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1. Introduction

1.1 The concept of immunoglobulin G4-related sclerosing disease

Immunoglobulin G4 (IgG4) is the rarest subclass of IgG, which is numbered 1 through 4 in the order of their discovery and serum concentration, and normally constitutes only 3 to 6% of the total IgG fraction (Oxelius, 2008). IgG4 antibody has unique structural and functional properties, and the production of IgG4 appears to be driven in part by T helper 2 (Th2) cytokines that mediate allergic responses and IgE production (Nirula et al., 2011). The presence of IgG4 autoantibody in bullous skin diseases and high serum IgG4 concentration in patients with atopic dermatitis, bronchial asthma and bullous skin diseases have indicated that IgG4 plays an important role in these diseases (Jones et al., 1988; Jarvis et al., 2007). However, little attention had been paid to IgG4, before Hamano et al. revealed that serum IgG4 concentration was markedly elevated in patients with sclerosing pancreatitis (also called autoimmune pancreatitis) in 2001 (Hamano et al., 2001). Moreover, the same group also reported that the lesions of sclerosing pancreatitis and retroperitoneal fibrosis had abundant infiltration of IgG4-positive plasma cells (Hamano et al., 2002). Since then, many extrapancreatic lesions that share the same histopathological and immunohistochemical features as autoimmune pancreatitis have been reported in various organs, and the distinct clinicopathological disease entity, termed “IgG4-related sclerosing disease”, was established, because irrespective of origin of the organ, these lesions show common clinicopathological features (Kamisawa & Okamoto, 2008; Cheuk & Chan, 2010).

1.2 Clinicopathological features of IgG4-related sclerosing disease

The characteristic clinical features of IgG4-related sclerosing disease are as follows: mostly middle-aged and elderly are affected, male predominance, multiple synchronous or metachronous lesions can be seen in different organs, and the presentation of the patients depend on the involved site(s).

Laboratory tests show that high serum IgG, IgG4, and IgE concentrations, and usually low titers of autoantibodies, such as antinuclear antibodies and rheumatoid factor. In particular, high serum IgG4 concentration (>135mg/dL) is the most important diagnostic factor of IgG4-related sclerosing disease.

Dramatic response to steroid therapy is another characteristic clinical finding of IgG4-related sclerosing disease; a decline in the serum IgG4 level and a reduction of lymphocytes
and IgG4-positive plasma cells in the involved tissues are frequently observed (Cheuk & Chan, 2010) (Table 1).

<table>
<thead>
<tr>
<th>Age</th>
<th>Mostly middle-aged and elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male predominance</td>
</tr>
<tr>
<td>Presentation</td>
<td>Symptom due to involved site(s) (usually mass formation)</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td>Elevated IgG, IgG4 and IgE, especially IgG4 (&gt;135mg/dL)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Dramatic response to steroid therapy</td>
</tr>
</tbody>
</table>

Table 1. Clinical features of IgG4-related sclerosing disease

Pathologically, IgG4-related sclerosing disease is usually non-circumscribed and can extend into the surrounding tissues. The triad of pathological features of IgG4-related sclerosing disease is dense lymphoplasmacytic infiltration, sclerosis and obliterative phlebitis (Cheuk & Chan 2010) (Table 2). The variable proportion of the lymphoplasmacytic infiltrates and sclerosis in each case is responsible for the spectrum of histopathological patterns, such as pseudolymphomatous, mixed and sclerosing types (Cheuk & Chan, 2010).

In the pseudolymphomatous type, the presence of dense lymphocytes and plasma cells without atypia are the predominant features, and reactive lymphoid follicles are commonly observed. Eosinophil infiltration is also occasionally seen. The mixed pattern, which is the most common histological subtype of IgG4-related sclerosing disease, is characterized by the presence of patchy dense lymphoplasmacytic infiltration and sclerosis. Lastly, the sclerosing type is characterized by the predominance of sclerosis with patchy aggregates of lymphocytes and plasma cells.

The presence of obliterative phlebitis, which represents veins affected by segmental or circumferential transmural lymphoplasmacytic infiltrates, resulting in luminal occlusion, is also a characteristic finding of IgG4-related sclerosing disease.

