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Case Report

A giant prolactinoma in a uremic patient with massive proteinuria: a case report and lessons learned

Yuechong Cui, Bin Zhu, Fei Zheng

Department of Obstetrics and Gynecology, Yiwu Maternity and Children Hospital, Jinhua 322000, Zhejiang, China

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Abstract: Prolactinomas are the most common functional pituitary tumors. We present a rare case of a young man with atypical symptoms of hyperprolactinemia, but who suffered from massive proteinuria with increased urinal PRL excretion. The patient did not respond to dopamine agonist therapy or increased dose of bromocriptine and did not convert cabergoline. Because of the precarious anatomic site of the prolactinoma in which the macroadenoma with sellar and suprasellar extension wrapped around the left internal carotid artery, he received endoscopic endonasal partial surgery for giant pituitary adenoma. Unfortunately, he had persistent hyperprolactinemia. Moreover, the patient and his family strongly disagreed with the renal biopsy. Despite dietary treatment and anti-proteinuric drug therapy, proteinuria persisted and the renal function deteriorated rapidly. The present case study reviews the relationship between prolactinoma and chronic renal failure, as well as the massive proteinuria.

Keywords: Prolactinomas, dopamine resistance, proteinuria, uremia

Introduction

Prolactinomas are the most common hormone-secreting pituitary tumors. Patients typically present with clinical manifestations of hyperprolactinemia, including galactorrhea and oligomenorrhea or amenorrhea in women, hypogonadism in men, and mass effects, such as headaches and visual field disturbances [1, 2]. Hyperprolactinemia occurs commonly in patients with chronic kidney disease [3]. In addition, uremic patients exhibit impaired responsiveness to the prolactin suppressive effects of dopamine. Proteinuria could occur in patients with hyper-functional pituitary tumors, mainly acromegaly, which is a disease characterized by excessive secretion of GH [4]. However, clinical reports of prolactinomas in a patient with massive proteinuria are rare. Herein, we describe a case of a giant prolactinoma in a uremic man with massive proteinuria.

Case report

A 27-year-old man was admitted to our hospital because of worsening hypertension. His blood pressure was > 140/90 mmHg 1 year ago and proteinuria with was detected on medical examination, his GFR decreased gradually. The patient was asymptomatic but occasionally had headache exacerbated by hypertension (blood pressure more than 180/120 mmHg) in the last week. Except for high blood pressure, the remainder of the physical examination was normal. Because of the complaint of occasionally headache and severe hypertension, a CT scan of the brain was performed. Surprisingly, CT scan showed the existence of a pituitary tumor. Subsequently, MRI scan of the brain was performed and the results showed the presence of a pituitary macroadenoma with sellar and suprasellar extension and wrapped around the left internal carotid artery (**Figure 1A** and **1B**).

We treated the hypertension with phenylacetic acid amlodipine (10 mg/day) combined with doxazosin (4 mg/day) and diltiazem (180 mg/day). One month later, his blood pressure was still > 140/90 mmHg. Consistent with a giant pituitary tumor, the serum prolactin level was extremely high (> 10,000 μIU/mL, normal range: 86-324 μIU/mL), while thyroid-stimulating hormone, free thyroxine, growth hormone, follicle-stimulating hormone, luteinizing hormone, corticotropin, cortisol, and testosterone values were normal. Strikingly, severe protein-

