Endovascular Repair and Adjunctive Immunosuppressive Therapy of Aortic Involvement in Behçet’s Disease

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WHAT THIS PAPER ADDS
This study will guide surgeons in the evaluation and treatment of patients with aortic involvement of Behçet’s Disease before endovascular surgery.

Objectives: Aortic aneurysm is a serious problem in Behçet’s disease, but open surgical therapy carries the risk of recurrent pseudoaneurysm. Here the outcomes of endovascular repair and adjunctive immunosuppressive therapy for aortic disease in Behçet’s disease are presented.

Materials: This was a retrospective study. Between 2002 and 2012, nine patients with Behçet’s disease (8 male, median age 41 years, range 33–60 years) were treated by endovascular stent grafting for abdominal or thoraco-abdominal aortic pseudoaneurysm.

Methods: Computed tomography angiography revealed infrarenal pseudoaneurysm in six (66.6%) patients and suprarenal pseudoaneurysm in three (33.3%). Patients received immunosuppressive therapy with oral prednisolone (60 mg/day) and cyclophosphamide (200 mg/day) for 2 weeks or more before the procedure, and intravenous hydrocortisone (200 mg/day) combined with cyclophosphamide (200 mg/day) for 3 days after the procedure. Thereafter, oral immunosuppressive therapy was continued for 2 years.

Results: A straight tube graft was implanted in seven patients and a bifurcated graft in two patients. Two stage procedures (debranching before endovascular therapy) were performed in three patients for thoraco-abdominal aortic pseudoaneurysms. Stent grafting was successful in all patients, without any peri-operative complications. However, two patients needed abdominal exploration later: one for seroma around the graft and the other for a fistula between the duodenum and the graft. No recurrence of aneurysm was observed during a mean follow up of 40 ± 16 months. One patient died in the 15th month from a non-vascular cause.

Conclusions: Endovascular stent graft implantation and adjunctive immunosuppressive therapy seems to be safe and effective in the treatment of aortic involvement in Behçet’s disease, but this approach needs further evaluation.

INTRODUCTION

In 1937, Turkish dermatologist Hulusi Behçet first described the disease that bears his name. The disease consists of recurrent ulcers in oral and genital mucosae and relapsing uveitis.1,2 Although the cause of Behçet’s disease is unknown, the disease is a multisystem inflammatory disorder with gastrointestinal, ophthalmological, neurological, cardiovascular, musculoskeletal, and urogenital involvement.2,3 Vasculitis is the predominant histopathological lesion, which may affect blood vessels of any size.4 Vascular lesions occur in 25–30% of Behçet’s disease patients, the most frequent being deep venous thrombosis, especially in the lower extremities.4–7 Usually, both arteries and veins are involved; pure arterial involvement is rare. Aortic lesions such as aneurysms, occlusions, and pseudoaneurysms can cause life threatening complications5 and increase mortality and morbidity rates.5

The abdominal aorta is the most common site of arterial involvement in Behçet’s disease, followed by the pulmonary, femoral, popliteal, and carotid arteries in that order. Conventional open surgery is the most frequently used treatment for the arterial lesions in Behçet’s disease patients.5 Pseudoaneurysm at the site of the anastomosis is
one of the most serious complications after open repair. Recent studies have shown that endovascular stent grafting may offer an alternative treatment for arterial aneurysms in Behçet’s disease.\(^4\)\(^{10}\)\(^{11}\)\(^{12}\)\(^{13}\)\(^{14}\) Also, endovascular treatment combined with immunosuppressive therapy has been reported to be associated with better post-operative results and lower recurrence rates than open repair.\(^4\)

In this study, the outcome of endovascular stent graft implantation and adjunctive immunosuppressive therapy for the treatment of abdominal or thoraco-abdominal aortic aneurysms in Behçet’s disease has been evaluated.

**MATERIALS AND METHODS**

Between 2002 and 2012, nine consecutive patients (8 male), with a median age of 41 (33–60) years, with Behçet’s disease underwent endovascular stent grafting either for abdominal or thoraco-abdominal aortic aneurysm. All patients had been referred to the department from the rheumatology clinic with a diagnosis of Behçet’s disease. The diagnosis was made according to the criteria of the International Study Group of Behçet’s Disease.\(^2\) Four (44.5%) patients were asymptomatic; three of them were followed by the rheumatology department and one was diagnosed incidentally (during abdominal ultrasonography); five (55.5%) had back pain.

