Aortic intramural hemorrhage: A distinct disease entity with mystery

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1. Introduction

Aortic intramural hemorrhage (IMH), characterized by the absence of an intimal tear and thus of flow communication between the true and false lumen, is one of the disease processes that comprise the spectrum of acute aortic syndrome (AAS). IMH was first described by Krukenberg in 1920 as "aortic dissection (AD) without an intimal tear" (1). IMH is a hemorrhage into the medial layer and can propagate longitudinally or circumferentially, but it does not rupture into the lumen. IMH presents with symptoms similar to those of classic (typical) AD and may have similar morbidity and mortality rates (2,3), but the pathologic differences between IMH and AD are well established (Figure 1). IMH has a lower morbidity, but some aspects of IMH are still a mystery.

2. IMH: A precursor to classic dissection or a distinct disease entity?

It’s reported that IMH progressed to AD in 12-47% patients (4). IMH is associated with a clinical profile and prognosis similar to those of classic dissection, and the same treatment strategy was recommended for both IMH and AD (5,6). IMH was assumed to be a hyperacute stage of AD and a precursor to classic dissection, but in fact the pathology, etiology, and natural history of IMH and AD differ considerably (Table 1).

The location of an IMH within the media is quite different from AD. The distinguishing feature of IMH is its exterior location within the media near the adventitia, whereas AD extends into the media in closer proximity to the intima (7). Data from the International Registry of Acute Aortic Dissection (IRAD) have revealed that IMH tends to involve the descending aorta (42% type A IMH and 58% type B), in contrast to classic AD, which principally involves the ascending aorta (73% type A AD and 27% type B) (8). A similar conclusion was reached by Song et al. (9). The average age of patients presenting with intramural hematoma ranged from 58 to 71 years (median age: 68 years) (2,8,10-15), which is much older than the average of patients with classic AD (median age: 61 years) (16). The prevalence

**Summary**

Aortic intramural hemorrhage (IMH) is one of the disease processes that comprise the spectrum of acute aortic syndrome (AAS) with clinical manifestations and a mortality rate similar to those of classic aortic dissection (AD). However, IMH should be considered as a distinct disease entity rather than a precursor to classic dissection because of differences in their pathology, etiology, natural history, and imaging findings. Multidetector computed tomography (CT) is recommended as the first-line diagnostic imaging modality for IMH, but transesophageal echocardiography (TEE) and magnetic resonance imaging (MRI) are also helpful. There is still debate over the appropriate treatment of IMH. Medical treatment of type B IMH appears effective and safe, while surgical treatment is recommended for type A IMH. Thoracic endovascular aortic repair (TEVAR) is a promising treatment for selected patients, and more clinical evidence needs to be assembled.

**Keywords:** Aortic intramural hemorrhage, pathology, imaging, treatment
The prevalence of Marfan syndrome is significantly lower in patients with intramural hematoma (9). Symptoms of chest pain, frequently severe and abrupt, are noted in most patients with IMH or AD. Unlike patients with classic AD, patients with type A IMH are less likely to present with aortic regurgitation, and patients with IMH are less likely to present with pulse deficits (8). Pericardial effusions or cardiac tamponade are more likely to occur in patients with type A IMH than in those with type A AD (21% vs. 9%) (3,17). There are marked differences in the natural remodeling process in AD and IMH when medically treated (18,19). Without surgical intervention, the most common and expected remodeling process in AD is a persistent double-channel aorta with the frequent development of aortic aneurysm as a result of uninterrupted flow communication between the true and false lumen through an intimal tear. In IMH, a high rate of complete resorption of the initial aortic pathology is observed in imaging follow-up, which is unimaginable in AD.

All of this evidence supports the conjecture that IMH is a distinct disease entity rather than a precursor to classic dissection.

3. Epidemiology: Does IMH vary geographically and among ethnic groups?

AAS is rare, occurring in 2 to 3.5 per 100,000 person-years, and IMH varies widely as a form of AAS (20-22). In early studies, the incidence of IMH as a form of AAS appeared to differ geographically. South Korean and Japanese studies reported that its incidence generally ranged from 22.9% to 53% (3,18,23,24), whereas Western studies reported a lower incidence of 5.7-10% (8,10,21). This discrepancy may be due to ethnic or geographical differences. In addition, the lack of a uniform definition of IMH, as well as different methods of evaluation and treatment algorithms, may also account for this discrepancy. Moreover, most studies on IMH from Japan and South Korea are based on data from a few centers rather than an overall nationwide database, so the potential for publication bias should

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Table 1. Differences between aortic IMH and AD

