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Case Report

Adrenal Cortical Carcinoma with Inferior Vena Cava and Right Atrium Involvement: A Report of an Unusual Presentation with a Literature Review

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Abstract: Background: Adrenal cortical carcinoma (ACC) is a rare and aggressive malignant tumor with an estimated prevalence of 0.5–2 cases per million people. For patients with advanced or metastatic disease, the prognosis is very poor, and death usually occurs in the first 24 months after diagnosis. Some cases of ACC with invasion of the inferior vena cava (IVC) and the right atrium (RA) have been reported. Methods: We herein report an additional case of IVC and RA involvement in ACC in a 61-year-old woman with no relevant past medical history. Results: The patient underwent heart surgery to remove neoplastic thrombi in the IVC and RA; abdominal surgery to remove the adrenal mass was performed one month later, when the patient's clinical condition was stable. Conclusions: The histologic and immunohistochemical features, as well as the differential diagnosis, are highlighted herein.

Keywords: adrenal cortical carcinoma; inferior vena cava; atrium; metastasis; differential diagnosis

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1. Introduction

Adrenal cortical carcinoma (ACC) is a rare and aggressive malignant tumor, with an estimated prevalence of between 0.5 and 2.0 cases per million people. It is associated with a high degree of malignancy, and the 5-year survival rate ranges from 15% to 35% depending on various factors including the stage at diagnosis and the effectiveness of treatment interventions [1,2]. Surgical resection remains the primary treatment modality, with a focus on achieving complete excision of the tumor. However, recurrence occurs in a significant proportion of patients, with rates ranging from 20% to 85% depending on the possibility of achieving a radical excision and the stage of disease at the time of surgery [1–4]. For patients diagnosed with stage III or IV ACC, the prognosis is particularly grim, as the disease is often resistant to conventional therapies, and death typically occurs within the first 24 months after diagnosis, largely due to the aggressive nature of the cancer and the lack of effective treatment options for advanced stages [1–4].

The most common metastatic sites for ACC are the liver, lungs, and lymph nodes, with distant metastasis often signifying a transition to more advanced disease stages. The tumor's ability to invade surrounding structures is also a major factor contributing to poor outcomes. Notably, invasion of the inferior vena cava (IVC) has been observed in a significant number of cases, which can lead to further complications [5–17]. In severe instances, there have been reports of direct extension of the tumor into the right atrium (RA) of the heart, a condition that is closely associated with a particularly poor prognosis due to its impact on cardiac function and the potential for rapid systemic spread [5–17]. This direct extension can complicate both surgical and non-surgical treatment approaches,

limiting therapeutic options and further worsening the survival outlook for affected patients. Despite advancements in surgical techniques, the challenge of managing ACC at advanced stages remains a critical issue in oncology, necessitating the exploration of alternative therapeutic strategies, including targeted therapies and immunotherapies, to improve outcomes for those diagnosed with this aggressive cancer.

2. Case Presentation

We herein report the case of a 61-year-old woman with obesity and no relevant past medical or surgical history. She presented to the emergency room with signs and symptoms of acute heart failure. All her laboratory work-up results, including her plasma free metanephrine, potassium, and aldosterone levels, were within normal ranges.

A chest and abdominal CT scan was performed, which showed a voluminous neoplastic mass involving the right side of the abdomen (10 × 7.5 cm), presumably arising from the right adrenal gland. The mass showed contrast enhancement and extended into the liver by contiguity, and other sub-centimetric liver nodules were found, supposedly of a metastatic nature. A parenchymal nodule of 3.5 cm was also found in the medium lobe of the right lung, as well as neoplastic thrombi in the IVC and RA. Therefore, a cardiac computed tomography angiography (CTA) was also performed, confirming the presence of a bilobed, inhomogeneously hypodense mass in the RA (5 × 3 cm), in continuity with the IVC (Figure 1).

