Acta Chirurgica Belgica

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/tacb20

Effective multimodal management of a giant adrenocortical carcinoma

Camille Pairon, Alexandra Dili, Claude Bertrand, Lionel D'Hondt, Caroline Fervaille & Julian Donckier

To cite this article: Camille Pairon, Alexandra Dili, Claude Bertrand, Lionel D'Hondt, Caroline Fervaille & Julian Donckier (2022): Effective multimodal management of a giant adrenocortical carcinoma, Acta Chirurgica Belgica, DOI: 10.1080/00015458.2022.2040109

To link to this article: https://doi.org/10.1080/00015458.2022.2040109

Accepted author version posted online: 09 Feb 2022.

Effective multimodal management of a giant adrenocortical carcinoma

.

Camille Pairon [a], Alexandra Dili [b], Claude Bertrand [b], Lionel D'Hondt [c], Caroline Fervaille [d], Julian Donckier [a].

[a] Department of Endocrinology, Université Catholique de Louvain, CHU UCL Namur (Site Godinne), B-5530 Yvoir, Belgium

[b] Unit of Digestive, Endocrine and General Surgery, Department of Surgery, Université Catholique de Louvain, CHU UCL Namur (Site Godinne), B-5530 Yvoir, Belgium

[c] Department of Oncology, Université Catholique de Louvain, CHU UCL Namur (Site Godinne), B-5530 Yvoir, Belgium

[d] Department of Pathology, Université Catholique de Louvain, CHU UCL Namur (Site Godinne), B-5530 Yvoir, Belgium

Corresponding author: Julian Donckier, Department of endocrinology, Université Catholique de Louvain, CHU UCL Namur (Site Godinne), Av. Docteur G. Thérasse 1, B-5530 Yvoir, Belgium. Tel: +3281423281; E-mail: julian.donckier@chuuclnamur.uclouvain.be

Word count: 1557 for paper including 245 for abstract

ABSTRACT

Background: Adrenocortical carcinoma is a rare and aggressive tumour. The only curative treatment is surgery with negative margins. In most series, the average lesion size ranges from 5.5 to 15 cm.

Methods: We report the case of a 27-year-old female with hyperandrogenism and Cushing syndrome due to a right adrenocortical carcinoma of 19.7 cm.

Results: The tumour abutting on liver and vena cava and the presence two nodules in liver required extensive surgery including a right posterior sectionectomy and an en bloc resection of the adrenal mass together with the right kidney and the gallbladder. The vena cava was also resected with a reconstruction using a pericardial patch since it was invaded on its border. Pathological examination confirmed an adrenocortical carcinoma, with tumour invasion of vessels, tumour capsule, vena cava and two metastases in the liver (pT4N0M1). All margins were negative. Three months after surgery, two lung nodules, cardio-phrenic and internal mammary adenomegalies were noticed on a PET/CT scan, justifying the initiation of chemotherapy, alongside with mitotane. After a 10-month follow-up, CT scan was stable excepted for a lung nodule growing from 4 to 7 mm. Targeted stereotaxic radiotherapy was then administered. Twenty-two months after surgery, the patient has improved considerably and all signs of hyperandrogenism and Cushing syndrome have resolved.

Conclusion: This case of adrenocortical carcinoma illustrates one of the largest tumours among those reported. It demonstrates the feasibility and effectiveness of a multimodal approach in its treatment even if it is giant and at high risk.

Key Words: adrenocortical carcinoma, Cushing's syndrome, hyperandrogenism

1. Introduction

Adrenocortical carcinoma is an uncommon and extremely aggressive tumour, with a poor prognosis. The incidence is one to two per million population/year [1-4]. The only curative management is surgery [3, 5-7]. The 5-year survival rate ranges from 16 to 47%, depending on the presence of metastatic lesions [1, 2]. In most series, the average lesion size ranges from 5.5 to 15 cm [2, 5]. We report the case of a patient with a 22-month follow-up after removal of a giant adrenocortical carcinoma, one of the largest tumours among those reported.

2. Case report

A 27-year-old female was referred for investigation of hyperandrogenism. The patient had a 6-month history of amenorrhoea, unexplained weight gain, acne, hirsutism, facial erythrosis, high blood pressure and palpitations. On physical examination, pulse rate was 109/min and blood pressure 161/115 mmHg. Purple striae were observed on the abdomen and flanks. A mass was palpated in the right flank and right hypochondrium. Routine laboratory findings showed a haemoglobin level of 17.3 g/dL and normal fasting plasma glucose, electrolytes, renal and thyroid function. CEA was negative. A diagnostic assessment showed a high urine free cortisol of 297 µg/24 hours (normal < 60). At 8 p.m., serum cortisol was raised to 27.4 µg/dL (normal 2.7-10.4) with a plasma ACTH at 3.89 pg/ml (normal 4-49). Other investigations showed increased levels of DHEA sulfate (856 µg/dL; normal 54-400), total testosterone (3.54 ng/mL; normal 0.057-0.77), free

