CLINICO-PATHOLOGIC CONFERENCE

(A weekly clinical and pathologic case conference participated jointly by members of the Departments of Internal Medicine and Pathology of the Chulalongkorn Hospital, Faculty of Medicine, Chulalongkorn University, and by the third and fourth year medical students)

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(PALPITATION – SWEATING – HYPERTENSION – DYSPNEA)

A twenty – nine – old Thai woman was admitted to the hospital because of paroxysmal dyspnea and orthopnea.

Three years previously, after her fourth delivery of a normal child, she had the onset of paroxysmal attacks of intense bilateral headache, associated with profuse sweating, nervousness, palpitation and dyspnea. Her period began to be irregular and scanty.

Two year ago, she was told that she had hypertension and was treated at Songkla hospital for two months.

One year prior to this admission, a diagnosis of hyperthyroidism was made and she was instituted with antihyroid drugs for 4 months without clinical improvement.

The symptoms continued with increase in frequency and severity. Nocturnal dyspnea and fainting spells on stan ding were noted. She lost 8 kgs. in weight in three years inspite of normal appetite.

Past history was unremarkable except for a histosy of abortion at 3 months, one year before admission.

There was no history of hyperten sion, diabetes or thyroid diseases in the family.

Physical examination on admission revealed a thin, nervous young female in no acute distress. The temperature was 36.5° C, the pulse, 120 and the respirations, 20/min. The blood pressure was 180 systolic, 100 diastolic, equal in both arms and legs. The neck veins were not distended. The skin was moist and marked tremor of outstretching hands was observed. The lungs were clear. The heart was not enlarged by percussion ; heaving apex beat and the rate was increased. No abdominal masses or bruit were detected. Pulses were equal in all extremities. There was no edema. The optic fundi were normal.

Hb. 9 gm%, Wbc 8,800 with normal differential count.

The urine showed sugar 3,$^{+}$ albumin neg, sediment normal.

The BUN 21 – 37.5 mg%., creatinine 1.2–1.6 mg.%, sodium 140 mEq/L potassium 4.8 mEq/L chloride 108 mEq. /L. CO_2 12 mEq/L, FBS 90 mg% glucose tolerance test : fasting blood sugar 90 mg %. ½ hr. 156 mg%, 1 hr. 208 mg%, 2 hr. 248 mg%, 3 hr, 176 mg%.

24 hour – urine : Total volume 720 c.c, urea – N 888 mg, creatinine 101 mg%,

sodium 64 mEq/L, potassium 33 mEq/L, chloride 54 mEq/L, osmolarity 591 mOsm, creatinine clearance 42 ml./min

Urinary vanillylmandelic acid 37 mg./24 hr.

Renogram showed definite delay in both parenchymatous and excretory phase bilaterally.

Chest X-ray and Intravenous pyelography - normal.

The EKG showed sinus tachycardia, rate 120/min, left ventricular hypertrophy, non specific ST-T change.

The radioactive iodine uptake was normal at 27% dose in 48 hrs.

Serum thyroxine 11 μg% (normal 7-14 μg%)

During hospitalization her blood pressure ranged between 250/140 to 120/80. Postural hypotension was noted.

She was treated with phenobarbital and later, inderal 40 mg twice a day for 3 days, with a slight decrease in her pulse rate. Inderal was discontinued on the 8th hospital day. On the 10th hospital day because of continue rapid heart rate and nocturnal dyspnea, she was digitalized with digoxin. She was given 6 tablets (1.5 mg.) over 2 days, on the following day, while being moved from her bed to wheelchair, she developed cardiac arrest. The patient died on the 12th hospital day.

Dr. Srisuda Sitprija :

This 29 yearold Thai woman had a history of hypertension for two year duration and had been treated as such in a provincial hospital. When admitted to our hospital, she was found to have a moderate degree of hypertension - that is- a diastolic blood presure of about 100 mm./Hg. There was no retinal vascular changes and the urine finding showed negative test for albumin, white and red cells. There was slight retention of blood urea nitrogen and the creatinine clearance was semewhat low, 42 ml./min.