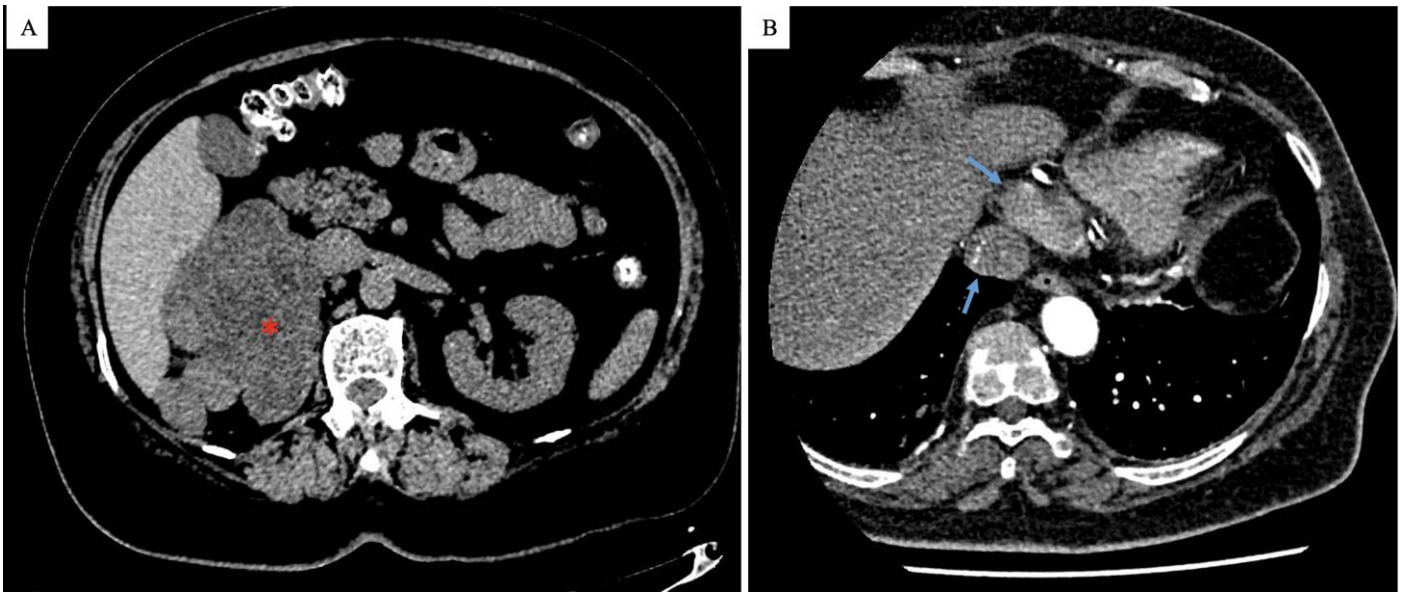

Figure 1. (**A**) Abdominal CT scan showing a voluminous neoplastic mass involving the right side of the abdomen (10 × 7.5 cm), presumably arising from the right adrenal gland, with liver involvement (*); (**B**) a cardiac computed tomography angiography (CTA) showing a bilobed, inhomogeneously hypodense mass in the RA, in continuity with the IVC (arrows).

Due to the risk of neoplastic embolism into the pulmonary artery, once the patient was stabilized, she underwent emergency heart surgery to remove the neoplastic thrombi from the IVC and the RA; the possible removal of the primary tumor was postponed.

The surgical specimens were sent to the Pathology Department. Gross examination of the RA mass revealed a 4.5 cm solid, whitish tumor; the IVC mass was a 5.5 cm thrombus with the shape of a blood vessel, with the same gross features as the atrial mass.

Histologically, both the RA and IVC masses shared the same morphological features. The tumors showed a nested growth pattern and were composed of cells with clear to slightly eosinophilic cytoplasm, and nuclei with moderate atypia and prominent nucleoli (which were clearly identifiable at 10× magnification). The tumor nests were separated

by thin fibrous septa with prominent vasculature, consisting of thin-walled, sometimes dilated, blood vessels. Areas of necrosis were found, as well as brisk mitotic activity (>50 mitoses/50 HPF) and some atypical mitotic figures (Figure 2).

