Long-term outcome after surgical treatment of arterial lesions in Behçet disease

Akihiro Hosaka, MD, Tetsuro Miyata, MD, Hiroshi Shigematsu, MD, Kunihiro Shigematsu, MD, Hiroyouki Okamoto, MD, Shigeyuki Ishii, MD, Takuya Miyahara, MD, Kota Yamamoto, MD, Daisuke Akagi, MD, Mikiko Nagayoshi, MD, and Hirokazu Nagawa, MD, Tokyo, Japan

Objective: Surgical treatment of arterial lesions associated with Behçet disease (BD) is often complicated by graft occlusion and recurrence of aneurysms. The purpose of this study was to clarify the long-term outcome of surgical intervention for arterial involvement in BD.

Methods: Ten patients with BD (9 men, 1 woman) who underwent surgical treatment for arterial aneurysms between 1980 and 2004 were included in the study. The age of patients at the first operation ranged from 36 to 69 years (mean, 50.4 ± 9.0 years). The mean period between the onset of BD and that of arterial manifestations was 8.0 ± 5.0 years. We retrospectively reviewed their postoperative courses, including survival, graft occlusion, formation of anastomotic false aneurysms, and the development of aneurysms at different sites. The Kaplan-Meier method was used to calculate the chronologic incidence of complications after surgery.

Results: The mean follow-up period was 133 ± 92 months, ranging from 5 to 285 months. One patient died of rupture of a dissecting aortic aneurysm after undergoing several surgical interventions for multiple aneurysms. There were five graft occlusions among 21 grafts. The cumulative primary graft patency rate in the infrainguinal region was 83.9% at 3 years. Five anastomotic false aneurysms formed among 49 anastomoses between grafts and host arteries. The overall cumulative incidence of formation of anastomotic pseudoaneurysm was 12.9% at 5 and 10 years. All of them formed within 18 months after surgery. Development of new aneurysms in different arteries was observed in two patients.

Conclusions: Early occurrence of anastomotic false aneurysm is characteristic of BD. Further investigation is necessary to establish effective postoperative treatment. (J Vasc Surg 2005;42:116-21.)

Behçet disease (BD) is a chronic multisystemic disorder typically characterized by the triad of recurrent oral and genital ulceration and relapsing uveitis. The etiology remains unknown, but it is speculated that autoimmunity triggered by bacterial or viral infection or other environmental factors plays a role.1,2 The various clinical manifestations of the disease include mucocutaneous, ocular, articular, neurologic, cardiovascular, gastrointestinal, and pulmonary involvement. The underlying histopathologic feature is systemic vasculitis affecting veins, arteries, and capillaries.3

Arterial involvement in the disease is rare, but aneurysm formation frequently is complicated by fatal rupture, which makes surgical treatment necessary.4 However, surgeons often are challenged by graft occlusion and aneurysm formation at the anastomotic site or in other arteries during the postoperative course.5-10 Yet, because of the rarity of the disease, there is little information about the incidence of complications after vascular surgery in patients with BD. In this study, we retrospectively reviewed the postoperative course of patients with BD with arterial involvement who underwent surgical intervention, to clarify the long-term outcome of treatment.

METHODS

The study included 10 patients with BD with arterial involvement (9 men, 1 woman) who underwent surgical treatment between 1980 and 2004. The diagnosis of BD was confirmed using the criteria of the International Study Group for Behçet’s Disease.11 Six of the male patients were smokers. The female patient had a history of hypertension; other patients did not have a medical history of hypertension, hyperlipidemia, or diabetes mellitus. Six patients had a history of venous involvement; 3 had a history of superficial thrombophlebitis, 2 had a history of deep venous thrombosis, and 1 had a history of both. No patient had the complication of pulmonary artery aneurysm. In all cases, the first surgical intervention was performed for aneurysmal lesions. The age of patients at the time of the first operation ranged from 36 to 69 years, with a mean ± standard deviation of 50.4 ± 9.0 years. The mean period between the onset of BD and that of vascular manifestation was 8.0 ± 5.0 years, ranging from 0 to 16 years. There was no operative death during the study period.

