Case Report

Primary non-functional extra-adrenal adrenocortical carcinoma

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ABSTRACT

We present the case of a 52-year-old Jordanian man who was admitted to hospital due to a left sided abdominal mass that was discovered during a routine physical examination. The huge abdominal tumor was initially suspected to be a retroperitoneal sarcoma based on the ultrasound and computed tomography findings. Cytological analysis of the fine needle aspiration smears was unable to define the origin of this mass, and suggested a sarcoma. During laparotomy, the mass was found not connected to the adrenal gland. Only histopathological and immunohistochemical examination of the surgical specimen allowed the diagnosis of adrenocortical carcinoma. This tumor most likely has risen from an extra-adrenal rest. From a review of the medical literature, this case appears to be unique as the first well documented histologically and immunohistochemically reported case of extra-adrenal adrenocortical carcinoma.

Saudi Med J 2003; Vol. 24 (3): 301-304

Adrenocortical carcinoma (ACC) is a relatively rare endocrine tumor, which is more common in women than in men with an incidence of approximately 0.5-2 cases per million per year.[1] It tends to occur in bimodal age distribution with peaks in the first and fifth decades.[2,3] The tumors are classified as functional or nonfunctional, depending on tumor production of corticosteroid, mineralocorticoid, androgen, or estrogen. In children functional tumors are more common, whereas nonfunctional tumors are more common in older patients.[2,3] The etiology of ACC is not known but cigarette smoking and use of oral contraceptives has been suggested to increase the risk of adrenal cancer.[4] They usually present in children due to functionality and in older patients due to mass effect or when metastasis has occurred.[3] Diagnosis is delayed as most patients present with large masses and with late stage of the disease, which is too late for curative resection. Consequently it is commonly associated with a poor prognosis with an overall 5-year survival rate varying between 10%-35%.[5-8] The data on the natural history and response to therapy of patients with this malignancy has often been conflicting. The objective of this case report is to document what we believe the first reported case of extra-adrenal histologically confirmed ACC.

Case Report. A 52-year-old man was referred to our surgical department with abdominal pain, weakness, malaise and 3 kg weight loss of 7 months duration. Physical examination revealed a large palpable mass in the left upper abdomen. On admission, the hematological and biochemical profiles were normal. The mass was investigated by abdominal ultrasonography followed by computed tomography (CT), which revealed a well-circumscribed left retroperitoneal mass 20 x 15 cm in diameter lying between the spleen, stomach, tail of pancreas, colonic splenic flexure, and left kidney and left adrenal gland (**Figure 1**). The radiologist suggested that this might represent a retroperitoneal tumor most probably a lipoma, fibroma or liposarcoma. Cytological analysis of

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Received 16th September 2002. Accepted for publication in final form 23rd November 2002.

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Figure 1 - Abdominal computerized tomography scan showing a well-circumscribed left retroperitoneal mass 20 x 15 cm in diameter lying between the spleen, stomach, tail of pancreas, colonic splenic flexure, and left kidney and left adrenal gland.

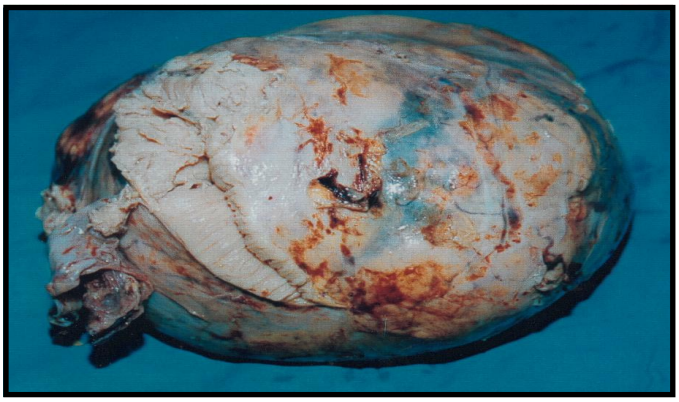

Figure 2 - Excised tumor, ovoid in shape, well circumscribed, whitish, soft mass with a smooth lobulated surface, measuring 19 x 15 x 9 cm.

