

# Adrenal cortical carcinoma with non-islet cell tumor hypoglycemia: A case report

YUNPENG LI<sup>1\*</sup>, RUI YANG<sup>2\*</sup>, LIANG ZHANG<sup>3</sup>, JIAN WANG<sup>4</sup>, FAYING YANG<sup>1,5</sup>,  
SONG TU<sup>1,5</sup>, JUN QIAN<sup>5</sup> and JIAXI YAO<sup>1,5</sup>

<sup>1</sup>Department of Urology, Hexi University Affiliated Zhangye People's Hospital, Zhangye, Gansu 734000, P.R. China;

<sup>2</sup>Xiangya Medical College, Central South University, Changsha, Hunan 410013, P.R. China; <sup>3</sup>Department of Surgery, Shandan County Traditional Chinese Medicine Hospital, Zhangye, Gansu 734000, P.R. China; <sup>4</sup>Department of Pathology,

Hexi University Affiliated Zhangye People's Hospital, Zhangye, Gansu 734000, P.R. China;

<sup>5</sup>Institute of Urology, Hexi University, Zhangye, Gansu 734000, P.R. China

Received November 8, 2024; Accepted February 14, 2025

DOI: 10.3892/ol.2025.14971

**Abstract.** Adrenal cortical carcinoma (ACC) is a rare invasive cancer with a poor prognosis. ACC often manifests with hyperglycemia and Cushing syndrome. Hypoglycemia is an unusual manifestation of this malignant tumor; therefore, the diagnosis and management of patients with ACC and hypoglycemia is extremely challenging. The current study presents the case of a 53-year-old woman who experienced recurrent, uncontrolled hypoglycemia and episodes of hypoglycemic coma. The patient was diagnosed with right-sided ACC and successfully treated with surgery. Hypoglycemic episodes associated with ACC are extremely rare. Moreover, the clinical diagnosis is often challenging owing to its similarity to multiple other diseases. Recurrent severe hypoglycemic comas, if not addressed promptly, can lead to patient death. Therefore, it is necessary to monitor patients with such rare diseases in clinical practice and make an accurate diagnosis promptly to ensure timely and effective treatment. This report of an ACC case with non-islet cell tumor hypoglycemia aims to raise awareness among clinical physicians.

## Introduction

Adrenal cortical carcinoma (ACC) is a rare endocrine tumor with an annual incidence rate of 0.5 to 2 cases per million individuals globally, accounting for 0.02-0.2% of all cancer-related deaths (1). The male-to-female ratio of patients with ACC is ~1.5:1, with ACC being more common in middle-aged women aged 40-50 years. The prognosis of patients with ACC is poor, with an average 5-year survival rate of 32-45% (2). Furthermore, >50% of patients exhibit excessive adrenal cortex hormone levels, with adrenocorticotropic hormone (ACTH) secretion by adrenal tumor cells, leading to ACTH-dependent Cushing's syndrome (3,4). Tumor-induced hypoglycemia may manifest in cases with late-stage tumors or paraneoplastic syndrome; nonetheless, this presentation is rare (5). Hypoglycemic symptoms have been proposed to be related to insulin overdose, with patients experiencing drowsiness, fatigue and even hypoglycemic coma. Hypoglycemia is often sporadic in patients with cancer and caused by physiological factors such as prolonged fasting. Pathological hypoglycemia is generally reported in patients with insulin-secreting tumors, non-islet cell tumors, myeloma, lymphoma, leukemia and metastatic tumors (6,7).

While the most common manifestations of ACC are hyperglycemia and Cushing's syndrome, tumor-associated hypoglycemia is relatively rare, with non-islet cell tumor hypoglycemia (NICTH) being a severe and rare malignant presentation of paraneoplastic syndrome (8). The incidence rate of NICTH is four times lower than that of insulinoma, mainly owing to insulin-like growth factor II (IGF-II) secretion by the tumor (9). NICTH may be associated with paraneoplastic syndrome caused by tumor cell secretion of IGF-II (10). ACC has been reported in various neuroendocrine and adrenal tumors in patients with recurrent hypoglycemia (11). Tumor resection remains the definitive treatment for hypoglycemia and related hormonal complications in patients with ACC and hypoglycemia (8,12). The current report presents the case of a middle-aged woman diagnosed with right-sided ACC based on recurrent hypoglycemic episodes.

