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Huge Hematoma as First Manifestation of Adrenocortical Carcinoma: A Case Report

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Data Interpretation D
Manuscript Preparation E
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Patient: Male, 38-year-old
Final Diagnosis: Adrenocortical cancer
Symptoms: Acute pain in right side flank
Medication: —
Clinical Procedure: —
Specialty: Endocrinology and Metabolic • Oncology • Surgery

Objective: Rare disease

Background: Adrenocortical carcinoma (ACC) is a rare malignancy associated with unfavorable prognosis. It is mainly diagnosed in the fifth or sixth decade of life. Symptoms of ACC are associated with hormonal activity, presence of metastases, and size of the tumor. The treatment and prognosis depend on the stage of the disease assessed with the ENSAT staging system.

Case Report: A 38-year-old White man was admitted to our department from the city hospital due to a huge hematoma of the right adrenal gland (130×100 mm). On admission, the patient's condition was stable, and no active bleeding or other complications were present. Therefore, initially, conservative treatment was performed. The control CT scan showed reduction of the hematoma (90×80 mm). Due to the unknown character of the tumor and the sudden onset of bleeding, the patient was prepared for elective surgery according to the phaeochromocytoma surgery protocol. Following preparation, the patient underwent right-sided adrenalectomy. In the postoperative histopathological examination, adrenocortical carcinoma was diagnosed, which allowed the patient to receive appropriate oncological treatment.

Conclusions: There is currently no clear algorithm for the management of adrenal hemorrhage. A hemodynamically unstable patient requires urgent surgical treatment. Patients in good general condition should be prepared for early elective surgery.

Keywords: Adrenal Gland Neoplasms • Adrenocortical Carcinoma • Hemorrhage

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Background

Adrenocortical carcinoma (ACC) is a rare malignancy, with estimated prevalence of 1-2 cases in 1 million, associated with unfavorable prognosis. ACC is mainly diagnosed in the fifth or sixth decade of life, at a mean age of 55 years old. In about 60% of cases, ACC is a hormonally functional neoplasm [1-3].

Patients with ACC may be divided into 3 groups in terms of the clinical presentation of the disease. In the first group the symptoms are secondary to the excessive hormone production. The second groups of patients present mainly non-specific symptoms caused by the effect of the mass, including abdominal pain, fulness, or early satiety. The third group includes patients in whom the lesion was detected during imaging examinations performed due to other reasons (incidentaloma) [1,4,5].

Several features in imaging examinations can show the malignant character of the lesion, such as: irregular shape with poorly-defined boarders, internal hemorrhages, necrosis, calcifications, density of the lesion >10 HU (Hounsfield units) in the computed tomography (CT), lack of or small areas of intracytoplasmic lipid in MRI (Magnetic Resonance Imaging) or rapid growth >2 cm/year [6].

The treatment of ACC is a complex process. The only curative approach is complete surgical resection of the lesion. There is still no consensus concerning the operation technique—conventional open surgery or laparoscopy. In other adrenal tumors, especially ones smaller than 6 cm, laparoscopy is the criterion standard. However, in ACC some experts prefer a conventional approach regardless of lesion size. Adjuvant therapies aim to reduce the recurrence rate. The prognosis depends on the stage of the disease (proliferation index/staging), serum cortisol concentration, the completeness of the surgical resection, and introduction of adjuvant therapies. Five-year survival ranges from 16% to 40% but increases to 60% to 80% when the tumor is limited to the adrenal gland [6,7].

We report a case of a 38-year-old White man, in whom the adrenal hemorrhage (AH) was the first symptom of the ACC

Case Report

A 38-year-old White man was admitted to a city hospital due to acute, right-sided, localized, flank pain. He had no concomitant disorders. In his previous examination (abdominal ultrasound) there was no mention of any adrenal lesions. On admission, the patient was in a stable state, with blood pressure (BP) 135/80 mmHg, and without tachycardia. In the abdominal ultrasound examination, a large, retroperitoneal hematoma was diagnosed on the right side. The subsequent contrast-enhanced computed tomography (CT) scan confirmed a large (13×10 cm) retroperitoneal, right-sided hematoma secondary to the bleeding to the adrenal tumor. The patient was transferred to the Department of General, Endocrine, and Vascular Surgery of the Medical University of Warsaw.

