Prognosis of Aortic Intramural Hematoma With and Without Penetrating Atherosclerotic Ulcer
A Clinical and Radiological Analysis

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Background—Advances in imaging techniques have increased the recognition of aortic intramural hematomas (IMHs) and penetrating atherosclerotic ulcers (PAUs); however, distinction between IMH and PAU remains unclear. We intended to clarify differences between IMH coexisting with PAU and IMH not associated with PAU by comparisons of clinical features, imaging findings, and patient outcome to derive the optimal therapeutic approach.

Methods and Results—We performed a retrospective analysis of 65 symptomatic patients with aortic IMH. There were 34 patients with IMH associated with PAU (group 1) and 31 patients with IMH unaccompanied by PAU (group 2). Involvement of the ascending aorta (type A) was more frequent in group 2 (8 of 31, 26%), whereas most of the patients in group 1 had exclusive involvement of the descending aorta (type B) (31 of 34, 91%). Patients were subdivided into 2 categories, those with clinical progression and those with stable disease. Forty-eight percent of patients in group 1 and 8% in group 2 were in the progressive category (P=0.002). Clinical and radiological findings were compared between those group 1 patients who had a progressive disease course (n=12) and those who were stable (n=13). Sustained or recurrent pain (P<0.0001), increasing pleural effusion (P=0.0003), and both the maximum diameter (P=0.004) and maximum depth (P=0.003) of the PAU were reliable predictors of disease progression.

Conclusions—This study suggests a difference in disease behavior that argues for the prognostic importance of making a clear distinction between IMH caused by PAU and IMH not associated with PAU. IMH with PAU was significantly associated with a progressive disease course, whereas IMH without PAU typically had a stable course, especially when limited to the descending thoracic aorta. (Circulation. 2002;106:342-348.)

Key Words: aorta ▪ prognosis ▪ imaging ▪ atherosclerosis

Over the past decade, advances in vascular imaging technology have led to increasing recognition of aortic intramural hematomas (IMHs) in patients with acute aortic syndromes. Considered by many to be a variant of aortic dissection, the pathogenesis of IMH still remains unclear. Two different pathophysiological processes can lead to intramural hematoma formation. One is IMH without intimal disruption; in this entity, it is believed that spontaneous rupture of aortic vasa vasorum is responsible for hematoma formation within the aortic wall. The other type of IMH is associated with an atherosclerotic ulcer that penetrates into the internal elastic lamina and allows hematoma formation within the media of the aortic wall. Because the prognostic impact of the location of IMH and its standard treatment have been considered similar to those for classic aortic dissection. It is generally accepted that patients with type B (exclusive involvement of the descending aorta) IMH can be managed conservatively in the absence of disease progression, whereas early surgical interventions are recommended for type A (involvement of the ascending aorta) IMH. On the other hand, Coady et al recently reported that the prognoses of acutely symptomatic hospitalized patients with penetrating atherosclerotic ulcers (PAUs) was worse than those with classic aortic dissection due to a higher incidence of aortic rupture.

We reviewed 65 symptomatic patients with aortic IMH. Thirty-four patients had a PAU that was considered to be the cause of IMH, whereas 31 had no evidence of a PAU. The objective of this study was to clarify the differences between IMH associated with PAU and IMH without PAU in terms of...
Angiography, increased signal intensity of thickened aortic wall for MRI and no flow within the locally thickened aortic wall for CT. A post-contrast image shows no opacification of the thickened aortic wall. The arrow indicates internal deviation of the intimal calcification in the ascending and descending aortic wall (arrowheads). C, Contrast CT shows PAU and associated IMH (arrow). A GIU in the involved aorta (Figure, C). In the patients who had prominent atherosclerotic disease, tiny ulcerated lesions of a few millimeters in size were observed occasionally. These lesions often were accompanied by atheromatous plaques and intimal calcification and were typically recognized as an irregularity along the luminal surface of the aortic wall in contrast-enhanced CT images (Figure, D). These tiny ulcers were seen irrespective of the IMH extent and represented intimal atheromatous plaque ulcerations (11 cases in group 1 and 4 cases in group 2). They were easily distinguished from the typical appearance of a deeper PAU.

