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Aortitis and Aortic Aneurysm in Systemic Vasculitis

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1. Introduction

Vasculitis encompasses a heterogeneous group of disorders characterized by inflammation of blood vessels. Inflammation affects vessels of any type and size, and causes a wide range of clinical manifestations, depending on the vascular bed involved. The preferential size of involved vessels and the targeted tissues determine the clinical presentation and serve as key elements for classification (Watts & Scott, 2009). Vasculitis may occur as a primary process or may be secondary to an underlying disease such as infection, malignancy or other systemic autoimmune or chronic inflammatory diseases. Blood vessel inflammation results in abnormal vascular remodelling with the potential of severe clinical consequences. In some instances, inflammation leads to intimal hyperplasia resulting in vascular stenoses and ischemia of the tributary tissues. In other settings, inflammation causes disruption of the vessel wall architecture leading to aneurysm formation and eventual dissection or rupture.

Aortitis is the term used to define inflammation of one or more layers of the aortic wall and may have an infectious or non-infectious origin (Gornik & Creager, 2008). Non-infectious aortitis is usually part of the spectrum of vascular involvement occurring in primary large-vessel vasculitis including giant-cell arteritis (GCA) of the elderly and Takayasu's arteritis (TAK). Aortitis is a major component of these diseases and may lead to severe complications including aortic aneurysm, dissection or stenosis.

Aortitis may also present as a circumscribed condition named isolated aortitis. This term refers to aortitis incidentally found at the time of histopathological examination of aortas obtained from necropsy studies or from patients who have undergone surgical repair of aortic aneurysm or aortic valve replacement. Existing studies are retrospective and most patients have not been prospectively and systematically evaluated in search for a systemic vasculitis or other chronic inflammatory diseases. There is some controversy about whether isolated aortitis is a specific condition or represents an incomplete view of a systemic disease.

Occasionally, aortitis may occur in the setting of other primary systemic vasculitis, particularly antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (Chirinos et al., 2004; Lee et al., 2008), and other autoimmune disorders or chronic inflammatory diseases (i.e. sarcoidosis, Crohn's disease, ankylosing spondylitis, Behçet's disease, Cogan's disease, and IgG4-related disease) (Domenech et al., 2005; Gluth et al., 2006; Palazzi et al.,

2010; Stone, 2011; Weiler et al., 2000; Okada et al., 1997). The main causes of primary and secondary aortitis are summarized in table 1.
Chronic periaortitis is an additional form of aortic inflammation that encompasses a variety of conditions and is characterized by inflammatory involvement of the outer layer of the aorta and surrounding tissues. Chronic periaortitis may occasionally occur in patients with small-medium sized vessel vasculitis.
This chapter will particularly focus on aortic inflammation and its consequences in the context of the primary large-vessel vasculitis.

NON INFECTIOUS AORTITIS	
Primary vasculitis	
Large-vessel vasculitis	Giant-cell arteritis Takayasu's arteritis
Other vasculitis	Granulomatosis with polyangiitis (Wegener's) Microscopic polyangiitis
Vasculitis associated with chronic inflammatory or autoimmune conditions	
	Rheumatoid arthritis Sarcoidosis Systemic lupus erythematosus Behçet disease Cogan syndrome HLA-B27 associated spondyloarthropaties Crohn's disease Relapsing polychondritis IgG4-related disease
Isolated aortitis	
Chronic periaortitis	
	Retroperitoneal fibrosis Inflammatory abdominal aortic aneurysm Perianeurysmal aortitis
INFECTIOUS AORTITIS	
Bacterial	*Salmonella spp* *Staphylococcus spp* *Streptococcus pneumoniae* *Treponema pallidum spp*
Mycobacterial	*Mycobacterium tuberculosis*

Table 1. Causes of aortic inflammation

2. Aortic inflammation in primary systemic vasculitis

2.1 Vasculitis leading to aortic inflammation

Primary large-vessel vasculitis encompasses GCA and TAK which represent the most common disorders associated with non-infectious aortitis. Although histologically similar, GCA and TAK are considered distinct disease entities based on demographic and clinical features. While GCA affects aged people and is usually associated with cranial symptoms, TAK predominantly affects patients younger than 40 years, primarily involves the aorta and its major branches but generally spares the cranial arteries. These features usually allow a clear clinical differentiation between these two vasculitides. However the increasing recognition of large-artery involvement in GCA during the past decade widens the overlap features between both entities and some authors suggest that they may be part of the spectrum of a single disorder (Maksimowicz-McKinnon & Hoffman, 2009).

2.1.1 Giant-cell arteritis

GCA is a systemic vasculitis involving large and medium sized vessels in patients older than 50 years. The preferential involvement of the cranial arteries determines the classical symptoms of GCA (headache, jaw claudication, scalp tenderness) and its more frequent vaso-occlusive complication (visual loss usually due to anterior ischemic optic neuritis). About half of the patients have polymyalgia rheumatica and the majority have prominent systemic symptoms (fever, anemia of chronic disease type, and weight loss) and elevation of acute phase reactants.

Although early descriptions of GCA identified the cranial arteries as the main target of the disease, subsequent reports indicated more widespread vascular involvement (Hunder, 2006). First report of aortic involvement was in 1937 (Sproul & Hawthorne, 1937) and described post-mortem chronic diffuse inflammation with giant cells in the aorta and iliac arteries of two men without apparent premortem symptoms of vasculitis. Over the following years, additional cases were reported (Bonnin & Lander, 1956; Cardell & Hanley, 1951; Cooke & Cloake, 1946; Heptinstall et al., 1954) confirming the potential of GCA to involve large-vessels.

In 1972 Ostberg (Ostberg, 1972) systematically investigated the aorta and its major branches in necropsies from 13 patients with GCA. Inflammatory involvement of the aorta was present in 12 out of the 13 patients (90%). Although the necropsy nature of this survey may be biased towards the inclusion of more severe cases, these findings suggest that aortic involvement might be frequent in GCA.

