A CASE OF PHAEOCHROMOCYTOMA

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Phaeochromocytoma is a tumour arising from the chromaffin cells of the adrenal medulla. Occasionally, and especially in children it originates in chromaffin tissues outside of the adrenal glands *e.g.* in the inter-renal area, in the organs of Zuckerkandl, in the para-aortic region and under or just outside the capsules of the abdominal sympathetic ganglia. The majority of these tumours is found within the abdomen and pelvis. Of the intra-abdominal phaeochromocytomata, almost all occur in/or near the adrenal glands in the adult. In children, about 10-15% occur in extra-adrenal sites. Rarely, such a tumour may present as a mediastinal mass, or may even occur in the carotid body in the neck.

Phaeochromocytoma is a rare but well documented tumour. Fraenkel in 1886 was the first to describe the clinical syndrome of paroxysmal hypertension, sweating, headaches and pallor produced by a phaeochromocytoma (vide Stephens, 1961). The first successfully treated case of phaeochromocytoma was reported by Roux in 1926 followed by Charles Mayo's in 1927. In 1929, 30 cases were recorded in the literature by Rabin. A decade later the figure stood at 90. By 1952, Symington and Goodall collected 283 cases from published reports. One of the more recent series of such cases is that published by Priestley et al (1963) who recorded their experience with 71 cases, surgically treated.

We report below a patient with phaeochromocytoma, which we believe to be the first case of phaeochromocytoma diagnosed pre-operatively and successfully treated by surgery, in Singapore.

CASE REPORT

A Chinese housewife, L.T.T., aged 40 years, saw a general practitioner because of severe recurring headaches of 3 months duration. No abnormal physical findings were found and the blood pressure recorded was 110/80 mm. Hg. She was thought to have migraine and was given symptomatic treatment but she found no relief and the attacks of headaches became more frequent. She was then referred to hospital and the following history obtained. Since 1½ years previously she has had sudden paroxysmal attacks of a throbbing fronto-temporal headache associated with palpitation and the feeling of generalised weakness. These attacks initially occurred once a month or so but increased in frequency so that now she was having them once or twice a week. Each attack was usually precipitated by a sudden fright or jolt and occurred more often in the evening. It usually began with palpitation and a sense of fear, associated with dyspnoea and generalised weakness. These symptoms were soon followed by severe throbbing frontal and bitemporal headache and blurring of the vision. At the same time she also experienced coldness of the lower extremities with pallor of the face and palms. The duration of each attack was about ½ - 1 hour. There was no giddiness, sweating, tremors or fits. Micturition and menstrual histories were normal, but she was constipated at the time of admission. Appetite was not increased and she did not notice any undue weight loss.

On clinical examination she was noted to be of medium build with no evidence of hypermetabolism. The pulse rate was 80/min., and regular. The blood pressure was found to be 170/120 mm.Hg. and during her stay in hospital varied between 120-160 mm.Hg. systolic and 90-120 mm.Hg. diastolic. The peripheral pulses were palpable and equal. The cardiovascular system was otherwise normal and no abnormalities were found in the respiratory, gastro-intestinal and central nervous systems except for a palpable right kidney. The fundi was normal.

Routine blood and urine examinations were normal—Hb.: 86% (12·73 gm.); W.B.C.: 4300/c.mm. (P.60%; L.36%; M.2%; and E.2%); urine: no albumin, microscopic examination normal; serum cholesterol: 200 mgm%; serum electrolytes: K-3·9 mEq/L.; Na-139 mEq/L. and Cl-113 mEq/L. Oral glucose tolerance test showed a normal curve; basal meta-

