Nonsurgical Management of a Patient with Hypopituitarism Secondary to Nonfunctioning Pituitary Macroadenoma: A Case Report

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Abstract

Pituitary adenoma is a benign neoplasm of pituitary gland. Pituitary adenoma, particularly a macroadenoma, may produce mass effect symptoms by compressing surrounding tissues. Due to pituitary function as a neuroendocrine organ, pituitary adenoma may also cause multiple endocrine disturbances. The authors report the case of a 39-year-old male patient presenting with chronic headache and history of seizure. MRI imaging revealed pituitary macroadenoma with optic chiasm compression. Further diagnostic workup indicated secondary hypogonadism and adrenal insufficiency. The patient was given hormone replacement therapy and was then advised for surgery, but the patient refused any surgical procedure. Subsequent follow-ups were somewhat difficult due to poor patient adherence. Nevertheless, appropriate management of pituitary adenoma is needed to achieve optimal result.

Keywords: *pituitary adenoma, macroadenoma, clinically nonfunctioning, hypopituitarism*

Introduction

Pituitary adenoma is a group of benign neoplasms arising from pituitary gland, comprising of 10-20% of all intracranial tumors [(1)] and more than 90% of intrasellar tumors [(2)]. Prevalence of pituitary adenoma is reportedly to be around 80-100 cases per 100.000 [(3)], but many studies found the actual number might be far greater, because many are asymptomatic and could only be detected from incidental findings on imaging or autopsy [(4)]. Based on its size, pituitary adenoma can be classified into macroadenoma (≥10 mm) and microadenoma (<10 mm). Pituitary adenoma can also be categorized based on its hormonal activity as functioning or nonfunctioning. This differentiation is important because they have different management approach. We reported a case of a male patient, aged 39, with partial hypopituitarism secondary to clinically nonfunctioning macroadenoma.

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Case Report

A 39-year-old male was referred from a rural general hospital to our outpatient clinic with a complaint of 1 year of worsening headache. He described the headache as continuous heavy sensation in the head bilaterally. The headache had varying frequency and duration in a nonspecific fashion and only partially responded to analgesics. The patient also had a history of a seizure in previous week which lasted only a few minutes and he fell unconscious during the seizure. It only happened

once and there was no previous history of seizure before nor thereafter.

Head MRI scan (Figure 1) revealed a solid intrasellar lesion with regular clear boundaries, isointense on T1 and T2 with rim contrast enhancement, with approximately 19x22x29 mm in size, which extended into suprasellar region and abutted the optic chiasm, compressing the latter to anterior and superior, which was suggestive of a pituitary adenoma. No other structural abnormalities were found.