More recently, other authors have investigated the prevalence of aortitis in specimens obtained from patients who underwent aortic reconstructive surgery because of aortic aneurysm, aortic dissection or aortic valve insufficiency. Table 2 summarizes the main findings of these studies (Burke et al., 2008; Gelsomino et al., 2005; Homme et al., 2006; Kerr et al., 2000; Liang et al., 2009; Miller et al., 2006; Nesi et al., 2009; Pacini et al., 2008; Rojo-Leyva et al., 2000). Histopathologic analysis of removed aortic fragments revealed chronic inflammation in about 1,7 to 8,7% of patients subjected to aortic surgery. Patients with aortic inflammation were predominantly women and the age average was 65 years. Among these patients, 5-20% had an underlying chronic inflammatory disease, mainly GCA. The design of these retrospective studies is not aimed to estimate the frequency of aortic involvement in GCA but underlines the fact that GCA accounts for a significant proportion of complicated inflammatory aortitis.

In the past decade, the vast development of imaging techniques has facilitated the non-invasive detection of signs suggestive of aortic inflammation in living individuals in early

phases, before the development of clinically relevant aortic complications (Pipitone et al., 2008) (Figures 1 and 2). In this setting, three prospective studies have been conducted to determine the prevalence of aortitis in patients with recent-onset GCA. Blockmans et al. performed a systematic 18F-Fluorodeoxyglucose (FDG) Positron Emission Tomography (FDG-PET) to 35 newly diagnosed GCA patients and found FDG uptake suggestive of active inflammation in both the abdominal and the thoracic aorta in approximatelly half of the patients (Blockmans et al., 2006). Agard et al. studied 22 patients with computed tomography angiography (CTA) during the first month after GCA diagnosis. Although some of these patients had received treatment at the time of the CTA, the authors demonstrated radiological signs of aortitis in 45% of patients in the thoracic aorta and in 23% in the abdominal aorta. Finally, in a prospective study performed by the authors in 40 newly diagnosed GCA patients using CTA, radiologic findings suggesting aortitis were detected in 65% of patients, which represents the higher prevalence of aortitis found by means of imaging techniques (Cid et al., 2009; Prieto-Gonzalez et al., 2009).

Reference	Specimen	NIA (%)	Gender (M/F)	Age (mean)	LVV	Other diagnosis	Isolated aortitis (%)	Treatment	Follow-up (mo)	New aneurysms
Kerr, 2000	1069 TA and AA	19 (1,7)	7/12	73	19 GCA	-	-	0	12-48	-
Rojo-Leyva, 2000	383 TA 681 AA	52 (4,3)	17/35	63	4 GCA 1 TAK	1 SLE 1 SS, 1 IBD 1 RPF 1 RF 1 GPA 1 PAN	36 (69,2)	11 GC	1-144	6 (untreated)
Gelsomino, 2005	386 TA and aortic valve	NA	1/9	74	10 GCA	-	-	2 GC	-	1 AAA (untreated)
Homme & Miller, 2006	513 TA and aortic valve	45 (8,7)	8/37	64	14 GCA 6 TAK	2 RA 1 rective arthritis	21 (46,6)	19 GC	35-196	7 (3 untreated)
Burke, 2008	NA	52	16/36	58	5 GCA	1 Crohn 1 SLE 1 SNA	44 (84,6)	-	-	-
Pacini, 2008	788 TA	38 (4,8)	14/24	73	30 GCA 1 TAK	1 Behçet 1 SLE	5 (0.6)	0	26-125	1 (AAA)
Nesi, 2009	338 TA	7 (2)	2/5	>65	7 GCA	-	-	-	-	-
Pacini, 2008	788 TA	38 (4,8)	14/24	73	30 GCA 1 TAK	1 Behçet 1 SLE	-	0	26-125	1 (AAA)

AA: abdominal aorta; AAA: abdominal aortic aneurysm; GC: glucocorticoids; GCA: giant-cell arteritis; NIA:non- infectious aortitis; IBD: inflammatory bowel disease; IS: inmunosupressive agents; LVV: large-vessel vasculitis; M/F: male/female; mo: months; PAN: polyarteritis nodosa; SLE: systemic lupus erythematosus; SNA: seronegative arthritis; SS: systemic sclerosis; RA: rheumatoid arthritis; RPF: retroperitoneal fibrosis; RF: rheumatic fever; TA: thoracic aorta;TAK: Takayasu's arteritis; GPA: granulomatosis with polyangiits (Wegener's), NA: no available information.

Table 2. Prevalence of aortitis and associated diseases in surgical specimens.

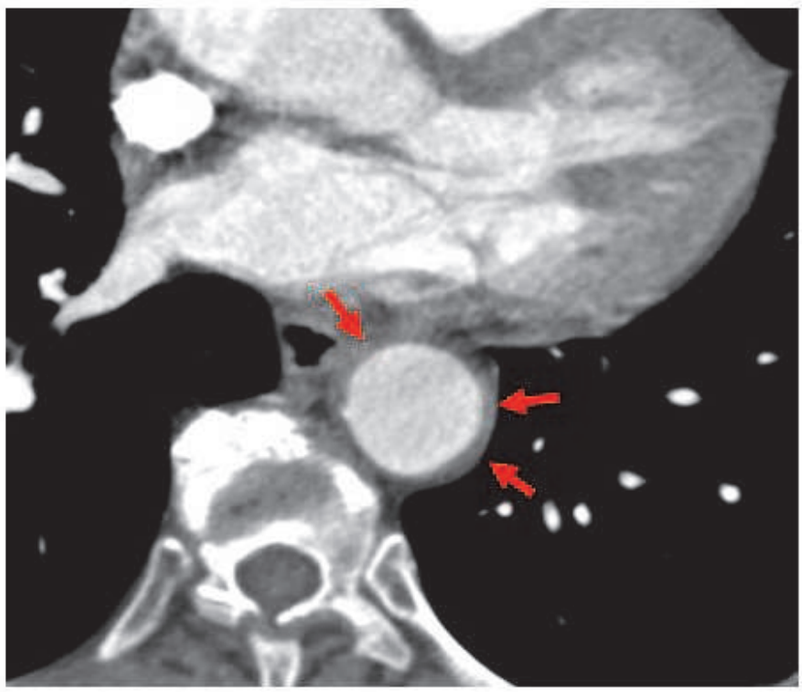

Fig. 1. Cross-sectional view of a CT angiography of a patient with newly diagnosed GCA displaying a marked circumferential thickening of the aortic wall.

