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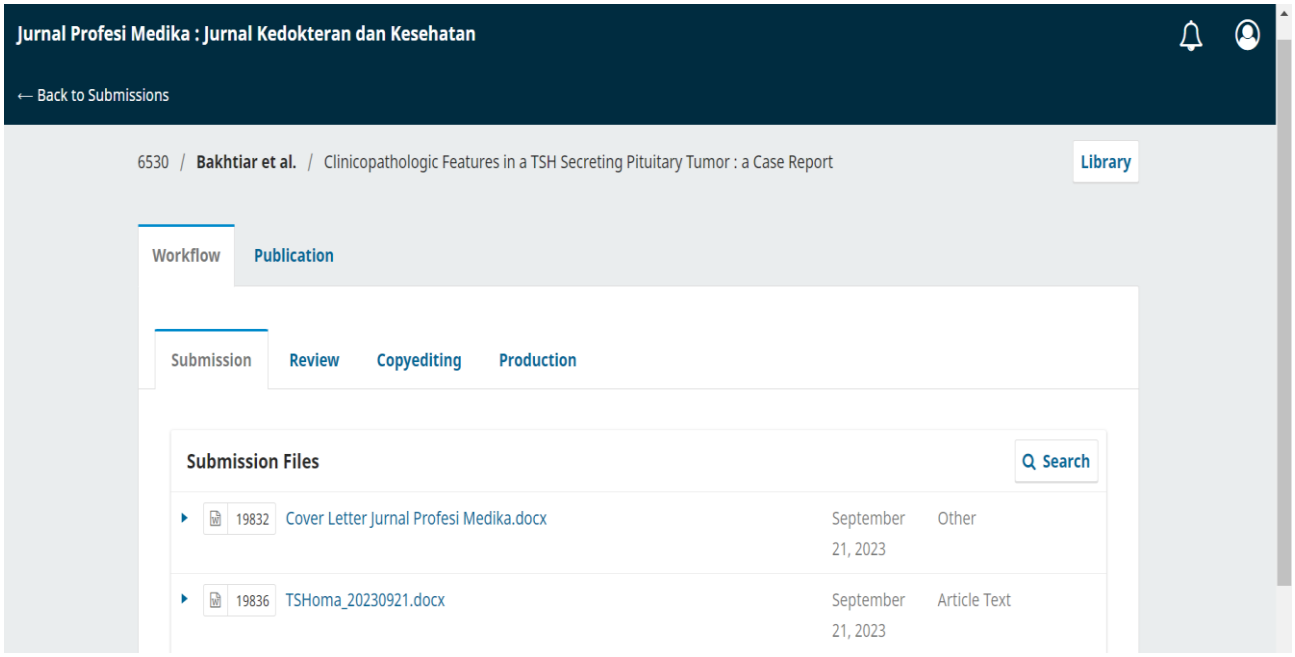
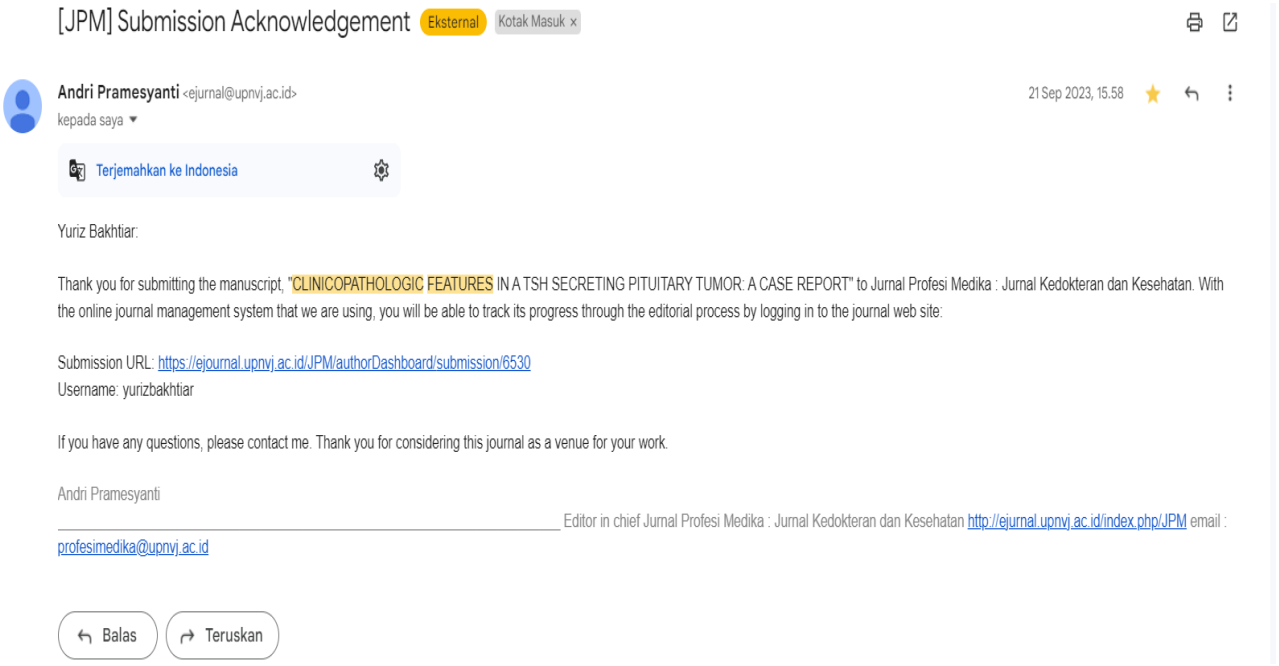
Submission Received-Original Paper





