Recurrent oncocytic adrenocortical carcinoma: implementing diagnostic criteria in a case report with the longest survival

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INTRODUCTION: *Oncocytic adrenocortical tumors represent a subtype of the adrenal cortex neoplasms. These tumors can be divided into oncocytomas, oncocytic neoplasms of uncertain malignancy and carcinomas (OACs). To date, only 34 cases of OAC have been reported.*
CASE EXPERIENCE: *We reported a case of a 54-year-old male patient with a history of laparoscopic right adrenalectomy for an OAC and subsequent chemotherapy for a recurrence. He was referred to our emergency room for diffuse abdominal pain, vomit, change in bowel habits, fever, asthenia. He underwent a laparotomy and a complete excision of the known bilobate lesion. The histopathological findings matched the features of a recurrent OAC. No chemotherapy was administered after surgery and the patient was disease-free after a follow-up of twenty-eight months.*
RESULTS - DISCUSSION: *The most questionable issue in treating adrenocortical oncocytic neoplasms is the determination of malignancy. According to the Helsinki Score, which is the best prognostic system, the primary lesion was an OAC. We also implemented the score systems to the recurrent lesion, that seemed to be malignant. We believe that the adjuvant treatment can delay a recurrent lesion development, but finally, radical surgical excision is necessary. Moreover, we reported the longest survival after the primary adrenalectomy.*
CONCLUSIONS: *This study described the first case of recurrent oncocytic adrenocortical carcinoma with the longest follow-up. Adrenocortical oncocytoma is an extremely rare tumor of the adrenal gland with variable biological behavior without definitive consensus about diagnostic criteria. This was also the first case in which different histopathological criteria have been implemented in a recurrence.*

KEY WORDS: Oncocytic adrenocortical carcinoma, Surgical oncology, Survival

Introduction

Oncocytic adrenocortical tumors represent a rare subgroup (1/10) of the neoplasms of the adrenal cortex [1]. Oncocytic adrenocortical neoplasms are ordinarily nonfunctioning and they are found predominantly in adults. Up to now, only 193 cases have been reported in the literature, and the last largest series of cases have been described by Karine Renaudin et al. in 2018 [2]. By histological definition, oncocytic adrenal tumors are composed of at least 50% oncocytes and they could be defined as pure (>90% oncocytes) or mixed (50-90%) [2]. Oncocytic adrenocortical tumors may be divided into oncocytomas," oncocytic neoplasms of uncertain malignancy, and carcinomas (OACs).

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Oncocytic neoplasms of uncertain malignancy, and carcinomas (OACs). Over 50% of oncocytic adrenocortical tumors are classified as carcinomas because of the overestimation of their carcinogenic potential. This is due to the multiplicity of scoring systems adopted: nowadays, the Weiss system [3] seems not to be appropriate. Instead, the Linn-Weiss-Bisceglia system has better prognostic efficacy. Conversely, the recently introduced Helsinki Score has been accepted as a more accurate system, as far as it involves a combined evaluation of morphological and immunohistochemical parameters [4]. We reported a case of a recurrent oncocytic adrenocortical carcinoma.

Case Experience

This case report has been described in accord with SCARE criteria and PROCESS guidelines [5,6].
A 54-year-old man, known for having an unresectable relapsed adrenocortical carcinoma, was referred to our emergency room for severe dyspnea, asthenia, tachycardia, diffuse abdominal pain, vomit, change in bowel habits, fever. This patient has already been referred to our department in the past and discharged since the mass was considered inoperable. The physical examination confirmed the already known palpable middle abdominal mass, associated with bilateral lower limb edema.