We investigated the long-term postoperative outcome, including survival, graft occlusion, formation of anastomotic false aneurysms, and development of aneurysms at different sites. The postoperative follow-up protocol of our institution included careful physical examination and measurement of ankle and brachial blood pressures every 1 to 6 months. Since the late 1980s, regular surveillance using
JOURNAL OF VASCULAR SURGERY
Volume 42, Number 1

Hosaka et al

either echography, angiography, or computed tomography additionally has been performed every 6 to 12 months. The diagnosis of anastomotic pseudoaneurysm was confirmed by intraoperative macroscopic findings or postoperative pathologic examination. In cases of graft occlusion, the proximal anastomosis was kept in the follow-up for analysis of the formation of anastomotic false aneurysms because it continued to be exposed to systemic blood pressure. On the other hand, the distal anastomosis exposed to low blood pressure after graft occlusion was excluded from the analysis.

Data are presented as mean ± standard deviation unless otherwise stated. The Kaplan-Meier method was used to calculate the chronologic primary patency rate of the graft and the occurrence of anastomotic false aneurysm.

RESULTS

The profiles of arterial lesions and surgical interventions and the postoperative course are summarized in Tables I and II. The graft material was selected according to the operator’s choice. All anastomoses were made using a wide-bite running suture technique. Endarterectomy was not performed in any of the cases. Autogenous veins used for grafts were closely examined preoperatively and intraop-eratively to exclude pre-existing changes associated with the disease. Postoperative medication was determined by the rheumatologists at our institution and depended on the systemic inflammatory status and general condition of each patient and on the side effects of the drugs. The mean follow-up period was 133 ± 92 months, ranging from 5 to 285 months. Two patients (cases 6 and 10) were lost to follow-up (at 228 and 68 months after the first operation, respectively). One patient (case 7) died during the study period.

We experienced five graft occlusions, all of which occurred among 14 grafts in the infrainguinal region (incidence per graft, 35.7%). The cumulative primary graft patency rate ± standard error in this region was 83.9% ± 10.4% at 3 years. Five grafts in the aortic or iliac region and 2 in the upper extremity remained patent.

A total of 5 anastomotic false aneurysms formed among 49 anastomoses between the graft and the host artery (incidence per anastomosis, 10.2%); 2 anastomotic false aneurysms each in cases 4 and 10, and 1 in case 6. Of them, 1 formed at the proximal anastomosis of the femoral artery, 2 at the distal anastomosis of the popliteal artery, 1 at the proximal anastomosis of the axillary artery, and 1 at

Table I. Profiles of arterial lesions and operations

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at operation</th>
<th>Indication for operation</th>
<th>Surgical procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58</td>
<td>Thoracoabdominal aortic aneurysm</td>
<td>Tube graft (wDG) + visceral arterial reconstruction</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>AAA + right CIA aneurysm</td>
<td>Bifurcated graft (aortobiiliac, wDG)</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>Left CFA aneurysm</td>
<td>EIA-DFA bypass (kDG) + kDG-popliteal bypass (HUVG)</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>Left SFA aneurysm</td>
<td>Femoropopliteal bypass (kDG)</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>Right SFA aneurysm</td>
<td>SFA-popliteal-peroneal sequential bypass (AVG)</td>
</tr>
<tr>
<td>6</td>
<td>46</td>
<td>Right popliteal aneurysm</td>
<td>Interposition (AVG)</td>
</tr>
<tr>
<td>7</td>
<td>47</td>
<td>ANA at popliteal artery + occlusion of AVG</td>
<td>Interposition (AVG)</td>
</tr>
<tr>
<td>8</td>
<td>44</td>
<td>Bilateral CIA aneurysm</td>
<td>Interposition (kDG)</td>
</tr>
<tr>
<td>9</td>
<td>36</td>
<td>Occlusion of popliteal graft</td>
<td>Interposition (AVG)</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>Left axillary aneurysm</td>
<td>Ligation of subclavian artery</td>
</tr>
<tr>
<td>11</td>
<td>50</td>
<td>ANAs at axillary and brachial arteries</td>
<td>Ligation of subclavian artery</td>
</tr>
<tr>
<td>12</td>
<td>50</td>
<td>Increased size of distal ANA</td>
<td>Aneurysmectomy</td>
</tr>
</tbody>
</table>

