PROLACTIN-SECRETING PITUITARY MACROADENOMA PRESENTING WITH MASS EFFECTS, HORMONAL DEFICIENCIES, AND NEUROGENIC DIABETES INSIPIDUS: A CASE REPORT AND REVIEW OF LITERATURE

ABSTRACT

To report and review a case of prolactin-producing pituitary tumor presenting with mass effects, hormonal deficiency, and neurogenic diabetes insipidus in a nulliparous woman of Afro-Caribbean descent. The patient presented with dull-aching headaches associated with worsening vision, nausea, and vomiting. The patient also complained of polyuria, nocturia, thirst, polydipsia, and weight gain. Physical examination showed bilateral visual field defects, while investigations revealed hypernatremia and elevated plasma osmolality but decreased urine sodium concentration, osmolality, and specific gravity.

Results of the hormonal profile showed high plasma prolactin levels, a low plasma concentration of the antidiuretic hormone, and decreased levels of other anterior pituitary hormones. Imaging revealed a large, uncalcified, cystic pituitary mass extending into adjacent structures and compressing the optic chiasm and internal carotid artery. The outcome of the water deprivation and desmopressin administration tests were consistent with neurogenic diabetes insipidus, and a diagnosis of prolactin-producing pituitary macroadenoma with mass effects, hormonal deficiencies, and neurogenic diabetes insipidus was made. The patient was commenced on medical treatment and referred for histopathological diagnosis and definitive treatment. This report highlights the coexistence of neurogenic diabetes insipidus with a prolactin-producing pituitary macroadenoma presenting with mass effects.

Key Words: Pituitary adenoma, Pituitary macroadenoma, Hypopituitarism, Neurogenic diabetes insipidus.

INTRODUCTION

Pituitary adenomas are benign tumors arising from cells of the anterior lobe of the pituitary gland. In the general population, pituitary adenomas account for 10-15% of all intracranial tumors. [1] Several population-based studies have been conducted in different parts of the world to report the prevalence of these tumors. A study in Iceland reported a prevalence rate of 115.57 cases per 100,000 people [2]. A similar prevalence rate of 94 cases per 100,000 people was reported by Daly et al. from a cross-sectional survey conducted in a province in Liege, Belgium [3]. In another study conducted in Banbury (Oxfordshire), UK, by Fernandez et al., they reported a prevalence rate of 77.6 cases per 100,000 individuals in the population studied. Fernandez A. et al. also showed that pituitary adenomas were more common in females (66.7%) compared to males (33.3%), although the nonfunctional adenoma (NFA) subtype occurred predominantly in males. Their study also showed that microadenomas were more common at a frequency of 58.7% compared to 41.3% for macroadenomas [4]. In recent decades the prevalence of these tumors has been rising due to increasing awareness within the medical community, access to hormonal assays, and advances in diagnostic imaging. In a meta-analysis conducted by Ezzat et al., they reported a prevalence rate as high as 14.4% from postmortem samples and 22.5% from imaging studies, with an average of 16.7% in the general population. In comparison, the prevalence rate for pituitary macroadenomas was 0.16 – 0.20% [5].

Pituitary adenomas are classified based on size, hormonal activity, or immunohistochemistry of the cell type of origin [6]. A comprehensive classification system based on immunohistochemistry, the presence or absence of secretory products, and various other ultrastructural features was published by WHO in 2004 [7]. Pituitary adenomas are classified as microadenomas, macroadenomas, and giant pituitary adenomas based on their size. Pituitary adenomas smaller than 1cm in dimension are described as microadenomas, while those greater than or equal to 1cm in size are described as macroadenomas. Giant pituitary adenomas are greater than 4cm in dimension and tend to be invasive with significant mass effects and destruction of the sella turcica. [2, 8]. On the basis of hormonal activity, which is most useful clinically, pituitary adenomas are classified into functional and nonfunctional adenomas (NFA) (1). While functional pituitary adenomas arise from hormonally active cell type(s) and secrete one or more hormones, nonfunctional pituitary adenomas (NFA) arise from inactive cells and do not secrete hormones but may exert mass effects from compression of adjacent structures, leading to hormonal deficiencies [9]. Examples of functional pituitary adenomas include prolactinomas, growth hormone-secreting pituitary adenomas, adrenocorticotrophic hormone-secreting pituitary adenomas (ACTHomas), thyroid-stimulating hormone-producing pituitary adenomas (TSHomas) and gonadotrophic hormone-secreting pituitary adenomas [2, 8, 10, 11, 12]. In a study conducted in Iceland on 410 patients with pituitary adenomas, 43% were found to be non-functional adenomas, 40% were prolactin-secreting adenomas, 11% were growth hormone (GH) secreting adenomas, and 6% were adrenocorticotropic hormone (ACTH) secreting adenomas. Functional plurihormonal pituitary adenomas (PHAs) have also been described and account for 10 – 15% of all pituitary adenomas. This subtype may be monomorphous with one functional cell type or plurimorphous with two or more functional cell

