Cardiac involvement in Wegener’s granulomatosis

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Abstract
Wegener’s granulomatosis is a systemic inflammatory disorder of unknown aetiology. The protein clinical presentations depend on the organ(s) involved and the degree of progression from a local to a systemic arteritis. The development of serological tests (antineutrophil cytoplasmic antibodies) allows easier diagnosis of a disease whose incidence is increasing. This is particularly helpful where the presentation is not classic—for example “overlap syndromes”—or where the disease presents early in a more localised form. This is true of cardiac involvement, which is traditionally believed to be rare, but may not be as uncommon as has hitherto been thought (≤ 44%). This involvement may be subclinical or the principal source of symptoms either in the form of localised disease or as part of a systemic illness. Pericarditis, arteritis, myocarditis, valvulitis, and arrhythmias are all recognised. Wegener’s granulomatosis should therefore be considered in the differential diagnosis of any non-specific illness with cardiac involvement. This includes culture negative endocarditis, because Wegener’s granulomatosis can produce systemic upset with mass lesions and vasculitis. Echocardiography and particularly transoesophageal echocardiography can easily identify and delineate cardiac and proximal aortic involvement and may also be used to assess response to treatment.

Case report
A 25 year old man was admitted with a two week history of intermittent palpitation after upper respiratory tract symptoms. There was no past history of note other than coincidentally found “aortic and mitral systolic bruits” some five years previously.

On admission the patient was apyrexial with no rash or splinter haemorrhage; his pulse was 77/min; blood pressure 100/70 mm Hg; and he had a 3/6 ejection systolic murmur and a 2/4 early diastolic murmur. There was no evidence of neuropathy.

Initial investigations showed normal urine analysis, chest radiograph, full blood count, plasma chemistry, thyroid function tests, C reactive protein, erythrocyte sedimentation rate, and autoantibodies (antineutrophil cytoplasmic antibodies). Smooth muscle, double stranded DNA, antiplatelet, antinuclear factor, anticardiolipin, rheumatoid factor, thyroid microglobulin and thyroglobulin, antinuclear factor and gastric parietal cell). Immune complex ratio at 0.75 and complement levels were normal. Four sets of blood cultures showed no growth. Antistreptolysin O titres were not raised and throat swabs were negative to bacterial culture. The electrocardiogram showed a normal PR interval and right bundle branch block. Transthoracic echocardiography showed a normal sized left ventricle with good contraction. The aortic valve appeared bicuspid with what was initially thought to be a subvalvar membrane in the left ventricular outflow tract. There was moderate aortic incompetence on Doppler echocardiography. A 24 h echocardiogram showed intermittent supraventricular tachycardia for which the patient was given metoprolol. The symptoms recurred and his medication was converted to verapamil. The patient was intolerant of this drug and his antitachycardic treatment was changed to flecainide.

The patient remained unwell and was admitted elsewhere with severe malaise, weakness, weight loss, and recurrent palpitation. On examination he had multiple splinter haemorrhages. The previously noted murmurs were unchanged. The erythrocyte sedimentation rate was 45 mm in the first hour and the C reactive protein concentration was more than four times that of normal.

Keywords: Wegener’s granulomatosis; myocarditis and aortitis; transoesophageal echocardiography

The incidence of Wegener’s granulomatosis, a systemic disorder of unknown aetiology, appears to have increased.1 2 This finding may be the result of an increased awareness and easier, earlier diagnosis allowing less severe, more localised forms of the disease to be recognised. There has also been a true increase in incidence due to an expanding elderly population which is at greater risk.3 4 The mode of presentation is protean5 7 depending in part on which organs are affected. Cardiac involvement can vary from subclinical to the primary organ affected, although this is thought to be rare.6 11 Using a case from our institution, we describe for the first time the transoesophageal echocardiographic features of Wegener’s myocarditis and aortitis and give an illustrated review of the heart in Wegener’s granulomatosis.
Cardiac involvement

RVOT, right within the of interventricular membranous is seen. also thickened. Middle sinuses. The aortic wall thickened by involvement right panel: SVC, superior ascending aorta; LA, left atrium; AO, aorta; RPA, right pulmonary artery; ASC AO, ascending aorta; MPA, main pulmonary artery; LA, left atrium; RA, right atrium; RVO2, right ventricular outflow tract; AO, aorta; IVS, interventricular septum; RV, right ventricle; LV, left ventricle.