Immunohistochemical studies revealed abundant IgG4-positive plasma cell infiltration, and the ratio of IgG4-/IgG-positive plasma cells is usually up to 40% (Cheuk & Chan 2010).

| a) Lymphoplasmacytic infiltration with/without lymphoid follicles and frequent eosinophil infiltration |
| b) Sclerosis |
| c) Obliterative phlebitis |
| d) No myofibroblast proliferation |
| e) Abundant IgG4-positive plasma cell infiltration |
| f) The ratio of IgG4-/IgG-positive plasma cells >40% |

Table 2. Pathological features of IgG4-related sclerosing disease

1.3 The spectrum of IgG4-related sclerosing disease

The concept of IgG4-related sclerosing disease has been expanded to include various organs since the first identification in the pancreas (autoimmune pancreatitis). Many extrapancreatic organs, such as bile duct (Zen et al., 2004), liver (Zen et al., 2004), salivary gland (Kitagawa et al., 2005), lacrimal gland (Sato et al., 2008), lung (Zen et al., 2005), breast (Zen et al., 2005), kidney and urinary tract (Watson et al., 2006; Cornell et al., 2007; Kim et al., 2011), prostate (Nishimori et al., 2007), retroperitonum (Hamano et al., 2002),
central nervous system (Chan et al., 2009; Shimatsu et al., 2009), thyroid (Li et al., 2011), nasal cavity (Ishida et al., 2009; Moteki et al., 2010), skin (Cheuk et al., 2009) and lymph node (Cheuk et al., 2008; Sato et al., 2010) (Table 3), have been shown to have the same histopathological findings and abundant IgG4-positive plasma cell infiltration as autoimmune pancreatitis. In addition, recently, a part of inflammatory aortic aneurysm has been regarded as a spectrum of IgG4-related sclerosing disease (Kasashima et al., 2008, 2009, 2010; Ishida et al., 2009). Multiple synchronous or metachronous lesions can be seen in different organs in the patients with IgG4-related sclerosing disease.

<table>
<thead>
<tr>
<th>Pancreas</th>
<th>Autoimmune pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile duct</td>
<td>Sclerosing cholangitis</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>Sclerosing cholecystitis</td>
</tr>
<tr>
<td>Liver</td>
<td>Inflammatory pseudotumor, hepatitis</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>Sclerosing sialadenitis (Küttner's tumor)</td>
</tr>
<tr>
<td>Lacrimal gland</td>
<td>Sclerosing dacryoadenitis (Mickulicz’s disease)</td>
</tr>
<tr>
<td>Nasal cavity</td>
<td>Inflammatory pseudotumor, rhinosinusitis</td>
</tr>
<tr>
<td>Lung</td>
<td>Inflammatory pseudotumor (plasma cell granuloma), interstitial pneumonia</td>
</tr>
<tr>
<td>Breast</td>
<td>Sclerosing mastitis</td>
</tr>
<tr>
<td>Kidney and urinary tract</td>
<td>Tubulointerstitial nephritis, inflammatory pseudotumor</td>
</tr>
<tr>
<td>Prostate</td>
<td>Prostatitis</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Hypophysitis, sclerosing pachymeningitis</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Hashimoto’s thyroiditis</td>
</tr>
<tr>
<td>Aorta</td>
<td>Inflammatory aortic aneurysm</td>
</tr>
<tr>
<td>Retroperitoneum</td>
<td>Retroperitoneal fibrosis</td>
</tr>
<tr>
<td>Skin</td>
<td>Cutaneous pseudolymphoma</td>
</tr>
<tr>
<td>Lymph node</td>
<td>Lymphadenopathy</td>
</tr>
</tbody>
</table>

