of Peripheral Aneurysms in Patients with Behcet's Disease

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Abstract *Introduction:* Our aim was to report our experience with 23 patients presenting with 32 peripheral aneurysms secondary to Behcet's disease (BD) and their outcome after vascular surgery.

Methods: The study was retrospective in nature. Except for those presenting with aneurysm rupture, patients underwent surgery after treatment of acute inflammatory lesions. All aneurysms appeared to be pseudo-aneurysms. Graft interposition with polytetrafluoroethylene or saphenous vein was most commonly employed. Postoperatively, all patients were put on immunosuppressive and antiplatelet therapy. Follow-up was done every 6–12 months, complications recorded and managed appropriately.

Results: All the patients were males. The mean age at diagnosis of a peripheral aneurysm was 41.0 ± 9 years. There were 17 (53%) femoral, 8 (25%) popliteal, two carotid, two external iliac, two brachial and one internal iliac aneurysms. Fourteen (61%) patients had a single peripheral aneurysm while nine had two. Surgery was performed for all initially presenting 23 aneurysms. Six patients with multiple peripheral aneurysms had surgery for their second asymptomatic aneurysm. The mean follow-up period was 84 ± 62 months. Of 29 aneurysms operated on, 7 (24%) anastomotic pseudo-aneurysms and 11 (38%) graft occlusions developed. Five (22%) patients underwent major lower extremity amputations. Six (26%) mortalities were recorded. *Conclusion:* Surgery for peripheral aneurysms in BD is warranted in many instances. Results of operation can be improved by prolonged monitoring. However, despite all efforts, peripheral aneurysm involvement in BD worsens the prognosis.

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Behcet's disease (BD) is a multisystemic disorder that mainly affects males between 20 and 40 years of age in the Mediterranean, Middle East and Japan. The main histological feature is a type of inflammatory vasculitis that affects vessels of all sizes.¹ It is characterised by the classic triad of urogenital ulcerations, chronic eye inflammation and skin lesions, but the prognosis is largely determined by involvement of the cardiovascular, gastrointestinal and central nervous systems.²

Vascular complications (vasculo-Behcet disease), noted in 7–29% of patients,³ gravely affect the course of the disease. Veins are more frequently affected, resulting in both superficial thrombophlebitis and deep vein thrombosis, which occur in 30–40% of patients.⁴ Arterial lesions, however, pose a greater risk. Involvement of a major artery is seen in 1.5–2.2% of patients³ often in the form of rapidly expanding aneurysms² which may be complicated by fatal rupture, making surgical treatment necessary.⁵ However, there is the challenge of graft occlusion and aneurysm formation at the anastomotic site or in other arteries during the postoperative course.^{5–7} Yet, because of the rarity of the disease, there is little information about the incidence of complications after vascular surgery in patients with BD.⁸ In this study, we reviewed, retrospectively, the characteristics of patients who underwent vascular surgery for peripheral aneurysms secondary to BD and their outcome, excluding aortic and pulmonary aneurysms.

Methods

The study was a retrospective analysis of the hospital records of 23 patients who presented with 32 peripheral aneurysms secondary to BD and underwent vascular surgery between January 1987 and February 2010. Most of the patients were referred from the centre for BD in our institution, which has a database of over 3000 BD patients. The study was approved by the institutional ethics committee. The diagnosis of BD was established using the criteria of the International Study Group for Behcet's Disease (Table 1).⁹

Table 1 Diagnostic criteria of Behcet disease.^a

Major symptoms	Minor symptoms
Recurrent genital ulcerations	Gastrointestinal features
Aphthous ulceration or scarring	Arthritis
Eye lesions	Family history
Skin lesions	Arthralgia
Positive pathergy test	Cerebral nervous system involvement
	Arterial occlusion or aneurysms
	Epididymitis
	Deep vein thrombosis
	Subcutaneous phlebitis

^a Recurrent oral ulceration; minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient, recurring at least three times in one 12-month period; and two of the symptoms in the table.

