

# Massive adrenal incidentalomas and late diagnosis of congenital adrenal hyperplasia in prostate cancer

Xin Feng and Gregory Kline

Division of Endocrinology, Department of Medicine, University of Calgary, Calgary, Alberta, Canada

Correspondence  
should be addressed  
to G Kline

**Email**

[Gregory.Kline@albertahealthservices.ca](mailto:Gregory.Kline@albertahealthservices.ca)

## Summary

In a 61-year-old Caucasian male with prostate cancer, leuprolide and bicalutamide failed to suppress the androgens. He presented to endocrinology with persistently normal testosterone and incidental massive (up to 18 cm) bilateral adrenal myelolipomas on CT scan. Blood test did not reveal metanephrine excess. The patient was noted to have short stature (151 cm) and primary infertility. Elementary school photographs demonstrated precocious puberty. Physical examination revealed palpable abdominal (adrenal) masses. Abiraterone and glucocorticoid treatment was commenced with excellent suppression of testosterone. Genetic testing revealed a mutation in *CYP21A2* confirming 21-hydroxylase-deficient congenital adrenal hyperplasia (CAH). Association of large myelolipomas with CAH has been reported in the literature. Our case highlights the importance of considering CAH in patients with non-suppressed testosterone despite androgen deprivation therapy. Large myelolipomas should raise the suspicion of congenital adrenal hyperplasia.

## Learning points:

- Adrenal myelolipomas are rare benign lesions that are more common in patients with longstanding untreated congenital adrenal hyperplasia thought to be due to ACTH stimulation.
- Consider undiagnosed congenital adrenal hyperplasia in patients with adrenal myelolipoma.
- Glucocorticoid replacement may be an efficacious treatment for patients with prostate cancer and CAH. Abiraterone therapy has a risk of adrenal crisis if glucocorticoids are not replaced.

## Background

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder of the steroid synthesis pathways. The most common form of CAH is 21-hydroxylase deficiency, representing 90–95% of CAH patients and causes a spectrum of adrenal insufficiency and virilization. Non-classical or partial CAH results from a milder enzyme deficiency compared to the classic form with an incidence estimated at approximately 1 in 1000 worldwide (1). The diagnosis may be suspected clinically but relies on genetic testing for confirmation. Although most patients are diagnosed in their childhood, there are reports of diagnosis of classical CAH in the sixth and seventh

decades of life (2). There exist increasing evidence of its association with adrenal tumors (3).

Prostate cancer is the most common cancer among Canadian men (excluding non-melanoma skin cancer) accounting for 21% of all new cancer cases in men in 2016 (4). Abiraterone has been used for the treatment of castration-resistant prostate cancer, and there is emerging evidence for its use in castration-sensitive prostate cancer (5). Abiraterone inhibits 17 $\alpha$ -hydroxylase/C17,20-lyase to decrease not only adrenal androgen production but also cortisol production (6).

## Case presentation

A 61-year-old Caucasian male with prostate cancer was unresponsive to leuprolide and bicalutamide with persistent testosterone levels of 8–14 (nmol/L). Initial cancer staging imaging noted bilateral adrenal masses 18.2×16.2×14 cm on the left and 6.4×8.7×7.8 cm on the right diagnosed as myelolipomas (Fig. 1). These were determined to be non-functioning with normal serum-free metanephrines (0.34, normal: <0.49 nmol/L) and normal serum-free normetanephrines (0.74, normal: <0.89 nmol/L). There was no clinical evidence of cortisol excess, and there was no history of hypertension or hypokalemia. He was admitted to hospital for lethargy and fatigue thought to be due to excessive narcotic use. Dexamethasone was initiated as an adjunctive pain management therapy, to which he responded rapidly with improved mentation and feeling of well-being. The serum testosterone decreased to 1.5 nmol/L after the introduction of dexamethasone. He was started on abiraterone and the dexamethasone was subsequently tapered to prednisone 5 mg daily; repeat testosterone levels were suppressed below the limit of detection.

