ANNALI ITALIANI DI CHIRURGIA

Digital Edition
*e-publish on-line*
ISSN 2239-253X
Direttore Nicola Picardi

# Adrenocortical carcinoma metastasis.
## A long story

*Ann Ital Chir, 2022; 11* - Dec. 27
pii: S2239253X22038555
Online Epub

Federico Mascioli*, Paolo Ossola**/***, Luca Esposito***, Andrea Ascione****, Simone Zilahi De Gyurgyokai*****

**Department of General Surgery, Casa di Cura Pierangeli, Pescara, Italy*
***Department of General Surgery, Gradenigo-Humanitas Hospital, Turin, Italy*
****Department of General Surgery, Pietro Valdoni, Sapienza University of Rome, Italy*
*****Department of Radiological Oncological and Anatomopathological Science, Sapienza University of Rome, Italy*
******Department of Radiological Oncological and Anatomopathological Science, Vascular and Interventional Radiology Unit, Sapienza University of Rome, Italy*



**Adrenal carcinoma metastasis. A long story.**

INTRODUCTION: *Adrenocortical Carcinoma (ACC) is an uncommon adrenal tumor with a predilection for the female population.*
CASE REPORT: *A 55-year-old woman was referred to our attention to undergo laparoscopic cholecystectomy for symptomatic gallstone disease. She underwent a left adrenalectomy for ACC 5 years before; the follow-up was negative for relapse. During the preoperative study an Ultrasound Scanner study demonstrated a liver lesion in S6 - S7, confirmed by a Magnetic Resonance. A PET identified also a lesion on L1 vertebra. The hepatic US-guided biopsy resulted positive for ACC metastasis. After a muldisciplinary evaluation, the patients underwent a local approach to treat both hepatic and vertebral lesions. Laparoscopic cholecystectomy was performed in order to prevent biliary and pancreatic complications. The minimally invasive technique was adopted in order to reduce surgical trauma in oncological patients, even the previous abdominal surgery and percutaneous hepatic treatment. The patient is alive, with no recurrence after 12 months from local treatments.*
CONCLUSION: *This is a very unusual case of double ACC metastases, discovered after the end of standard follow-up and locally treated. The patient is recurrence-free 12 months after these procedures. Minimally invasive approach to treat symptomatic cholecystectomy was used in order to avoid pancreato-biliary complications. This study emphasized the necessity to realize tailored protocols for the follow-up of rare neoplasia, as ACC.*

KEY WORDS: Adrenocortical carcinoma, Cholecystectomy, Liver metastasis, Thermoablation

## Introduction

Adrenocortical Carcinoma (ACC) is a rare adrenal tumor with an incidence rate ranging between 0.7 and 2 cases per million per year [1,2].

An exceptional high incidence was reported in Southern Brazil where, because of the high prevalence (50-80% in pediatric population) of p. R337H low-penetrance allele of *TP53,* the ACC new diagnosis during childhood accounting for 2.9-4.2 per million annually [3].
ACCs have a bimodal distribution in diagnosis: the first peak is described during childhood (5 years old), the second during the fifth decade of life.
Even if no specific risk factors are clearly identified, ACC has a predilection for female population (female to male ratio of 1.5-2.5:1), probably for the estrogen activity in growth-cells promotion [3,4].

*Pervenuto in Redazione Giugno 2022. Accettato per la pubblicazione Agosto 2022*
*Correspondence to: Dott Federico Mascioli, Specialista in Chirurgia Generale, Via Sallustio 21, 65127 Pescara, Italy (e-mail: mascioli-federico@gmail.com)*

*Clinical presentations for ACC varies:*
1. 40-60% ACCs are defined "functional" and are associated with signs and symptoms of hormonal production (i.e. Cushing syndrome, sexual hormone hypersecretion), 20-30% patients complain non specific symptoms (i.e. aspecific abdominal pain);
2. 20-30% of ACCs are asymptomatic and diagnosed incidentally during imaging exams [3-5].
Unfortunately, about 50% of ACCs patients are diagnosed with a metastatic disease: the commonest sites of metastases are: liver (47%), lungs (43%), lymph nodes and bone (25%) [6]. Interestingly in 5% of cases also in the contralateral gland is individuated a neoplasm: in these cases, the diagnostic challenge is to known if the second lesion is synchronous or metachronous.
Surgery represents the only curative chance for primitive tumors; however, in case of recurrence an universally codified protocol is not yet available.
We present a case of late onset ACC metastasis, incidentally discovered during a preoperative study for cholecystectomy.