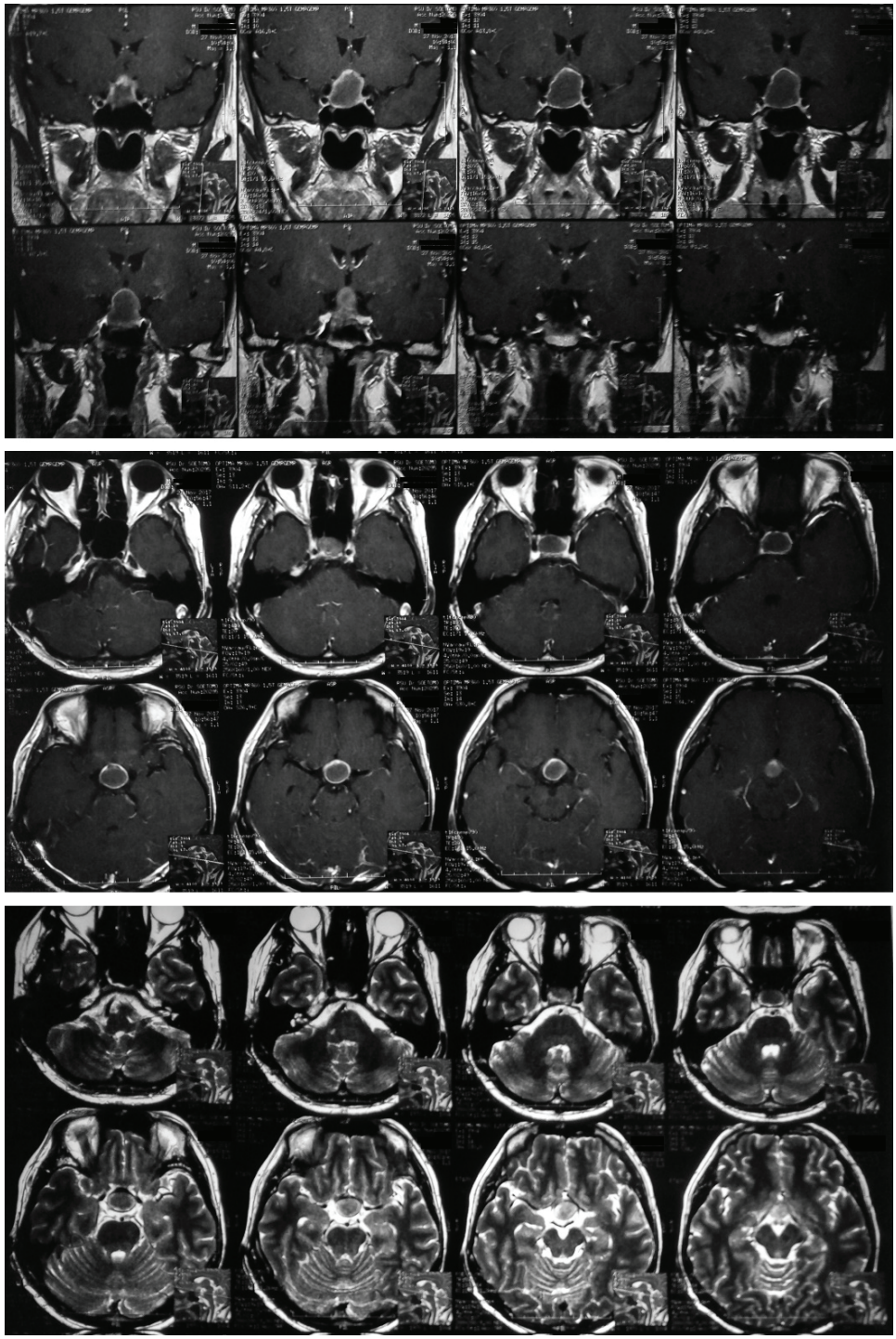

Figure 1. Contrast MRI of the brain on various planes and sequences. (*top*) T1-weighted coronal. (*middle*) T1-weighted axial. (*bottom*) T2-weighted axial.

Hormonal panel evaluation results were as follows: serum morning cortisol 0.8 mcg/dL (N: 4.3-22.4 mcg/dL), ACTH 28 pg/mL (N: 20-52 pg/mL), LH 0.12 mIU/mL (N: 1.5-9.3 mIU/mL), FSH 0.66 mIU/mL (N: 1.4-18.1 mIU/mL), testosterone 5.17 ng/dL (N: 241-827 ng/dL), prolactine 3.01 ng/mL (N: 2.1-17.7 ng/mL), TSH 1.62 mIU/mL (N: 0.55-4.78 mIU/mL), and FT4 0.94 ng/dL (N: 0.89-1.76 ng/dL). Other basic laboratory tests including complete blood count, serum electrolytes and glucose levels were within normal limit.

Further history taking and physical examination revealed diminished secondary male sexual characteristics and decreased libido within the past 6 months, although the patient was at first did not realizethat his condition was interrelated. The patient was already married for 15 years and had 2 children from his marriage, aged 10 and 7 years old. Although the patient did not feel any visual disturbance that he might be aware of, the patient was referred to ophthalmology departement for evaluation and was subsequently assessed with bitemporal hemianopia.

Based on the examination results, the patient was diagnosed with nonfunctioning pituitary macroadenoma with secondary hypopituitarism, manifesting as secondary hypogonadism and adrenal insufficiency. The patient was referred to neurosurgery department for further management. He was advised for surgery, but unfortunately he refused, asking for more time to discuss it with his family.

