CASE REPORT

Pituitary Macroadenoma with Hypogonadism in 30-year-old Liver Cirrhosis Patient: A Case Report

Alexander Kam[1*], Dinda Aprilia[1], Eva Decroli[1], Syafril Syahbuddin[1]

1 Metabolic Endocrinology and Diabetes Division, Internal Medicine Department, Medical Faculty, Universitas Andalas, Padang, Indonesia/Dr. M. Djamil General Hospital

*Corresponding author:
Alexander Kam, MD.
Metabolic Endocrinology and Diabetes Division, Internal Medicine Department, Medical Faculty, Universitas Andalas, Padang, Indonesia/Dr. M. Djamil General Hospital, Padang, Indonesia

ABSTRACT

Pituitary macroadenomas can suppress pituitary hormone secretion, one of which is the gonadotropin hormone, causing hypogonadism. The condition of hypogonadism can increase the risk of non-alcoholic fatty liver disease (NAFLD), which can then become liver cirrhosis. A 30-year-old man came to the hospital with decreased consciousness and hematemesis melena. From physical examination, laboratory, and pituitary magnetic resonance imaging (MRI). The patient was diagnosed with pituitary macroadenoma, hypogonadotropic hypogonadism, primary hypothyroidism, acute adrenal insufficiency, and liver cirrhosis. The patient was given hydrocortisone therapy, correction of electrolyte levels, hypoglycemia protocol, levothyroxine 100 mg/day, and management of hematemesis melena. After that, Sustanon 250 mg was given every two weeks intramuscularly. The patient went home in good condition and was planned for neurosurgery consultation for transsphenoidal resection. After the injection of Sustanon, the patient experienced increased penile length and testicular volume. The condition of hypogonadism in patients with pituitary macroadenoma can be a risk factor for NAFLD, which can then progress to liver cirrhosis. NAFLD and liver cirrhosis also can cause hypogonadism in men by several mechanisms. The patient has been well-managed and experienced clinical improvement.

Keywords: pituitary macroadenoma, hypogonadism, liver cirrhosis, therapeutic intervention

INTRODUCTION

A pituitary adenoma is the most common type of pituitary tumor. Based on the size of the widest diameter, pituitary adenomas can be divided into microadenoma (<1 cm) and macroadenoma (>1 cm). Pituitary adenoma can be classified as non-functioning pituitary adenoma (NFPA) and functioning pituitary adenoma, based on their hormone-secreting capabilities. Both pituitary adenomas can suppress the secretion of pituitary hormones, one of which is the gonadotropin hormone, causing hypogonadism. In men, hypogonadism is a condition of testosterone deficiency.[1,2] Testosterone deficiency in men is associated with increased visceral adipose tissue (VAT) and insulin resistance, which are some of the factors that cause metabolic syndrome. VAT and insulin resistance are important in non-alcoholic fatty liver disease (NAFLD) pathogenesis. Chronic liver damage in NAFLD can lead to the progression of NAFLD to non-alcoholic steatohepatitis (NASH), advanced fibrosis, and liver cirrhosis.[3] One of the most common causes of liver cirrhosis is NAFLD. Therefore, this case is discussed to see the relationship between hypogonadism and possibly acromegaly that arises due to pituitary macroadenoma and the incidence of liver cirrhosis in this patient.[4]

CASE ILLUSTRATION

A 30-year-old man comes to the hospital with a decreased level of consciousness and hematemesis-melena. From the anamnesis, this patient complained of child-like voice, small penis size and, no axillary and pubic hair growth. The patient did not complain of chronic headaches and visual field disturbances. From the physical examination, he was somnolent, with blood pressure 100/75 mmHg, pulse 78 times/minute, respiratory rate 20 times/minute, temperature 37^0C, body weight 53 kg, height 166 cm, and body mass index (BMI) 19.23 kg/m^2. Other physical examination findings were pale conjunctiva, collateral veins, Schuffner grade 4 spleen, ascites, bilateral pretibial edema, penile length 1 cm, right testicular volume 3 cc, and left testicular volume 2 cc.

From laboratory examination, hemoglobin 4.4 gr/dl, hematocrit 16%, platelets 112,000 mm^3, random blood glucose 73 mg/dl, sodium 115 mmol/l, potassium 3.9 mmol/l, chloride 79 mmol/l, HbsAg (-), and antiHCV (-). On further laboratory tests, we found LH <0.09 mIU/ml (0.57 - 12.07 mIU/ml), FSH 0.14 mIU/ml (0.95 - 11.95 mIU/ml), testosterone <2.5 ng/ml (249 - 836 ng/ml), TSH 5.7 ·IU/ml (0.27 - 4.2 mIU/ml), free T4 6.94 pmol/L (12 - 22 pmol/l), ACTH 7.5 pg/ml (7.2 - 63.3 pg/ml), cortisol 7.5 ·g/dl (3.7 - 19.4 ug/dl), IGF-1 18 ng/ml (41 - 246 ng/ml), GH < 0.05 ng/ml (< 3 ng/ml), and prolactin 5.01 ng/ml (3.46 - 19.4 ng/ml). An abdominal ultrasound examination revealed liver cirrhosis, and esophagoduodenoscopy revealed grade I-II esophagol variceal with portal hypertension gastropathy. On pituitary MRI examination, it was found suggestive of a macroadenoma with size 17.04 x 17.07 x 13.26 mm^3.