## Case Report

A 55-year-old woman was referred to our surgical department to undergo laparoscopic cholecystectomy for symptomatic gallstone disease. Her past medical history was silent except for a parathyroidectomy due to primitive hyperparathyroidism and left open adrenalectomy for ACC 5 years before.
The pathological report of the adrenal neoplasia described a cortical borderline lesion with oncocytic aspect (mitosis 5/50 HPF, no vascular invasion, CK8-18 negative, MIB1: 16%, synaptophysin: negative, melan A: negative).
The follow up for ACC was negative for recurrence. During the preoperative study for the treatment of gallbladder disease, the Ultrasound Scanner (US) study demonstrated a liver lesion in S6 - S7 (Fig. 1A). For this finding, a Magnetic Resonance (MR) with hepatic specific contrast study was performed with the confirmation of a 28 mm T2 hyperintense hepatic nodule, hypointense in late hepatic specific phase (Fig. 1B, C).
A total body Positron Emission Tomography Scan (PETCT) with 18 FDG scan identified two abnormal uptakes: One in the hepatic tissue and the other on the first lumbar (L1) vertebra.
The hepatic US-guided biopsy resulted positive for ACC metastasis with Ki67 of 2% (Fig. 2). Morphologic and immunohistochemical findings are consistent with cortical adrenal origin for the lesion in exam. Its localization in the liver parenchyma supports the diagnosis of metastatic adrenocortical carcinoma.
The low mitotic frequency and relatively benign morphology frame this neoplasm as low grade.
The patient underwent a multidisciplinary discussion: the simultaneous presence of the hepatic and vertebral lesion represented a contraindication for a surgical upfront approach; so a local ablative treatment was scheduled for both hepatic and vertebral secondarisms.
Hepatic ablation was performed under ultrasound guidance under general anesthesia, with a 14G antenna into the nodule (ablation time 10 minutes; power 100 Watt), through intercostal approach, followed by needle track ablation. Post-procedural US revealed the correct ablation zone without signs of bleeding (Fig. 3).
The bone recurrence on L1 was treated with stereotactic radiotherapy.
After twelve months of the ablative treatment the Patient has no recurrence and undergone the planned cholecystectomy for symptomatic gallstone disease.

## Discussion

ACC is a rare endocrine malignancy with a high risk of relapse and metastasization (60-80% if no adjuvant therapy was administered [7], even if the primary tumor is surgically completely removed at an early stage [8].
Patients with a disease free interval superior to 12 months after primary resection had a better prognosis, with a median survival of 6.6 years [9].
Adjuvant therapy with mitotane seems to reduce postoperative recurrence (38%) and postoperative death (31%) [7].



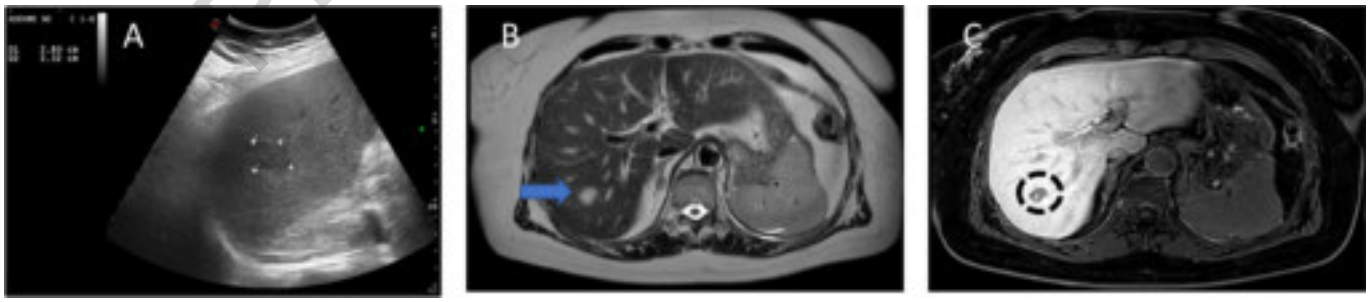


Fig. 1: Hepatic Lesion: A US scan, A) 28 mm single hepatic in liver segment VII, without contact with the Glisson's capsule, B) T2 section showed an hyperintense lesion (arrow), C) the hepatic lesion (circle) during hepato-specific contrast injection.