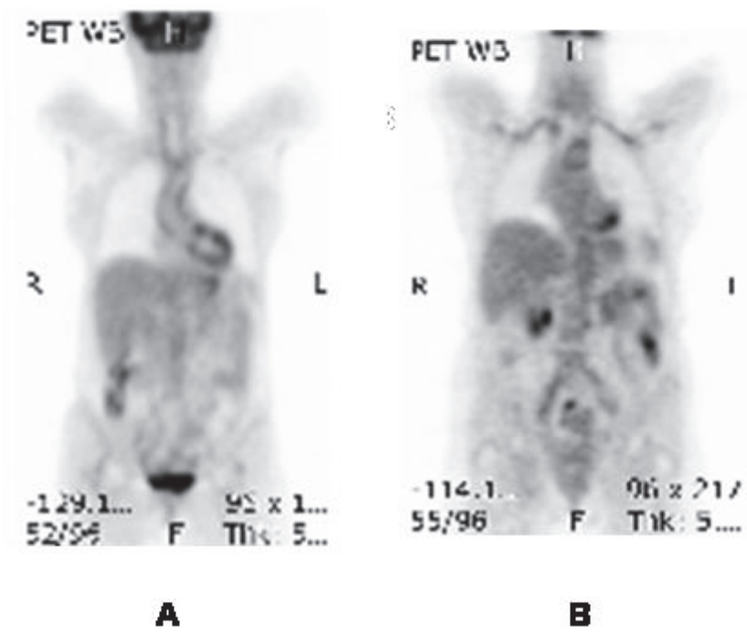

Fig. 2. ^{18}F-FDG-PET scan of a patient with GCA prior to corticosteroid treatment.
(A) Markedly abnormal uptake of ^{18}F-FDG in the ascending thoracic aorta and carotid arteries. (B) Increased ^{18}F-FDG uptake in the aortic arch, abdominal aorta, iliac, subclavian and axillary arteries.

2.1.2 Takayasu's arteritis

TAK is a rare chronic inflammatory granulomatous disease of unknown aetiology that affects predominantly young women. It has a worldwide distribution but higher prevalence has been reported among Asian populations. TAK primarily affects the aorta and its major branches. Pulmonary arteries can also be involved (Kerr et al., 1994; Mwipatayi et al., 2005). Aortitis may affect either an aortic segment or involve the entire aorta. Although there is considerable variability in disease expression between different geographical areas, the initial vascular lesion frequently occurs in the middle or proximal segment of the left subclavian artery close to the aorta. In Japanese patients, aortitis has been described mostly in the ascending aorta and the aortic arch whereas in Indian patients inflammation apparently occurs firstly in the abdominal aorta, subsequently extending towards the thoracic segments. (Hata et al., 1996). Aortic involvement is very common in TAK. In different series of patients with TAK who underwent imaging studies, aortic involvement had been detected in more than 70% of cases.

2.1.3 Isolated aortitis

Vasculitis limited to the aorta has been found in post-mortem studies or has been incidentally diagnosed in specimens obtained from surgical repair of aortic aneurysms. The prevalence of isolated aortitis in the general population is unknown due to the subclinical course of this entity.

In a retrospective review of 1204 aortic surgical specimens obtained over a 20-year period at the Cleveland Clinic, idiopathic aortitis was found in 52 patients (4.3%) (Rojo-Leyva et al., 2000). Sixty-nine percent of these patients had no previous history of systemic vasculitis and only 31% of patients had prior history of systemic illnesses known to be associated with aortitis. Indications for surgery in patients with isolated aortitis consisted of manifestations related to aortic aneurysm (large aneurysm size or progressive enlargement, aortic dissection, or aortic valve dysfunction), or coronary artery disease and only in 1 patient aortitis was detected at the time of thymoma ressection. In 96% of patients with aneurysm formation and idiopathic aortitis, the disease was only identified within the thoracic aorta whereas aortic aneurysms not associated with idiopathic aortitis occurred predominantly in the abdominal aorta (67%).

In another recent retrospective study, noninfectious aortitis was detected in 64 patients of a series of 766 patients with ascending thoracic aneurysm who underwent surgical repair, representing 8.4% of the series. The majority of patients were asymptomatic or had aneurysm-related symptoms only, being aneurysm incidentally discovered in a chest x-ray or echocardiography. The majority of aortitis (81.3%) were of the isolated variant, with no history of chronic inflammatory diseases. Among the remaining, GCA was the entity more frequently associated with aortitis. Eighty-nine percent of patients with noninfectious aortitis (57/64) underwent vascular imaging, and additional vascular abnormalities were present in 72% of them. Additional imaging findings included stenoses and/or ectasia of the major aortic branches (42.1%), descending thoracic aneurysm (31.6%), descending thoracic and abdominal aneurysms (21.1%), and abdominal aneurysms (7%). The median follow up in this study was 15.4 months, which was insufficient to determine the outcome of these additional vascular abnormalities (Liang et al., 2009). Data from these and other surgical series are summarized in table 2.

Therefore, in the majority but not all patients with apparently isolated aortitis, a more widespread involvement indicating systemic large-vessel vasculitis or an associated

condition can be detected. Existing studies assessing potentially associated diseases in these patients are retrospective and almost certainly underestimate the prevalence of pre-existing conditions because many patients with incidentally discovered aortitis had not been systematically subjected to an extensive clinical evaluation or imaging study.

2.1.4 ANCA-associated vasculitis

Large-vessel involvement and associated complications such as aortic stenoses, aneurysm, or dissection have been occasionally reported in patients with small-medium sized vessels such as ANCA- associated vasculitis, particularly granulomatosis with polyangiitis (Wegener's) (GPA). Reported cases, have well-sustained diagnosis and have no epidemiologic, clinical or histopathologic features of GCA or TAK that might suggest misclassification (Chirinos et al., 2004). These findings suggest that aortitis may be part of the spectrum of vascular involvement in ANCA-associated vasculitis.

