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Case Report

Pituitary Microadenoma Presenting with Panhypopituitarism and Hyponatremia: A Case Report

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ABSTRACT

The prevalence of pituitary adenomas is rising as more are incidentally reported on Magnetic Resonance Imaging (MRI) and Computerized Tomography (CT) imaging studies. While most exist without causing clinical symptoms or laboratory abnormalities, a non-functional sellar mass can initially present with panhypopituitarism. We present a case of pituitary microadenoma that presented with severe hyponatremia and panhypopituitarism. This patient had a non-functional pituitary microadenoma and was hospitalized many times for hyponatremia before finally being diagnosed with panhypopituitarism.

Keywords: Pituitary adenomas; Magnetic resonance imaging; Computerized tomography; Hyponatremia, Panhypopituitarism.

INTRODUCTION

The pituitary gland is about the size of a pea and is divided into two anatomical sections based on location and hormone production, anterior and posterior. It is located in the brain, housed in the sella turcia for protection. It serves as the master gland of the body, controlling most other endocrine glands and producing over 8 hormones that act all over the body. The anterior pituitary gland produces growth hormone, prolactin, luteinizing hormone, follicle-stimulating hormone, adrenocorticotropic hormone and thyroid-stimulating hormone; while the posterior pituitary gland produces vasopressin and oxytocin. Pituitary adenomas are a diverse group of tumors that arise from this gland and can contain hormone-producing tissue (functional) or non-hormone producing tissue (non-functional) [1]. They can be associated with increased morbidity and mortality to their aberrant hormonal production, and mass effect on the body (e.g., hypopituitarism) [2].

Classically, pituitary adenomas are classified according to their size as microadenomas (diameter <1 cm) and macroadenomas (diameter >1 cm); microadenomas are more common [3,4]. With increased use of radiological investigations through CT and MRI imaging, the number of incidentally detected pituitary masses has increased over the last few decades. Several studies estimate the prevalence of pituitary adenomas to be anywhere from less than 1% to over 30% amongst the general population with the best estimating around 17% [3-6]. However, since most pituitary microadenomas exist without causing any clinical symptoms or non-specific symptoms, it is difficult to accurately measure their prevalence [2-4,7].

Most pituitary adenomas are sporadic, but associated germline mutations are increasingly identified with up to 43% of cases reporting a significant family history for pituitary adenoma 8, 9. One germline mutation in the aryl hydrocarbon receptor-interacting protein (AIP) has been identified in both families with multiple cases of pituitary in their lineage (20%) and amongst sporadic cases (3.6 to 20%) [8,9]. Since existence of the AIP mutations and other germline mutations (MEN1, CDKN1B, PRKAR1A, SDHx) predisposes to pituitary adenoma development but has low penetrance (20-23%), the clinical consequences of the mutations remain unclear [8]. Therefore, no formal guidelines about genetic testing for pituitary adenoma patients currently exist [8,10]. However, the presence of AIP mutations has been associated with more aggressive tumors causing significant hormonal deviations, such as panhypopituitarism [8,9]. Furthermore, while current guidelines

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exclude the majority of pituitary microadenomas (most often found as incidentalomas on routine screening) from endocrine or genetic workup, there is evidence to suggest that even non-secreting microadenomas may not be clinically harmless [4,11]. This implicates the need for further research to create evidence-based guidelines on screening (e.g., genetic screening, in-depth endocrine testing) for patients with incidental or newly diagnosed pituitary microadenomas [10].

CASE REPORT

A 69-year-old Caucasian man was seen for initial evaluation in our endocrinology clinic for a pituitary microadenoma in November 2018. His past medical history was notable for hypertension, hyponatremia, hyperlipidemia, hypothyroidism, anxiety, depression, and history of prostate cancer. Social history was negative for active or past tobacco use, alcohol or illicit drug use. Home medications were fentanyl 50 mcg/h patch, levothyroxine 100 µg tablet daily, lisinopril 10 mg tablet daily, ranitidine 75 mg tablet daily, simvastatin 40 mg tablet daily, sodium chloride 1 g tablet 3 times a day, and over-the-counter medications including apoaequorin, coenzyme Q 10, garlic 1000 mg, turmeric 500 mg, melatonin and methylsulfonylmethane.