Transoesophageal echocardiography was performed after transfer to our hospital, in an attempt was confirmed but in addition marked thickening and echodense reflection were seen circumferentially from the wall of the aortic root in the first 2–3 cm and from the atrial and ventricular septa, with a fibromuscular mass obstructing the left ventricular outflow tract, producing a pressure gradient of 36–40 mm Hg as assessed by continuous wave Doppler examination (fig 1). The patient continued to receive triple antibiotic treatment without improvement while other possible causes of aortitis were excluded.

No evidence was found to suggest ankylosing spondylitis (HLA B27 negative), Reiter's syndrome or syphilis (antitreponemal antibody negative). Antineutrophil cytoplasmic antibodies were not seen with indirect immunofluorescence of ethanol fixed neutrophils exposed to the patient's serum. The patient did, however, give a vague history of rhinorrhoea and nose bleeds, raising the suspicion of Wegener's granulomatosis. He was reviewed by an otolaryngologist and a septal biopsy specimen was taken which showed acute inflammation without granuloma or vasculitis. The patient then developed haemoptysis with an ill defined opacity at the right base in the chest radiograph. This was thought to be beyond the reach of percutaneous or transbronchial biopsy. In a further attempt to gain histological proof of Wegener's granulomatosis, transoesophageal echocardiography was repeated, showing progression of the aortitis with marked thickening of the aortic wall. Guided myocardial biopsy was performed. Biopsy specimens taken from the interatrial septum, right ventricular apex, and right atrial side of the posterior aortic wall showed only non-specific inflammation. Repeat indirect immunofluorescence for antineutrophil cytoplasmic antibody, two weeks after it was initially performed, was strongly positive with a diffuse granular staining pattern. This was subsequently confirmed, both on repeat indirect immunofluorescence and after solid phase radioimmunoassay, on a sample sent to the University of Cambridge Laboratory at Addenbrookes Hospital. They reported antibody levels as 73% of a known positive serum (normal < 16%).

The patient showed no improvement with intravenous antibiotics but treatment with cyclophosphamide and prednisolone produced an excellent symptomatic response. The erythrocyte sedimentation rate, C reactive protein concentration and, chest radio graphy and electrocardiogram findings normalised. Antineutrophil cytoplasmic antibody became undetectable but aortic incompetency remained. Repeat transoesophageal echocardiography showed marked improvement of aortitis (fig 2). Unfortunately, the patient became increasingly short of breath, without any serological evidence of reactivation of Wegener's granulomatosis as assessed by C reactive protein concentration and repeat indirect immunofluorescence. Diastolic blood pressure was unrecordable, echocardiography showed progressive dilatation of the left ventricle and he was referred for aortic valve surgery. The aortic valve at surgery showed a shrunken right coronary cusp. Pathological examination showed localised inflammation but no evidence of
vasculitis. Symptoms of breathlessness were greatly improved after surgery.

A subglottal stenosis, which required resection, was subsequently discovered in the patient. Pathological analysis of the tracheal biopsy specimens showed organising granulation tissue with areas of acute superficial inflammation compatible with Wegener’s granulomatosis.

The patient continued to feel well while receiving cyclophosphamide and prednisolone. Initial attempts to reduce the steroid dosage, however, produced a symptomatic relapse requiring reintroduction of higher doses. Currently three years after diagnosis, steroid medication has been reduced and cyclophosphamide has been converted to azathioprine.

**Discussion**

Wegener’s granulomatosis is typically characterised by granulomatous inflammation of the respiratory tract and internal organs with a generalised necrotising vasculitis and glomerulonephritis. It was first defined as a distinct clinical syndrome in 1936, but had previously been described by Klinger in 1931 and McBride in 1897. The onset is often insidious, the mode of presentation depending on the organs affected and the extent to which the disease has progressed from local involvement to a truly systemic arthritis.