To evaluate any difference in the natural history of the disease between the 2 IMH groups, 49 of 65 patients were divided into 2 categories, those with a progressive disease process and those with stable disease. The other 16 patients (9 in group 1 and 7 in group 2) were excluded from this analysis because the observation of these patients was interrupted by an operation. A progressive disease course was defined as an increase in IMH size (longitudinal or radial) over the interval between imaging studies, evolution of the IMH to double-barreled dissection, or aortic rupture. A stable disease course was defined as an IMH that regressed spontaneously or had no interval change between imaging studies in an otherwise hemodynamically stable patient. The observation period was usually the extent of the index hospitalization; however, when pertinent follow-up information was available, it was included in the analysis.

**Indicators and Predictors of Disease Progression in Patients With IMH and PAU**

To identify the predictors of disease progression in patients with IMH associated with PAU, clinical and radiological findings were compared between those who had a progressive disease course (n=12) and those with stable disease (n=13). The clinical findings of age, sex, history of hypertension, extent of disease (Stanford classification), and presence of concomitant aortic aneurysm were evaluated. Each patient’s pain response to antihypertensive therapy was also analyzed. The imaging characteristics evaluated included the presence of pleural effusion at time of hospital admission and any interval radiological changes, including number, location, maximum diameter, and maximum depth of PAU, maximum diameter and maximum wall thickness of the aorta involved with IMH, and extent of IMH defined by aortic segments involved. In patients with multiple PAUs (n=7), the maximum diameter, depth, and location of the largest PAU were assessed.

**Statistical Analysis**

Data are expressed as mean±SD or as proportions. Comparisons between patients in group 1 and 2 and patients with progressive versus stable disease course were made with the χ² test for categorical variables and unpaired Student’s t test for continuous variables. A probability value <0.05 was considered statistically significant.
Results

Overall Patient Characteristics
The study population consisted of 34 men and 31 women with a mean age of 69 ± 9.5 years. Of the 65 patients, 60 (92%) had an acute IMH (admitted within 2 weeks of the onset of symptoms), and 5 (8%) had a chronic IMH (admitted >2 weeks after the onset of symptoms). Forty-six (71%) of the patients were transferred from other hospitals with a diagnosis of aortic IMH or suspected aortic dissection. No patient had a previous history of major trauma or the Marfan syndrome.

IMH With PAU Versus IMH Without PAU

Patient Characteristics
The clinical features of the patients in groups 1 and 2 are summarized in Table 1. Although not statistically significant (P = 0.08), the patients in group 1 were slightly older. Involvement of the ascending aorta (type A) was more frequent in group 2, whereas most of the patients in group 1 had type B morphology (P = 0.07). In terms of clinical history, there was no significant difference between the groups.

Morphological Features of IMH
The morphological features of IMH in group 1 and 2 patients are detailed in Table 2. Type A IMH was more frequent in group 2. There was no difference in the longitudinal extent of the IMH as represented by the numbers of involved aortic segments (P = 0.88).

Treatment and Prognosis
The treatment and clinical course of the patients in group 1 and 2 are summarized in Table 3.

Type A IMH in Group 1
Three patients underwent graft replacement of the ascending aorta within 4 days of the onset of symptoms, with 2 survivors.

Type A IMH in Group 2
Five patients underwent surgery within 4 days of their first symptoms. Four were successfully treated by ascending aortic graft replacement, and 1 patient died from septic complication 11 days after surgery.
Of the 31 patients with type B IMH in group 1, 17 (55%) were treated medically. In this subset, 3 deaths from progression of disease were observed at a mean of 9.3 days (range: 4 to 17 days) after the onset of symptoms. All 3 patients died from aortic rupture caused by a PAU.

Eight of 31 patients (26%) underwent graft replacement between 3 and 37 days (mean 9.6 days) after the onset of symptoms. Three had a ruptured PAU and 4 others had signs of impending rupture, eg, poorly controlled pain (n=4), increased mediastinal or pleural effusion (n=4), or increased PAU size (n=2).

Endovascular repair of PAU with stent-graft placement was performed in 6 (19%) of the 31 type B patients in group 1, between 1 and 49 days (mean: 17.5 days) after symptom onset. Stent-graft deployment was successful in all. One patient underwent emergency stent-graft placement for a ruptured PAU in the proximal descending aorta. Five patients showed signs of impending rupture, including persistent pain (n=4), increased pleural effusion (n=4), increased PAU size (n=1), and pseudoaneurysm formation (n=3). In all cases, the full extent of the PAU and pseudoaneurysm, but not the entire length of the IMH, were covered by the stent-graft. Pain and pleural effusion lessened in 5 patients. One patient died from a massive cerebral hemorrhage 3 days after the stent-grafting.