Our patient reported a history of a 35-pound weight loss over 6-8 months with a stable weight maintained in recent months, generalized weakness, and occasional nausea. He denied vomiting, dizziness, orthostatic symptoms, galactorrhea, and reported no significant changes in his facial features, shoe size or ring size. On detailed questioning, patient reported 5 hospitalizations for hyponatremia since July 2017. In May 2018, he was diagnosed with central hypothyroidism during evaluation of his persistent hyponatremia. Thyroid function tests at this time showed low free T4 of 0.29 ng/dL (0.6–1.24 ng/mL), low Free T3 of 1.3 pg/mL (2.3–4.2 pg/mL) with low normal thyroid stimulating hormone (TSH) of 1.06 uIU/mL (0.300-4.000 ulU/mL) (Table 1).

His last hospitalization for hyponatremia was in June 2018 when he was provisionally diagnosed with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) based on laboratory evaluation (labs) showing a serum sodium of 118 (135-146 mmol/L), serum osmolality 246 (275-295 mOsm/L), urine osmolality 237 (52-1200 mOsm/L), urine sodium 57 (42-20 mmol/L), testosterone < 2.5 (193-740 ng/dL), PSA <0.01 (1.65-4.10 ng/ml) and AM cortisol 11 mcg/dL (Table 1). The patient's serum sodium improved with normal saline infusion and urea, and he was discharged home on oral salt tablets. MRI of the brain was performed in October 2018 to evaluate his central hypothyroidism, which showed a 3 x 6 x 9 mm hypoenhancing nodule in the left lateral pituitary with no evidence of optic chiasm compression. The patient was then referred to our endocrinology clinic for further management.

Given high clinical suspicion for adrenal insufficiency and hypopituitarism, labs were ordered for evaluation of pituitary functions. His labs were consistent with central adrenal insufficiency along with panhypopituitarism and showed an abnormal ACTH stimulation test (0 min cortisol 4 mcg/dl, 30 min cortisol 9 mcg/dl, and 60 min cortisol 10 mcg/dL) with low normal ACTH of 21.9 (7.2-63.3 pg/ml), low insulin like growth factor -1 (IGF-1) of 39 (47-192 ng/mL) and low prolactin of 1.3 (4.04-15.2 ng/mL) (Table 1). Thyroid function tests were normal on levothyroxine replacement. Thus, the patient's hyponatremia was most likely due to adrenal insufficiency and central hypothyroidism. Therefore, salt tablets were discontinued, a maintenance dose of hydrocortisone was initiated, and levothyroxine was continued. The patient felt significantly better over next few weeks and follow up labs showed normal thyroid function and serum sodium level.

Table 1: Lab Values.

Date	Lab Type	Lab Value (reference range)
05/2018	Free T4	0.29 ng/dL (0.6–1.24 ng/mL)
05/2018	Free T3	1.3 pg/mL (2.3–4.2 pg/mL)
05/2018	TSH	1.06 uIU/mL (0.300-4.000 ulU/mL)
06/2018	Sodium	118 mmol/L (135-146 mmol/L)
06/2018	Serum osmolality	246 mOsm/L (275-295 mOsm/L)
06/2018	Urine osmolality	237 mOsm/L (52-1200 mOsm/L)
06/2018	Urine sodium	57 mmol/L (42-20 mmol/L)
06/2018	Testosterone	< 2.5 ng/dL (193-740 ng/dL)
06/2018	PSA	<0.01 ng/ml (1.65-4.10 ng/ml)
06/2018	AM cortisol	11 mcg/dL
10/2018	ACTH stimulation test	0 min cortisol 4 mcg/dL 30 min cortisol 9 mcg/dL 60 min cortisol 10 mcg/dL
10/2018	ACTH	21.9 (7.2-63.3 pg/mL)
10/2018	IGF-1	39 (47-192 ng/mL)
10/2018	Prolactin	1.3 (4.04-15.2 ng/mL)

DISCUSSION

Typically pituitary microadenomas most often are non-functioning with no pituitary dysfunction. With careful follow-up, growth over time can occur in 10% of microadenomas [12].