2.1.5 Chronic periaortitis

Chronic periaortitis includes several modalities of aortic inflammatory involvement including retroperitoneal fibrosis, inflammatory aortic aneurysm and perianeurysmal retroperitoneal fibrosis. The last two conditions convey aortic dilatation. The abdominal aorta is most frequently involved. Retroperitoneal fibrosis is idiopathic in most cases but may occur in the context of small and medium sized vessel vasculitis, particularly GPA. It has also been described in association with microscopic poliangiitis and its renal limited variant, and hepatitis C virus-associated cryoglobulinemia. Idiopathic retroperitoneal fibrosis may accompany other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, autoimmune thyroiditis) or may be part of other fibrosing disorders including orbital pseudotumor, mediastinal fibrosis, sclerosing cholangitis, and Riedel's thyroiditis. Histopathologically there is a marked aortic adventitial inflammation with inflammatory involvement of vasa vasorum extending towards the retroperitoneal small vessels and retroperitoneum itself. Inflammatory changes are thought to trigger a fibrotic response of variable intensity (Vaglio et al., 2003; Levine et al., 2006).

2.2 Clinical manifestations derived from aortitis

Aortic inflammation is usually asymptomatic until complications derived from inflammation -induced vascular remodelling occur. Clinical manifestations are dominated by other components of the associated disease. In patients with GCA cranial, systemic and polymyalgic symptoms dominate the clinical picture. TAK disease is usually more silent and indolent and initial manifestations are frequently derived from involvement of the aortic branches (vascular bruits, weak or absent pulses, limb claudication, hypertension, dizziness or light-headedness) (Kerr GS et al., 1994; Macsimowicz-Mckinnon et al., 2007). Aortitis may contribute to the inflammation-associated non-specific signs and symptoms such as fever, anemia, weigh loss or malaise highly frequent in GCA and also present in a substantial proportion of TAK patients. Complications derived from aortitis are usually manifest and patients may present with severe symptoms related to aortic aneurysm enlargement or rupture (i.e. chest pain, abdominal pain, back pain) or aortic valve insufficiency (i.e. dyspnea and heart failure,) (Garcia-Martinez et al., 2008; Nuenninghoff et al., 2003a; Nuenninghoff et al., 2003b).

2.3 Histopathological features

Aortitis is characterized by patchy areas of medial necrosis and focal loss of medial smooth muscle cells, along with adjacent infiltration of lymphocytes, plasma cells, and histiocytes. Multinucleated giant cells, if present, are generally found at the borders of necrotic zones. The aorta of TAK patients may show thickening of the aortic wall with fibrotic rindlike adventitia, and intense medial and adventitial inflammation with granulomas. It can be indistinghishable from aortitis found in GCA. In general, histological features of non-infectious aortitis are similar and there are no specific features helpful in distinguishing isolated aortitis from GCA or TAK (Kerr et al., 2000; Miller et al., 2006; Gravanis, 2000; Hall et al., 1985; miller et al., 2006).

2.4 Diagnosis and assessment of aortic inflammation

In GCA, diagnosis is usually obtained by temporal artery biopsy. The detection of aortitis may have diagnostic usefulness in patients with suspected GCA when temporal artery biopsy is not informative or is unavailable. In TAK, the diagnosis is largely based on the combination of clinical information, laboratory evaluation, and diagnostic imaging (Mukhtyar et al., 2009). Imaging is an essential tool for the diagnosis of TAK because the involved vessels are not routinely available for histopathologic examination and in both conditions imaging techniques play a critical role in evidencing aortitis. Among imaging modalities, percutaneous intravascular angiography has been traditionally the gold standard investigation for the diagnosis of TAK, providing high-quality images of the arterial lumen frequently altered in involved vessels. Typical lesions appear as long, smooth, tapered stenoses or sometimes complete occlusions intermingled with areas of dilatation. Collateral circulation is often prominent because of the slow progression of the disease. Modern non-invasive diagnostic modalities including ultrasonography, PET-scan, computed tomography scanning and magnetic resonance angiography have progressively replaced conventional angiography for diagnosis of large vessel involvement because of their reduced risks and the ability to provide information not only about the lumen but also about the vessel wall. Specific MRI sequences such as delayed contrast-enhanced MRI may allow the detection of edema and arterial wall thickening at a reversible stage, prior to the development of luminal stenosis. MRI/MRA may provide useful information avoiding the risks associated with arterial puncture, iodinated contrast load and radiation exposure. Currently, conventional angiography is basically used to guide endovascular intervention procedures or to combine imaging with the detection of central blood pressure in patients with significant limb artery stenoses.

Systematic evaluation of patients with large-vessel vasculitis with imaging studies such as color duplex ultrasonography (US), CTA, FDG-PET, angiography, and magnetic resonance imaging (MRI) or MR angiography (MRA) has been performed by several investigators (Agard et al., 2008; Andrews et al., 2004; Andrews & Mason, 2007; Blockmans et al., 2008; Blockmans et al., 2009; Both et al., 2008; Hautzel et al., 2008; Henes et al., 2008; Narvaez et al., 2005; Pipitone et al., 2008; Prieto-Gonzalez et al., 2009; Walter et al., 2005; Webb & Al-Nahhas 2006). These techniques offer different but complementary information to assess large vessel involvement with relative advantages and disadvantages which are summarized in Table 3 (Tso E et al., 2002; Blockmans et al., 2009; Cid et al., 2009;).

Technique	Findings	Advantages	Disadvantges
Color Dupplex US	Wall thickening Hipoechoic halo Reduced pulsation Stenoses/occlusions /dilatations Lumen patency assessment	Inexpensive Repeatable No radiation No IV contrast needed Communication with the patient during the procedure Good resolution for small arteries	Not suitable for structures below air or bone
MRI/MRA	Wall thickening Contrast enhancement Stenosis/occlusions /dilatations Lumen patency assessment	No radiation Repeatable	Expensive Not suitable for patients with claustrophhobia No feasible with metal devices Limited resolution for small vessels Gadolinium contrast contraindicated if impaired renal function
CTA	Wall thickening Contrast enhancement Stenosis/occlusions /dilatations Lumen patency assessment	Rapid and available Inexpensive Repeatable	Contraindicated if renal insufficiency or iodine allergy Radiation exposure
FDG-PET	FDG uptake by metabolically active cells such as inflammatory infiltrate	Repeatable Whole body assessment	Expensive Not widely available No lumen patency assessment No resolution for vessels < 4 mm Setting and results not standardized Requires normal blood glucose concentration Not suitable for cranial arteries due to strong cerebral uptake
Angiography	Lumen patency assessment (smooth, long and tapered stenoses or occlusions)	Therapeutic procedures (angioplasty and/or stent placement) High resolution for small vessels Central blood pressure detection	Invasive Radiation Contraindicated if renal insufficiency or iodine allergy No information about the vessel wall