On admission, the patient was in stable condition, with BP 130/80 mmHg, heart rate (HR) 80/min, hemoglobin (HGB) 11 g/dl, and red blood cells (RBC) 3.55 [10^6/μL]. On the second day following admission, the control CT scan showed a 98×85×80 mm right-sided adrenal hematoma, with density of 55 HU, without features of active bleeding. Due to the undetermined character of the adrenal tumor, following the suggestions of the MDT (multidisciplinary team), the individually

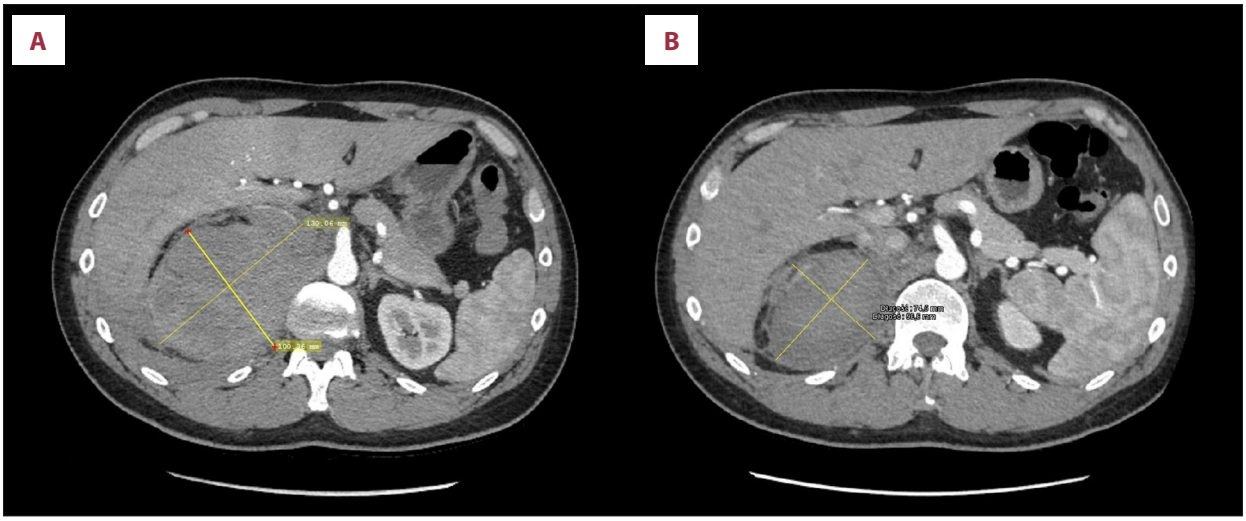

Figure 1. (**A**) Initial angio-CT scan of the abdominopelvic cavity shows the adrenal hematoma of 130×100 mm; (**B**) Angio-CT scan 3 weeks after the first examination shows decreased size of the hematoma to 90×60 mm.

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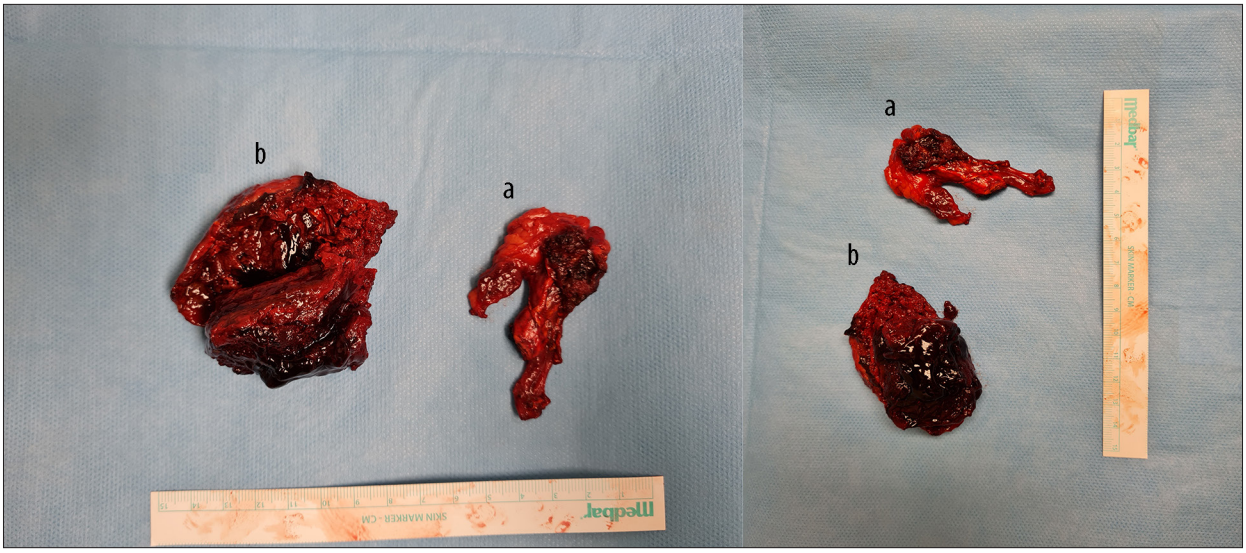

