



Case Report

Case Report: Secondary Amenorrhea with Hyperprolactinemia due to Pituitary Macroadenoma

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ABSTRACT

Introduction: Secondary amenorrhea has a broad etiology, so each case must be studied in depth. One of the causes of secondary amenorrhea is a state of hyperprolactinemia caused by a mass in the anterior pituitary. Pituitary macroadenoma patients may be asymptomatic or have a hormone imbalance or mass impact symptoms. Tumors in asymptomatic patients might be identified during a routine head imaging examination for unrelated medical issues.

Case Presentation: A 24-year-old unmarried woman with complaints of headache, blurred vision, and worsening for one year ago. The patient complained of not having menstruation in the past five years ago, with a history of previous normal menstruation. On physical examination, found breast and pubic Tanner stage 5. On laboratory examination, it was found FSH (2.21), Oestradiol (20.23), and Prolactin (1365.47). On an MRI of the head examination on April 14, 2021, a solid intrasellar mass of suspected pituitary macroadenoma was found with a size of \pm 1.3 cm x 1.4 cm x 1.6 cm.

Conclusion: Secondary amenorrhea caused by hyperprolactinemia due to pituitary macroadenoma is a rare case (40%). First-line therapy for prolactinomas is dopamine agonist administration because most pituitary macroadenomas respond to dopamine agonists.

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INTRODUCTION

Amenorrhea is a condition where a woman does not experience menstruation at the time of menstruation as it should or is called not menstruating during the menstrual period. Two types of amenorrhea classification are primary amenorrhea and secondary amenorrhea. Primary amenorrhea is when a person has never had a menstrual period and is 16 years old or older with signs of secondary sex; or 14 years if there is no sign of secondary sex. Secondary amenorrhea is when a person experiences menstruation or a regular menstrual cycle but then does not have menstruation for three months or more in a row [1,2].

Amenorrhea can result from inherited disease or dysfunction at any level in the system and can involve more than one mechanism. For example, polycystic ovary syndrome (PCOS) involves several interrelated pathophysiological mechanisms at various levels, including the ovary, pituitary, and hypothalamus [1].

Secondary amenorrhea is caused by the following, the use of oral or injectable contraceptive drugs such as birth control pills or *Depo-Provera*; stress due to the use of certain types of medicines; consequences of low body weight from the presence of thyroid disorders; regular weight training such as long-distance running, especially if low body fat; and the presence of abnormalities of the egg (ovarian) such as due to chemotherapy or the

appearance of ovarian cysts. In addition, deviations from the normal anatomy of the female reproductive organs can also cause amenorrhea.

Pituitary tumors can disrupt hormone balance by causing increased production of pituitary hormones. Pituitary tumor lesions can affect the surrounding normal tissue, reducing pituitary gland function, known as hypopituitarism. Pituitary macroadenomas are benign epithelial neoplasms consisting of anterior pituitary cells. Primary pituitary malignancies are sporadic. Evidence shows that pituitary adenomas develop in stages and an irreversible initiation phase followed by tumor propagation. The growth of pituitary tumors is a monoclonal process with multiple factors involved. Heredity, hormonal effects, and genetic mutations are among the causes. Most pituitary tumors are monoclonal, indicating that they derive from mutated pituitary cells. However, the precise pathophysiological mechanisms/molecular components causing pituitary adenomas remain unclear. The importance of mutational genetics was shown in a study that found individuals with pituitary tumors from four families in Ireland had the same mutations as patients from the 18th century who had mediated gigantism by pituitary tumors. Several pituitary tumors can develop as a result of the clinical condition. Pituitary adenomas (most common prolactinomas) are related to parathyroid tumors and islets Langerhans in multiple endocrine neoplasia type 1 (MEN 1), an autosomal dominant genetic condition. McCune-Albright syndrome is distinguished by skin lesions, polyostotic fibrous dysplasia, and hyperfunction endocrinopathy. The syndrome results from somatic activator mutations of the alpha subunit of the Gs protein, which impacts tissue responses to adenylate cyclase-mediated hormonal signaling. The most prevalent pituitary tumor in McCune-Albright syndrome is somatotropinoma, which causes acromegaly. The identical mutation is seen in several large somatotropinomas in cases of sporadic acromegaly. Carney Complex is an autosomal dominant disorder that is distinguished by pigmented skin lesions (lentigines, blue nevus), primary pigmented nodular adrenal disease, acromegaly, Sertoli cell tumors, melanocytic schwannoma, and cardiac myxoma [3,4].