<table>
<thead>
<tr>
<th>Items</th>
<th>IMH</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intimal flap</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>Communication between true and false lumen</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>Location within the media</td>
<td>exterior</td>
<td>interior</td>
</tr>
<tr>
<td>Descending aorta involvement</td>
<td>more</td>
<td>less</td>
</tr>
<tr>
<td>Epidemiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (y)</td>
<td>68</td>
<td>61</td>
</tr>
<tr>
<td>Prevalence of Marfan syndrome</td>
<td>lower</td>
<td>higher</td>
</tr>
<tr>
<td>Clinical manifestation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>less</td>
<td>more</td>
</tr>
<tr>
<td>Pulse deficits</td>
<td>less</td>
<td>more</td>
</tr>
<tr>
<td>Pericardial effusions</td>
<td>more</td>
<td>less</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>more</td>
<td>less</td>
</tr>
<tr>
<td>Natural history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete resorption</td>
<td>high rate</td>
<td>very low rate</td>
</tr>
</tbody>
</table>

AD, aortic dissection; IMH, intramural hemorrhage.
also be seriously considered. However, recent studies from China and South Korea have cast some doubt on this conclusion. Data from 1,812 patients at 19 large hospitals in China indicated that the incidence of IMH was 4.7% (25), while Cho et al. in South Korea reported an incidence of 10.7% (26). These rates seem to roughly coincide with the reported incidence in the West. Thus, there may be no geographic or ethnic variability in IMH.

4. Pathology: Due to rupture of the vasa vasorum or a micro intimal tear?

Early studies did not find a typical intimal tear or flow communication between the true and false lumen through the tear in patients with IMH, so the hemorrhage may be the result of a rupture of the vasa vasorum, a contention that is substantiated by computed tomography (CT) and transesophageal echocardiography (TEE) findings (27,28). However, there is little direct clinical or experimental evidence to substantiate this contention. Crescentic aortic wall thickening mimicking an intramural hemorrhage has been reported due to iatrogenic injury such as coronary angioplasty (29) or insertion of a balloon pump (30). Recent studies using more sensitive imaging modalities have identified intimal tears in many cases of IMH (31-34). Moreover, Park et al. (33) and Uchida et al. (31) found a small intimal communication at the time of surgery.

All of these findings indicate that IMH may originate from small intimal tears rather than a rupture of the vasa vasorum. Thus, the ACC/AHA guideline states that "When the term IMH is used strictly, no intimal defect such as a tear or an ulcer is present. But in practice, the term is used loosely to mean a thrombosed false lumen regardless of a small defect" (35). In Japan, IMH is referred to as "thrombosed-type aortic dissection" (31). As imaging sensitivity improves, the rate at which very small intimal tears are detected will continue to increase. If this occurs, the incidence of "true IMH" as has been reported may decline. In actual clinical practice, IMH should mainly be diagnosed based on imaging findings if surgical inspection or autopsy cannot be performed.

5. Imaging: Which modality to choose?

IMH is diagnosed based on imaging. Contemporary imaging modalities, such as magnetic resonance imaging (MRI), CT, and TEE are used to diagnose IMH. Each has its advantages and limitations in clinical practice.

5.1. CT

Because of its widespread availability, high spatial resolution, rapid examination time, and complete anatomic evaluation of the thoracoabdominal aorta and major branch vessels, CT scan is the most common diagnostic modality with which to diagnose IMH (22,36), with a negative predictive value of approximately 100% (37). The hallmark non-contrast multidetector CT (MDCT) finding of IMH is eccentric crescent-shaped thickening of the aortic wall with high attenuation (60–80 HU) (indicative of blood products), which extends in a longitudinal fashion (38-40). The thickened wall is typically > 7 mm and doesn't enhance following contrast medium injection. IMH is classified using the Stanford classification. IMH is Stanford type A if eccentric (crescent-shaped) to circumferential thickening and brightness of the aortic wall are observed in the ascending aorta on unenhanced CT images, and all other forms are classified as Stanford type B (8). MDCT with a systematically delayed phase and millimeter-thin slices can increase the rate at which intimal anomalies are detected (41). Some CT imaging finding may be related to the poor prognosis of IMH, such as intimal erosion measuring > 10 mm (41), ulcer-like projections (ULPs; also referred to as intimal erosions) (34,41-45), an aortic diameter (with different cutoff, ≥ 50 mm (46), ≥ 48 mm (47), ≥ 41 mm (48)), and an intramural hematoma thickness > 10 to 11 mm (4,41,44,45,49).

