Endocrinología, Diabetes y Nutrición 71 (2024) 187–190

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

SCIENTIFIC LETTER

Addison's disease in metastatic neuroendocrine prostate cancer

Enfermedad de Addison en el cáncer de próstata neuroendocrino metastásico

We present the case of a 66-year-old male with a three-year history of high-grade (Gleason 5+4) prostate acinar adenocarcinoma with pelvic lymph node and multiple bone metastasis at presentation (September/2019). Besides active smoking, he had no relevant personal or familial medical history. During initial staging evaluation, CT scan documented a 2.0 cm left adrenal hypodense nodule (−25 Hounsfield Units) compatible with a lipid-rich adenoma and interpreted as incidentaloma. No hormonal work-up was performed. As decided by the Oncology team, he initiated long-term six-monthly androgen-deprivation therapy with leuprorelin and completed six cycles of palliative chemotherapy with docetaxel 75 mg/m^2 every three weeks. He had good clinical, biochemical (PSA levels decreased from 18.8 to less than 1.0 ng/ml) and imaging responses on conventional exams, with best response ''stable disease''. Nineteen months after diagnosis, the adrenal nodule grew, and a *de novo* contralateral nodule with 1.3 cm was documented. Both nodules underwent significant dimensional progression over the following 13 months (on the left to 5.0 cm and on the right to 4.5 cm) and exhibited features highly suspicious for metastasis on MRI. The pre-existing lymph node and bone disease continued stable and PSA levels also remained normal. The Endocrinology Department was then consulted to assess the hormonal status of the adrenal masses. Functional pheochromocytoma was excluded by normal plasma and 24-hour urinary metanephrines. There was evidence of primary adrenal insufficiency: morning cortisol 4.7 μg/dl (3.7–19.4), ACTH 765.8 pg/ml (7.2–63.3), aldosterone <3.7 ng/dl (upright position 3.7–31.0), direct renin concentration 179.0 μIU/ml (upright position 4.2–59.7), K+ 5.2 mEq/l (3.4–5.1). Clinically he complained of moderate asthenia, anorexia, weight loss and low normal blood pressure for five months. On physical examination he had mucocutaneous hyperpigmentation and blood pressure 90/59 mmHg. He was placed on hydrocortisone at supraphysiological doses with marked clinical improvement; and later de-escalated hydrocortisone to physiological doses combined with fludrocortisone. The cancer restaging studies showed no changes: full-body CT and gastrointestinal endoscopy studies were negative for suspicious lesions and 18F-FDG PET/CT only revealed moderate adrenal uptake (left SUVmax 5.3; right SUVmax 4.1) and slight prostate uptake. To clarify the metastasis origin, an adrenal mass biopsy was then performed and revealed a poorly differentiated malignant epithelial neoplasm with immunohistochemical staining positive for CK AE1/AE3, synaptophysin, chromogranin and PSA; Ki67 >50%. This result was compatible with prostate small-cell neuroendocrine carcinoma. Serum chromogranin A was 72 ng/ml (<102). It was decided to start chemotherapy with cisplatin (75 mg/m^2) and etoposide (100 mg/m^2 D1-3) every three weeks, with parallel doubling of hydrocortisone dose. After four months of chemotherapy (six cycles), he obtained ''partial response'' with a 30% decrease in the metastasis size on MRI (the left reduced to 3.6 cm and the right to 3.2 cm). Bone scintigraphy continued to show stable disease and full-body CT scan did not reveal new lesions. Biochemically, PSA levels slightly increased after treatment but still within the normal range (from 0.6 ng/ml to 2.4 ng/ml). Due to the aggressive behaviour of the neuroendocrine component and good response to chemotherapy, a multidisciplinary team discussion was carried out, and the decision was made for radiotherapy to the adrenal metastasis.

To our knowledge, this is the first report of a prostate small-cell neuroendocrine carcinoma probably developed after cancer therapies, presenting with adrenal metastasis and concomitant Addison's disease.[1–5] Small-cell neuroendocrine prostate carcinoma is rare, usually presents mixed with classic adenocarcinoma and is associated with early and multiple visceral metastasis.[6] It can arise *de novo* or, more frequently, after exposure to hormonal and non-hormonal therapies as a resistance mechanism.[6,7] In fact, up to 30% of metastatic castration-resistant prostate cancer cases have immunohistochemical features of neuroendocrine differentiation.[7] Small-cell neuroendocrine prostate carcinoma is highly aggressive and portends a poor prognosis with rapid disease progression and limited survival.[6,7] Chemotherapy regimens of small-cell lung cancer have been used due to their pathological and biological similarity, but with very limited efficacy.[6] Nonetheless, our case is intriguing as the neuroendocrine component had a more indolent behaviour, ''lower than expected'' tumour burden and a surprising imaging response. The adrenal glands are very unusual sites of prostate metastasis,[8] with only seven reported cases.[1–5,9] Initially, we thought a prostate origin unlikely given its rarity and apparent stable disease, so other primary sites of adrenal metastasis were searched; nevertheless, the investigation was compatible with prostatic origin. A prostate cancer with atypical metastatic behaviour and normal PSA levels should raise suspicion for neuroendocrine differentiation and resistance to therapy[7]; in this setting, CgA may be a useful biomarker.[7] The occurrence of primary adrenal insufficiency due to bilateral adrenal metastasis (of any origin) is quite uncommon,