Prolactinomas are a common type of pituitary tumor. Systematic post-mortem autopsy studies show that small pituitary tumor affects around a quarter of the population in the United States. Around 40% of these pituitary tumors release prolactin; however, most are not clinically significant since they cause no symptoms or issues. Pituitary tumors significantly impact the health of around 14 persons out of every 100,000 [5]. The causes of primary amenorrhea in prolactinomas include disturbances in the hypothalamus, which

interacts with the pituitary gland, which functions to regulate the menstrual cycle; the presence of diseases of the pituitary can affect the function of the pituitary gland in regulating the menstrual cycle; abnormal chromosomes and the presence of obstruction or blockage in the vagina, such as the presence of a membrane that blocks the menstrual pathway.

Although research into the mechanism of abnormal cell development is underway, the origin of many pituitary tumors, including prolactinomas, is unclear. Most pituitary tumors occur sporadically, meaning the family does not inherit them. Prolactinoma is a defining feature of MEN1. A few families appear prone to prolactinomas but do not appear to have MEN1. The gene that causes prolactinoma has not yet been entirely identified [5].

In most cases, the absence of clinical indications of hormonal hypersecretion causes a substantial delay in diagnosis. As a result, pituitary adenomas are frequently identified when they are massive enough to substantially affect surrounding tissues, resulting in symptoms such as headache, vision disturbances, and cranial nerve impairment. Other infrequent signs include hyperprolactinemia caused by pituitary stalk deviation and pituitary apoplexy. Unintentional imaging scans can diagnose some incidences for other reasons known as pituitary incidentalomas [5,6].

Pituitary gland enlargement can also induce local symptoms such as headaches associated with increasing pressure when the cerebrospinal fluid system is obstructed or vision disturbances due to the pituitary gland's proximity to the optic nerve [5,6].

Patients with pituitary macroadenoma may be asymptomatic or have hormone balance disorders or mass effect complaints. Tumors in asymptomatic patients may be discovered during a routine head imaging examination for unrelated medical issues. Magnetic resonance imaging (MRI) and computed tomography (CT) scans have increased the frequency of diagnosis of pituitary tumors. The effects of pituitary hormones depend on the hormones involved. Panhypopituitarism can occur when all of the pituitary hormones are deficient. Larger tumors make it more likely to affect most hormones. The anterior pituitary cells are less vulnerable to mass stimulation. Somatotrophs and gonadotrophs are the most susceptible, but corticotropes and thyrotropes are more resistant. A distinct clinical sign, mainly due to the tumor's hormonal activity, is hyperprolactinemia which occurs with amenorrhea, infertility, hypogonadism, and galactorrhoea. Hyperprolactinemia can be caused by elevated hormone secretion by prolactinomas, or it might be caused by stalk compression by macroadenomas from hormonal activity. It is a very common sequel to pituitary macroadenoma [2,3,7].

The most prevalent neuro-ophthalmologic symptoms are visual abnormalities produced by suprasellar growth of the adenoma compressing the optic chiasm. The degree and location of nerve compression determine the type of visual defect. Diplopia may occur due to nerve compression induced by parasellar extension of the adenoma in the oculomotor nerve, and the fourth, fifth, and sixth cranial nerves may also be implicated. However, the most common visual field impairment associated with pituitary tumors is bitemporal hemianopia, which occurs in around 40% of patients [5,6,8].

Pituitary tumors or pituitary adenomas are relatively common neoplasms, accounting for 10-20% of all intracranial tumors. In general, pituitary tumors are benign and cause symptoms, clinical consequences, mass effect, and hormonal secretory activity, which are the main indications for surgery. Pituitary tumors are found incidentally in approximately 10% of patients who undergo radio-imaging brain imaging for other indications. This tumor is also the second most common tumor according to histopathology in patients aged 20-35 years according to the Central Brain Tumor Registry of the United States (CBTRUS) [9].

CASE PRESENTATION

A 24-year-old unmarried woman with complaints of headache, blurred vision, and worsening since one year ago. The patient complained of not having menstruation in the last five years (when she was 19), with a history of regular menstruation. History of menarche at the age of 13 years with a duration of 4 days, regular, 30-day cycle, changing pads 2x/day, no pain during menstruation. The patient had no history of pregnancy or breastfeeding. There was no change in eating habits and physical activity or exercise. There was no change in body weight, history of trauma or fracture, drug use, and history of other chronic diseases. There is a history of headaches, especially in the back of the head, in the past six months ago, but no visual disturbances. There is no family history of cancer.