testosterone (4 ng/dL; normal 0.10-1.6), 17-OH-progesterone (940.4 ng/dL; normal 11-108) and delta4 androstenedione (> 1080 ng/dl; normal 50-470). A diagnosis of ACTH-independent Cushing's syndrome associated with hyperandrogenism was made. A computed tomographic (CT) scan showed a voluminous right adrenal lesion (13.3 x 12 x 19.7 cm) (figure 1). Surgical exploration was performed without showing peritoneal carcinomatosis. An intraoperative echography showed a voluminous right mass invading the postero-lateral side of the liver as well as an isolated lesion in segment II that was removed by a wedge resection. The main tumour occluded the vena cava. A hepatotomy was performed between segment VI-VII and V-VIII along the right lateral scissura including a removal of the right hepatic vein. The right adrenal mass was resected en bloc together with the right kidney, the gallbladder and the postero-lateral sector of the liver. A resection of the vena cava was performed with a reconstruction using a pericardial patch since it was invaded on its right lateral border over a height of 3 cm. Pathological examination revealed a 19 x 14 x 10.5 cm adrenocortical carcinoma, with tumour invasion of vessels, tumour capsule, vena cava and two metastases in segments VI and VII of the liver. All margins were negative. Four lymph nodes were normal. Tumour examination showed more than 20 mitoses per 50 high power field. These findings implied a pT4N0M1 staging or a stage IV according to the ENSAT (European Network for the study of Adrenal Tumors) classification. Microsatellite instability was absent and the Ki67 score was 15-20%. The lesion in segment II was a haemangioma. After surgery, glucocorticoid replacement therapy was given. Three months after surgery, two lung nodules (5 and 3 mm), cardio-phrenic and internal mammary adenomegalies were noticed on a PET/CT scan, justifying the initiation of chemotherapy including Etoposide, Doxorubicin and Cisplatin (EDP), alongside with mitotane. The patient benefited from 6 EDP-type chemotherapy courses and mitotane was continued thereafter. The main side effect was fatigue. After a 10-month follow-up, CT scan was stable excepted for a lung nodule growing from 4 to 7 mm. Targeted stereotaxic radiotherapy was then administered. Twenty-two months after surgery, the patient has improved considerably and

all signs of Cushing syndrome and hyperandrogenism have resolved. Total testosterone, DHEA sulfate and delta4 androstenedione have remained below the normal range since the operation and urinary free cortisol was always < 60 µg/24 hours under glucocorticoid replacement therapy.

3. Discussion

We here report the case of a young female patient with an adrenocortical carcinoma of 19.7 cm. According to a meta-analysis published in 2016, regrouping 27 studies from 1950 to 2011 and including around 6306 patients [2], the mean size of those lesions ranges from 5.5 to 15 cm which makes our case exceptional regarding the size of the tumour. This type of tumour is most often diagnosed between 46 and 55 years [3, 5-6], our patient being younger. She also had a vena cava involvement, which is reported in less than 10% and is usually associated with an increased risk of hepatic and or pulmonary metastatic lesions [6]. This is what occurred in our patient. Since this meta-analysis, no other series have been published.

The only curative treatment of adrenocortical carcinoma is a surgical resection, with negative margins. This surgery can be performed laparoscopically only for tumours less than 6 cm according to the guidelines of the European Society of Endocrinology [3, 6]. Surgery also includes lymphadenectomy and resection of metastatic lesions when necessary [3, 8]. In our patient, given the size of lesions, there was no other choice than extensive open surgery. Achieving R0 resection positively impacts the prognosis of the disease. According to a recent study [5, 9], mean survival rate was 96.3 months and 5-year survival rate was 64.8 % after R0 resection. On the opposite, the mean overall survival was only 25.1 months and 5-year survival rate 33.8% after R1 resection. Patients having infiltrated lymph nodes had a higher recurrence rate [2, 5]. In the event of a local or metastatic recurrence, surgery is also the first-line therapy if R0 resection is achievable [3, 7,

10]. The surgical resection in our patient was considered as RO. However, it is to note that in case of metastases, the 5-year survival ranges from 0 to 28 % [3].

After this surgery, the patient was too frail to consider immediate adjuvant therapy. In the interval, she suffered a rapid recurrence within 3 months, with appearance of lung and lymph node metastases. Mitotane and chemotherapy were then initiated. Given the extent of lesions, local therapies were not possible. From a medical standpoint, mitotane, an adrenocorticolytic drug, is the best adjuvant therapy [10-11]. The European Society of Endocrinology recommends the use of mitotane as adjuvant therapy for patients with a significant risk of recurrence: disease with a high histological grade (and a Ki-67 index > 10%), large tumour or intraoperative tumour spillage [5]. Mitotane can also be given as a first therapy in the context of unresectable ACC, or for the treatment of recurrence of the disease after surgery. The recommended treatment duration is 5 years for patients at high risk regardless of the stage of the disease. A Phase-3 FIRM-ACT study [11] compared the effectiveness of Mitotane combined with EDP (etoposide, doxorubicin and cisplatin) chemotherapy, versus Mitotane combined with Streptozotocin. Mitotane combined with EDP chemotherapy was proven superior in terms of overall 1 year survival (26.1% vs 7.2%) but more side effects were induced.