types (13). Slow-growing and nonfunctional microadenomas discovered on radiological and postmortem examinations are widely reported in the literature and are known as incidentalomas. Using immunohistochemistry staining, pituitary adenomas are classified into pink-staining or acidophilic adenomas; which account for about 45% of all cases, and blue-staining or basophilic adenomas; which are less than 20% of all cases. The pink-staining tumors include prolactinomas and growth hormone-secreting pituitary adenomas while blue-staining tumors include ACTHomas, TSHomas, and gonadotrophic hormone-secreting adenomas. Nonfunctional pituitary adenomas that stain positive for synaptophysin have also been identified and are described as null-cell pituitary adenomas. [2] [14] [27]

Amongst all pituitary adenomas, prolactinomas are the most common, accounting for about 29% of all pituitary adenomas. Clinically, prolactinomas present with galactorrhea-amenorrhea and infertility in females, while decreased libido, impotence, and infertility are commonly seen in males. Recognizing the clinical manifestations of the hormonal imbalances present in these tumors helps to guide the classification and management of patients and determine their prognosis. Generally, prolactinomas can be managed medically with dopamine agonists or somatostatin analogs to suppress prolactin synthesis and secretion. [1] However, the treatment of choice is endoscopic transsphenoidal surgical resection. Radiotherapy is also available as another treatment option for cases that are not responsive to both surgical and medical treatment.

CASE REPORT

A 42-year-old nulliparous woman presented to the clinic with a headache described as a dull-aching pain over the past year. Her complaint was associated with progressively worsening vision, nausea, and vomiting. She also complained of thirst, polyuria of about 6 – 9 L/day, nocturia, and polydipsia. Over the past two years, she has experienced a weight gain of about 10kg and a six-month history of amenorrhea. She denied breast discharge, neck swelling, or heat or cold intolerance. There was no history of head injury, hearing loss, tinnitus, nystagmus, or vertigo in her. A review of symptoms revealed poor sleep, muscle weakness, fatigue, and bone pains in her shoulder and pelvic regions. There was no fever, cough, shortness of breath, chest pain, or palpitations. Past history was positive for poorly controlled high blood pressure, seasonal allergies, and a mood disorder. She, however, admitted to poor compliance with her routine medications, which included lisinopril 10mg, nifedipine 30mg, and atorvastatin 25mg daily. History of use of alcohol, nicotine, or other recreational drugs was negative, and her family history was not contributory.

Physical examination on presentation showed an anxious but well-oriented middle-aged female who was afebrile, not pale, with bilateral pedal edema. Vital signs revealed a body temperature of 98F, a pulse rate of 69/min, blood pressure of 153/102mmHg, and a respiratory rate of 14/min. Her BMI was 36.57kg/cm2. Findings on chest and abdominal examinations were normal. The visual assessment showed a mild refractive error and bilateral visual field defects (Figure 1), with normal findings on the Ishihara test.

The results of the investigations conducted are documented below.