Patient's Medical History

The patient had a past medical history of alcoholic liver disease and, six years earlier, previous laparoscopic right adrenalectomy, with histological diagnosis of oncocytic adrenal carcinoma, with diffuse architecture, abundant necrosis, doubtful vascular and sinusoidal invasion, Ki-67 20%.
Twenty-three months after the adrenalectomy, intra-peritoneal recurrences in the peri-splenic and posterior-gastric area (diameter 4,5cm), with other minor recurrences were reported after a CT scan. A fine-needle aspiration biopsy of the posterior-gastric mass was performed (cytologic sample: oncocytic carcinoma). The patient received chemotherapy with mitotane, cis-platinum, and EDP (epirubicin, docetaxel, and cisplatin). After 14 months, a CT-scan revealed a constant volume of the posterior-gastric lesion (20x12 mm), but also a modest enlargement of the sub-hepatic lesion.
After 13 months, the sub-hepatic and posterior gastric lesions have grown to 49 and 23mm respectively but, after another 7 months, on continued therapy with mitotane, the bilobate sub-hepatic lesion has reduced to 44 mm, while the posterior gastric one showed a larger diameter of 19mm. After another 8 months, that is five years after surgery, a control CT scan showed an enlargement of the bilobate sub-hepatic lesion (12x8 and 15x8 cm) with hypodense, colliquative central zone, high vascularized peripheral zone, circumscribed margins, but without colon and vessels invasion. On the basis of oncologist's opinion, patient's poor clinical conditions, and bad prognosis, chemotherapy was temporarily interrupted. After nine months, just one month before the patient was referred to our emergency room, the oncologists had confirmed discontinuation of any kind of antitumoral treatment.

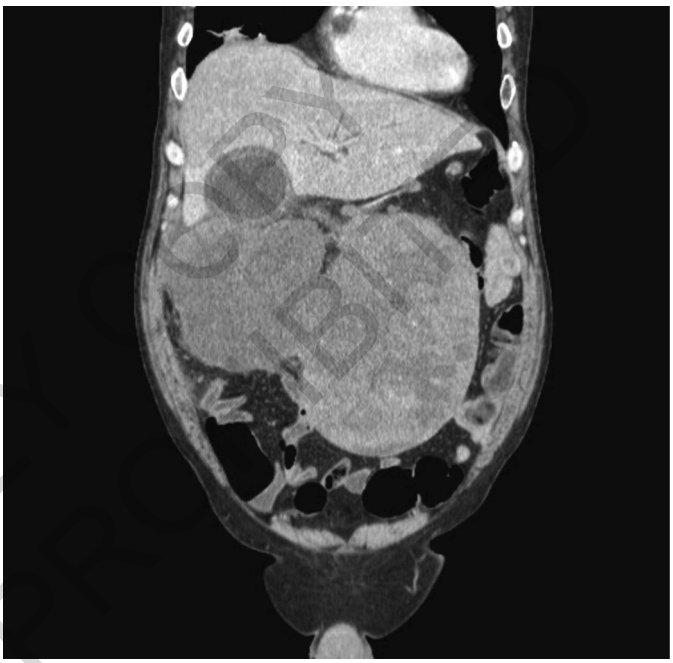

Fig. 1: The CT scan (coronal view) shows a well-defined bilobate enhancing lesion.

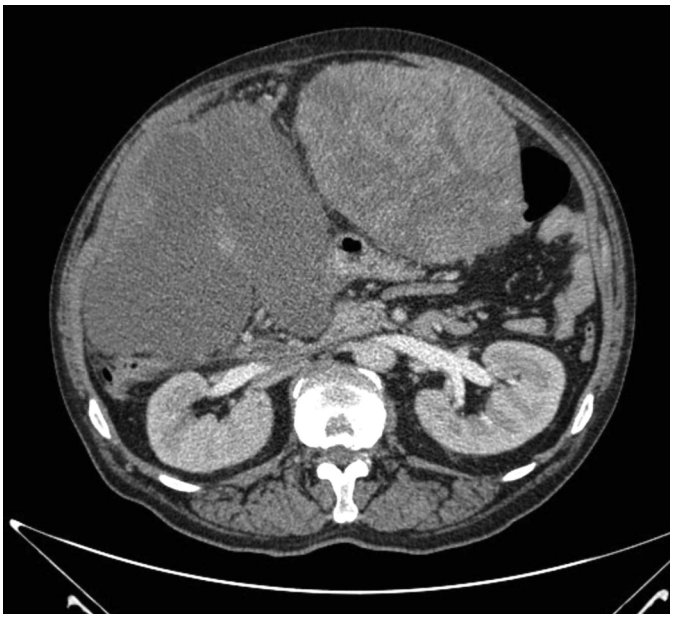

Fig. 2: The CT scan (axial view): the lesion is attached to the anterior abdominal wall and compresses the inferior vena cava.

