Surgery for Aortic Disease

Impact of New Development of Ulcer-Like Projection on Clinical Outcomes in Patients With Type B Aortic Dissection With Closed and Thrombosed False Lumen

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Background—The purpose of this study was to investigate the clinical importance of newly developed ulcer-like projection (ULP) in patients with type B aortic dissection with closed and thrombosed false lumen (AD with CTFL), which is better known as aortic intramural hematoma.

Methods and Results—A total of 170 patients with acute type B AD with CTFL were admitted to our institution from 1986 to 2008 and treated initially with medical therapy. There were 31 late deaths, including 9 cases of aortic rupture. The actuarial survival rates of all patients were 99%, 89%, 83% at 1, 5, and 10 years, respectively. A total of 62 (36%) patients showed new ULP development within 30 days from the onset. Patients who had ULP showed significantly poorer survival rates than patients who did not have ULP ($P=0.037$). Development of ULP was also associated with a significant increase in adverse aorta-related events ($P<0.001$). In addition, patients with ULP in the proximal descending thoracic aorta (PD) showed significantly higher aorta-related event rates than patients without ULP in the PD ($P<0.001$). Initial aortic diameter (hazard ratio, 3.55; $P=0.001$) and development of ULP in PD (hazard ratio, 3.79; $P=0.003$) were the strongest predictors of adverse aorta-related events.

Conclusions—Initial aortic diameter and development of ULP in the PD are both strong predictors of adverse aorta-related events in patients with type B AD with CTFL. Patients with newly developed ULP should be more carefully followed up with close surveillance imaging than those without ULP. (Circulation. 2010;122[suppl 1]:S74–S80.)

Key Words: aorta ■ follow-up studies ■ mortality ■ prognosis ■ and survival

The natural history of aortic dissection with closed and thrombosed false lumen (AD with CTFL), which is generally known as aortic intramural hematoma (IMH), continues to be debated.1–3 Despite a controversy in the management of type A AD with CTFL, it is generally accepted that patients with type B AD with CTFL can be treated conservatively.2,4–8 However, a considerable proportion of patients with type B AD with CTFL have life-threatening complications including organ ischemia and aortic enlargement and rupture, which require surgical intervention.1,4,9,10 Risk stratification must be necessary for proper treatment of patients with type B AD with CTFL.

Development of ulcer-like projection (ULP) appears to be associated with a higher incidence of disease progression under medical therapy, whereas the absence of ULP may suggest a stable disease course in patients with AD with CTFL.7,11 ULP has been described as a localized collection of contrast material within the aortic wall,12–14 but its distinct clinical and pathological entity has not been well investigated in a large study cohort. Moreover, a complete understanding of the behavior of these entities is complicated by confusion generated in the literature, in which many series combine analysis of those lesions involving the ascending aorta with those involving the descending aorta.12,15,16 In the present study, we focused on patients with type B AD with CTFL and investigated the natural history and clinical importance of development of ULP in patients with type B AD with CTFL.

Methods

Patient Characteristics

From 1986 to 2008, 170 patients (105 male and 65 female) with acute type B AD with CTFL were admitted to our institution within 48 hours from the onset. The mean age of all patients was 69±10 years. Diagnoses were established by contrast-enhanced computed tomography (CT) and/or transesophageal echocardiography (TEE). AD with CTFL was diagnosed as same criteria as those of IMH; a crescentic or circular high attenuation area along the aortic wall without contrast enhancement in CT and regional aortic wall thickening in TEE without evidence of direct flow communication.
Treatment

All patients were treated initially with medical therapy. Our initial therapeutic goal during the acute phase included the elimination of pain and the reduction of systolic blood pressure to 100 to 120 mm Hg. To achieve adequate blood pressure control, oral antihypertensive drugs such as β-blockers, calcium channel antagonists, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers were administered during the hospitalization, in addition to intravenous administration of antihypertensive drugs in the acute stage. CT or TEE was repeated once per week during the acute stage. CT scans were then obtained 2 or 3 times per year and at the onset of new symptoms suggesting complications. Patients who demonstrated aortic rupture or aortic enlargement (maximum diameter of the affected aorta ≥60 mm or rapid enlargement of the affected aorta or ulcer-like lesion) during follow-up were referred for surgical repair and underwent urgent operation.