Regarding prognosis, several factors have been reported such as tumour stage, resection status, the patient's general condition, the proliferation marker Ki-67 and cortisol excess but only the latter two factors had a robust association with prognosis [3, 4, 11-12]. Thus, our patient with an ENSAT stage IV, a Ki-67 index >10 % and hypercortisolism was at high risk of recurrence.

Besides conventional therapies, a role of immunotherapy has been investigated in advanced adrenocortical carcinoma by five clinical trials [13]. However, results are heterogeneous with low rates of overall responses and progression free survival. Mechanisms underlying immunotherapy resistance requires further studies.

Interestingly, despite recurrence on imaging, no hormone hypersecretion was evidenced. We assume that the small size of the lesions may account for this dissociation.

In conclusion, this case illustrates one of the largest adrenocortical carcinoma among those reported. It also demonstrates the feasibility and effectiveness of a multimodal approach in the treatment of such a tumour even if it is giant and at high risk.

Disclosure statement:

The authors report no conflict of interest

References

1. Benassai G, Desiato V, Benassai G, Bianco T, Sivero L, Compagna R et al. Adrenocortical carcinoma: what the surgeon needs to know. Case report and literature review. Int J Surg 2014; 12: S22-8.
2. Langenhuijsen J, Birtle A, Klatte T, Porpligia F, Tinsit MO. Surgical management of adrenocortical carcinoma: impact of laparoscopic approach, lymphadenectomy, and surgical volume on outcomes-A systematic review and meta-analysis of the current literature. Eur Urol Focus 2016; 1: 241-50.
3. Fassnacht M, Dekkers OM, Else T, Baudin E, Berruti A, De Krijger RR et al. European Society of Endocrinology practical guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2018; 179: G1-G46.
4. Fassnacht M, Assie G, Baudin E, Eisenhofer G, de la Fouchardiere C, Haak HR et al. Adrenocortical carcinomas and malignant phaeochromocytomas: ESMO-EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020; 31: 476-90.

5. Mirallié E, Blanchard C, Caillard C, Rodien P, Briet C, Mucci S et al. Adrenocortical carcinoma: impact of surgical treatment. Ann Endocrinol (Paris) 2019; 80: 308-13.
6. Gaujoux S, Weinandt M, Bonnet S, Reslinger V, Bertherat J, Dousset B. Surgical treatment of adrenal carcinoma. J Visc Surg 2017; 154: 335-43.
7. Zini L, Porpiglia F, Fassnacht M. Contempory management of adrenocortical carcinoma. Eur Urol. 2011; 60: 1055-65.
8. Porpiglia F, Miller BS, Manfredi M, Fiori C, Doherty GM. A debate on laparoscopic versus open adrenalectomy for adrenocortical carcinoma. Horm Cancer 2011; 2: 372-7.
9. Margonis GA, Kim Y, Prescott JD, Tran TB, Postlewait LM, Maithel SK et al. Adrenocortical Carcinoma: Impact of Surgical Margin Status on Long-Term Outcomes. Ann Surg Oncol 2016; 23: 134-41.
10. Terzolo M, Angeli A, Fassnacht M, Daffara F, Tauchmanova L, Conton PA et al, Adjuvant mitotane treatment for adrenocortical carcinoma. N Engl J Med 2007; 356: 2372-80.
11. Fassnacht M, Terzolo M, Allolio B, Baudin E, Haak H, Berruti A et al. Combination chemotherapy in advanced adrenocortical carcinoma. N Engl J Med 2012; 366: 2189-97.
12. Beuschlein F, Weigel J, Saeger W, Kroiss M, Wild V, Daffara F et al. Major prognostic role of Ki67 in localized adrenocortical carcinoma after complete resection. J Clin Endocrinol Metab 2015; 100: 841-49.
13. Araujo-Castro M, Pascual-Corrales E, Molina-Cerrillo J, Alonso-Gordoa T. Immunotherapy in adrenocortical carcinoma: predictors of response, efficacy, safety, and mechanisms of resistance. Biomedicines. 2021; 9: 304.

Legend for figure 1

Computed tomographic (CT) scan showing a voluminous and heterogeneous right adrenal tumour. The mass contained intramural necrosis and calcifications and abutted on liver tissue and vena cava. Contiguous hepatic invasion could be suspected with two nodules in segment VII and one in segment II. Chest and bones were normal. A section of the tumour shows the immunostaining for Ki67 with a 15-20 % score (magnification x20).