**In-Hospital Mortality**

Overall, the in-hospital mortality rate was 16% in group 1 and 19% in group 2. Disease progression was the cause of death in 4 patients (12%) in group 1 and 1 patient (3%) in group 2 (P=0.20).

**IMH Disease Course in Groups 1 and 2**

The natural history of IMH in both groups is shown in Table 4. An interval increase in IMH was observed in 5 patients with type B IMH in group 1, between 4 and 35 days (mean: 13.8 days) after initial symptom onset. This was related to progression of the PAU in all cases. There were no patients in group 2 who had an increase in IMH size.

Evolution to a classic double-barreled dissection occurred in 4 patients, including 1 with type A and 2 with type B IMH in group 1, and 1 patient with a type A IMH in group 2. This pathological evolution occurred between 2 and 7 days (mean 4.5) after the onset of symptoms. All 4 patients died: 3 from aortic rupture and 1 from an acute myocardial infarction related to the ascending aortic dissection.

Compared with group 2, patients in group 1 with IMH had a more progressive disease course (P=0.002). This was most

| TABLE 4. Disease Course of IMH in Group 1 and 2 Patients |
|------------|------------|------------|--------------|
|            | Group 1 (n=25) | Group 2 (n=24) | P      |
| Stable course | 13          | 22          |        |
| No change     | 11          | 20          |        |
| Regression    | 2           | 2           |        |
| Progressive course | 12 | 2 |        |
| Aortic rupture | 4           | 1           |        |
| IMH expansion | 5           | 0           |        |
| Propagation to double-barreled dissection | 3 | 1 |        |

* Patients who developed aortic rupture.
evident in those with a type B IMH (24 in group 1; 21 in group 2), where patients with an associated PAU clearly had more clinical progression \((P=0.002)\).

**Indicators and Predictors of Disease Progression in IMH Patients With PAU**

A comparison of clinical and radiological findings between PAU patients with progressive and stable disease is shown in Table 5.

**Clinical Factors**

Uncontrollable pain was a significant indicator of disease progression \((P=0.0001)\). Slightly more women than men had a stable disease course \((P=0.07)\). There were no significant differences in age, Stanford disease classification, or presence of hypertension or associated aortic aneurysm between the patients with a progressive disease course and those with a stable process.

**Radiological Factors**

Although pleural effusion was commonly seen in patients with either a progressive or stable IMH, an interval increase in the pleural effusion was a significant indicator \((P=0.0003)\) of progressive disease in those with a PAU. In terms of the initial size of the PAU, the maximum diameter and maximum depth in patients with progressive disease were \(21.1\pm8.0\) mm and \(13.7\pm4.2\) mm, respectively. Both values were significantly greater than those measured in patients with stable disease \((P=0.004\) and \(0.003\), respectively). If a threshold of \(20\) mm is used for maximum PAU diameter, the positive and negative predictive values for disease progression are \(100\%\) and \(71\%\), respectively. If a value for maximum PAU depth is set arbitrarily at \(10\) mm or greater, the positive and negative predictive values are \(80\%\) and \(88\%\), respectively. PAUs in patients with progressive disease were usually proximal \((P=0.01)\), with the proximal descending thoracic aorta being the most common site.

**TABLE 5. Comparison of Clinical and Radiological Features Between Patients With Progressive and Stable Disease Courses**

