# Three strokes and a heart attack in a fit and relatively young woman

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**Mirdhu Wickremaratchi*, Tom Hughes*, Charles Warlow†, Maggie Hourihan‡, Alistair Lammie§**
*Departments of Neurology, ‡Neuroradiology and §Pathology, University Hospital of Wales, Heath Park, Cardiff, UK and †Department of Clinical Neurosciences, University of Edinburgh, Edinburgh, UK;
E-mail: Tom.Hughes@UHW-TR.wales.nhs.uk
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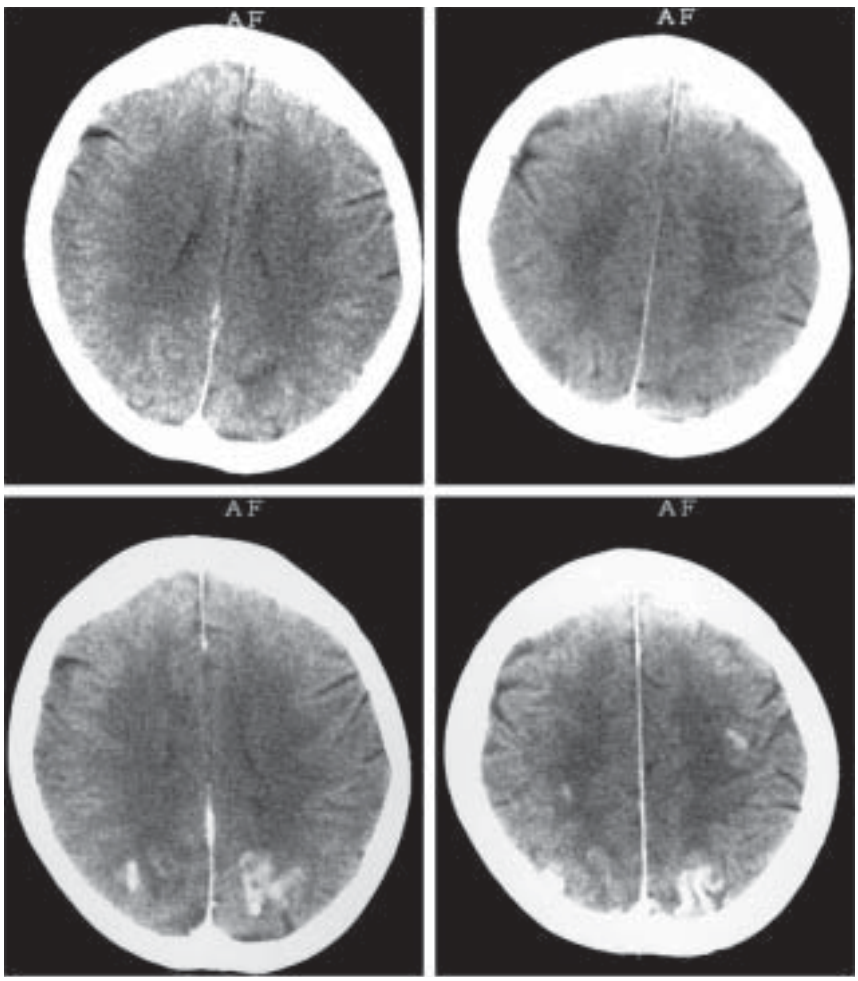
## THE STORY

A 52-year-old female presented on 3 July 2001 with the sudden onset of nausea, vomiting and double vision. On admission she was drowsy and vague with a right hemiparesis, poor coordination of the right side, and a right inferior homonymous quadrantinopia. A CT brain scan on 4 July excluded intracerebral haemorrhage and was repeated with and without contrast on the 16 July (Fig. 1). She gradually improved and was discharged home 2 weeks later, independently mobile.

On 12 August 2001 she was woken by central crushing chest pain. An ECG showed acute inferior myocardial infarction and the troponin T level was raised at 1.78. Thrombolysis was not given. Six hours after admission she became drowsy and weak down the left side. There was difficulty with voluntary control of gaze, left sided visual inattention, a left hemiparesis and bilateral extensor plantars. Brain CT showed infarction in part of the right middle cerebral artery territory. The next day she became cold and clammy. An ECG suggested lateral extension of the myocardial infarct. She was drowsy, BP 180/95, pulse 120 bpm, afebrile and there was no neck rigidity. Over the next 2 weeks she improved. A transthoracic echocardiogram revealed apical dyskinesia with an ejection fraction of 76%. Coronary angiography was considered to be too risky because of her neurological condition. Secondary prevention with an ACE inhibitor and aspirin was recommended.