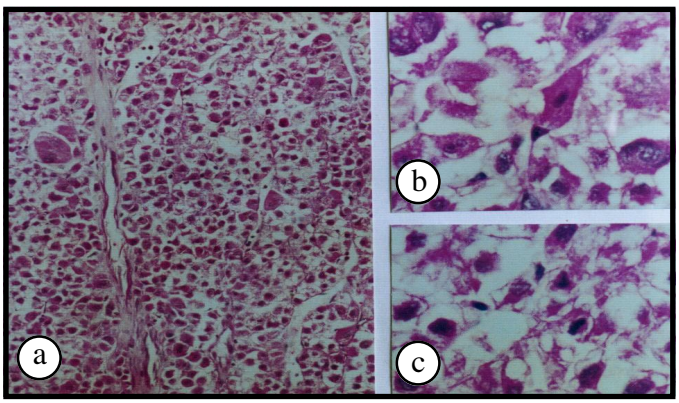

Figure 3 - Histopathological sections of the tumor. **a)** Low power view shows a highly cellular tumor showing diffuse and poorly defined nesting patterns (hematoxylin and eosin x 10). **b)** The neoplastic cells are large rounded to polygonal and have abundant vacuolated and fine granular eosinophilic cytoplasm with highly pleomorphic large nuclei (hematoxylin and eosin x 40). **c)** A mitotic figure is shown in the center of the field (hematoxylin and eosin x 40).

the fine needle aspiration (FNA) smears was unable to define the origin of this mass, and highly suggested a sarcoma as the initial diagnosis.

Laparotomy revealed a huge ovoid, well-circumscribed, whitish, soft mass having a smooth lobulated surface, measuring 19 x 15 x 9 cm and weighing 1950 gm arising outside the Gerota's fascia and lying between the left kidney, left adrenal gland, spleen, stomach, tail of pancreas and the splenic flexure of the colon. The mass was not attached to any of these structures and appeared to arise from the retroperitoneal space. There was no evidence of metastasis. An apparently complete surgical resection of the mass was performed (**Figure 2**), but adrenalectomy was not carried out. The cut sections showed homogenous whitish-gray tissue with scattered spots of hemorrhage. Histopathological examination (**Figure 3**) revealed a highly cellular tumor, which was growing in diffuse and poorly, defined nests. The neoplastic cells were large rounded to polygonal with abundant vacuolated and fine granular eosinophilic cytoplasm with highly pleomorphic large nuclei, some of which were multinucleated. There was mild mitotic activity with a mitotic rate of 3/50 high power field. A thin fibrous capsule surrounded the tumor. Focally at the rim of the tumor, there were nests and cords of vacuolated epithelial cells, reminiscent of adrenal gland tissue. Vascular invasion was not identified in the sections.

Immunohistochemical studies were performed on the tumor paraffin sections. The stains revealed that the neoplastic cells were positive for vimentin, synaptophysin, inhibin-alpha and melan A (clone A 103); they were negative for cytokeratin, epithelial membrane antigen, chromogranin A, desmin, and S-100 protein. Periodic acid-schiff and reticulin stains were not contributory. The pathological diagnosis was a malignant neoplasm most consistent with ACC. Faced with this unexpected diagnosis, detailed endocrine evaluation was carried out to rule out a possible functioning carcinoma, and all the hormonal studies were normal. The final diagnosis was that this patient had hormonally inactive ACC. According to the MacFarlane system as modified by Sullivan et al,[9] the patient was classified as stage I tumor. The patient had an uneventful post-operative course. He did not receive additional chemotherapy. Another abdominal CT scan was performed one month after the operation and revealed a normal looking left adrenal gland. On clinical and radiological (CT) follow-up for 25 months postoperatively he remained well with no evidence of recurrence of his tumor.

Discussion. The frequency of ACC among patients operated on for incidentally discovered adrenal tumors is 6-16%.[10-12] The diameter of these tumors ranged between 3 and 30 cm, and the weight varies between 12 to 4750 gm.[8] The tumor diameter is correlated with the risk of cancer; a cutoff at 5 cm has been suggested to discriminate between benign and malignant lesions.[10]

