Perianeurysmal Fibrosis: a Relative Contra-indication to Endovascular Repair

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Objective: perianeurysmal fibrosis (PAF) with involvement of neighbouring viscera can render open repair of inflammatory aneurysms technically difficult and therefore hazardous. For this reason, endovascular repair (EVAR) has been advocated as the preferred approach for this condition. EVAR is known to induce a systemic inflammatory response in patients but the nature of the local response remains unknown. If significant, such a response could exacerbate rather than ameliorate PAF. The aim of the study was to examine the incidence, course and consequences of perianeurysmal fibrosis detected by computerised tomography (CT) before and after EVAR.

Material and Methods: the clinical records of patients treated by EVAR and followed for at least 6 months were reviewed. Pre and post-operative CT images were independently graded for PAF by three radiologists according to a standard protocol.

Results: PAF was documented preoperatively in six out of a total of 61 patients. In two of these PAF worsened after EVAR resulting in ureteric obstruction and hydronephrosis requiring ureteric stents. In the remaining 4 patients PAF did not reduce postoperatively. PAF of low grade developed postoperatively in 10 out of 55 patients (18%) in whom there was no evidence of PAF on preoperative imaging. Median follow-up was 18 months (range 6–36 months). The development of periaortic fibrosis de novo postoperatively was statistically significant (McNemar’s test; \( p = 0.002 \)).

Conclusion: EVAR does not seem to reverse PAF if this is present preoperatively and it induces this condition in approximately one sixth of patients without evidence of preoperative PAF. The potential for this adverse inflammatory local response should be taken into account when considering EVAR for treatment of aneurysms with perianeurysmal fibrosis and must be weighed against the perceived benefits of this approach.

Key Words: Inflammatory aneurysm; Endovascular repair; Perianeurysmal fibrosis; Periaortic fibrosis; Surveillance.

Introduction

Inflammatory abdominal aortic aneurysms (IAAA) form a distinct clinical entity accounting for between 3 and 15% of all infrarenal aortic aneurysms.1–3 Involvement of the ureter is seen in up to a quarter of these patients.4 Conventional repair of IAAA can be challenging and is associated with a higher mortality and morbidity than repair of non-inflammatory aneurysms.5,6 Often the planes of surgical dissection are obscured by fibrotic adhesions rendering the duodenum, the left renal vein and other adherent structures prone to iatrogenic injury.7 Endoluminal repair can be performed without these risks in suitable patients and has been proposed as a safer alternative.8,9

In animals endovascular repair has been shown to evoke an immediate local inflammatory response around the stent-graft within the aneurysm and in the perianeurysmal tissue.10,11 Longer-term evolution of such periaortic inflammation has not been documented previously in animal models or in humans. This study was conducted to establish the incidence, extent and implications of radiological changes consistent with inflammation in the perianeurysmal tissue following EVAR.

Material and Methods

Details of all patients undergoing EVAR at our institution were entered prospectively into a computer database. Patients with a minimum of 6 months follow-up were entered into the study. Follow-up surveillance
Table 1. Grading of periaortic fibrosis used in the study.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No fibrosis</td>
</tr>
<tr>
<td>1</td>
<td>Fibrosis &lt;3 mm thick</td>
</tr>
<tr>
<td>2</td>
<td>Fibrosis 3-4 mm thick</td>
</tr>
<tr>
<td>3</td>
<td>Fibrosis 5-6 mm thick</td>
</tr>
<tr>
<td>4</td>
<td>Fibrosis 7-8 mm thick</td>
</tr>
<tr>
<td>5</td>
<td>Fibrosis &gt;8 mm thick</td>
</tr>
</tbody>
</table>

demonstrates slight late enhancement with contrast due to its abundant capillary network13 (Fig. 1).

In order to minimise the subjectivity inherent in image analysis, a representative set of 6 images (Fig. 1) of aneurysms with varying degrees of periaortic thickening, graded as shown in Table 1 was composed. This set of images was used as reference throughout the study. Two Consultant radiologists (RGW and PCR) and one final year Higher Radiology Trainee (AA) interpreted all the films and reported independently. Another author (SRV) collated the reports to identify any discrepancies. In the event of disagreement between reviewers, the images were re-evaluated by all reviewers together and a final consensus was agreed in all cases. Discrepancy in the grading of periaortic fibrosis of one grade only was not subjected to this process. In this circumstance the majority opinion was accepted.