Now, what is the cause of hypertension in this woman ; Could it be from renal diseases or the findings of slight renal impairment were in effect, a result of hypertension from other causes? This is one of the key questions which I shall attempt to answer.

Coarctation of the aorta is another cause of hypertension, but is quite remote to occur in this woman because several blood pressure determination showed similar result both in the arm and leg measurements.

The biggest group of the cause of hyperternsion is primary renal disease. Before discussing further, I would like to see what the X-ray man could tell us about the findings in this case.

Dr. Gaysorn Vajarapongse :

The film of the chest showed normal contour of the heart. Its size is in an upper normal limit, otherwise it is essen tially normal. Both lungs showed slight vascular thickening around the hilar regions. No fluid was noted in either pleural cavity. The lung parenchyma was clear.

The plain KUB and the intravenous pyelography showed normal sized kidneys. The excretory function appeared normal although there appeared to be a slight delay of excretion from the right side. No calyceal deformity is noted on either side.

Dr. Srisuda :

The renogram suggests insufficiancy of the excretion function of both kidneys. We know that sometimes in chronic pyelonephritis, No clinical manifestations pertaining to infection are present. The

urine findings may be entirly normal especially if it also has low specific gravity. Unfortunatly no record on urine specfic gravity is given in the protocal. However, the urine osmolarity in twenty four hour was 541 mOsm which may include some of the glucose. Calculating from the amount of salutes excreted ; the renal power of concentration appears to be unaltered. Therefore chronic pyelon ephritis as a primary cause of hypertension in this woman is quite unlikey.

Another common cause of renal hypertension is glomerulonephritis. All stages of glomerulonephritis may produce hypertension especially in the chronic variety. The kidneys which may be visualized in X-ray examination are usually enlarged in the early stage and become smaller or contracted in the late stage. However, in some cases, the kidneys may be normal in size in all stages. In this case, both kidneys were of normal size. The urine findings which are most helpful in glomerulonephritis were not observed in this patient ; even albumin was not detected in the urine.

Another possibility that should be considered as a cause of hypertension is diabetic glomerulosclerosis. This patient had 3 plus urine sugar and the glucose tolerance test showed a diabetic type curve. One of the most common indication of diabetic glomerulosclerosis is proteinuria which was absent in this patient.

Because of the absence of albumin in her urine, all of these primary renal causes of hypertension are less likely.

Protean systemic vascular diseases ; the so-called collagen diseases such as systemic lupus erythematosus, polyarteritis nodosa etc. may very well produce hypertension but there is nothing in the history and physical examination in this case that would suggest vascular disorders.

Renoprival hypertension is an uncommon cause of hypertension and the urinalysis may be entirely normal. This condition is caused by renal arterial obstruction whether it is a compression, stenosis, thrombosis or others. The renogram would be very helpful.

Dr. Makumkrong Poshayachinda :

The renagram showed definite delay of both parenchymatous and excretory function on both kidneys, which is due to decrease vascular perfussion to the kidneys.

Dr Srisuda:

Renogram has a chief value in the indication of renal blood flow. The finding in this patients might explain the decrease in creatinine clearance and retention of blood urea nitrogen. We still, however, have to find an answer to the question why was to renal vascular flow reduced in this woman? I shall leave this for a momant.

Another group of primary cause of hypertension which we must consider is a disorder of endocrine system. There is nothing in the protocol which might indicate Cushing's syndrome in this woman; the urinary potassium was low; this finding is against primary aldosteronism.

Pheochromocytoma is another rare cause of hypertension; from the history, the symptoms and signs of sweating, nervousness, palpitation, tachycardia and loss of body weight, they were indications of hypermetabolism. Since she had a normal thyroid function, but with diabetic glucose tolerance curve and increase urinary VMA excretion, pheochromocytoma seems to be the most likely cause of hypertension in this patient. In fact, all of the students think that this is a typical case of pheochromocytoma.