Serum Chemistry

Test	Patient Results	Reference Range
Serum sodium	160mmol/L	135 – 145mmol/L
Serum potassium	4.1mmol/L	3.5 – 5mmol/L
Blood urea nitrogen (BUN)	4.6mg/dl	6 – 24mg/dl
Serum calcium	8.5mg/dl	8.5 – 10.2mg/dl
Serum osmolality	365mOsm/kg	275 -290 mOsm/kg

Blood Glucose

Test	Patient Results	Reference Range
Random blood glucose	146mg/dl	<200mg/dl
HBA1c	6.1%	<6.5%

Lipid Profile

Test	Patient Results	Reference Range
Serum low density lipoprotein (LDL)	5.3mmol/L	<3.4mmol/L
Serum cholesterol	7.0mmol/L	<2.5mmol/L

Hormonal Profile

Test	Patient Results	Reference Range
Serum prolactin	127.7ng/ml	<20ng/ml
Serum follicle-stimulating hormone (FSH)	2.6IU/L	4.5 – 21.5IU/L
Serum luteinizing hormone (LH)	3.9IU/L	5 – 21.5IU/L
Serum thyroid-stimulating hormone (TSH)	0.1mU/L	0.5 – 5.0mU/L
Serum thyroxine (T4)	0.3ng/dL	0.7 – 1.9ng/dL
Serum cortisol	3.2mcg/dL	5 – 25mcg/dL
Serum antidiuretic hormone (ADH)	0.5pmol/L	0.9 – 4.6pmol/L

Urine Chemistry

Test	Patient Results	Reference Range
Urine sodium	19mEq/L	>20mEq/L

(UNa)		
Urine osmolality	35mOsm/kg	50 – 1400mOsm/kg
Urine Specific gravity (SG)	1.001	1.005 – 1.030
Beta-hCG	Negative	

Urine volume and osmolality, showed no significant change with the water deprivation test. However, desmopressin administration improved these parameters moderately, with serum osmolality also increasing to 295mOsm/Kg.

The MRI scan showed a large, uncalcified, cystic pituitary mass in the sella turcica measuring 2.46 x 3.16 x 2.69cm in dimension, extending superiorly into the diaphragmatic sella with compression of the optic chiasm and laterally into the cavernous sinus with 50% compression of the internal carotid artery. (Figure 2) The pituitary tumor and the extent of local invasion are better appreciated on the multimedia attachments labeled 1 to 16. (Figure 3)

