Case Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2019, Vol. 47(5) 2288–2295

DOI: 10.1177/0300060519840896
journals.sagepub.com/home/imr
SAGE

Treatment of gynecomastia with prednisone: case report and literature review

Yansheng Jin* **and Maoxiao Fan***

Abstract

This study aimed to report a unique case of primary adrenal insufficiency that was accompanied by painful gynecomastia, which was resolved by treatment with prednisone. Enlargement of the left breast with continuous weakness and generalized nausea in a male was discovered 3 months before admission. Magnetic resonance imaging of the brain was normal 1 month before presentation. A physical examination revealed that the diameter of the left breast was 5 cm and the height was 3 cm. Laboratory investigations revealed hyponatremia, with a low serum cortisol level and an elevated prolactin level. Hyperprolactinemia was suspected because of adrenal deficiency that was directly or indirectly associated with increased prolactin levels. Thus, a diagnosis of hyperprolactinemia was confirmed. Ultrasonography of the left breast showed glandular tissue hyperplasia. In the present study, treating adrenal insufficiency with prednisone relieved both gynecomastia and hyponatremia. However, gynecomastia regression and hyponatremia resolution were observed when prednisone was stopped. Gynecomastia completely resolved by re-administering prednisone. Therefore, treating the underlying disease is essential so that prednisone can be given in a timely manner.

Keywords

Gynecomastia, prednisone, primary adrenal insufficiency, hyponatremia, cortisol, prolactin, hyperprolactinemia

Date received: 29 October 2018; accepted: 7 March 2019

Introduction

Gynecomastia is one of the rarest symptoms in adrenal insufficiency.[1] This study reports the case of a patient with painful gynecomastia resulting from primary

Department of Internal Medicine, Suzhou Wuzhong People's Hospital, Suzhou, Jiangsu Province, China

*These authors contributed equally to this work.

Corresponding author:
Yansheng Jin, Department of Internal Medicine, Suzhou Wuzhong People's Hospital, 61 North Dongwu Road, Suzhou, Jiangsu Province, 215128, China.
Email: jys0120@163.com

adrenal insufficiency. The patient was treated with prednisone, resulting in symptom resolution. However, prednisone is theoretically known to cause gynecomastia.[2] Clinically, reports of painful gynecomastia being resolved with prednisone treatment are lacking, and this study may change the routine clinical practice in a meaningful way.

Case report

A 69-year-old male Chinese patient sought medical help for left breast fullness and ongoing malaise. His illness began 3 months before admission, with progressive unilateral breast enlargement that was accompanied by spontaneous pain. The patient complained of increasing weakness, nausea, and decreased appetite. After 2 months, he was diagnosed with hyponatremia. The serum sodium level was 122 (normal range [NR], 135–145) mmol/L. A brain MRI showed normal results (Figure 1). He was then treated with a sodium supplement. However, the symptoms did not improve. His medical history revealed that he had been infected with pulmonary tuberculosis 30 years ago, which had completely resolved at that time. He denied a history of hypertension, diabetes mellitus, nephropathy, cardiac dysrhythmia, or any familial diseases. The patient did not smoke tobacco, drink alcohol, or take any other medications recently. On examination, he was thin, with slightly low blood pressure. His skin, including the face, hands, palm lines, areola, foot back, and belt, appeared hyperpigmented. Additionally, the left breast was 5 cm in diameter and 3 cm in height. It was painful upon palpation, with an elastic consistency, and was nonadherent to the superficial and deep layers. No nipple retraction, skin dimpling, nipple discharge, or bleeding occurred. No alterations were found in the right breast. An examination of the patient's body systems showed normal secondary sex characteristics and external genitalia. Abdominal, neurologic, and thyroid examinations yielded normal findings.

Initial laboratory tests revealed the following: serum sodium, 128.3 (NR, 135.0–145.0) mmol/L; serum chloride, 92.8 (NR, 96.0–108.0) mmol/L; and serum potassium, 4.5 (NR, 3.5–5.3) mmol/L. Subsequent

