Abstract. Adrenocortical carcinomas are rare tumors in adults. They can be hormonally active and detected by a hormonal excess, or be non-secretory tumors. In the latter case, they become symptomatic after a long period of growth, usually after they have already invaded the surrounding tissues. In these cases, multiple visceral resections are sometimes required in order to obtain a complete R0 resection. We present the case of a 65-year-old patient who was addressed to our service for a giant abdominal tumor with compression phenomena in whom we performed a complete resection en bloc with left nephrectomy and adrenalectomy, distal pancreatectomy, splenectomy, left colectomy and para-aortic lymph node dissection. The early postoperative course was uneventful, the patient was discharged eight days after surgery. The histopathological findings revealed an adrenocortical carcinoma with no lymph node metastases.

Adrenocortical carcinomas are rare but lethal tumors, representing the second most aggressive endocrine malignancy after anaplastic thyroid cancer (1). Up to 60% of patients present adrenocortical hormonal excess, which sometimes helps the clinician to diagnose the patient at an earlier stage of the disease. Asymptomatic cases with no hormonal secretion, also known as incidentalomas, are usually diagnosed in advanced stages, when the tumor has already reached large dimensions, invaded the surrounding tissues or already given rise to distant metastases (2, 3). We present the case of a 65-year-old male in whom multiple visceral resections were performed in order to remove a large retroperitoneal tumor measuring 35×30×25 cm. The postoperative course was favorable with no signs of recurrence after one year of follow-up; this fact enables us to consider the aggressive surgical approach to be perfectly justified even in older patients.

Case Report

The patient was initially diagnosed with a retroperitoneal tumor three years before the current presentation, at which time he formally refused the surgical procedure. He was later addressed to our service for a giant abdominal tumor associated with abdominal diffuse pain, subocclusive syndrome and important caval compression syndrome with significant lower limb edema. The clinical examination revealed a large abdominal tumor developed in the left side of the abdomen with collateral venous circulation (Figure 1) and important edema of the inferior limbs. The preoperative computed tomographic scan showed a large retroperitoneal tumor invading the left colon, completely encasing the left kidney and its pedicle in immediate contact and exerting compression on the abdominal aorta and inferior cava vein; it developed into and shifted aside the mesentery, being in close contact with the superior mesenteric artery and vein. It also showed no demarcation limit to the body and tail of the pancreas. However, the tumor had respected the vertebral column and seemed to have no invasion into the retroperitoneal great vessels hence the decision to attempt resection was made.

Intraoperatively, we found no criteria of non-resectability in accordance with the preoperative imaging; the tumor was resected en bloc with the left kidney and adrenal gland,
corporeo-caudal pancreatectomy, splenectomy and left colectomy (Figure 2-5). Systematic para-aortic and paracaval lymph node dissection was also performed (Figure 6). The removed specimen weighed 18.5 kg and measured 35×30×25 cm (Figure 7 and 8).

Histopathological evaluation was performed after cutting serial 3-μm sections from paraffin blocks and staining with hematoxylin and eosin (HE). HE-stained sections showed the presence of tumoral proliferation with round, polygonal, multinucleate cells, with intense eosinophilic cytoplasm and hyperchromic nuclei with relatively frequent mitoses (Figure 9). Areas of hyalinization and necrosis were also seen; lymph nodes presented sinus histiocytosis without metastases.

Immunohistochemistry (IHC) was performed on 3-μm sections from 10% formalin-fixed paraffin-embedded tissues using an indirect two-stage technique performed with a polymer based detection system (EnVision™ Dual Link System-HRP; DAKO, Carpinteria, CA, USA). Tissue
sections were spread on poly-L-lysine-coated slides, immersed in three changes of xylene and rehydrated using a graded series of alcohol. Antigen retrieval was performed in a microwave oven. In each section, endogenous peroxidase was blocked by 20-min incubation in 3% hydrogen peroxide. The sections were incubated with primary antibodies to: S100 protein (polyclonal, 1:400; DAKO), Vimentin (V9, 1:50desmin (D33, 1:50; DAKO), MNF116 (MNF116, 1:50; DAKO), inhibin (AMY82, 1:100; Leica), calretinin (CAL6, 1:100; Leica), Myogenin (Myf-4) (Lo26, 1:20; Leica), melanA (A103, 1:50; Leica) chromogranin A

Figure 5. The final aspect after removing the tumor. The superior mesenteric vessels are completely dissected.

Figure 6. Complete para-aortic lymph node dissection.

Figure 7. The specimen: the tumor was removed en bloc with distal splenopancreatectomy, left colectomy and left nephrectomy.

Figure 8. The macroscopic aspect of the sectioned tumor.
(5H7, 1:100; Leica), synaptophysin (27G12, 1:100; Leica), SMA (1A4, 1:200; DAKO) and Ki67 (Mib-1, 1:100; DAKO) at room temperature for 1 h. The DAKO EnVision Detection System-HRP was then applied for 30 min. Finally, the sections were incubated in 3´3-diaminobenzidine for 5 min, counterstained with Meyer’s hematoxylin and mounted. The slides was examined and photographed on a Leica DM750 Microscope. Negative controls were obtained by replacing the primary antibody with non-immune serum. As a positive control, an adrenal tissue section was used.

Immunohistochemically, the tumor cells presented diffuse strong expression for vimentin (Figure 10) and synaptophysin (Figure 11) with focal positive immunostaining for melan A (Figure 12) and calretinin (Figure 13), while Ki67 was positive in about 15% of the tumor cells (Figure 14).