---

*Correspondence to:* Dr Jiaxi Yao, Department of Urology, Hexi University Affiliated Zhangye People's Hospital, 67 Xihuan Road, Ganzhou, Zhangye, Gansu 734000, P.R. China  
E-mail: 16111210057@fudan.edu.cn

Dr Jun Qian, Institute of Urology, Hexi University, 67 Xihuan Road, Ganzhou, Zhangye, Gansu 734000, P.R. China  
E-mail: qianjun0936@163.com

\*Contributed equally

*Abbreviations:* ACC, adrenal cortical carcinoma; IGF-II, insulin-like growth factor II; NICTH, non-islet cell tumor hypoglycemia

*Key words:* ACC, hypoglycemia, non-islet cell tumor, rare

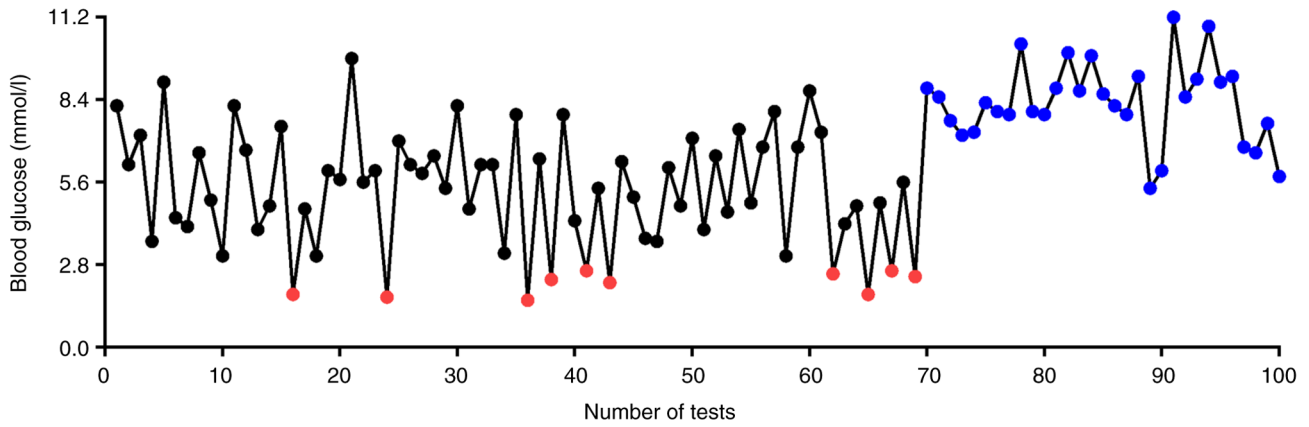


Figure 1. Trend of blood glucose changes in the patient. Black dots represent preoperative blood glucose within the normal range, red dots represent preoperative hypoglycemia and blue dots represent postoperative blood glucose within the normal range.