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CLINICOPATHOLOGIC FEATURES IN A TSH-SECRETING PITUITARY TUMOR: A CASE REPORT

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ABSTRACT

Thyrotropin-stimulating hormone-producing adenoma (TSHoma) is a rare cause of hyperthyroidism. Patients with this condition are often diagnosed when the tumor has already grown significantly, as the diagnosis of TSHoma is frequently delayed and confused with primary hyperthyroidism. Our case describes a 60-year-old woman with a goiter who was referred to our center from the otolaryngology department. Her thyroid panel in endocrinology showed elevated free hormone levels (fT3: 4.6 mg/ml and fT4: 1.93 mg/ml) and an unsuppressed TSH: 12.85 µ mIU/l, suggesting central hyperthyroidism. A thyroid gland sample obtained by a fine needle aspiration biopsy did not show malignant cells. An MRI scan of the pituitary gland revealed a macroadenoma with KNOSP grade 1. She underwent transsphenoidal surgery for the tumor. Histopathology revealed an acidophilic adenoma with the expression of TSH and prolactin by immunostaining. The proliferation rate, as indicated by MIB-1 staining, was only 0.6%. The decrease in thyroid hormones after the operation confirmed the effectiveness of the surgery. In conclusion, TSHoma, a rare tumor associated with hyperthyroidism, requires a careful diagnosis for effective management. Our article serves as reference material for understanding cases of pituitary-secreting tumors in Indonesia.

Keywords: Pituitary adenoma; TSHoma; Hyperthyroid; Transsphenoidal surgery

INTRODUCTION

Thyrotropin stimulating hormone-producing pituitary adenoma (TSHoma) is a relatively rare tumor with a prevalence of less than 2%.[1] The patients usually show symptoms of hyperthyroidism (sweating, palpitation, weight loss, and diffuse goiter), and are often misdiagnosed and treated for Grave's disease.[2] The diagnose of TSHoma was firstly reported in 1970 by Radioimmunoassay.[3]

In the past, the diagnosis of TSHoma often occurred during the invasive macroadenoma stage, making effective therapy difficult. However, the procedure of diagnosing hyperthyroidism has been greatly improved by the invention of sensitive immunometric assays, which are frequently used as the main test for thyroid function. This development makes it possible to recognize unsuppressed TSH secretion. This has led to an increase in the number of TSHoma diagnoses at early stages, before the macroadenoma phase. This shift has led to an increased diagnosis of patients who exhibit normal or elevated TSH levels, alongside elevated concentrations of free thyroid hormones.[4, 5]

Conversely, magnetic resonance imaging (MRI) examinations have gained popularity, increasing the likelihood of incidentally discovering pituitary tumors.[6] Patients with resistance to thyroid hormones (RTH) may also exhibit signs and symptoms of hyperthyroidism. Additionally, their thyroid function test results may resemble those reported in TSHoma. This form of RTH, characterized by greater resistance in the pituitary than in peripheral tissues, is known as pituitary RTH (PRTH)[2, 7, 8]

The clinical significance of these rare conditions comes from the complex challenges in terms of diagnosis and treatment. Failing to distinguish between these distinct diseases can lead to serious consequences, such as incorrect thyroid treatment for individuals with central hyperthyroidism or unnecessary pituitary surgery for those with RTH. Conversely, early

identification and appropriate management of TSHoma can help prevent the development of neurological and endocrinological complications. These complications include visual impairments due to optic chiasm compression, headaches, and hypopituitarism.[9]