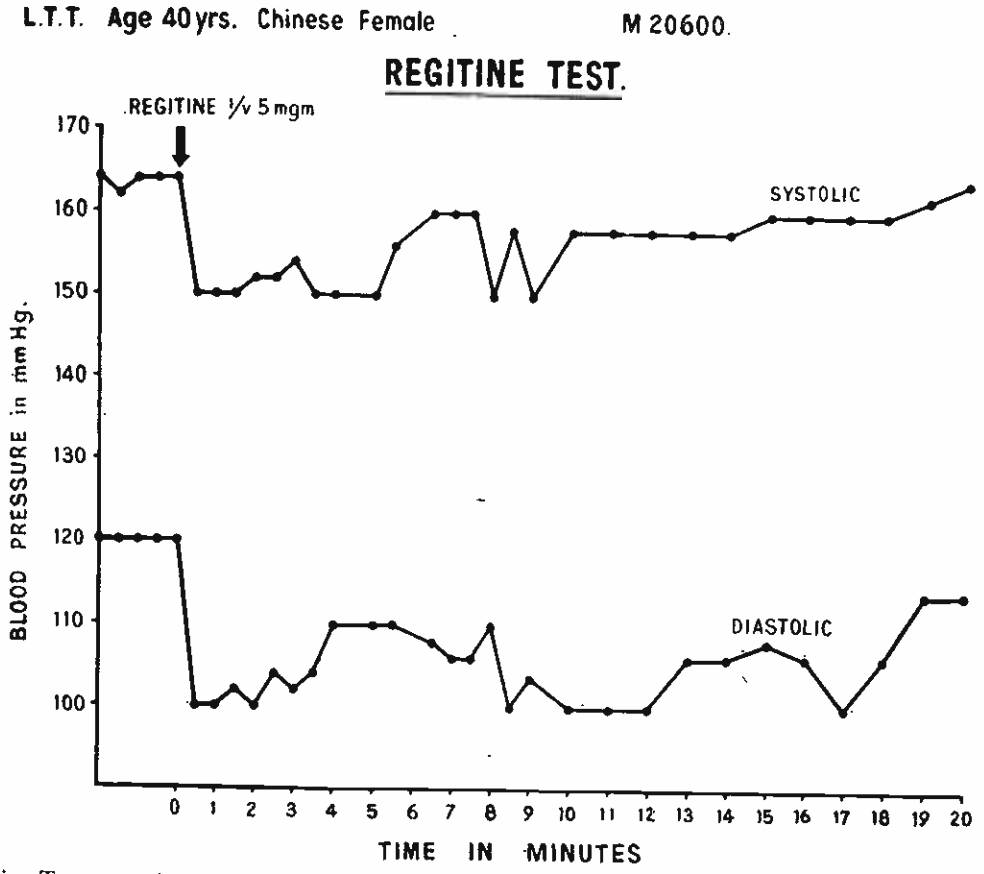

Fig. 1. Regitine Test: negative result. The blood pressure fell by only 15 mm. Hg. systolic and 20 mm. Hg. diastolic.