In hyperfunction of adrenal medulla, similar clinical pictures may also occur. This lesion is very uncommon.

Other chromaffin tissue hyperfunction such as tumor of the extra-adrehal chromaffin tissue in paravertebral sympathetic chain may produce the same manifestation as a result of increase epinephrine production.

In pheochromocytoma, patients may develop renal changes as a result of :-

1. Unilatral renal ischemia due to compression of ipsilatral renal artery by the extraadrenal mass which may be located at the hilus of the kidney.

2. Unilateral renal artery stenosis from localized intimal hyperplasia.

The renogram as has been shown, showed bilateral involvement thus, these two possibilities can be excluded.

3. Subinitmal edema of the renal arteries. The edema is known to occur following intraluminar pressure increase and seems to be more prominent in the arteries than in arterioles. Catecholamines have been attributed for the induction of morphologic alteration in the arterial wall which subsequently developed into occlusive arteriosclerosis.

4. Artreiolar nephrosclerosis usually is of milder degree. This is probably the most common and the most likely lesion which our patient here is having; impairment of the vascular flow in both kidneys as seen in the renogram is compatible.

The final question is : what is the cause of death in this patient ? The mode of death is sudden and concievably, the most common cause of sudden death lies in the heart. This woman developed dyspnea, orthopnea, heaving apex beat, tachycardia and she had left ventricular hypertrophy. All of these features certainly appears to have qeen manifestations of compensative phase of hypertensive heart disease. We are all aware of the effect of catecholamines on the cavdiovascular system which may be:-

1. a direct effect on the conduction pathway of the heart resulted in cardiac arrhythmia.

2. a toxic effect to the heart muscle causing myocarditis.

3. an effect to the arterial wall causing morphologic change in the intima. The lesion begins with edema of the subintima which later on develops to arteritis of the vessel.

Arrthythemia, as we all know, is a common manifestation when there is a paroxysm of hypertension. This woman developed arrythmia while being moved from bed to a wheel - chair. This manuveur might have stimulated the production of catecholamines which in turn caused cardiac arrythmia e.g. ventricular tachycardia or ventricular fibrillation and cardiac arrest ensued.

Therefore, I shall say that this patient had pheochromocytoma, intraadrenal type. All of the other features seem best explained on the basis of catecholamines effect on cardiovascular system.

Clinical Diagnosis

1. Pheochromocytoma, intraadrenal;
2. Renal arteritis
3. Arteriolar nephrosclerosis, mild.

Cause of Death:

Cardiac arrythmia - ventricular fibrillation

Dr. Chaveng Dechakaisaya:

The figure of 37 mg/24 Hr. of VMA is somewhat low for pheochromcytoma, I would like to know what was the method used in this patient ? Another question is : did the patient had arteriorapghy ? I think arteriography is very helpfal in locating intradrenal pheochromocytoma.

Dr. Srichitra Bunnag:

Our method of VMA determination used give normal value of 4 – 17 mg./24 hours. I agree that the figure is rather low but we did it once only. Aortography was not performed in this case because of her condition and fear of complications. I again agree that arteriography is of great benefit in this curable form of hypertension.

Dr. Sunit Chandraprasort:

There seems to be little doubt that this patient did not have pheochromocytoma. The presenting symptoms of hypermetabolism is interesting. From the clinical picture alone one could not at all exclude hyperthyroidism in this patient. The thyroid function test however, as had been performed in this patient unequivocally excluded thyroid hyperfunction.

Dr. Prasan Tangchai

The heart weighed 480 gms. The hypertrophy involved principally the left ventricle in which its thickness measured 1.7 cm. The papillary muscles were thick and very porminent. No valvular lesions were present. Both lungs were edematous and congested. The liver was slightly enlarged and congested. Microscopically, there was centrolobular hemorrhagic necrosis, obviously a result of cardiac insufficiency and hypotension superimposed on severe chronic passive congestion due to heart failnre.