The patient was then given hormone replacement therapy to correct hormonal deficiency caused by hypopituitarism. Before initiating testosterone replacement, serum PSA level was 0.02 ng/dL and hematocrit was 45%. The patient was subsequently given 250 mg of testosterone injection (a mixture of 30 mg testosterone propionate, 60 mg testosterone phenylpropionate, 60 mg testosterone isocaproate, and 100 mg testosterone decanoate) intramuscularly every 4 weeks. For glucocorticoid substitution, the patient was given methylprednisolone 4 mg orally in the morning once daily. On subsequent laboratory evaluations, serum PSA levels and hematocrit were always within normal limit, while serum testosterone levels were fluctuating, ranging from 82.45 to 277.75 ng/dL. One major problem concerning the patient's treatment was poor adherence. The patient was unable to attend our clinic regularly because he lived in rural area very far away from the city, making optimal treatment and follow-ups somewhat difficult.

Discussion

Diagnostic workup for pituitary macroadenoma involves imaging modalities of sellar region, assessment of pituitary hormones function, and optic pathway evaluation. CT and MRI of the sellar region are the preferred imaging modality in detecting pituitary adenoma, with the latter is considered to be more sensitive [4].

Clinical symptoms and signs in patients with pituitary adenoma can generally be classified into mass effect-related symptoms and endocrine abnormalities arising from hormonal overproduction leading to hyperpituitarism. Males were more associated with neurological symptoms such as visual disturbances and seizures, while females were more likely to present with symptoms related to sexual function disturbances such as menstrual disturbances, galactorrhea, infertility, and hirsutism [5]. Still, many do not exhibit symptoms and discovered by chance (incidentaloma).

Based on its hormonal activity, a pituitary adenoma can be classified into functioning and nonfunctioning. Among the functioning pituitary adenomas, prolactin-producing tumor (prolactinoma) is the most frequent type [4,6]. Other functioning pituitary adenomas producing GH, ACTH, TSH, or LH are also reported in studies but they are less common.

Clinically nonfunctioning pituitary adenoma (NFPA) is defined as pituitary adenoma which is not hormonically active, that is, not associated with clinical syndromes caused by overproduction of any pituitary gland hormones [7]. Most pituitary adenomas are clinically nonfunctioning [8]; approximately 50%

of microadenomas and 80% of macroadenomas belong to this group [2]. NFPA could be categorized further based on transcription factor expression and immunohistochemistry (IHC) staining into silent pituitary adenoma (at least one positive transcription factor expression or IHC staining) and null-cell adenoma (negative transcription factor expression and IHC staining) [1].

Clinically nonfunctioning pituitary microadenomas usually do not cause signs or symptoms, while the main complaints in clinically nonfunctioning macroadenomas are largely related to mass effects including headache, visual field defects, and hypopituitarism. Approximately 40-60% of patients have headache as one of their main symptoms which might be caused by increased intracranial pressure or dura mater stretch. Visual field defect is present in 58% of macroadenoma cases, which has typical bitemporal pattern [9].

Hypopituitarism may occur due to pituitary stalk compression (and thus inhibits signals from hypothalamus) and also compression of the surrounding healthy pituitary tissue by the growing mass [2]. In 60-85% patients with nonfunctioning pituitary macroadenoma, at least one pituitary hormone deficiency is present, while panhypopituitarism is less frequent. Among these hormones, gonadotropin deficiency is the most common and accounts for more than 80% of cases, followed by somatotropin deficiency in 70% of cases; while thyrotropin and corticotropin deficiency present in 20-50% of cases [10]. Different literatures report somatotropin deficiency as the most common, followed by gonadotropin, corticotropin, and thyrotropin deficiency [9,11].

In our case, a tumor size of ≥10 mm on imaging leads the diagnosis of a macroadenoma, which was accompanied by optic chiasm compression. This explains mass effect symptoms in our patient, including headache, seizure, and visual field defect. A very low serum morning cortisol accompanied by a low-normal level of ACTH is indicative of secondary adrenal insufficiency. Low level of serum testosterone combined with low levels of both FSH and LH suggests secondary hypogonadism.

Management of pituitary adenoma generally consists of several main strategies: surgery, radiotherapy, and medical treatment (using dopamine agonists and somatostatin analogs). Existing hypopituitarism should also be managed accordingly by administering hormone replacement therapy.