Clinical Follow-Up and CT Evaluation

All patients were followed at the outpatient clinic every 4 to 8 weeks after discharge. Further follow-up was done by the referring physician. Follow-up was available for 144 patients and was achieved by a direct contact in 37% of the patients and by telephone in the remaining patients. A total of 26 patients could not be contacted and were lost at a mean of 4.1 years after the onset. Mean follow-up period was 7.1±4.9 years (1008 patient-years). Adverse aorta-related events were defined by a composite of aortic rupture, horizontal and longitudinal development of classic aortic dissection (development with typical "double-channel aorta" with intimal flap), aortic enlargement (≥60 mm), and surgical aortic repair.

New development of ULP was assessed by comparing the initial and follow-up CT images within 30 days from the onset. We also evaluated the location of ULP: (1) proximal descending thoracic aorta (PD), from distal to the left subclavian artery to the level of pulmonary artery bifurcation, (2) mid descending thoracic aorta (MD), from the level of pulmonary artery bifurcation to the level of center of the left atrium, (3) distal descending thoracic aorta (DD), from distal to the left subclavian artery to the diaphragm, (4) suprarenal abdominal aorta (SR), and (5) infrarenal abdominal aorta (IR) as previously reported (Figure 1).

This study was approved by the Institutional Review Board of Kobe City Medical Center General Hospital. Waiver of informed consent was obtained, given the nature of the study.

Statistical Analysis

Categorical variables are described as number and percent and compared by the χ² test or Fisher exact test as appropriate. Continuous variables are described as mean±SD and compared with unpaired t tests. Survival rates are expressed as mean±SE percentages. Survival analysis was performed by Kaplan-Meier analysis, and differences in survival between groups were examined with the
log-rank test. To determine predictors for adverse aorta-related events during follow-up period, the Cox proportional hazards model was used to estimate the risk of the following potential variables: age, sex, hypertension, hyperlipidemia, diabetes mellitus, smoking, maximum aortic diameter, maximum false lumen diameter, the presence of ULP, and the presence of ULP in the PD. We plotted log (time) versus log (−log (survival)) stratified by each significant risk factor and evaluated whether the plotted lines were parallel. Those variables for which probability values were <0.20 in univariable analyses, and proportionality assumptions were generally fair were included in the multivariable analysis. The multivariable Cox proportional hazard model was built by stepwise variable selection with entry and removal exit criteria set at \( P < 0.05 \) and \( P < 0.10 \), respectively. Because of the small sample size, exact confidence intervals (CI) and probability values are reported for the multivariable models. Data analyses were performed with SPSS software (version 17.0; SPSS, Inc, Chicago, Ill).

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Overall Patient Characteristics and Clinical Outcomes

Clinical features of all 170 patients are summarized in Table 1. Of the 170 patients, 62 (36%) showed new development of ULP within 30 days from the onset, whereas 108 did not show any ULP (Figure 2). No patients had new ULP after 30 days from the onset. The prevalence of hypertension, diabetes mellitus, hyperlipidemia, and history of smoking did not show any significant difference between patients with and without new ULP development. Antihypertensive medications were not significantly different between the groups. Twelve patients showed LCP at initial CT images. During follow-up, 5 of the 12 patients showed localized aortic dissection without aortic enlargement. Two patients showed aortic enlargement (≥60 mm), whereas 10 patients had no aorta-related events during long-term follow-up. A representative case of patients with LCP who showed no aorta-related events is depicted in Figure 3A through 3C, and a representative case of patients with LCP who showed aortic enlargement is depicted in Figure 3D through 3F.

The 30-day mortality rate of all patients was 0.6% (n=1). Patients were followed from 1.0 to 22.8 years, with a mean of 7.1 years. After hospital discharge, there were 31 late deaths including 2 operative deaths. The actuarial survival rates of all 170 patients were 99±2%, 89±3%, and 83±4% at 1, 5, and 10 years, respectively. Patients with newly developed ULP had significantly poorer actuarial survival rate than patients without newly developed ULP (\( P = 0.037 \), Figure 4A).
Of 170 patients with type B AD with CTFL, 5 patients showed early adverse aorta-related events within 30 days from the onset and underwent emergent surgery; 4 patients were complicated with impending aortic rupture or aortic rupture; and 1 patient had progression to classic double-barreled aortic dissection, which caused lower-limb ischemia. Besides, 2 patients complicated with aortic rupture had lower-limb ischemia (n=1) and visceral ischemia (n=1) caused by hypotensive shock. A total of 22 patients had late adverse aorta-related events after 30 days from the onset, and 15 of these underwent surgical repair. As a result, a total of 27 patients had adverse aorta-related events during the whole study period. Patients with newly developed ULP had significantly poorer adverse aorta-related event-free survival rates than patients without newly developed ULP (P<0.001; Figure 4B).

