Journal of BUON **13:** 425-428, 2008

Association of an oversized adrenal cortical adenoma with expression of pheochromocytoma-like neurosecretory features

I.N. Nomikos[1], A. Zizi-Serbetzoglou[2], G. Matsakis[1], J. Elemenoglou[2], N.C. Vamvakopoulos[3]

[1]Department of Surgery (B΄ Unit), "Metaxa" Cancer Hospital, Piraeus; [2]Department of Pathology, "Tzanion" General Hospital, Piraeus; [3]Department of Biology and Genetics, University of Thessalia Medical School, Larissa, Greece

Summary

Abnormal stimulation of adrenal function may be either direct, affecting similarly cortical and medullary secretion, or indirect affecting primarily the medulla. Indirect activation of clinically detectable adrenomedullary function may develop as a physical consequence of a non-functional adrenal tumor exerting pressure on the medulla by its size, location and direction of growth. Our case of an oversized and overweight adrenal tumor associated with expression of late-onset pheochromocytoma-like clinical symptoms may be explained by the physical indirect rather than the biological direct activation of adrenomedullary function like hyperplasia or cancer.

Key words: adrenal tumor, pheochromocytoma

Introduction

Identification of abnormal adrenal mass may be an incidental finding of computerized tomography (CT) performed for unrelated reasons that requires proper clinical evaluation and management [1,2]. The decision for surgical removal of non-secretory adrenal mass depends largely on its size [3]. Functional adrenal tumors usually hypersecrete characteristic bioactive products, in direct accordance to their cortical or medullary origin and represent surgically correctable causes of hypertension that must be resected regardless of size. Apparent discordance between clinical and pathological adrenal phenotypes has been noted in rare neoplasms of mixed, intermediate-type, corticomedullary cells co-expressing cortical and medullary features [4]. The size and degree of differentiation of neurosecretory adrenal cortical neoplasms or pseudopheochromocytomas detected so far vary, with an upper size limit rarely approaching 10 cm diameter or a ceiling of weight approaching that of the adrenal gland [2,4]. We report herein a case with association of an oversized and overweight adrenal cortical adenoma with expression of pheochromocytoma-like neurosecretory features.

Case presentation

A 42-year-old man was admitted to the department of surgery with a large mass arising from the right adrenal gland that was found on a CT of his abdominal cavity (Figure 1A), recommended by his primary care physician during the investigation of his arterial hypertension that was resistant to medical treatment. The patient revealed that he suffered from occasional anxiety attacks with sweat and palpitations for the last 6 months.

Physical examination was unremarkable, except a blood pressure of 170/95 mm Hg and a pulse of 105 beats per minute. Routine blood tests revealed slightly elevated hematocrit and blood glucose. Urinary levels of catecholamines (epinephrine and norepinephrine) and their metabolites (vanillyl mandelic acid - VMA)

Correspondence to: Iakovos Nomikos, MD. 55 Psarron Street, Koridallos 181 20, Piraeus, Greece. Tel. & Fax: +30 210 49 64 241, E-mail: nomikosj@otenet.gr

Received 26-10-2007; Accepted 10-12-2007

were elevated. Magnetic resonance imaging (MRI) disclosed clearly the adrenal origin of the mass (Figure 1B). No other retroperitoneal or abdominal abnormal masses were found.

Under the working diagnosis of pheochromocytoma the patient was scheduled to undergo surgery in two weeks. He was prescribed an oral regimen of phenoxybenzamine and encouraged to drink plenty of fluids. Preoperative preparation was uneventful. One day before surgery he was admitted to the surgical ward and received infusion of fluids along with a β-blocker (propranolol).

The patient was submitted to exploratory laparotomy by an abdominal (anterior) approach and resection of his tumor (right adrenalectomy). There were no other tumors in the abdomen and surgery was finished without any hemodynamic problems. Few hours after completion of the procedure the patient developed progressively hypovolemic shock due to intraabdominal bleeding. A re-laparotomy was unavoidable for the control of hemorrhage, which was coming from the suddenly decompressed veins of the tumor bed. His subsequent recovery was uneventful and was discharged on the 8th postoperative day.

Urinary catecholamine levels measured at 3 and 6 months after surgery were back in the normal range and ^{131}I-MIBG (meta-iodo-benzyl-guanidine) scanning at 6 months showed no accumulation of the radioactive drug either in the removed tumor bed or elsewhere in the abdominal cavity.

Four years after surgery the patient remains disease free with no sign of malignancy or recurrence.

Pathological findings

Gross findings

The right adrenal gland was converted into a sizeable 19×10×7 cm tumor weighting 650 g and was removed intact. The lesion presented extensive necrotic regions with no signs of disruption of the surrounding fibroadipose capsule. The specimen had yellow-red, focally hemorrhagic appearance suggestive of a cortical adenoma and was submitted intact for microscopic evaluation.