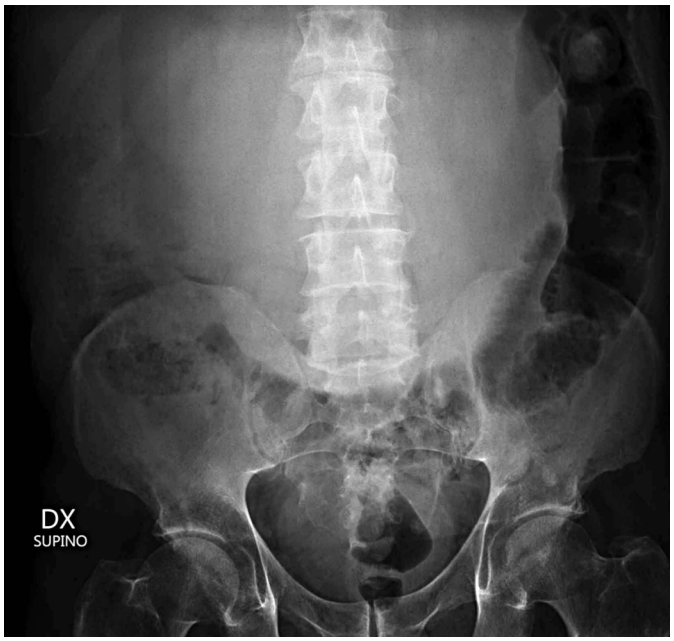

Fig. 3: Dorsal decubitus abdomen X-ray: ventral and lateral dislocation of the intestinal loops.

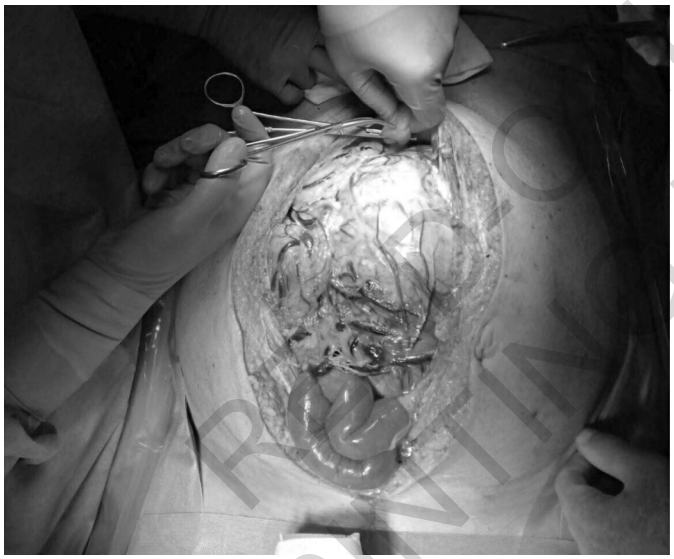

Fig. 4: Median laparotomy. The hypervascular lesion appears.

