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EXEMPLAR

Cardiac involvement in Wegener's granulomatosis

N E R Goodfield, S Bhandari, W D Plant, A Morley-Davies, G R Sutherland

Abstract

Wegener's granulomatosis is a systemic inflammatory disorder of unknown aetiology. The protean 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.

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

Department of Cardiology, Royal Infirmary, Edinburgh
N E R Goodfield
S Bhandari
A Morley-Davies

Department of Renal Medicine, Royal Infirmary, Edinburgh
W D Plant

Department of Cardiology, Western General Hospital, Edinburgh
G R Sutherland

Correspondence to:
Dr N E R Goodfield,
Department of Cardiology,
Royal Infirmary,
1 Lauriston Place,
Edinburgh EH9 9YW.

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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.[2-4] The mode of presentation is protean[5-7] 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.[8-11] 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.

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 (antimitochondrial, smooth muscle, double stranded DNA, intrinsic 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 electrocardiograph 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 antiarrhythmic 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. The

electrocardiogram showed first degree heart block in addition to the right bundle branch block. Six sets of blood cultures were negative for bacterial growth. Serological analysis for atypical organisms (coxiella, chlamydia, mycoplasma, psittacosis) and fungal precipitins were also negative. A clinical diagnosis of culture negative infective endocarditis was made and intravenous triple antibiotic treatment started.

Transoesophageal echocardiography was performed after transfer to our hospital, in an attempt to confirm the clinical diagnosis. Aortic incompetence with no evidence of vegetations 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.

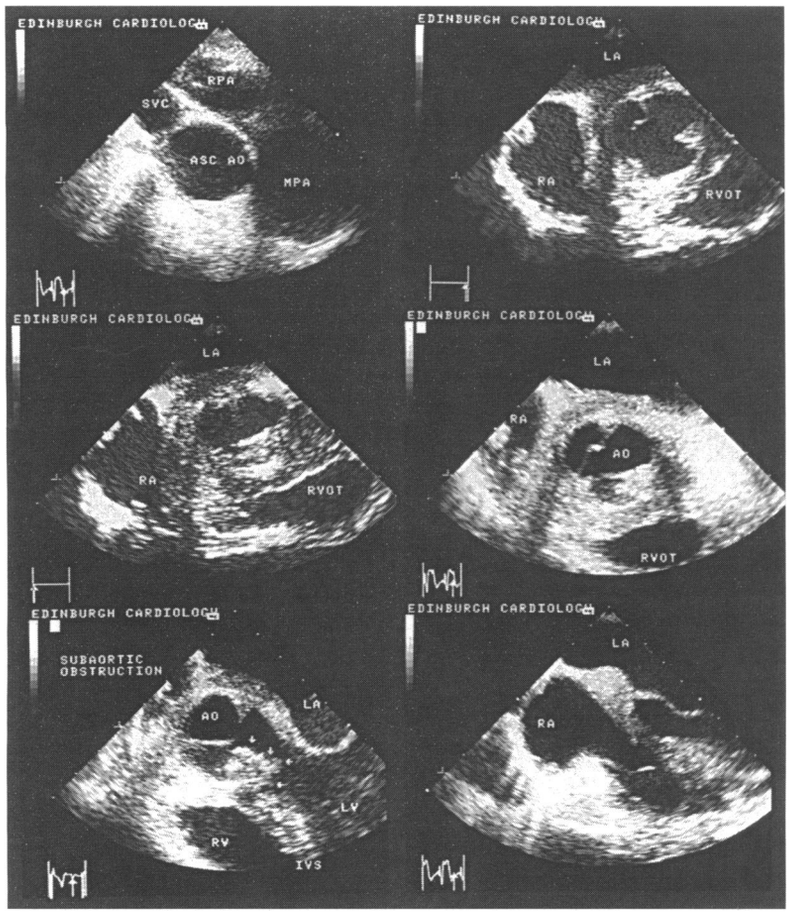

Figure 1 Initial pretreatment transoesophageal echocardiograms showing the features of aortic root and left ventricular outflow tract involvement in the patient described in the text. Upper left panel: transverse plane transoesophageal view at the level of the pulmonary artery. Note that walls of the ascending aorta above the aortic sinuses, the superior vena cava and the right pulmonary artery are of normal thickness. Upper right panel: the transverse plane transoesophageal probe has been advanced to the level of the upper aortic sinuses. The aortic wall thickened in a concentric manner with a ground glass appearance. The anterior wall of the right ventricular outflow tract and the right atrial medial wall are also thickened. Middle left panel: the probe has been advanced slightly further and increased thickening of the aortic root and atrial wall is seen. Middle right panel: the probe has been advanced to the level of the aortic valve, where maximal aortic root involvement is seen. Lower left panel: advancing the probe further a large mass lesion in the area of the membranous interventricular septum is seen, (arrows), which produced a pressure gradient within the outflow tract of 35–40 mm Hg as assessed by continuous wave Doppler. Lower right panel: retraction of the probe and angulation towards the atrial septum demonstrated involvement by Wegener's tissue of the anterior portion of the interatrial septum. The tissue of the foramen ovale and superior rim of the atrial septum was normal in thickness and appearance. SVC, superior vena cava; RPA, right pulmonary artery; ASC AO, ascending aorta; MPA, main pulmonary artery; LA, left atrium; RA, right atrium; RVOT, right ventricular outflow tract; AO, aorta; IVS, interventricular septum; RV, right ventricle; LV, left ventricle.