because it requires massive destruction (>90%) of the adrenal cortex.[2,10] The estimated rates of primary adrenal insufficiency in this specific context vary in the range of 3–8%[10] and, to our knowledge, only two cases with prostate origin (adenocarcinoma) have been reported.[1,2] It is, however, important to raise awareness on this matter, as adrenal insufficiency may be overlooked in the oncology setting due to overlapping symptoms. Some authors consider that screening is only indicated in patients with signs and symptoms suggestive of adrenal insufficiency and should ideally rely on ACTH stimulation testing, since basal cortisol levels may be ''normal'' in patients with advanced malignancy due to the ''stressed'' adrenal response.[10] From our experience, in the context of prostate cancer and bilateral adrenal masses, we advise early consideration of metastatic involvement and systematic hypocortisolism exclusion, besides hormonal hypersecretion. Indeed, addressing adrenal insufficiency can improve patient quality of life and prevent fatal decompensations. Although the adrenal burden of our patient decreased, we believe hypoadrenalism is probably permanent; moreover, radiotherapy is a major contributor to adrenal hypofunction. As such, the patient benefits from lifelong hormonal supplementation and clinical surveillance. We provide new evidence on the natural history of a high-grade prostate adenocarcinoma transforming into a small-cell neuroendocrine carcinoma after androgen-deprivation therapy and docetaxel. Progression of prostatic disease can manifest with the unexpected endocrinological picture of bilateral adrenal metastasis causing Addison's disease and requires multidisciplinary management. Acknowledging atypical manifestations of metastatic disease reduces diagnostic delay and may improve overall management.

Ethical approval

Written informed consent for publication was obtained.

The publication of the manuscript was approved by the Local Ethics Committee.

Authors' contributions

Francisca de Brito Marques performed: conceptualisation; writing-original draft; writing-review and editing.

Ana Paula Marques performed: writing-review and editing.

Francisco Simões de Carvalho performed: writing-review and editing.

Helena Magalhães performed: conceptualisation; writing-review and editing.

Funding

This work received no grants from any funding agencies in the public, commercial or not-for-profit sectors.

Conflicts of interest

The authors declare that they have no conflicts of interests.

Acknowledgements

The authors would like to thank all the physicians who were involved in the management of our patient.

References

1. Navarro M, Felip E, Garcia L, Bellmunt J, Jolis L, Morales S, et al. Addison's disease secondary to prostatic carcinoma. A case report. Tumori. 1990;76:611–3.
2. Mirtsching BC, Freeman DA. Adrenal insufficiency and stage D carcinoma of the prostate. South Med J. 1992;85:196–7. Available from: https://pubmed.ncbi.nlm.nih.gov/1738889/ [cited 07.11.23].
3. Sakamoto N, Eto M, Ando S. Surgical excision of a metastatic adrenal lesion in a patient with prostatic cancer. Int J Urol. 1999;6:38–40. Available from: https://pubmed.ncbi.nlm.nih.gov/10221863/ [cited 07.11.23].
4. Long MA, Husband JE. Features of unusual metastases from prostate cancer. Br J Radiol. 1999;72:933–41. Available from: https://pubmed.ncbi.nlm.nih.gov/10673942/ [cited 07.11.23].
5. Kawahara T, Taguchi H, Yamagishi T, Udagawa K, Ouchi H, Misaki H. A case of bilateral adrenal and pleural metastases from prostate cancer. Case Rep Oncol. 2009;2:217–9. Available from: https://pubmed.ncbi.nlm.nih.gov/20737040/ [cited 07.11.23].
6. Hu J, Han B, Huang J. Morphologic spectrum of neuroendocrine tumors of the prostate: an updated review. Arch Pathol Lab Med. 2020;144:320–5. Available from: https://pubmed.ncbi.nlm.nih.gov/31644322/ [cited 07.11.23].
7. Arman T, Nelson PS. Endocrine and paracrine characteristics of neuroendocrine prostate cancer. Front Endocrinol. 2022;13:1012005. Available from: https://pubmed.ncbi.nlm.nih.gov/36440195/ [cited 07.11.23].
8. Spartalis E, Drikos I, Ioannidis A, Chrysikos D, Athanasiadis DI, Spartalis M, et al. Metastatic carcinomas of the adrenal glands: from diagnosis to treatment. Anticancer Res. 2019;39:2699–710.
9. Muñoz López AY, Domínguez Castillo RE, Rodenas Gil EA, Navarro Ruesga I, Morales Montor JG, Pacheco Gahbler C. Primary neuroendocrine prostate cancer with adrenal gland metastasis. Urol Case Rep. 2022;40:101896. Available from: https://pubmed.ncbi.nlm.nih.gov/34745894/ [cited 07.11.23].
10. Tallis PH, Rushworth RL, Torpy DJ, Falhammar H. Adrenal insufficiency due to bilateral adrenal metastases – a systematic review and meta-analysis. Heliyon. 2019;5:e01783.

Francisca de Brito Marques[a,*], Ana Paula Marques[a], Francisco Simões de Carvalho[a], Helena Magalhães[b]

[a] *Department of Endocrinology, Pedro Hispano Hospital, Matosinhos Local Health Unit, Rua Dr. Eduardo Torres, 4464-513 Senhora da Hora, Matosinhos, Portugal*
[b] *Department of Medical Oncology, Pedro Hispano Hospital, Matosinhos Local Health Unit, Rua Dr. Eduardo Torres, 4464-513 Senhora da Hora, Matosinhos, Portugal*

* Corresponding author.
E-mail address: franciscadbmm@gmail.com
(F. de Brito Marques).

https://doi.org/10.1016/j.endinu.2024.01.011