Our patient developed panhypopituitarism despite only having a small pituitary microadenoma (3 x 5 x 9mm). Currently, there is not enough evidence to justify the cost of hormonal evaluation for pituitary dysfunction in patients with pituitary microadenomas less than 5mm in diameter [4,10,13]. Existing guidelines limit recommendations for a detailed endocrine workup in patients with pituitary macroadenomas (>/=1cm) or large microadenomas (>5mm) due to a higher prevalence of hypopituitarism [4,7,10]. However, these guidelines rely on expert opinion and clinical judgment rather than evidence-based

research [4,7,10]. While the prevalence of panhypopituitarism is low amongst patients with pituitary microadenomas (<1 cm), it is not negligible nor are the clinical effects on those who have it [3]. Yuen KC et al. [11] evaluated 38 patients with microadenomas (measuring 2 mm to 9 mm) and showed panhypopituitarism (deficiency in 3 or more anterior pituitary hormone axis) in one of the 38 patients. A study by Diederich et al evaluated 28 cases of hyponatremia due to hypopituitarism [14]. In the study, all but 3 cases with chronic hypopituitarism were undiagnosed until a hospital admission for symptomatic hyponatremia, and 12 out of 28 cases had recurrent episodes of hyponatremia requiring up to four hospital admissions [14]. This suggests hypopituitarism had not been considered as a potential etiology for hyponatremia.

For these patients, as with the patient presented in this case report, delayed recognition of the effects of pituitary dysfunction from an adenoma resulted in multiple hospitalizations from severe electrolyte imbalances and life-threatening conditions. The smallest recorded microadenoma with reported pituitary dysfunction in the literature was 2 mm [11]. Therefore, a differential diagnosis for patients presenting with hyponatremia and a clinical picture suggestive for SIADH should include hypopituitarism. This early recognition and a thorough endocrine workup are crucial [14]. While the current guidelines exclude smaller pituitary microadenomas from a full clinical workup, it is known that pituitary macroadenomas may also be nonsecretory with normal pituitary function. Therefore, we postulate that tumor size may not be an appropriate exclusion criterion for clinical and laboratory evaluations for hypopituitarism. Rather other pituitary adenoma characteristics and individual patient-specific features such as genetic markers and proteomics need to be evaluated in future studies as determinants of risk of pituitary dysfunction.

CONCLUSION

Management of a pituitary adenoma is inherently expensive due to its chronic nature, requiring decades of management that include costly laboratory tests and imaging studies. Given increased detection rates of pituitary microadenomas with advancements in imaging techniques, there is an urgent need for further studies to better understand pituitary adenoma characteristics and individual patient-specific features to help identify subsets of patients with pituitary microadenomas who are at high risk for hypopituitarism. Further understanding of patient specific risk factors for hypopituitarism will help develop cost effective and personalized approaches for precise management of pituitary microadenomas. Recent studies have begun to identify genetic mutations, such as AIP, that are associated with pituitary adenoma predisposition and may serve as important future diagnostic tools in evaluating the extent and nature of adenomas and incidentalomas rather than being limited to size. At this time genetic evaluation is not recommended unless there is a consistent family history due to the low prevalence of these markers (~5%) 10. Current recommendations for macroadenomas and larger microadenomas include an evaluation for hypopituitarism. Transphenoidal resection remains the treatment of choice for all functional adenomas other than prolactinomas, which may be effectively managed with medical therapy alone. For patients who do not achieve an adequate response to surgery or medical therapy in tumor size or hormone levels, radiation therapy may be considered. This case highlights the importance of further research to identify which patients with pituitary microadenomas would benefit from a more in-depth endocrine workup upon initial.

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