## Investigation

At referral to endocrinology, the patient was noted to have short stature at 151 cm (height potential: 171.5 cm based on mid-parental height) with his siblings 18–23 cm taller than him. He provided school photographs demonstrating initial tall stature and precocious puberty at age 9 years with early masculinizing features and presence of longstanding hyperpigmentation. However, by the end of high school, he recalled being the shortest person in the class. Later in life when presenting with infertility, he was noted to be azoospermic although no diagnosis was provided. At the present evaluation, he declined testicular examination but reported a history of small testes.

Genetic testing demonstrated bi-allelic mutations in *CYP21A2*; one complete gene deletion and the other having a C518T>A (I172N) mutation. The diagnosis of simple virilizing 21 $\alpha$ -hydroxylase deficiency (CAH) was made. Measurements of 17-hydroxyprogesterone and ACTH were not taken due to his required use of abiraterone and prednisone as it would not have altered management.

## Treatment

The patient continued on prednisone 5 mg by mouth daily in conjunction with abiraterone to suppress



**Figure 1**  
CT scan of abdomen (coronal and axial). Arrows indicate adrenal masses.

endogenous androgen production as well as to prevent adrenal insufficiency.

## Outcome and follow-up

Unfortunately, the patient deceased due to metastatic prostate cancer shortly after the diagnosis of congenital adrenal hyperplasia was made.



## Discussion

We present the first reported case of a patient presenting with massive adrenal incidental myelolipomas in the context of castration-resistant prostate cancer.

Congenital adrenal hyperplasia presents as a spectrum of disease depending on the residual enzyme activity. There can be multiple abnormalities in the adrenal hormone synthesis pathways. The most common form involves mutation in *CYP21A2*, resulting in variable deficiency of 21-hydroxylase (21OHD). The majority of cases of classic 21OH deficiency are detected on routine newborn screening or with evidence of virilization, ambiguous genitalia and elevated 17-OH-progesterone. However, it is more difficult to detect males with mild forms of this condition, as the 17OH progesterone may not be significantly elevated at birth and partial deficiencies may not present with adrenal insufficiency or salt wasting.

Our patient presented to medical attention diagnosed with castration-resistant prostate cancer. His short stature and precocious puberty suggests the presence of excess adrenal androgens from an early age. CAH has a strong genotype–phenotype correlation, which highlights the importance of genetic testing and counseling. Patients with del/I172N mutations (such as our patient) present most commonly as simple virilizing (53/72 cases) (7) as compared with salt wasting (18/72 cases) (7) or non-classic (1/72) (7). The delayed diagnosis in his sixth decade of life is unusual given his genetic mutation. Biochemical screening would not have been done at the time of his birth.

Suppression of endogenous testosterone is vital to managing prostate cancer to reduce tumor growth. His persistently elevated testosterone was likely from adrenal overproduction due to undiagnosed CAH. This elevation in testosterone was glucocorticoid responsive, which would decrease endogenous ACTH and thus decrease androstenedione and testosterone production (8). The decreased testosterone levels after dexamethasone therapy likely reflects this. Furthermore, abiraterone was later used for his second-line management of castration-resistant prostate cancer, which can itself precipitate adrenal insufficiency via inhibition of cortisol biosynthesis. It is crucial to treat patients on abiraterone concurrently with physiologic glucocorticoid replacement to prevent this. It was especially important that our patient received replacement as he was at risk of developing adrenal insufficiency due to undiagnosed CAH and potentially compromised cortisol biosynthesis at baseline.

This case also shows the importance of considering the diagnosis of CAH in apparent ‘castration-resistant’ prostate cancer, especially in the presence of adrenal myelolipomas, due to the important therapeutic considerations noted earlier. There are numerous reports of men with simple virilizing CAH undiagnosed until later in the sixth and seventh decades (2). While ours is the second case of CAH in the context of castration-resistant prostate cancer reported in the literature (8), it is the first reported case to our knowledge of CAH and prostate cancer treated with abiraterone. This is especially relevant given the recent trials demonstrating the efficacy of abiraterone in castration-sensitive prostate cancer (5) where patients with undiagnosed CAH may not be identified prior to prostate cancer therapy.