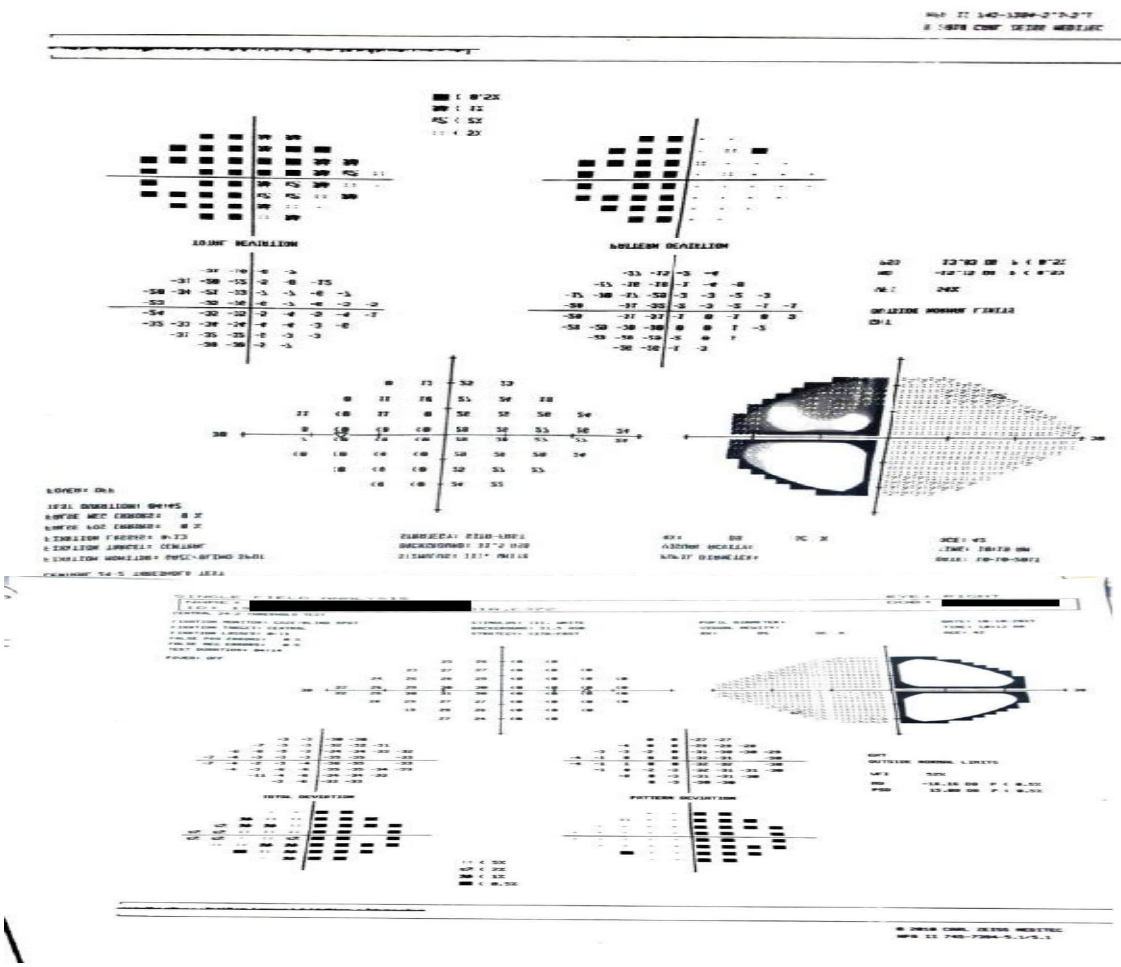

Figure 1: Visual field examinations showing multiple abnormalities bilaterally (homonymous hemianopia and quadrantanopia). Source: Caribbean Kidney and Medical Center (Library).