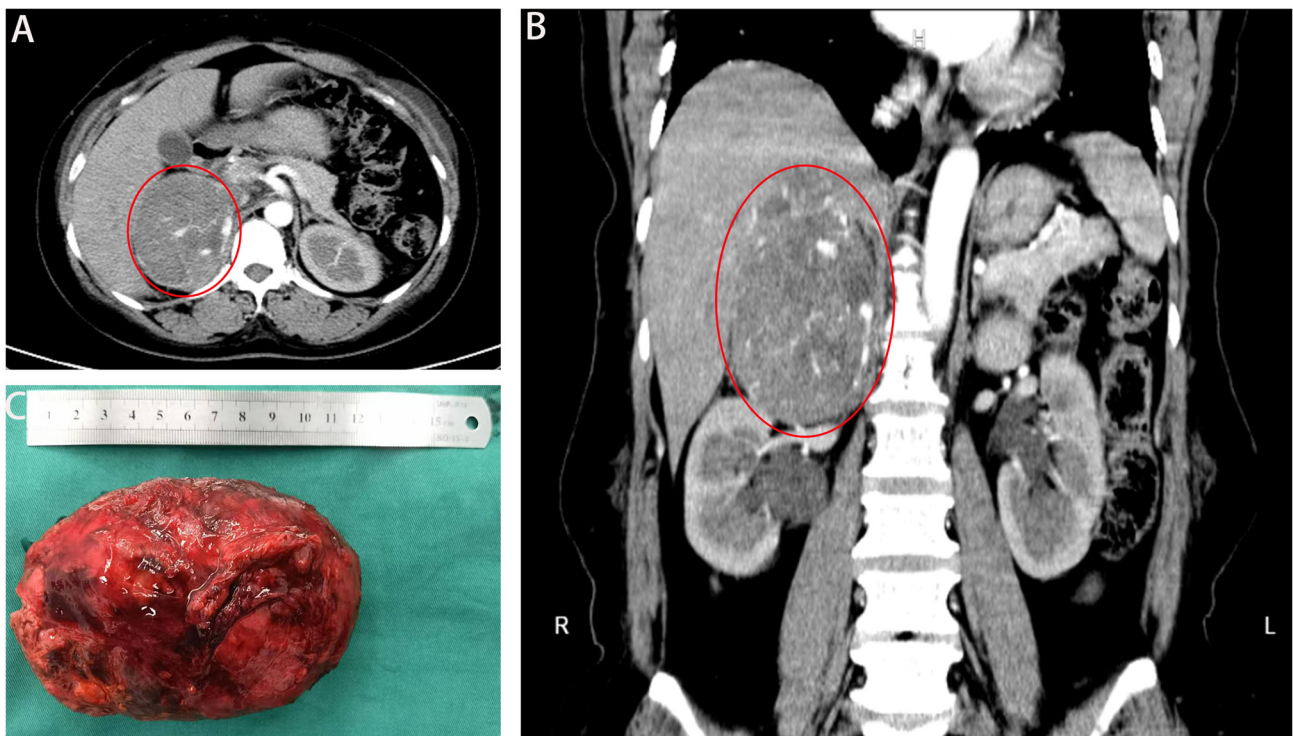


Figure 2. Imaging manifestations and specimens of right ACC. (A) Computed tomography cross section scan, (B) computed tomography coronal section scan and (C) resection of the tumor specimen. The tumor is circled in red.

### Case report

A 53-year-old woman was admitted to the Affiliated Hospital of Ningxia Medical University (Yinchuan, China) in May 2024 with abdominal pain and recurrent hypoglycemic coma. The patient continued to experience hypoglycemic coma episodes during hospitalization, which improved with active symptomatic glucose supplementation treatment. However, the cause of these episodes remained unidentified. Even after discharge, the patient experienced hypoglycemic coma episodes while resting at home. For further diagnosis and treatment, the patient visited Hexi University Affiliated Zhangye People's Hospital (Zhangye, China) in July 2024. The patient's vital signs were evaluated upon admission, and were all within normal ranges (blood pressure, 140/90 mmHg; body

temperature, 36.3°C; heart rate, 76 beats/min; and respiratory rate, 16 breaths/min). The patient had right upper abdominal tenderness, a palpable mass, facial acne and obesity, with a body weight increasing from 54 to 69 kg in the past 2 months. The patient experienced mental distress and general fatigue, the patient exhibited weight gain and redistribution of body fat, resulting in the characteristic appearance of a moon face and buffalo hump. Laboratory examination revealed a normal white blood cell count, creatinine level and coagulation, accompanied by hypokalemia (potassium level, 2.64 mmol/l; normal reference range, 3.5-.5 mmol/l). The cortisol level at 4:00 p.m. was 610.54 nmol/l (normal reference range, <276 nmol/l) and did not normalize after treatment with oral dexamethasone (2 mg, once every 6 h) for 2 days. Moreover, the patient's ACTH level was 4.09 pg/ml (normal reference