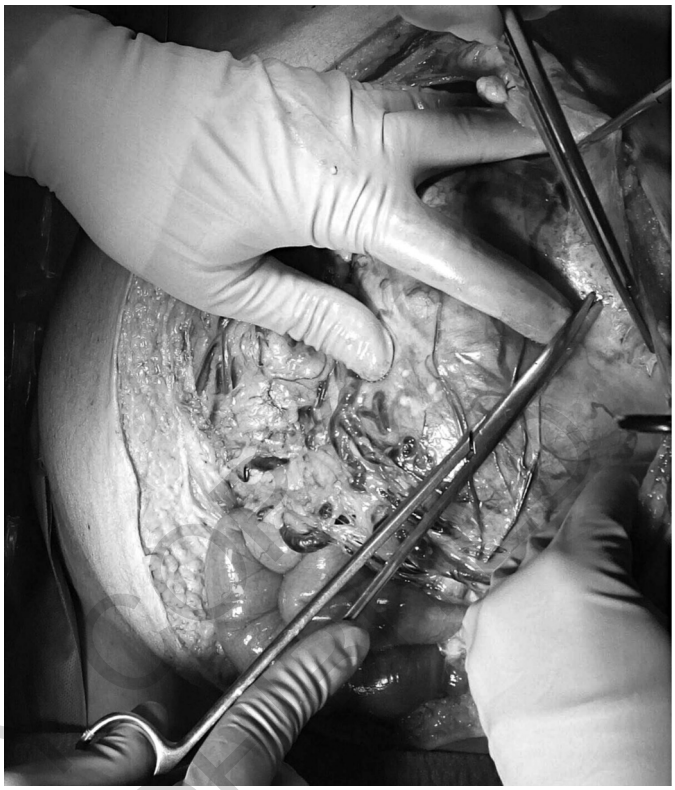

Fig. 5: The lesion is detached from the anterior abdominal wall.

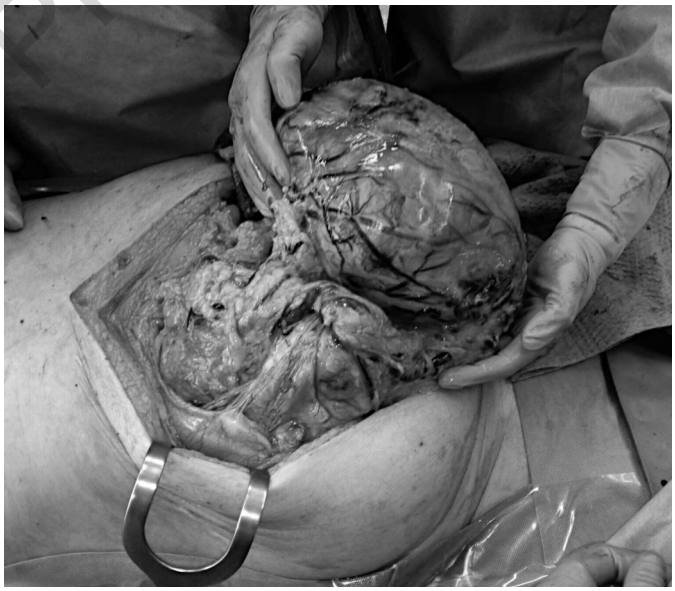

Fig. 6: The left lobe is flipped and excised.

Primary Care, Evaluation, and Surgical Procedure

Hospital admittance was required, infusive and antibiotic therapy were administered and total-body CT-scan with contrast (Figs. 1, 2) revealed a volumetric gain (diameter >15cm) of the bilobate lesion, in comparison with the previous CT images. The adjacent intestinal loops appeared to be compressed and dislocated by the mass, like the X-rays had suggested before (Fig. 3), and a moderate enlargement of the intrahepatic and extrahepatic bile ducts was also described. Considered the number of past ER admittances, the altered venous return, the absence of other extra-abdominal localizations, after a multidisciplinary discussion, an exploratory laparotomy was undertaken in more stable clinical conditions.