The diagnosis of peripheral aneurysm secondary to BD was made when a patient with a prior diagnosis of BD presented with such an aneurysm. For patients without prior diagnosis of BD, the diagnosis was considered when the patient was a young male presenting with solitary or multiple aneurysms together with venous disease of the lower extremities and confirmed after pre- or post-operative BD work-up by the BD centre in our institution. Diagnostic work-up for aneurysms included duplex examination, magnetic resonance angiography and computed tomographic angiography (Fig. 1A). Contrast angiography was performed rarely for fear of puncture site complications in patients with BD. Indications for surgical intervention included symptomatic and ruptured aneurysm, regardless of size. On the other hand, depending on the active status of BD characterised by an increased erythrocyte sedimentation rate, high C-reactive protein, and/or high white blood cell count, asymptomatic aneurysms were operated upon when rapidly expanding or when they became large with size 4–5 times that of the normal artery.

Except in emergency situations, we tried to operate the patient only after effective treatment of the acute inflammatory phase of the disease. Hence, preoperatively, most of the patients were on immunosuppressives or the immunomodulator colchicine.

At surgery, all aneurysms appeared to be pseudo-aneurysms (Fig. 1B). The surgical technique employed mostly was graft interposition with polytetrafluoroethylene (PTFE) or saphenous vein (Fig. 1C). In general, PTFE grafts were used for the repair of aneurysms occurring in bigger arteries such as iliac or femoral arteries or when a saphenous vein of suitable size and quality could not be found on Duplex. For smaller vessels, saphenous vein graft was preferred. Ligation was performed in some cases when bypass was not feasible for aneurysms presenting as an emergency or for postoperative infected grafts. During graft interposition, reconstruction was always attempted in a disease-free appearing segment of the artery. Autogenous veins used for grafts were closely examined preoperatively and intraoperatively, by inspection and palpation, to exclude pre-existing thrombophlebitis associated with the disease.

Postoperatively, all patients were put on combinations of azathioprine (Imuran[®]; GlaxoSmithKline, UK), methylprednisolone (Prednol[®]; Mustafa Nevzat, Turkey), colchicine (Colchicum Dispert[®]; Dr. F. Frik, Turkey) and acetylsalicylic acid (Aspirin[®]; Bayer AG, Germany) as determined by the BD centre in our institution.

Follow-up was done every 6–12 months with history, physical examination and Doppler ultrasonography of upper and lower extremities, carotid arteries, abdominal aorta and iliac arteries. Incidents of postoperative complications including graft infection or occlusion pseudo-aneurysms at anastomotic sites and development of new aneurysms at different sites were recorded and managed appropriately.

Statistical analysis

Data are presented as mean \pm standard error of mean. Analyses were performed using the SPSS 15.0 software package (SPSS Inc, Chicago, IL, USA). Comparisons between