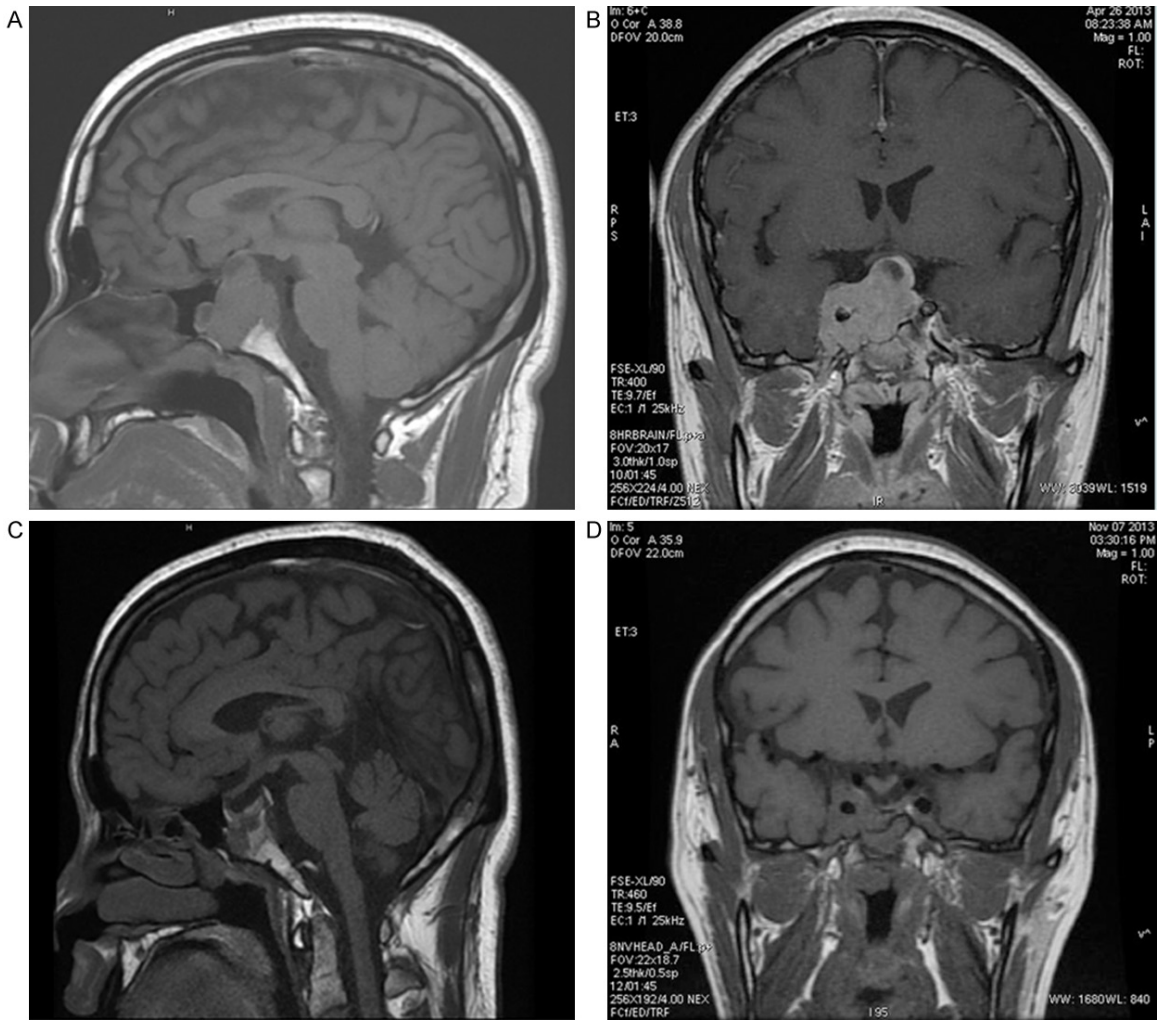

Figure 1. Magnetic resonance imaging scan of the brain before and after surgery. MRI scan of the brain showed the presence of a pituitary tumor with sellar and suprasellar extension that was wrapped around the left internal carotid artery. A, B. Sagittal and coronal T1-weighted MRI of brain scan on admission. C, D. Sagittal and coronal T1-weighted MRI of brain scan after surgery.

uria was observed. A basic urinalysis showed 3+ protein. Quantified proteinuria in a 24-hour urine collection was 8690.5 mg. Urine protein electrophoresis confirmed non-selective proteinuria (α1-microgrobulin, 16.0 mg/dl; microalbumin, 201 mg/dl; IgG, 26.9 mg/dl; transferrin, 13.2 mg/dl), and urine prolactin was 6870.0 pg/ml. Renal function was impaired: BUN, 13.7 mmol/L; urine creatinine, 323 μmoL/L; eGFR 38 ml/min/1.73 m^2. Therefore, chronic glomerulonephritis was diagnosed based on the history of 1 year of proteinuria and decreased eGFR. Kidney biopsy should be performed to determine the nature of renal disease with the impaired renal function. Unfortunately, the patient and his family strongly disagreed with the renal biopsy. A low-protein diet was recommended as anti-proteinuric therapy.

Additionally, the prolactinoma was treated with bromocriptine (2.5 mg/d), while the patient did not respond to dopamine agonist therapy, even after increased dose of bromocriptine (15 mg/d orally) and converted cabergoline (4.5 mg per week). Because of the precarious anatomic site of the prolactinoma, he received endoscopic endonasal partial surgery for giant pituitary adenoma (**Figure 1C** and **1D**). Histopathology revealed an atypical adenoma of the pituitary with nuclear atypia, immunohistochemical staining for prolactin was positive (**Figure 2**).

After 5 months of therapy, his condition continued to deteriorate; specifically, proteinuria persisted within the nephrotic range (protein, 0.97 g/24 h; urine volume, 400 ml/24 h) and renal function was worsening (BUN, 42.56 mmol/L;