The right adrenal gland was transformed into a large globular mass weighing 150 gm. On cutting it was dark brown and lobulated. The cortical yellowish substance was still recognizable at the periphery (Fig. 1.) The tumor cells were large polygonal with ample granular cytoplasm. Yellowish to dark brown pigment granules were numerously pressnt. Areas of hyperchromatism, pleomorphism and mitoses were observed sparingly. The granules were fine or coarse,amphophilic as well as acidophilic. No evidence of invasion and metastasis was noted. (Fig. 2.).

There are four basic aspects concerning diagnosis and natural history of pheochromoctyma. In this patient, it is obvious that the tumor is functioning, secreting catecholamines as evident by vascular hypertension, cardiomegaly and an increase in VMA in urine. The aspect of tissue diagnosis is not very difficult. The cellular characteristic, the present of chromaffin granules and the pattern of the tumor make the diagnosis readily possible. As for the aspect of malignancy of this tumor it has been known that malignant pheochromocytoma is rare. There are less than 30 cases of malignant pheochromocytoma reported in the literature up to 1968, and some authorities even doubt its authenticity of the malignant behavior of this tumor.[1] Sherwin[6] found three malignant pheochromocytomas among 107 tumors studied. In malignant variety, spindle cell are usually present instead of polygonal granular cell of benign pheochromocytomas.

The kidneys were slightly smaller than normal. The cortices showed benign arteriolar nephrosclerosis bilaterally. The juxtaglomerular apparatus showed an increase in the cell number. A few glomoruli showed partial hyalinization while the wall of the afferent arterioles were thickened. (Fig.3).

There was generalized fibrous thickening of the intima of muscular arteries. No arteritis was noted elsewhere. No significant atheromatous changes were observed. It has been shown in hypertension induced in experimental animal that there is intimal edema, endothelial intracellular edema and increase in suftated mucopolysaccharides content of the arterial wall.[3] Whether this association indicates

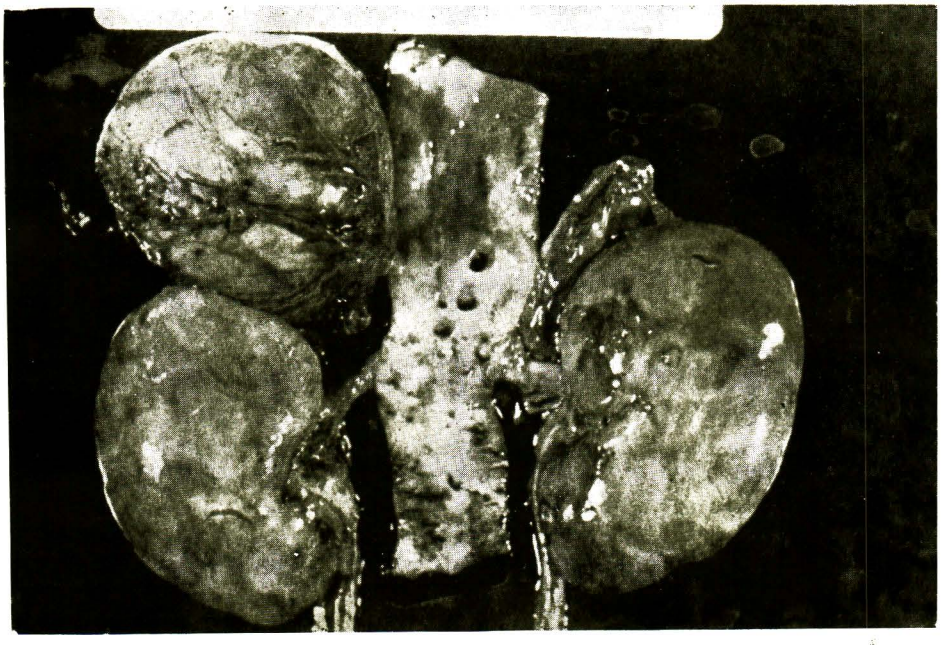

Figure 1. A large globular tumor mass at the upper pole of the right kidney in the region of rightadrenal gland. The tumor is well encapsulated.