Adrenal myelolipomas are a type of rare benign mesenchymal and stromal tumor of the adrenal cortex composed of adipose tissue and bone marrow elements that accounts for approximately 6% of adrenal incidentalomas (9). Those greater than 10 cm are termed giant, and only 12% of adrenal myelolipomas are bilateral (9). These masses are usually hormonally inactive but have been associated with androgen production and hypertension (9). There is a higher incidence of bilateral myelolipomas in patients with longstanding and untreated CAH (10) with over 40 reported cases (3), which supports the theory that chronically elevated endogenous ACTH acts to stimulate growth of the adrenal tissue (9). There have been reports of adrenal nodules regressing in size with improved control in patients with 21OH deficiency (11). Patients presenting with incidentally found adrenal myelolipomas should be screened for classic CAH.

## Case conclusion

Simple virilizing congenital adrenal hyperplasia was the likely cause of the difficult to suppress androgens in this patient. This clinical scenario also demonstrates the importance of considering CAH in patients with large myelolipomas.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

### Funding

This research did not receive any specific grant from any funding agencies in the public, commercial or not-for-profit sector.



#### Author contribution statement

G K is the named physician of the patient and was involved in conceiving, editing and submission of the work. X F is an endocrine trainee who was responsible for writing the initial manuscript, editing and submission of the work.

#### References

- 1 El-Maouche D, Arlt W & Merke DP 2017 Congenital adrenal hyperplasia. *Lancet*. Epub. (doi:10.1016/S0140-6736(17)31431-9)
- 2 Nerموen I, Folling I, Vegge K, Larmo A, Nedrebo BG, Husebye ES & Lovas K 2009 Two adults with adrenal myelolipoma and 21-hydroxylase deficiency. *Case Reports in Medicine* **2009** 916891. (doi:10.1155/2009/916891)
- 3 Westcott GP, Sadeghi-Nejad A, Munoz-Pena J, Blau A, Goodman M & Siegel RD 2017 Gender reversal and bilateral giant adrenal myelolipomas in a 46,XX patient with 21-hydroxylase deficiency: case report and review of the literature. *AACE Clinical Case Reports* **3** e217–e224. (doi:10.4158/EP161343.CR)
- 4 Committee CCSA 2017 *Canadian Cancer Statistics 2017*. Toronto, ON: Canadian Cancer Society.
- 5 Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, Ozguroglu M, Ye D, Feyereabend S, Protheroe A, *et al.* 2017 Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *New England Journal of Medicine* **377** 352–360. (doi:10.1056/NEJMoa1704174)
- 6 Ang JE, Olmos D & de Bono JS 2009 CYP17 blockade by abiraterone: further evidence for frequent continued hormone-dependence in castration-resistant prostate cancer. *British Journal of Cancer* **100** 671–675. (doi:10.1038/sj.bjc.6604904)
- 7 New MI, Abraham M, Gonzalez B, Dumic M, Razzaghy-Azar M, Chitayat D, Sun L, Zaidi M, Wilson RC & Yuen T 2013 Genotype-phenotype correlation in 1507 families with congenital adrenal hyperplasia owing to 21-hydroxylase deficiency. *PNAS* **110** 2611–2616. (doi:10.1073/pnas.1300057110)
- 8 Ragnarsson O, Johannsson G, Geterud K, Lodding P & Dahlqvist P 2013 Inadequate testosterone suppression after medical and subsequent surgical castration in a patient with prostate cancer. *BMJ Case Reports* **2013**. (doi:10.1136/bcr-2013-010395)
- 9 Shenoy VG, Thota A, Shankar R & Desai MG 2015 Adrenal myelolipoma: controversies in its management. *Indian Journal of Urology* **31** 94–101. (doi:10.4103/0970-1591.152807)
- 10 Nerموen I, Rorvik J, Holmedal SH, Hykkerud DL, Fougner KJ, Svartberg J, Husebye ES & Lovas K 2011 High frequency of adrenal myelolipomas and testicular adrenal rest tumours in adult Norwegian patients with classical congenital adrenal hyperplasia because of 21-hydroxylase deficiency. *Clinical Endocrinology* **75** 753–759. (doi:10.1111/j.1365-2265.2011.04151.x)
- 11 Giacaglia LR, Mendonca BB, Madureira G, Melo KF, Suslik CA, Arnhold IJ & Bachega TA 2001 Adrenal nodules in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency: regression after adequate hormonal control. *Journal of Pediatric Endocrinology and Metabolism* **14** 415–419.

Received in final form 21 September 2017

Accepted 3 October 2017