wDG, Woven Dacron graft; AAA, abdominal aortic aneurysm; CIA, common iliac artery; CFA, common femoral artery; EIA, external iliac artery; DFA, deep femoral artery; kDG, knitted Dacron graft; HUVG, glutaraldehyde-tanned human umbilical vein graft; TP trunk, tibioperoneal trunk; ANA, anastomotic false aneurysm; PTA, posterior tibial artery; AVG, autogenous vein graft; SFA, superficial femoral artery.
the distal anastomosis of the brachial artery. The incidence per anastomosis was: infrainguinal, 3 of 27 anastomoses (11.1%); aortic or iliac, 0 of 18 anastomoses (0%); upper extremity, 2 of 4 anastomoses (50%). Two formed at the anastomosis of a knitted Dacron graft (2 of 24 anastomoses of Dacron grafts, 8.3%), and the other 2 at the anastomosis of an autogenous vein graft (3 of 23 anastomoses, 13.0%). The mean interval between the operation and the diagnosis of anastomotic false aneurysm was 10.8 ± 5.1 months, ranging from 6 to 17 months. The overall cumulative incidence of anastomotic false aneurysm ± standard error was 12.9% ± 5.4% at 5 and 10 years (Figure).

Three patients had aneurysms of different arteries, either simultaneously or metachronously. An aneurysm of the superficial femoral artery (SFA), 19 mm in diameter, was found 5 years after surgical treatment of an aneurysm of the contralateral common femoral artery (CFA) in case 3. The lesion has been under close observation for 12 years, and had enlarged to reach 28 mm in diameter at the last follow-up. Surgical intervention is now under consideration. This patient underwent two operations for aneurysmal degeneration of a glutaraldehyde-tanned human umbilical vein graft. Pathologic examination of the aneurysmal parts of the impaired grafts revealed no specific findings characteristic of BD. In case 5, an infrarenal abdominal aortic aneurysm, 3 cm in diameter, was diagnosed at the same time as an aneurysm of the SFA. The aneurysm of the SFA was treated surgically, and the aortic aneurysm has been under observation. The size of the latter has not changed during 6 months of follow-up. Metachronous multiple aneurysms of the bilateral popliteal and common iliac arteries, SFA, and ascending aorta developed in one patient (case 7), all of which were treated surgically. Twenty-four years after the first operation for popliteal aneurysm, the patient died of rupture of an acute dissecting aneurysm of the descending aorta.

Table II. Profiles of postoperative course and number of occluded grafts, anastomotic false aneurysms, and new aneurysms of different arteries

<table>
<thead>
<tr>
<th>Case</th>
<th>Medication</th>
<th>Graft occlusion</th>
<th>Anastomotic false aneurysm</th>
<th>New aneurysms at different sites</th>
<th>Duration of follow-up (months)</th>
<th>Final status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>160</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>C, CS</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>98</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>AC, AP</td>
<td>2</td>
<td>—</td>
<td>1</td>
<td>212</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>AP</td>
<td>1</td>
<td>2</td>
<td>—</td>
<td>44</td>
<td>Alive</td>
</tr>
<tr>
<td>5</td>
<td>C, CS, AC</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>6</td>
<td>Alive</td>
</tr>
<tr>
<td>6</td>
<td>C, AP</td>
<td>1</td>
<td>1</td>
<td>—</td>
<td>228</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>7</td>
<td>AC, AP</td>
<td>1</td>
<td>—</td>
<td>6</td>
<td>173</td>
<td>Died, rupture of TAA</td>
</tr>
<tr>
<td>8</td>
<td>AC</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>53</td>
<td>Alive</td>
</tr>
<tr>
<td>9</td>
<td>C</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>285</td>
<td>Alive</td>
</tr>
<tr>
<td>10</td>
<td>AP</td>
<td>—</td>
<td>2</td>
<td>—</td>
<td>68</td>
<td>Lost to follow-up</td>
</tr>
</tbody>
</table>

C, Colchicine; CS, corticosteroid; AC, anticoagulant; AP, antiplatelet agent; TAA, thoracic aortic aneurysm.