Investigation

On examination, the general condition was good with compos mentis consciousness. Tanner breast and pubic hair stage 5. Galactorrhoea was not found. Laboratory examination found FSH (2.21), estradiol (20.23), and prolactin (1365.47). On MRI examination of the head, it was found that there was a suspicion of a dense intracellular mass of pituitary macroadenoma measuring $\pm 1.3 \text{ cm} \times 1.4 \text{ cm} \times 1.6 \text{ cm}$. Perimetry and fundoscopic examination by right and left ophthalmologists did not reveal any abnormalities.

Treatment

The patient was given dopamine agonist oral therapy bromocriptine once a day with a 2.5 mg dose. The patient planned a 6-month MRI evaluation with monthly monitoring of clinical status and prolactin levels.

Outcomes and Follow Up

The patient did a check-up every month, and the complaint of headache reduced since the first month of treatment with bromocriptine. The decrease in prolactin levels until the ninth month reached the level of prolactin treatment (92.1).

DISCUSSION

Amenorrhea patient history in the last five years (when she was 19). History of menarche at the age of 13 years with a duration of 4 days, regular, 30-day cycle, changing pads 2x/day, no pain during menstruation. The patient had no history of pregnancy or breastfeeding. There was no change in eating habits and physical activity or exercise. There was no change in body weight, history of trauma or fracture, drug use, and history of other chronic diseases. There is a history of headaches, especially in the back of the head, but no visual disturbances in the last six months. On physical examination, there was no abnormality of the thyroid gland. Physical examination refers to a disease based on the findings. Physical examination in amenorrhea can cause certain diseases. The patient also found elevated serum prolactin. Elevated serum prolactin can cause amenorrhea by inhibiting gonadotropins [1,2].

The mechanism of hyperprolactinemia that causes anovulation and amenorrhea is related to disruption or inhibition of the normal hypothalamic GnRH pulse rhythm that causes inadequate or even low levels of gonadotropin secretion. This affects the increase in circulating prolactin velocity and will stimulate an increase in hypothalamic dopaminergic neuron activity, which promotes prolactin secretion and inhibits GnRH neurons. Impaired GnRH pulsatility due to excess prolactin causes mild ovulatory dysfunction, anovulatory, or even severe hypogonadotropic hypogonadism, depending on the degree of suppression of gonadotropin secretion. Mild hyperprolactinemia (20-50 ng/mL) can only lead to a short luteal phase due to poor preovulatory follicular development. Moderate hyperprolactinemia (50-100 ng/mL) frequently results in oligomenorrhea or amenorrhea, but greater prolactin levels (>100 ng/mL) typically result in significant hypogonadism with low estrogen levels and clinical symptoms such as genitourinary atrophy and loss of bone mass [1].

Cabergoline is a selective dopamine receptor type 2

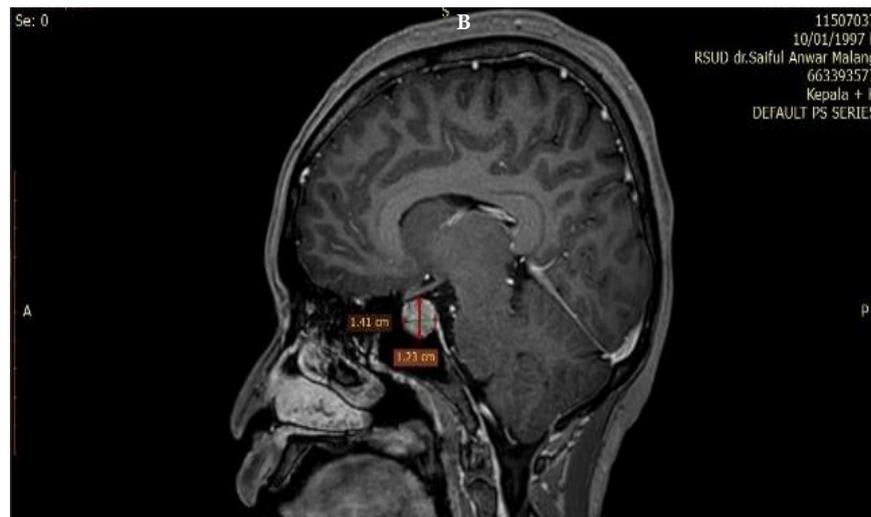


Fig. 1. Head MRI T1 sagittal view. A solid intrasellar mass of suspected pituitary macroadenoma was found