Table 3. Imaging techniques applied to assess large-vessel vasculitis

3. Aortic complications in patients with large-vessel vasculitis

Aortitis may eventually lead to aortic complications in patients with large-vessel vasculitis. After the initial inflammatory injury, abnormal vascular remodelling may eventually cause aortic structural damage and clinical complications such as aortic aneurysm, dissection, or aortic valve insufficiency secondary to aortic root dilatation (Salvarani et al., 2008). Patients with GCA tend to develop complications derived from aortic dilatation or dissection whereas patients with TAK more commonly develop aortic stenosis but may also develop dilatation of the ascending aorta and aortic valve insufficiency.

3.1 Aortic complications in patients with GCA

GCA patients are at an increased risk of developing aortic complications. In a retrospective population-based study, GCA patients were 17.3 times more likely to develop thoracic aortic aneurysms and 2.4 times more likely to develop abdominal aortic aneurysms during follow-up than individuals of the same age from the general population (Evans et al., 1995). The prevalence of aortic complications during follow-up ranged from 9.5 to 18% in three series of patients with GCA (Evans et al., 1995; González-Gay et al., 2004; Nuenninghoff et al., 2003a). Table 4 summarizes the main results of these studies.

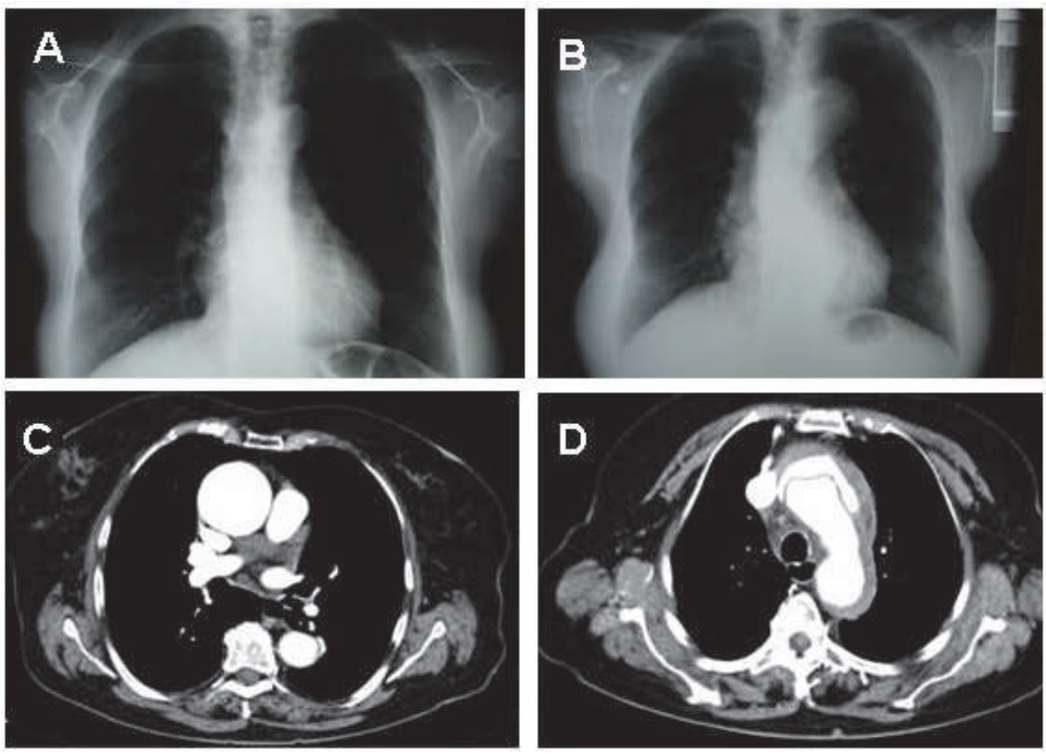

Fig. 3. (A) Chest x-ray of a 68 -years old woman at the time of GCA diagnosis. (B) Four years later the chest radiograph of the same patient showed mediastinum broadening and aortic aneurysm was confirmed by CT-scan. (C) CT scan of another patient wit GCA demonstrating an aneurysm with a maximum diameter of 5 cm at the ascending thoracic aorta. (D) Aortic dissection at the ascending aortic segment in a patient with GCA presenting with chest pain.

	Evans (n=96)	Nuenninghoff (n=168)	González-Gay (n=210)	García-Martínez (n=54)
Design of the study	Retrospective	Retrospective	Retrospective	Prospective cross-sectional evaluation
GCA diagnosis	1950-1985	1950-1999	1981-2001	1995-2001
Follow-up	8.6 yr (1 mo – 28 yr)	7.6 yr (3.9 – 13.5)	Not recorded	5.4 yr (4-10.5)
Aortic complications	16 (16.6%)	30 (18%)	20 (9.5%)	12 (22.2%)
Type of aortic complication	2 TAD at GCA diagnosis 9 TAA 5 AAA	18 TAA 16 AAA	16 TAA 6 AAA	11 thoracic dilatation/aneurysm 1 AAA
Time of complication discovery after GCA diagnosis	TAA: 5.75 yr (2.5 mo-20 yr) AAA: 2.5 yr (1.3-7.6)	TAA: 10.9 yr (4.5-13.3) TAD: 1.1 yr (0.2-2.1) AAA: 6.3 yr (1.1-13.3) AAD: 7.6 yr	3.2 yr (0-13.5)	5.4 yr (4-10.5)
Histophatologic aortitis	4 / 6	5 / 7 in TA 0 / 1 in AA	Not recorded	0/2 (*)
CS treatment	1 yr (< 1 mo-4.2 yr)	Not recorded	Not recorded	Patients were treated uniformly and those with ASD were able to withdraw CS in a shorter period of time

TAA: thoracic aortic aneurysm; TAD: thoracic aortic dissection; AAA: abdominal aortic aneurysm; AAD: abdominal aortic dissection; CAD: coronary artery disease; yr: years; mo: months;.
ASD: aortic structural damage (aneurysm or dilatation)
(*) Only scattered small infiltrates were observed.