Aortic aneurysms were imaged with thoraco-abdominal computed tomography angiography (CTA). The specialized endovascular team evaluated all CTA images before the procedure to measure the diameter of the aneurysm and select the appropriate stent graft (Fig. 1). In this cohort, six patients (66.6%) had infrarenal abdominal aortic pseudoaneurysm and three (33.3%) had suprarenal pseudoaneurysm (Table 1). Vascular involvement in Behçet’s Disease may occur in multiple sites. Interestingly, no co-existing lesions, such as peripheral pseudoaneurysm or occlusion (femoral, popliteal, subclavian, etc.), were shown in the CTA images. The CTA images showed that all the aortic pathologies were saccular pseudoaneurysms. The aneurysm sacs were irregular and filled with thrombus without any calcification, which differs from atherosclerotic aneurysms. The mean diameters were 5.6 cm and 6 cm for infrarenal and suprarenal pseudoaneurysms respectively. In spite of the contained rupture, patients were clinically stable before intervention. For follow up, CTA was performed in all patients post-operatively during the first, sixth, and 12th month, and yearly thereafter (Fig. 2). The same radiologist evaluated all the CTA scans.

Before endovascular procedures, full blood count and biochemical markers were measured in all patients. Eight of the nine patients received immunosuppressive therapy, consisting of oral prednisolone at least 2 weeks before (60 mg/day) and cyclophosphamide 3 days (200 mg/day) before the procedure. All patients were monitored to control hemodynamics for risk of rupture. Biochemical tests were performed daily to check possible side effects of
immunosuppressive therapy. An endovascular stent graft was implanted when the inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) had declined to the normal range. In an asymptomatic patient whose aneurysm was diagnosed incidentally during urogenital examination, immunosuppressive therapy was first started after endovascular treatment with the administration of intravenous hydrocortisone (200 mg/day) and cyclophosphamide (200 mg/day) for 3 days, based on the erythrocyte sedimentation rate and C-reactive protein values; then oral medication was started as the maintenance treatment.

For all patients, the post-operative immunosuppressive drug dosages were adjusted by a rheumatologist, on the basis of the patient’s symptoms and the erythrocyte sedimentation rate.

### Table 1. Demographic and operative patient data.

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Aneurysm location</th>
<th>Type of stent graft</th>
<th>Graft size (diameter/length)</th>
<th>Additional procedure</th>
<th>Result/Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>40</td>
<td>M</td>
<td>Infrarenal AAA</td>
<td>Tube</td>
<td>28 mm/8 cm</td>
<td>None</td>
</tr>
<tr>
<td>Patient 2</td>
<td>39</td>
<td>M</td>
<td>Type 4 TAAA</td>
<td>Y graft</td>
<td>26 mm/10 cm</td>
<td>Visceral debranching</td>
</tr>
<tr>
<td>Patient 3</td>
<td>41</td>
<td>M</td>
<td>Infrarenal AAA</td>
<td>Tube</td>
<td>22 mm/8 cm</td>
<td>None</td>
</tr>
<tr>
<td>Patient 4</td>
<td>60</td>
<td>M</td>
<td>Infrarenal AAA</td>
<td>Y graft</td>
<td>23 cm, 12–14 mm (the body), 12–10 mm (counterside)</td>
<td>None</td>
</tr>
<tr>
<td>Patient 5</td>
<td>41</td>
<td>M</td>
<td>Type 4 TAAA</td>
<td>Tube</td>
<td>34 mm/15 cm</td>
<td>Visceral debranching</td>
</tr>
<tr>
<td>Patient 6</td>
<td>59</td>
<td>F</td>
<td>Type 4 TAAA</td>
<td>Tube</td>
<td>34 mm/20 cm</td>
<td>Visceral debranching</td>
</tr>
<tr>
<td>Patient 7</td>
<td>46</td>
<td>M</td>
<td>Infrarenal AAA</td>
<td>Tube</td>
<td>22 mm/10 cm</td>
<td>None</td>
</tr>
<tr>
<td>Patient 8</td>
<td>33</td>
<td>M</td>
<td>Infrarenal AAA</td>
<td>Tube</td>
<td>24 mm/10 cm</td>
<td>None</td>
</tr>
<tr>
<td>Patient 9</td>
<td>45</td>
<td>M</td>
<td>Infrarenal AAA</td>
<td>Tube</td>
<td>24 mm/10 cm</td>
<td>None</td>
</tr>
</tbody>
</table>