This means the clinical manifestations are protean and the condition should be considered in the differential diagnosis of any multisystem disorder. The diagnosis is primarily based on characteristic clinical features combined with specific organ involvement and histological findings (table 1). These traditional classification systems, however, may discriminate poorly between related diseases. This difficulty in classification accounts for the existence of the so-called “overlap syndromes” where the clinical characteristics are mixed and the pathological features disparate or non-specific (table 2). In Wegener’s granulomatosis the characteristic granulomata may be absent or difficult to identify in the biopsy material obtained in any one case. This difficulty in obtaining histopathological confirmation leads to a delay in diagnosis; in a series of 158 patients reported by Hoffman et al., the mean time to diagnosis was 12 years.

**Table 1** Systemic vasculitides

<table>
<thead>
<tr>
<th>Vessel involvement</th>
<th>Classical organ involvement</th>
<th>Granuloma</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wegener’s granulomatosis</td>
<td>Small-medium sized vessels</td>
<td>Upper and lower respiratory tract, necrotising vasculitis and glomerulonephritis</td>
<td>Present</td>
</tr>
<tr>
<td>Microscopic polyarteritis nodosa</td>
<td>Small vessels and/or small-medium sized arteries</td>
<td>Necrotising glomerulonephritis, necrotising vasculitis (respiratory tract)</td>
<td>Absent</td>
</tr>
<tr>
<td>Takayasu’s arteritis</td>
<td>Aorta and major branches</td>
<td>No glomerulonephritis—renal involvement via arteritis</td>
<td>Present</td>
</tr>
<tr>
<td>Kawasaki syndrome</td>
<td>Small, medium and large arteries, including coronary arteries</td>
<td>Common in young oriental females; ANCA very infrequently positive</td>
<td>Absent</td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td>Aorta and major branches, especially extracranial branches of carotid artery</td>
<td>ANCA sometimes positive—antineutrophil G</td>
<td>Absent</td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
<td>Small-medium sized vessels</td>
<td>Respiratory tract, necrotising vasculitis</td>
<td>Present</td>
</tr>
<tr>
<td>Henoch-Schoenlein purpura</td>
<td>Small vessels</td>
<td>Skin, gut, glomerulonephritis, joints</td>
<td>Absent</td>
</tr>
</tbody>
</table>

ANCA, antineutrophil cytoplasmic antibody; c-ANCA, cytoplasmic ANCA; p-ANCA, perinuclear ANCA.
from onset of symptoms to diagnosis was 15 months with a range of immediate to 15 years. Diagnosis is now facilitated, however, following the development of both indirect immunofluorescence and solid phase radioimmunoassay for antineutrophil cytoplasmic antibodies.23

Wegener’s granulomatosis is classically associated with a detectable antineutrophil cytoplasmic antibody which shows a cytoplasmic distribution, as opposed to a perinuclear. This former pattern (fig 3) is associated with circulating antineutrophil cytoplasmic antibody against the proteinase-3 antigen, a component of neutrophil primary granules.24 These serological tests are both sensitive (> 95%) and specific (> 80%)25 26 and not only simplify diagnosis but also allow an immunological component to be included in classification systems.32 26 Realisation of the importance of the underlying immunological mechanism as opposed to the clinicopathological syndrome it produces helps to reduce the problems inherent within the old classification systems with their confusing taxonomy. This use of serological testing rather than reliance only on clinicopathological features means that less severe more localised forms of the disease can be recognised and the reported range of organ involvement may well alter.

Cardiac manifestations, previously said to be uncommon6–11 may not be so rare27 (table 3). In reviewing these and other series15–38 and Keifer Lehmann40 and Grant et al27 identified a wide discrepancy in the reported incidence of cardiac involvement. These variations may reflect the variable natural history of the disease,29 the source of the patients,27 34 the specialty of the group investigating the patients,37 the size of the population studied,15 24 or the availability of techniques such as echocardiography to diagnose subclinical cardiac involvement before death.