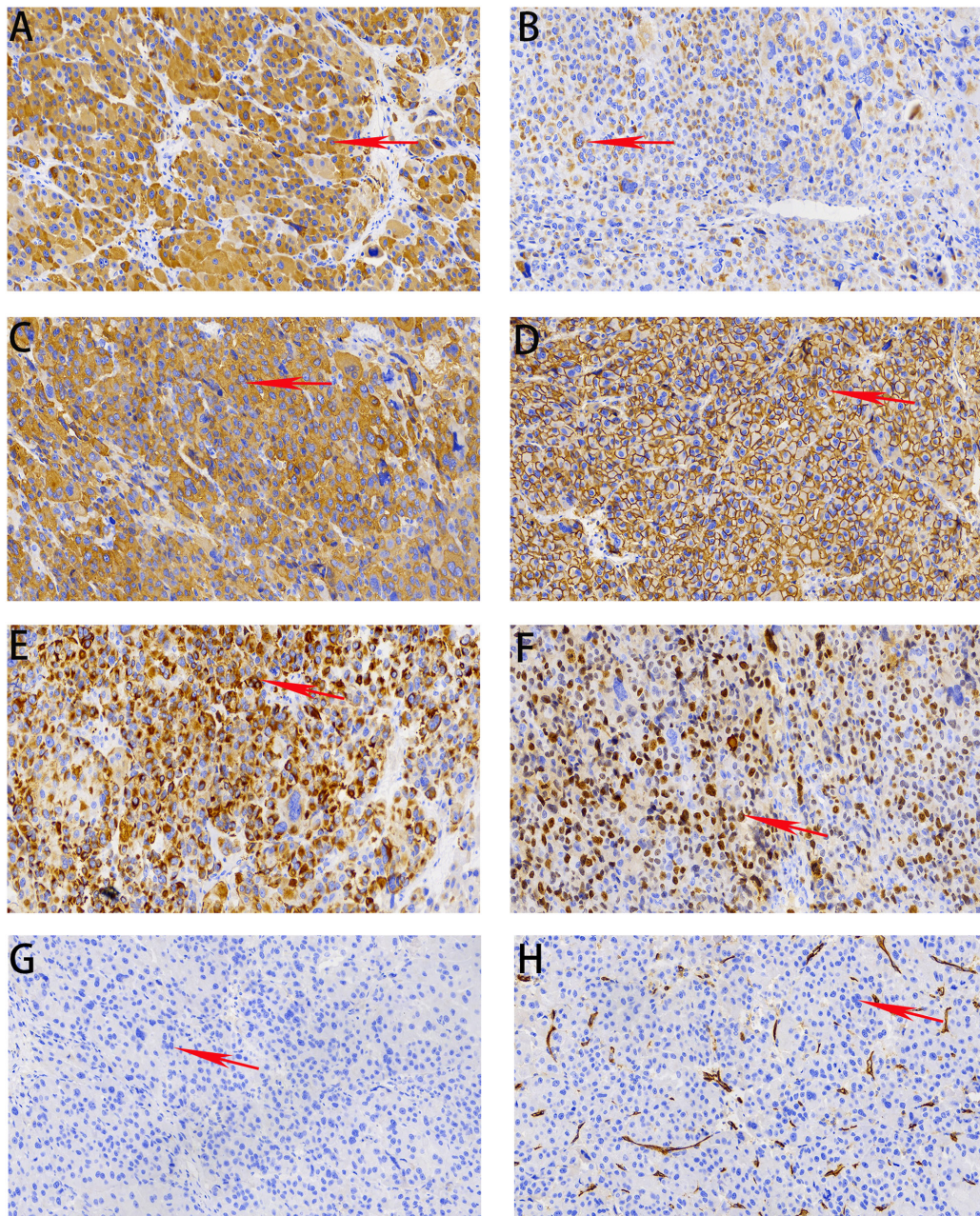


Figure 3. Immunohistochemical staining. Positive staining for (A) inhibin- $\alpha$ , (B) melan-A, (C) synaptophysin, (D) CD56, (E) pan-cytokeratin, and (F) Ki-67. Negative staining results for (G) chromogranin A and (H) CD31. Red arrows indicate tumor cells. Original magnification, x200.

range, 7.26-62.73 pg/ml) and the aldosterone-to-renin ratio was 2.01 (normal reference range, <5.7). The patient had a history of multiple hypoglycemia episodes induced by an unknown cause before hospitalization. Post-hospitalization, the patient underwent an average of seven daily blood glucose monitoring tests; however, 10 episodes of hypoglycemia occurred before surgical treatment despite regular glucose monitoring (Fig. 1).

Abdominal computed tomography revealed a 12-cm malignant tumor in the right adrenal gland, liver S7 invasion with the right inferior phrenic artery as the blood supply, superior vena cava invasion, and the right renal artery and vein closely attached to the lower edge of the lesion (Fig. 2A and B). During hospitalization, patients often experience symptomatic hypoglycemia, needing continuous glucose infusion to prevent the recurrence of hypoglycemia. The patient was administered

an intravenous glucose infusion (10% glucose 1,000 ml), oral glucose (20% glucose 100 ml), starch supplemented with blood potassium (3 g potassium chloride) and oral potassium chloride (potassium chloride sustained-release tablets, 1 g three times a day) daily. After the blood potassium and glucose levels stabilized, the patient underwent an open right adrenal tumor resection (Fig. 2C). Immunohistochemistry was performed on 4- $\mu$ m paraffin-embedded tissue sections during postoperative analysis. Slides were heated at 60°C for 2 h, dewaxed in