Operative mortality and morbidity of both early and late surgery are summarized in Table 2. Although 3 patients with ULP underwent descending aorta replacement and 3 with ULP underwent partial or total arch replacement due to progression of aortic dilatation in the late phase, 2 without ULP underwent descending and ascending aorta replacement due to dilation of descending aorta and type A aortic redissection, respectively. There was 1 early operative death caused by uncontrollable bleeding in patients with ULP and 2 late operative deaths, 1 caused by perioperative cerebral infarction in patients with ULP and 1 caused by postoperative pneumonia in patients without ULP. Besides, 9 patients, all with newly developed ULP, died of aortic rupture before receiving emergency operation. Of these, 4 patients had been recommended surgical repair for aortic dilatation but had rejected. The other 5 patients had not been followed up with serial imaging study.

Table 3. Locations and Progression of ULPs

<table>
<thead>
<tr>
<th>Progression* of ULP/Development of ULP</th>
<th>Patients With ULP</th>
<th>Patients Without ULP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descending thoracic aorta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>13/22 (59%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid</td>
<td>3/15 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal</td>
<td>2/8 (25%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal aorta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suprarenal</td>
<td>2/11 (18%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infrarenal</td>
<td>2/6 (33%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>22/62 (35%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Progression was defined as aortic rupture, development of classic aortic dissection, significant aortic enlargement (>60 mm), or surgical aortic repair.

Of 62 patients with newly developed ULP, progression to adverse aorta-related event was confirmed in 22 patients (35%). The incidences of adverse aorta-related event were 59% (13/22) in PD, 20% (3/15) in MD, 25% (2/8) in DD, 18% (2/11) in SR, and 33% (2/6) in IR (Table 3). Patients with ULP in the PD had significantly poorer adverse aorta-related event-free survival rates than patients with ULP in other segments (MD, DD, SR, and IR) (P<0.001, Figure 5). Besides, in the total study population, patients with ULP in the PD had significantly poorer adverse aorta-related event-free survival rates than patients without ULP in the PD (P<0.001, Figure 6).

Predictors of Adverse Aorta-Related Events

Table 4 shows the results of univariable and multivariable analyses for predictors of adverse aorta-related events. Maximum aortic diameter ranged from 24.1 to 58.3 mm and was significantly larger in patients with adverse aorta-related events than those without adverse aorta-related events (39±5 versus 34±5, P<0.001), whereas maximum false lumen diameter ranged from 6.2 to 19.3 mm and was not significantly different (11±4 versus 10±3, P=0.12). On multivariable Cox regression analysis, maximum aortic diameter and development of ULP in the PD were confirmed as the
The strongest independent predictors of adverse aorta-related events (hazard ratio, 3.55; 95% CI, 1.79 to 7.04; \( P < 0.001 \); hazard ratio, 3.79; 95% CI, 1.57 to 9.17; \( P = 0.003 \), respectively).

**Discussion**

The present observational study reports the largest series on clinical outcomes of acute type B AD with CTFL. The main findings of this study were as follows: (1) Development of ULP is associated with poorer survival rate and event-free rate in patients with type B AD with CTFL, and (2) initial aortic diameter and development of ULP in the proximal descending aorta are the principal risk factors for future aorta-related events in patients with type B AD with CTFL.

Our study population consisted of the patients who had crescentic or circular aortic wall thickening on CT or TEE without apparent flow communication, who were generally diagnosed as having IMH. Because IMH is thought to be originated from bleeding in the aortic wall media caused by rupture of the vasa vasorum, absence of intimal tear and flow communication between true and false lumens has been considered as essential for the diagnosis. However, in the present study, almost one third of the study patients showed ULP during the clinical course, which suggested new intimal disruption. Although this process has been believed to be reentry tear formation secondary to hematoma expansion, \(^{14}\) it might be possible that these patients initially had intimal tear but completely thrombosed false lumen without flow communication between true and false lumens. Because complete identification of intimal tear without flow communication in the entire aorta is not possible with current imaging modalities, it is difficult to know precisely whether intimal tear exists or not at the onset and to understand the genesis of the aortic pathology of these patients. The term “aortic intramural hematoma” (IMH), which is originally based on the pathogenesis, might be inappropriate to represent these diverse pathological conditions of the disease entity. Therefore, in this study, we used the term “aortic dissection with closed and thrombosed false lumen” (AD with CTFL) instead of “IMH” for the diagnosis.