Over the next 5 months she became mobile but had persisting visual problems that limited her participation in therapy and made her dependent on ward staff. Although she was able to give a detailed description of her environment in soft lighting, and could recognize people, shapes and objects she felt that the images were fragmented. She could not, reliably, reach out to something she could see. On examination on 8 January 2002 she was healthy and well nourished. General medical examination was unremarkable; height 162 cm, weight 58 kg. She was

**Figure 1** Pre (top) and post contrast (bottom) CT scans. The images demonstrate a small focal area of low density in the left frontal lobe and low densities in both parieto-occipital lobes. Post contrast there is enhancement that is more extensive in the parieto-occipital lobes, reflecting areas of ischaemic damage.



fully orientated, gave a good account of herself, and had good insight into her problems. Her speech was normal although a detailed language assessment suggested some high level difficulty with word finding and the organization and sequencing of responses. On testing near vision she could identify – if given sufficient time – individual letters (N6), and construct the relevant word correctly, but found reading very difficult. Her hand-writing was illegible. Pupils and fundi were normal. She was unable to shift gaze voluntarily to objects of interest and had difficulty reaching accurately under visual guidance. There was a left inferior homonymous quadrantinopia. She was unable to draw the numbers on a clock or copy a simple diagram. She had a mild left hemiparesis but was able to walk independently with one stick.

On 20 January she suddenly developed a left hemiparesis. A CT scan of the head on 21 January showed a huge right cerebral infarct (Fig. 2). Over the next 48 h she deteriorated and died on 24 January

For the 6 years prior to becoming unwell she had experienced attacks of classical migraine once or twice per year; on two occasions there had been a visual disturbance. She had not been able to tolerate a number of different types of hormone replacement therapy. However she was generally well and in the week before the first episode in July 2001 she had climbed to the top of Cader Idris (892 m) for the first time. There was no family history of neurological disease and she had not been on any medication. She did not smoke and drank only small amounts of alcohol. There was no history of recreational drug use.

## INVESTIGATIONS

The following investigations were normal throughout the course of her illness: urea, electrolytes, glucose, liver function, calcium, thyroid function, B12, folate, C-reactive protein, cholesterol, triglyceride, prothrombin time, activated partial thromboplastin time, thrombin time, ANCA (C and P). A mild thrombocytopenia at the time of the heart attack (platelet count $39–79 \times 10^9$/L) resolved spontaneously. Haemoglobin and white cell count were normal throughout. Cultures of blood and urine were negative. Anticardiolipin antibodies were not detected and a lupus anticoagulant screen, including a dilute Russell's Viper Venom time, was normal. In August 2001 the ESR was 43 mm/h, falling to 7 mm/h in October. In August 2001

At this age, with no family history or risk factors for vascular disease, the most likely causes are arterial dissection or embolism from or through the heart

