·临床病理讨论·

**Clinicopathological Conference**

# A 64 year old woman with longterm paroxysmal dizziness

**(the ninth case)**

Case presentation

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A female patient of 64 year old was admitted to the hospital due to paroxysmal dizziness for 10 years with progression for 3 years.

The patient has suffered from paroxysmal dizziness since 1992, which persisted for minutes, even hours. Then she was diagnosed as "essential hypertension" due to the blood pressure measured as 160/100 mmHg. Her condition didn't get relieved after routine antihypertensive therapy, even got more severe in 1997. Her blood pressure was usually elevated suddenly as high as 170 – 220/70 – 90 mmHg, and decreased to the normal range within minutes or hours. Furthermore, she also had headache, perspiration, paleness and palpitation. "Pheochromocytoma in both adrenal glands" was highly suspected in 2001 because hyper-reactive regions above the superior poles of both kidneys were found by the abdominal radioisotope scanning in Beijing hospital and the 3-methoxy-4-hydroxy-mandelic acid (VMA) in the urine was slightly elevated although that in the serum was within the normal range.

The past history consisted of paroxysmal chest compressing, chronic pyelonephritis, cholecystectomy and duodenal ulcer. The patient didn't have the family history of hypertension.

Physical examination: general condition was relatively well, with blood pressure of 180/90 mmHg. No rales were heard in both lung fields. The cardiac boarder enlarged to the left side, moderate systolic murmur was heard in the apex and pulmonary regions. Slight tenderness was found in the upper abdomen and local point of ureter. Vascular murmur was heard in the region 1.0 – 2.0 cm from the umbilicus. ECG indicated "hypertrophy of left ventricle". The main primary diagnosis was "hypertension, suspicious of pheochromocytoma".

After hospitalization, the sudden change of the patient's blood pressure still occurred for 5 – 6 times in spite of combined antihypertensive medication of prazosin, amlodipine and indamol. CT scan of both kidneys and adrenal glands revealed a shadow with very low density in right kidney and an enlargement in left adrenal gland, which was confirmed by enhanced CT scan. Coronary angiography did not discover obvious lesion while 20% stenosis in right renal artery was found by renal angiography. The catecholamine level detected in different segments of circulation was as follows:

**Tab 1 Catecholamine detection in systemic circulation** (pmol/ml)

| Item | Norepinephrine (NE) | Epinephrine (E) |
|---|---|---|
| Left renal vein | 8.04 | 4.31 |
| After provocation test | 5.15 | 0.71 |
| Right renal vein | 5.77 | 1.10 |
| Inferior cava vena | | |
| Above renal vein | 5.7 | 1.10 |
| Below renal vein | 5.53 | 0.12 |
| Femoral vein | 5.79 | 2.72 |
| Femoral artery | 5.32 | 1.52 |

The patient was transferred to the department of urology for further surgical therapy.

## Clinical Discussion

*Dr. Du Xinping*: This case had following characteristics: (1) Elderly patient, the BP usually fluctuated widely because of functional degeneration of pressure sensor. (2) Features of attack: increase in blood

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pressure (170 - 220/70 - 90 mmHg), especially the systolic pressure, became more and more frequent and with spells of headache, sweating, palpitation and pallor of the face. (3) Examination of blood and urine: VMA and CA were normal. (4) Accompanying symptoms: chest pain similar to angina pectoris. (5) Accompanying diseases: nephropyelitis, duodenal ulcer, cholelithiasis. (6) Video examination: 20% stenosis of right renal artery was discovered by angiography and hyperreactive regions above the superior poles of both kidneys were found by the abdominal radioisotope scanning. Coronary angiography did not show obvious lesion. (7) The catecholamine level detected in different segments of circulation was higher in left side than that in right side. (8) Pathologic discovery: adrenal cortical and medullary hyperplasia. (9) Treatment: blood pressure was refractory to standard antihypertensive treatment.

Impression diagnosis: (1) Pheochromocytoma: the wide fluctuation in blood pressure and dramatic spells of symptoms as well as catecholamine level detected in different segments of circulation in this patient can alert physician to the possibility of this diagnosis. (2) Essential hypertension: eldery, stenosis of right renal artery, increase in catecholamine secretion from adrenal gland were factors resulting in wide fluctuation of BP.