AAA = abdominal aortic aneurysm; F = female; HA = hepatic artery; LRA = left renal artery; M = male; RRA = right renal artery; SMA = superior mesenteric artery; TAAA = thoraco-abdominal aortic aneurysm; TC = Coeliac trunk.

Death due to non-vascular cause.

### Figure 2.

(A) Patient with suprarenal abdominal aortic pseudoaneurysm. (B) Control angiogram of the visceral bypass grafts before endovascular procedure. (C) Intra-operative view of visceral grafts. (D) Three dimensional reconstruction image of the aneurysm 4 months after graft implantation. SMA = superior mesenteric artery.
blood tests were done for all patients at each follow up. Two patients were lost to follow up. Physical examination continued for 2 years, without any significant changes. The event free survival rate was 67%. Immunosuppressive therapy was continued during the second years, respectively. The event free survival rate was 100% and 88% at the first and second years, respectively. The event free survival rate was 77%, and for the entire follow up period was 67%. Immunosuppressive therapy was continued for 2 years, without any significant side effects. Two patients were lost to follow up. Physical examination and blood tests were done for all patients at each follow up visit on a routine basis; CTA was performed to confirm stent graft patency, leakage, and pseudoaneurysm, 1, 6, and 12 months after the operation and every year subsequently. No pseudoaneurysms or graft occlusions were encountered. The diameter of the aneurysm sac had decreased in all patients at the sixth month (Fig. 1). Patient 5 required abdominal exploration 15 months after the operation for a suspected abscess, which revealed seroma around the abdominal debranching grafts; no additional procedures were needed. Patient 6 experienced back pain, high fever, and weight loss after 24 months. CTA showed a fistula between the duodenum and the vascular graft, with air bubbles around the bypass graft to the superior mesenteric artery. Laparotomy revealed a fistula. The duodenum was resected, the abscess was drained, and the visceral graft was replaced and covered with omentum to prevent re-infection.

Table 2. Target vessels and graft properties used for debranching.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Target vessel</th>
<th>Graft size and type</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Hepatic artery</td>
<td>6 mm, ringed PTFE</td>
</tr>
<tr>
<td></td>
<td>Superior mesenteric artery</td>
<td>8 mm, ringed PTFE</td>
</tr>
<tr>
<td></td>
<td>Right renal artery</td>
<td>6 mm to 5 cm, Viabahn graft</td>
</tr>
<tr>
<td>5</td>
<td>Left renal artery</td>
<td>5 mm, ringed PTFE</td>
</tr>
<tr>
<td></td>
<td>Superior mesenteric artery</td>
<td>8 mm, ringed PTFE</td>
</tr>
<tr>
<td></td>
<td>Right renal artery</td>
<td>5 mm, ringed PTFE</td>
</tr>
<tr>
<td>6</td>
<td>Coeliac trunk</td>
<td>8 mm, Ringed PTFE</td>
</tr>
<tr>
<td></td>
<td>Left renal artery</td>
<td>6 mm, Ringed PTFE</td>
</tr>
<tr>
<td></td>
<td>Superior mesenteric artery</td>
<td>8 mm, Ringed PTFE</td>
</tr>
<tr>
<td></td>
<td>Right renal artery</td>
<td>6 mm, Ringed PTFE</td>
</tr>
</tbody>
</table>

PTFE = polytetrafluoroethylene.