5.2. TEE

2D Transthoracic echocardiography (TTE) is not recommended for diagnosis of IMH (22); IMH can be detected and monitored with TEE but not with aortography (27,50). TEE has a sensitivity of 96.5-100% and a specificity of 91-98.5% in the diagnosis of IMH(12,16). TEE is superior to other imaging modalities because it allows direct observation of the aortic intima, and flow communication can be depicted with the Doppler technique. TEE is widely available, portable, convenient, fast, and it is exceptional at depicting pericardial effusion, the presence, degree, and mechanism(s) of aortic regurgitation, and LV function, which is important for unstable patients. Moreover, TEE can also be used in the operating room, facilitating early detection of IMH as well as possible complications (51). One characteristic TEE finding of IMH is the presence of an "echo-free space or echolucent area" within the thickened aortic wall (22). There is no Doppler evidence of communication between the hematoma and the true lumen, but there may be some color Doppler flow within the hematoma (22,52). Although TEE requires esophageal intubation, images are acquired at the bedside and can immediately be interpreted. In a limited number of patients, contrast injection helps to reveal direct flow communication through the microtear into the echo-free space (9). The main disadvantage of TEE is the "blind spot" of
the distal ascending aorta and proximal arch because of interposition of the air-filled trachea and the main bronchus (22,53). A further disadvantage is that TEE may also cause upper gastrointestinal injuries (54).

5.3. MRI

MRI has a sensitivity of approximately 100% in the diagnosis of IMH, and MRI has the advantage of a very high signal-to-noise ratio and a high contrast resolution with the ability to characterize the vascular wall far better than CT or TEE. However, MRI is less frequently used because of its relative lack of availability and longer scan time in comparison to CT (55). MRI is able to diagnose intramural bleeding in the acute phase (< 7 days) because the hematoma shows an isointense signal (black) on T1-weighted images (blood appears black) and a hyperintense signal (bright white) on T2-weighted images (blood appears white) (22). In contrast, a chronic IMH (> 7 days) on T1-weighted images appears hypointense (bright) as the hematoma evolves and degenerates, whereas a chronic IMH on T2-weighted images is less intense than an acute IMH (55,56). MRI can also be useful in follow-up. Ma et al. (57) reported a 6-year follow-up of a spontaneous IMH with a cardiovascular magnetic resonance examination.

5.4. Recommendation

In conclusion, CT is recommended as the first-line diagnostic imaging modality for IMH, particularly in the emergency room. TEE can be available at bedside or in the operating room. When findings on CT or TEE are equivocal, MRI may prove helpful.

6. Treatment: Medical treatment or surgical intervention, open surgery or thoracic endovascular aortic repair (TEVAR)

IMH is a potentially lethal condition with a mortality of 24% (36% with type A IMH and 12% with type B) (58). Studies have reported that the mortality of IMH is similar to that of classic AD (8,18,21). Twenty years of experience in Japan indicated that the 30-day mortality rate was 6% with emergent open surgery and 4% with supportive medical therapy; the actuarial survival rate of all patients was 96.3% at 1 year, 94.3% at 5 years, and 89.5% at 10 years (59). Medical treatment may alleviate an IMH by decreasing the hematoma thickness (59). All patients with IMH should receive initial medical therapy to control pain and blood pressure (level I, grade C) (36). TEVAR is safe and effective in treating IMH and also contributes to ideal remodeling of the affected aorta (60,61).

Overall consensus regarding a treatment strategy has yet to be reached. Medical therapy is recommended more often in Asia (62), while surgical treatment is recommended more often in Europe and the US (35,36). The clinical outcomes for treatment of IMH are shown in Table 2, and differences due to geography and

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Table 2. Reported outcomes for treatment of intramural hemorrhage (IMH)

<table>
<thead>
<tr>
<th>Country</th>
<th>Type A/B</th>
<th>Type A</th>
<th>Type B</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>0-23.5</td>
<td>(13,14,69)</td>
<td>(2,13,19,26,48,71,72)</td>
</tr>
<tr>
<td>Japan</td>
<td>4-23.5</td>
<td>0-165</td>
<td>10-165</td>
</tr>
<tr>
<td>South Korea</td>
<td>0-7.1</td>
<td>0-33.3</td>
<td>0-6.7</td>
</tr>
<tr>
<td>IRAD</td>
<td>4-90</td>
<td>14-59</td>
<td>2-5</td>
</tr>
<tr>
<td>Italy</td>
<td>3.8-7.8</td>
<td>23.7-42.9</td>
<td>5</td>
</tr>
<tr>
<td>France</td>
<td>/</td>
<td>/</td>
<td>15-15</td>
</tr>
<tr>
<td>Sweden</td>
<td>/</td>
<td>/</td>
<td>28.5</td>
</tr>
<tr>
<td>Germany MR</td>
<td>/</td>
<td>/</td>
<td>18</td>
</tr>
<tr>
<td>Austria</td>
<td>/</td>
<td>/</td>
<td>8</td>
</tr>
<tr>
<td>Canada</td>
<td>/</td>
<td>/</td>
<td>0</td>
</tr>
<tr>
<td>USA</td>
<td>/</td>
<td>/</td>
<td>6-44</td>
</tr>
<tr>
<td>Argentina</td>
<td>19</td>
<td>0</td>
<td>4-10</td>
</tr>
<tr>
<td>Classification</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Mortality in hospital; †† Mortality during follow-up. Germany MR: Germany Multicenter Registry.