*Dr. Zhang Jian*: I agree with what Dr. Du had said. According to clinical manifestations characterized by systemic paroxymal hypertension, headache, palpitation and sweating and according to the results of various examinations and tests, it is easy to correctly diagnose. However, we should take the possibility of extra-adrenal medullary pheochromocytoma into account because the serum concentrations of epinephrine and norepinephrine were not significantly elevated after the provocative tests. Further examinations are needed for diagnosis and management.

*Dr. Liu Li*: The case had following characteristics: (1) A 64-year-old woman suffered from paroxysmal dizziness for 10 years, which was aggravated and accompanied by headache and sweating for 3 years. She had past history of chronic pyelonephritis, coronary heart disease, cholecystectomy and duodenal ulcer. (2) The blood pressure increased abruptly as high as 170 - 220/70 - 90 mmHg without possible precipitating factors accompanied by headache, sweating, palpitation and pallor of the face. All these symptoms can be alleviated without any treatment in a few minutes. Poor response to therapy which was usually effective. (3) Physical examination: BP 180/90 mmHg. No rales were heard in both lower lung fields. The heart rate was 64/min and the rhythm was regular, Slight pain was found in upper abdomen and vascular murmur was also found in abdomen. Both limbs had no edema. (4) Laboratory tests: VMA in urine was higher than normal. Electrocardiogram showed hypertrophy of left ventricle. Radioisotope assay revealed that regions above the superior poles of both kidneys exhibited higher ability in absorbing the radioisotope, most likely indicating pheochromocytoma in both adrenals.

According to the present history, physical examination and other assistant examinations, I would like to put forward the diagnosis of secondary hypertension caused by renal disease. The most common causes were listed below: (1) Renal parenchymal diseases such as acute glomerulonephritis. Although the patient has a past history of chronic pyelonephritis, she had normal renal function and there was no evidence of renal insufficiency caused by chronic pyelonaphritis which led to hypertension. (2) Renal vascular disease: in this case, 20% stenosis in right renal artery was found by renal angiography. The renal vascular hypertension, however, should be persistent instead of intermittent. (3) Adrenal disease: All evidences including typical history and assistant examination confirmed that hypertension was caused by pheochromocytoma. The NE in left renal vein was obviously higher than that in right side. Besides, enhanced CT scan also confirmed that there was a shadow with very low density in right kidney and an enlargement in left adrenal.

*Dr. Wu Haiyun*: This elderly female patient had following characteristics: (1) 10-year history of hypertension which fluctuated widely and responded poorly to the commonly used antihypertensive regimens, accompanied by attacks of severe dizziness; (2) Spells of headache, sweating, palpitation and pallor of the face with marked increase in blood pressure, especially the systolic pressure, which became more and more frequent. The attacks lasted from minutes to hours, sometime

associated with chest pain; (3) 26-year intermittent urinary tract symptoms with a presumed diagnosis of "chronic pyelonephritis"; (4) A relatively normal physical examination results except a left upper bruit; (5) A test of urine VMA taken one year before at another hospital showed slightly higher than normal.

My differential diagnoses include the following:

1. Primary hypertension: Any hypertensive disease can initiate a spell of symptoms, although some, including pheochromocytoma and renal vascular hypertension, do so at a higher rate than primary hypertension does. However since primary hypertension accounts for over 90 percent of all patients, it should be considered first even in hypertensive patients with paroxysmal attacks, but spontaneous normalization of blood pressure and refractory to standard antihypertensive treatment in this patient demands more rigorous studies to rule out secondary causes.

2. Renal parenchymal disease: The patient's history and anemia suggest the probability of chronic pyelonephritis, which, either unilateral or bilateral, may cause hypertension. However, in pyelonephritic patients with hypertension but fairly normal renal function, renin level is usually high, and so the ACEIs are usually very effective in the control of hypertension in these patients.

3. Renal vascular hypertension: Hypertension with a suggestive abdomnal bruit in this patients is an index of suspicion of renal vascular hypertension, but poor response to ACEIs makes this diagnosis less likely.