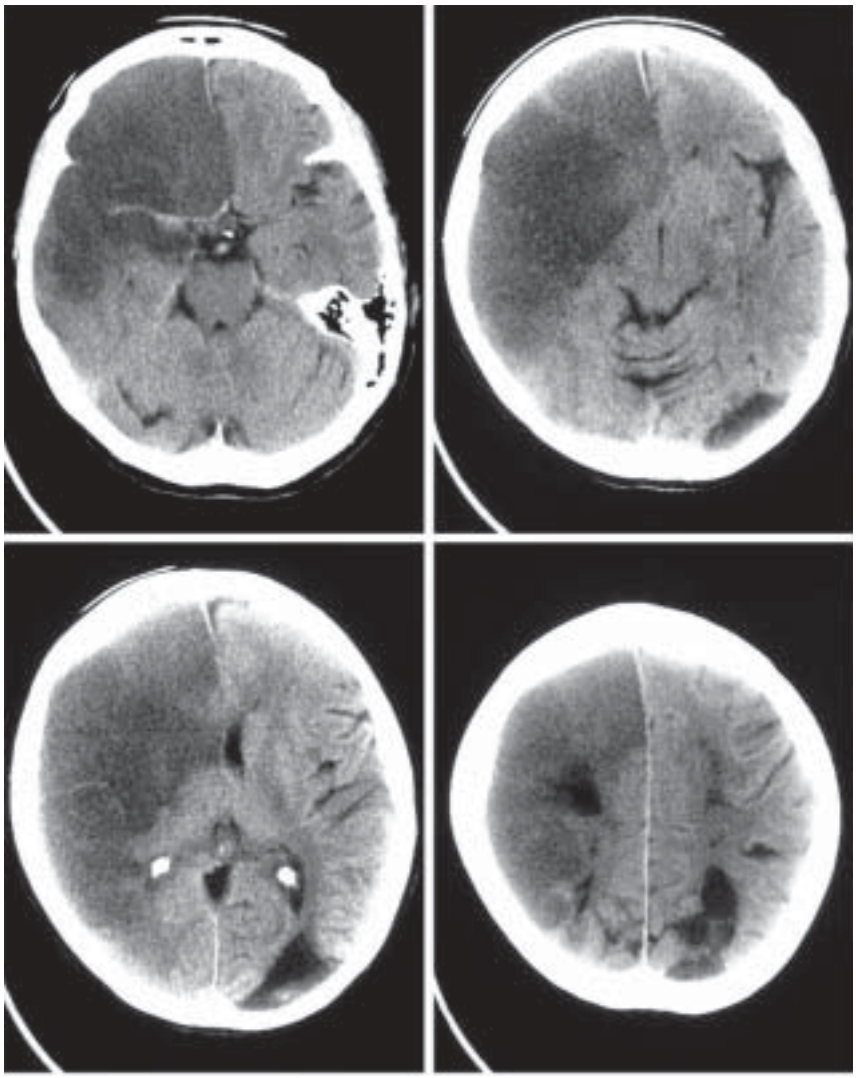


**Figure 2** Non-contrast CT scan demonstrating acute infarction in the right frontal and anterior temporal lobes with mass effect.

antithrombin III was 132%, protein C-chromogenic 150%, and activated protein C resistance 2.42.

## THE STORY EXPLAINED?

### Professor Charles Warlow

The simplistic approach is that here is a relatively young woman who has had three strokes and a heart attack, all due to atheroma, which, after all, is a generalized vascular disorder affecting several arteries. A more sophisticated neurological approach is to add that she also had some interesting neuropsychological problems, particularly with vision, and to spend some time dissecting these to illuminate how the brain works. However, I want to know what stops the brain working and how to fix it, or at least to stop any recurrence. So why should a woman at this relatively young age with no vascular risk factors or family history of neurological disease – and I shall assume cardiac disease too – who was fit enough to be scrambling over the Welsh mountains, have had a stroke in the first place? But was the first event on 3 July 2001 a stroke? Yes. It came on suddenly – at a stroke – and the clinical features suggested very strongly that there were focal lesions in the distribution of the posterior circulation with brain stem (the vomiting and diplopia) and left occipital lobe features (the right homonymous quadrantinopia). Something embolic had probably shot up the basilar artery, broken up, and fragments occluded the circulation to the brainstem and left occipital lobe. Indeed, an unenhanced brain CT the next day ruled out the highly unlikely possibility of haemorrhage as the cause of the stroke (because there would have to have been two simultaneously, which, although not impossible, is unlikely), and the later scan, with and without contrast (Fig. 1), showed enhancement, presumably luxury perfusion, in infarcts in both occipital areas. The lack of any visible infarction in the brain stem does not mean there was no infarct there – not even the more sensitive MR is sensitive enough to pick up all infarcts in the brain stem or anywhere else. There also looked as though there might have been some other small infarcts, in the middle cerebral artery territories on the left *and* right – perhaps there had been embolism from somewhere into the anterior circulation too, or maybe this patient had an unusually extensive posterior cerebral artery territory of supply. The imaging did not look at all like venous infarcts and nor like the stroke-like lesions one can see in the posterior area of the brain in MELAS.

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So what caused all this? At this age, with no family history or risk factors for vascular disease, the most *likely* causes are arterial dissection or embolism from or through the heart (Warlow *et al*. 2001). Despite the past history of migraine with visual aura, this is not a migrainous stroke because it came on far too quickly and without the typical migrainous spread and intensification, and there was no headache. Being unable to tolerate HRT is a red herring.

We are not told whether there was a recent history of neck trauma to cause vertebral dissection, but then was she actually asked whether she had recently had a whip lash in a car crash or been grabbed around the neck during play with a grandchild, or had someone attempted to strangle her? Unlikely, and even less than unlikely as the story unfolds later with a heart attack and more strokes. We are not told whether she had ultrasound of her neck arteries, or indeed any arterial imaging at all. Also, even at this first stroke stage I would have looked very hard at her heart with a transthoracic if not a transoesophageal echocardiogram. We know there was no thrombophilia, which although a cause of venous thrombosis is a vanishingly rare cause of arterial thrombosis, and anyway there was no personal or family history of recurrent thromboses.