Figure 2. Adrenal gland with hematoma after surgical excision. **a**) Adrenal gland with hematoma; **b**) Hematoma.

adjusted, maximal, well-tolerated daily dose of doxazosin of 8 mg (4 mg every 12 hours) was introduced. The laboratory tests results, which were available 3 weeks later, showed increased level of DHEA-S of 513.5 ug/dl, morning cortisol level 17.7 ug/dl, evening cortisol level 14.9 ug/dl, normetanephrine concentration 110.62 pg/ml (N<113.8 pg/ml), metanephrine concentration of 11.84 pg/ml (N<88 pg/ml,) and very low methyltyramine level below the testing method sensitivity threshold.

During this 3-week period, the patient had an angio-CT scan of the abdominopelvic cavity performed, which showed decreased hemorrhage size to 90×60mm (**Figure 1**). Despite the decline in hemorrhage volume, the patient was not disqualified from surgical treatment.

After 25 days, the patient was admitted to our department again for an elective surgery. The patient was stable, with RR 135/90 mmHg, HR 90/min, HBC 13.80 g/dl, and RBC 4.77 [10^6/µL]. Due to the initially large size of the hemorrhage and expected difficult intra-operative conditions due to infiltration of the retroperitoneal space, we performed conventional open surgery with intraperitoneal approach. Intraoperatively, a large retroperitoneal infiltration encompassing the vena cava inferior and diaphragm was identified. After successful dissection of the hemorrhage from the infiltrating tissues, the adrenal gland, with initially identified adrenal capsule rupture (most probably secondary to hemorrhage), was successfully dissected and excised following the adrenal vessels ligation. All the excised tissues were sent for histopathological examination (**Figure 2**). The postoperative period was uncomplicated and the patient remained stable, with BP 120/75 mmHg, HR 80/min, HGB 10 g/dl, and RBC 4.29 [10^6/µL]. The patient was discharged from the hospital on the 4th day after surgery.

Histopathological examination revealed adrenal carcinoma with low proliferation and low mitotic index, 4 points according to the Weiss scoring system, and Helsinki score of 3.5 points (**Figure 3**). The necrosis was reported to be of vascular origin. Our patient is currently undergoing adjuvant chemotherapy with Mitotane and Cisplatin. The adrenal bleeding was the first manifestation of the adrenal carcinoma. No ACC was suspected in any previously performed examinations.

Discussion

In almost 60% of cases, ACC are hormonally active, in 30-40% it manifests with symptoms of Cushing syndrome, while another 20-30% of patients have hypercortisolemia and virilization of gynecomastia. In other cases, the diagnosis is related to effect of tumor growth or metastases to lungs (45%), liver (42%), lymph nodes (24%), and bones (5-20%).

In our patient, the performed hormonal tests did not permit diagnosis of ACC (DHEA-S 513.5 ug/dl, morning cortisol level 17.7 ug/dl, evening cortisol level 14.9 ug/dl, normetanephrine concentration 110.62 pg/ml (N<113.8 pg/ml), metanephrine concentration 11.84 pg/ml (N<88 pg/ml), and the very low methyltyramine level was below the testing method sensitivity threshold. Preoperatively, there was no basis for suspicion of a malignant process.

The treatment and prognosis depend on the stage of the disease assessed with the ENSAT staging system, which defines 4 stages of disease. Stage 1 (tumors <5 cm) and stage 2 (>5 cm) do not exceed the gland. Stage 3 extends into surrounding tissues (adipose tissue, lymph nodes), while in stage 4 distant metastases are present [6].