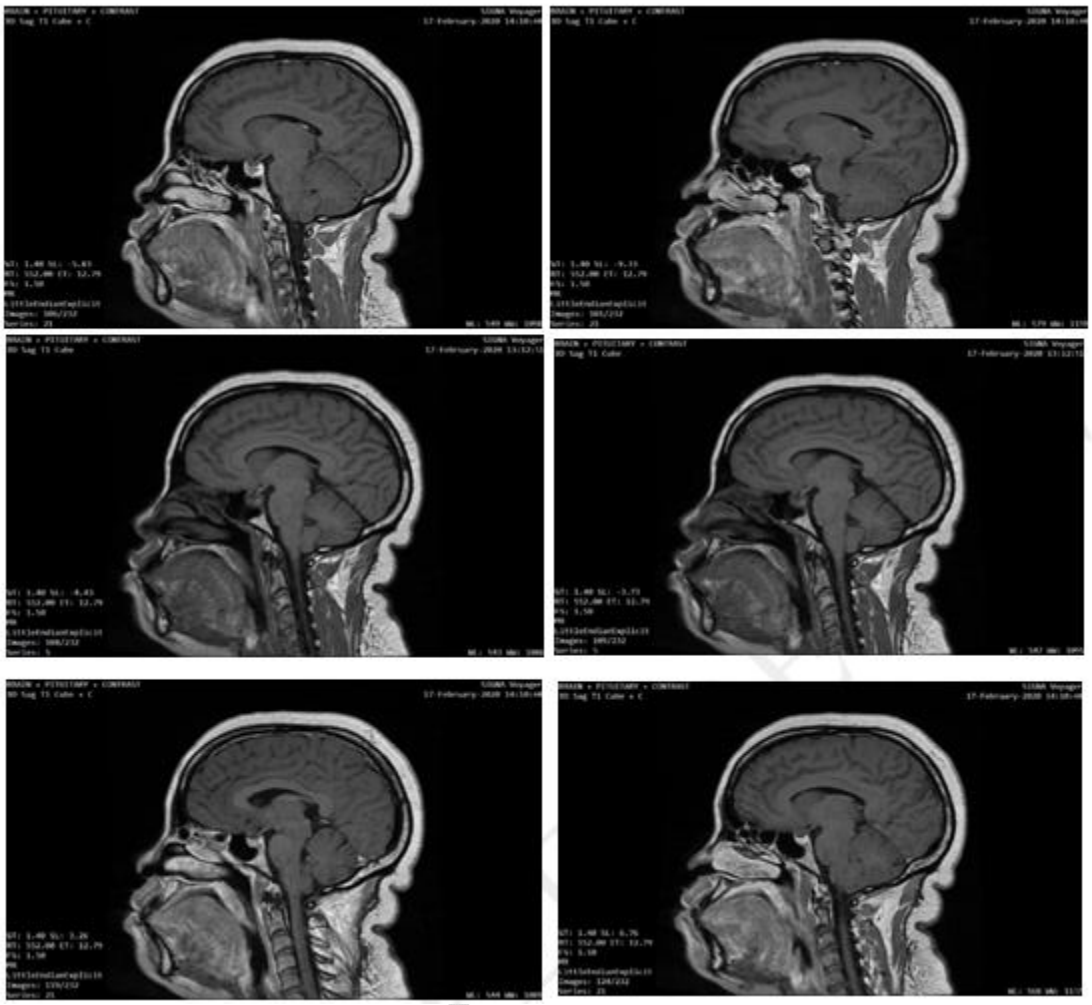

Figure 2: Baseline magnetic resonance imaging (MRI) showing the multilayer sagittal sections of the patient with an uncalcified mass on the sella turcica pushing anteriorly and downward. Source: Caribbean Kidney and Medical Center (Library).

M media 1.mp4
M media 2.mp4
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Figure 3: Multimedia (MM) 1 to 16 demonstrated differing visual layers of the pituitary tumor. The MRI scan (Brain) showed a large, uncalcified, cystic pituitary mass in the sella turcica measuring 2.46 x 3.16 x 2.69cm in dimension, extending anterior-superiorly into the diaphragmatic sella with compression of the optic chiasm, and laterally into the cavernous sinus with compression 50% of the internal carotid artery—source: Caribbean Kidney and Medical Center (Library).

Given the patient's history and the physical and investigation findings, an assessment of a prolactin-producing pituitary macroadenoma with mass effects, hormonal deficiencies, and neurogenic diabetes insipidus was made. She was commenced on oral bromocriptine (Parlodel) 2.5mg daily and intranasal desmopressin spray (DDVAP) 20mcg twice daily. She was also referred for a neurosurgery consult in Barbados for further evaluation and definitive treatment. At the time of documentation of this report, the patient was stable and awaiting further evaluation.

DISCUSSION

Pituitary adenomas are unique tumors arising from the cells of anterior pituitary gland. Most are slow-growing and benign; however, invasive pituitary adenomas with aggressive behavior have been described in the literature. Pituitary adenomas are monoclonal neoplasms in origin. Several molecular mechanisms involved in the pathogenesis of pituitary adenomas have been described, although the precise molecular mechanisms remain unknown. These factors include altered growth factors, epigenetic changes in cell-cycle regulators, abnormal hormonal milieu, abnormal intrapituitary microenvironment, and inherited germline and somatic or sporadic mutations [14].

Anatomically, the pituitary gland is a pea-sized gland that sits inferior to the hypothalamus in the pituitary fossa or sella turcica, a basketlike saddle-shaped depression of the sphenoid bone. The gland is covered in this fossa by the diaphragmatic sella of the dura matter. The gland is surrounded on its superior aspect by the optic chiasm, inferiorly by the sphenoid bone, and laterally by the cavernous sinus.