Cumulative incidence of anastomotic false aneurysm after bypass grafting in patients with Behçet disease.
DISCUSSION

Previous studies documented that the prevalence of arterial involvement ranged from 2.2% to 18%, with marked male predominance. A high proportion of cases with arterial lesions are also complicated by venous involvement. The reported interval between the onset of BD and that of arterial manifestation is 5 to 9 years. In the present series of 10 cases, 9 patients were male, 6 had a history of venous complications, and the mean duration of BD before the initial arterial manifestations was 8.0 years, which were comparable with previous reports. The reason for the predominance of vascular involvement in male subjects remains unclear. Six of 9 male patients included in the present study were smokers, while none of them had other cardiovascular risk factors. In the series of 25 cases with arterial lesions in BD (23 men and 2 women) reported by Le Thi Huong et al, no patient had cardiovascular risk factors except for 1 smoker. Taking these data into account, the male predominance cannot be explained only by factors predisposing to the atherosclerotic changes in vessels. On the other hand, the influence of sex hormones or genetic peculiarity has been indicated.18,19

Although occlusive lesions tend to take a rather benign course, aneurysms complicating BD are apt to grow rapidly and sometimes result in fatal rupture. Because of the risk of rupture, aneurysmal lesions in BD should be treated surgically if they are large or are increasing in size. However, the postoperative course is often complicated by graft occlusion and recurrence of aneurysms, leading to a relatively high mortality rate. Indeed, the cause of death of the only patient who died during the study period in the present series was rupture of an acute dissecting aneurysm of the descending aorta, which followed multiple aneurysms. The survival rate after the onset of arterial involvement in BD is reported to be 83% and 66% at 5 and 15 years, respectively, showing a poorer prognosis of BD with arterial lesions compared with the overall survival rate of patients with BD.17,22

Pathologically, arterial lesions in BD are characterized by intense inflammation primarily involving the media and adventitia. A specific histologic feature of BD is leukocyte accumulation around the vasa vasorum. Infiltration of inflammatory cells, mainly neutrophils, lymphocytes, and plasma cells, leads to destruction of the media and fibrous thickening of the intima and adventitia. Weakening of the arterial wall causes dissection of the vessel, with subsequent formation of a true aneurysm, or perforation of the vessel wall, triggering development of a false aneurysm or arterial dissection. The most common site of aneurysm formation is the aorta, followed by the pulmonary and iliacal arteries. Vessel occlusion associated with BD can also be attributed to intimal thickening and endothelial dysfunction caused by vasculitis. Ozoran et al documented a high plasma level of von Willebrand factor induced by inflammation of vessels, which could enhance platelet aggregation, and a high level of plasminogen activator inhibitor caused by platelet accumulation on the damaged endothelial surface, which might inhibit fibrinolytic activity. On the other hand, Guerazzi et al reported that acquired protein S deficiency caused by autoantibodies might be one of the causes of thrombogenicity of BD. The presence of anticardiolipin antibodies in patients with BD has been shown in several studies. These underlying thrombotic diatheses might predispose to the development of occlusive changes in vessels.

We could not investigate the cause of graft occlusions because pathologic examination of the occluded grafts was not performed in any of the cases. Systemic procoagulative tendency and intimal thickening caused by inflammation of native arteries may be an explanation for the high incidence of postoperative graft occlusion. Le Thi Huong et al experienced six graft occlusions in 10 patients with BD who underwent bypass grafting during a mean follow-up period of 69 months. Tuzun et al reported that of 17 patients with BD who were treated with arterial bypass surgery, graft occlusion developed in 3 during a mean follow-up period of 47 months. In our series, grafts became occluded in 4 of 10 patients during a relatively longer mean follow-up of 133 months, with a cumulative primary patency rate of 83.9% at 3 years in the infragenital region. All of the four patients had been treated with antiplatelet therapy postoperatively, and two had also received anticoagulants. More intense preventive measures, including high-intensity anticoagulant therapy, might be necessary to prevent graft occlusion in patients with BD.

Anastomotic pseudoaneurysm is another postoperative complication that is considered to occur frequently in BD patients and is sometimes life-threatening, although its incidence has never been elucidated. We encountered 5 anastomotic false aneurysms among 49 anastomoses between the graft and the host artery during the study period, with a cumulative incidence of 12.9% at 5 and 10 years. We excluded anastomoses between the grafts from the analysis because the relationship between BD and complications at these anastomoses is not clear. On the other hand, the anastomotic false aneurysms formed in case 4 were included because graft infection occurred after the formation of pseudoaneurysms and we considered that they were probably related to BD.