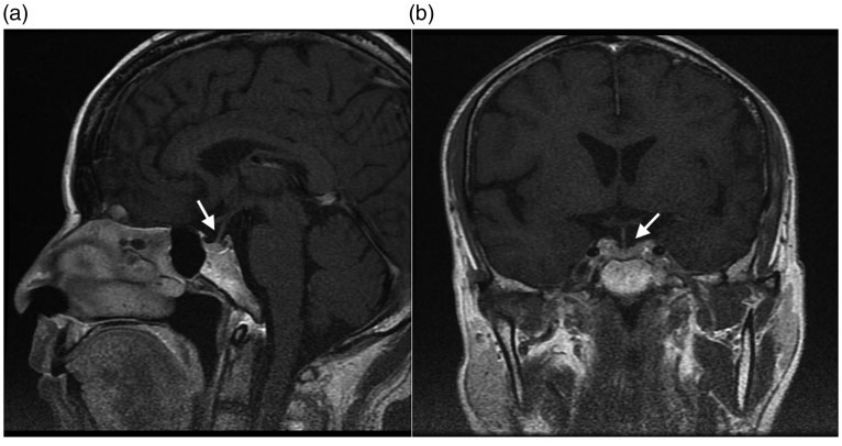

Figure 1. Intracranial MRI of the patient demonstrated no abnormalities in the hypothalamus, pituitary gland, or pituitary stalk. The white arrow indicates that the pituitary gland and pituitary stalk were a normal size. Left image (a), sagittal view; right image (b), coronal view.

hormonal investigations found a relatively low morning cortisol level of 27.6 (NR, 138–690) nmol/L (Table 1). In a work-up for gynecomastia at this point, the plasma prolactin level was high at 661.06 (NR, 54–340) μIU/mL. Adrenocorticotropic hormone (ACTH) and aldosterone (ALD) levels were normal (Table 1), and routine test results for liver, renal, thyroid, and immunologic function were within normal limits. Ultrasonography of the left breast showed glandular tissue hyperplasia (Figure 2). A positron emission tomography–computed tomography scan of the chest revealed a 1.8×1.6 cm^2 mass in the right lung, which showed fluorodeoxyglucose uptake with a standard uptake value maximum of 5.0. This, along with biopsy test results, suggested obsolete pulmonary tuberculosis (Figure 3).

Table 1. Hormone levels in the study.

Hormone	Level	Normal range for males
Cortisol	27.6 nmol/L (morning)	Morning 138–690 nmol/L Afternoon 69–345 nmol/L
Prolactin	661.06 μIU/mL	54–340 μIU/mL
Adrenocorticotropic hormone (ACTH)	15.7 pg/mL (morning)	Morning 10.0–46.0 pg/mL Mid-night <10 pg/mL
Aldosterone (ALD)	64.48 pg/mL (decubitus position)	Decubitus position 12.0–150.0 pg/mL Standing position 70.0–350.0 pg/mL
Luteinizing hormone (LH)	7.8 mIU/mL	1.1–25 mIU/mL
Follicle stimulating hormone (FSH)	8.08 mIU/mL	1.5–11.8 mIU/mL
Estradiol	30.58 pg/mL	<87 pg/mL
Testosterone	3.71 ng/mL	2.2–10.5 ng/mL
Dehydroepiandrosterone sulfate	102.39 μg/dL	5–253 μg/dL
Progesterone	0.13 ng/mL	<2.75 ng/mL

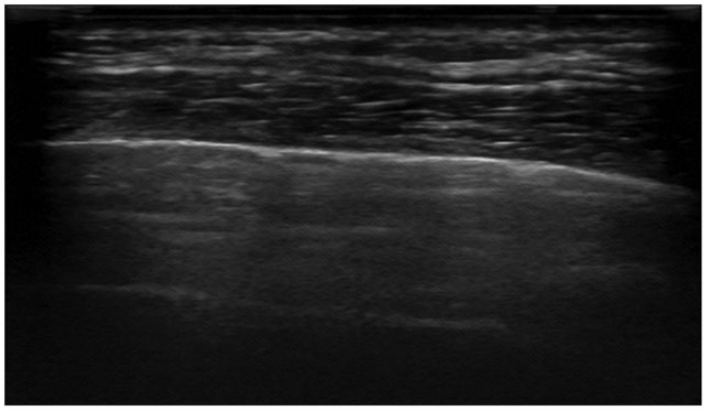

Figure 2. Doppler ultrasonography of the left breast showed glandular tissue hyperplasia. The mammary glands were arranged in a regular pattern with clear layers. The glands were an uneven thickness, presenting a smooth and intact boundary, with a thickened internal echo, disordered structure, and uneven distribution. No solid nodular or cystic formations were present.