CASE PRESENTATION

A 60-year-old woman was referred from the otolaryngology department to the neurosurgery department. She presented with a slight goiter and had no prior medical treatment history. The goiter, located on the right side, had a 2-cm diameter, and exhibited a firm texture without tenderness. A comprehensive physical examination, including a neurological assessment, revealed no notable findings. Upon admission, her skin appeared moist, with no signs of finger tremors or weight loss. Ophthalmological examination showed no visual disturbances. All other physical examinations fell within normal limits. Her pulse rate was 80/min, and her blood pressure measured 116/60 mmHg.

Laboratory examinations indicated normal blood count and biochemical data. Following the oral administration of 75g of glucose, her plasma glucose levels exhibited a hyperglycemic pattern. They increased from 107 mg/dl to a peak of 207 mg/dl at 60 minutes, before decreasing to 175 mg/dl at 120 minutes. Endocrinology panel results revealed elevated serum fT3 (4.6 mg/ml) and fT4 (1.93 ng/dl) levels. Additionally, the serum TSH level was high at 12.85 μIU/ml. The molar ratio of TSH-a to TSH in serum was 3.27. The 123-I uptake of the thyroid gland over 24 hours was 60.98%. TRAb and TSBAb tested negative, at 8% and 144%, respectively. Both anti-T3 and anti-T4 antibodies were negative, and antithyroglobulin antibodies were also absent.

Serum TSH levels did not respond to intravenous administration of 0.2 mg thyrotropin-releasing hormone (TRH test); the basal level remained at 12.49 μIU/ml, peaking at 13.96 μIU/ml. No paradoxical response of serum TSH level was observed after intravenous administration of 0.1 mg LH-releasing hormone (LH-RH test), 100 μg GH-releasing hormone (GRH test), or 100 μg corticotropin-releasing hormone (CRH test). Subcutaneous administration of 50 μg of sandostatin (octreotide acetate) resulted in a decrease in serum TSH levels from 13.33 μIU/dl to 10.09 at 1 hour and 7.59 at 8 hours.

Basal plasma levels of other pituitary hormones and their responses to hypothalamic hormones were within normal limits. Prolactin (PRL) was 11.9 ng/ml and increased to 28.0 during the TRH test; LH and FSH were 14.4 mIU/ml and 26.8 mIU/ml, increasing to 47.6 and 35.5 in the GnRH test, respectively. GH was 0.8 ng/ml and increased to 5.2 in the GRH test; ACTH was 11.6 pg/ml and increased to 291.0 in the CRH test. MRI identified a KNOSP grade 1 pituitary adenoma with a maximal diameter of 15 mm (Figure 1).

Based on these findings, a TSH-producing pituitary tumor was strongly suspected. A transsphenoidal hypophysectomy was performed, successfully removing the tumor. In the days following the operation, serum TSH, fT3, and fT4 levels briefly decreased and reached 0.45 μIU/ml, 2.1 pg/ml, and 1.92 ng/ml, respectively, one-month post-operation. The responses of plasma prolactin, LH, FSH, GH, and ACTH levels to the administration of TRH, GnRH, GRH, and CRH were normal, as were their basal levels. A response of serum TSH levels was observed in the TRH test. Subsequent MRI of the head showed no residual tumor.

Light microscopic and immunohistochemical findings showed that the resected pituitary tumor was a pituitary adenoma constituted of acidophilic cells. It exhibited stromal fibrosis and harbored calcification (psammoma bodies). Immunohistochemically, anti-TSH antibodies stained most of the tumor cells strongly (Fig. 2B). Furthermore, tumor cells were stained with anti- PRL antibodies (Fig. 2C). There were no cells stained with anti-GH, anti-LH, anti-FSH and anti-ACTH antibodies. Proliferation rate of MIB-1 staining showed only 0.6%. Hormonal data of post-surgery is showed in the table. 1.