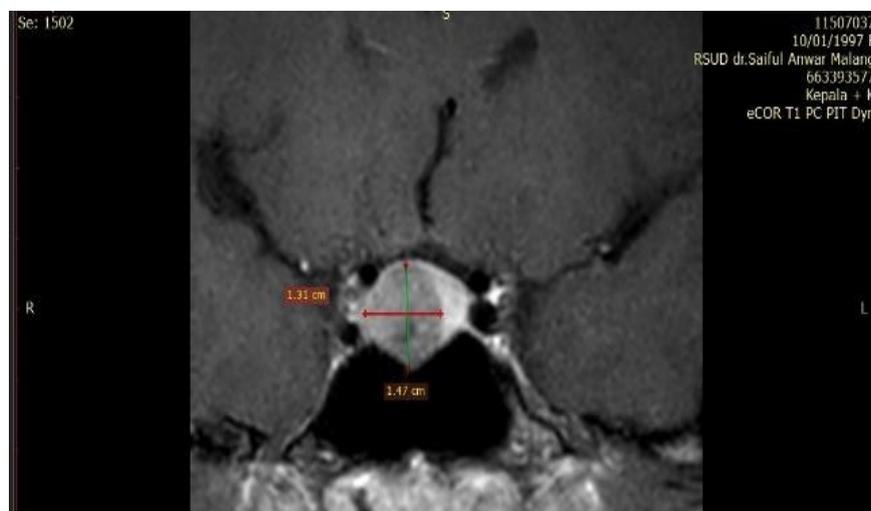


Fig. 2. Head MRI T1 coronal view

Minimal clinical symptoms, antipsychotic medication type, and prolactin level confound hyperprolactinemia's diagnosis and pathogenesis. The use of MRI aids in diagnosing pituitary microadenoma and the subsequent treatment of choice with bromocriptine. Pituitary MRI is recommended for individuals whose etiology of hyperprolactinemia is unknown due to therapy. Pituitary tumors can cause disorders by causing increased secretion of pituitary hormones. The lesions could disrupt the normal tissue around the pituitary gland, reducing its effectiveness (hypopituitarism) [10].

Dopamine agonists are the first-line therapy of choice for women with lactotroph-secreting functional prolactin adenomas of all sizes because they effectively lower prolactin levels and reduce tumor size by more than 90% [1].

agonist, which has a more negligible effect but greater potency and is also more effective than bromocriptine in restoring normal prolactin levels in women with lactotrophic adenomas. As a result, many consider it a better choice. However, even at relatively low doses, Cabergoline usage over an extended period may raise the risk of hypertrophic valvular heart disease, whereas bromocriptine does not. Therefore, some consider it a better and safer option for cabergoline for patients who are intolerant or resistant to bromocriptine. Treatment should be started at a low dose to minimize side effects (e.g., bromocriptine 1.25 mg at bedtime; cabergoline 0.25 mg twice weekly) and increased gradually, guided by evaluation of serial prolactin levels obtained at approximately monthly intervals. Dopamine agonists are the best initial treatment for women with prolactin-secreting macroadenomas and are the best but not the only treatment option for microadenomas. As in women

with unexplained hyperprolactinemia who have an adenoma, treatment can fit the patient's needs and goals.

reported that surgery, The Endoscopic Endonasal Transsphenoidal Approach (EETA), normalized