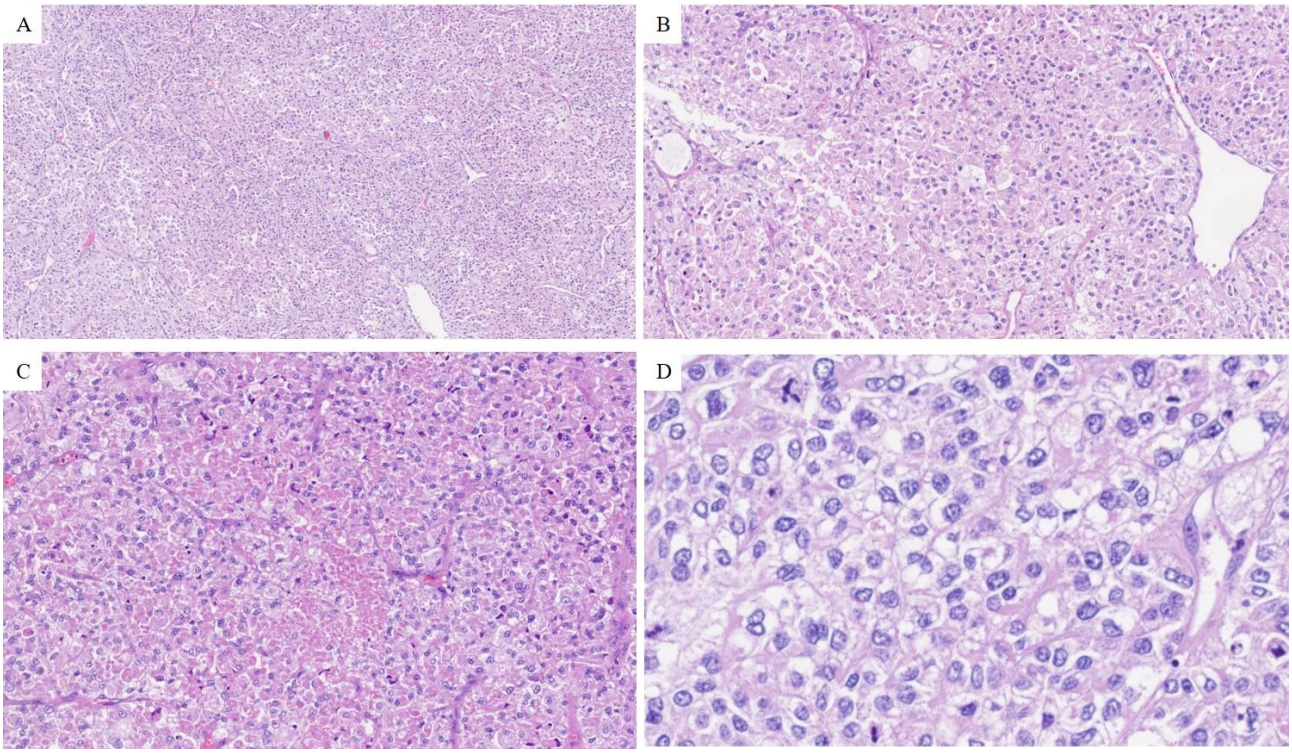

Figure 2. (**A**) The tumor exhibited a nested growth pattern, with nests separated by thin fibrous septa with prominent vasculature, consisting of thin-walled, sometimes dilated, blood vessels; (**B**) tumor cells showed clear to slightly eosinophilic cytoplasm, and nuclei with moderate atypia and prominent nucleoli; (**C**) areas of necrosis were found; (**D**) the tumor showed brisk mitotic activity and some atypical mitotic figures.

The main differential diagnoses included an ACC and a clear-cell renal cell carcinoma (CC-RCC) with invasion of both the adrenal gland and the IVC, extending into the RA. Immunohistochemical analysis was therefore performed as previously described [18], and the antibodies tested included SF1, PAX8, CD10, inhibin, Melan-A, chromogranin A, synaptophysin, and Ki67. Immunohistochemical analyses for the p53, β-catenin, and "mismatch repair" (MMR) proteins were also performed. The tumor showed immunoreactivity to SF1, inhibin, Melan-A, chromogranin A, and synaptophysin, with a Ki67 > 50%, whereas PAX8 and CD10 were negative (Figure 3). Accordingly, a diagnosis of metastatic adrenal cortical carcinoma (ACC) was finally rendered.