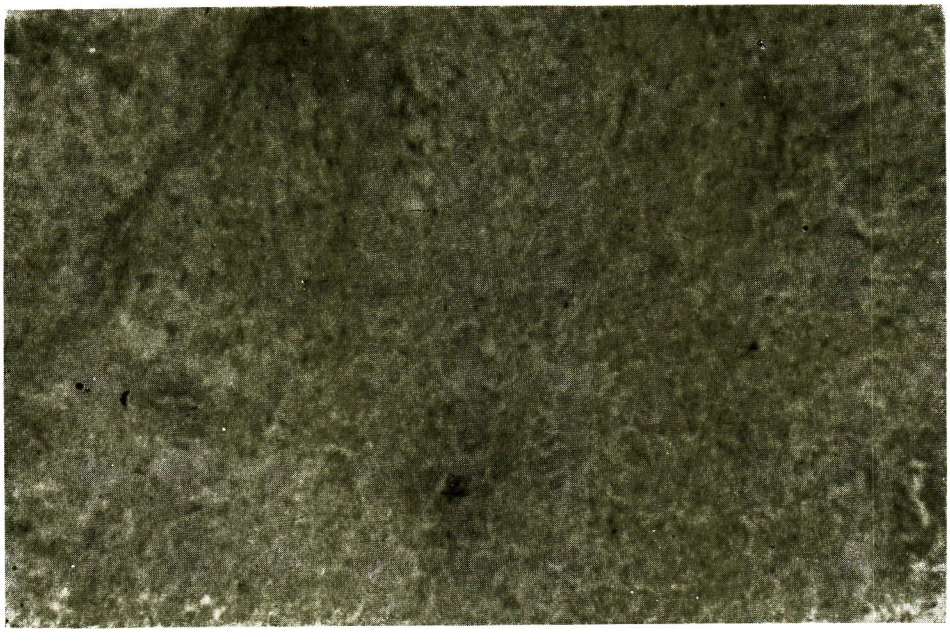

Figure 2. A section through the tumor reveals solid masses of large polygonal or round cells with small nuclei. H & E x 100

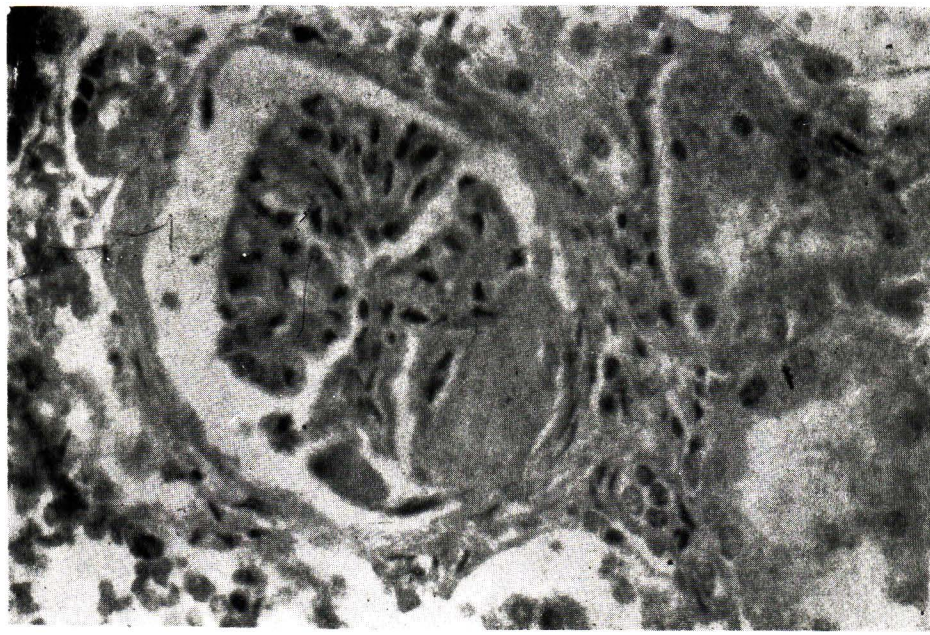

Figure 3. A glomerulus showing pericapsular fibrosis and partial hya; inization. H & E x 100

