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A Case of Pheochromocytoma with Associated Cushing's Syndrome

Mariam Gachechiladze[1*], Tomas Tichy[1], Ivo Uberall[1], Daniela Skanderova[1], Frysak Zdenek[2], Tudos Zbynek[3], Filip Ctvrtlik[3] and Josef Skarda[1]

[1]*Department of Clinical and Molecular Pathology, Palacky University, Olomouc, Czech Republic*

[2]*Department of Nephrology, Rheumatology and Endocrinology, Faculty Hospital Olomouc, Olomouc, Czech Republic*

[3]*Department of Neurology, Palacky University, Olomouc, Czech Republic*

Abstract

Cushing's syndrome is rarely caused by high levels of ectopic Adrenocorticotropic Hormone (ACTH) secretion and only few cases caused by pheochromocytoma are described in the literature. Cushing's syndrome caused by ectopic ACTH secretion from pheochromocytoma. Here we present a case of 38-year-old woman with cushing's syndrome due to benign pheochromocytoma. Diagnosis was based on clinical examination and standard histopathological and immunohistochemical investigation.

Keywords: Pheochromocytoma; Cushing's syndrome; Immunohistochemical; Adrenocorticotropic hormone

Introduction

Pheochromocytoma develops from the chromaffin cells in the adrenal medulla and varies from benign to malignant variants. Rarely, pheochromocytomas are characterized with ectopic production of various hormones and cytokines, including adrenomedullin, IL-6 and Adrenocorticotropic Hormone (ACTH). Cushing's syndrome caused by ectopic ACTH secretion from pheochromocytoma is rare and only a few cases are described in English literature to date. Here we present a case of 38-year-old woman with cushing's syndrome due to benign pheochromocytoma [1].

An Adrenal Incidentaloma (AI) is defined as an adrenal lesion that is discovered when a radiological study is performed for indications other than suspected adrenal disease. All patients with an AI should be evaluated for hypercortisolism, pheochromocytoma and (if hypertensive) hyperaldosteronism [2]. A combination of pheochromocytoma and cushing's syndrome due to pathology in same adrenal gland is extremely rare. There are few case reports suggesting the different etiologies for this association, namely, pheochromocytoma secreting Adrenocorticotropin Hormone (ACTH) or its precursors, corticomedullary mixed tumors and focal adrenocortical hyperplasia [3].

Here, we report a case of AI with the clinical and biochemical evidence of both pheochromocytoma and sub-clinical cushing's syndrome.

Case Presentation

38-year-old diabetic female patient, who was previously treated for Holmes tremor, hemorrhagic stroke and arterial hypertension presented at III internal clinic of faculty hospital Olomouc, at the department of endocrinology with cushingoid appearance, severe hypokalemia of undefined origin [4]. Due to high levels of adrenocorticotropic hormone, Magnetic Resonance (MR) imaging of pituitary gland has been performed. However, no changes were found. Subsequent PET/CT scan identified the tumor mass in the right adrenal gland, with high hormonal activity [5]. There were no signs of metastatic disease and clinical diagnosis of hormonally active adrenal tumor with cushing's syndrome was made. Patient received pre-operative treatment with alpha-beta blockers, as well as with anti-hypokalemic and anti-diabetic treatment and laparoscopic adrenalectomy of the right adrenal gland has been performed [6].

Macroscopic description

Unfixed 75 × 55 × 30 mm tissue was received at the department of clinical and molecular pathology, Palacky university Olomouc and faculty hospital Olomouc [7]. The size of tumor mass was 50 × 30 × 30 mm, brownish-red cysts up to 7 mm and blood were found on macroscopic examination. Tissue was fixed in 10% neutral buffered formalin. After fixation tumor mass with size 40 × 30 × 30 mm with surrounding adipose and adrenal tissue (40 × 30 × 10 mm) were examined and photographed. Macroscopically tumor was present at the lateral edge of adrenal gland [8].

Microscopic description

Histomorphological examination of surgical material showed the microscopic features of pheochromocytoma, with average nuclear polymorphism and increased nuclear hyperchromasia in some cells. There was no necrosis, lymphovascular invasion and mitotic activity at 10 HPF present. Some cells were characterized with enlarged cytoplasm and ganglioid appearance [9]. Ganglioneuronal or glioma structures were not detected. On reticullin stain classic architecture of pheochromocytoma was present. Some tumor nests were slightly enlarged. However, diffuse solid growth were not present. Immunohistochemical investigation showed the positivity for

***Corresponding author:** Mariam Gachechiladze, Department of Clinical and Molecular Pathology, Palacky University, Olomouc, Czech Republic, E-mail: mariam.gachechiladze@upol.cz

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chromogranin, synaptophysin and S100. ACHT positivity was present in 20% of tumor cells. S100 was positive in sustentacular tumor cells and Ki67 index was only 1%. Tumor was negative for melan A and inhibin. Final Pheochromocytoma of the Adrenal Gland Scaled Score (PAAS) was defined as 2 and therefore the diagnosis of benign pheochromocytoma was made. In addition to pheochromocytoma, the hyperplasia of adrenal cortex was also present [10].