The tumor showed diffuse p53 expression and the loss of MSH6 nuclear expression, while the remaining MMR proteins (MLH1, PMS2, and MSH2) were retained; no nuclear expression of β-catenin was identified. Based on the results of MMR protein expression (loss of MSH6), a genetic consultation for Lynch syndrome was suggested in the pathology report.

The patient was transferred to the semi-intensive care unit two days after heart surgery and was discharged a few days later when clinical conditions stabilized. Post-operatively, the patient's clinical condition was stable, so the possibility of further surgical treatment was taken into consideration.

One month later, the patient underwent abdominal surgery to remove the adrenal mass and liver nodules. Histological examination showed an adrenal cortical tumor with the same morphologic features previously found in the IVC and RA thrombi, but a more pronounced nuclear pleomorphism and a minor clear-cell component were detected, as well

as more extensive necrotic areas and capsular, sinusoidal, and venous invasion (Figure 4). The tumor also showed a diffuse growth pattern > 33%, so the Weiss score was 9/9 [19].

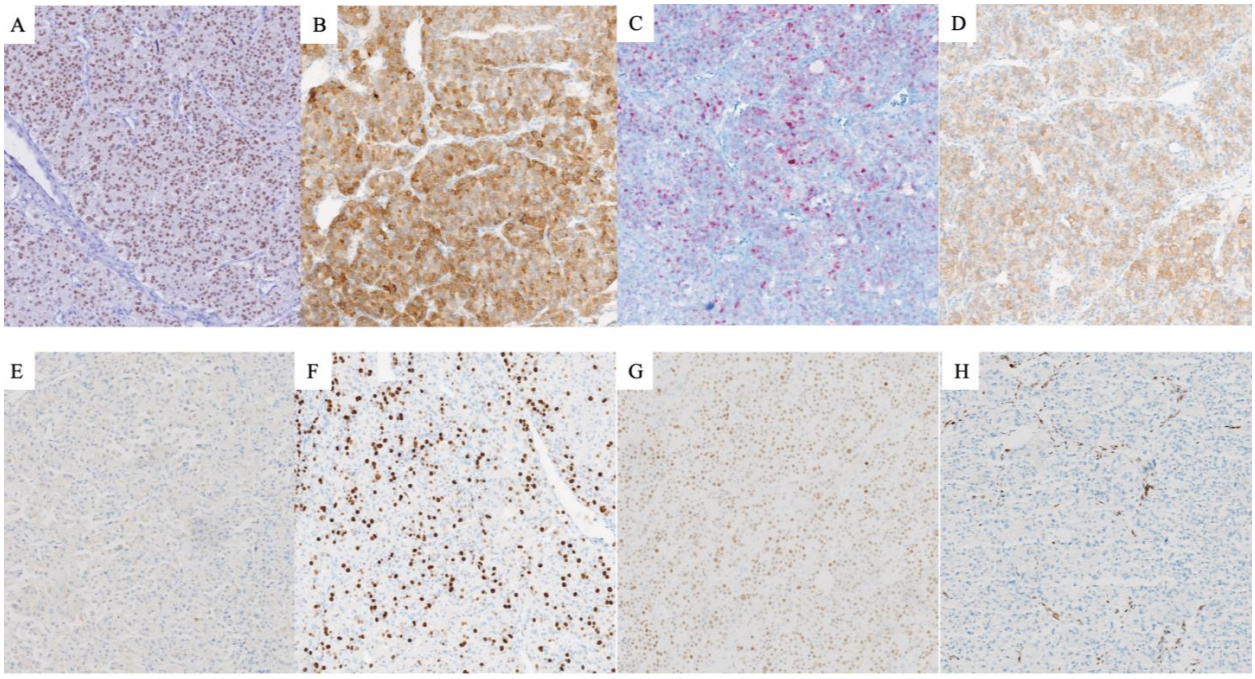