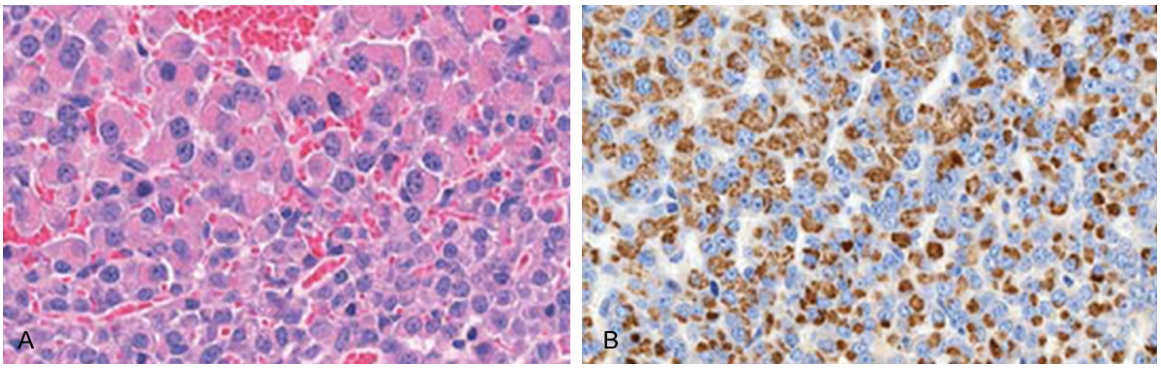

Figure 2. Histopathology illustrations for pituitary adenoma. A. Histopathology revealed an atypical adenoma of the pituitary and the tumor cells with nuclear atypia were diffusely arranged in strands (HE staining, ×400); B. Immunohistochemical staining for prolactin (×400).

urine creatinine, 1311 umoL/L; and eGFR 4.36 ml/min/1.73 m^2). Moreover, he had nausea, vomiting, dyspnea, and symptoms of congestive heart failure. In addition, the BNP was abnormal (1152 pg/mL). With a diagnosis of uremia, dialysis was initiated. However, the patient had persistent hyperprolactinemia (> 10,000 μIU/mL) during follow up.

Discussion

Hyperprolactinemia can occur as a consequence of pharmacologic alteration in the pathway that controls prolactin secretion, or physiologic or pathologic effects on prolactin production and clearance, such as pregnancy, lactation, hypothyroidism, chronic liver disease, chest wall injury or lesion, end-stage renal disease, or neoplastic disease [1, 5]. In our case the extremely high concentration of prolactin was primarily attributed to the prolactinoma. Another underestimated pathologic entity in which the prolactin concentration rises is chronic kidney disease (CKD). It has been reported that the levels of various polypeptide hormones, including prolactin, are increased in rats experimental models of uremia, which is suggested by an insufficient glomerular filtration rate for prolactin clearance [6]. Similarly, a patient who presents with CKD has diminished physiologic oscillations of prolactin and the prolactin secretion circadian rhythm disappears, which leads to a longer half-life of prolactin and a lower metabolic clearance rate in the circulation with renal insufficiency [7].

Our patient had severe proteinuria when he was first admitted to the hospital with impaired renal function. Unfortunately, the patient and his family strongly disagreed with the renal biopsy. Despite dietary treatment and anti-proteinuric drug therapy, proteinuria persisted and the renal function deteriorated rapidly. Clearly, CKD had a great effect on proteinuria. In addition, the role of hyperprolactinemia could not be underestimated. The man was detected with massive urine prolactin, similar to a previous case. Heras reported a case in which disappearance of nephrotic-range proteinuria was related to dopamine agonist treatment in a patient with a giant prolactinoma, and the mechanism was due to hypersecretion of prolactin or other tumor-related proteins that filter the glomerulus freely overcoming tubular reabsorption and appearing as a urinary protein [8].

Pharmacologic therapy with a dopamine agonist is first-line treatment for prolactinomas [9]. In our case, the man did not respond to medical therapy. Several possible mechanisms of dopamine resistance in prolactinoma were addressed, including reduced density of D2 dopamine receptors, dysregulation of cell proliferation, and differentiation and alterations in intracellular signal transduction pathways [2, 5]. In addition, uremic patients exhibit marked resistance to the prolactin suppressive effects of dopamine [3, 10], while the mechanism of dopamine resistance with hyperprolactinemia in uremia is not totally understood. In this case, the patient had renal insufficiency, thus we presumed that accumulation of uremic toxins and disturbance of the endocrine and neurologic systems by uremia, disrupted the regulation of prolactin metabolism and the pathway that controls prolactin secretion.

In the following years, the man underwent hemodialysis treatment for irreversible end-stage renal disease, however, the prolactin

level remained high. Others have reported dialysis was unassociated with or even have an elevated serum prolactin levels [11, 12]. Moreover, although the well-known functions of prolactin are related to reproduction, this hormone was also considered to regulate angiogenesis [13], and abnormalities in blood vessel growth have been associated with various pathologies, such as preeclampsia and hypertension [14, 15]. In this case, it became difficult to treat the elevated blood pressure probably owing to hyperprolactinemia, which would damage the systemic vascular endothelium and remodel vessels.

We describe a rare case of a giant prolactinoma in a uremic young man with massive proteinuria and increased urinal PRL excretion. Although the absence of a cause-and-effect relationship between proteinuria counteraction with anti-hyperprolactinemia therapy, we suggest that urine prolactin was one of the proteins in the urine of this patient. Meanwhile, the man suffered intractable hyperprolactinemia, as well as with the refractory hypertension and renal failure, accordingly, therefore we speculate that they can interact with each other, and further investigations are needed in these areas.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Zheng Fei, Yiwu Maternity and Children Hospital, 320 South Gate Street, Yiwu, Jinhua 322000, Zhejiang, China. Tel: +8615057943512; E-mail: 928721201@qq.com

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