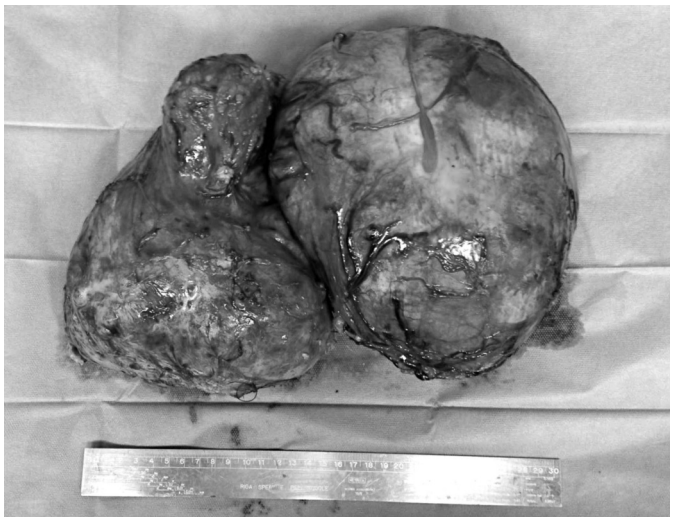

Fig. 7: The 22x18x15cm and 19x18x15cm bilobate lesion once removed.

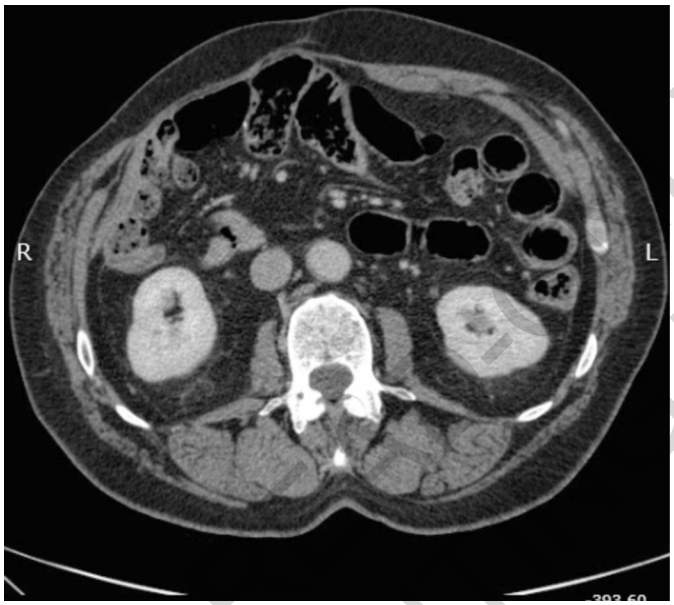

Fig. 8: CT scan. The patient is disease-free 28 moths after surgery.

A median laparotomy was performed. The voluminous hypervascular lesion (Fig. 4) was detached from the anterior abdominal wall, to which it was strongly adherent (Fig. 5), and from the visceral peritoneal attachments. A resection of the right, transverse colon, and the distal ileum was necessary due to the marked adhesion of the neoplastic lesion with the mesocolon. A separate excision of the two lobes of the lesion was completed (Fig. 6), and a side-to-side ileocolic anastomosis was performed. Neither intraoperative or postoperative complications occurred, and the patient was discharged 13 days after surgery, after a period of kinetic and respiratory rehabilitation.

Results

Histopathological Findings

Macroscopically, the two lobes of the lesion (Fig. 7) had the subsequent dimensions and weight: 22x18x15 cm and 19x18x15 cm; 3100 g and 2800 g respectively. The most sizeable one was solid and capsulated, the section had a grey-yellow color, a multi-nodular appearance, a soft consistency, and was focally hemorrhagic and necrotic. The second lesion had a nodular appearance. The sectional view showed a yellowish multinodular tissue with interposed grey sclerotic tissue and hard and elastic texture. Microscopically, both lesions were composed of pleomorphic cells, with irregular-shaped nuclei, dense chromatin, prominent nucleoli (high nuclear grade, based on Fuhrman criteria [7]), and eosinophilic cytoplasm. Rare multinuclear cells were identified, as well as large and multifocal necrotic areas and intratumoral fibrous branches. 10 mitoses per 50-high power field were reported. The Ki-67 index was 15%. The immunophenotype was Inhibin positive (focally), Melan-A positive, Vimentin positive, Calretinin positive (focally), Synaptophysin positive, CD56 positive, Chromogranin negative, Cytokeratin negative, S100 negative, and TTF-1 negative. The histopathological findings matched the features of a recurrent oncocytic carcinoma with an adrenal origin.