**Statistical methods**

McNemar’s test for paired data was applied to evaluate the statistical significance of development of periaeurysmal fibrosis *de novo* postoperatively.

**Results**

A total of 61 patients were identified to have undergone EVAR between February 1996 and June 1999, with at least 6 months’ follow-up. Median duration of follow-up was 18 months.

**Evaluation of CT images**

There were major disagreements among the three observers in relation to two patients. In one patient, two observers found no periaeurysmal thickening at any stage, while the third observer reported Grade 5 thickening. Following re-evaluation of this set of images the consensus opinion was that the reported periaortic thickening was in fact erroneous interpretation of bowel adjacent to the aneurysm sac.
Table 2. Evolution of periaortic fibrosis grading when noticed on preoperative imaging.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Grade of PAF at intervals after EVAR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-operative</td>
</tr>
<tr>
<td>A</td>
<td>5</td>
</tr>
<tr>
<td>B</td>
<td>4</td>
</tr>
<tr>
<td>C</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>2</td>
</tr>
<tr>
<td>F</td>
<td>1</td>
</tr>
</tbody>
</table>

(Gr 1 = <3 mm, Gr 2 = 3–4 mm, Gr 3 = 5–6 mm, Gr 4 = 7–8 mm and Gr 5 = >8 mm).

The final report for this patient was therefore that there was no periaortic fibrosis at any stage. In another patient, two observers reported Grade 1 periaortic fibrosis in the preoperative scan. The third observer who originally reported absence of fibrosis agreed to the presence of Grade 1 fibrosis at the consensus reporting.

The remaining 59 patients had a total of 241 sets of CT scans reported. Among these there were minor disagreements in relation to 9 sets. In all cases this was resolved by one observer revising his grading of fibrosis by one grade to comply with the grading of the other two where the reports were in agreement.

Patients without periaortysmal fibrosis at any stage

In 45 patients there was no periaortysmal fibrosis at any stage before or after operation.

Patients with pre-operative periaortysmal fibrosis

Six patients were considered to have periaortic fibrosis on preoperative imaging. Among these patients, two were diagnosed preoperatively on clinical and imaging grounds to have inflammatory aneurysms. The periaortic fibrosis in the remaining four was noted on retrospective review. The severity of periaortic fibrosis of these patients before repair and during follow-up is presented in Table 2. A brief history of each of these patients is given here.

Patient A. This 71-year-old man underwent endovascular repair with an AneuRx stent-graft (Medtronic Inc, CA, U.S.A.) following a diagnosis of inflammatory aneurysm. Preoperative bilateral ureteric obstruction was relieved by placement of double J stents and steroid therapy commenced. Preoperative films showed Grade 5 periaortysmal fibrosis and this was still present 24 months after operation. The ureteric stents were removed after 3 months but bilateral hydronephrosis recurred with gross dilatation of both pelvicalyceal systems at 17 months after operation (Fig. 2). This required replacement of ureteric stents while on continued steroid therapy.

Patient B. This 57-year-old woman underwent uncomplicated endovascular repair of a 50 mm inflammatory AAA with a Vanguard stent-graft (Boston Scientific Corp, NJ, U.S.A.). Preoperative imaging revealed Grade 4 periaortysmal fibrosis with partial obstruction of the left ureter and mild dilatation of the pelvicalyceal system. She was therefore commenced on oral steroid therapy. The periaortysmal fibrosis remained at Grade 4 but the ureteric obstruction and hydronephrosis worsened so that it became necessary to insert a double J ureteric stent 6 months after operation. The ureteric stent was removed 6 months later without recurrence of hydronephrosis despite the fact that Grade 4 periaortysmal fibrosis persisted at 36 months after operation.
follow-up images up to 6 months showed Grade 1 perianeurysmal fibrosis on review. He died 8 months postoperatively of unrelated cause.

Patient E. This 56-year-old underwent endovascular repair of a 54 mm aneurysm using a Vanguard (Boston Scientific Corp, NJ, U.S.A.) device. A preoperative diagnosis of inflammatory aneurysm was not made. The perianeurysmal fibrosis was of Grade 2 preoperatively and showed no signs of resolution at 18 months after operation.