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Progressive Course (n=12)</th>
<th>Stable Course (n=13)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.0±7.6</td>
<td>71.8±10.9</td>
<td>0.84</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>7/5</td>
<td>3/10</td>
<td>0.07</td>
</tr>
<tr>
<td>Type A/B</td>
<td>1/11</td>
<td>0/13</td>
<td>0.29</td>
</tr>
<tr>
<td>Hypertension, yes/no</td>
<td>10/2</td>
<td>9/4</td>
<td>0.41</td>
</tr>
<tr>
<td>Aortic aneurysm, yes/no</td>
<td>3/9</td>
<td>6/7</td>
<td>0.27</td>
</tr>
<tr>
<td>Uncontrollable pain, yes/no</td>
<td>9/1</td>
<td>1/12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Radiological findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At initial diagnosis, yes/no</td>
<td>10/2</td>
<td>10/3</td>
<td>0.69</td>
</tr>
<tr>
<td>Interval change (increased/no change/decreased)</td>
<td>9/1/0</td>
<td>0/8/2</td>
<td>0.0003</td>
</tr>
<tr>
<td>Initial evaluation of PAU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum diameter of PAU, mm</td>
<td>21.1±8.0</td>
<td>11.6±4.0</td>
<td>0.004</td>
</tr>
<tr>
<td>Maximum depth of PAU, mm</td>
<td>13.7±4.2</td>
<td>7.4±3.5</td>
<td>0.003</td>
</tr>
<tr>
<td>Numbers of PAU</td>
<td>1.2±0.4</td>
<td>1.5±0.9</td>
<td>0.23</td>
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<tr>
<td>Location of PAU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asc</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Arch</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>MD</td>
<td>1</td>
<td>3</td>
<td>0.01</td>
</tr>
<tr>
<td>DD</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>SRA</td>
<td>0</td>
<td>1</td>
<td></td>
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<tr>
<td>Initial evaluation of aorta</td>
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<td></td>
<td></td>
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<tr>
<td>Maximum diameter of aorta, mm</td>
<td>48.1±4.3</td>
<td>46.3±9.7</td>
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<tr>
<td>Maximum thickness of aorta wall, mm</td>
<td>17.4±4.4</td>
<td>14.4±4.1</td>
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<td>IMH involved segment numbers</td>
<td>3.25±1.06</td>
<td>3.92±0.76</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Values are mean±SD or n. PAU indicates penetrating atherosclerotic ulcer; Asc, ascending aorta; PD, proximal descending thoracic aorta; MD, middle descending thoracic aorta; DD, distal descending thoracic aorta; and SRA, suprarenal abdominal aorta.
There were no significant differences in maximum aortic diameter and maximum aortic wall thickness over the extent of IMH, or in the number of involved aortic segments between those IMH patients with and without progressive disease ($P = 0.61$, $0.16$, and $0.08$, respectively).

**Discussion**

**History and Incidence of IMH**

Aortic IMH was first described in 1920 by Krukenberg as “dissection without intimal tear” and was considered a distinct entity at autopsy. In 1988, Yamada et al reported the CT and MRI findings of this condition. They predicted that the frequency of detection of this variant of aortic dissection would increase in the future as CT and MRI became more widely employed. Indeed, aortic IMH has been recognized increasingly more frequently in patients with acute aortic syndromes. In large autopsy series, the incidence of IMH in patients with aortic dissection is reported to range from 4% to 13%. In this series, 66 (9%) of 725 patients had an IMH, a frequency that is consistent with that reported from autopsy series.

**Comparison Between IMH With PAU and IMH Without PAU**

**Clinical Features**

Previous reports indicate that both IMHs and PAUs commonly affect elderly patients with a history of hypertension. Although the mean age of both groups of IMH patients is older than that for patients with classic dissection, the patients in group 1 were slightly older than those in group 2 (mean age: 71.0 and 66.9 years, respectively). Hypertension and concomitant thoracic and abdominal aortic aneurysm were commonly seen in both groups, with no apparent difference in incidence between groups 1 and 2.

There was a significant difference in the Stanford type of IMH between groups 1 and 2. Most of the patients in group 1 had a type B IMH (31 of 34, 91%). Type A IMH was slightly more common (8 of 31, 26%) in group 2 than in group 1 ($P = 0.07$). These results are consistent with previous reports that showed that a PAU is typically located in the descending thoracic aorta. In terms of the frequency of type A IMH without associated PAU, Coady et al reported that 5 (29%) of 17 patients had this finding, similar to the prevalence found in this study. Of note, there was no difference in the extent of IMH between groups 1 and 2.

**Treatment and Prognosis**

In many institutions, the standard therapy over the past decade for patients with type A IMH has been early surgical graft replacement. Therefore, most of the patients with a type A IMH in this study were treated surgically. As a result, the prognosis of patients with a type A IMH in both groups 1 and 2 was more favorable than that reported in other series where early operative repair was not performed.

In patients with a type B IMH, there was a significant difference in treatment and prognosis between groups 1 and 2. Twenty (87%) of the 23 type B patients in group 2 were treated exclusively by antihypertensive therapy without complications. In contrast, among the 17 patients in group 1 who were treated medically, there were 3 deaths from aortic rupture.

Among the 31 patients with a type B IMH in group 1, 8 underwent surgical intervention and 6 were treated with endovascular methods. Endovascular treatment with a stent-graft successfully covered the PAU in all 6 patients without early pseudoaneurysm formation. Given that PAUs tend to occur in elderly patients with severe atherosclerosis and other comorbidities that put them at high surgical risk, in our limited experience, this minimally invasive endovascular approach may have considerable advantages in this disease compared with conventional open surgical repair.