So the story moves on and a month later she has a clearcut history, ECG and tropinin positive heart attack. She was not given thrombolysis, perhaps because she came into hospital too late, or maybe the recent stroke was regarded as a contraindication, or maybe the physicians were worried about something else – the lowish platelet count perhaps. They must have become extraordinarily worried when within 6 hours of admission she had another stroke – the clinical features suggested a right hemisphere lesion with weakness down the left side, and left visual inattention. The brain CT next day showed an infarct in the expected place, part of the middle cerebral artery territory. To add insult to injury, the myocardial infarct extended laterally from the original inferior location. However, from the

heart point of view she recovered surprisingly well, the ejection fraction of 76% was very normal and there was just some apical dyskinesia on the transthoracic echocardiogram.

So what caused this second ischaemic stroke, and indeed the more or less simultaneous heart attack? I can't believe this was all due to widespread atheroma in the coronary and cerebral arteries, becoming unstable in two places simultaneously even though there is some evidence that plaque instability can be provoked by systemic factors (Rothwell *et al* 2000). She is too young for widespread atheroma, particularly without any vascular risk factors or family history. In fact, there are not that many reasons for more or less simultaneous heart attack and brain attack; the underlying cause of this patient's problem must be somewhere in Box 1.

The final ischaemic stroke in January 2002 was fatal. This time it was another left hemiparesis, and the brain CT on the following day (Fig. 2) showed a huge fresh right middle cerebral arterial territory infarct, along with the old infarcts and perhaps some others that may have been subclinical in the left cerebral hemisphere – we had hints of those right from the first stroke. Not surprisingly she died a few days later.

So let's go back to the causes of simultaneous brain and heart attack (Box 1)

- The August stroke was far too quick after the heart attack to be due to embolism from clot forming in the left ventricle overlying the myocardial infarct.
- Clot can form quite quickly in a fibrillating atrium but she was not in atrial fibrillation so that is out.
- Paradoxical embolism due to a deep venous thrombosis (DVT) complicating the heart attack? Again the stroke was too quick after the onset of the heart attack, a DVT probably would not yet have formed.

Furthermore, none of these three possibilities can explain the stroke a month earlier unless one supposes that the apical dyskinesia was longer standing and due to an earlier subclinical myocardial infarct. But, for what it is worth, not only was no intracardiac thrombus seen on the echo but thrombus is far more likely with large anterior than inferior infarcts.

Instrumentation of the aorta and coronary arteries can cause an embolic stroke just after a heart attack, but she didn't have coronary angiography.

This is not a haemodynamic ischaemic stroke due to a drop in cerebral perfusion pressure because she didn't have a cardiac arrest and she was not hypotensive. These sort of strokes are more often in boundary zone areas *between* arterial territories and here they were very much within arterial territories on CT, and anyway what about the other two strokes that were not associated with a heart attack?

Could she have had a systemic vasculitic disorder affecting the coronary as well as the brain arteries? I think not. The classical one is Kawasaki disease but this is an acute febrile systemic illness in infants and children with rash and lymphadenopathy. There was no hint of vasculitis here – no malaise, weight loss, or multiorgan involvement; a normal ESR (apart from in the aftermath of the heart attack and second stroke), C-reactive protein and haemoglobin. There were no anticardiolipin antibodies and the ANCA was negative but then it usually is in large vessel vasculitides. Very few vasculitides affect arteries the size of the main stem of the middle cerebral artery as must have been involved in this patient's final stroke, they mostly involve smaller arteries and veins. Two that do

**Box 1 Causes of simultaneous – or more or less simultaneous – brain attack and heart attack**

- Thrombus forming over an acute myocardial infarct of the left ventricle and embolizing to the brain.
- Atrial fibrillation and embolism from the left atrium.
- Paradoxical embolism through the heart.
- Instrumentation of the aorta, coronary arteries or heart valves.
- Hypotension and ischaemic stroke due to impaired cerebral perfusion.
- Vasculitis.
- Heparin-induced thrombocytopenia.
- Aortic arch dissection.
- Embolism from the heart to the brain, and to the coronary arteries.
- Haemorrhagic stroke due to therapeutic thrombolysis, heparin, aspirin, etc.