4. Pheochromocytoma: The wide fluctuation in blood pressure and dramatic symptoms of the spell in this patient can alert any physician to the possibility of this diagnosis, and refractory to standard treatment heightened this suspicion. Despite the borderline results of urine VMA and plasma CA in the tests a year ago, which may result from samples collected during the "silent period" of the pheochromocytoma, this diagnosis still could be highly suspected.

*Dr. Zhao Yusheng*: The feature of the case was a 64-year-old woman, who suffered from a fluctuation of blood pressure for 10 years. pheochromocytoma was suspected because of the clinical history, fluctuated blood pressure and slightly elevated VMA in the urine. An enlarged left adrenal gland was found from computerized tomograghic scan. Left adrenalectomy was performed and the result was consistent with adrenal cortical and medullary hyperplasia found by pathologic examination. However, the patient has a past history of paroxysmal chest compressing for 8 years. ECG indicated hypertrophy of left ventricle. The patient was suspected to have coronary artery disease. But the coronary angiography did not show obvious lesion, while 20% stenosis of right renal artery was found by renal angiography, which indicated that the coronary artery disease could be ruled out. Thus, the paroxysmal chest compressing associated with severe hypertension in the absence of a significant coronary stenosis may possibly be related to a concomitant coronary and systemic vasoconstriction secondary to the adrenal cortical and medullary hyperplasia, which induced a high catecholamine content in circulation.

## Pathological discussion

*Dr. Gao Jie, Yin Tong*: Obvious hyperplasia, without apparent tumor on the surface of left adrenal gland during operation could be found. Macroscopically, a nodule measured 0.5 cm in diameter with cut section in gray to tan color was found. Microscopically, cortical and medullary components could be seen in the nodule. The orderly arranged adrenal zones were destroyed. Increased zona reticularis and fasciculata formed several small nodules, cords or nests with interludes of hyperplastic medullary cells. In this case, the diameter of adrenal hyperplasia was smaller than 1 cm. Pheochromocytoma can be considered when the diameter of medullary hyperplasia exceeds 1 cm. Finally, the pathological diagnosis is "adrenal cortical and medullary hyperplasia".

*Dr. Yin Tong*: Pheochromocytoma is introduced to describe an adrenal medullary tumor that darkens after exposure to potassium dichromate. It releases epinephrine or norespinephrine (or both) and, in some cases, dopamine into the circulation, causing hypertension and other signs and symptoms.

Most adrenal pheochromocytomas contain a mixture of norepinephrine and epinephrine with a predominance of norepinephrine. The typical pheochromocytoma is often described as an encapsulated mass measuring 3 to 5 cm in

diameter and weighing less than 100 g. On cross section, the tumors are usually gray to tan in color; however, exposure of the cut surface to light and air results in the formation of brown to yellow adrenochrome and noradrenochrome pigments.

Microscopically the tumors are composed of small, intermediate-sized or large cells that may be arranged in cords, small nests, or alveolar structures. The cytoplasm is generally granular and faintly basophilic. Nuclei are round to ovoid and vesicular with coarsely clumped chromatin and usually a single prominent nucleolus.

Hyperplasia of adrenal medulla is a distinct disease, which may cause symptoms similar to those of pheochromocytoma. It may be nodular or diffuse and is always bilateral. The medulla appears more prominent than usual. The cut surfaces reveal expansion of medullary tissue into both alae or tail of the gland with or without nodule formation.

Microscopically the medullary cells may increase in size and have abundant eosinophilic to amphophilic cytoplasm. Mitotic figures are sometimes present. It was suggested that there is a close relationship between adrenal medullary hyperplasia and the development of pheochromocytomas.

Immunohistochemical studies on adrenal medullary hyperplasia have revealed antigenic profiles similar to those seen in the normal adrenal medulla.

Cortical nodule, small nodules composed of cortical tissue and located in the periadrenal region are common. These nodules do not have clinical significance. They increase in number with age but are not correlated with hypertension, diabetes, or cardiovascular disease.