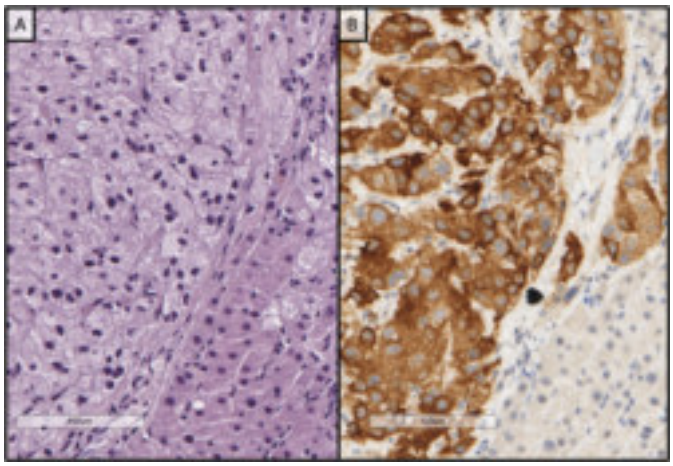

Fig. 2: Liver biopsy: A) A population of cells with granular clear cytoplasm, nested growth pattern and no obvious atypia is seen interfacing with normal hepatocytes (lower right) (H&E, 20x), B) Inhibin immunohistochemistry showing diffuse immunoreactivity in the cytoplasm of this cell population (Inhibin immunostain, 20x).

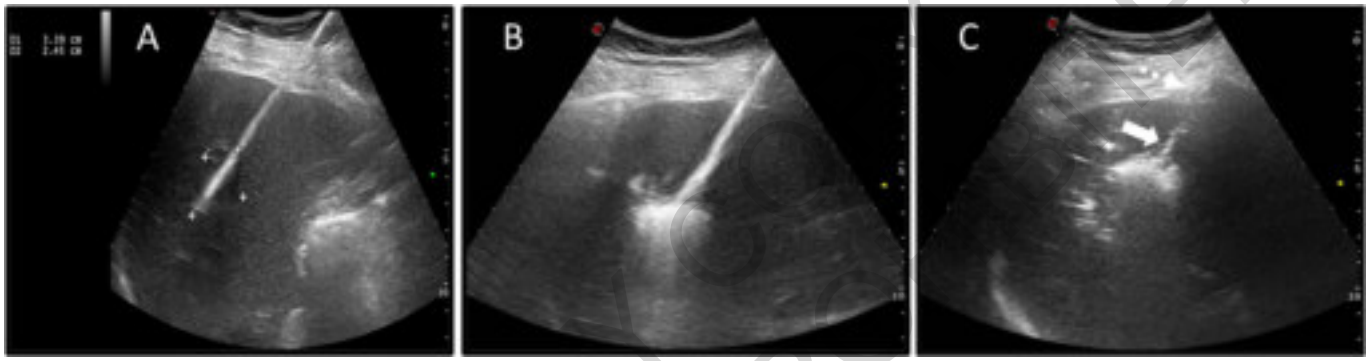

Fig. 3: Ablation Procedure: A) US-guided 14 G antenna positioning into the nodule in standard way, B) Correct ablation zone corresponding to nodule position, C) Needle track (white arrow) and capsular entry site (dotted white arrow) ablation after ablation time.