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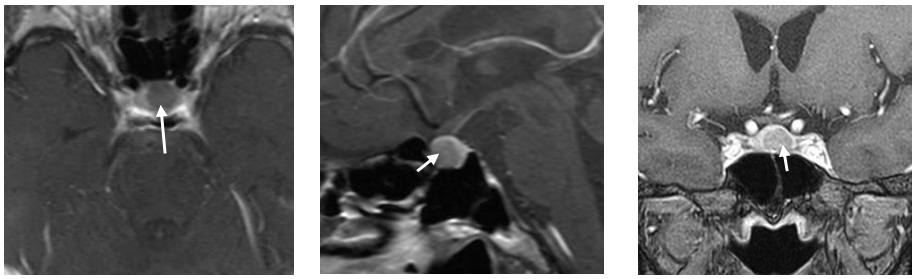

Figure 1. Pre operation MRI showed KNOSP grade 1 of pituitary adenoma (arrow) with maximal diameter 15 mm.

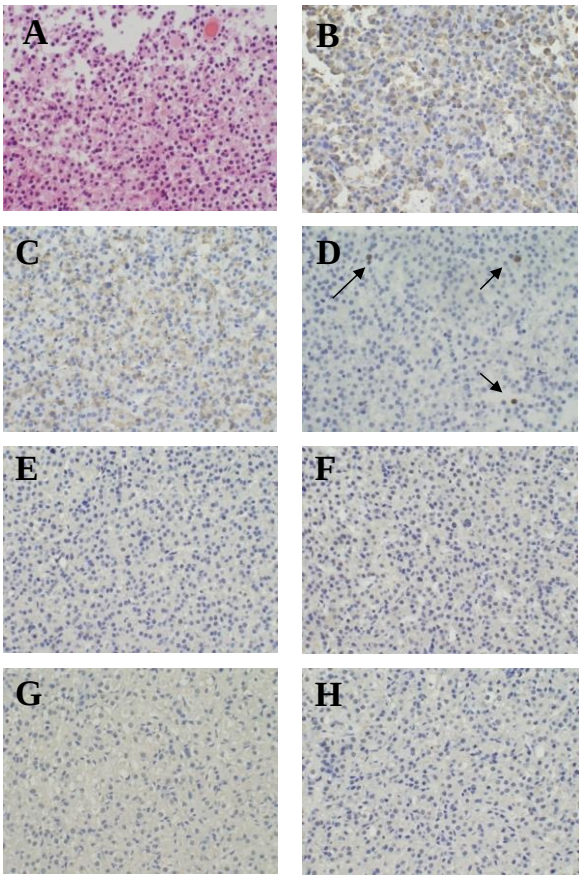

Figure 2. Hematoxilyn eosin staining revealed acidophilic adenoma with psammoma body (A), Immuno-histochemical staining of 2-µm sections of tumor tissue (x200), cytoplasm was stained with

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an anti-TSH antibody (B), anti-prolactin antibodies, and (C) and nuclei were stained with an anti-MIB-1 antibody "arrow" (D). (E, F, G, H) negative stained by anti-antibody of GH, ACTH, LH and FSH.

Table 1. Pre- and post-surgical hormonal panel

Hormonal Panel	Pre-Operation	Post-Operation	Normal Range
TSH TRH test sandostatin (octreotide acetate) test	**12.85 µIU/ml** **peak : 13.96 µIU/ml** **13.33 µIU/dl → 10.09 (1 h) and 7.59 (8 h)**	4,18 µIU/ml peak : 35.61 µIU/ml	0.5-5.0 µIU/ml;
fT3	**4.6 pg/ml**	2.1 pg/ml	2.3-4.0 pg/ml
fT4	**1.93 ng/ml**	1.92 ng/ml	0.9-1.7ng/ml
ratio of alpha subunit to serum TSH	3.27	Nd	TSHoma → 1.0
TRAb	8%	Nd	≤ 15%
TSAb	144%	Nd	< 180%
TGAb	≤ 0.3 U/ml	Nd	≤0.3 U/ml
TPOAb	≤ 0.3 U/ml	Nd	≤0.3 U/ml
LH, FSH Gn-RH test	14.4 mIU/ml 26.8 mIU/ml peak → LH: 68.5 FSH: 48.7	11.9mIU/ml 26.1 mIU/ml peak → LH: 58.9 FSH: 44.9	0.5-100 mIU/ml 1.3-120 mIU/ml
GH GRH test OGTT	0.8 ng/ml peak 10.6 Nadir → 0.1	1.4 ng/ml peak → 6.0	5.0-25.0µg/dl
PRL TRH test	11.9 ng/ml peak 28.0	7.1 ng/ml peak 45.4	2.9-40.8 ng/ml
ACTH CRH test	11.6 pg/ml peak 291.0	12.0 pg/ml peak 108.0	5.0-46.0 pg/ml
Serum cortisol	15.2 µg/dl	10.8 µg/dl	5-25.0µg/dl
Urinary cortisol	36.4 µg/day	Nd	11.2-80.3 µg/day