Microscopic findings

The morphologic and immunocytochemical light microscopic findings converged to a working diagnosis of adrenocortical adenoma consisting primarily of compact acidophilic cells. The tumor contained small clusters of neoplastic cells separated by a thin layer, focally swollen with thin-walled vessels. Neoplastic cells had big round unequally sized nuclei with distinct nucleoli and were large, mainly polyhedral, with compact eosinophilic content, compared to the weakly colored, soft-microbubble-like cytoplasm of normal cells. No infiltration of vessels or capsule was observed in the microscopy sections examined (Figure 2). Im-

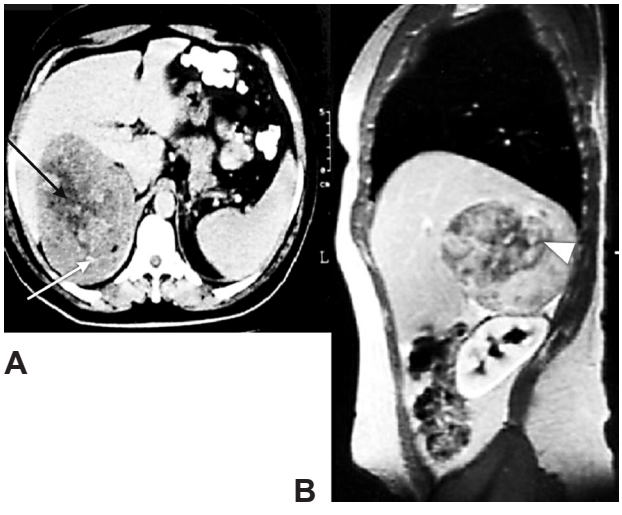

Figure 1. Diagnostic imaging of adrenal mass: **A:** CT visualization of a large tumor on the right adrenal gland with areas of necrosis causing heterogeneous appearance of the parenchyma (black arrow). It is evident the presence of few small-sized calcifications (white arrow) and the clear margins of the mass from the surrounding structures. **B:** MRI shows clearly the adrenal origin of the mass (open arrowhead).

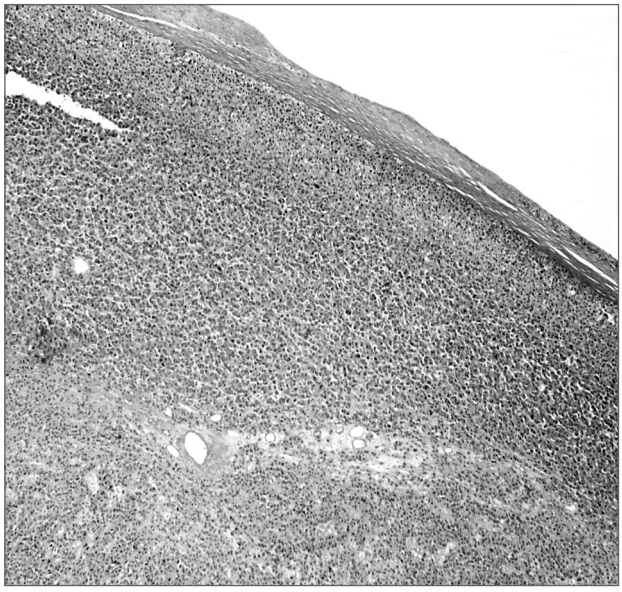

Figure 2. The tumor was composed mainly of compact cells arranged in small nests (H & E × 200).

munohistochemical analysis for nuclear antigen Ki-67 expression revealed a low mitotic rate of about 1% and was negative for most medullary pheochromocytoma and chromaffin cell markers tested (chromogranin, GFAP, S-100 protein and vimentin) and positive for inhibin.

Working diagnosis

The apparent conflict between clinically-based preoperative working diagnosis of pheochromocytoma with the postoperative histopathologic findings of adrenocortical adenoma pointed towards the direction of a tumor with dual corticomedullary properties originating from mixed intermediate-type cells co-expressing cortical and medullary features. These autonomously neurosecreting tumors, however, in addition to their mixed histological features, are relatively small upon resection due to their early functional detection as a consequence of their associated clinical symptoms. Failure to detect medullary immunocytochemical landmarks in the excised material suggested its non-functional adrenocortical adenoma-like origin with the potential explanation of its associated clinical neurosecretion being related to its unusual size and weight in some rather indirect fashion. Elevated catecholamine levels have been associated with the pressure on the splanchnic nerves imposed by the tumor or with adrenomedullary hyperplasia [5]. The histologic findings along with the normalization of clinical features following removal of the tumor, pointed against adrenomedullary hyperplasia as a potential causative agent of neurosecretion. Our proposed working diagnosis for this apparently late-onset clinical hypertension observed was that the oversized and overweight adrenocortical adenoma physically primed adrenomedullary neurosecretion through its gain in weight primarily and in connection to its location and direction of growth within the gland. This diagnosis was consistent to and supported by available evidence like presence of benign, non-metastatic, not fully differentiated, non-functional, slow-growing, as a result of low mitotic rate, features.

Discussion

Incidentally discovered adrenal masses include adrenocortical tumors of mesodermal origin such as adenoma, carcinoma or aldosterinoma, adrenomedullary tumors of neural crest origin such as benign or malignant pheochromocytoma and of neuroectodermal origin such as neuroblastoma and neuroganglioma [6]. Metastatic tumors are also found in the adrenal gland [7].