Recurrence treatment is not completely standardized: radical surgery seems to be the best approach, but the indications are very strict (low grade lesion, low proliferation index, a singular localization).
In our case two lesions are individuated: one in the liver and one in L1; at the hepatic biopsy the liver lesion was G2 with ki 67 of 2%: for this reason surgery was not proposable.
As in the Mawardi et al.[11] and the Berget et al.[12] cases, the first differential diagnosis was between primary liver tumor and hemangioma. The diagnosis was made with US-guided fine needle biopsy.
When recurrences are not resectable, trans-catheter arterial chemoembolization [10] or percutaneous radiofrequency represent an option.
In Literature, cases of late onset metastases, are infrequent: Mawardi et al. [11] reported a case of a liver metastasis [17] years after primary resection, and Berget et al.[12] a unique liver metastasis 23 years after complete adrenal resection [12]. In both cases the primary tumor was a stage II, superior to 15 cm of diameter.
In our case, the gallbladder disease needs to be treated in order to avoid pancreatic complications. However, the previous abdominal major surgery, the chronic cholecystitis, and the transcutaneous ablation determined the formation of straight peritoneal and visceral adhesion in the hepatic area: this condition is known as "difficult abdomen", and normally approached by laparotomy.
In this case, minimally invasive approach, the gold standard for gallbladder surgery [13-14] was adopted in order to reduce the surgical-related immunosuppression and the overall post-laparotomy complications (i.e. pulmonary, cardiologic, etc.) [15,16].
In conclusion this is a very unusual case of double ACC metastases, discovered after the end of standard followup and locally treated. The bone metastasis was treated with radiotherapy and the hepatic lesion was ablated with a good oncological result. The patient is recurrence-free 12 months after these procedures.
This study emphasized the necessity to realize tailored protocols for the follow-up of rare tumors: in particular the extension over 5 years of clinical and instrumental studies in order to prevent late onset relapses.

## Riassunto

L'adenocarcinoma del surrene (ACC) è un tumore raro con predilizione per il sesso femminile.
In questo articolo viene presentato il caso di una donna di 55 anni con una storia medica caratterizzata da una surrenectomia sinistra laparotomica per ACC bor-

derline avvenuta 5 anni prima. La paziente è giunta alla nostra attenzione al termine del regolare follow-up con una sintomatologia riconducibile a colelitiasi. Lo studio ecografico dell'addome preoperatorio riscontrava una lesione epatica. La risonanza magnetica con mezzo di contrasto epatospecifico confermava tale lesione ad aspetto evolutivo. La paziente veniva dunque sottoposta a PET con evidenza di una ulteriore lesione vertebrale di analoghe caratteristiche a livello di L1. La biopsia della lesione epatica risultava positiva per cellule di ACC. Il caso veniva discusso multidisciplinariamente con indicazione a trattamento locale delle due lesioni. La colecistectomia laparoscopica veniva eseguita al termine delle procedure ablative, con lo scopo di evitare possibili complicanze della patologia litiasica.
La tecnica mininvasiva, sebbene più difficoltosa a causa del precedente chirurgico e delle aderenze legate alla procedura ablativa epatica, è stata ritenuta imprescindibile al fine di ridurre il trauma chirurgico in un paziente oncologico. Attualmente, dopo 12 mesi dal trattamento, la paziente è in vita senza segni di ripresa di malattia.

## References


1. M, Al-Judaibi B, P: *Hepatic metastasis from adrenocortical carcinoma fifteen years after primary resection.* Saudi J Gastroenterol, 2012; 18(2):140-2, doi: 10.4103/1319-3767.93821.

2. Kiseljak-Vassiliades K, Bancos I, Hamrahian A, Habra M, Vaidya A, Levine AC, 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, 2020; 26(11):1366-383, doi: 10.4158/DSCR-2020-0567, Epub 2020; Dec 14, PMID: 33875173, PMCID: PMC8058447.

3. Else T, Kim AC, Sabolch A, Raymond VM, Kandathil A, Caoili EM, Jolly S, Miller BS, Giordano TJ, Hammer GD: *Adrenocortical carcinoma*. Endocr Rev, 2014; 35(2):282-26, doi: 10.1210/er.2013-1029, Epub 2013; Dec 20, PMID: 24423978, PMCID: PMC3963263.