Figure 3. (**A**) Immunohistochemical analysis showed diffuse nuclear staining for SF1; (**B**) diffuse cytoplasmic staining for inhibin; (**C**) heterogeneous cytoplasmic staining for Melan-A; (**D**) synaptophysin heterogeneous cytoplasmic staining is shown; (**E**) PAX8-negative staining ruled out clear-cell renal cell carcinoma; (**F**) the neoplastic cells exhibited a high proliferative index, assessed with Ki67; (**G**) P53 overexpression in tumor cells; (**H**) MSH6 loss is shown.

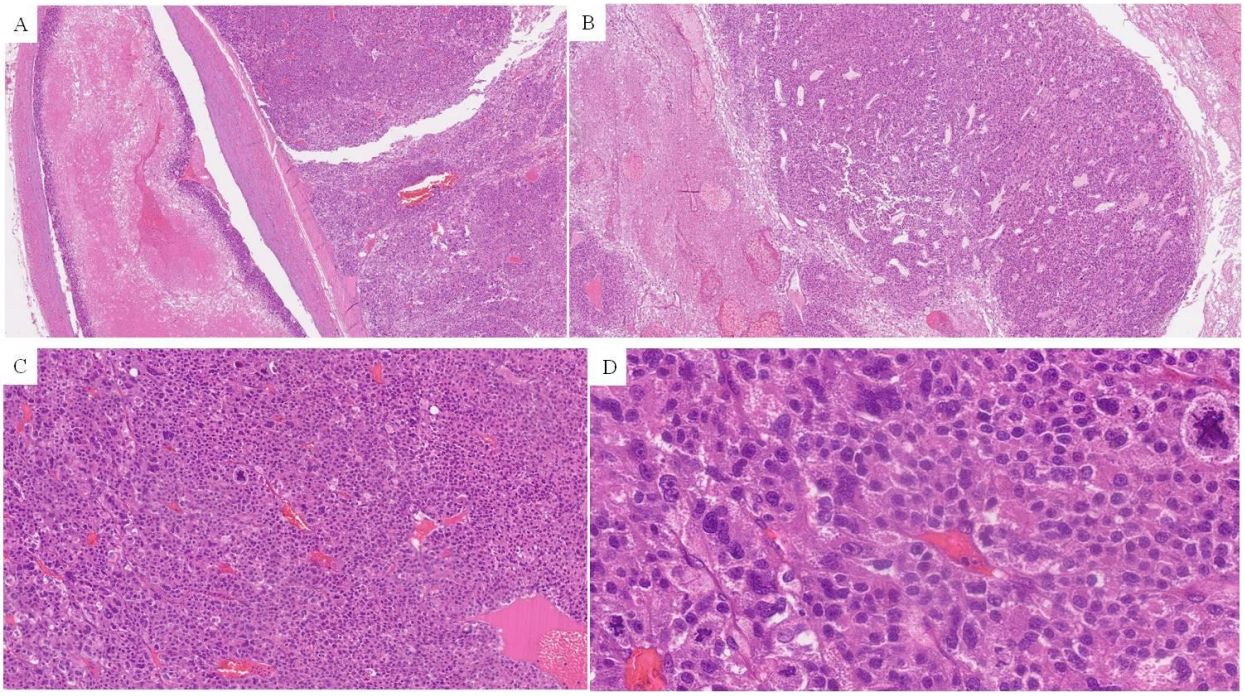

Figure 4. (**A**) Adrenal tumor showing easily identifiable venous invasion; (**B**) large necrotic areas were found; (**C**) with higher magnification, striking nuclear pleomorphism can be seen; (**D**) numerous mitoses were identified, including atypical mitotic figures.

The tumor had metastasized to the liver, and the immunophenotype was the same as that found in the IVC and RA thrombi.

After surgery, the patient underwent adjuvant chemotherapy with mitotane and radiation therapy of the tumor bed and is living at present with no evidence of additional metastatic lesions on a total body CT scan, after 6 months of follow-up.