xylene and dehydrated by a gradient concentration of alcohol. After retrieving and blocking the endogenous peroxidase and non-specific staining with 3% (v/v) hydrogen peroxide and normal goat serum, the sections were incubated with primary antibody overnight at 4°C. The slides were then incubated with HRP-conjugated goat anti-mouse/rabbit IgG

secondary antibody for 30 min at 37°C. Finally, they were visualized by DAB solution (Dako; Agilent Technologies, Inc.) and counterstained with haematoxylin. The quantity of the positively stained cells was measured using a light microscope. Postoperative pathological analysis using immunohistochemistry revealed a high-grade ACC according to the Weiss criteria (13), with the following results: Partially positive for rabbit anti-human melan-A (cat. no. ab51061; 1:1,000; Abcam); positive for mouse anti-human Inhibin- $\alpha$  (cat. no. ab273454; 1:1,000; Abcam), rabbit anti-human synaptophysin (cat. no. ab32127; 1:400; Abcam), rabbit anti-human CD56 (cat. no. ab220360; 1:1,000; Abcam), rabbit anti-human pan-cytokeratin (cat. no. ab308262; 1:2,000; Abcam) and rabbit anti-human Ki-67 (cat. no. ab16667; 1:200; Abcam); and negative for rabbit anti-human chromogranin A (cat. no. ab308262; 1:2,000; Abcam) and rabbit anti-human CD31 (cat. no. ab308262; 1:50; Abcam) (Fig. 3). Postoperative follow-up revealed that the patient recovered well from the tumor resection. However, due to slow healing of the open surgical wound, the patient was discharged half a month later with significant weight loss but a better mental state than before. No further episodes of hypoglycemia or hypokalemia were observed. The possibility of recurrence is high, but the patient is satisfied with the control of hypoglycemia and bloating symptoms, and is followed up monthly.