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 incompetence 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

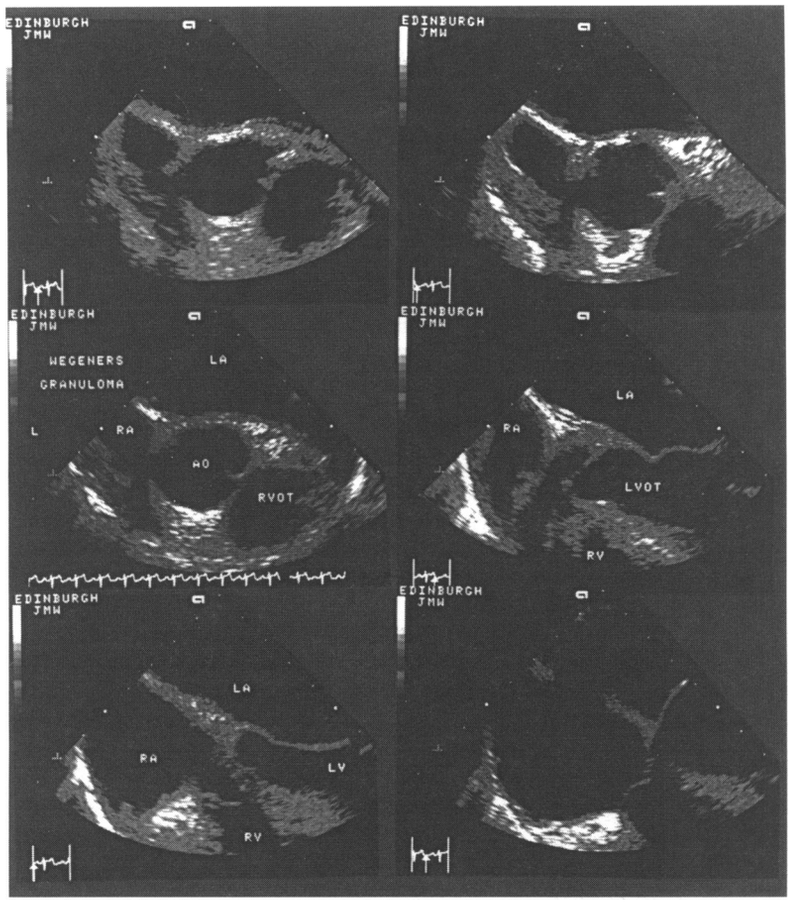

Figure 2 Transverse plane transoesophageal echocardiograms 6 weeks after starting treatment with cyclophosphamide and prednisolone. Upper left panel: the aortic root is cut in transverse section at the level of the left coronary artery. Note that the previous thickening seen in fig 1 is largely absent. Upper right, middle left and middle right panels: sequential sections are demonstrated by introducing the probe further through the aortic valve and into the left ventricular outflow tract. Note that gross thickening of the aortic root and hyperechogenicity are now mostly absent. The mass lesion in the left ventricular outflow tract has resolved. Continuous wave Doppler examination from the apex confirmed normal flow velocities in the left ventricular tract after treatment. Lower left and right panels: the probe was retracted to examine the atrial septum; the previous thickening has largely resolved. These features were considered to indicate resolution of Wegener's granulomatosis from the aortic root and the upper left ventricular outflow tract. LA, left atrium; RA, right atrium; RVOT, right ventricular outflow tract; AO, aorta; RV, right ventricle; LV, left ventricle; LVOT, left ventricular outflow tract.