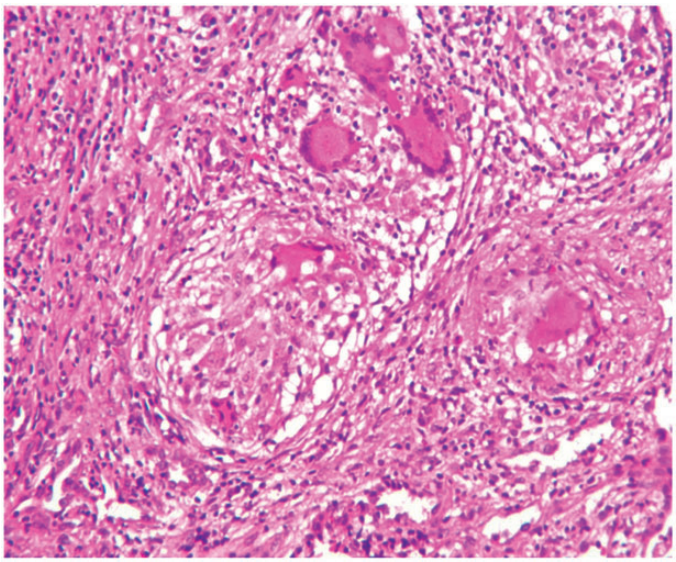

Figure 3. Histology revealed infiltration of the classic tubercular nodule with Langerhans cells in the right lung mass tissue (hematoxylin and eosin stain, 200× magnification). The pathology of the right lung mass showed a granulomatous inflammation.

Based on the presence of gynecomastia with persistent hyponatremia, normal intracranial MRI, and a low serum cortisol level, he was diagnosed with primary adrenal insufficiency. Prednisone (7.5 mg once daily) was added to his medication. The pain in his breast then rapidly disappeared and gynecomastia slowly decreased. After treatment with prednisone, the serum cortisol and blood sodium levels also gradually increased to normal limits (267 nmol/L and 139 mmol/L, respectively). However, breast pain recurred quickly when prednisone treatment was stopped based on the doctor's suggestion. Gynecomastia and hyponatremia subsequently reappeared within a few days. Prednisone therapy was then restarted, and the gynecomastia improved and hyponatremia was also resolved. The prolactin level decreased to a normal level within 1 month. Over a period of 4 years, the patient returned for follow-up evaluations. He still requires prednisone supplementation at a dose of 2.5 mg daily, and the patient has been satisfied with this therapy. No persisting breast enlargement or noticeable decrease in the blood sodium level occurred within 4 years. Written informed consent was obtained from the patient to publish his case. This study was approved by the ethics committee of Suzhou Wuzhong People's Hospital.

Discussion

Gynecomastia is the benign enlargement of glandular breast tissue in men.[3] A study showed that up to two-thirds of adult men experience some degree of gynecomastia.[4] Although gynecomastia may be clinically benign, it is sometimes accompanied by underlying medical conditions.[5] This study examined a male patient with unilateral gynecomastia and hyponatremia, which were his dominant clinical symptoms, and he was diagnosed with adrenal insufficiency. With the manifestations of cortisol deficiency, low blood pressure,

hyperpigmentation, and normal intracranial MRI, primary adrenal insufficiency may be suspected. Gynecomastia is commonly bilaterally, although unilateral gynecomastia may also appear and is often left-sided, which was similar to what was observed in the patient in this study.[6] Additionally, painful gynecomastia is a special symptom of primary adrenal insufficiency. However, primary adrenal insufficiency complicated with both painful gynecomastia and hyponatremia has not been reported.

Gynecomastia seems to result from physiologic or nonphysiologic conditions. When the estrogen-to-androgen reaction is disrupted in a male, it leads to proliferation of breast glands.[7] Physiologic gynecomastia is relatively universal in neonates, adolescents, and aged men.[8] The course of physiological gynecomastia varies from reversible changes in puberty to permanent age-related manifestations.[9] However, nonphysiologic gynecomastia may rarely develop in association with chronic diseases (such as hypogonadism, hepatocirrhosis, and uremia), medication use, and neoplasms.[10] Additionally, nonphysiologic gynecomastia may cause local pain. The patient in this study also had spontaneous breast pain. Pain may be present if a new onset of the disease occurs.[11] Moreover, limited laboratory tests and imaging workup to determine the potential reasons for gynecomastia need to be performed. Laboratory testing to measure hepatic transaminase, serum creatinine, and thyroid-stimulating hormone levels in patients should be conducted. In this study, liver, kidney, and thyroid function tests excluded the associated medical conditions. Further work-up includes screening laboratory tests and imaging examinations of the hypothalamus, pituitary, and adrenal glands.[12] Overall, hormonal testing, including the levels of total and bioavailable testosterone, estradiol, prolactin, and luteinizing hormone, can indicate pituitary, gonadal, and extragonadal endocrinopathies, and neoplasms. In men, breast ultrasonography is suggested to assess gynecomastia.[13] A routine breast biopsy should not be performed in patients with gynecomastia.[10] However, if cancer is suspected, a breast biopsy should be taken to exclude malignancy.[14]