## Discussion

ACC is a rare, highly invasive endocrine tumor with excessive adrenal cortex hormone secretion first manifesting as increased cortisol levels in most patients (14). Hypercortisolism can cause masculinization and Cushing's syndrome in these patients. Some patients also have paraneoplastic syndromes, including hyperreninemic aldosteronism (15). In the present case, recurrent hypokalemia was closely associated with aldosterone secretion; however, cases of concomitant hypoglycemia are extremely rare with a poor prognosis (16,17). Khadka *et al* (17) reported the case of a 30-year-old man with ACC metastasis and hypoglycemia symptoms. The patient died after 2 months of chemotherapy. Karimi *et al* (16) reported the case of a 26-year-old woman with hypoglycemia caused by an ACC secreting cortisol and androgens. The patient was treated with mitotane, but eventually succumbed to the disease a few months later. The present patient experienced a potentially fatal hypoglycemic coma repeatedly before hospitalization; however, the specific cause of hypoglycemia was not identified, and the patient was treated only with a high-glucose infusion. For patients with frequent hypoglycemic episodes, the priority is to prevent a hypoglycemic coma or even death. However, owing to the unpredictability of the tumor-induced hypoglycemia, access to glucose is important. If hypoglycemia symptoms are observed, timely glucose supplementation, either orally or through intravenous administration is necessary, as it is the only preventive approach currently available. Thus, curing the tumors is the fundamental and effective method to eliminate these tumor-induced hypoglycemic episodes.

NICTH is a rare paraneoplastic syndrome, second only to insulinoma in causing tumor-induced hypoglycemia (18). NICTH is less commonly associated with ACC. The main

pathophysiological mechanism of NICTH in ACC is the secretion of the 10- to 20-kDa IGF-II resulting in the insulin-like activity of the tumor (19). Abnormal transcription and expression of the tumor IGF-II gene leads to increased secretion abnormalities. Currently, hypoglycemia in ACC has been proposed to be caused by excessive IGF-II secretion activating insulin receptors and promoting glucose uptake (20,21). Furthermore, inhibition of glycogen breakdown and gluconeogenesis induces severe recurrent hypoglycemia. Moreover, 25-30% of the patients are diagnosed with ACC only after tumor metastasis, making them ineligible for surgery owing to the lack of specific clinical manifestations and obvious symptoms during early ACC, making an early diagnosis difficult (22,23). Numerous primary hospitals in China do not perform blood tests for ACC; therefore, patients with recurrent hypoglycemia are not diagnosed or treated in a timely and effective manner.

Surgical resection is the gold-standard treatment for ACC, and mitotane is the only drug approved by the US Food and Drug Administration and European Medicines Agency for ACC treatment (15,24). Mitotane combined with cytotoxic chemotherapy, etoposide, doxorubicin and cisplatin has been reported to be associated with good response rates in patients with ACC (25). However, adjuvant treatment is needed post-surgery for giant ACC. Patients with metastases cannot undergo surgery and can only be administered systemic drug therapy. However, a number of countries, including China, have not yet approved these therapies, and patients do not receive effective treatment. In the present case, after surgical treatment, the patient's hypoglycemic symptoms were quickly controlled and the hypoglycemia was no longer evident. The hypokalemia gradually improved and the patient experienced marked weight loss. Tumor-associated hypoglycemia can be treated with glucose supplements and glucagon. Supplementation with glucocorticoids can stimulate gluconeogenesis, inhibiting IGF-II after surgery, preventing adrenal crises in patients, and providing sustained benefits in hypoglycemia treatment (26). Therefore, glucocorticoids are routinely administered in Hexi University Affiliated Zhangye People's Hospital before and after surgery, and the patient stopped using them after discharge without any adrenal-related complications.