The first line and the most effective treatment for clinically NFPA is surgery, particularly in symptomatic macroadenoma. Without surgery, 50% will progress within the next 5 years, while only 10% might regress spontaneously [2]. Surgery is indicated if there is optic chiasm compression or visual field defects which ensue from the compression. In these cases, visual function preservation or recovery should be the main goal of treatment. Approximately 78% of patients are reported to have improvement in visual field after surgery. However, only 30% of patients undergoing surgery obtain improvement in pituitary functions [7]. These possible outcomes should be carefully discussed with the patient before surgery along with other surgical risks. Other mass effects such as headache could also be a consideration for surgery, although in a more individual approach. In NFPA without optic chiasm compression, the decision regarding surgical treatment should be tailored individually [2].

Regarding surgical method, transsphenoidal approach is preferred because it has lower complications rate and perioperative mortality risk compared to transcranial approach. Some complications that might occur after surgery (less than 5% of cases) include new visual disturbance, cerebrospinal fluid leakage, fistula, meningitis, and diabetes insipidus [7]. Newer endoscopic resection method has comparable efficacy and safety [12]. While combination of surgery and radiotherapy is reported to have lower risk of tumor recurrences than surgery alone [7], it must be noted that radiotherapy is not recommended in all cases, but may be considered when there is large residual tumor postoperatively or tumor recurrence.

Medical treatment using dopamine agonists and somatostatin analogs are considered to be adjunct therapy in functioning pituitary adenoma [6]. However, the effectiveness of these medications in the treatment for NFPA has not been proven [3,13]. Therefore, currently there is no recommendation for using these drugs in NFPA.

Hypopituitarism due to pituitary adenoma might be permanent despite tumor removal; therefore, the patient may require hormone replacement for a lifetime. Complete assessment of pituitary function is needed to detect hypopituitarism in one or more axis, although panhypopituitarism is less frequent. Management of hypopituitarism should be done on an individual basis. In our case, the patient develops secondary adrenal insufficiency and hypogonadism.

For glucocorticoid substitution, hydrocortisone use is recommended, with daily dose of 15-25 mg in single or divided doses. In our patient, we used methylprednisolone in its equivalent doses because oral hydrocortisone was not available in our center. It should be noted that there is no universal consensus on appropriate treatment for glucocorticoid replacement. There is also no objective monitoring parameter available. Doses should be adjusted based on clinical grounds, which can be increased 2-3 times the usual dose during mild illness or surgery and 10 times in major illness or surgery for a short time [14]. Overcorrection for prolonged period should be avoided to prevent undesirable adverse effects.

Secondary hypogonadism in males can be treated either with testosterone or gonadotropin formulations. Gonadotropin administration is preferred if fertility is desired [14]. Our patient already had 2 children from his marriage and did not have a plan to have another child; therefore, fertility is not an issue. The patient was then given intramuscular testosterone injection as replacement therapy which should have been administered every 3-4 weeks but unfortunately our patient only managed to visit our clinic every 2-3 months. Nevertheless, this formulation was chosen because it was the most readily available in our center and more convenient for the patient considering patient's poor adherence.

Serum PSA and hematocrit level must be monitored during testosterone replacement treatment. An increase > 1.4 ng/mL of serum PSA from baseline within the first 12 months of treatment or a level >4 ng/mL is an indication for further urologic evaluation. Testosterone treatment should be stopped if hematocrit level is >54% until it decreases to a safe level and then might be reinitiated in a reduced dose. Serum testosterone level should be maintained in mid-normal range (400-700 ng/dL) during treatment and evaluation should be made midway between injections [15,16]. In our patient, baseline serum PSA and hematocrit levels were normal and there was no significant increase throughout therapy. However, achieving treatment goal was challenging since his serum testosterone never reached recommended level due to suboptimal treatment which was influenced by social and economic difficulties.

Conclusion

Patient with pituitary adenoma should be evaluated for mass effects related symptoms and complete pituitary axis function in order to give appropriate treatment. Management of pituitary adenoma should be made on individual basis. For symptomatic clinically nonfunctioning macroadenoma, surgery is the first line treatment. Based on data from previous studies, visual disturbance will improve in almost 80%, while pituitary function will improve in only 30% of cases after surgery. Patients with hypopituitarism may need continuous long term hormonal replacement to maintain physiological function. This case is reported to highlight the importance of appropriate workup and management of a clinically nonfunctioning macroadenoma.

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Ethical Clearance: All procedures were in accordance with the ethical standards of the Ethics Committee of Dr. Soetomo General Hospital, Surabaya, Indonesia. Written consent was obtained from patient

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