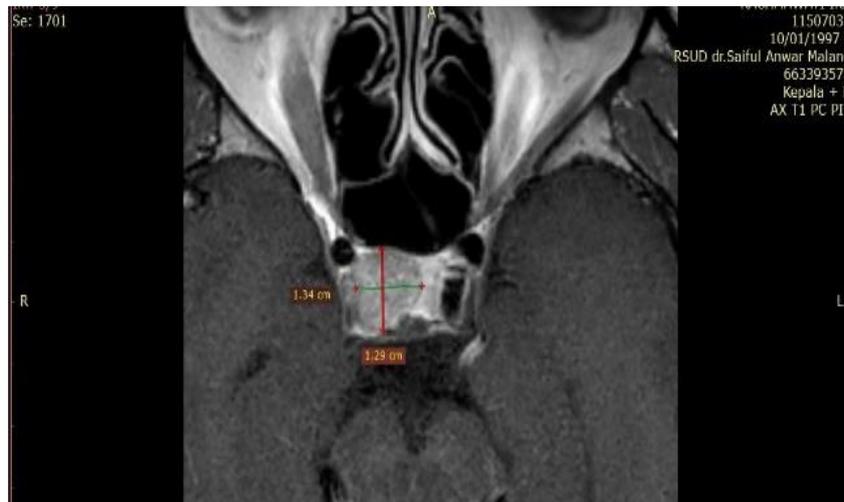


Fig. 3. Head MRI T1 axial view

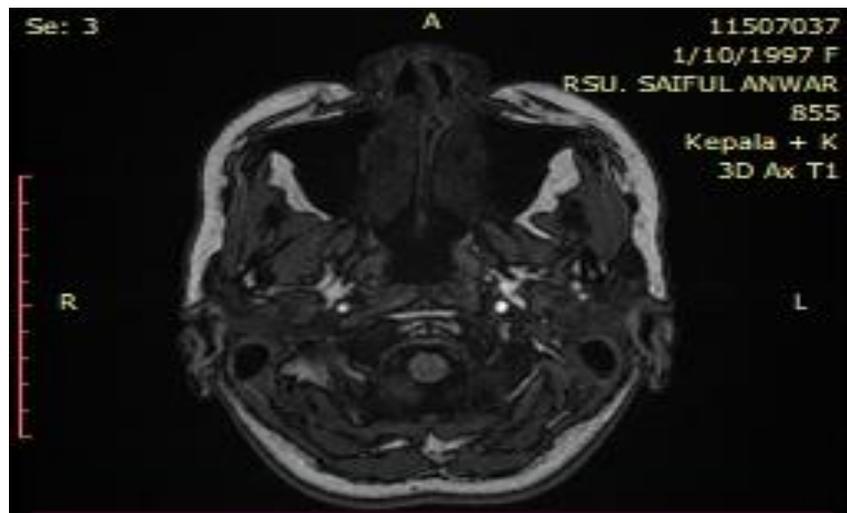


Fig. 4. The superior appearance of pituitary tumor

Therapy with dopamine agonists is better for ovulation induction and those with bothersome galactorrhea. According to the need for contraceptives, others may be treated with physiological cyclic estrogen/progestin therapy, or combined hormonal contraceptives are given orally or vaginally), and they have no risk of stimulating tumor growth. However, it is prudent to monitor the serum prolactin level approximately every six months and repeat the MRI 1-2 years after diagnosis to re-evaluate the adenoma size [1].

Traditional radiotherapy uses external beam radiation for complete surgery in inoperable cases or patients who refuse surgery. Disadvantages of this method include delayed onset of action and high incidence of panhypopituitarism [1,11]. A study of dopamine agonist-resistant prolactinoma patients

prolactin levels in 36% of patients not treated with dopamine agonists and 15% of patients treated with postoperative dopamine agonists. Improvement of clinical condition and decrease in total prolactin level 79.70% (before surgery 198.10 ng/mL, after measurement 40.20 ng/mL) in patients with pituitary macroadenoma with hyperprolactinemia after administration of Bromocriptine 2.5 mg daily for 14 days Hospitalization and EETA surgery [12].

A woman with prolactinoma should consult her doctor before planning a pregnancy so that she can be thoroughly assessed before conception. This assessment often includes an MRI scan to determine tumor size and an examination with visual field measures. The doctor will advise stopping Bromocriptine or Cabergoline when the patient becomes pregnant. Patients should consult

an endocrinologist immediately if symptoms develop, especially vision changes, headaches, vomiting, nausea, urination, excessive thirst, or lethargy. Medication with bromocriptine or cabergoline can be continued, and additional treatment may be required if symptoms develop due to tumor growth during pregnancy [1].

CONCLUSION

The cause of amenorrhea has many determinants. Amenorrhea diagnostic plot can be used, namely from secondary based on history, physical examination findings, and related examinations. Secondary amenorrhea patients with elevated serum prolactin levels are recommended to perform a head MRI to diagnose pituitary adenoma. Hormone-secreting macroadenomas are very sensitive to drug therapy; therefore, surgery and radiation are rarely used in treatment.

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CONFLICT OF INTEREST

The authors state that they have no conflicts of interest.

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