The present study has some limitations. Although the patient had a huge tumor invading the liver and underwent surgical treatment, standard postoperative adjuvant therapy with mitotane was not administered, decreasing the treatment efficacy. The patient received radiotherapy and chemotherapy in the Department of Oncology, and new complications may still require close follow-up.

In recent decades, the understanding of ACC pathology has gradually led to its recognition and familiarity. However, ACC has a poor prognosis with a low 5-year survival rate and complex surgical and perioperative management (27). Therefore, treatment is challenging, and the early symptoms of patients need to be closely monitored and physical examinations need to be conducted to detect and treat ACC at an early stage to improve the patient's prognosis.

## Acknowledgements

Not applicable.

## Funding

This study was funded by grants from the Hexi University 14th Science and Technology Innovation Project (grant no. 164).

## Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

## Authors' contributions

YPL, RY and JXY contributed to the drafting of the manuscript and the design of the study. LZ, JW, FYY, ST and JQ contributed to the conceptualization and design of the study. ST and JXY assisted with the completion of the surgery. JQ and JXY confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

## Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Hexi University Affiliated Zhangye People's Hospital (approval number B2024-018).

## Patient consent for publication

The patient provided written informed consent for the publication of this report.

## Competing interests

The authors declare that they have no competing interests.

## References

1. Torti JF and Correa R: Adrenal Cancer [M]. StatPearls. Treasure Island, 2025.
2. Wang Z, Deng JH, Wang X, Liu Y, Chen JY and Zhang YS: Changes in WHO classification of adrenal tumors and new ideas for multi-dimensional diagnosis and treatment. *Zhonghua Wai Ke Za Zhi* 62: 1001-1007, 2024 (In Chinese).
3. Yip L, Duh QY, Wachtel H, Jimenez C, Sturgeon C, Lee C, Velázquez-Fernández D, Berber E, Hammer GD, Bancos I, *et al*: American association of endocrine surgeons guidelines for adrenalectomy: Executive summary. *JAMA Surg* 157: 870-877, 2022.
4. Kiseljak-Vassiliades K, Bancos I, Hamrahian A, Habra M, Vaidya A, Levine AC and Else T: American association of clinical endocrinology disease state clinical review on the evaluation and management of adrenocortical carcinoma in an adult: A practical approach. *Endocr Pract* 26: 1366-1383, 2020.
5. Iglesias P and Díez JJ: Management of endocrine disease: A clinical update on tumor-induced hypoglycemia. *Eur J Endocrinol* 170: R147-R157, 2014.
6. Siddiqui M, Vora A, Ali S, Abramowitz J and Mirfakhraee S: Pasireotide: A novel treatment for tumor-induced hypoglycemia due to insulinoma and non-islet cell tumor hypoglycemia. *J Endocr Soc* 5: bvaa171, 2020.
7. Axelrod L and Ron D: Insulin-like growth factor II and the riddle of tumor-induced hypoglycemia. *N Engl J Med* 319:1477-1479, 1988.
8. Kim SW, Lee SE, Oh YL, Kim S, Park SH and Kim JH: Nonislet cell tumor hypoglycemia in a patient with adrenal cortical carcinoma. *Case Rep Endocrinol* 2016: 5731417, 2016.
9. Marchetti KR, Pereira MA, Lichtenstein A and Paiva EF: Refractory hypoglycemia in a patient with functional adrenal cortical carcinoma. *Endocrinol Diabetes Metab Case Rep* 201: 16-0101, 2016.