Because all of the patients in the present study, including those who were operated on in the early 1980s, have undergone surveillance imaging using either echography, angiography, or computed tomography, we consider that the possibility of missing anastomotic pseudoaneurysms is very low. The reported incidence of anastomotic pseudoaneurysm after vascular reconstruction in patients with atherosclerotic disease varies from 2% to 15% per anastomosis depending on the length of follow-up, site of anastomosis, and method of diagnosis. A previous study from our institution documented that the incidence of anastomotic false aneurysm after surgical treatment of patients with Takayasu arteritis, another disease with systemic noninfectious vasculitis, was 8.2% during a mean follow-up of 17 years, excluding anastomoses made distal to the femoral artery. This rate is comparable to the incidence of
anastomotic false aneurysm above the iliac artery of 9.1% in the present series (2 of 22 anastomoses). Taking these data into account, we could not reach a conclusion that there seems to be a higher risk of formation of anastomotic false aneurysms in patients with BD compared with that in atherosclerotic disease or Takayasu arteritis. However, a notable observation in the present study was that all anastomotic false aneurysms were detected within 18 months postoperatively. McCabe et al. reported that the development of anastomotic false aneurysm of the femoral artery was diagnosed on average of 6.2 years after surgery in patients with atherosclerotic disease. In patients with Takayasu disease, the mean interval between the operation and the diagnosis of anastomotic false aneurysm was 9.8 years. The anastomotic fragility in patients with BD might be attributable to weakening of the arterial wall caused by fulminant inflammation. The early occurrence of anastomotic false aneurysm indicates the difficulty in determining an appropriate site for anastomosis of a graft with solid arterial wall, preoperatively or intraoperatively. Macroscopic inspection might not be sufficient to clearly identify a disease-free portion of artery. As for the graft material, we preferred Dacron grafts to expanded polytetrafluoroethylene grafts because of easy handling and good healing characteristics. We cannot reach any conclusion on the optimal graft type or useful surgical technique to avoid anastomotic complications because of the small number of cases included in the present study. However, suturing with wide bites at vessels distant from the diseased artery, if possible, might lower the risk, as recommended for surgical treatment of atherosclerotic disease.

Tuzun et al. introduced ligation as a means of surgical treatment for extremity aneurysms, because the likelihood of finding an intact artery is low in BD patients. They reported 8 cases of extremity aneurysms (1 carotid, 1 subclavian, 4 superficial femoral, 1 popliteal, and 1 posterior tibial artery aneurysm) treated with ligation after confirming an adequate stump pressure. In our series, a subclavian artery was ligated without disabling ischemia in one patient (case 10) after formation of two anastomotic false aneurysms after bypass grafting. This approach could be an effective treatment without the risk of anastomotic complications in some circumstances. However, it could result in significant functional impairment of the limb. We have therefore opted for bypass grafting as the first choice of intervention to secure a good functional outcome. Recently, Park et al. showed the possible usefulness of stent-graft insertion in the management of aneurysms in BD. Because the outcome of this technique in the long term remains unclear, we have not considered using it in patients with BD. Further investigation with longer follow-up would elucidate the safety and effectiveness of stent-graft placement for arterial lesions in BD.

Postoperative corticosteroid therapy and systemic immunosuppression with azathioprine, chlorambucil, or cyclophosphamide have been suggested as efficacious preventive medication for arterial relapse including the formation of aneurysms at anastomotic sites and in other arteries. In the present series, two of the patients were treated with corticosteroids and none was treated with immunosuppressive drugs after surgical intervention. One patient who received corticosteroid therapy (case 2) had no arterial relapse for 98 months postoperatively; the other (case 5) had no sign of recurrence for 5 months, either, with no change in size of an untreated aortic aneurysm. On the other hand, 5 of 8 patients who were not under corticosteroid treatment experienced new aneurysm formation. We cannot reach any conclusion regarding the effectiveness of postoperative steroid administration from our data, but it is likely that patients without corticosteroid or immunosuppressive therapy are highly susceptible to recurrence of arterial lesions. Further studies are necessary to clarify whether postoperative medical treatment can improve the prognosis of patients with BD with arterial involvement.

We thank Hiroyuki Koyama, MD, Jun-o Deguchi, MD, Hideo Kimura, MD, and Tatsu Nakazawa, MD from University of Tokyo, Japan, for assistance with preparation of the manuscript.

REFERENCES


Submitted Jan 10, 2005; accepted Mar 9, 2005.