DISCUSSION

In our case, the basal serum levels of fT3, fT4, and TSH were indicative of inappropriate TSH secretion, which can result from TSH-producing tumors or selective PRTH. The notably high TSH-a subunit to TSH molar ratios in this patient essentially ruled out the latter diagnosis. Symptoms of hyperthyroidism are typically observable, although occasionally they appear less severe than expected, possibly due to their prolonged duration. Some untreated TSHoma patients may present with clinically normal thyroid function. Furthermore, in patients with mixed TSH/GH adenomas, hyperthyroid can be obscured by those of acromegaly. This underscores the importance of regularly measuring TSH and FT4 levels in patients with pituitary tumors.[10-14]

Even in patients who have previously undergone partial thyroidectomy, a goiter is almost always present because TSH hyperstimulation can cause the regrowth of thyroid residue. Uni- or multinodular goiter is

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common, accounting for approximately 70 to 80 percent of reported cases, but the development of functional thyroid anatomy seems to be rare. Given that differentiated thyroid carcinomas have been reported in several patients, it is recommended to monitor thyroid nodule(s) and perform fine needle aspiration biopsy (FNAB) in cases of TSHoma. A prior study revealed that thyroid cancer was present in 3 out of 62 patients (4.8%) with TSHoma.[15]

Despite similar prevalence of antithyroid autoantibodies in circulation (anti-thyroglobulin or Tg-Ab, and anti-thyroid peroxidase or TPO-Ab) as the general population, some patients developed post-pituitary surgery Graves' disease. Others showed bilateral exophthalmos due to autoimmune thyroiditis, and isolated unilateral exophthalmos resulted from pituitary tumor invasion into the orbit.[15-17] An endocrinology evaluation of this patient was performed. The results of hormonal and thyroid panel indicated a secondary hyperpituitarism, which is caused by TSHoma without any associated disease.

In the immunohistochemical examination, we defined acidophilic pituitary adenoma with double immunoreactivity of TSH and prolactin staining. Simultaneous overproduction of PRL and/or GH and/or LH and FSH in TSH-producing pituitary adenoma has been reported.[18] A previous review revealed a total of 598 cases of TSHoma, including 450 (75.2%) cases of pure TSHoma, 148 (24.8%) cases of mixed TSHomas, 90 (15.1%) cases of mixed TSH/GHomas, 50 (8.4%) cases of TSH/PRLomas, and 8 (1.3%) cases of mixed TSH/FSH/LHomas.[19]

Transsphenoidal sinus removal of the tumor was performed in this patient. Total removal was successfully accomplished in this case, although the large tumors are typically difficult to completely remove due to their significant fibrosis and local invasion of the cavernous sinus, internal carotid artery, and optic chiasm. Parameters of this result are shown from post-operation MRI (fig. 3). Complication due to TSS was not defined. We think that TSS is the first choice for therapy because of its advantages, and associated higher curability when TSHoma is treated in the early stages.[20, 21]

In this case, a routine follow-up for hormonal status is most important for ensuring the curability of a patient (fig. 4). The previous study showed that an immediate measurement of TSH levels after surgery is a strong predictor for remission. The recurrence rate of TSHoma with TSS approach was found to be 38.9%.[22]

In Indonesia, reports of TSHoma cases have not been well-documented. Although TSHoma cases are very rare, proper diagnosis and early management showed a good result. Our study highlights the importance of understanding TSHoma cases, as managements such as TSS, FNAB, and the assessment of TSH, ft3, and ft4 hormone levels are already viable within several Indonesian institutions. Future case reports of pituitary-secreting tumors with more effective diagnosis and management in Indonesia are therefore expected.