The correlation between histopathological studies and immunohistochemistry sustained the diagnosis of an adrenocortical carcinoma. At one-year follow-up, the patient is free of any recurrent disease.

Discussion

Adrenocortical carcinomas are rare tumors, with an estimated incidence of 1-6 patients in every one million habitants, and usually discovered in patients between 40 and 50 years of age (1). The main classification is related to the tumor capacity for hormonal secretion. While cases presenting hormonally active tumors can be more easily diagnosed at an early stage due to the systemic signs of hormonal excess, inactive tumors usually grow for a long period of
time and become symptomatic when they reach large dimensions, inducing compression or invasion of the surrounding viscera. Up to 40% of these tumors remain non-functional throughout their evolution (2). Distinction between benign and malignant lesions is hard on preoperative imagistic studies; however, lesions which surpass 10 cm in size are more likely to be malignant (4, 5). The most important characteristics of these malignant tumors are related to their capacity to invade the surrounding viscera and to invade the vascular space, inducing precocious metastases.

When it comes to the most appropriate therapeutic approach, most authors consider that aggressive surgery is the only potentially curative option (2, 6-8). Allolio et al. consider that complete surgical resection offers the best chance for long-term survival in patients with stage I-III adrenocortical carcinoma (4); however, even if an R0 resection is achieved, these patients should be confined to oncology Clinics for adjuvant chemo-irradiation in order to increase disease-free survival. In cases in which recurrent disease appears, surgery should be considered as a first-line option. The same study concluded that only in cases diagnosed at stage IV of the disease or presenting recurrent disseminated disease should systemic therapy with mitotane be considered as a first-line therapy (4).

Contrarely to Allolio et al.’s study, Livithis et al. considered that surgery can improve survival even in cases diagnosed with metastatic disease. In their they included study 367 patients diagnosed with adrenocortical carcinoma with median tumor size of 10 cm at the time of diagnosis, 37% of patients presented with localized disease, while 17% and 46% presented regional and metastatic disease, respectively. One-year and 5-year survival was: 92%/62% for patients with localized disease; 73%/39% for those with regional invasion; and 24%/7% for those with metastatic disease (9).

The most important prognostic factors are complete resection, absence of lymph-node invasion and a lower tumoral stage (6, 10-12). In order to achieve R0 resection, multiple visceral resections are needed, and regularly include lymphadenectomies. Another important fact in order to reduce the local risk of recurrence is keeping the tumor capsule intact (10).

Once an adequate surgical procedure is performed, the pathological study plays the central role in determining the histopathological and immunohistochemical features which provide a proper assessment of these patients. The presence of nuclear atypia, frequent mitoses (more than 5 per 50 high-power-fields), vascular and capsular invasion, necrosis and broad fibrous bands are signs suggestive of malignancy. Additional information regarding prognosis are brought by immunohistochemical studies; a higher expression of Ki67 (>10%) is usually associated with poor prognosis. Other specific markers which confirm the presence of an adrenocortical carcinoma are D11, inhibin-α, melan A, chromogranin A, and cyclin E (7).

Kokal et al. in their study introduced 10 cases diagnosed with adrenocortical carcinomas over 12 years; tumor weight ranged between 350 and 1,800 g (with a mean value of 799.3 g), while size ranged from 5 to 21 cm (with an average of 10 cm). In order to confirm the diagnosis, the authors used a panel of antibodies which included vimentin, synaptophysin, melan A, calretinin, inhibin, SMA, cytokeratin and Ki-67. Staining for vimentin and synaptophysin was positive in eight cases, melan A in six, calretinin in four, while Ki 67 was found to be >20% in all 10 cases. Cytokeratin and SMA were negative in all patients. Their study demonstrated the
importance of vimentin, synaptophysin, melan A, calretinin inhibin, SMA, cytokeratin and Ki67 in order to establish a positive diagnosis of adrenocortical carcinoma and to provide a differential diagnosis with other similar malignancies, especially renal cell carcinoma (15). Sangoi et al. also demonstrated the utility of calretinin, melan A and inhibin in order to differentiate adrenocortical carcinomas from metastatic clear cell renal carcinomas (16).

In our case, decision making in performing surgery and risk-benefit evaluation was made easier by the important signs and symptoms of compression, debilitating the patient, with important consequences for his quality of life. On one hand, the apparent feasibility of an R0 resection at preoperative evaluation, which in a suspected retroperitoneal sarcoma seems to have the greatest impact on survival prognosis, and on the other hand, necessity for symptom palliation, strongly encouraged us to propose major surgery with an undeniable degree of risk to a reluctant patient who initially refused surgery at a time when it was more easily achievable and with less tissue sacrifice.

Conclusion

Adrenocortical carcinoma is a rare and aggressive malignancy which seems to be best controlled through wide surgical excision with negative margins. To the best of our knowledge, this is the largest adrenocortical carcinoma described in literature. In our case, it seems that the complete resection ensured good local and systemic control of the disease. Absence of locoregional lymph node metastasis possibly accounted for a more indolent biology of a tumor, with a documented evolution of at least three years contributing to a good oncological evolution despite the large dimensions of the tumor. It must also be noted that important multi-visceral resection in an older patient can be accompanied by low morbidity, encouraging resection whenever estimated on preoperative examinations as being achievable without residual tumor tissue.

References