Clinical evaluation of an incidental adrenal mass uses a combination of patient's medical record, physical examination and laboratory tests to assess its secretory status and size. Current diagnostic guidelines propose unconditional removal of any adrenal mass secreting detectable levels of bioactive products regardless of size. A non-secretory mass smaller than 3 cm and between 3 and 6 cm should be monitored and followed by biochemical tests and CT, respectively. A mass larger than 6 cm has a significant risk of being a carcinoma and should be resected regardless of secretory function. Worth noting is the discrepancy between the size of the tumor and its benign character. In the presented case, the combination of medical records, clinical symptoms, response to preoperative preparation and postoperative follow-up, diagnosed pheochromocytoma. This diagnosis was not confirmed by the histologic structure of the tumor, which although not fully differentiated, pointed towards the direction of adrenocortical formation. The interior anatomic position may explain in part the increased susceptibility of the adrenal medulla to physical influence by extraneous adrenocortical formations similar to the case presented herein. Therefore, in addition to biological, physical priming of adrenal function should be considered in tumors with poor mitotic activity presenting late-onset functional clinical symptoms, if detected by CT scan in an already advanced oversized and overweight condition.

CT finds 90-95% of all pheochromocytomas larger than 1 cm and is sufficient in most of the cases. MRI has a similar resolution. In our case, due to the increased size of the tumor, MRI was very helpful in defining the accurate origin of the tumor. ^{131}I-MIBG scan detects the preferential accumulation of radioactive MIBG in pheochromocytoma relative to other chromaffin tissues with 80% accuracy. Because it examines the entire body, it can be an useful initial diagnostic tool or a follow-up test to assess recurrent tumor growth.

In pheochromocytoma, histological criteria do not predict malignant potential and the only definite determinant of malignancy is documented recurrence. Other risk factors may include young age and positive staining for proliferation markers like MIB-1 [8].

Unless incidentally discovered at an early stage, non-functional adrenal masses may continue to grow unnoticeable until detected by physical exploratory means in benign non-metastatic types, or through their biological metastatic effects in malignant types [9]. Basic [10] and clinical [11,12] advancements to homeostatic management may help resolve diagnostic dilemmas in adrenal medicine, while preserving the delicate balance between anticipated gain in medical benefit and associated diagnostic cost [13].

Conclusion

Oversized and overweight adrenocortical adenomas may physically induce pheochromocytoma-like neurosecretion and cause clinical hypertension in the absence of direct medullary activation by either hyperplasia or cancer.

References

1. Caplan RH, Strutt PI, Wickus GG. Subclinical hormone secretion by incidentally discovered adrenal masses. Arch Surg 1994; 129: 291-296.
2. Mansmann G, Lau J, Balk E, Rothberg M, Miyachi Y, Bornstein SR. The clinically inapparent adrenal mass: update in diagnosis and management. Endocr Rev 2004; 25: 309-340.
3. Graham DJ, McHenry CR. The adrenal incidentaloma: guidelines for evaluation and recommendations for management. Surg Clin North Am 1998; 7: 749-764.
4. Ivsic T, Komorowski RA, Sudakoff GS, Wilson SD, Datta MW. Adrenal cortical adenoma with adrenalin-type neurosecretory granules clinically mimicking a pheochromocytoma. Arch Pathol Lab Med 2002; 126: 1530-1553.
5. Komminoth P, Roth J, Schroeder S, Saremaslani P, Heitz PU. Overlapping expression of immunohistochemical markers and synaptophysin mRNA in pheochromocytomas and adrenocortical carcinomas: implications for the differential diagnosis of adrenal gland tumors. Lab Invest 1995; 72: 424-431.
6. Young WF. Management approaches to adrenal incidentalomas. A view from Rochester, Minessota. Endocrinol Metab Clin 2000; 29: 159-185.
7. Sidhu S, Gicquel C, Bambach CP et al. Clinical and molecular aspects of adrenocortical tumorigenesis. ANZ J Surg 2003; 73: 727-738.
8. Clarke MR, Weyant RJ, Watson CG, Carty SE. Prognostic markers in pheochromocytoma. Hum Pathol 1998; 29: 522-525.
9. Nawar R, Aron W. Adrenal incidentalomas: a continuing management dilemma. Endocr Rel Cancer 2005; 12: 585-598.
10. Vamvakopoulos NC. Sexual dimorphism of stress response and immune/inflammatory reaction: The corticotropin releasing hormone perspective. Mediat Inflamm 1995; 4: 163-174.
11. Nomikos IN, Vamvakopoulos NC. Correlating functional staging to effective treatment of acute surgical illness. Am J Surg 2001; 182: 278-286.
12. Nomikos IN, Malizos C, Vamvakopoulos NC. Protective and damaging effects of healing. Wounds 2006; 18: 177-185.
13. Stone JH. Incidentalomas-Clinical correlation and translational science required. N Engl J Med 2006; 354: 2748-2749.