The patient was diagnosed with pituitary macroadenoma, hypogonadotropic hypo-gonadism, primary hypothyroidism, acute adrenal insufficiency, and hepatic cirrhosis with hematemesis melena. The patient was given hydrocortisone therapy, correction of electrolyte levels, hypoglycemia protocol, levothyroxine 100 mg/day, and management of hematemesis melena. After that, Sustanon 250 mg every two weeks intramuscularly. The patient went home in good condition and was scheduled for another pituitary hormone examination and neurosurgery consultation for transsphenoidal resection. At the follow-up after six times of injection of Sustanon, he has experienced deepening voice and erection. In physical examination, it was found that the penis had increased in length to 5 cm, and the volume of the right and left testicles had increased to 4 cc and 3 cc, respectively. However, the patient still has not experienced axillary and pubic hair growth.

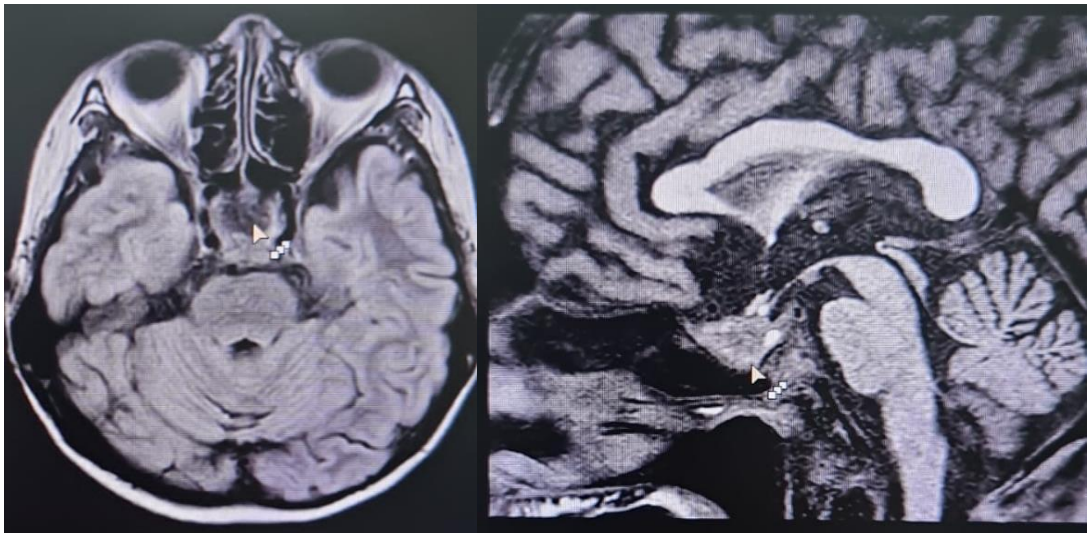

Figure 1. Pituitary MRI Result

Figure 2. Patient profile

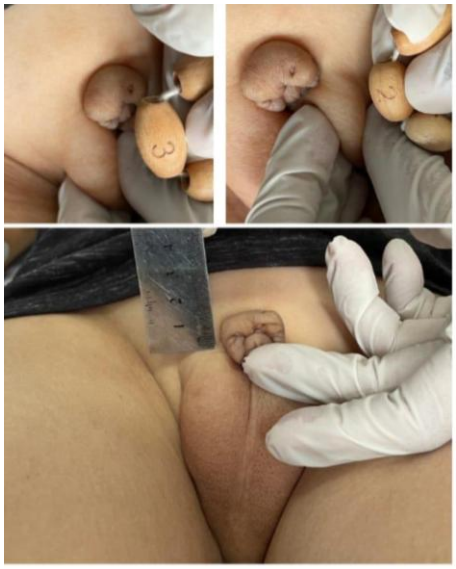

Figure 3. Genital examination before Sustanon therapy

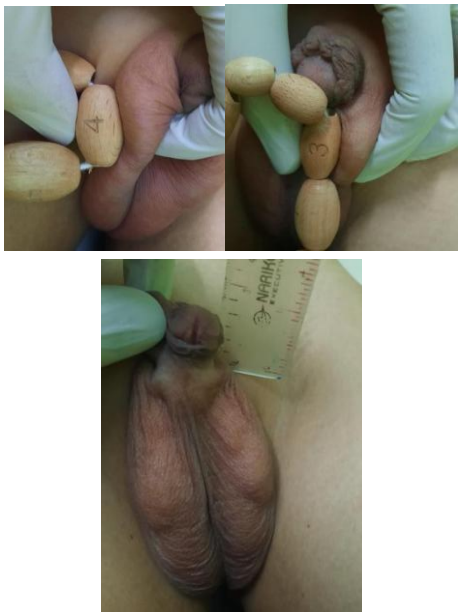

Figure 4. Genital examination after Sustanon therapy

DISCUSSION

A pituitary adenoma is the most common cause of pituitary tumors. The most common types of pituitary adenomas are prolactinoma and non-functioning pituitary adenoma (NPFA). NPFA is a tumour originating from adenohypophysis cells characterized by the absence of hypersecretion from these cells. In NPFA, there can be suppression of some pituitary cells, which will then cause a deficiency of one or several pituitary hormones. Thus, it is recommended for patients with NPFA and other pituitary tumours to check the pituitary hormone panel. Pituitary hormone deficiency can be asymptomatic, so by examining the pituitary hormone panel, disorders that can occur due to pituitary hormone deficiency can be managed earlier. In this patient, it is planned to examine IGF-1, ACTH, and prolactin to determine the condition of other pituitary hormones.[1,5]

Approximately 30% of NPFA patients are asymptomatic and diagnosed with NPFA based on incidental findings on MRI. Symptoms of headache and visual field disturbances are found in approximately 60% of NPFA patients. The incidence of NPFA with hypogonadism is about 60%. Hypogonadism and growth hormone (GH) deficiency are the most common hormonal abnormalities in NPFA.[1,5] Hwang et al. (2023) stated that several hormone deficiencies that result from NPFA are associated with NAFLD, which are GH, thyroid, and testosterone. Testosterone deficiency is associated with the occurrence of metabolic syndrome.[6] Testosterone deficiency in men is associated with increased visceral adipose tissue (VAT) and insulin resistance, which are some of the factors that cause metabolic syndrome. VAT and insulin resistance have an essential role in the pathogenesis of NAFLD. Several other studies support the relationship between testosterone deficiency and NAFLD. NAFLD is a chronic liver disorder that can then progress to liver cirrhosis.[3,6]