It is generally accepted that patients with type B AD with CTFL can be treated conservatively in the absence of disease progression.\(^{11}\) However, some cases can have complications develop or surgical treatment necessitated.\(^{1,9,10}\) In a report of the International Registry of Aortic Dissection, among 51 patients with IMH alone at initial diagnosis, 8 (16%) progressed on serial imaging studies.\(^{9}\) In the present study, 27 of 170 (16%) showed progression during follow-up. Moreover, the mortality rate of patients undergoing surgical intervention for aortic aneurysm is still relatively high.\(^{19,20}\) Therefore, prediction of aorta-related events including aortic enlargement or rupture must be important in patients with type B AD with CTFL.

ULP can be often identified during follow-up in patients with AD with CTFL. ULP has been considered as direct flow communication between true and false lumen\(^{12}\) and might suggest a new intimal disruption or the intimal tear, which occurred at the onset and could be revealed in follow-up.

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**Table 4. Univariable and Multivariable Predictor Analysis of Adverse Aorta-Related Events**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariable Predictors</th>
<th>Multivariable Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>( P^* )</td>
</tr>
<tr>
<td>Age†</td>
<td>1.027 (0.99–1.07)</td>
<td>0.22</td>
</tr>
<tr>
<td>Female</td>
<td>1.19 (0.55–2.57)</td>
<td>0.66</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.51 (0.18–1.48)</td>
<td>0.22</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.10 (0.51–2.38)</td>
<td>0.81</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.89 (0.36–2.21)</td>
<td>0.80</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.18 (0.55–2.52)</td>
<td>0.68</td>
</tr>
<tr>
<td>CT findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum aortic diameter‡</td>
<td>4.10 (2.02–8.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum false lumen diameter§</td>
<td>1.75 (0.93–3.27)</td>
<td>0.08</td>
</tr>
<tr>
<td>Appearance of ULP</td>
<td>7.05 (2.65–18.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Location of ULP in PD</td>
<td>7.35 (3.45–15.67)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Cox regression analysis.
† Per year; ‡ per 10-mm increment; § per 5-mm increment.
imaging studies due to thrombolysis of superficial thrombus. Previous studies demonstrated that newly developed ULP tended to lead to aortic enlargement and progression to overt dissection.7,12 Besides, ULP was reported to be significantly associated with a progressive disease course.11 Our results agreed with these reports indicating the importance of ULP. In the present study, newly developed ULP frequently occurred in the proximal descending aorta and the proximal location was of particular importance in the prediction of future aorta-related events. Thus, our results suggest that early intervention could be considered for patients with ULP in the proximal descending aorta.

Previous pathological or clinical studies demonstrated a “microtear” or small intimal communication in patients with AD with CTFL,21,22 which raised new issues concerning the “microtear” or small intimal communication in patients with AD with CTFL. The “microtear” may also cause development of new ULP. In the present study, we excluded patients who showed apparent longitudinal flow communication within thickened aortic wall or typical double-barreled false lumen in the initial CT images. However, patients with “microtear,” which was seen on the initial CT images as LCP, were included in the study population because complete identification of “microtear” in the entire aorta is not possible with current imaging modalities. Although “microtear” did not affect initial treatment plan in the present study, it may be a clue to clarify the pathogenesis of the study patients. Unfortunately, because surgery was not performed in most of our patients, we could not assess the prevalence and clinical importance of “microtear.” Further studies with newer imaging technologies would be necessary to clarify pathophysiological importance of “microtear” in AD with CTFL.

Endovascular treatment with a stent-graft has been recently considered as a less invasive alternative to open surgical graft replacement for patients with complicated type B AD.23–26 However, it is still controversial whether or not prophylactic stent-grafting can reduce the risk of late surgery or death among patients with initially uncomplicated type B AD or IMH.25,26 When aortic rupture is imminent, outcome of surgical treatment in terms of operative mortality and morbidity has not improved substantially in the past decades despite the progress of medical and surgical treatment.19,20 Considering a progressive disease course of newly developed ULP, prophylactic surgical or endovascular intervention may provide considerable benefit in these patients compared with conservative medical treatment.

Clinical Implications
On the basis of our data, patients with type B AD with CTFL generally have favorable long-term outcomes. However, patients with newly developed ULP should be more carefully followed up with serial CT or MRI examination than those without ULP because they frequently progress and require surgical or percutaneous aortic repair during follow-up. Moreover, ULP in the PD is the principal risk factor for progression. Among patients with type B AD with CTFL, the finding of new ULP development in PD may identify a high-risk group in whom prophylactic stent-grafting would be beneficial.

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Disclosures
None.

References


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