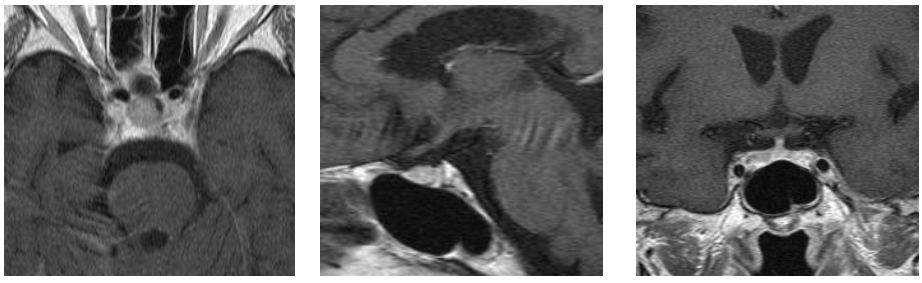

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Figure 3. Post-operation MRI

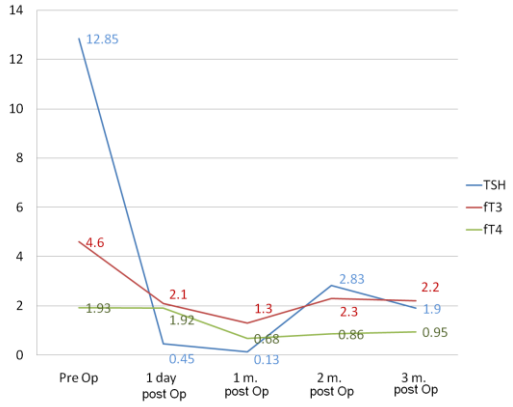

Figure 4. TSH, fT3, and fT4 level pre- and post-operation.

CONCLUSION

TSHoma is a rare tumor that can be difficult to diagnose, but it is important to consider in patients with hyperthyroidism. Early diagnosis and treatment of TSHoma can help prevent complications and improve the patient's outcome. This article is expected to serve as reference material for understanding pituitary-secreting tumor cases in Indonesia.

ACKNOWLEDGMENT

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DECLARATIONS

YZ and SF were the doctors in charge of the presented case and helped with manuscript preparation. IK contributed to the manuscript writing and submission. MTA was the senior advisor of this study. The authors declare that they have not received any external funds for this paper. There is no conflict of interest. No additional information is available for this paper.

REFERENCES

1. Asioli S, Righi A, Iommi M, Baldovini C, Ambrosi F, Guaraldi F, et al. Validation of a clinicopathological score for the prediction of post-surgical evolution of pituitary adenoma: retrospective analysis on 566 patients from a tertiary care centre. Eur J Endocrinol. 2019;180(2):127-34.
2. Beck-Peccoz P, Lania A, Beckers A, Chatterjee K, Wemeau JL. 2013 European thyroid association guidelines for the diagnosis and treatment of thyrotropin-secreting pituitary tumors. Eur Thyroid J. 2013;2(2):76-82.
3. Hamilton CR, Jr., Adams LC, Maloof F. Hyperthyroidism due to thyrotropin-producing pituitary chromophobe adenoma. N Engl J Med. 1970;283(20):1077-80.
4. Dutta A, Jain N, Rai A, Gupta R, Dhandapani S, Bhansali A, et al. The outcome of TSHoma from a tertiary care institute in India. Surg Neurol Int. 2021;12:161.
5. Yamada S, Fukuhara N, Horiguchi K, Yamaguchi-Okada M, Nishioka H, Takeshita A, et al. Clinicopathological characteristics and therapeutic outcomes in thyrotropin-secreting

DOI: https://doi.org/10.33533/jpm.....