RESULTS

All procedures were performed successfully without peri-operative complications, and no patient required conversion to open repair. A tube stent graft was implanted in five patients with infrarenal aneurysms and in two patients with suprarenal aneurysms. Bifurcated stent grafts were implanted in one patient in each anatomical location. Aortography was performed at the end of the procedures to verify the appropriate placement of the stent graft. No endoleaks were documented. Upon completion of the 3 day medical treatment therapy the patients were discharged.

Two stage procedures were used in three patients who had ruptured type 4 thoraco-abdominal aortic aneurysms. The visceral debranching procedure was performed first followed by the endovascular procedure, to prevent intestinal and renal ischemia. A single main graft, as a source of inflow, was anastomosed to the common iliac artery (Fig. 2). Endograft implantation was performed on the same day after the completion of the visceral bypass. Information about the bypass grafts is shown in Table 2.

Endovascular stent grafting was performed under spinal or general anesthesia, depending on the patient's condition. Surgical exploration of the femoral artery was done on one side and percutaneous puncture on the opposite side. Surgical arteriotomies were closed with 6/0 polypropylene sutures. High pressure compression was applied to the percutaneous puncture site for 8 hours after the procedure. There were no procedure related complications.

The mean follow up was 40 ± 16 months. One patient died during the 15th month from a non-vascular cause. The patients' survival rate was 100% and 88% at the first and second years, respectively. The event free survival rate during the first year was 77%, and for the entire follow up period was 67%. Immunosuppressive therapy was continued for 2 years, without any significant side effects. Two patients were lost to follow up. Physical examination and blood tests were done for all patients at each follow up visit on a routine basis; CTA was performed to confirm stent graft patency, leakage, and pseudoaneurysm, 1, 6, and 12 months after the operation and every year subsequently. No pseudoaneurysms or graft occlusions were encountered. The diameter of the aneurysm sac had decreased in all patients at the sixth month (Fig. 1). Patient 5 required abdominal exploration 15 months after the operation for a suspected abscess, which revealed seroma around the abdominal debranching grafts; no additional procedures were needed. Patient 6 experienced back pain, high fever, and weight loss after 24 months. CTA showed a fistula between the duodenum and the vascular graft, with air bubbles around the bypass graft to the superior mesenteric artery. Laparotomy revealed a fistula. The duodenum was resected, the abscess was drained, and the visceral graft was replaced and covered with omentum to prevent re-infection.

DISCUSSION

In this study, endovascular stent graft implantation combined with immunosuppressive therapy for the treatment of aortic pseudoaneurysm in Behçet’s disease was evaluated. The major finding was that the operation was performed successfully in most patients, with low morbidity and mortality rates. Indeed, no peri-operative complications occurred, and the only death was unrelated to the operation.

The expression of vasculitis due to Behçet’s disease may be in many clinical forms. Although, aneurysm and pseudoaneurysm are mostly seen in the arterial system, thrombosis occurs in the venous system. Arterial aneurysms are the most serious ones because of the inherited high risk of rupture.11 The abdominal aorta is the most common location of aneurysms in Behçet’s disease, followed by the pulmonary and femoral arteries.16–18 Until recently, open surgical therapy was the only treatment option for these aneurysms. Unfortunately, that approach often resulted in the development of pseudoaneurysm or leakage at the anastomotic sites, or graft occlusions during the post-operative period.5,12,13,19,20 Schneider et al. reported a case with early graft occlusion and late pseudoaneurysm formation after an aneurysmectomy and prosthetic revascularization for abdominal aortic and left femoral artery aneurysms.19 Hosaka et al. reported a study of 10 patients with Behçet’s Disease who underwent open surgery for arterial involvement. They observed five graft occlusions and five anastomotic pseudoaneurysms during the post-operative follow up period.21 Several studies have shown similar results for graft occlusions after peripheral bypass surgery.18,21,22 The pathological mechanism of post-operative graft occlusion is unclear. Some authors believe that the systemic pro-coagulative state and inflammatory activity in patients with Behçet’s disease might lead to wall thickening and occlusions in both native arteries and implanted grafts.21