The clinical presentations of pituitary adenomas generally depend on the tumor size and functional status and include progressive mass effects, visual field defects, and endocrine manifestations [7, 25]. Mass effects are common features of functional and nonfunctional macroadenomas and may present as headaches, visual field defects from compression of the optic chiasm and cranial nerves, and hormonal deficiency due to the suppression of functional cells. [2] The endocrine effects may present as hormonal excess from functional tumors or hormonal deficiency from the mass effect of the tumor and suppression of functional cells. Asymptomatic presentation is, however, known to be very common in patients with the diagnosis made as incidental findings on routine MRI scans. Pituitary apoplexy, a rare endocrine emergency from sudden hemorrhage or infarction of an existing pituitary adenoma, may also occur. The condition presents as a life-threatening emergency with sudden and severe

headaches, vision loss, and acute hormonal deficiencies from the suppression of functional cells. [15]

In this case report, the clinical presentations seen may be explained by the functional status and mass effects of the macroadenoma. Headaches and visual field defects are common, as reported in this patient. While the tumor size is known to correlate with visual impairment, it does not correlate with the presentation of headaches. About 40% - 60% of patients are known to present with visual field defects, with bitemporal hemianopsia being the most common presentation, while bitemporal quadrantanopia may also occur. With tumor growth, a suprasellar extension may compress the optic chiasm and present with visual field defects or stretch the dural sheath and present with headaches. [1][17] The lateral extension of the tumor into the cavernous sinus may also occur, with compression of the internal carotid artery, as reported in this patient, or compression of the oculomotor, trochlear, and trigeminal nerves, which may present as diplopia. [1, 18, 19]

The patient was evaluated as a case of a prolactin-producing pituitary macroadenoma with hormonal deficiencies presenting with secondary hypothyroidism, secondary hypogonadism, secondary hypocortisolism, and neurogenic diabetes insipidus. Hyperplasia of prolactin-secreting acidophils led to prolactinoma and hyperprolactinemia observed in the patient. However, the transport of dopamine down the portal vessels to the anterior pituitary may be disrupted by the compressive effects of the tumor on the pituitary stalk. The loss of the inhibitory effect of dopamine on prolactin synthesis from the stalk effect thus contributed to the hyperprolactinemia seen in the patient. [19][20][28]

In patients with pituitary macroadenomas, hypopituitarism may result from mass effects and suppression of functional cells of the anterior pituitary and present with hormonal deficiencies, observed in this patient.[1][21][22] Deficiency of posterior pituitary hormones may also occur in the setting of compression of the pituitary stalk, neurodegeneration of axons, and disruption of axoplasmic transport. [22] These mechanisms explain the impaired hormonal profile and the low levels of serum FSH, LH, TSH, and ADH seen in the patient. [9][23][24] Elevated serum prolactin levels are also known to exert negative feedback on the thyroid axis physiologically, decreasing thyrotropin-releasing hormone (TRH) synthesis and secretion. This mechanism would contribute to hypothyroidism by decreasing the synthesis and secretion of thyroid-stimulating hormone (TSH) from thyrotrophic cells of the anterior pituitary and thyroid hormones (free T4) from the follicular cells of the thyroid gland. In addition to the mass effects of the macroadenoma and suppression of thyrotrophic cells in the anterior pituitary, the negative feedback of elevated serum prolactin levels on the thyroid axis contributes to the presentation of hypothyroidism (low TSH and T4), fatigue, and weight gain seen in the patient. [16, 26, 27, 28] Other manifestations of hypothyroidism that may be seen include cold intolerance, constipation, and bradycardia.

The low serum luteinizing hormone (LH), low follicle-stimulating hormone (FSH), and secondary hypogonadism seen in the patient can also be explained by multiple mechanisms. The inhibitory effect of elevated serum prolactin on the synthesis and pulsatile release of gonadotrophin-releasing hormone downregulates the hypothalamic-pituitary-ovarian axis. [17][18][19][20][21]

In addition, the mass effects of the macroadenoma may cause suppression of gonadotrophic cells of the anterior pituitary, contributing to the secondary hypogonadism seen in the patient. The classical manifestations of hypogonadism in women include inhibition of follicular development and ovulation from decreased FSH and LH, infertility, amenorrhea, and galactorrhea. In men, common clinical findings include reduced libido, erectile dysfunction, and infertility. Gynecomastia, bone pains, osteopenia, and osteoporosis are additional presentations of hypogonadism that may be seen in both sexes. [23] Suppression of functional corticotropic cells of the anterior pituitary by the tumor presents with secondary hypocortisolism (ACTH and cortisol deficiency) seen in this patient. Expected clinical manifestations include fatigue, dizziness, nausea, vomiting, abdominal pain, arthralgia, low-stress tolerance, low blood pressure, and weight loss, some of which were seen in the patient. The deficiency of growth hormone (GH) may also occur from similar mechanisms and present with fatigue, increased adiposity, and weight gain. [17][18][19][20]