Table 3. The spectrum of IgG4-related sclerosing disease

2. IgG4-related inflammatory aortic aneurysm

Inflammatory aortic aneurysm (IAA), first described by Walker et al. in 1972, is a distinct clinicopathological entity (Walker et al., 1972). They reported that approximately 10% of 187 patients undergoing resection of abdominal aortic aneurysm was IAA. The key distinguishing features of IAA from atherosclerotic aortic aneurysm are as follows: a) marked thickening of the aortic wall, b) fibrosis of the adjacent retroperitoneum, and c) rigid adherence of the adjacent structures to the anterior aneurysmal wall (Walker et al., 1972). Histopathologically, IAA of the abdominal aorta shows a striking fibrosclerotic change in the adventitia with dense lymphoplasmacytic infiltration (Hellmann et al., 2007). Patients with IAA of the abdominal aorta are younger than patients with atherosclerotic abdominal aortic aneurysm (Paravastu et al., 2009). The clinical symptoms are usually non-specific, such as abdominal and back pain, fever, and general fatigue (Paravastu et al., 2009). Laboratory tests reveal that white blood counts and C-reactive protein levels are usually elevated (Walker et al. 1972). Elevated serum IgG concentration and the presence of
autoantibodies are also frequently observed in the patients with IAA of the abdominal aorta (Vaglio A et al., 2003; Jagadesham et al., 2008) IAA preferentially develops in the infrarenal abdominal aorta, and their presence in the ascending aorta and aortic arch is extremely rare (Ishida et al., 2009).

In 2008, Kasashima et al. proposed that IAA of the abdominal aorta can be divided into two subgroups: “IgG4-related” and “non-IgG4-related” (Kasashima et al., 2008). They reported that 4 of 10 patients with IAA of the abdominal aorta had high serum IgG concentration and abundant IgG4-positive plasma cell infiltrates in the aneurysmal wall, which are identical to the clinicopathological features of IgG4-related sclerosing disease. Henceforth, IgG4-related IAA of the thoracic aorta have also been reported (Ishida et al., 2009; Kasashima et al., 2010)

2.1.1 Abdominal aortic aneurysm

As shown Kasashima et al., there are clinicopathological differences between IgG4-related and non-IgG4-related IAA of the abdominal aorta (Kasashima, et al. 2008, 2009). With regard to incidence rate, IgG4-related IAA of the abdominal aorta accounts for 5% of all surgically resected abdominal aortic aneurysms, and 57% of IAA of the abdominal aorta (Kasashima et al. 2009).

<table>
<thead>
<tr>
<th>Age/Gender</th>
<th>No difference</th>
<th>No difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneurysmal diameter</td>
<td>More frequency of abdominal or back pain in non-IgG4-related cases</td>
<td>More frequent in IgG4-related cases</td>
</tr>
<tr>
<td>Symptom</td>
<td>More frequent in IgG4-related cases</td>
<td>(food or drug allergy, bronchial asthma and rheumatoid arthritis)</td>
</tr>
<tr>
<td>History of autoimmune and allergic diseases</td>
<td>No difference</td>
<td>Markedly higher in IgG4-related cases</td>
</tr>
<tr>
<td>Serum IgG</td>
<td>Higher in IgG4-related cases</td>
<td>Thicker in IgG4-related cases</td>
</tr>
<tr>
<td>Serum IgG4</td>
<td>More numerous in IgG4-related cases</td>
<td>More higher in IgG4-related cases</td>
</tr>
<tr>
<td>Serum IgE</td>
<td>More higher in non-IgG4-related cases</td>
<td>More frequent in IgG4-related cases</td>
</tr>
<tr>
<td>Adventitial thickening</td>
<td>More frequent in IgG4-related cases</td>
<td>More frequent in IgG4-related cases</td>
</tr>
<tr>
<td>IgG-positive cells</td>
<td>More frequent in IgG4-related cases</td>
<td>More frequent in IgG4-related cases</td>
</tr>
<tr>
<td>IgG4-positive cells</td>
<td>More frequent in IgG4-related cases</td>
<td>More frequent in IgG4-related cases</td>
</tr>
<tr>
<td>IgG4/IgG cells ratio</td>
<td>More frequent in IgG4-related cases</td>
<td>More frequent in IgG4-related cases</td>
</tr>
<tr>
<td>Neutrophils infiltration</td>
<td>More frequent in IgG4-related cases</td>
<td>More frequent in IgG4-related cases</td>
</tr>
<tr>
<td>Eosinophils infiltration</td>
<td>More frequent in IgG4-related cases</td>
<td>More frequent in IgG4-related cases</td>
</tr>
<tr>
<td>Lymphoid follicles</td>
<td>More frequent in IgG4-related cases</td>
<td>More frequent in IgG4-related cases</td>
</tr>
<tr>
<td>Obliterative phlebitis</td>
<td>More frequent in IgG4-related cases</td>
<td>More frequent in IgG4-related cases</td>
</tr>
</tbody>
</table>

Table 4: Clinicopathological differences between IgG4-related and non-IgG4-related inflammatory aortic aneurysms of the abdominal aorta.