**Natural History of PAU**

There exists widespread confusion in the literature about disease behavior of the PAU. Stanson et al found PAUs to be malignant, but most of these patients had acutely symptomatic, Harris et al and Quint et al reported a lower incidence of life-threatening complications in a patient sample where asymptomatic patients were enrolled. The considerable difference in prognosis probably can be explained by the differences in patient substrate (symptomatic versus asymptomatic). In our series, all patients (group 1) were asymptomatic, and this may explain a higher incidence of disease progression. A more aggressive approach should be considered for acutely symptomatic patients.

**Relationship Between IMH and PAU**

In previous reports of IMHs, many investigators have identified PAUs as a cause of IMHs, whereas others have considered PAUs and IMHs to be distinct, unrelated entities. Indeed, a lack of agreement in the terminology used in the literature to describe IMH and PAU is clearly evident. Because our results suggest a major difference in prognosis according to whether the IMH coexists with PAU or without a PAU, it is important to distinguish these 2 types of IMH. Practically speaking, this differentiation must be made by imaging techniques because clinical separation is not possible.

**Indicators and Predictors of Disease Progression in Patients With PAU**

We are not aware of reports in which predictive factors of disease progression were investigated in patients with IMHs associated with a PAU. Persistent or recurrent pain despite aggressive treatment and an interval increase of pleural effusion were significant and important indicators of disease progression.

As for the implications of initial PAU size, maximum diameter and depth both correlated significantly with disease progression. Patients with a PAU that initially measured 20 mm or more in maximum diameter or 10 mm or greater in maximum depth have a high risk of disease progression and thus should be considered candidates for early surgical or endovascular repair.

In addition, it is apparent that not only PAUs in the ascending or arch but also those in the proximal descending aorta had a more malignant course ($P = 0.01$) compared with
that observed for PAUs in the middle and distal descending aorta. Possible explanations for this tendency include greater hemodynamic stress within the proximal aortic wall or a greater preponderance of elastin over collagen in the media of the proximal aorta compared with the descending thoracic aorta.\textsuperscript{18} Regardless of the exact pathophysiological mechanism, early aggressive treatment with either open surgical or endovascular stent-graft repair is prudent for patients with IMH and a proximal PAU, especially in those with uncontrollable pain and/or increasing pleural effusion.

Limitations of This Study
A weakness of this study is the lack of strict diagnostic uniformity in the patient selection. We defined a diagnostic criterion as “absence of a visible intimal flap or tear identified by any imaging technique,” however, because of differences in the relative abilities of each imaging modality to detect intimal disruption and the evolution in technology that has improved image resolution over the 10-year study period, the diagnostic data used to select patients in this study were not absolutely comparable. Thus, the validity of inferences made from results of this study is questionable.

Another limitation is related to the end points. We defined an IMH expansion as “an increase in IMH size over the interval between imaging studies,” and a stable disease course as one that “regressed spontaneously or had no interval change between imaging studies.” To reliably compare individual courses of disease, it is ideally necessary to predetermine the timing of imaging studies for the evaluation of interval changes. For example, it would be optimal if baseline studies were obtained at clinically equivalent starting points (eg, at the onset of symptoms), and then follow-up examinations performed at regular prescribed intervals. Because of the constraints imposed by the retrospective nature of this study, however, it is only possible to review studies performed at clinically required intervals.

Conclusions
This study suggests substantial differences in the clinical features and the patients’ prognoses in patients with an IMH caused by PAU and those with an IMH not associated with a PAU. Patients with IMH due to a PAU commonly had a progressive downhill clinical course, particularly when symptomatic, even when the IMH was limited to the descending thoracic aorta. In comparison, patients with an IMH without an ulcer were typically fairly stable, particularly when the IMH was limited to the descending aorta. Thus, these 2 types of IMH should be distinguished clinically and, more importantly, be managed differently. In terms of treatment for patients with an IMH without a PAU, most with a type B IMH can be treated conservatively with aggressive blood pressure control. On the other hand, those with a type A IMH should be treated with early surgical repair.\textsuperscript{5,6,15} When the IMH is associated with a PAU, urgent surgical aortic graft replacement should be considered not only for patients with a type A IMH, but also for those with a type B IMH, especially if persistent pain and/or interval increase in pleural effusion are present.

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References
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