Anastomotic pseudoaneurysm is another life threatening complication, occurring after open repair of Behçet’s disease.
Suturing of prosthetic graft to an already inflamed artery is the main reason for this complication. There are various options to reduce the high recurrence rate of anastomotic pseudoaneurysms. Kalko et al.\textsuperscript{23} treated 16 patients and 18 aneurysms using an open surgical technique. They suggest using immunosuppressive therapy (glucocorticoid and cyclophosphamide) before surgery if the patient is hemodynamically stable and performing the anastomosis on disease free arterial walls. Apart from urgent patients, Kalko et al.\textsuperscript{23} preferred to wait until the inflammatory markers diminished, otherwise immunosuppressive therapy was given after surgery. Tüzün et al.\textsuperscript{22} reported eight peripheral aneurysms treated by ligation after confirming stump pressure. Kwon et al.\textsuperscript{11} used prosthetic wrapping on the proximal anastomotic site in all cases of graft interposition and omental wrapping for infrarenal aortic aneurysms to prevent recurrence. In addition, they performed a patch closure technique, but the patch closure technique was associated with a high aneurysm recurrence rate (62.5%).\textsuperscript{11} Post-operative corticosteroid therapy and systemic immunosuppression have been suggested as efficacious preventive medication for anastomotic pseudoaneurysm.\textsuperscript{18,22} Hosaka et al.\textsuperscript{21} reported long-term results after surgical treatment of arterial lesions in Behçet’s disease. They reported no arterial relapse in patients treated with corticosteroid after surgery. Moreover, they reported that five of eight patients who did not receive corticosteroids had experienced new aneurysm formation.\textsuperscript{21}

In 1998, Vasseur et al.\textsuperscript{14} performed the first endovascular treatment in Behçet’s disease to treat aorto-iliac aneurysms. After that experience, other investigators tried this less invasive surgical alternative. Liu et al.\textsuperscript{10} reported 10 patients with pseudoaneurysm due to Behçet’s disease who underwent endoluminal stent graft implantation; they experienced no peri-operative complications. However, the authors lost one patient 8 months after the procedure due to rupture of a recurrent aneurysm. Park et al.\textsuperscript{15} reported that one of seven patients developed recurrence at the distal landing zone of the stent graft. Thus, aneurysms can recur in Behçet’s disease patients even after endovascular grafting. It has been suggested that recurrence of aneurysms after stent graft implantation might occur because of chronic tissue inflammation at the edge of the stent graft.\textsuperscript{15}

Because of the high rate of recurrence of aneurysms after vascular operation in Behçet’s disease patients, most vascular surgeons today believe that surgical treatment without additional immunosuppressive therapy is not adequate.\textsuperscript{21} Aneurysm formation in Behçet’s disease is different from that of degenerative aneurysms; the main problem in the aortic aneurysms of Behçet’s disease is that active inflammation can destroy the aortic wall. Predictably, any vascular operation on the aneurysms can cause new weak areas at the anastomotic sites and lead to the development of new aneurysms. Ozeren et al.\textsuperscript{16} proposed that fewer invasive techniques combined with medical therapy would give better results than open surgery. Nitecki et al.\textsuperscript{17} compared open surgery and endovascular repair techniques for abdominal aortic aneurysm in Behçet’s disease. They reported high recurrence with pseudoaneurysm formation in the open surgery group and none in those treated endovascularly.\textsuperscript{19} Endovascular repair of aortic aneurysms was preferred in the current study, combined with immunosuppressive therapy with the intention of reducing the severity of vascular inflammation and thus decreasing the likelihood of aneurysm recurrence. Recurrent aneurysms were not observed. Although solid evidence supporting the superiority of the combined endovascular and medical approach for aortic aneurysms in Behçet’s disease is lacking, it is believed that all such patients should be given immunosuppressive therapy before and after stent graft implantation. The total endovascular approach with a fenestrated endograft may be a better option in patients with thoraco-abdominal aneurysm to minimize surgical risk.

On the basis of limited experience, endovascular stent graft implantation combined with immunosuppressive therapy appears to be an efficacious treatment for aortic aneurysms in Behçet’s disease. The endovascular approach is less invasive than open surgery, and immunosuppressive therapy may help to prevent recurrence of aneurysms. Further, prospective studies on a larger scale are warranted.

**CONFLICT OF INTEREST**

None.

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None.

**REFERENCES**