10. Fukuda I, Hizuka N, Takano K, Asakawa-Yasumoto K, Shizume K and Demura H: Characterization of insulin-like growth factor II (IGF-II) and IGF binding proteins in patients with non-islet-cell tumor hypoglycemia. *Endocr J* 40: 111-119, 1993.
11. Ishikura K, Takamura T, Takeshita Y, Nakagawa A, Imaizumi N, Misu H, Taji K, Kasahara K, Oshinoya Y, Suzuki S, *et al*: Cushing's syndrome and big IGF-II associated hypoglycaemia in a patient with adrenocortical carcinoma. *BMJ Case Rep* 2010: bcr07.2009.2100, 2010.
12. Sinclair TJ, Gillis A, Alobuia WM, Wild H and Kebebew E: Surgery for adrenocortical carcinoma: When and how? *Best Pract Res Clin Endocrinol Metab* 34: 101408, 2020.
13. Kamai T, Murakami S, Arai K, Ishida K and Kijima T: Association of Nrf2 expression and mutation with Weiss and Helsinki scores in adrenocortical carcinoma. *Cancer Sci* 13: 2368-2377, 2022.
14. Gaujoux S, Weinandt M, Bonnet S, Reslinger V, Bertherat J and Dousset B: Surgical treatment of adrenal carcinoma. *J Visc Surg* 154: 335-343, 2017.
15. Puglisi S, Calabrese A, Basile V, Pia A, Reimondo G, Perotti P and Terzolo M: New perspectives for mitotane treatment of adrenocortical carcinoma. *Best Pract Res Clin Endocrinol Metab* 34: 101415, 2020.
16. Karimi F, Dehghanian A, Fallahi M and Dalfardi B: Pure androgen-secreting adrenocortical carcinoma presenting with hypoglycemia. *Arch Iran Med* 22: 527-530, 2019.
17. Khadka S, Mandal S, Kasireddy V, Ghimire S, Maganti T and Mols-Kowalczewski B: Hypoglycemia in a patient with hypercortisolism and adrenocortical carcinoma: A paradoxical entity. *J Adolesc Young Adult Oncol* 11: 122-125, 2022.
18. Douillard C, Jannin A and Vantghem MC: Rare causes of hypoglycemia in adults. *Ann Endocrinol (Paris)* 81: 110-117, 2020.
19. Scalia P, Marino IR, Asero S, Pandini G, Grimberg A, El-Deiry WS and Williams SJ: Autocrine IGF-II-associated cancers: From a rare paraneoplastic event to a hallmark in malignancy. *Biomedicines* 12: 40, 2023.
20. Miller BS, Rogol AD and Rosenfeld RG: The history of the insulin-like growth factor system. *Horm Res Paediatr* 95: 619-630, 2022.
21. Holly JMP, Biernacka K and Perks CM: The neglected insulin: IGF-II, a metabolic regulator with implications for diabetes, obesity, and cancer. *Cells* 8: 1207, 2019.
22. Phan AT: Adrenal cortical carcinoma-review of current knowledge and treatment practices. *Hematol Oncol Clin North Am* 21: 489-507; viii-ix, 2007.
23. Angelousi A, Kassi E and Kaltsas GA: Adrenocortical Carcinoma. *Endotext* [Internet]. MDText.com, Inc., South Dartmouth, MDText.com, Inc.; 2025.
24. Fassnacht M, Dekkers OM, Else T, Baudin E, Berruti A, de Krijger R, Haak HR, Mihai R, Assie G and Terzolo M: European society of endocrinology clinical practice guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European network for the study of adrenal tumors. *Eur J Endocrinol* 179: G1-G46, 2018.
25. Fassnacht M, Terzolo M, Allolio B, Baudin E, Haak H, Berruti A, Welin S, Schade-Brittinger C, Lacroix A, Jarzab B, *et al*: Combination chemotherapy in advanced adrenocortical carcinoma. *N Engl J Med* 366: 2189-2197, 2012.
26. Deng JH, Li HZ, Ji ZG, Zhang Y and Liu GH: Comprehensive treatment of adrenal cortical carcinoma. *Beijing Da Xue Xue Bao Yi Xue Ban* 51: 298-301, 2019 (In Chinese).
27. Yeap BT, Teah KM, Tan JBG and Azizan N: Case report: A giant hemorrhagic adrenocortical carcinoma causing cardiorespiratory embarrassment. *Ann Med Surg (Lond)* 71: 102996, 2021.



Copyright © 2025 Li et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.