Abdominal CT and magnetic resonance imaging (MRI) are the radiological modalities used in the evaluation of adrenal tumors. Tutuncu and Gedik[12] suggested that the optimal diagnostic approach is to consider the results of the biochemical tests and a review of anatomical qualities depicted on CT or MRI while taking into account the previous clinical epidemiological data. While CT and MRI have some limitations as they are able to definitely characterize only a minority of adrenal tumors such as simple cyst, myelolipoma, and obvious local malignant invasion, adrenocortical scintigraphy allows more accurate categorization of these tumors.[13] Venography should be performed prior to adrenal tumor surgery to detect or exclude thrombotic tumor masses in the suprarenal vein, renal vein or inferior vena cava.[1] Endocrinal hormonal studies are essential in all cases of adrenal tumors irrespective of history and physical examination.[13] The result of FNA in adrenal tumors may be disappointing as in the present case. Normal adrenocortical tissue on cytological studies from FNA may represent inadvertent sampling of adjacent normal adrenocortical tissues or the presence of a well-differentiated ACC.[13]

Our patient represents a difficult case. The unique feature in this case was the uncommon location of the ACC. The differential diagnosis based on the morphologic features included paraganglioma, clear cell sarcoma, and renal cell carcinoma (RCC). These were ruled out based on the immunohistochemical findings of positive vimentin, synaptophysin, inhibin-alpha and melan A, suggesting an adrenal origin of the tumor cells. Adrenocortical carcinoma have been reported to express these markers.[14-21] Once melanoma is excluded, the presence of immunoreactivity for melan A practically excludes any other carcinoma that may enter into the differential diagnosis of ACC.[14] The diagnosis of ACC versus RCC may be difficult morphologically. Melan A and inhibin-alpha, are most often reported to be reactive with ACC but not with RCC.[15,16] Sharma et al[22] studied the comparison between the cytomorphology of ACC and RCC. They suggested that the presence of cells in sheets with a central, thin-walled vascular core (endocrine vascular pattern); monomorphic cell population; eccentric nuclei; focal dramatic anisonucleosis; and focal spindling with crushing is a prominent feature of ACC in contrast to RCC, which show mainly an acinar pattern with only a focal endocrine pattern, well-defined cytoplasmic angles and projections, and cytoplasmic vacuolations.[22]

In our patient the tumor was located outside of Gerota's fascia and postoperative CT scans showed intact left adrenal and kidney. Combining the operative, radiological, morphologic and immunohistochemical findings, we favored an ACC that most likely arose from an extra-adrenal rest as the final diagnosis. We believe that the large size, abundant cytological atypia, diffuse architecture, eosinophilic cytoplasm and the presence of mitotic figures all support the diagnosis of ACC. Radical surgical resection remains the only form of effective potentially curative approach for ACC as it was proven that it is safe and prolongs survival, so it is recommended for all patients with resectable tumors, including those patients with recurrent disease.[1,2,5,23] Resection is also recommended for those patients with nonfunctioning adrenal tumors because there are no exclusion criteria for malignancy, and non-operative treatment has not been clearly defined.[24] We did not give our patient chemotherapy. There is no consensus concerning adjuvant therapy. Mitotane is the most accepted chemotherapeutic agent and is the most often used to treat ACC. Its efficacy in prolonging survival is limited and still unsatisfactory.[2,3,6] Only 35% of patients treated with mitotane had a clinical response, and treatment of metastatic disease with mitotane has limited success.[3] For the patients whose tumors respond to mitotane, survival is prolonged.[5] The prognosis of patients with ACC is poor. Recurrence and metastasis are extremely common even in those patients who had complete resection,[2] therefore a prolonged and vigilant follow-up is essential. A study from Lahey Clinic showed that 48% of patients had endocrine symptoms, 19% had involvement of the inferior vena cava by tumor thrombus, and 32% had metastatic disease. The 5-year survival rate was 26%. Age below 54-years, localized disease, nonfunctioning tumor status and completeness of surgical resection were associated with better prognosis.[23] Early diagnosis in addition to optimization of therapeutic protocols through multicenter trials may improve prognostic aspects of ACC.[6,7] The clinical factors that are of prognostic significance for long-term survival are early stage, nonfunctioning tumor, relatively younger age at diagnosis and the curative resection performed.[8,23] On the basis of this we believe that our patient has a good prognosis because all these factors are present in his case.

In conclusion this appears to be a unique case of extra-adrenal ACC. To the best of our knowledge, no similar cases have been previously reported.

Acknowledgment. I would like to thank Dr L. Jeffrey Medeiros, from the University of Texas, MD Anderson Cancer Center in Houston, and Dr. Hassan Khaldi from the Pathology Department, Jordan University of Science & Technology for their expert opinion regarding the histopathology of this tumor. Dr. Anne Marie McNicol from the Department of Pathology, Glasgow Royal Infirmary, United Kingdom for revising the manuscript.

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