Follow-Up

It was decided not to administer any chemotherapy medication and to set a close follow-up. After oncological evaluation no chemotherapy regimen was suggested in this patient. Nine months after surgery, the total-body CT-scan revealed no sign of relapse nor recurrence. Even twenty-eight months after surgery, the patient was disease-free (Fig. 8).

Discussion

Oncocytic adrenocortical carcinoma is a rare tumor. To date, 34 cases of oncocytic adrenocortical carcinoma have been reported, according to Lin-Weiss-Bisceglia criteria [2]. The majority of these neoplasms are non-functioning, but, in a few cases, abnormal hormonal serum and urinary levels were documented [8,9,10]. In our patient a non-functioning OAC was observed and we tried to match and compare our findings to literature data.
The most problematic issue in treating these tumors is the determination of malignancy. According to other reports, the Weiss score overrates the malignancy, and for this reason the Lin-Weiss-Bisceglia was adopted. More specifically, an oncocytic tumor is considered as malignant if it shows one of the major criteria (more than 5 mitoses/50 HPF, atypical mitotic figures, and

venous invasion); conversely, the presence of one to four minor criteria (presence of necrosis, sinusoidal invasion, capsular invasion, and size > 10 cm and/or weight > 200 g) indicates uncertain malignant potential [11]. According to the patient's clinical history, Weiss criteria defined the lesion as suspicious for malignancy, whilst Lin-Weiss-Bisceglia criteria indicated an uncertain malignant potential. Although these criteria were used for primary tumors in the literature, we tried to implement the criteria for the relapse histological sample: it matched Lin-Weiss-Bisceglia score for malignancy. More recently the Helsinki score has been validated as the most relevant prognostic system since it evaluates the morphological features and includes the Ki-67 proliferation index [2]. It is calculated as follows: 3 points for a mitotic count > 5/50 HPF + 5 points for the presence of necrosis + the absolute value of Ki-67 proliferation index. The Helsinki score demonstrates a poor prognosis for oncocytic neoplasms, having a score of 19 or more. Concerning the primary tumor, the patient's clinical history data indicated malignancy (Helsinki score >19). Even in this case, we implemented the Helsinki score to the recurrence reaching 23. As regards immunohistochemistry, we referred to a Japanese work, which reviewed the features of 17 oncocytic adrenocortical carcinomas reported in the literature [12]. It was reported that 93,3% and 75% of these carcinomas express Vimentin and Inhibin respectively, and so does the tumor displayed in this case report. Besides, both Melan-A and Synaptophysin, which resulted to be positive in 20% and 50% of cases respectively, were found to be positive in our case. Lastly, Chromogranin A was reported as negative in all oncocytic adrenocortical carcinoma in the literature, and so was in our case of recurrence. In a patient with excised lung metastasis of OAC [13], a Calretinin and CD-56 positivity, and a TTF-1 and S-100 negativity were reported, just like that observed in our patient.

Due to the aggressive behavior and constant relapse of OACs, the standard treatment for these tumors is the complete surgical excision, whenever possible, according to the patient's performance status [13]. Nevertheless, there is an extensive debate about the multimodal therapeutic approach which should follow the radical surgical excision of the primary tumor. Some studies have shown that adjuvant mitotane can delay and eventually prevent recurrences [14,15]. According to Kazushi Tanaka et al. [16], mitotane seemed to be effective after surgery. In our patient for almost two years after the primary adrenalectomy, no adjuvant therapy was given. Then recurrences occurred, and chemotherapy was administered. Although this adjuvant treatment probably delayed the recurrent lesions enlargement, a radical surgical excision was eventually necessary to prevent fatal complications.