Table 4. Studies evaluating aortic complications in patients with GCA

Overall, these studies suggest that aortic aneurysms are late complications, usually detected several years after the diagnosis of GCA, even in patients that have achieved sustained remission and have been able to withdraw corticosteroid therapy. Only 10% of patients with GCA evaluated by CT angiography imaging exhibit slight dilatation of the aortic wall at the time of diagnosis (Prieto-Gonzalez et al., 2009). Apparently, aortic dissection may occur in earlier phases even in the absence of aortic aneurysmal disease and sometimes represents the initial event leading to the diagnosis of GCA. In this setting, aortic dissection may occur in patients with active inflammation which is demonstrated by histopathologic examination of the aortic specimen obtained after surgical repair or necropsy (Lie, 1995; Nuenninghoff et al., 2003a). Although the entire aorta may be involved, aneurysms and dissections

preferentially develop in the thoracic segments, mainly the ascending aorta. Although survival rates are not decreased in patients with GCA, the development of aortic rupture is a catastrophic event that carries high morbidity and mortality (Evans et al., 1995; Nuenninghoff et al., 2003a).

In a prospective cross-sectional analysis of 54 GCA patients who were screened with a defined protocol after a median follow-up of 5.4 years (range 4-10.5 years), García-Martínez A et al found significant aortic structural damage (aneurysm or dilatation) in 22% of patients which was higher than the prevalence observed in previous retrospective studies (García-Martínez et al., 2008). Almost half of the patients in this cohort were candidates to surgical repair because of the size of the aneurysm. The ascending aorta was the segment involved in three quarters of patients. Aortic structural damage was significantly more frequent in men and was not associated with the presence of traditional cardiovascular risk factors. When these patients were re-screened after longer follow-up (median 8.8 years, range 8-10.5) additional aortic aneurysms appeared in few additional patients who had non-dilated aortas in the initial study and one of them developed aortic dissection. Histopathological study of the aorta of this patient did not evidence persistence of active aortic inflammation but there was marked loss and disruption of elastic lamelae.

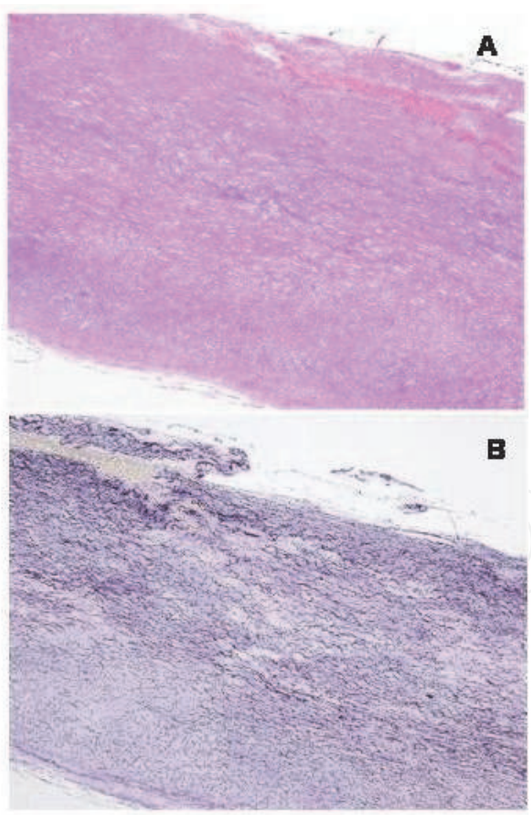

Fig. 4. Post-mortem aortic specimen obtained from a patient who died from aortic dissection 9 years after the diagnosis of GCA. A) Hematoxylin-eosin staining showing absence of inflammation. B) Orcein staining of a serial section disclosing extensive disruption of the elastic fibres, probably due to the initial injury.

Persistence of inflammatory infiltrates has been described in some aortic specimens obtained from necropsies or from patients with aortic aneurysm that have undergone surgery years after the diagnosis of GCA (Evans et al., 1995; Lie, 1995; Nuenninghoff et al., 2003a; Zehr et al., 2005). As a result of these findings, aortic complications are considered to be the result of persistent aortic inflammation and the ensuing weakening of the aortic wall. However, in a prospective cross-sectional evaluation, persistence of clinically or analytically detectable disease activity was not found to be associated with increased risk of aortic structural damage (García-Martínez A et al 2008). Patients with aortic dilatation experienced less relapses during follow-up, had lower corticosteroid requirements and exhibited lower acute-phase reactants than patients without aortic aneurysm or dilatation. Histopathological review of the aortic wall in patients who underwent surgery for aneurysm repair evidenced only minimal inflammatory infiltrates but important loss and disruption of elastic lamellae even in areas devoid of inflammation, probably as a consequence of the initial injury (Figure 4). The aneurysmal aortic wall exhibited increased expression of matrix metalloproteinase (MMP)-2 but not MMP-9 which suggests ongoing remodelling process more than persistent aortic inflammation (García-Martínez et al., 2008). Thus, aortic dilatation develops as a consequence of complex and probably multifactorial mechanisms. On the basis of these studies it is likely that aortic inflammation and subsequent maladaptative remodelling determine the weakening of the aortic wall, which subjected to mechanical stress, may eventually undergo dilatation and aneurysm formation over time.

The life-threatening nature of the potential complications derived from aortic structural damage makes mandatory to subject GCA patients to a continuous surveillance by clinical examination and imaging, even patients in long-term sustained remission. The best cost-benefit screening procedure has not been established but a reasonable approach would include performance of a chest X-ray and abdominal US examination every one or two years and echocardiogram if aortic bruits are detected.

3.2 Aortic complications in patients with Takayasu's arteritis

As the disease progresses abnormal vascular remodelling leads to the combination of arterial stenosis/occlusion with arterial aneurysms. However, while stenotic lesions appear in almost all patients with TA only 27% of patients develop arterial aneurysms (Kerr GS et al., 1994). Symptoms derived from involvement of the aortic branches, usually dominate the clinical picture and may combine with symptoms derived form aortic involvement. Patients may experience symptoms due to vertebrobasilar insufficiency (vertigo, syncope), upper- and lower-extremity claudication, transient ischemic attacks or stroke, coronary heart disease, or mesenteric ischemia, among others.