I think embolism from the heart to the brain is the most likely possibility, but we would have to suppose that emboli got not just to the brain but also to the right coronary or left circumflex artery to give her the inferior myocardial infarct

are very unlikely here. Giant cell arteritis affects older people and there really should be a raised ESR and/or systemic features. We are not told of this lady's racial origin and Takayasu's disease can occur in whites as well as orientals, but again it has systemic features, at least in its early stages, there is often neck pain, and we are not told about absent peripheral and neck pulses.

Could she have had the rare thrombotic disorder seen with prolonged heparin use, associated with thrombocytopenia? I think not. She only had thrombocytopenia around the time of the heart attack and although that may have been due to heparin (if she was given it, which we are not told), clearly it can be nothing to do with the earlier and later strokes when the platelet count was normal. The same reasoning goes for thrombotic thrombocytopenic purpura, and disseminated intravascular coagulation, but these rarely cause stroke-like syndromes.

Aortic dissection might have been the cause of the ischaemic strokes with the dissection affecting the major vessels arising from the arch as well as the right coronary artery to cause the heart attack. There isn't always chest or interscapular pain or aortic regurgitation, but we are not given any information about the neck arteries from ultrasound or indeed told any arm or neck pulses were absent. The falling platelet count might have been due to a large transmural haematoma in the aortic arch, or maybe this is a bit far-fetched, but a suspected dissection would certainly have stopped any thrombolytic treatment for the MI. Against this diagnosis is what she was treated with – just an ACE inhibitor and aspirin, which are standard practice after an ordinary MI. If she had had a dissection she would probably have had far more aggressive blood pressure lowering with beta blockers, and even surgery if her neurological state was up to it. Also she was not hypotensive, which one might expect in dissection; her BP was actually a bit up at 180/95.

I think embolism from the heart to the brain is the most likely possibility, but we would have to suppose that emboli got not just to the brain but also to the right coronary or left circumflex artery to give her the inferior myocardial infarct. Whilst that can happen, it is very rare – emboli don't often seem to go round 90 degree bends, although one wonders why not if the blood itself does. Cardiac tumours can embolize to the brain but even the most common – myxoma – is very rare and there are usually systemic features that she did not have – malaise, weight loss, temperature, anaemia, raised ESR and so on (Reynen 1995). An even rarer possibility is a papillary fibroelastoma, a benign tumour that grows on cardiac valves and here there are no systemic features and, because it can grow on the aortic valve, acute myocardial infarction due to coronary artery occlusion has been well described (Bevilacqua & Corredoira 2002). However, no tumour was seen on the echo but she didn't have the more sensitive transoesophageal echocardiogram. Sarcomas of cardiac valves have also been described, and even secondaries to the heart but these are usually to the right side and so wouldn't embolize to the brain, and there is no hint of malignancy about this case. I suppose there might have been something going on at the apex of the left ventricle to explain the dyskinesia, but not a cardiomyopathy of the sort that might be associated with systemic embolism. Vegetations on the aortic valve might have got into the coronary arteries as well as the brain but she didn't have infectious endocarditis – no murmurs, no malaise, no fever, no valve lesions on the echo, negative blood cultures and ischae-

mic events over 7 months, which is too long. She seemed far too well to have non-bacterial thrombotic 'marantic' endocarditis of the sort one can get with cancer or other debilitating disease, and I don't think she had systemic lupus erythematosus so Libman–Sacks endocarditis is out. Embolism through the heart seems unlikely too. Although transthoracic is not as good as transoesophageal echo for detecting patent foramen ovale, and she did not have bubble contrast, there was no reason for her to have a deep venous thrombosis and then paradoxical embolism.

The cause of the problem must have been in or near her heart so I would have involved a cardiologist, even right from the first stroke and urged him or her to investigate the heart and aortic arch extremely thoroughly (Chambers 2002). Was there a cardiac tumour, clot in the left atrial appendage, or vegetations on the valves that were missed on transthoracic echo, or a dissected aorta or even some very rare tumour on the aortic valve or thererabouts? So I will come down on some sort of tumour in the heart, or more likely on the aortic valve, and a papillary fibroelastoma would be the best fit because of the lack of systemic features, and the embolism to the coronary as well as to the cerebral circulation.