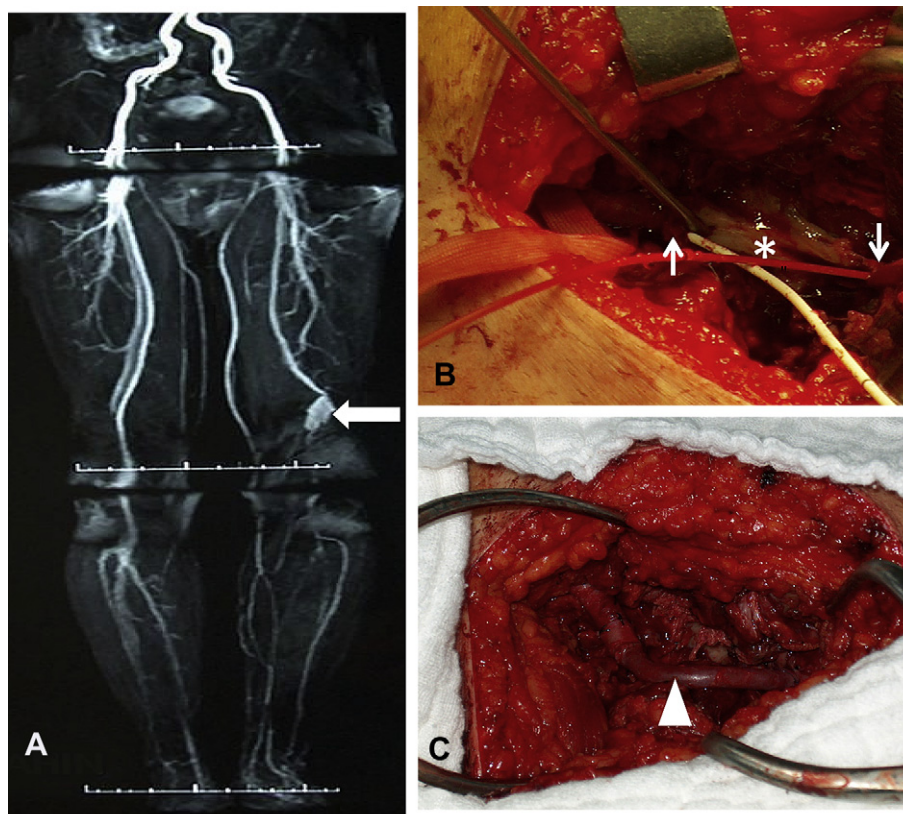


Figure 1 A. Magnetic resonance angiogram of a patient with a symptomatic left popliteal artery aneurysm (broad arrow). B. Intraoperative appearance of the same popliteal aneurysm. Catheters were inserted into proximal and distal lumen (arrows) showing the intact posterior wall of the artery (*). C. After saphenous vein graft (arrow head) repair of the same aneurysm.

groups were made using Fisher's exact test for categorical variables and Student's *t*-test for continuous variables.

Results

All patients were male. The mean age at diagnosis of a peripheral aneurysm was 41.0 ± 8.6 years (20–60 years) and the mean time interval between diagnosis of BD and development of a peripheral aneurysm was 6.1 ± 5.1 years (0–18 years). For 12 patients, this was within 5 years of acquiring a diagnosis of BD.

Preoperatively, 11 patients were on immunosuppressives, whereas nine were on colchicine alone.

There were a total of 32 peripheral aneurysms among 23 patients (Table 2). Multiple peripheral aneurysms were commonly encountered. Fourteen (61%) patients had a single peripheral aneurysm, while 9 (39%) had two. The mean size of peripheral aneurysms was 5.9 ± 3 cm (3–15 cm). It must be noted that patients were only diagnosed as having multiple aneurysms during investigation for symptoms perceived to be due to their initially presenting peripheral aneurysm or during their follow-up reviews.

Six (26%) patients with peripheral aneurysms also had aortic aneurysms (AAs). Two patients initially presenting with a femoral aneurysm had already been operated for an AA. Likewise, one patient first presenting with a popliteal aneurysm had already had surgery for his AA, while

another later developed an AA. One patient with bilateral external iliac aneurysms (EIAs) later developed an AA. The patient presenting with an internal carotid (ICA) aneurysm had an abdominal AA repaired before developing the peripheral aneurysm and later also developed a thoracoabdominal AA.

Twenty (87%) patients had already been diagnosed with BD, only one of whom presented with aneurysm rupture, whereas all three patients without a prior diagnosis presented with aneurysm rupture ($p < 0.05$) associated with signs of peripheral nerve compression.

Surgery was performed for all initially presenting 23 aneurysms, four as emergency operations to treat rupture. Six of nine patients with multiple peripheral aneurysms had surgery for their second aneurysm at a later date (Table 2). Surgery was not performed for one brachial and two femoral aneurysms. The two femoral aneurysms were each encountered in patients who had already had surgery for a contralateral femoral aneurysm. Both were asymptomatic, appeared stable during reviews with low BD activity markers, hence a policy of watchful waiting was adopted. One of them, however, after undergoing multiple salvage operations for postoperative complications of his first femoral aneurysm finally had a hip disarticulation, and died later. The brachial aneurysm not operated upon was encountered in a patient who had previously had surgery for a contralateral brachial aneurysm. Due to increased BD activation, surgery of his symptomatic brachial aneurysm

Table 2 Operations performed for peripheral aneurysms and outcome.

Aneurysm	#	Operation performed	#	Complications	#	Amputation	Mortality
External iliac artery	2	Graft interposition ^a	2	Wound with graft infection	1	—	
				Anastomotic pseudo-aneurysm	1		
Internal iliac artery	1	Ligation	1	—	—	—	—
Femoral artery	17	Graft interposition ^a	14	Wound infection ^b	2	4	6 ^c
				Ligation	1	Wound with graft infection	1
				Graft infection ^d	4		
				Graft occlusion	6		
				Anastomotic pseudo-aneurysm	5		
				Haemorrhage	1		
Popliteal artery	8	Graft interposition ^a	7	Wound infection ^b	2	1	—
				Ligation	1	Graft infection ^d	1
				Graft occlusion	4		
				Anastomotic pseudo-aneurysm	1		
Common carotid artery	1	Graft interposition ^a	1	Graft occlusion	1	—	—
Internal carotid artery	1	Graft interposition ^a	1	—	—	—	—
Brachial artery	2	Graft interposition ^a	1	—	—	—	—

^a Polytetrafluoroethylene or saphenous vein graft.