(Translator: Ma Jing)

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# 肾上腺髓质增生一例

## 1 病历摘要

患者,女性,64岁,因发作性头晕、眼花10年,加重伴头痛、出汗3年于2002年7月1日入院。患者1992年无明显诱因出现发作性头晕,无头痛,持续数分钟至数小时不等。曾于当地医务室量血压160/100 mmHg,诊断为高血压病,间断服用复方降压及其他药物(具体不详)降压治疗,症状无明显缓解,仍时有发作,血压控制在110~120/70~80 mmHg之间。1997年上述症状加重,每次发作较突然,测血压高达170~220/70~90 mmHg,伴头痛、出汗、面色苍白,持续数分钟至数小时后血压渐下降至正常范围。上述症状反复发作,血压时高时低,波动明显,应用洛汀新、心痛定等药物,病情无明显缓解。2001年5月17日于北京医院行腹部核医学检查发现双肾的上极上方处存在显影剂高摄取区域。可疑双侧肾上腺嗜铬细胞瘤或髓质增生。化验VMA(3-甲氧基-4-羟基苦杏仁酸,3-methoxy-4-hydroxy-mandelic acid)略高于正常,但CA不高。2002年6月11日及23日患者无明显诱因两次出现上述症状,当时测压为220/90 mmHg,并伴有心前区闷痛,并向左肩部放射。持续4 h后疼痛方缓解,血压降至正常。

既往发作性气短8年。反复尿频、尿急30年,诊断为"慢性肾盂肾炎"26年。1995年因胆石症行胆囊摘除术。十二指肠球部溃疡6年。无高血压家族史。入院查体:体温36.5 ℃,脉搏64次/min,呼吸18次/min,心律齐,心尖部及肺动脉瓣听诊区可闻及2/6级收缩期杂音,$A_2 > P_2$。腹平软,上腹部轻度压痛,无反跳痛,季肋点、上输尿管点、中输尿管点压痛,肝脾肋下未及,全腹叩诊鼓音,移动性浊音阴性,脐旁左侧1~2 cm处可闻及血管杂音。双下肢不肿。心电图:窦性心律,左室肥厚。入院诊断为:(1)高血压,原因待查,嗜铬细胞瘤?(2)冠心病,稳定性心绞痛;(3)慢性肾盂肾炎;(4)胆囊摘除术后。

入院后经哌唑嗪、络活喜、寿比山联合降压及支持对症治疗,患者血压控制不理想,先后出现5次血压急剧升高(最高达190/120 mmHg,心痛定等常规降压效果不佳,15~30 min后自行降至140/90 mmHg),伴头痛、出汗、面色苍白及心动过速发作。血、尿、便常规在正常范围内。

双肾及肾上腺CT平扫示左肾上极低密度影,左肾上腺内肢饱满,增强CT显示右肾等密度、增强及低密度病变,左肾上腺较饱满,右肾囊肿可能性大。冠脉造影结果:右优势型冠状动脉,LM、LAD、LCX、RCA未见明显病变。肾动脉造影发现右肾动脉开口20%狭窄。停服降压药3 d后,肾静脉分段

取血测儿茶酚胺结果:左肾静脉 NE(去甲肾上腺素)8.04 pmol/ml、E(肾上腺素)4.31 pmol/ml;激发后 NE 5.15 pmol/ml, E 0.71 pmol/ml; 右肾静脉 NE 5.77 pmol/ml,E 1.10 pmol/ml。左/右肾静脉 NE 比值为 1.39。腔静脉 NE 正常值为 0.62 ~ 3.24 pmol/ml。下腔静脉肾静脉开口下 NE 5.53 pmol/ml、E 0.12 pmol/ml。股静脉 NE 5.79 pmol/ml, E 2.72 pmol/ml。股动脉 NE 5.32 pmol/ml、E 1.52 pmol/ml。