4. Palomba G, Dinuzzi VP, Palumbo MACR, Impero SL, Sivero GD, De Palma M, Aprea G: *Management of pheochromocytoma during pregnancy from diagnosis to laparoscopic adrenalectomy. A case report and review of literature*. Ann Ital Chir, 2021; 92:254-59.

5. Rodgers SE, Evans DB, Lee JE, Perrier ND: *Adrenocortical carcinoma*. Surg Oncol Clin N Am, 2006; 15(3):535-53, doi: 10.1016/j.soc.2006.05.005, PMID: 16882496.

6. Cuesta MA, Bonjer HJ, van Mourik JC: *Endoscopic adrenalectomy: the adrenals under the scope?* Clin Endocrinol (Oxf), 1996; 44(3):349-51, doi: 10.1046/j.1365-2265.1996.679501.x, PMID: 8729535.

7. Tang Y, Liu Z, Zou Z, Liang J, Lu Y, Zhu Y: *Benefits of adjuvant mitotane after resection of adrenocortical carcinoma: A systematic review and meta-analysis*. Biomed Res Int, 2018; 4:2018:9362108, doi: 10.1155/2018/9362108, PMID: 29967789, PMCID, PMC6008618.

8. Lalli et al: *Next step mechanism driving acc metastasis. The complete resection of the tumor is the only therapeutic chance*.

9. Datrice NM, Langan RC, Ripley RT, Kemp CD, Steinberg SM, Wood BJ, Libutti SK, Fojo T, Schrump DS, Avital I: *Operative management for recurrent and metastatic adrenocortical carcinoma*. J Surg Oncol, 2012; 105(7):709-13, doi: 10.1002/jso.23015, Epub 2011; Dec 20, PMID: 22189845, PMCID, PMC4136651.

10. Cazejust J, De Baère T, Auperin A, Deschamps F, Hechelhammer L, Abdel-Rehim M, Schlumberger M, Leboulleux S, Baudin E: *Transcatheter arterial chemoembolization for liver metastases in patients with adrenocortical carcinoma*. J Vasc Interv Radiol, 2010; 21(10):1527-32, doi: 10.1016/j.jvir.2010.05.020, PMID: 20801688.

11. Mawardi M, Al-Judaibi B, Marotta P: *Hepatic metastasis from adrenocortical carcinoma fifteen years after primary resection.* Saudi J Gastroenterol, 18(2):140-2, doi: 10.4103/1319-3767.93821, PMID: 22421721, PMCID: PMC3326976.

12. Bergeat D, Rayar M, Beuzit L, Levi Sandri GB, Dagher J, Merdrignac A, Tanguy L, Boudjema K, Sulpice L, Meunier B: *An unusual case of adrenocortical carcinoma with liver metastasis that occurred at 23 years after surgery.* Hepatobiliary Surg Nutr, 2016; 5(3):265-8, doi: 10.21037/hbsn.2016.03.05, PMID: 27275470, PMCID, PMC4876254.

13. Di Bartolomeo N, Mascioli F, Ciampaglia F: *Minilaparoscopic cholecystectomy a one year record*. Ann Ital Chir, 2015; 86:528-31, PMID: 26899137.

14. Ossola P, Mascioli F, Coletta D, et al.: *Evidence on postoperative abdominal binding: A systematic review with meta-analysis of randomized controlled trials.* Surgeon, 2021; 19(4):244-251. doi: 10.1016/j.surge.2020.07.003.

15. Coletta D, Mascioli F, Balla A, Guerra F, Ossola P: *Minilaparoscopic cholecystectomy versus conventional laparoscopic cholecystectomy: An endless debate*. J Laparoendosc Adv Surg Tech A, 2021; 31(6):648-56, doi: 10.1089/lap.2020.0416, Epub 2020; Aug 21.

16. Boo YJ, Kim WB, Kim J, Song TJ, Choi SY, Kim YC, Suh SO: *Systemic immune response after open versus laparoscopic cholecystectomy in acute cholecystitis: A prospective randomized study*. Scand J Clin Lab Invest, 2007; 67(2):207-14, doi: 10.1080/00365510601011585.