Liver cirrhosis is a condition of liver fibrosis with several causal factors. Some common factors that cause liver cirrhosis are hepatitis B and C infection and NAFLD. In this patient, markers of hepatitis were negative. The natural progression from acute infection to cirrhosis takes 20-30 years. Thus, liver cirrhosis in this patient is suspected to be caused by the metabolic syndrome experienced by the patient due to testosterone deficiency.[4] A liver biopsy examination is the gold standard to prove liver cirrhosis caused by NAFLD. However, this patient was not able to undergo the procedure because of the mortality risk due to this procedure.[7]

Several studies have also reported the effect of hepatic cirrhosis on hormonal disorders. Kim et al. (2017) reported that liver cirrhosis can cause hypogonadism in men with impaired LH pulsatility, blunted gonadotropic response, and downregulation of GnRH production due to increased proinflammatory cytokines. Estrogen in male patients with liver cirrhosis increases due to decreased estrogen clearance, increasing the estrogen/androgen ratio.[8]

In NAFLD conditions, several hypotheses emerge, such as the bidirectional relationship between metabolic syndrome and hypogonadism and the hypothesis of a low sex hormone binding globulin (SHBG) relationship in NAFLD, which is the cause of decreased testosterone levels. The SHBG theory is supported by Song and Choi (2022), who reported that sex hormone dysfunction has a role in the pathogenesis of NAFLD. SHBG is associated with low testosterone levels in men.[8,9]

In addition, Punekar et al. (2018) reported that liver cirrhosis can cause clinical hypothyroidism. The liver has an essential role in the peripheral conversion of T4 to T3 because type 1 deiodinase is a liver enzyme. The liver also plays a role in the synthesis of thyroid-binding globulin.[10] This patient also had acute adrenal insufficiency. Wentworth and Siragy (2022) reported that adrenal insufficiency is an underrecognized endocrine dysfunction in liver disorders. The circadian rhythm of cortisol is disrupted in liver cirrhosis, likewise with the metabolism of cortisol and the production of binding globulin. Another hypothesis linking adrenal insufficiency with liver cirrhosis is deficient intrinsic adrenal enzymatic activity and the suppressive effect of proinflammatory cytokines on the HPA axis.[11]

The pituitary macroadenoma in this patient was planned for transsphenoidal resection surgery. Two surgical techniques can be performed, which are transsphenoidal and transcranial. Transsphenoidal can be done through endoscopic and microscopic. Some research results state that transsphenoidal provides better results than transcranial.[5,12,13]