In the aorta stenoses/occlusions are mainly located at the aortic arch, the descending aorta and the abdominal aorta, and aortic aneurysms preferentially develop at the ascending thoracic aorta (Kerr et al., 1994; Mwipatayi, 2005). More than 70% of patients develop hypertension, mainly of renovascular origin but aortic stenosis leading to atypical aortic coarctation may also contribute. Blood pressure treatment and control may be a serious problem in these patients since arm blood pressure measurement may not be accurate. TAK patients may also develop aortic dilatation or aneurysm with risk of rupture. Aortic valve incompetence has been reported in up to one quarter of patients and is generally due to annular or ascending aortic dilatation but also as a result of secondary aortic valve changes such as fibrous thickening, retraction, and calcification. Congestive heart failure is present in up to one fourth of patients

who have TAK and usually occurs as a consequence of uncontrolled hypertension or aortic regurgitation (Kerr et al. 1994; Macksimowicz-Mckinnon et al. 2007).

4. Treatment of aortitis and aortic complications

Treatment of primary large vessel vasculitis is addressed to eliminate clinical symptoms and suppress inflammatory activity wherever it is present, including the aorta and its branches. However current therapies are not able to completely abrogate inflammation in most cases and are not able to prevent complications derived from inflammation-induced vascular remodelling which may need to be addressed with surgery or revascularization procedures. High dose glucocorticoids are the mainstay of initial therapy to induce remission in large-vessel vasculitis which must be combined with immunosuppressive agents in the majority of patients with TAK.

4.1 Giant-cell arteritis

Prednisone or equivalent is usually given to patients with GCA at 1 mg/Kg/day, up to 60 mg/day for 1 month with subsequent tapering. Low-dose prednisone is maintained for 2-3 years until complete discontinuation which is achieved by approximately half of the patients. Between 40-60% of patients experience a relapsing course. Methotrexate and azathioprine have shown modest corticosteroid sparing effects in clinical trials (Mahr et al. 2007; Hoffman et al. 2002; Cid et al., 2007) and can be used to reduce glucocorticoid exposure in patients with relapsing outcome or with glucocorticoid-related side effects (Mukhtyar et al., 2009). A randomized clinical trial did not show benefit of infliximab over placebo in maintaining remission in patients with newly-diagnosed GCA (Hoffman et al.,2007). Glucocorticoid treatment is usually adjusted according to remission of cranial, systemic or polymyalgic symptoms and normalization of acute phase reactants. Response of aortic inflammation has not been taken into account because the substantial prevalence of aortitis and its potential delayed complications has not been appreciated until very recently. Imaging techniques may have promise in assessing the effect of treatment on large-vessel inflammation but their sensitivity and specificity are not fully established and, at present, it is premature to adapt therapeutic adjustments to the persistence or resolution of imaging abnormalities.

Since the discovery that aortitis and aortic complications are frequent in GCA is relatively recent, there is no evidence supporting whether the discovery of aortic dilatation may have therapeutic implications. It is not clear whether aortic dilatation results from persistent subclinical inflammation, previous injury, abnormal remodelling, hemodynamic factors or a combination of these. Surgical aortic repair in GCA patients should be performed according to standard current guidelines for the general population with aortic disease and preferably in patients in remission (Zehr et al. 2005). Since GCA targets aged people, advanced age or co-morbidities may unacceptably increase the risk of elective surgery and convenience of surgical repair must be carefully weighted in an individual basis. Endovascular repair of aortic aneurysm may be an interesting option but the experience is limited. Moreover, most of the existing evidence regarding endovascular repair of aortic aneurysm has been obtained from abdominal and thoracic descending aneurysms. Endovascular repair of ascending aortic dilatation, common in GCA, is technically more difficult (The United Kingdom EVAR trial investigators, 2010a; The United Kingdom EVAR trial investigators, 2010b; Kolvenbach et al., 2011).

4.2 Takayasu arteritis

For TAK patients, an initial prednisone dose of 1 mg/Kg/day (max 60 mg/day) maintained for 1 month and gradually tapered is recommended. With this treatment, 93% of patients achieve disease remission. However, remission is sustained in only 20% of patients. More than 70% of patients need adjuvant therapy and long-term low-dose glucocorticoid is frequently required by most patients. Recommendations about immunosuppressive agents are based on open-label studies. Methotrexate, azathioprine and mycophenolate are the most frequently used. Open-label studies support the potential usefulness of infliximab for refractory patients (Mukhtyar et al., 2009; Molloy et al., 2008)

TAK is a chronic relapsing disease and flares and anatomic progression of vascular lesions occur in the majority of patients during follow-up.

One of the challenges in TAK is to find better surrogate markers of disease activity and ongoing inflammation. Clinical data are often non-specific and acute-phase reactants may be unreliable indicators. Previous studies of patients undergoing periodic imaging surveillance showed inconsistencies in the relationship between acute-phase reactants and the development of new vascular lesions during follow-up. In a review of patients with clinically inactive disease, new angiographic changes appeared in 60% of them and surgical aortic biopsy specimens revealed histological evidence of persistent inflammatory infiltrates in 44% of the samples (Kerr et al., 1994).

Serial imaging has been used for long in the follow-up of patients with TAK since symptoms usually occur when severe disruption of the normal vascular architecture has occurred. Serial imaging is very useful in detecting new lesions or changes in the existing ones and allows an objective assessment of disease stability or progression. MRI angiography may reveal early signs of vascular inflammation in patients with TAK and is currently being evaluated as a potential tool to assess disease activity and response to treatment in prospective clinical studies (Andrews & Mason 2007). However, qualitative changes suggestive of active disease versus fibrotic scarring do not always accurately predict response to therapy. (Tso et al., 2002) .

Vascular remodelling and scarring may lead to fixed vascular lesions that will not be reversed by pharmacologic therapy. Revascularization or surgical repair should be considered if stenotic or occlusive lesions lead to significant haemodynamic effects with ischemic symptoms, or if aneurysmal enlargement results in increased risk of rupture, dissection or in case of aortic valve regurgitation (Mukhtyar et al., 2009).