Many studies have reported a more indolent outcome in patients with OACs in comparison with conventional adrenocortical carcinomas [2,13]. Wong et al. have reported that the overall median survival for patients with OAC is 58 months, while the median survival of patients with conventional adrenocortical tumors is between 14 and 32 months [17]. In this study, we reported survival of twenty-eight months after the second surgical intervention, and overall survival of more than 8 years after the primary adrenalectomy.

Conclusions

The adrenocortical oncocytoma is a rare tumor with or without function. Surgical removal is still the major treatment method.

At the best of our knowledge the maximum follow-up time reported for patients with OACs is 59 months. Our patient seems the first case of recurrent oncocytic adrenocortical carcinoma with the longest follow-up of 99 months [2], and with different histopathological criteria implemented in a recurrent form of OAC. To improve treatment strategies large clinical series with molecular studies, precise diagnosis criteria, and detailed follow-up are needed. This could allow us to better understand the behavior of this type of rare adrenocortical tumors.

Riassunto

I tumori oncocitici della corteccia surrenale possono essere suddivisi in oncocitomi, neoplasie oncocitiche ad incerto potenziale maligno e carcinomi oncocitici (OACs) e più del 50% surrenali è classificato come carcinoma per sovrastima del potenziale di malignità, data una certa discordanza delle scale di score adottate. Finora, in letteratura sono stati descritti solo 34 casi di carcinomi oncocitici della corteccia surrenale.

Viene qui presentato il caso clinico di un uomo di 54 anni, già sottoposto a surrenectomia destra per via laparoscopica, per l'asportazione di un OAC. Successivamente, per una recidiva locale, il paziente era andato incontro a cicli di chemioterapia con mitotano, cis-platino, ad EDP (epirubicina, docetaxel, cisplatino). Ciononostante, cinque anni dopo la surrenectomia, alla TC addome di controllo, la recidiva locale aveva raggiunto le caratteristiche di una lesione bilobata di circa 12x8 e 15x8 cm. Sulla base del parere oncologico, delle condizioni cliniche scadute del paziente e della cattiva prognosi, veniva controindicato qualunque tipo di trattamento, medico o chirurgico. In seguito, il paziente si è recato presso il pronto soccorso del nostro Istituto, per dolori addominali diffusi, vomito, alvo alterno, febbre, astenia, ipotensione, con instabilità emodinamica. Dopo stabilizzazione dei parametri vitali, in regime di urgenza è stato sottoposto ad una laparotomia esplorativa, e quindi a completa exeresi della lesione bilobata. Il referto dell'esame istologico riportava: "recidiva di carcinoma oncocitico della corteccia surrenale". In seguito a tale intervento,

non è stato somministrato alcun farmaco chemioterapico e ad un follow-up di 28 mesi il paziente è stato considerato libero da malattia.
La problematica maggiore è dunque quello della determinazione del grado di malignità nel caso di neoplasie oncocitiche della corteccia surrenalica. Secondo lo Score di Helsinki, valutato come il miglior sistema prognostico, il caso illustrato rappresentava un carcinoma oncocitico, anche considerando la lesione recidiva: erano soddisfatti i criteri di malignità. In letteratura è stato dimostrato che il trattamento adiuvante è in grado di ritardare lo sviluppo di recidive, ma, in questo studio, l'intervento chirurgico si è rivelato essere una procedura necessaria e salvavita. Molti studi hanno riportato una migliore prognosi nei pazienti con OAC, rispetto ai pazienti con carcinoma surrenale convenzionale. Il presente studio riporta il maggior periodo di sopravvivenza dopo la surrenectomia primaria (più di 8 anni) e dopo l'intervento d'urgenza nella recidiva (28 mesi).
Questo caso clinico descrive un adrenocarcinoma oncocitico con il più lungo periodo di follow-up mai descritto in letteratura. In conclusione, l'oncocitoma del surrene è un tumore molto raro della ghiandola surrenale, avente un comportamento clinico variabile. Non vi è ancora un definito consenso riguardo ai criteri diagnostici. Il presente studio riporta il primo caso in cui i differenti criteri istopatologici sono stati applicati anche in una recidiva di malattia.

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