Patient F. This 63-year-old male underwent repair of a 55 mm aneurysm that was not clinically diagnosed to be inflammatory, using an Excluder device (WL Gore Associates, AZ, U.S.A.). The preoperative and postoperative images up to 6 months after the operation showed Grade 1 perianeurysmal fibrosis.

Patients without preoperative perianeurysmal fibrosis

Among the remaining 55 patients who did not have perianeurysmal thickening on preoperative imaging, 10 (18%) developed evidence of this condition on follow-up imaging. An example is given in Fig. 4. Grading and evolution of the postoperative fibrosis in these patients is given Table 3. The maximal aneurysm diameter decreased in 6 of these patients while it remained the same in two and increased in two. There was no relationship between postoperative change in aneurysm diameter and the development of perianeurysmal fibrosis.
Table 3. Grading of periaortic fibrosis that developed de novo after EVAR and its evolution.

<table>
<thead>
<tr>
<th>Patient</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
<th>36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>D</td>
<td>1</td>
<td>1</td>
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<tr>
<td>E</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>F</td>
<td>3</td>
<td>5</td>
<td>0</td>
<td></td>
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<tr>
<td>G</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>H</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>I</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
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</tr>
<tr>
<td>J</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

(Gr 1 = <3 mm, Gr 2 = 3–4 mm, Gr 3 = 5–6 mm, Gr 4 = 7–8 mm and Gr 5 = >8 mm).

Table 4. Summary of results (No. of patients).

<table>
<thead>
<tr>
<th>Fibrosis post-EVAR</th>
<th>No fibrosis post-EVAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>45</td>
</tr>
</tbody>
</table>

Case report

One of these ten patients developed late clinical complications that resulted in his death. He had undergone endovascular repair of a 60 mm aneurysm with a Stentor endograft (Mintec Inc, La Ciatot, France) at the age of 76 years. There was no evidence of peri-aneurysmal fibrosis preoperatively. At 6 months after operation there was evidence of Grade 5 peri-aneurysmal fibrosis that had disappeared at 12 months. There was no ureteric involvement at any stage. He died of sepsis 24 months after EVAR at another hospital. Postmortem examination revealed pneumonia and an infected aortic stent-graft.

The other 9 patients with periaortic fibrosis that developed de novo after operation have remained free from clinical complications.

A summary of the results is shown in Table 4. The probability that perianeurysmal fibrosis developing de novo after operation was observed by chance was calculated as less than less than 2 in 1000 (McNemar’s test; p<0.002). The risk of developing perianeurysmal fibrosis de novo was calculated to be 16.4% (95% CI 6.6%–27.1%).

Discussion

The option of repairing an inflammatory aortic aneurysm by endoluminal means is attractive because it might be expected to reduce the operative risk compared to open repair. This supposes that endoluminal exclusion of the aneurysm has a beneficial effect on or at least does not make worse the perianeurysmal fibrosis. It is accepted that after open repair the perianeurysmal fibrosis usually regresses.14,15 This is not necessarily the case after endovascular repair.

Endovascular repair of AAA is known to induce an inflammatory response.10,11 The explanations considered for this include expression of a local immune reaction and this is also one of the theories proposed to explain the aetiology of inflammatory aneurysms. The longer-term effects of this local inflammatory response have not previously been documented.

Despite using established parameters for reporting periaortic fibrosis,16 it is acknowledged that the interpretation of CT images is relatively subjective. To minimise the risk of error and bias all films were reported by three radiologists independently and any disagreements resolved by group discussion. This happened only in two patients where the senior radiologists gave identical reports while the more junior member diagnosed the presence of periaortic thickening on one occasion and its absence in another. Among the remaining 241 sets of images, 232 were interpreted identically by all three observers. The remaining nine had two observers reporting identically but the third grading the fibrosis lower by one grade. There was therefore a high degree of concurrence among the observers and good adherence to accepted standards of reporting.
McNemar’s test for paired data showed strong statistical significance for the observation of de novo peri-aneurysmal fibrosis after endovascular repair. However the clinical “significance” of this study lies in the fact that none of the inflammatory aneurysms treated showed a resolution of fibrosis. This together with the finding that a high proportion (10/46) of non-inflammatory aneurysms developed periaortic fibrosis de novo after EVAR signals the need for caution in advising this method for the treatment of patients with established inflammatory aneurysms.