## 2 临床病理讨论

该患者的特点有:(1)老年女性。(2)发现高血压10年,其血压波动较大,于短时间内急剧升高,达170~220/70~90 mmHg,伴头痛、出汗、面色苍白。反复阵发性发作,且以收缩压升高为主。(3)近5年来出现胸痛,每次发作持续数分钟至数小时,其发作有逐年加频趋势。(4)既往有尿频、尿急史26年,伴有肾盂肾炎,十二指肠溃疡,胆囊结石。(5)查体,左上腹部可闻及血管杂音,余无明显异常。(6)1年前在外院查尿 VMA 略高于正常,血 CA 在正常范围。肾静脉分段取血测儿茶酚胺:左侧明显高于右侧。心电图:左室肥厚。影像学检查:冠脉造影正常,右肾动脉20%狭窄。腹部核医学检查双肾上极上方处对显影剂摄取增加。(7)降压药对血压控制不理想。

### 2.1 诊断及其鉴别

2.1.1 原发性高血压病 各种原因引起的高血压均可出现该患者表现出的发作性症状。虽然在嗜铬细胞瘤及肾血管性高血压中其发生率更高,但由于原发性高血压占高血压病患者的90%以上,因此在诊断时仍应首先考虑。但该患者在症状发作的间歇期,血压可自行降至正常,其高血压对常规治疗反应不佳,使该诊断值得怀疑。

2.1.2 肾实质性高血压 该患者有20余年的尿路刺激症状史,应考虑到慢性肾盂肾炎引起的高血压的可能。患者虽然有慢性肾盂肾炎病史,但无肾功能损害,无肾功能不全表现,如患者肾功能正常,则高血压主要由血浆肾素水平升高引起。ACEI 类药应有较好疗效。该患者对多种药物治疗不敏感,故不支持慢性肾盂肾炎所致高血压。

2.1.3 肾血管性高血压 该患者血压波动大,有发作性的血压骤升,特别是左上腹可闻及血管杂音,应疑及肾血管性高血压的可能。老年患者肾动脉狭窄多由动脉粥样硬化斑块引起。该患者可能在原发性高血压病的基础上,出现了肾动脉粥样斑块性阻塞,后者再促发了高血压的加重和剧烈波动。该患者行肾动脉造影示右肾动脉20%狭窄,但肾动脉狭窄所致高血压应为持续性,而患者为阵发性,故不支持本病所致。

2.1.4 嗜铬细胞瘤 本病临床相对少见。但该患者有典型的发作性头痛、心悸、出汗"三联征",常规降压药治疗效果不佳,高度提示本病的可能。虽然1年前外院查尿 VMA 仅略高于正常,血 CA 不高,但如采集标本时,患者处于症状发作的间歇期,血尿儿茶酚胺及其代谢产物水平可在正常范围。入院后查肾动脉分段血测儿茶酚胺,左肾静脉 NE 明显高于右侧,CT 提示左肾上腺饱满,均支持嗜铬细胞瘤。但应注意,激发试验后左肾静脉内儿茶酚胺浓度并没有明显升高,故应考虑肾上腺髓质外嗜铬细胞瘤之可能。进一步完善检查以明确诊断,以利治疗。

总之,综合患者病史,诊断以嗜铬细胞瘤可能性大。应在患者症状发作时采集血尿标本,检测儿茶酚胺及其代谢物水平 以确定诊断。

患者经泌尿外科会诊后以"(1)嗜铬细胞瘤?(2)慢性肾盂肾炎;(3)高尿酸血症;(4)胆囊摘除术后"于8月13日转入泌尿外科行进一步手术治疗。术中见左侧肾上腺内侧支增生明显,表面未见明显肿瘤。手术切除内侧及部分外侧支,纵行剖开见一0.5 cm 大小的腺瘤样组织,送检病理。术后半年随访,患者未再服用降压药物,血压稳定在 100~140/70~85 mmHg。

病理所见:肾上腺皮髓质增生,皮髓质细胞排列方式不规则,失去正常肾上腺组织皮质各带分层排列的规律。髓质细胞分布亦呈巢状或索状穿插于增生的皮质细胞之间。此例皮髓质增生的区域 < 1 cm。

病理论断:左肾上腺皮髓质增生。

鉴别诊断:嗜铬细胞瘤:当肾上腺髓质增生 > 1 cm 时提示嗜铬细胞瘤,形态上增生的髓质细胞形态与嗜铬细胞瘤的细胞相似。

(马晶 赵玉生 侯允天 整理)