Clinically, there are no differences in patient age, gender and aneurysmal diameter between IgG4-related and non-IgG4-related IAAs, however, IgG4-related cases are characterized by less frequent association with abdominal or back pain. The history of autoimmune diseases (such as rheumatoid arthritis and idiopathic thrombocytopenic purpura), bronchial asthma and food or drug allergy are more frequent in IgG4-related cases than non-IgG4-related cases. Characteristically, serum IgG4 concentration is significantly elevated in IgG4-related
cases (>135 mg/dL), although serum IgG concentration is not different in both groups. In addition, IgE concentration is higher in IgG4-related cases. Aneurysmal rupture is more common in non-IgG4-related cases, because severe thickening of the aneurysmal wall and adhesion to the surrounding tissue may prevent rupture in IgG4-related cases (Kasashima et al., 2010) (Table 4).

Most reported cases of IgG4-related IAA of abdominal aorta have no association with other IgG4-related sclerosing diseases, however, some cases of IgG4-related IAA of the abdominal aorta with autoimmune pancreatitis have been reported (Ito et al., 2008; Tseng et al., 2009; Matsuki et al., 2010).

Pathologically, IgG4-related IAA fundamentally has the similar histopathological findings of IgG4-related sclerosing disease. IgG4-related IAA is characterized by significant thickening of the adventitia more so than non-IgG4-related cases (Figure 1), although all IAA cases generally have marked thickening of the adventitia (Figure 6). In IgG4-related cases, dense lymphoplasmacytic infiltrates with lymphoid follicles are observed in the adventitia (Figure 2). Eosinophil infiltration and perineural lymphoplasmacytic infiltration are common findings of IgG4-related cases (Figure 3), however, neutrophil infiltration is rarely seen. In contrast, neutrophil infiltration is occasionally seen in non-IgG4-related cases. In most IgG4-related cases, obliterative phlebitis, one of the characteristic findings of IgG4-related sclerosing disease, is present in the adventitia (Figure 4), although obliterative phlebitis is also observed in some non-IgG4-related cases, but at much lower frequency.

Atherosclerotic change is also observed in IgG4-related cases, because both IgG4-related and non-IgG4-related IAAs commonly affect middle-aged to elderly persons. However, atherosclerotic intimal thickening is more intense in non-IgG4-related cases (Kasashima et al., 2010).

Immunohistochemically, abundant IgG4-positive plasma cell infiltrate is observed in the adventitia of IgG4-related IAA (Figure 5), in contrast to non-IgG4-related IAA, which harbor only a few IgG4-positive plasma cells (Figure 7). The ratio of IgG4-/IgG-positive plasma cells is markedly higher in IgG4-related cases (usually >60%) as compared to non-IgG4-related cases (Kasashima et al., 2009).
Fig. 2. Histopathological findings of IgG4-related inflammatory aortic aneurysm (H.E. stain). Lymphoplasmacytic infiltration and sclerosis in the adventitia.

Fig. 3. Histopathological findings of IgG4-related inflammatory aortic aneurysm (H.E. stain). Perineural lymphoplasmacytic infiltration is occasionally observed.
Fig. 4. Elastica van Gieson stain clearly showing obliterative phlebitis in the adventitia in IgG4-related inflammatory aortic aneurysm.

Fig. 5. Immunostaining for IgG4 in IgG4-related inflammatory aortic aneurysm. Abundant IgG4-positive plasma cell infiltration.
Fig. 6. Histopathological findings of non-IgG4-related inflammatory aortic aneurysm (H.E. stain). Lymphoplasmacytic infiltration and sclerosis are shown in the adventitia.