The cause of gynecomastia in males can be determined by a clinical assessment. Information on the gynecomastia characteristics, breast examination, systemic symptoms, and weight alteration in the previous few months should be obtained.[15] Some common etiologies can be ruled out, such as hypogonadism, hormone-secreting malignancies, pseudogynecomastia, hyperthyroidism, severe hepatic dysfunction, renal failure, hemodialysis treatment, or adverse pharmacologic effects. Hormones may contribute to the progression of gynecomastia. In the patient in this study, morning serum ACTH, ALD, luteinizing hormone, follicle-stimulating hormone, estradiol, testosterone, dehydroepiandrosterone sulfate, and progesterone levels were within normal limits. Subsequent hormonal investigations revealed a relatively low morning cortisol level, with an increased prolactin level. However, the relationship between the serum prolactin level and gynecomastia development has not been described completely. Clinically, high serum prolactin levels in some men with hyperprolactinemia leads to the development of gynecomastia.[16] However, hyperprolactinemia is rare in patients with gynecomastia. The differential diagnosis of gynecomastia, as demonstrated in a series of adult patients with gynecomastia, includes approximately 9% of all-cause hyperprolactinemia.[11] Based on previous studies, hypogonadism and androgen deficiency were probably caused by hyperprolactinemia, and therefore, these conditions might alter the progesterone and androgen receptors, leading to gynecomastia.[15]

Additionally, pituitary adenomas producing prolactin may also induce hyperprolactinemia.[17] A single serum prolactin measurement is enough to confirm hyperprolactinemia, and the pituitary tumor usually correlates with the serum prolactin levels.[18] Prolactin is a hormone with multiple biological actions and it is synthesized by the anterior pituitary gland.[19] However, ACTH production by the pituitary tumor and modest hyperprolactinemia may develop because of adrenocortical insufficiency; however, prolactin production because of primary adrenal insufficiency is rare.[20] Adrenal insufficiency should be considered to be a very rare cause in the differential diagnosis of hyperprolactinemia. Akçay et al.[21] reported the case of a patient who presented with primary adrenal insufficiency, which was associated with hyperprolactinemia and a pituitary tumor. Plasma levels of prolactin were found to decrease after glucocorticoid, mineralocorticoid, and bromocriptine therapy. Lever et al.[22] reported that four patients with autoimmune Addison's disease had associated hyperprolactinemia. However, the exact relationship between prolactin, hyperprolactinemia, and primary adrenal insufficiency in the progression of gynecomastia remains unclear. Because the prolactin level decreased and gynecomastia responded well to the treatment with prednisone in this study, the possibility of primary adrenal insufficiency with gynecomastia was considered. Kelver et al.[20] reported the case of a patient with primary adrenal deficiency who presented with hyperprolactinemia; the patient's prolactin levels returned to normal with corticosteroid replacement therapy. These data supported the evidence for the influence of corticosteroids on prolactin regulation.

In the last few years, new therapeutic methods for gynecomastia have been recommended. For male patients with painful gynecomastia, the therapeutic method was directed toward curing the primary disease.[23] Because there is a lack of prospective therapies for gynecomastia, empirical treatment is often suggested. In this study, the male patient presented with a rare case of primary adrenal insufficiency with painful gynecomastia and persistent hyponatremia. Successful treatment of primary adrenal insufficiency with prednisone might relieve gynecomastia and hyponatremia. The rarity of this clinical condition may be why it is a poorly understood phenomenon. Prednisone, a corticosteroid, is theoretically known to cause gynecomastia. In the case of a boy who was diagnosed with Addison's disease, prednisone treatment inexplicably caused gynecomastia, which is a rare occurrence.[2] In this study, the patient was diagnosed with primary adrenal insufficiency, and he received a low dose of prednisone. When prednisone treatment was initiated, hyponatremia resolved within several days, and gynecomastia symptoms improved. However, when the patient stopped taking the prescribed prednisone, hyponatremia recurred and pain upon palpation re-appeared. Followed re-administration of prednisone therapy, the gynecomastia symptoms improved and hyponatremia resolved. The prolactin level returned to normal 1 month after prednisone was administered. The patient's condition improved with this therapeutic regimen, with no persisting breast enlargement and a noticeable increase in blood sodium. However, there is little evidence supporting the use of corticosteroid replacement therapy to treat gynecomastia. The lack of information on the balance between its benefits and possible harms should be highlighted to candidate patients.