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.[12] It was first defined as a distinct clinical syndrome in 1936,[13 14] but had previously been described by Klinger in 1931[15] and McBride in 1897.[16 17] 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 arteritis.[12 18] This means the clinical manifestations are protean and the condition should be considered in the differential diagnosis of any multisystem disorder.[5-7] The diagnosis is primarily based on characteristic clinical features combined with specific organ involvement and histological findings (table 1). These traditional classification systems,[19 20] however, may discriminate poorly between related diseases.[2 21] 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).[18] In Wegener's granulomatosis the characteristic granulomata may be absent or difficult to identify in the biopsy material obtained in any one case.[6 12] This difficulty in obtaining histopathological confirmation[5 18] leads to a delay in diagnosis; in a series of 158 patients reported by Hoffman *et al*[22] the mean time

Table 1 Systemic vasculitides

	Vessel involvement	*Classical organ involvement*	*Granuloma*	*Comments*
Wegener's granulomatosis	Small–medium sized vessels	Upper and lower respiratory tract, necrotising vasculitis and glomerulonephritis	Present	c-ANCA classically present
Microscopic polyarteritis	Small vessels and/or small–medium sized arteries	Necrotising glomerulonephritis, necrotising vasculitis (respiratory tract)	Absent	p-ANCA classically present
Classic polyarteritis nodosa	Small–medium sized arteries	No glomerulonephritis—renal involvement via arteritis	Absent	Microaneurysm formation; ANCA very infrequently positive
Takayasu's arteritis	Aorta and major branches		Present	Common in young oriental females; ANCA very infrequently positive
Kawasaki syndrome	Small, medium and large arteries, including coronary arteries		Absent	ANCA very infrequently positive Children; associated mucocutaneous lymph node syndrome; ANCA sometimes positive—anticathepsin G
Giant cell arteritis	Aorta and major branches, especially extracranial branches of carotid artery		Absent	< 50 years of age; associated polymyalgia rheumatica; ANCA very infrequently positive
Churg–Strauss syndrome	Small–medium sized vessels	Respiratory tract, necrotising vasculitis	Present	Eosinophilia and asthma/allergic rhinitis; ANCA infrequently positive
Henoch–Schoenlein purpura	Small vessels	Skin, gut, glomerulonephritis, joints	Absent	IgA immune deposits, adults or children; ANCA very infrequently positive

ANCA, antineutrophil cytoplasmic antibody; c-ANCA, cytoplasmic ANCA; p-ANCA, perinuclear ANCA.

Table 2 "Overlap syndromes"—systemic vasculitides manifesting mixed clinicopathological features

Overlap syndrome
Polyarteritis/Wegener's granulomatosis
Giant cell arteritis/Churg–Strauss syndrome/Wegener's granulomatosis
Polyarteritis/Churg–Strauss syndrome
Temporal arteritis/polyarteritis
Takayasu's arteritis/polyarteritis
Polyarteritis/cutaneous vasculitis
Henoch-Schoenlein purpura/polyarteritis
Systemic necrotising vasculitis

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%)[21 25] and not only simplify diagnosis but also allow an immunological component to be included in classification systems.[3 23 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.

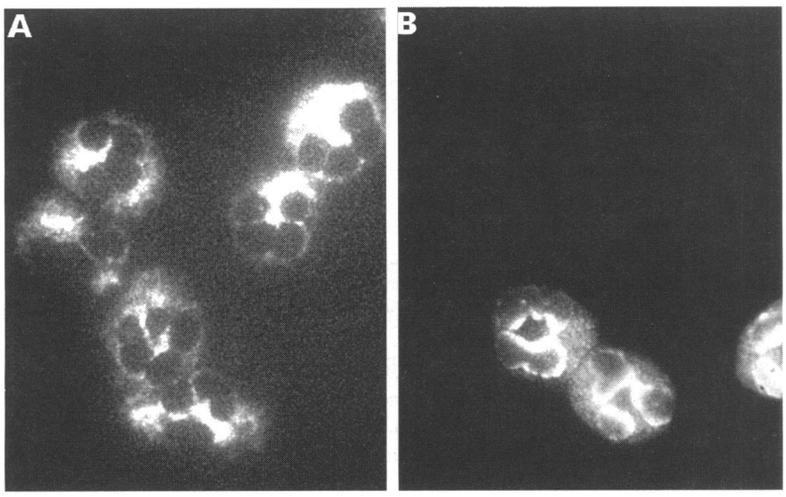

Figure 3 Indirect immunofluorescence of ethanol fixed neutrophils exposed to the serum of patients with systemic vasculitis. Fluorescein labelled antihuman antibodies identify two classical patterns. (A) Diffuse cytoplasmic pattern of antineutrophil cytoplasmic antibody which tends to be associated with Wegener's granulomatosis and a circulating antibody against proteinase-3. (B) Localised pattern of perinuclear antineutrophil cytoplasmic antibody which tends to be associated with microscopic polyarteritis and a circulating antibody against myeloperoxidase.