Forstot et al60 retrospectively analysed reported cases of patients with cardiac involvement: about 50% had pericarditis, 50% coronary arteritis, 25% focal myocarditis, and 21% valvulitis or endocarditis, with the conduction system involved in 17% and myocardial infarction in 11%.

PERICARDITIS
Pericarditis and effusion have been reported alone18 41 and in conjunction with other cardiac abnormalities15 40 and may be unexpectedly found at postmortem examination.40 41 present acutely as tamponade,46 48 or as chronic constriction.27 46 49 In a few cases pericarditis may be secondary to myocardial infarction or uraemia due to renal involvement.27

ARTERITIS
Generalised arteritis may produce a systemic illness with fever, malaise, and weight loss,41 which may mimic infective endocarditis. More localised arteritis is recognised, affecting the coronary arteries producing coronary artery stenoses,38 myocardial infarction,41 44 and death.44 46 47 53 Inflammation may also involve the aorta both proximally, causing dilatation,27 and distally, causing retroperitoneal inflammation.44 Proximal aortic involvement has previously been noted at postmortem examination1 12 44 53 and in our case this was demonstrated by transoesophageal echocardiography. The transoesophageal characteristics of aortic and cardiac involvement in Wegener’s granulomatosis have never previously been described and in our case this technique also proved useful in following the response to treatment.

MYOCARDITIS
Myocarditis with granulomata is recognised20 52 and can produce acute cardiac failure.40 44 45 56 It may later progress to

Table 2 “Overlap syndromes”—systemic vasculitides manifesting mixed clinicopathological features

<table>
<thead>
<tr>
<th>Overlap syndrome</th>
<th>Polyarteritis/Wegener’s granulomatosis</th>
<th>Giant cell arteritis/Churg-Strauss syndrome/Wegener’s granulomatosis</th>
<th>Temporal arteritis/polyarteritis</th>
<th>Takayasu’s arteritis/polyarteritis</th>
<th>Polyarteritis/cutaneous vasculitis</th>
<th>Henoch-Schoenlein purpura/polyarteritis</th>
<th>Systemic necrotising vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>No of patients</td>
<td>Heart</td>
<td>Respiratory</td>
<td>Renal</td>
<td>Joints</td>
<td>Skin</td>
<td>Eye</td>
</tr>
<tr>
<td>McDonald and DeRemee46</td>
<td>108</td>
<td>69</td>
<td>42</td>
<td>14</td>
<td>22</td>
<td>95</td>
<td>11</td>
</tr>
<tr>
<td>Anderson, et al26</td>
<td>264</td>
<td>&lt;4</td>
<td>63</td>
<td>60</td>
<td>20</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>DeRemee, et al26</td>
<td>50</td>
<td>4</td>
<td>70</td>
<td>46</td>
<td>16</td>
<td>12</td>
<td>74</td>
</tr>
<tr>
<td>Hoffman, et al21</td>
<td>158</td>
<td>&lt;8</td>
<td>85</td>
<td>77</td>
<td>67</td>
<td>46</td>
<td>52</td>
</tr>
<tr>
<td>Faucci, et al32</td>
<td>85</td>
<td>12</td>
<td>94</td>
<td>85</td>
<td>67</td>
<td>45</td>
<td>58</td>
</tr>
<tr>
<td>Garrett et al41</td>
<td>50</td>
<td>17</td>
<td>86</td>
<td>33</td>
<td>40</td>
<td>33</td>
<td>37</td>
</tr>
<tr>
<td>Walron37</td>
<td>18</td>
<td>28</td>
<td>100</td>
<td>83</td>
<td>56</td>
<td>44</td>
<td>39</td>
</tr>
<tr>
<td>Bronfman, et al95</td>
<td>21</td>
<td>29</td>
<td>100</td>
<td>81</td>
<td>57</td>
<td>48</td>
<td>43</td>
</tr>
<tr>
<td>Pinching, et al36</td>
<td>18</td>
<td>44</td>
<td>100</td>
<td>94</td>
<td>77</td>
<td>66</td>
<td>77</td>
</tr>
</tbody>
</table>
cardiomyopathy. The cardiitis may also affect the atria or produce mass lesions within the ventricles. These in turn may result in arrhythmia or obstruction, as in our patient who had both tachyarrhythmia and a detectable gradient across the left ventricular outflow tract. The single previous patient reported with a cardiac mass in Wegener's granulomatosis underwent surgical resection, although appropriate chemotherapy induced regression of the mass in our case.