Fig. 7. Immunostaining for IgG4 in non-IgG4-related inflammatory aortic aneurysm. Only a few IgG4-positive plasma cells are detected in the adventitia.
2.1.2 Thoracic aortic aneurysm

In 2009, IgG4-related IAA of the aortic arch was first reported, and this report suggested that IgG4-related aortic lesion can occur in the thoracic aorta, as a counterpart of IgG4-related IAA of the abdominal aorta (Ishida et al., 2009). Since then, subsequent studies have revealed the clinicopathological features of IgG4-related lesions of the thoracic aorta. IgG4-related thoracic aortic lesions often represent aneurysmal cases, and several cases of lymphoplasmacytic aortitis without dilatation of the aorta are included in this entity, which may represent an early phase of IgG4-related aortic aneurysm (Kasashima et al., 2010; Stone et al., 2010). Kasashima et al. reported that 4% of all surgically resected thoracic aortic lesions (which corresponded to 7% of thoracic aortic aneurysm) was IgG4-related. (Kasashima et al., 2010). These cases included inflammatory aneurysm, lymphoplasmacytic aortitis, and atherosclerotic aneurysms (Kasashima et al., 2010). Stone et al. reported that IgG4-related sclerosing lesions of thoracic aorta accounted for 9% of noninfectious thoracic aortitis and 75% of lymphoplasmacytic aortitis (Stone et al., 2010). These patients show similar clinical features to IgG4-related IAA of the abdominal aorta with a predilection for elderly males, medical history of bronchial asthma and allergy, and elevated white blood cell count and C-reactive protein levels. IgG4-related aortic aneurysm of the thoracic aorta develops frequently in the aortic arch and saccular form aneurysm (Kasashima et al., 2010). In addition, fibrous adherence to the surrounding tissue is more frequent as compared to non-IgG4-related cases (Kasashima et al., 2010).

Pathologically, IgG4-related IAA of the thoracic aorta also shows similar findings to IgG4-related IAA of the abdominal aorta including thickening of the adventitia, dense lymphoplasmacytic infiltration, obliterative phlebitis, frequent eosinophil infiltration, lymphoid follicle formation, and infrequent neutrophil infiltration. Immunohistochemically, abundant IgG4-positive plasma cell infiltration and high ratio of IgG4-/IgG-positive plasma cells (>60%) are observed (Ishida et al., 2009; Kasashima et al., 2010). Interestingly, aortic dissection has been reported as one manifestation of IgG4-related lesions in the thoracic aorta (Stone et al., 2009, 2010). In such case, inflammation is denser in the media than in the adventitia, and medial laminar necrosis is also observed (Stone et al., 2009, 2010).

Some cases of IgG4-related lesions of the thoracic aorta associated with other IgG4-related sclerosing lesions, such as pancreas, submandibular gland and lymph node, have been reported (Stone et al., 2010).

2.2 Diagnostic criteria for IgG4-related IAA

The diagnostic criteria for IgG4-related IAA of the abdominal aorta have been previously outlined (Kasashima et al., 2009), and a recent study have found that these criteria may also be appropriate for IgG4-related thoracic aortic aneurysm (Kasashima et al., 2010).

a. Diffuse fibrous thickening of the adventitia (>4mm)

b. Abundant lymphoplasmacytic infiltrates

c. Numerous IgG4-positive plasma cells (60/ high-power fields)

d. Ratio of IgG4-/IgG-positive plasma cells >60%
Takayasu arteritis must be taken into consideration during diagnosis of IgG4-related IAA of the thoracic aorta. Takayasu arteritis is well known as a “pulseless disease”, which chiefly strikes young women, especially in Asian and South American countries, and mainly involves the ascending aorta, aortic arch, and their main branches, leading to the characteristic clinical findings of pulselessness and ophthalmic and/or cerebral disorders (Numano et al., 2000). Histopathologically, Takayasu arteritis is characterized by involvement of all three layers of the arterial wall, thickened adventitia with lymphocyte and histiocyte infiltrates, destruction of smooth muscles and elastic fiber network of the medina, occasional medial necrosis and intimal fibrosis and/or atherosclerotic changes (Numano, 2000). The inflammatory process appears to begin at the vaso vasorum in the adventitia and these inflammatory processes result in stenosis of vessel lumina and sometimes induce aneurysmal formation (Numano, 2000). IgG4-related IAA does not show vascular stricture and stenosis. Thus, the differential diagnostic features include patient’s age, histopathological findings, especially involvement of all three arterial wall layers found only in Takayasu arteritis, and immunohistochemical findings for IgG4. In addition, epithelioid granuloma, giant cells, and fibrinoid necrosis are extremely rare in IgG4-related IAA (Kasashima et al. 2010).