Cardiac manifestations, previously said to be uncommon[6 8–11] may not be so rare[27] (table 3). In reviewing these and other series[35–38] and Keifer Lehmann[39] and Grant *et al*[27] identified a wide discrepancy in the reported incidence of cardiac involvement. These variations may reflect the variable natural history of the disease,[39] the source of patients,[27 34] the specialty of the group investigating the patients,[29] the size of the population studied,[32–34] or the availability of techniques such as echocardiography to diagnose subclinical cardiac involvement before death.

Forstot *et al*[40] 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 alone[33 41] and in conjunction with other cardiac abnormalities[42–45] and may be unexpectedly found at postmortem examination,[46 47] present acutely as tamponade,[48] or as chronic constriction.[27 49 50] In a few cases pericarditis may be secondary to myocardial infarction or uraemia due to renal involvement.[32]

ARTERITIS

Generalised arteritis may produce a systemic illness with fever, malaise, and weight loss,[4 21] which may mimic infective endocarditis. More localised arteritis is recognised, affecting the coronary arteries producing coronary artery stenoses,[51] myocardial infarction,[8 41] and death.[46 47 52 53] Inflammation may also involve the aorta both proximally, causing dilatation,[27] and distally, causing retroperitoneal inflammation.[54] Proximal aortic involvement has previously been noted at postmortem examination [9 12 44 55] 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 recognised[30 52] and can produce acute cardiac failure.[11 41 44 45 56] It may later progress to

Table 3 Organ involvement in Wegener's granulomatosis

Reference	*No of patients*	*Organ involvement (%)*							
		Heart	*Respiratory*	*Renal*	*Joints*	*Skin*	*Eye*	*Ear, nose and throat*	*Nervous system*
McDonald and DeRemee[28]	108		69	42		14	22	95	11
Anderson, *et al*[29]	265	<4	63	60	20	25	14	75	
DeRemee, *et al*[19]	50	4	70	46		16	12	74	22
Hoffman, *et al*[22]	158	<8	85	77	67	46	52	92	23
Fauci, *et al*[30]	85	12	94	85	67	45	58	91	22
Garrett *et al*[31]	30	17	86	33	40	33	37		10
Walton[7]	56	27	48	25	34	46	23	89	
Fauci and Wolff[32]	18	28	100	83	56	44	39	94	22
Wolff, *et al*[33]	21	29	100	81	57	48	43	95	24
Pinching, *et al*[34]	18	44	100	94	77	66	77	94	44

cardiomyopathy.[8 30] The carditis may also affect the atria[12 45] or produce mass lesions within the ventricles. These in turn may result in arrhythmia[42] 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[42] 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[27] or left ventricle, but primary valvulitis is also recognised.[9 10] It occurs both alone[50 57 58] and as part of either widespread endocarditis or pancarditis.[41 44 51] This may result in a mistaken diagnosis of culture negative infective endocarditis which fails to respond to antibiotic therapy[6] 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.[43] All degrees of conduction defect are recognised, from intraventricular conduction defects[34 40] (as in our case) through first[27 49] and second degree to complete heart block.[34 40 49 59 60] These may require permanent pacing but will occasionally correct with treatment.[40 49 60]

The most common arrhythmias are atrial tachycardia and atrial fibrillation or flutter.[32 34 43 47 49] Ventricular arrhythmia has been noted[40] in association with dilated cardiomyopathy,[30] ischaemia[33 46 47] and secondary to cardiac masses.[42]

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 protean 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 risks 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.

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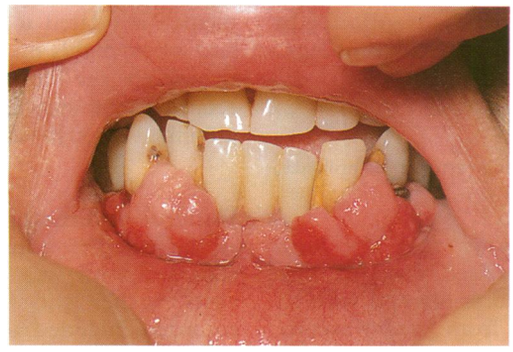
SHORT CASES IN CARDIOLOGY

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 thrombolytic therapy to reopen an occluded saphenous vein graft to the right coronary artery on two occasions in 1993, and directional coronary atherectomy 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.



Severe inflammatory gingival hyperplasia causing pain, swelling, and bleeding. Plaque and calculus are also visible.

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 amlodipine[4] 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 antiseptic washings to control plaque are thought to be an essential part of the management to prevent recurrence. Gingivectomy is sometimes required.

Cardiothoracic Centre, Liverpool
D R Ramsdale
J L Morris
P Hardy

Correspondence to:
Dr D R Ramsdale, Department of Cardiology, The Cardiothoracic Centre, Thomas Drive, Liverpool L14 3PE.

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