^b Wound infection without graft infection.

^c One patient also had an ipsilateral popliteal aneurysm operated upon.

^d Graft infection without wound infection.

was postponed and the patient put on immunosuppressives but he was lost to follow-up.

The mean follow-up period was 83.9 ± 61.5 months (2–226 months). Four patients were lost to follow-up and 13 (57%) are still alive.

Complications

Surgical repair of peripheral aneurysms in BD was associated with a substantial number of early and late complications (Table 3).

Six complications (in four patients) occurred after operations for 6 second aneurysms as compared to the 24

complications (in 15 patients) encountered in operations for 23 initially presenting aneurysms.

Of a total of 29 aneurysms operated on, 7 (24%) anastomotic pseudo-aneurysms developed in seven patients. Two were associated with graft thrombosis, three with graft infection, one with postoperative haemorrhage and one occurring alone (Table 2). All patients developing anastomotic pseudo-aneurysms were re-operated.

There were also 11 (38%) graft occlusions developing in 10 patients (Table 2). While all the graft occlusions associated with other complications ended with amputation eventually, those presenting without other associated complications were followed up without reoperation because patients only had claudication without showing any signs of critical ischaemia. One of the two patients who underwent carotid artery aneurysm repair developed graft occlusion 1 year later without any evidence of cerebrovascular symptoms. Hence, late graft occlusions without anastomotic pseudo-aneurysms or infection were associated with mild symptoms. It is worth noting that duplex surveillance did not show signs of impending failure in grafts that eventually were occluded, although it revealed paraanastomotic aneurysms and perigraft fluid collections.

Five PTFE and two saphenous graft infections were encountered. Choice of graft material did not influence outcome in terms of graft infection which may be due to the small numbers involved.

Five (22%) patients underwent major lower extremity amputations, only one (4%) of whom was done in-hospital. All five developed graft occlusions after aneurysm repair; two in association with anastomotic pseudo-aneurysms and three with graft infection. Post-amputation mortality rate was 40%.

Six (26%) mortalities were recorded during the follow-up. One occurred in hospital after major amputation. The causes of late death included gastrointestinal haemorrhage,

Table 3 Complications after surgery for initially presenting peripheral aneurysms.

	Preop treatment (20 patients)	No preop treatment (3 patients)
<i>Early complications</i>		
Wound infection ^a	2	1
Wound with graft infection	2	
Haemorrhage	1	
Graft occlusion	1	
Total	6	1
<i>Late complications</i>		
Anastomotic pseudo-aneurysm	6	
Graft infection ^b	4	
Graft occlusion	7	
Total	17	

^a Wound infection without graft infection.

^b Graft infection without wound infection.

intracranial aneurysmic mass and sepsis from graft infection in one patient each, while the cause could not be determined for the other two patients. Four of the patients had undergone multiple re-operations either for postoperative complications or for their second aneurysms.

Discussion

Behcet aneurysm has the tendency to be multiple and can involve any artery. The most common site of aneurysm formation is the aorta, followed by the pulmonary and femoral arteries.^{10,11}

Various investigators including Tuzun et al.,¹² Kalko et al.,¹ Iscan et al.² and Hosaka et al.⁸ have reported on the long-term outcome of surgery for aneurysms secondary to BD in which they present a mixture of patients with both central and peripheral aneurysms. This is understandable because of the rarity of the disease making it difficult to gather large populations of patients. This is the first study, with the largest population to date, to assess the long-term outcome of surgery for peripheral aneurysms alone, presenting 32 of such aneurysms in 23 patients.

The prevalence of arterial involvement in BD has been estimated at 2.2–18%, with marked male predominance.^{3,5,13,14} The reported interval between the onset of BD and that of arterial manifestation is 5–9 years.^{5,11,13} In our series, all the patients were male and the mean duration before the appearance of peripheral aneurysms was 6.1 years.

Three (13%) of our patients, who had no previous diagnosis of BD, presented with aneurysm rupture compared to only one (5%) of 20 patients who already had a diagnosis. It may be that not being a known BD patient – and hence probably not being on medication and more importantly not being in a surveillance programme – contributed to peripheral aneurysm presenting as an emergency.