Syphilitic aortitis is also included in the differential diagnosis, because it is also characterized by frequent aneurysmal formation and lymphoplasmacytic infiltration in the adventitia. Lymphoplasmacytic infiltration accompanying destruction of the medina and endarteritis obliterans of the vaso vasorum are usually observed in syphilitic aortitis (Heggteviet 1962), but not in IgG4-related IAA. The serological examination for Treponema pallidium agglutination is also useful.

| a) Non-IgG4-related IAA | b) Takayasu arteritis | c) Syphilitic arteritis |

Table 5. Chief differential diagnoses of IgG4-related IAA

3. The association with chronic periaortitis

Chronic periaortitis encompasses idiopathic retroperitoneal fibrosis, IAA and perianeurysmal retroperitoneal fibrosis (Jois et al., 2004). The histopathological characteristic are identical, which include periaortic fibrosis with extension to involve the adjacent structure, and lymphoplasmacytic infiltration in the aortic adventitia. These characteristic histopathological findings also correspond to IgG4-related sclerosing disease, and abundant IgG4-positive plasma cells infiltration is also observed in chronic periaortitis. Therefore, both retroperitoneal fibrosis and IgG4-related IAA of the abdominal aorta are recognized as a manifestation of “IgG4-related chronic periaortitis” (Kasashima et al., 2008, 2011), together with mediastinal fibrosis and IgG4-related IAA of the thoracic aorta (Ishida et al., 2009; Kasashima et al., 2011).

4. Treatment of IgG4-related IAA

Dramatic response to steroid therapy is the characteristic clinical finding of IgG4-related sclerosing disease. It is speculated that steroid therapy may be also effective in IgG4-related IAA, because adventitial thickening and fibrous adhesion to the surround organs may be
reduced (Kasashima et al., 2009). However, most of the reported cases of IgG4-related IAA were surgically resected cases, therefore, steroid therapy was not administrated and no data is available.

Recently, some cases of IgG4-related IAA in whom steroid therapy could reduce the aneurysmal wall thickening and fibrous adhesion of IAA, have been reported (Kasashima et al., 2010; Yabe et al., 2010). However, it must be considered that the risk of aneurysmal rupture might be elevated by the thinning of the adventitia. Additional clinicopathological studies are required to establish the treatment strategy for IgG4-related IAA.

Finally, multiple metachronous or synchronous development is one of the characteristic findings of IgG4-related sclerosing disease, therefore, systemic surveillance and follow-up are required in cases of IgG4-related IAA.

5. Conclusion

IgG4-related sclerosing disease is a distinct clinicopathological entity and may manifest as IAA of the thoracic and abdominal aorta. IgG4-related IAA shows characteristic clinical features, and histopathological diagnostic criteria of IgG4-related IAA have been recently proposed. However, further studies are needed to clarify the spectrum of IgG4-related vascular lesions and treatment strategy of IgG4-related IAA.

6. References


Etiology, Pathogenesis and Pathophysiology of Aortic Aneurysms and Aneurysm Rupture


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This book considers mainly etiology, pathogenesis, and pathophysiology of aortic aneurysms (AA) and aneurysm rupture and addresses anyone engaged in treatment and prevention of AA. Multiple factors are implicated in AA pathogenesis, and are outlined here in detail by a team of specialist researchers. Initial pathological events in AA involve recruitment and infiltration of leukocytes into the aortic adventitia and media, which are associated with the production of inflammatory cytokines, chemokine, and reactive oxygen species. AA development is characterized by elastin fragmentation. As the aorta dilates due to loss of elastin and attenuation of the media, the arterial wall thickens as a result of remodeling. Collagen synthesis increases during the early stages of aneurysm formation, suggesting a repair process, but resulting in a less distensible vessel. Proteases identified in excess in AA and other aortic diseases include matrix metalloproteinases (MMPs), cathepsins, chymase and others. The elucidation of these issues will identify new targets for prophylactic and therapeutic intervention.

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