VALVULITIS

Valve abnormalities may occur secondary to dilatation of the aortic root or left ventricle, but primary valvulitis is also recognised. It occurs both alone and as part of either widespread endocarditis or pancarditis. This may result in a mistaken diagnosis of culture negative infective endocarditis which fails to respond to antibiotic therapy and delay in the initiation of appropriate and potentially life saving treatment.

ARRHYTHMIA

Conduction abnormalities occur, possibly because of granuloma of the conduction system or arteritis of the atrioventricular nodal artery. All degrees of conduction defect are recognised, from intraventricular conduction defects (as in our case) through first and second degree to complete heart block. These may require permanent pacing but will occasionally correct with treatment.

The most common arrhythmias are atrial tachycardia and atrial fibrillation or flutter, and secondary to cardiac masses. Cardiac involvement in Wegener's granulomatosis is not as uncommon as generally thought, ranging from 6 to 44% of patients. It may take many forms and varies from the principal clinical feature to mild or subclinical disease. Involvement should be actively sought in patients with Wegener's granulomatosis and should be considered in patients with non-specific illness. In view of its protein clinical manifestations it should be considered early in the course of any apparent multisystem disorder including culture negative endocarditis, as it can similarly produce systemic upset with mass lesions and vasculitis. The risk of blind and potentially inappropriate antibiotic treatment for "culture negative endocarditis" are obvious. The possible differential diagnosis of Wegener's granulomatosis, now easily confirmed immunologically, should therefore be excluded early in the illness to reduce serious, long-term renal and pulmonary damage which may be fatal.

Echocardiography and particularly transoesophageal echocardiography can easily identify and delineate cardiac and proximal aortic involvement in Wegener's granulomatosis and may also have a potentially important role in following the response to treatment.
Cardiac involvement in Wegener's granulomatosis

SHORT CASES

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Cardiac involvement

CARDIAC INVOLVEMENT

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J Hardy

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SHORT CASES IN CARDIOLOGY

Gingival hyperplasia with nifedipine

David R Ramsdale, John L Morris, Phillip Hardy

A 57 year old man underwent coronary artery bypass surgery in 1981 and 1987, percutaneous transluminal coronary angioplasty and thrombolic therapy to reopen an occluded saphenous vein graft to the right coronary artery on two occasions in 1993, and directional coronary athrectomy to a proximal stenosis in the same graft. He had been taking nifedipine capsules between 1982 and 1987 and from February 1993 to January 1994 when he presented with a three month history of painful, swollen, and bleeding gums. Physical examination showed pronounced inflammatory gingival hyperplasia involving several papillae on the labial side of the lower anterior teeth (figure). The bulbous gingiva were red, shiny, and bled easily. There was periodontitis with plaque and calculus deposits. Treatment with nifedipine was stopped and he was advised to go for descaling and instructions on oral hygiene. Six months later the gingival hyperplasia had disappeared.

Although gingival hyperplasia is a well-known side effect of treatment with phenytoin, valproic acid, and cyclosporin, many physicians and cardiologists may not be aware that nifedipine,1 diltiazem,2 verapamil,3 and amloidine have been similarly implicated.

The nodular hyperplasia occurs mainly in the labial gingiva of the lower anterior teeth, around the maxillary molars or the interdental gingiva or both. Edentulous gums are unaffected. Histological examination shows hyperplasia, epithelial acanthosis with proliferation, reticulation, and elongation of the rete pegs.

Drug induced gingival hyperplasia usually regresses after nifedipine is stopped. Regression may take a few months. Rigorous oral hygiene including scaling, gingival massage, and antiplastic washings to control plaque are thought to be an essential part of the management to prevent recurrence.

Gingivectomy is sometimes required.