**Aneurysms with periaeurysmal fibrosis preoperatively treated by endoluminal stent-graft**

Six of the 61 patients in this series had preoperative periaeurysmal fibrosis based on CT findings. Following conventional repair of an inflammatory aortic aneurysm, the inflammatory change seen on imaging and systemic markers of inflammation regress in the majority of the patients.14,15 In this series of patients treated with EVAR there was no evidence of regression of fibrosis on imaging during follow-up ranging from 6 to 36 months (Table 2 and Fig. 4). In one patient with an IAAA, the ureteric obstruction which was present preoperatively remained troublesome after operation with continued requirement for ureteric stenting. Another patient with IAAA was able to tolerate post-operative removal of the ureteric stent even though there was no significant reduction in periaortic fibrosis. Both these patients received steroid therapy.

In four patients in this series, inflammatory change was diagnosed retrospectively on the basis of CT scans. One of these patients developed ureteric obstruction postoperatively due to increased fibrosis.

Reversal of the fibrotic response is a significant component of the aim of treatment of inflammatory aneurysms. In none of the 6 patients with preoperative periaortic fibrosis in this study was there any reduction in thickness of fibrosis on postoperative imaging with follow-up ranging from 6 months to 36 months. This suggests an “on-going” inflammatory process. Although endovascular repair is perhaps a lower risk option in suitable patients in the short term, it appears to be ineffective at reversing periaeurysmal fibrosis.

There are previous case reports of successful treatment of patients with inflammatory aneurysm by EVAR with resolution of systemic inflammatory markers.53 However in our series none of the patients with preoperative periaortic fibrosis demonstrated radiological evidence of remission of fibrosis. The expected lower mortality and morbidity associated with EVAR compared to open repair might justify this approach in some poor operative risk patients with inflammatory aneurysms. But on the basis of this study “inflammatory” aneurysm may also be regarded as a relative contra-indication to EVAR. Certainly the potential disadvantages associated with exacerbation of the inflammatory process must be weighed carefully against the perceived benefits.

Among the 55 patients who had no periaortic fibrosis noted on preoperative images, 10 patients (Table 3) (18%) developed periaortic thickening de novo during follow-up. This tended to be mild in most with some evidence of later regression. However as seen in two patients, it can be moderately severe. This study demonstrates for the first time that periaeurysmal fibrosis may develop de novo after EVAR with a risk of one in six. Figure 3 demonstrates one such patient. The long-term implications of such stent-graft induced periaortic fibrosis are not known. The distribution of fibrosis is similar to that seen in inflammatory aneurysms. Associated clinical complications were not observed in any of these patients. However the risk this might occur cannot be discounted.

The exact pathogenesis of periaeurysmal fibrosis in patients with inflammatory aneurysm remains unknown. Similarly any theories about the mechanisms responsible for the observations made in this study are at this stage speculative. One possibility is that the intraluminal devices themselves elicit a foreign body reaction despite the fact that the materials used in their construction are inert. But it is also interesting to speculate about the role of the intra-sac thrombus. Intra-sac thrombus or products of thrombus degradation have been implicated as a possible trigger of periaeurysmal fibrosis perhaps by eliciting an autoimmune response. If this was true, it would not be surprising to find that EVAR, which, in contrast to open repair, leaves the thrombus in-situ is not followed by regression of the inflammatory response. Also by eliciting new thrombosis in the sac EVAR might be expected to trigger de novo fibrosis in susceptible patients.

**Conclusion**

Although the potential for lower operative risk compared to open repair makes EVAR an attractive option for the treatment of inflammatory aneurysms this study shows that it may exacerbate the inflammatory

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process with later adverse clinical consequences. In all cases perianeurysmal fibrosis either persisted or increased following EVAR. Further more 1 in 6 aneurysms developed radiological periaortic fibrosis de novo after endovascular repair. While the full implications of this are unknown, evidence of perianeurysmal fibrosis on pre-operative CT scans needs to be taken into account as a possible adverse factor when considering the therapeutic options for patients with aneurysms. For those with established inflammatory aneurysms, the potential for the inflammatory change to be exacerbated must be carefully weighed against the perceived short-term advantages of EVAR.

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References


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