At least that is what I was going to suggest before I woke with a start at 5.30am on the morning of this clinicopathological conference, in the midst of a dream that was telling me that there were no cobras on Cader Idris, the Welsh mountain the patient had climbed the year of her death. Why cobras? Could this be something to do with another snake – vipers perhaps? The negative Russell Viper Venom test? And then the case suddenly made sense. The diagnosis must be the antiphospholipid syndrome (Greaves 1999) when the functional clotting tests (such as Russell's Viper venom) can be normal, and even the anticardiolipin antibodies can be negative if they are tested for in the midst of an acute stroke (Drenkard & Alarcon-Segovia 1989). Sterile vegetations are well described on the cardiac valves and can embolize. The slightly raised ESR, migraine and the lowish platelet count fit. And finally the alternative name of Hughes's syndrome is the same as the neurologist involved in her care – Tom Hughes, no relation, but a nice twist at the end of the case, typical of all the best crime stories.

## The post mortem – Dr Alistair Lammie

Consent was obtained from the relatives for an autopsy limited to the heart, great neck vessels and brain.

The brain was globally swollen with right-to-left midline shift, right uncal and subfalcine herniation and secondary (Duret) brainstem haemorrhage. There was an acute right total anterior circulation cerebral infarct, and large old bilateral anterior/middle cerebral artery borderzone infarcts extending from the level of the mid-hippocampus anteriorly almost to the occipital pole on both sides. There was occlusive thrombus in the distal right intracranial internal carotid artery, but no significant cerebral artery atheroma. Brain histology revealed multiple recent and organizing occluded vessels, mainly cortical. Multiple small cortical infarcts of varying age, not detected grossly, accompanied the larger regional infarcts.

The aortic arch, carotid and vertebral arteries showed fatty streaking only. The coronary ostea and arteries were widely patent. The heart contained a large, healing, posterolateral myocardial infarct, and multiple small, healed, organizing and recent infarcts. There was no mural thrombus. All the leaflets of the mitral and aortic valves bore small, loosely adherent, friable vegetations (Fig. 3), with no evidence of valve destruction or congenital valve abnormality. Valve histology showed non-destructive small platelet/fibrin vegetations, with no inflammation, organization or microorganisms (Fig. 4). Occlusive thrombo-emboli in heart, brain and kidney had the same histological appearance.

Permission was then granted for the autopsy to be extended, revealing a left pleural effusion, multiple renal infarcts, a small uterine body leiomyoma (fibroid) and an encapsulated left ovarian tumour ($6 \times 10 \times 10$ cm), comprising a large cyst with multiple pale grey and yellow mural tumour nodules. Histology showed a low-grade tubulopapillary variant of clear cell ovarian carcinoma (Fig. 5).

## Professor Warlow's diagnosis

Antiphospholipid antibody (Hughes's) syndrome with embolism of cardiac valvular vegetations to the brain and heart

## Autopsy diagnosis

Emboli to brain, heart and kidney from non-bacterial thrombotic ('marantic') endocarditis

