Postgraduate Medical Journal, (February 1984) **60**, 111–115

Phaeochromocytoma and acute cardiovascular death (with special reference to myocardial infarction)

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Summary

The causes of death, as determined by autopsy, in 10 patients dying from the acute effects of phaeochromocytoma were myocardial infarction (five patients), left ventricular failure (two patients), cerebral haemorrhage (two patients) and circulatory collapse with malignant phaeochromocytoma (one patient). Most patients died shortly after admission during the course of a fulminant cardiovascular illness and the underlying tumour was unsuspected in eight instances. The clinical features and post-mortem cardiovascular findings are reviewed.

KEY WORDS: atheroma, left ventricular failure, cerebral haemorrhage, myocardial disease.

Introduction

When the clinical diagnosis of phaeochromocytoma is made, the patients have usually presented with characteristic paroxysmal or sustained hypertension and symptoms related to hypertension. In a significant proportion of cases, however, the lesion is only diagnosed at autopsy (Modlin *et al.*, 1979; Sutton, Scheepo and Lie, 1981). Many of this latter group of patients have presented with an acute, severe cerebrovascular or myocardial illness. This mode of presentation forms a less well known but important clinical expression of this rare tumour. Myocardial disease in patients with phaeochromocytoma may take the form of left ventricular hypertrophy as a consequence of severe prolonged hypertension (Engelman, 1977; Van Way *et al.*, 1974), as a catecholamine cardiomyopathy (Rose, 1974; Baker *et al.*, 1972; Shapiro, Trethowan and Singh, 1982; Alpert *et al.*, 1972), or, occasionally, as an acute myocardial infarction (Gupta, 1975; Priest, 1952; Boldt, Flexner and Ortner, 1957). The infarction may occur with or without demonstrable coronary artery disease. This paper examines the clinical and pathological features of 10 patients who died an acute cardiovascular death and who harboured a phaeochromocytoma.

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Patients

Examination of all clinical and autopsy records between 1961 and 1982 at Groote Schuur Hospital, Cape Town, revealed that there were altogether 34 patients in whom the diagnosis of phaeochromocytoma was made. Ten of these died an acute cardiovascular death, and form the basis of this article. The principal clinical features are presented in Table 1.

There were five males and five females and their mean age was 46 years. In the patients with pre-existing symptoms, the mean duration was 21 months, the shortest history being of 1 day and the longest of 3 years. The primary presenting complaint (which in the majority of cases was new and of recent onset) was chest pain or dyspnoea in six patients and one each of epigastric pain, a 'flu-like' illness (with abdominal pain) and 'attacks' suggestive of catecholamine excess together with abdominal pain. The last patient had no cardiovascular symptoms and died of cardiovascular collapse during a laminectomy. Case 1 was known to have maturity onset diabetes and four additional patients had glycosuria recorded during the course of their illness. Cases 1 and 4 were known smokers; there was no record whether or not the remaining patients smoked.

Four of the six patients with chest pain and dyspnoea were found to be in left ventricular failure. Paroxysmal hypertension was recorded in four patients and sustained hypertension in three. Of interest was the fact that three patients of the group were normotensive. Retinopathy was recorded in half the cases. The electrocardiogram (ECG) showed left ventricular hypertrophy in four cases and evidence of myocardial infarction in three patients.

In eight patients, the attending clinicians did not

TABLE 1: Clinical features of patients

Case	Sex	Age	Presenting symptoms	Principal signs	Highest recorded blood pressure (mmHg)	Retinopathy	ECG	Working diagnosis	Comment
1	M	43	Chest pain, headaches, 'attacks'	None	Paroxysmal 280/180	Grade II	LVH	Phaeochromocytoma	Patient refused operation
2	M	47	Chest pain	LVF	Paroxysmal 160/130	Grade II	LVH	Hypertensive heart disease	Unsuspected
3	F	58	Angina on effort, dyspnoea	LVF	190/115	Grade II	Myocardial infarction	Ischaemic heart disease	Unsuspected
4	M	42	Dyspnoea, abdominal pain	Sweating	125/90	Grade II	Myocardial infarction	Pulmonary embolus	Sudden death
5	F	34	Dyspnoea, haemoptysis	LVF	200/120	—	—	Hypertensive heart disease	Unsuspected
6	F	78	Epigastric pain	Epigastric mass	180/100	—	Myocardial infarction	Gastric carcinoma	Unsuspected died during barium meal
7	M	38	'Flu-like' illness, abdominal pain	Pleural effusion	130/85	—	—	Viral illness	Unsuspected
8	F	32	'Attacks', throbbing epigastrium	None	Paroxysmal 170/110	Grade IV	LVH	Phaeochromocytoma	Died 48 hr postoperatively
9	F	20	Dyspnoea, headaches, haemoptysis	LVF	Paroxysmal 180/110	—	LVH	Hypertensive heart disease	Unsuspected
10	M	50	—	—	120/80	—	—	—	Died undergoing laminectomy