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Stanford classification are evident.

The management of IMH depends on the clinical status of the patient and Stanford classification. Management will be difficult if one of the following aspects is present: persistence of chest pain despite medical treatment, hemodynamic instability, signs of an aortic rupture (periaortic hemorrhage), depth of ULP > 10 mm, maximum aortic diameter > 55 mm, or a rapid increase in the aortic diameter during hospitalization (63).

6.1. Type B

The mortality rate for initial medical treatment of type B IMH is 0-19% in hospital and 0-11.7% during follow-up (Table 2). The mean mortality rate related to aortic events was 5.4% within 3 years (63). Patients diagnosed with type B IMH were initially treated medically with beta blockers and other antihypertensive therapies. A study has reported a mortality rate of 8% for medical treatment and that type B IMH has a better prognosis without surgical intervention (58). Open surgical treatment of type B IMH results in a mortality rate of 0-20% in hospital and a mortality rate of 0-40% during follow-up (Table 2). The mean mortality rate is 23.2% within 3 years (63). TEVAR is an effective and promising way to manage IMH because it is relatively less invasive and causes fewer complications (13). A study on TEVAR has noted a mortality rate of 0-28.5% in hospital and a mean mortality rate of 7.1% within 3 years (63). Although TEVAR causes complication similar to those noted in other aortic diseases, endoleaks might occur more frequently when using TEVAR to treat an acute IMH (64,65).

Initial medical treatment is recommended for type B IMH with no complications (35,36). If comorbidities are present with type B IMH, the European Society of Cardiology (ESC) (36) and Mussa et al. (16) recommend TEVAR, but the 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines recommend surgery without distinguishing between open surgery and TEVAR (35).

6.2. Type A

The optimal initial treatment strategy for type A IMH may still be individualized. A study has reported a high mortality rate for type A IMH in hospital (26.6%) and a higher rate for medical treatment (40%) than for surgical treatment (24.1%) (8). A study in Japan indicated that 47.2% (17/36) of patients with type A IMH who received medical treatment also needed surgery. Urgent surgical repair is not necessary for all patients with type A IMH to achieve favorable surgical outcomes with careful follow-up using imaging (11). The mortality rate for initial medical treatment of type A IMH ranges from 4.3% to 40% in hospital and 11.8-40% during follow-up. Initial medical treatment and timed surgical therapy seem to be associated with a higher early mortality rate in patients with type A IMH, although the mortality rates did not differ significantly (14.4% vs. 10.1%, p = 0.36) (66). However, another study in Japan reported that medical treatment and timed surgical therapy resulted in no aortic dissection-related mortality and no aortic dissection-related events in patients who underwent surgical repair with a mean follow-up of 24.3 months (67). This suggests that type A IMH is more likely to progress, regardless of the diameter of the aorta, and, thus that prompt surgical repair should be performed (68). However, Uzuka et al. (67) recommended that emergency or urgent surgery not be considered for a hemodynamically stable patient unless the diameter of the ascending aortic was ≥ 50 mm or the thickness of the thrombosed false lumen was ≥ 10 mm. The mortality rate for open surgical treatment of type A IMH was 0-42.9% in hospital and 0-27.1% during follow-up (Table 2). The clinical use of TEVAR in selected patients with type A IMH resulted in good clinical outcomes (Table 2). This procedure offers low morbidity and mortality rates, representing a feasible therapeutic option especially for elderly patients with comorbidities.

Open surgery is recommended for type A IMH with comorbidities (16,35,36). Management of type A IMH with no comorbidities has yet to be determined, although Mussa et al. (16) recommended medical treatment.

7. Conclusion

IMH is one of the disease processes that comprise the spectrum of AAS with clinical manifestations and a mortality rate similar to those of classic AD. However, IMH should be considered as a distinct disease entity rather than a precursor to classic dissection. Imaging and surgical findings have revealed that a micro intimal tear may be the cause of IMH. IMH appeared to vary geographically and among ethnic groups, but recent studies have called that conclusion into question. MDCT is recommended as the first-line diagnostic imaging modality for IMH, while TEE and MRI are also helpful. There is still debate over the treatment for IMH. Medical treatment seems to be effective and safe for type B IMH, while surgical treatment is recommended for type A IMH. TEVAR is a promising treatment for selected patients, and more clinical evidence needs to be assembled.

Acknowledgements

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