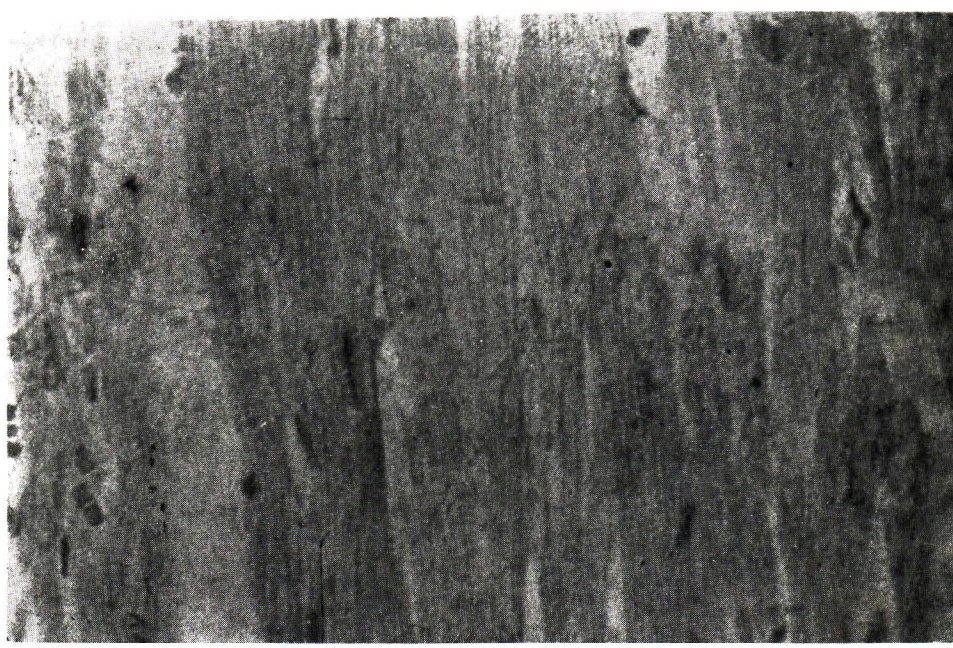

Figure 4. The myocardium fibers display blurring of the cross striation. The longitudinal myofibrils are distinct. Note numerous cross "banding" in some of the fibers, H & E x 100.

cause or effect of hypertension is however, controversial. Recent trends seem to favor that the changes in the vessel wall are the effect of hypertension[2] Nevertheless, there seems to be general agreement that intimal edema is related to intimal fibroplasia and arterial sclerosis.

Final Anaotomical Diagnosis

Primary

Pheochromocytoma of the right adrenal gland;

Hypertrophy ofthe myocardium, left. (Heart wt. 480 gms.); Arteriolosclerosis, generalized; Hyperplasia of the juxtaglomerular apparatus; Focal arteriolonephrosclerosis; Hypopolasia and vacuolation, left adrenal cortex; acute pulmonary edema and conges tion; Fibrillary myocardiopathy

The direct cause of this patient's death was certainly a myocartal failure.. The muscle cells showed bluring of cross striation, nuclear basophilism, mononuclaer cell in filtration and cross – bandings frequently observed in catecholamines fibrillary myocardiopathy in experimental animals[4,5]as well as incertain diseases notably, in subarachnoid hemorrhages, after cardiovascular surgery and in pheochromocytoma[5] (Fig.4). About one – third of this tumor produce norepinephrine alone, while in about two – third of the cases, both epinephrine and norepinephrine are secreted

Dr. Sunit:

I would like to comment that these functioning pheochromocytomas do secrete more adrenalin than noradrenalin. However certain number of the tumor is not functioning.

References:

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