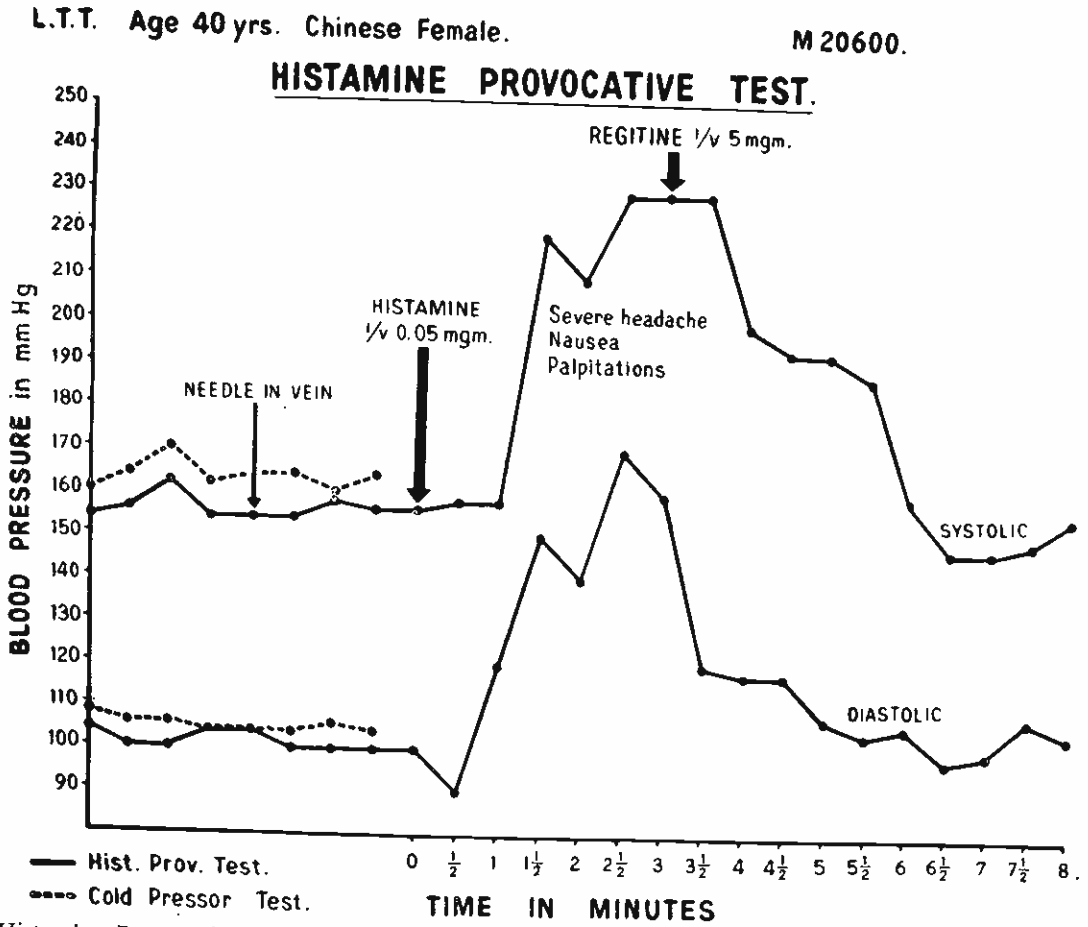

Fig. 2. Histamine Provocative Test: positive result. The blood pressure rose within two minutes to a maximum of 230/170 mm.Hg., a rise of more than 50 mm.Hg. systolic and 25 mm.Hg. diastolic. Note occurrence of symptoms with rise in blood pressure and fall in blood pressure after intravenous regitine.

bolic rate was minus 6% (Dubois); electrocardiograph was normal; roentgenograms of chest, abdomen and skull showed no abnormality and intravenous pyelography was normal.

On the basis of the clinical history and the finding of a paroxysmal hypertension a diagnosis of phaeochromocytoma was suspected and the following tests performed.

Regitine Test: An intravenous dose of 5 mgm. regitine (phentolamine) was given rapidly. The blood pressure fell from 165/120 to 150/100 mm.Hg. within a minute and was maintained at this level for about 4 minutes (Fig. 1). The test was thus negative as a positive result is one in which the fall in blood pressure is greater than 35 mm.Hg. systolic and 25 mm.Hg. diastolic occurring soon after injection and returning to its previous level after 10-15 minutes (Hume, 1960).

Histamine Test: An intravenous dose of 0·05 mgm. histamine phosphate was given rapidly. Within 2 minutes the basal blood pressure rose from 160/90 to 230/170 mm.Hg., with severe headache, nausea and palpitations. Administration of 5 mgm. regitine intravenously produced a fall in blood pressure to 200/120 mm.Hg. in 1 minute and to basal levels in 3 minutes (Fig. 2). A repeat test using 0·03 mgm. histamine intravenously produced an equally if not more marked rise in blood pressure (to 265/190 mm.Hg.) and improvement with regitine. This was a positive response as the blood pressure rose more than 50 mm.Hg. systolic and 25 mm. Hg. diastolic almost immediately (Hume, 1960) associated with production of symptoms and correction of the rise in blood pressure with regitine.

Urinary 3-methoxy-4-hydroxy-mandelic acid (Vanillyl mandelic acid or V.M.A.): Urine was collected over 24 hour periods and estimated for V.M.A. This was done on 3 occasions and the results obtained were as follows: 8·7 mgm./24 hours (26.10.64); 15 mgm./24 hours (30.10.64) and 4·1 mgm./24 hours (9.11.64). Vanillyl mandelic acid constitutes the major metabolite of the catecholamines and determination of the amount of this substance present in the urine is a useful screening procedure for detecting phaeochromocytoma. The second result was abnormal and highly suggestive of a phaeochromocytoma, as normally, less than 13 mgm. of V.M.A. are excreted in 24 hours (Lee Kum Tatt). In patients with phaeochromocytoma 15 to 200 mgm. or more may appear in the urine daily.

It was next decided to attempt to demonstrate and localise the tumour radiologically and a retro-peritoneal air insufflation was performed. Oxygen was introduced into the retro-peritoneal space and a large rounded mass measuring approximately $4\frac{1}{2} \times 4$ cm. was demonstrated lying over the upper pole of the right kidney. The left adrenal gland was of relatively small size (Fig. 3). The impression gained was that of a

Fig. 3. Retro-peritoneal air insufflation showing a large rounded mass lying over the upper pole of the right kidney. The left adrenal gland was of relatively small size.

right suprarenal tumour, most probably an adenoma and surgical removal of the tumour was advised and undertaken. The patient was admitted to hospital a week before surgery and given the following pre-operative preparation:

1. Sod. amytal tablets gr.3 nightly for 1 week.
2. Phentolamine tablets 40 mgm. 6 hourly for 3 days.

3. Inj. hydrocortisone I/M 100 mgm. b.d. for 2 days.
4. Sodium chloride tablets 5 gm. t.d.s. for 1 day.

OPERATION

The operation was performed through a transverse supraumbilical incision. A spherical, pink, fleshy tumour was located in the right adrenal gland. The left adrenal gland was normal. After ligating the vein leading from the tumour, the tumour and the right adrenal gland remnants were removed. The tumour measured $2\frac{1}{2} \times 1\frac{1}{2}$ cms. and weighed 52 gms. (Fig. 4). During surgery, while the tumour was being handled, the blood pressure rose to 200 mm.Hg. systolic and tachycardia and ventricular extrasystoles were noted. This was controlled with intravenous phentolamine. On removal of the tumour the blood pressure fell to 110/70 and during the immediate post-operative period and for the next few days hovered around 100-120/70-85 mm.Hg.

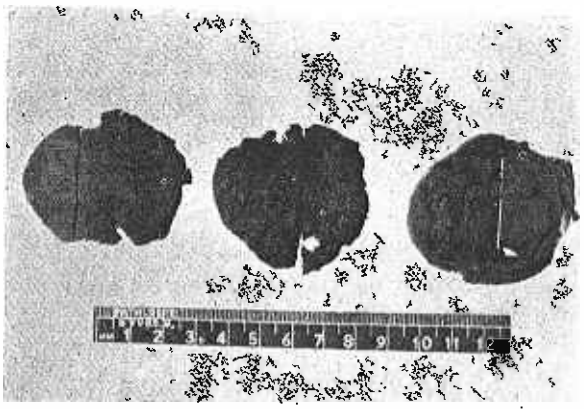

Fig. 4. Macroscopic appearance of tumour. The tumour was soft with nodular surface.

POST-OPERATIVE FOLLOW-UP

She developed a moderate fever during the early post-operative period and this was controlled by antibiotics. Hydrocortisone injections were continued intramuscularly for a further 2 days. Her post-operative course was on the whole quite uneventful and she did not have any hypotensive episodes.

She has been followed up for almost a year, has had no further attacks so far and feels generally well. Her blood pressure has remained around 130-150/90-95 mm.Hg. Repeated urinary V.M.A. levels after operation gave normal values of 5·4 mgm., 6·0 mgm. and 6·7 mgm. per 24 hours specimen.

BIOPSY REPORT

Sections show clusters of pleomorphic cells with abundant cytoplasm and large vesicular nuclei lying in a highly vascular stroma and surrounded by a capsule of compressed adrenal cortical tissue—phaeochromocytoma (Fig. 5).

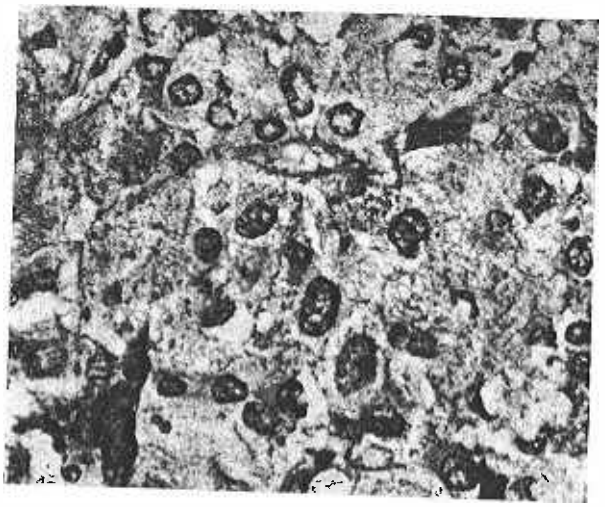

Fig. 5. Microscopic appearance of tumour showing clusters of pleomorphic cells with abundant cytoplasm and large vesicular nuclei.

DISCUSSION

Phaeochromocytoma is a rare cause of hypertension but it is a curable one and therefore must be considered in all cases of hypertension especially in the young when no immediate cause is obvious. Quite frequently a diagnosis is only made at autopsy and following death after anaesthesia or during surgery for other reasons (Coates and Rigal, 1961; Seward, 1961). Symington and Goodall (1953) who collected 283 cases from published reports found that as many as 67% were demonstrated at postmortem. With a high index of suspicion and a thorough investigation it is possible to diagnose more cases early as in this patient and achieve a successful result.