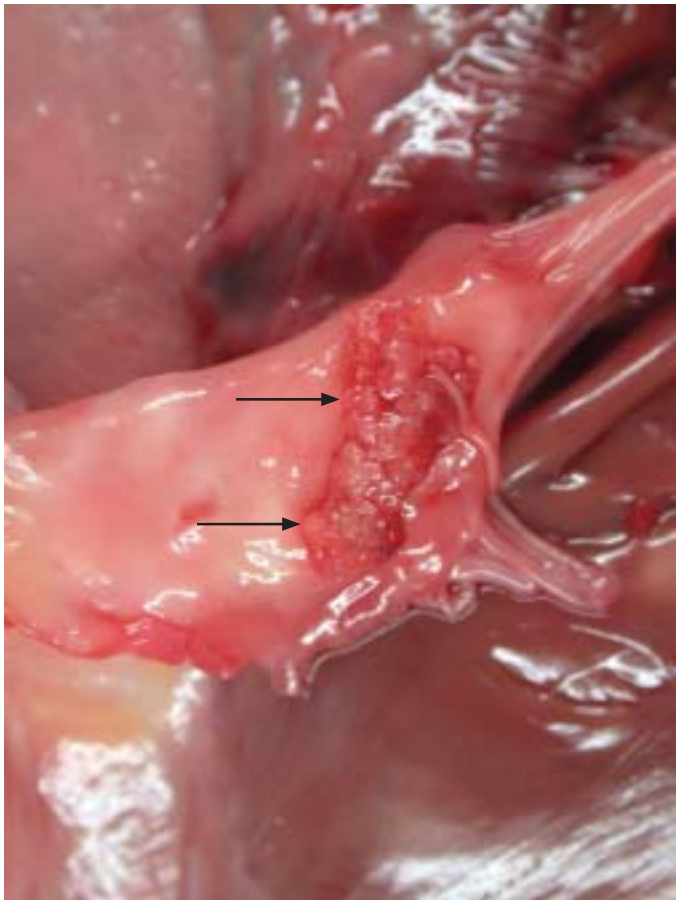

**Figure 3** Mitral valve leaflet at autopsy showing friable, loosely adherent vegetations on its free edge (arrows).

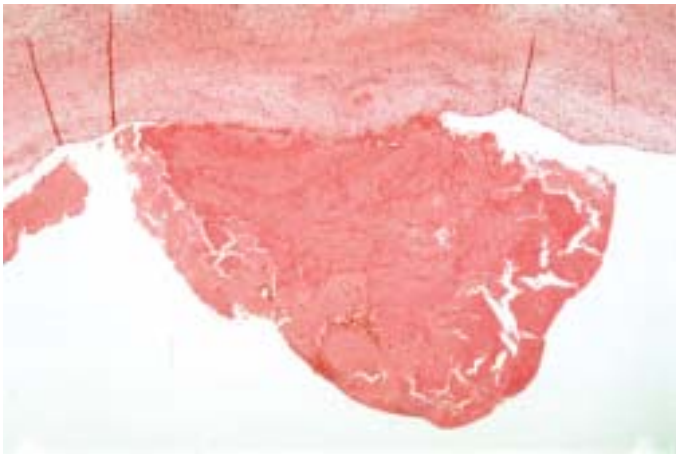

**Figure 4** Low power photomicrograph of aortic valve leaflet with attached platelet-fibrin thrombus, without inflammation or microorganisms (haematoxylin and eosin).

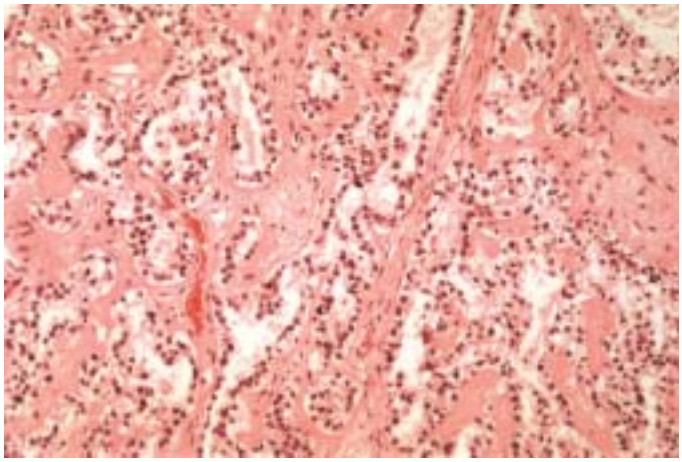

**Figure 5** Left ovarian cyst – papillary fibrovascular cores covered by mucin-secreting adenocarcinoma cells, with clear or pale cytoplasm (haematoxylin and eosin).

affecting the aortic and mitral valves, which in turn was due to a mucin-producing ovarian carcinoma.

## LITERATURE REVIEW

In 1865 Trousseau first described multiple venous thromboses, especially thrombophlebitis, as a complication of occult carcinoma (Raychaudhuri 1971). Non-bacterial thrombotic endocarditis (NBTE) was first described by Zeigler in 1888 (Lopez 1987), and then in 1938 Sproul described the association of carcinoma of the pancreas with widespread venous thrombosis, vegetations on cardiac valves and multiple arterial infarcts (Sproul 1938). NBTE denotes the presence of sterile, fibrin-platelet thrombus on structurally normal, or subtly degenerate, cardiac valves (Fayemi & Deppisch 1977; *BMJ* 1978). There are several reports, mainly retrospective autopsy studies, of malignancy-associated NBTE giving rise to embolic manifestations. Carcinomas that have been described in association with NBTE include pancreas, lung, stomach, ovary, colon, breast, kidney, gallbladder, prostate, and bile duct, as well as a variety of lymphomas, sarcomas, melanomas and leukaemias. A mucin-secreting adenocarcinoma is the commonest histology.