pituitary adenomas: a single-center study of 90 cases. J Neurosurg. 2014;121(6):1462-73.
6. Chaudhary V, Bano S. Imaging of the pituitary: Recent advances. Indian J Endocrinol Metab. 2011;15 Suppl 3(Suppl3):S216-23.
7. Beck-Peccoz P, Brucker-Davis F, Persani L, Smallridge RC, Weintraub BD. Thyrotropin-secreting pituitary tumors. Endocr Rev. 1996;17(6):610-38.
8. Beck-Peccoz P, Persani L, Mannavola D, Campi I. Pituitary tumours: TSH-secreting adenomas. Best Pract Res Clin Endocrinol Metab. 2009;23(5):597-606.
9. Beck-Peccoz P, Giavoli C, Rodari G, Lania A. Physiopathology, Diagnosis and Treatment of Secondary Hyperthyroidism. In: Casanueva FF, Ghigo E, editors. Hypothalamic-Pituitary Diseases. Cham: Springer International Publishing; 2017. p. 1-21.
10. Rabbiosi S, Peroni E, Tronconi GM, Chiumello G, Losa M, Weber G. Asymptomatic thyrotropin-secreting pituitary macroadenoma in a 13-year-old girl: successful first-line treatment with somatostatin analogs. Thyroid. 2012;22(10):1076-9.
11. Malchiodi E, Profka E, Ferrante E, Sala E, Verrua E, Campi I, et al. Thyrotropin-secreting pituitary adenomas: outcome of pituitary surgery and irradiation. J Clin Endocrinol Metab. 2014;99(6):2069-76.
12. Maisnam I, Dutta D, Jain R, Ghosh S, Mukhopadhyay S, Chowdhury S. Plurihormone secreting pituitary macroadenoma masquerading as thyrotoxicosis: Clinical presentation and diagnostic challenges. Indian J Endocrinol Metab. 2012;16(Suppl 2):S315-7.
13. Glynn N, Agha A. Unexpected clinical course during treatment of a TSH-secreting pituitary adenoma. Endocr Pract. 2013;19(4):e88-91.
14. Johnston PC, Hamrahian AH, Prayson RA, Kennedy L, Weil RJ. Thyrotoxicosis with absence of clinical features of acromegaly in a TSH- and GH-secreting, invasive pituitary macroadenoma. Endocrinol Diabetes Metab Case Rep. 2015;2015:140070.
15. Perticone F, Pigliaru F, Mariotti S, Deiana L, Furlani L, Mortini P, et al. Is the incidence of differentiated thyroid cancer increased in patients with thyrotropin-secreting adenomas? Report of three cases from a large consecutive series. Thyroid. 2015;25(4):417-24.
16. Kamoun M, d'Herbomez M, Lemaire C, Fayard A, Desailloud R, Huglo D, et al. Coexistence of thyroid-stimulating hormone-secreting pituitary adenoma and graves' hyperthyroidism. European thyroid journal. 2014;3(1):60-4.
17. Okuyucu K, Alagoz E, Arslan N, Taslipinar A, Deveci MS, Bolu E. Thyrotropinoma with Graves' disease detected by the fusion of indium-111 octreotide scintigraphy and pituitary magnetic resonance imaging. Indian Journal of Nuclear Medicine: IJNM: the Official Journal of the Society of Nuclear Medicine, India. 2016;31(2):141.
18. Beck-Peccoz P, Lania A, Beckers A, Chatterjee K, Wemeau JL. 2013 European thyroid association guidelines for the diagnosis and treatment of thyrotropin-secreting pituitary tumors. European thyroid journal. 2013;2(2):76-82.
19. Beck-Peccoz P PL, Lania A. Thyrotropin-Secreting Pituitary Adenomas 2022 [Available from: https://www.ncbi.nlm.nih.gov/books/NBK278978/ .
20. Yang C, Wu H, Wang J, Hu M, Xing X, Bao X, et al. Successful management of octreotide-insensitive thyrotropin-secreting pituitary adenoma with bromocriptine and surgery: A case report and literature review. Medicine (Baltimore). 2017;96(36):e8017.
21. Herguido NG, Fuentes ED, Venegas-Moreno E, Maorad LB, Flores-Martinez A, Ruiz PR, et al. Surgical Outcome and Treatment of Thyrotropin-Secreting Pituitary Tumors in a Tertiary Referral Center. World Neurosurgery. 2019;130:e634-e9.
22. Yang Y, Liu J, Deng K, Lu L, Zhu H, Lian X, et al. Clinical and therapeutic characteristics of pituitary TSH-secreting adenoma in adolescent-onset patients: six case studies and literature review. Frontiers in Endocrinology. 2021;12:771673.