In patients with pituitary adenomas, neurogenic diabetes insipidus rarely occurs as a coexisting presentation. In literature, it has, however, been widely reported as a complication following endoscopic transsphenoidal resection for a pituitary adenoma, with metastatic disease of the pituitary gland, or following steroid treatment for pituitary apoplexy. [21][22][23] In the absence of these associations, neurogenic diabetes insipidus seen in this patient most likely occurred with the growth of the pituitary macroadenoma, its stalk effect, neurodegeneration of axons of the magnocellular neurons descending from the supraoptic and paraventricular hypothalamic nuclei to the posterior pituitary and disruption of axoplasmic transport. [23][24] This mechanism explains the possible coexistence of neurogenic diabetes insipidus as a clinical manifestation of pituitary macroadenoma. The presentation is characterized by polyuria, nocturia, dehydration, thirst, and polydipsia in the presence of euglycemia and may be complicated by seizures. Psychiatric manifestations like depression, anxiety, apathy, emotional instability, and irritability may also be observed. [17][23]

The diagnosis of pituitary adenomas is usually made from clinical presentations, investigations, and imaging to rule out possible differentials and confirm the diagnosis. Generally, MRI scans are considered the imaging modality of choice for pituitary pathologies because of their multiplanar capability and soft tissue penetrance. [11][25][26] Treatment generally includes medical and surgical therapy. Dopamine agonists, somatostatin analogs, and growth hormone receptor antagonists are medications available for tumor shrinkage. [25] However, surgical decompression is especially preferred and should be considered in patients with compressive mass effects presenting with neurological deficits or visual field defects, in resistant cases, or when patients are intolerant of medications. The definitive treatment for pituitary adenomas is endoscopic trans-sphenoidal adenomectomy. The procedure is known to be potentially curative for microadenomas and smaller macroadenomas. [25][26] Radiotherapy and proton therapy

are additional treatment options to be considered when medical and surgical options become ineffective. [25][27] Replacement of hormonal deficiencies may also be necessary for patients. The prognosis depends on tumor size, the functional status of patients, and the presence of comorbidities. While the rate of growth of macroadenomas occurs at 12.5 per 100 patient-years (95% CI 7.9-17.2), microadenomas are known to grow at a lower rate of 3.3 per 100 patient-years (95% CI 2.1-4.5). [8][28][29]

CONCLUSION

Pituitary adenomas are common benign tumors in the general population. Although their prevalence has been rising in recent years, a pituitary macroadenoma presenting with hypopituitarism, hormonal deficiencies, and neurogenic diabetes insipidus, as reported in this case, remains uncommon. In literature, the association of neurogenic diabetes insipidus highlighted in this patient has been mostly documented as a complication following surgical treatment for pituitary tumors, steroid treatment for pituitary apoplexy, or metastatic disease of the pituitary gland. Thus, it is essential to recognize it as a possible presentation in patients with pituitary macroadenomas. This presentation also illustrates the importance of carefully evaluating hormonal deficiencies in patients with pituitary macroadenomas. In this case, we believe the presentation of neurogenic diabetes insipidus occurred from the stalk effect of the macroadenoma compressing the axons descending from hypothalamic nuclei to the posterior pituitary. Although surgical evaluation and histopathological assessment were unavailable when writing this report, this patient's clinical manifestations and investigation findings were consistent with the diagnosis of prolactin-producing macroadenoma with hypopituitarism, hormonal deficiency, and neurogenic diabetes insipidus.

DISCLAIMER

There is no conflict of interest between the authors, facilities, and the government. The aim of this research activity is to contribute to medical knowledge for academic purposes and to improve patient's clinical outcomes and quality of life. The authors funded the work alone and received no external financial support.

CONSENT AND ETHICAL APPROVAL

The Ministry of Health and Wellness, Saint Vincent the Grenadines, approved the research—consent form signed by the patient, witness, and physicians.

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