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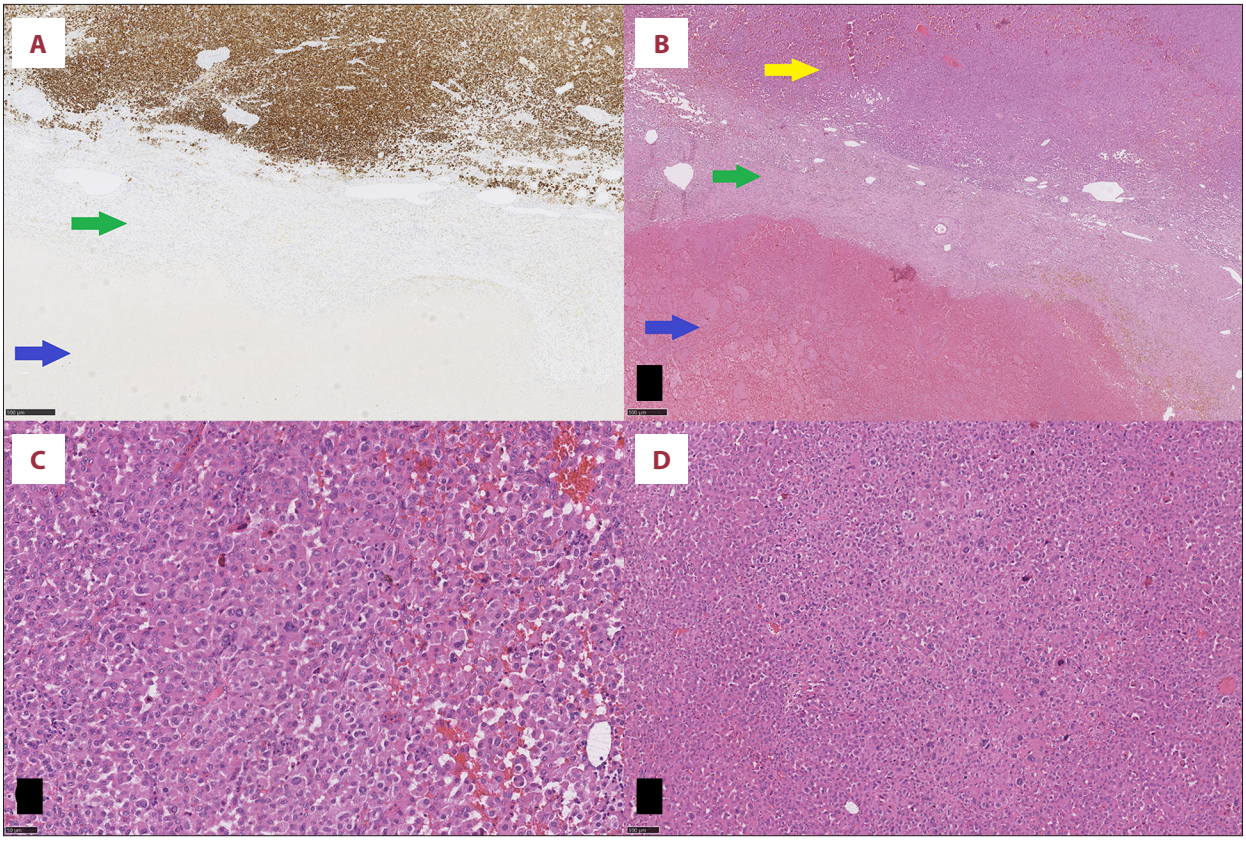

Figure 3. Postoperative histopathological examination. (**A**) (Hematoxylin and eosin staining) and (**B**) (immunohistochemical staining) were taken at low magnification and show hemorrhagic pseudocyst circuit in AAC, capsule, and hematoma content (yellow arrow indicates ACC, green arrow indicates the fibrous capsule, the blue arrow indicates blood and fibrine). (**C, D**) Show cells with compact, eosinophilic cytoplasm and nuclear pleomorphism (focally high nuclear grade).

There is a consensus that laparoscopy is the preferred surgical approach for adrenal tumors, but this is not the case with ACC, in which there are no clear guidelines concerning the selection of surgical approach. However, surgical excision with chemotherapy is associated with the best prognosis [2,6].