All the peripheral as well as the concomitant aortic aneurysms in our series appeared to be pseudo-aneurysms. A similar observation was made by Iscan et al.,² whereas some of the aneurysms in the Tuzun et al.¹² series were true aneurysms. As stated previously by Matsumoto et al.,¹⁵ most BD aneurysms are pseudo-aneurysms.

Graft interposition for patients in our series was with either PTFE or saphenous vein. Some investigators preferred only synthetic material for their surgeries, believing that vasculitis might be present in venous tissue and so avoiding

use of autologous grafts might decrease the long-term risk for complications.¹ From our series, choice of PTFE or saphenous vein did not influence outcome with respect to complication rates (data not shown).

The postoperative course is often complicated by graft occlusion and recurrence of aneurysms, leading to a relatively high mortality rate.¹⁰ In all, there were 30 incidents of complications occurring in 17 patients. Interestingly, only one incident – a case of early wound infection – occurred in a patient not on preoperative treatment. It appears that although putting patients on immunosuppressives or immunomodulators may save them from presenting with an aneurysm rupture, these medications may be associated with more postoperative complications.

Anastomotic pseudo-aneurysm formation is a postoperative complication that is considered to occur frequently in BD patients and is sometimes life threatening, although its incidence has never been elucidated.¹⁰ We encountered 7 (24%) anastomotic pseudo-aneurysms in seven patients. Analysis of similar patients from other series is given in Table 4. The anastomotic fragility in patients with BD might be attributable to weakening of the arterial wall caused by fulminant inflammation. There is also the difficulty of determining the appropriate site for anastomosis of a graft with solid arterial wall, preoperatively or intra-operatively. Macroscopic examination alone might not be sufficient to clearly identify a disease-free portion of the artery.

Graft occlusion is also common, possibly as a result of dysfunction of the endothelium.¹⁶ There were 11 (38%) graft occlusions developing in 10 patients (Table 4). Although graft occlusion is a frequent feature of surgical repair of peripheral aneurysms in patients with BD some patients, whose graft occlusion was not compounded with graft infection or anastomotic pseudo-aneurysm, tolerated the graft occlusion well by only presenting with mild symptoms. Hence, graft occlusion did not always result in loss of extremity.

Following salvage operations for complications encountered postoperatively, it is not very surprising that some patients undergo various degrees of amputations. All of our patients who underwent amputations had undergone re-operations after developing graft occlusions together with graft infection or anastomotic pseudo-aneurysms.

We recorded an overall mortality of 26% during the period with an in-hospital mortality of 4% (Table 4). Four of our patients who died had undergone multiple re-operations either for complications or for their multiple

Table 4 Results of analysis of operations performed for peripheral aneurysms.

	Koksoy et al.	Tuzun et al. ¹²	Kalko et al. ¹	Iscan et al. ²
Number of patients	23	15	12	5
Peripheral aneurysms operated on	29	18	12	6
Anastomotic pseudo-aneurysm	7	4	2	N/A
Graft occlusion	11	4	1	1
Amputation	5	0	N/A	1
Related mortality	6	2	0	0
Follow-up (months)	83.9	54.4	17	24.4

N/A: Not available.

aneurysms. This was also true for two patients from the Tuzun et al. series. Therefore, it may seem that the multiple operations that these patients undergo have a negative impact on their survival.

Stent-graft placement has recently been attempted as an alternative treatment for aortic and arterial aneurysms in patients with BD and it has been proved to be effective, safe and associated with an acceptable vascular complication rate and low mortality.^{17,18} However, it appears that the current experience with endovascular treatment in this specific subset of patients is limited.¹

Conclusion

A timely surgical approach to peripheral aneurysms in BD is warranted in many instances. The outcome after surgical intervention is adversely influenced by complications unique to the severe inflammatory nature of this disease. The early and late results of operation can be improved by prolonged monitoring. However, despite all efforts, peripheral vascular involvement brings with it a worsening of the prognosis. Due to the high rate of complications related to new pseudo-aneurysms at the anastomotic site and graft occlusions, it is suitable looking for other treatment modalities. Endovascular stent-graft repair of BD aneurysms might be a safe alternative to the surgical intervention.

Conflict of Interest

None.

Funding

None.

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