Diagnosis of phaeochromocytoma should be suspected when hypertension is found associated with a clinical history of attacks of headache, palpitation and tachycardia, sweating, weakness and pallor. Increased metabolic rate (with normal protein bound iodine), glycosuria and hyperglycaemia may be present and are helpful features. Loss of weight is often seen and patients with phaeochromocytoma tend to be thin. The hypertension may be sustained or paroxysmal. In adults only 20-50% show paroxysmal hypertension (Goldenberg et al., 1950; Kvale et al., 1957) while in children the majority (92%) show sustained hypertension (Hume,

1960). This patient showed a slight paroxysmal hypertension in the beginning (normal on the first visit, elevated on the second) and this later became sustained. It is now generally found that such tumours more frequently produce sustained hypertension than paroxysmal hypertension (Smithwick et al., 1950; Hume, 1960). In a few cases hypertension may be absent and Richmond et al. (1961) reported a young girl presenting with paroxysmal hypotension due to an adrenaline-secreting phaeochromocytoma. The diagnosis of phaeochromocytoma should also be considered in patients with or without hypertension, in whom severe hypertension develops on induction of anaesthesia or in whom unexplained hypotension develops following or during surgery.

Pharmacologic screening tests are useful aids in diagnosis but it must be remembered that they may not always be positive and that false positive results do occur. In this patient the regitine (phentolamine) test was negative but the histamine provocative test was positive. When doing a histamine provocative test, regitine must be at hand for use to reduce the blood pressure if it becomes alarmingly elevated as in this patient.

As it constitutes the major metabolite of the catecholamines estimation of vanillyl mandelic acid or 3-methoxy-4-hydroxy-mandelic acid (V.M.A.) in the 24 hour urine specimen is now largely used as a screening procedure. In some cases the urinary V.M.A. may not be elevated and for this patient only 1 of the 3 estimations was elevated above the normal value. In order to avoid false positive results, the patient should not be given aspirin, bananas or vanilla containing foods 48 hours before and during collection of the urine specimens. The differential determination of epinephrine and norepinephrine in the blood and urine has been used as an aid also in localisation of a phaeochromocytoma (Grollman, 1964). In patients in whom norepinephrine only is secreted, about $\frac{2}{3}$ of the tumours will be found in the area of the adrenal.

Localisation and visualisation of the tumour (especially in doubtful cases when the pharmacologic screening tests are negative or equivocal and the urinary V.M.A. values are within normal limits or only slightly elevated) can be done pre-operatively by retro-peritoneal air insufflation either by the peri-renal or pre-sacral routes. The tumour in this patient was localised by air insufflation and found at operation to be on the right side as in about 80% of all reported cases (Seward, 1961). Although the tumour may be localised radiologically before operation, it is still necessary at operation to examine the other adrenal gland carefully as well as the extra-adrenal sites in the abdomen where these tumours are known to occur. This is because the tumour may be multiple and in 10% of cases are bilateral as well as extra-adrenal in location (Hume, 1960).

Careful pre-operative management with oral phentolamine especially in patients with elevated blood pressures helps to prevent severe hypertensive crises during surgery. The value of this was first reported by Iseri et al. (1951) and has now been found to be very helpful in controlling and alleviating the symptoms and blood pressure before as well as during operation (Goldfien, 1963). Recently, Robertson (1965) advocates the pre-operative use of phenoxybenzamine to control the pressor response and pronethalol or propranolol for the tachycardia and arrhythmias. During the handling of the tumour, hypertensive crises with tachycardia and arrhythmia may still occur as in this patient and further intravenous phentolamine may be required. Following excision of the tumour and in the early post-operative period hypotensive crises, may occur, for which intravenous noradrenaline or metaraminol (aramine) are life saving drugs. This patient did not develop any hypotensive episodes at all.

The prognosis in patients treated for this tumour is very good especially when early diagnosis is made and before permanent cardiovascular, renal or cerebro-vascular disturbances occur. In patients diagnosed pre-operatively and with suitable pre-operative preparation, good anaesthetic and surgical management, the risk of surgery is small. In contrast, Goldfien found a mortality rate as high as 50% when patients are subjected to unrelated surgical procedures in undiagnosed cases.

SUMMARY

A case of phaeochromocytoma in a housewife aged 40 years, diagnosed and successfully treated by surgical removal of the tumour is reported.

A brief discussion of the clinical picture, diagnosis and management is given.

The necessity for early pre-operative diagnosis and careful operative control is stressed.

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