For correction of stenoses and occlusions of the aorta and its branches the largest body of experience comes from bypass graft procedures where good long-term outcomes have been achieved. On average, a 20 to 30% rate of restenosis or occlusion is reported on long-term follow-up. Revascularization can also be achieved by percutaneous transluminal angioplasty (PTA). PTA is less invasive than vascular surgery and is currently the revascularization procedure of choice. Angioplasty is usually successful but the rate of restenosis during follow-up is higher than with vascular surgery. Endovascular angioplasty has shown better outcomes for lesions that are short and not already occluded. To prevent restenosis, stents are currently used although conventional stents have been associated with high rates of failure in long-term follow-up studies. The long-term impact of angioplasty in patients with TAK is still uncertain because there have been no reports describing the outcome of angioplasty with or without stenting after periods longer than 10 years. Encouraging results have been reported with the use of drug-eluting stents in atheromatous

vascular disease. Their benefit in the treatment of patients with TAK needs to be determined (Liang et al., 2009).

In patients with hypertension, anatomical correction of lesions such as renal artery or aortic stenosis should also be performed. When needed, the most common procedure to repair aortic stenosis has been an aortoaortic bypass with the use of a prosthetic graft. Angioplasty with or without stenting may also be of use to treat discrete stenosis of the aorta. Aortic aneurysm should be repaired according to the current guidelines for general population. Aortic valve incompetence with aortic ring expansion may necessitate root and aortic valve replacement or valvuloplasty. Complex vascular reconstructions (i.e. complete aortic arch replacement) may be need by patients with multiple stenosis.

Patients with TAK have lower rates of sustained vessel patency for angioplasty and arterial bypass procedures than patients undergoing intervention for atherosclerosis or other vascular diseases. Failure has been associated with the presence of active disease at the time of surgery. Thus, in order to improve the life-span of the revascularized vessel and minimize the risk of surgical dehiscence, interventions should ideally be performed during inactive disease. However, when an earlier surgical intervention is mandatory it can also be successfully accomplished during the acute stage. In this scenario, treatment with steroids and/or immunosuppressive agents should be continued after surgery. Some authors recommend to carefully select the anastomotic site excluding inflamed vascular areas in order to avoid occlusion of the reconstructed vessel, anastomotic disruption or aneurysm development at the site of anastomosis (Ogino et al., 2008).

Recent advances in immunosuppressive and surgical therapies, including endovascular interventions, have improved the outcome of patients with TAK. However, longer follow-up studies are still necessary to get statistically valid conclusions about the impact of these therapies on the natural history of TAK. In addition, patients with TAK may develop accelerated atherosclerosis as a consequence of systemic chronic inflammation and long-term hypertension. Therefore, in order to improve the long-term outcome of these patients, a careful control of traditional vascular risk factors is crucial to prevent the potential vascular complications associated with atherosclerosis.

4.3 Isolated aortitis

Patients with incidentally discovered noninfectious aortitis should be evaluated for additional areas of arterial disease and for signs and symptoms of systemic inflammatory conditions potentially associated with aortitis. The evaluation should include a full patient interview, a complete physical examination with particular focus on the vascular system, and appropriate laboratory testing including acute phase reactants. Imaging of the entire aorta and its main branches with MRI or CTA to exclude abnormalities in other vascular beds should be considered.

It is not clear at present whether patients with incidentally discovered aortitis in whom a systemic vasculitis or systemic disease has been reasonably ruled out should receive therapy with glucocorticoids and/or immunosuppressants following resection of the affected aortic segment. Data from retrospective studies indicate that the longterm outcome of patients with isolated aortitis is generally good. However, in a retrospective study performed at the Cleveland Clinic in which 36 out of the 52 patients with idiopathic aortitis were followed for a mean of 3.25 years, 6 out of the 25 patients not receiving therapy after the initial surgery developed new aortic aneurysm during follow-up. Conversely, recurrent aneurysms were

not identified among 11 corticosteroid-treated patients, in spite that treatment schedule was not standardized and some patients received very short courses of corticosteroids (Rojo-Leyva F., et al 2008).

Therefore, the decision to treat with glucocorticoids or immunosuppressive agents should be individually considered, depending on the clinical presentation and the location and extent of inflammation. Patients with idiopathic aortitis require careful and periodic surveillance during follow-up because small case series have identified a propensity toward aneurysm formation in other vascular beds over time. Prospective follow-up studies of patients with isolated aortitis are required to further clarify this point.

5. Conclusions

Over the past decade, the improvement and wider use of imaging techniques has motivated an increasing appreciation of the relevance of aortic involvement in systemic vasculitis and its potential for severe complications. Persistent aortitis observed in some patients by means of imaging or histopathologic examination questions the ability of current therapies to completely suppress the inflammatory process in spite of the clinical remission of the initial symptoms. It remains to be determined whether patients with asymptomatic persistent signs of aortitis would benefit form more intensive therapy since recent data suggest that persistent low-grade subclinical inflammatory activity is not clearly associated with higher frequency of aortic complications. On the other hand, mechanisms involved in aortic dilatation are not completely understood. It is unclear at present whether aortic dilatation results from persistent subclinical activity, abnormal vascular remodelling following the initial injury, hemodynamic influences or a combination of factors. The indication and best method for elective repair of aortic dilatation or stenosis need to be delimitated. Awareness of aortic participation in systemic vasculitis raises a number of important questions and opens an exciting research agenda for coming years that will definitely benefit from multicenter collaboration

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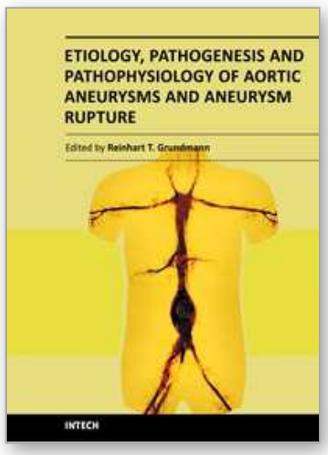

Etiology, Pathogenesis and Pathophysiology of Aortic Aneurysms and Aneurysm Rupture

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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.

How to reference

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