Clinical follow-up

After the operation, there was a noticeable decrease not only in cortisol, but also in ACTH level. Hydrocortisone substitution, mineral substitution set, re-alimentation started. Subjectively patient is without difficulties, gradually improving the glycemic profile, without the need for insulin. Currently patient is treated by PAD-metformin. Informed consent has been obtained from the patient for publication of the case report and accompanying images (Figure 1) [11].

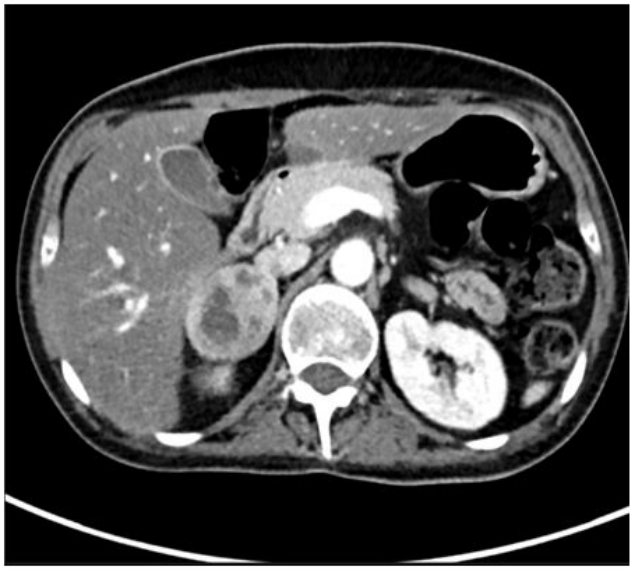

Figure 1: Clinical diagnosis of hormonally active adrenal tumor.

Results and Discussion

We have presented the rare patient with cushing's syndrome, caused by benign pheochromocytoma [12]. The diagnosis of pheochromocytoma was made based on standard histomorphological, histochemical and immunohistochemical investigation. On standard hematoxylin and eosin examination and histochemical examination by reticulin stain classical picture of benign pheochromocytoma was present. The diagnosis was further confirmed by immunohistochemical positivity of chromogranin A, synaphtopysin and S100 [13]. Differential diagnosis of pheochromocytoma includes adrenocortical carcinoma and small blue round cell tumors, including neuroblastoma. The later was excluded by histomorphological examination [14]. In addition, neuronal markers NeuN, GFAP and MAP-2 were negative. Adrenocortical carcinoma is usually positive for inhibin, melan A and calretinin. These markers were negative in our case and therefore adrenocortical carcinoma was excluded. The secretion of ACHT by pheochromocytoma was confirmed by ACHT immunohistochemistry (Figure 2) [15].

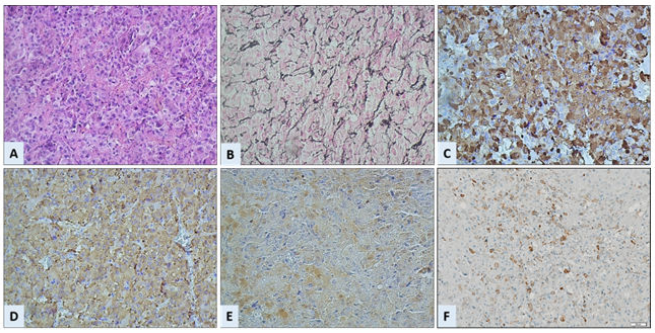

Figure 2: Standard histopathological and immune histochemical investigation.

Conclusion

There are up to 59 cases of pheochromocytoma associated cushing's syndrome previously described in literature, which were recently reviewed by Gabi et al. Most of the cases are presented with cushingoid appearance and marked hypokalemia similar to our case. However, subclinical cushing syndrome is also reported. In addition, some cases report increased hyperpigmentation due to unknown reasons. This characteristic was not seen in our patient. The unique characteristic of presented case it that patient was previously treated for Holmes tremor and was repeatedly hospitalized due to hypertension and stroke. Similar to the previously reported case by Goyal et al., and others patient's condition was significantly improved by adrenalectomy. The cortisol level was also significantly decreased. Our described case further highlights that cushing's syndrome due to pheochromocytoma is not related by malignant potential of pheochromocytoma and the course of the disease is benign after surgical treatment.

Conflicts of Interest

Authors declare no conflicts of interest.

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