LVH = left ventricular hypertrophy.
LVF = left ventricular failure.

suspect that there was an underlying phaechromocytoma, their working diagnoses being shown in Table 1. In retrospect it is not difficult to reconcile the clinical features with an underlying phaeochromocytoma; examination of the notes, however, suggests that the attending clinicians' concentration was so focussed on the cardiovascular problem that the possibility of phaeochromocytoma did not come to mind. In the remaining two cases, an antemortem diagnosis of phaeochromocytoma was made: case 1 refused surgery, after extensive and conclusive investigation and case 8 died of pulmonary oedema 48 hr after surgical removal of a phaeochromocytoma. These last two cases have been included as their mode of death was essentially similar to the undiagnosed cases.

All patients died during a short period of hospital admission in the course of a complicated and severe cardiovascular illness. In the unsuspected cases, a feature of the records was a failure ever to gain control of the clinical situation, whether it was cardiac failure, arrhythmia or hypertension. In retrospect this was hardly surprising as the medication was in all cases inappropriate and dangerous. Of the two patients where an antemortem diagnosis was made, case 1 was re-admitted comatose and died soon after, some 2 years after the diagnosis had been made and he had refused surgery, he having been managed on antihypertensive therapy. It is suspected that he was not drug compliant. The history of case 8 will be given in some detail.

The causes of death determined at autopsy are presented in Table 2; cerebral haemorrhage (two patients), myocardial infarction (five patients), left ventricular failure and ventricular fibrillation (two patients). The presence of an underlying phaeochromocytoma came as a surprise finding in eight of the 10 cases. The histology of the tumour in case 7 showed an undifferentiated neoplasm made up of tumour cells with large vesicular nuclei and abundant cytoplasm containing chromaffin granules consistent with the appearance of a phaeochromocytoma. There was no evidence of metastases or invasion. The patient died of circulatory collapse of undetermined cause. Four of the five patients dying from myocardial infarction had evidence of coronary artery disease. In case 8, a 32-year-old female, there was evidence of severe coronary atherosclerosis and in case 9, a 20-year-old female, who died from cerebral haemorrhage, the coronary vessels showed remarkably severe atheroma for a woman of that age.

Case report

A 32-year-old female was admitted with a 3-year history very suggestive of phaeochromocytoma: she had experienced attacks which consisted of throbbing headaches associated with pronounced sweating, nausea, flushing, rapid palpitations and a throbbing feeling in her epigastrium. The attacks would occur 3–4 times a day and lasted 5–10 min. She had been noted to be hypertensive after the birth of her child 3 years previously.

Examination revealed a paroxysmal blood pressure which varied between 210/120 and 150/100 mmHg. She had Grade II hypertensive retinopathy and an apex beat in the 5th interspace outside the midclavicular line. Palpation of her epigastrium produced a typical attack on one occasion. The ECG showed left ventricular hypertrophy and non-specific ST and T wave flattening. The vanillyl mandelic acid (VMA) level was 118·1 μmol/l (normal: 0–40). Computerized axial tomography demonstrated a 6 cm mass in relation to the upper pole of the right kidney. She was prepared for operative removal of a suspected phaeochromocytoma with alpha blockade using phenoxybenzamine for 14 days. Two days before operation propranolol was added. The operation was uneventful and a 6 cm tumour was removed. All medication was stopped postoperatively.

Eighteen hours after surgery, she developed pulmonary oedema without evidence of fluid overload, and died despite resuscitative measures. At autopsy the myocardium showed foci of myocytolysis, stromal collapse and interstitial fibrosis. The aorta showed early fatty streaking. In addition there was 50% narrowing of the left anterior descending artery by atherosclerosis. Histology of the mass was that of a benign phaeochromocytoma.

Discussion

Phaeochromocytoma may be unsuspected during life and come as a surprise finding at autopsy. This was the case in eight of our 34 cases (24%), 66% of a Mayo Clinic autopsy analysis (Sutton *et al.*, 1981) and 35% of the Hammersmith/Newcastle/Belfast survey (Modlin *et al.*, 1979). Retrospective examination of the clinical records of our cases revealed many features that could have been attributable to catecholamine excess, and yet the condition was never considered by the clinicians. In most of our cases the terminal illness was characterized by acute onset and inexorable progression. Egdahl and Chobanian (1966) have used the term 'acute' phaeochromocytoma and Weinberger (1963) has described the 'physiologically malignant' tumour, two descriptions that could easily be applied to our patients.