According to Penn (2017), indications for surgery for patients with NFPA are the presence of neurological disorders, vision, ophthalmoparesis, and obstructive hydrocephalus, asymptomatic tumors but threatening the occurrence of visual disturbances, signs of hypopituitarism, and acute pituitary apoplexy. This operation aims to decompress the optic nerve and chiasm and restore normal pituitary function.[12,13]

According to the guidelines of the Endocrine Society, it is recommended that male patients with hypogonadism receive testosterone to induce and maintain secondary sex characteristics and improve symptoms of testosterone deficiency. There are several preparations for administering testosterone, such as intramuscular, transdermal, pellets, and intranasal. Testosterone administration was continued and followed up in these patients despite tumor resection surgery.[14]

This patient was given an intramuscular injection of Sustanon 250 containing 30 mg of testosterone propionate, 60 mg of testosterone phenylpropionate, 60 mg of testosterone isocaproate, and 100 mg of testosterone decanoate every two weeks. After giving it six times, it has been found that the patient has experienced deepening voice, erections, and an increased in penile length and the testicular volume. However, the patient still has not experienced axillary and pubic hair growth.

Liver cirrhosis and hematemesis melena experienced by patients have been given therapy, and clinical improvement was obtained, likewise with acute adrenal insufficiency and hypothyroidism. During treatment, the patient experienced improvement and continued treatment at the outpatient clinic. Levothyroxine and hydrocortisone therapy was continued, and clinical improvement was found on follow-up. Sustanon, hydrocortisone, and levothyroxine will be given until the patient undergoes transsphenoidal resection for pituitary macroadenoma. After surgery, pituitary hormones level will be remeasured to determine the need for long-term therapy.

CONCLUSION

The condition of hypogonadism in patients with pituitary macroadenoma can be a risk factor for NAFLD, which can then progress to liver cirrhosis. The patient has been well-managed and experienced clinical improvement. The patient is prepared for transsphenoidal tumour resection.

REFERENCES

1. Melmed S. Pituitary masses and tumors. In: Melmed S, Auchus RJ, Goldfine AB, Koenig RJ, Rosen CJ, editors. Williams Textbook of Endocrinology. 14th ed. Philadelphia: Elsevier; 2020. p. 236-302.
2. Banskota S, Adamson DC. Pituitary adenomas: from diagnosis to therapeutics. Biomedicines. 2021;9(5):494.
3. Zhang Z, Chen C, Wang Y, Wang N, Chen Y, Lu Y, Xia F. The association of total testosterone with probable nonalcoholic steatohepatitis and nonalcoholic fatty liver disease fibrotic progression in men with type 2 diabetes: a cross-sectional study. Eur J Med Res. 2022;27:307.
4. Khullar V, Firpi RJ. Hepatitis C cirrhosis: new perspectives for diagnosis and treatment. World J Hepatol. 2015;7(14):1834-55.
5. Esposito D, Olsson DS, Ragnarsson O, Buchfelder M, Skoglund T, Johansson G. Nonfunctioning pituitary adenomas: indications for pituitary surgery and post-surgical management. Pituitary. 2019;22:422-34.
6. Hwang Y, Lee HW, Ahn SH, Lee EJ, Ku CR, Kim SU. Positive association between nonalcoholic fatty liver disease and growth hormone deficiency in patients with nonfunctioning pituitary adenoma. Front Endocrinol. 2023;13:1057769.
7. Mody A, White D, Kanwal F, Garcia JM. Relevance of low testosterone to non-alcoholic fatty liver disease. Cardiovasc Endocrinol. 2015;4(3):83-9.
8. Kim SM, Yalamanchi S, Dobs AS. Male hypogonadism and liver disease. In: Winters S, Huhtaniemi I, editors. Male Hypogonadism. Contemporary Endocrinology. Humana Press; 2017.
9. Song MJ, Choi JY. Androgens dysfunction in non-alcoholic fatty liver disease: role of sex hormone-binding globulin. Front Endocrinol. 2022;13:1053709.
10. Punekar P, Sharma AK, Jain A. A study of thyroid dysfunction in cirrhosis of liver and correlation with severity of liver disease. Indian J Endocrinol Metab. 2018;22(5):645-50.
11. Wentworth BJ, Siragy HM. Adrenal insufficiency in cirrhosis. J Endocr Soc. 2022;6(10):bvac115.
12. Penn DL, Burke WT, Laws ER. Management of non-functioning pituitary adenomas: surgery. Pituitary. 2017;21(2):145-53.
13. Pereira MP, Oh T, Joshi RS, Haddad AF, Pereira KM, Osoria RC, et al. Clinical characteristics and outcomes in elderly patients undergoing transsphenoidal surgery for nonfunctioning pituitary adenoma. J Neurosurg. 2020;49(4).
14. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2018;103(5):1715-44.