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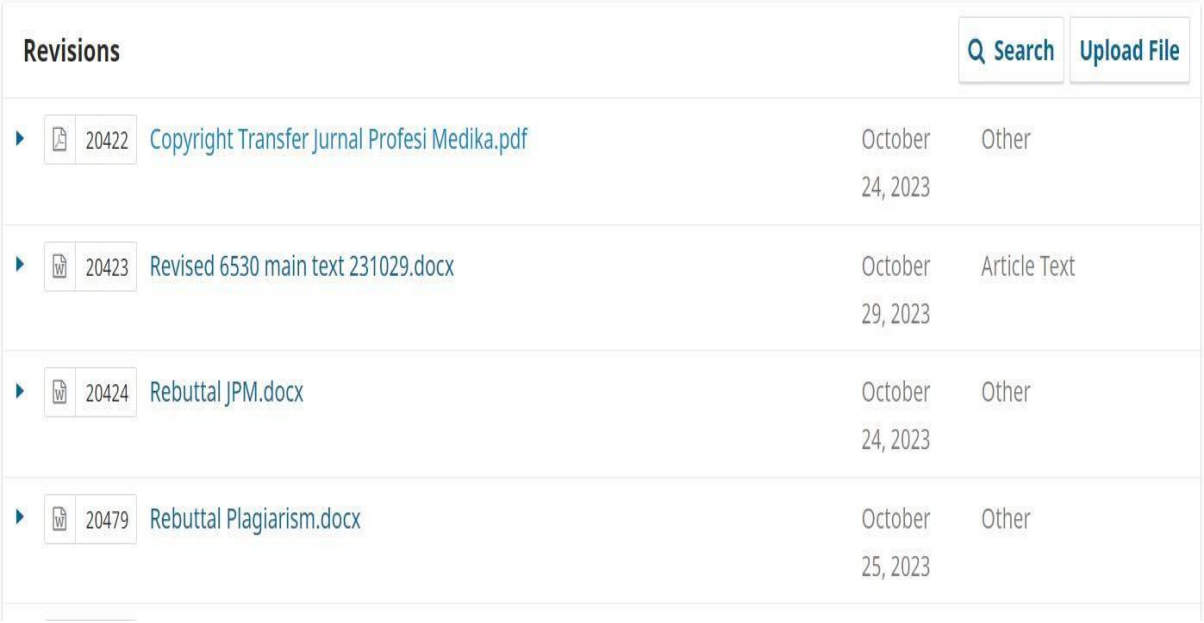

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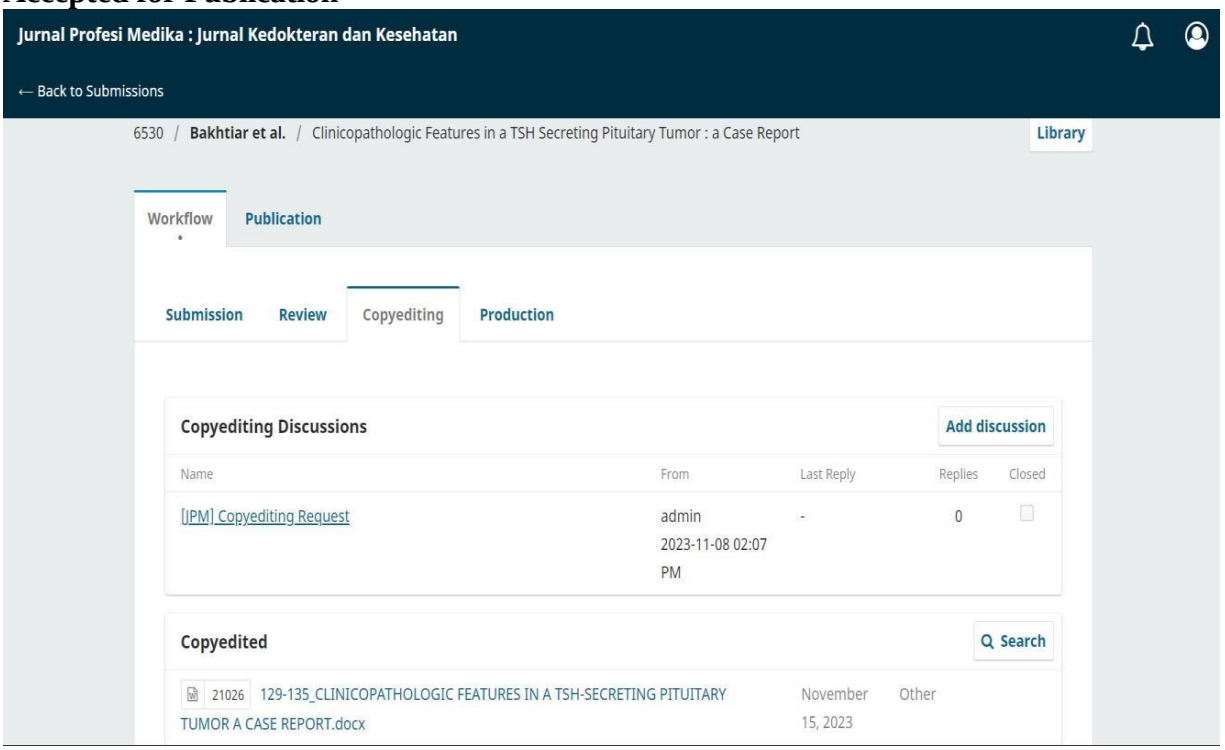

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Written by :
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Has been Accepted and will proceed to be published in Jurnal Profesi Medika : Jurnal Kedokteran dan Kesehatan Volume 17 No 2 2023.

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