The role of laparoscopy in stage 1 and 2 ACCs, according to ENSAT, is questionable. Several authors suggest that lesions >6 cm should be treated with a conventional, open surgical approach, highlighting the increased risk of adrenal capsule rupture, local and regional recurrent lesions, or peritoneal metastases following laparoscopy. On the contrary, supporters of a laparoscopic approach stress the quicker recovery and faster introduction of adjuvant therapy after laparoscopy. They also point out that a less invasive intervention may be associated with lower risk of spread of carcinomatous cells in the peritoneal cavity. According to the ESE (European Society of Endocrinology), the ACC should be excised completely with surrounding adipose tissue. Simultaneous resection of the ipsilateral kidney is not recommended [6]. The adjuvant treatment is chemotherapy based on the Mitotane, Cisplatin, Doxorubicin, and Etoposide. Better long-term results are reported in patients with small tumors in non-advanced stages, and in patients who received Mitotane immediately after surgical treatment.

In pathomorphological assessment, the Weiss score is most commonly used. It is based on: Fuhrman nuclear grade III/IV, mitotic rate >5/50 HPF, abnormal mitoses, percentage of clear cells, >1/3 diffuse architecture, presence of necrosis, venous invasion, sinusoid invasion, and capsular invasion. Each feature scores 1 point. Malignancy is diagnosed when the score is equal to or more than 3. The Helsinki score was developed to predict the prognosis and diagnose the metastasis of ACC. With the use of equation 3× mitotic rate (>5/50 high-power fields) + 5× presence of necrosis + proliferation index in the most proliferative area of the tumor, and a cut-off value of 8.5, the new scoring system can diagnose metastatic ACC with 100% sensitivity and 99.4% specificity [3,8-10].

In our patient the first and the only manifestation of the ACC was the intra-adrenal bleeding and consequent hemorrhage. There are very limited data in the literature concerning adrenal bleeding in adults and management in hemodynamically

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stable patients. The need for surgical intervention in active bleeding resulting in hypovolemic shock is unclear.

The management of patients with adrenal hemorrhage in stable condition without features of active retroperitoneal bleeding remains debatable. The most common adrenal lesions are benign adenomas and pheochromocytomas. Taking this issue into account, in hemodynamically stable patients, emergency surgery should not be performed. Patient with adrenal hemorrhage who are hemodynamically stable, without features of active bleeding, should be prepared for early elective surgery as is typical for patients with adrenal tumor such as phaeochromocytoma, the same s for patients without adrenal hemorrhage. The pharmacological preparation should last about 2 to 3 weeks [7,11].

According to the NANETS Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors, pre-operative α-blockade is mandatory in patients with pheochromocytoma or paraganglioma (as are patients with normal levels of catecholamines) to minimize the intra-operative and perioperative risk by protecting against release of catecholamines due to anesthesia and surgical manipulation of the tumor [12]. Due to the unknown character of the lesion and to minimize perioperative risk, our patient's surgery involved a multidisciplinary team (MDT), including endocrinology specialists, with an individually adjusted daily dose of 8 mg doxazosin (4 mg every 12 hours).

In our patient, the hemorrhage was the only factor that influenced the decision about performing surgery. Laboratory tests and imaging examinations (CT, MRI) failed to show any signs of malignancy. The patient did not present with any other symptoms suggesting adrenal pathology. There was no suggestion of an adrenal lesion in his previous abdominal ultrasound examinations. The first suggestion of a malignant process appeared in the postoperative histopathological examination.

Therefore, our team finds it necessary to perform surgery in adult patients with adrenal lesion of an unknown or not clearly defined character with bleeding of an unknown or undefined etiology. In our patient, it proved to be the first and the only symptom of malignant process – ACC.

Selection of the surgical approach should be individualized for each patient. The laparoscopic approach is feasible when bleeding is limited to the adrenal tumor. When the hematoma exceeds the adrenal tumor and is located in the retroperitoneal space, laparoscopy carries significant risk of damaging surrounding tissues or blood vessels. The hematoma also causes a local edema, which precludes clear identification of adrenal gland borders. In this situation, a conventional, open surgical approach seems safer because it allows for better visualization of the surgical field and anatomical structures. Due to the size of the hematoma, this approach was selected in our patient.

Conclusions

Adrenal bleeding may be the first and only manifestation of a malignant process, even at an early stage, when neither laboratory tests nor imaging examinations suggest a malignant etiology.

Our team finds it necessary to perform early elective surgery in adult patients with adrenal lesion of an unknown or not clearly defined character with bleeding of an unknown or undefined etiology, following standard 3-week pharmacological preparation.

Department And Institution Where Work Was Done

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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