3. Discussion

ACC is a rare tumor with aggressive behavior. The prognosis is related to the stage of the disease at diagnosis and to the possibility of radical surgery [1–4], with a 5-year survival rate ranging from 15% to 35% [1,2]. Surgery represents the therapeutic gold standard, but recurrence occurs in 20–85% of patients; recurrence is mainly due to an incomplete surgical excision and is related to the stage of disease, with advanced stages showing higher recurrence rates [1–4]. Patients with locally advanced (stage III) or metastatic (stage IV) disease have very poor prognosis, and death usually occurs in the first 24 months after diagnosis [1–4].

The main metastatic sites are the liver, lungs, and lymph nodes, but during the past few years, a few cases have been reported showing involvement of the IVC and, more rarely, of the RA [5–17] (Table 1).

Table 1. Summary of reported cases of adrenal cortical carcinoma involving the right atrium.

Study	N. of Cases	Age, Sex	Side of ACC	Tumor Size
Hisham et al. (2003) [5]	1	43 y, M	Left	14 cm
Chiche et al. (2006) [6]	4	Mean 42.25 y (range 15–65 y) 3 F, 1 M	Right in all 4 cases	NA
Kim et al. (2006) [7]	1	34 y, M	Right	17 cm
Peterffy et al. (2008) [8]	1	47 y, F	Right	NA
Kumar et al. (2011) [9]	1	1 y, M	Right	5 cm
Patil et al. (2013) [10]	1	30 y, F	Right	13 cm
Kumar et al. (2013) [11]	1	40 y, F	Right	10 cm
Annamaria et al. (2015) [12]	1	51 y, F	Right	8 cm
Levin et al. (2015) [13]	1	1.7 y, F	Right	NA
Wang et al. (2016) [14]	1	33 y, M	Right	18 cm
Alghulayqah et al. (2017) [15]	1	15 y, M	Right	11 cm
Castro-Dominguez et al. (2017) [16]	1	42 y, M	Right	22 cm
Szmyt et al. (2023) [17]	1	34 y, F	Right	23 cm
Present case	1	61 y, F	Right	10 cm

Abbreviations: y—years; M—male; F—female; ACC—adrenal cortical carcinoma; NA—not available.

On searching the literature, 16 reported cases were found of RA involvement in ACC. The group of patients with ACC with RA involvement comprised nine females (ten including the present case) and seven males, with a mean age of 35.4 years (range 1–65). The adrenal mass was located on the right side in all but one case, and this may be explained by anatomical reasons: the right adrenal vein drains directly into the IVC, whereas the left adrenal vein drains into the left renal vein. The mean tumor size was 13.7 cm (range 5–23 cm); for six cases, no data were available regarding tumor size. For all previously reported cases, the patients underwent surgery with resection of both the RA thrombus and adrenal mass, highlighting the importance of radical surgery for ACC. Unfortunately, in our case, the patient was in a life-threatening condition with signs and symptoms of acute heart failure; so, in an emergency situation, only heart surgery to remove the thrombi from the IVC and RA was performed, in order to stabilize the patient from a hemodynamic

point of view and to prevent the risk of neoplastic embolism into the pulmonary artery. We know from the literature that this is not the best approach to ACC [1–4], but the patient was not fit for a more complex surgery at the time. Abdominal surgery was performed later, when the patient had been stabilized from a hemodynamic point of view and could therefore undergo such a complex surgery. Due to the advanced stage of the disease, the patient also underwent adjuvant chemotherapy and radiotherapy.

This latter aspect highlights once more the need for a specialized center for the treatment of rare tumors, such as ACC, especially when they are diagnosed at an advanced stage, requiring complex multi-modal treatment. We believe that the most educational aspect of the case presented herein is that these patients, despite onset in an advanced stage of disease, can still benefit from a surgical approach to the primary tumor, especially if they are in good general condition. Therefore, the preliminary evaluation of the patient's clinical status seems to be crucial in choosing the optimal treatment even in cases of advanced disease.

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