Catecholamine-induced myocarditis and congestive cardiac failure are well-recognized features of phaeochromocytoma (Engleman, 1977; Van Way *et al.*, 1974). Less well documented, however, is the occurrence of myocardial infarction in patients with this tumour. We were able to find only nine cases

TABLE 2. Pathology

Case	Sex	Age	Aorta and large vessels	Heart	Coronary vessels	Cause of death
1	M	43	Moderate atheroma	Normal	Normal	Cerebral haemorrhage
2	M	47	Normal	Recent infarction, areas of focal ischaemia	Extensive occlusion LAD*, RAD† circumflex	Myocardial infarction
3	F	58	Moderate atheroma	Infarction of large areas	Extensive atheroma LAD	Myocardial infarction
4	M	42	Fatty streaking	Myocardial infarction	Normal	Myocardial infarction
5	F	34	Minor specks of atheroma	Normal	Normal	Left ventricular failure, ventricular fibrillation
6	F	78	Atheroma	Old and recent infarction	Occlusion RAD	Myocardial infarction
7	M	38	Normal	Normal	Normal	Malignant phaeochromocytoma Mode of death unknown
8	F	32	Normal	Myocardial degeneration	Coronary atherosclerosis 40% narrowing LAD	Left ventricular failure
9	F	20	Early atheroma	Normal	Severe atheroma for age	Cerebral haemorrhage
10	M	50	Normal	Myofibrillar degeneration	LAD, RAD occlusion	Myocardial infarction while undergoing laminectomy

*LAD = Left anterior descending; †RAD = Right anterior descending.

reported in the literature (Table 3) and to these add five further cases.

TABLE 3. Patients with proven phaeochromocytoma and myocardial infarction (from the world literature)

Reference	Age (years)	Sex
Bell *et al.*, 1962	49	F
Boldt *et al.*, 1957	56	F
Cushman, 1962	55	M
Hotchkiss *et al.*, 1967	70	—
	70	
Huddle *et al.*, 1982	—	—
Priest, 1952	22	M
Rossi *et al.*, 1968	34	M
Wilkens *et al.*, 1952	22	—

Infarction has been described as painless in some patients (Boldt *et al.*, 1957) and may occur with or without demonstrable coronary artery disease (Engelman, 1977). This analysis would support these contentions. Electrocardiographic evidence of myocardial ischaemia is not uncommon in phaeochromocytoma (Boldt *et al.*, 1957) and this is most likely to be related to the presence of coronary artery atheroma. Six of our 10 patients had significant vessel disease. Van Vliet and his co-workers found significant atheroma and more than 25% coronary vessel narrowing in 14 out of 26 patients whose hearts were examined histologically (Van Vliet, Burchell and Titus, 1966). A striking observation in our series was the finding of inappropriate atheroma for age in two cases: a 20-year-old female (case 9) who died of a cerebral haemorrhage had severe atheroma and a 32-year-old female (case 8) had greater than 50% narrowing of the left anterior descending coronary artery. Platelet aggregation stimulated by increased catecholamines has been postulated as a pathophysiological mechanism for severe irreversible postoperative pulmonary oedema (Sutton *et al.*, 1981). This, however, was not demonstrated in our patient (case 8) who had both narrowing of the coronary vessels and a catecholamine cardiomyopathy. Conceivably both of these factors contributed to her sudden pulmonary oedema and death.

These findings raise several clinical issues. Firstly, phaeochromocytoma should be considered in all patients presenting with an acute cardiovascular illness, particularly when conventional therapy fails to achieve control. Secondly, as it appears that the disease is associated with severe atheroma and cardiac disease and indeed may predispose to it, and as the actuarial survival for those patients who have had successful surgical resection is the same as for

normal people (Remine *et al.*, 1974), we urge that early diagnosis and treatment may prevent the cardiac morbidity and mortality.

Finally, the use of beta-blocking agents in patients with phaeochromocytoma should be carefully considered in the light of these findings. On the one hand, there is a persuasive argument for their use. Catecholamines are known to cause myocardial necrosis and focal myofibrillar degeneration and this is one hypothesis for the evolution of congestive cardiomyopathy (Van Vliet *et al.*, 1966; Rose, 1974). It is also possible that they may also stimulate the formation of atheroma. As the occurrence of myocardial infarction may be due to the effects of sudden beta stimulation on the heart and as beta blockade has been shown to decrease the incidence of sudden deaths due to myocardial infarction (Lubbe, 1978; Multicentre International Study, 1975; Opie, 1980), there is an attractive argument to use these agents in patients with phaeochromocytoma. On the other hand, beta blockade in this situation is not entirely without potential problems of a serious nature. Because of the negative inotropic effect of beta blockers, extreme caution it recommended in their use when congestive cardiac failure and myocarditis are present; they should only be given once adequate alpha blockade is established.

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(*Accepted* 29 *June* 1983)