In conclusion, this study is a special report of an older male patient with primary adrenal insufficiency with painful gynecomastia that was complicated by hyponatremia. These symptoms were resolved by prednisone treatment. This study is

instructive and meaningful to routine clinical practice. Additional investigation of this issue is needed to clarify the interactions between prolactin, prednisone, and primary adrenal insufficiency in the pathogenesis of gynecomastia.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Yansheng Jin http://orcid.org/0000-0002-4056-2644

References

1. Suryawanshi A, Middleton T and Ganda K. An unusual presentation of X-linked adrenoleukodystrophy. *Endocrinol Diabetes Metab Case Rep* 2015; 2015: 150098.
2. Pishdad GR, Pishdad P and Pishdad R. Breast enlargement with prednisone treatment. *Am J Med Sci* 2011; 342: 425–426.
3. Sollie M. Management of gynecomastia-changes in psychological aspects after surgery-a systematic review. *Gland Surg* 2018; 7: S70–S76.
4. Fagerlund A, Lewin R, Rufolo G, et al. Gynecomastia: a systematic review. *J Plast Surg Hand Surg* 2015; 49: 311–318.
5. Kratz JD, EI-Shazly AY, Mambuque SG, et al. Gynaecomastia in two men on stable antiretroviral therapy who commenced treatment for tuberculosis. *Malawi Med J* 2016; 28: 185–187.
6. Nuttall FQ, Warrier RS and Gannon MC. Gynecomastia and drugs: a critical evaluation of the literature. *Eur J Clin Pharmacol* 2015; 71: 569–578.
7. Fagerlund A, Cormio L, Palangi L, et al. Gynecomastia in patients with prostate cancer: a systematic review. *PloS One* 2015; 10: e0136094.
8. Lawrence SE, Faught KA, Vethamuthu J, et al. Beneficial effects of raloxifene and tamoxifen in the treatment of pubertal gynecomastia. *J Pediatr* 2004; 145: 71–76.
9. Oana Cristina V, Monica Mihaela C, Daniel I, et al. Histology of male breast lesions. Series of cases and literature review. *Maedica (Buchar)* 2018; 13: 196–201.
10. Telegrafo M, Introna T, Coi L, et al. Breast US as primary imaging modality for diagnosing gynecomastia. *G Chir* 2016; 37: 118–122.
11. Costanzo PR, Pacenza NA, Aszpis SM, et al. Clinical and etiological aspects of gynecomastia in adult males: a multicenter study. *Biomed Res Int* 2018; 2018: 8364824.
12. Barros AC and Sampaio Mde C. Gynecomastia: physiopathology, evaluation and treatment. *Sao Paulo Med J* 2012; 130: 187–197.
13. Yılmaz R, Cömert RG, Aliyev S, et al. Encapsulated papillary carcinoma in a man with gynecomastia: ultrasonography, mammography and magnetic resonance imaging features with pathologic correlation. *Eur J Breast Health* 2018; 14: 127–131.
14. Yuan WH, Li AF, Chou YH, et al. Clinical and ultrasonographic features of male breast tumors: a retrospective analysis. *PLoS One* 2018; 13: e0194651.
15. Narula HS and Carlson HE. Gynaecomastia-pathophysiology, diagnosis and treatment. *Nat Rev Endocrinol* 2014; 10: 684–698.
16. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, et al. Endocrine-disrupting chemicals: an endocrine society scientific statement. *Endocr Rev* 2009; 30: 293–342.
17. De Pue A, Lutin B and Paemeleire K. Chronic cluster headache and the pituitary gland. *J Headache Pain* 2016; 17: 23.
18. Bettencourt-Silva R, Pereira J, Belo S, et al. Prolactin-producing pituitary carcinoma, hypopituitarism, and Graves' disease-report of a challenging case and literature review. *Front Endocrinol (Lausanne)* 2018; 9: 312.
19. Lazopoulos A, Krimiotis D, Schizas NC, et al. Galactorrhea, mastodynia and gynecomastia as the first manifestation of lung

adenocarcinoma. A case report. *Respir Med Case Rep* 2018; 26: 146–149.
20. Kelver ME and Nagamani M. Hyperprolactinemia in primary adrenocortical insufficiency. *Fertil Steril* 1985; 44: 423–425.
21. Akçay G, Aral F, Ozbey N, et al. Pituitary macroadenoma in Addison's disease. *J Int Med Res* 1996; 24: 221–227.
22. Lever EG and McKerron CG. Autoimmune Addison's disease associated with hyperprolactinaemia. *Clin Endocrinol (Oxf)* 1984; 21: 451–457.
23. Carlson HE. Approach to the patient with gynecomastia. *J Clin Endocrinol Metab* 2011; 96: 15–21.