A Medline search from 1960 to the present day found 25 cases of stroke caused by malignancy-associated NBTE (Sproul 1938; Barron & Siqueira *et al*. 1960; Aguayo 1964; Raychaudhuri 1971; Kooiker & MacLean *et al*. 1976; Studdy 1976; Sack & Bell 1977; Kearsley 1982; Ojeda & Frost *et al*. 1985). In eight cases stroke was the presenting feature in a previously-well individual, as in this case (Table 1). In 11 cases there was a non-neurological presentation but stroke occurred before a diagnosis of NBTE was made. In six cases the presenting features were unclear but neurological symptoms preceded the diagnosis of NBTE and carcinoma. In none of these cases did the time from onset of neurological symptoms to death exceed 2 months, so our case was unusual in this respect. In some cases, multiple episodes of neurological dysfunction may have occurred (Rogers & Cho *et al*. 1987)

It is well known that malignancy may be associated with a hypercoaguable state, which, acting together with subtle damage to the heart valve surface, contributes to the pathogenesis of NBTE. What is not clear however, is whether the cerebrovascular consequences of cancer are all due to cardiac emboli or can be a result of in-situ intravascular thrombosis. Woimant *et al*. (1998) suggested the possibility of cerebral infarcts due to neoplasm-associated disseminated intravascular coagulation and occlusion of medium sized arteries, in the absence of NBTE.

**Table 1** Summary of published cases of previously-well patients presenting with stroke due to malignancy associated nonbacterial thrombotic endocarditis

| PATIENT (REF) | AGE | GENDER | PRESENTATION | VALVE | NEOPLASM | TIME BETWEEN STROKE ONSET AND DEATH |
|---|---|---|---|---|---|---|
| 1 (Kooiker *et al*. 1976) | 51 | F | R hemiparesis, non-fluent aphasia | Mitral | Mucinous cystadenoma of ovary | 3 days |
| 2 (Kooiker *et al*. 1976) | 58 | F | L hemiparesis, dysarthria | Aortic | Undifferentiated carcinoma of lung + 1° undifferentiated carcinoma small bowel | 6 weeks |
| 3 (Kooiker *et al*. 1976) | 54 | F | R hemiparesis, aphasia | Mitral | Giant cell carcinoma (site not given) | |
| 4 (Kooiker *et al*. 1976) | 68 | M | L hemiparesis | Aortic | Pancreas | |
| 5 (Kooiker *et al*. 1976) | 72 | M | Ataxia, vertigo, hemiparesis | Aortic | Prostate | |
| 6 (Barron *et al*. 1960) | 63 | F | Transient episodes L + R hemiparesis + dysphasia | Mitral | Anaplastic lung carcinoma | 2 months |
| 7 (Fayemi *et al*. 1977) | 61 | M | Difficulty reading + writing, hemiparesis | Aortic | Bladder carcinoma | 16 days |
| 8 (Fayemi *et al*. 1977) | 59 | M | Transient ischaemic attack 2 weeks prior, slurred speech + stupor | Aortic | Adenocarcinoma pancreas | 4 weeks |
| 9 (this case) | 52 | F | R hemiparesis, right inferior quadrantinopia | Mitral and Aortic | Tubulopapillary variant of clear cell carcinoma of the ovary | 7 months |

we have all been educated to be more clinically vigilant in the future – those looking after the patient, Professor Warlow, members of the Association of British Neurologists and the readers of *Practical Neurology*

Although several papers mention that the diagnosis of malignancy may be preceded by neurological symptoms, NBTE with cerebral events as the initial manifestation of systemic malignancy does not appear to have received the emphasis it deserves (Kooiker *et al.* 1976). Advances in imaging techniques may allow earlier detection of malignant disease and associated cardiac valve abnormalities but at the present there is no convincing evidence that anticoagulants prevent further thromboembolic events, nor are there reports of whether removal of the tumour alters outcome. NBTE should be considered a paraneoplastic complication of malignancy and included in the differential diagnosis in cases of cerebral embolism without an obvious source.

## IMPORTANT TAKE-HOME MESSAGES

- Non-bacterial thrombotic endocarditis associated stroke may be the first presentation of malignancy.
- The patient does not necessarily need to be cachexic to have malignancy associated non-bacterial thrombotic endocarditis.
- The vegetations may be too small to be visualized even by transoesophageal echocardiography, and so the diagnosis must be considered in patients with cerebral infarcts of uncertain origin, particularly if embolism from the heart seems clinically likely.
- The importance of post mortem cannot be emphasized enough: in this case the family could be told the reason for the strokes and heart attack, and we have all been educated to be more clinically vigilant in the future – those looking after the patient, Professor Warlow, members of the ABN and the readers of Practical Neurology.

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