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Kosova Journal of Surgery

KOSOVA JOURNAL OF SURGERY

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Volume 8
Issue 2
December 2024
ISSN: 3027-5008 (Online)
ISSN: 3027-5016 (Print)

www.kosovajournalofsurgery.net

Surgical treatment as an optimal solution for Dopamine Agonists resistant microprolactinoma: A case report

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Abstract

Background: Prolactinomas are the most common type of pituitary neuroendocrine tumors (PitNET). The treatment of PRL-secreting PitNET is medical, but in some conditions, surgery is needed.

Case presentation: We report a case of a 34-years-old female with a history of a resistant PitNET with active galactorrhea, treated with oral contraceptives at the age of 23 due to elevated PRL levels and irregular menstrual cycles. Magnetic Resonance Image (MRI) revealed a solid sellar lesion, 8 mm, suggesting a micro PitNET. Treatment with Cabergoline resulted in regular menstrual cycles with first pregnancy at 31. Two years after, galactorrhea reappeared and PRL was 175 μg/L, without changes in tumor size. Despite high dose of Cabergoline, PRL remained high. Resistance to Dopamine Agonists (DAs) was concluded and surgery was suggested.

Intervention: Endoscopic transsphenoidal surgery (ETSS) was performed resulting in gross total resection (GTR).

Outcome: Immediately after surgery the PRL levels returned to normal range.

Conclusion: It is crucial to identify in time DAs resistant prolactinomas and step up to surgery as the best treatment option, leading to GTR of microprolactinoma with satisfactory outcomes and normalization of PRL levels.

Introduction

Prolactinomas are the major cause of pathological hyperprolactinemia and the most common type of pituitary neuroendocrine tumors (PitNET) adenomas representing 53% of them all, and generally affecting women between 20 to 50 years old. In this age group, the females to males` ratio is 10:1, while after the sixth decade both sexes present the same frequency.[1,2] Epidemiological studies suggest a prevalence of 44-62 cases per 100 000 people from which around 80% of them are microadenomas.[3]
The clinical manifestations of patients diagnosed with microprolactinoma is related to hyperprolactinemia. Therefore, women classically present with oligo- or

amenorrhea, which is reported in almost 90% of all patients;[4] galactorrhea in 84% of patients, and sometimes infertility.[5,6] In contrary, males who mostly suffer from macroprolactinomas have symptoms related to mass effect more than hyperprolactinemia.[7] The treatment of Prolactin (PRL)-secreting PitNET is medical, but in some conditions surgery is necessary.

Case report

A 34-years-old female was referred to our department for a resistant PitNET with active galactorrhea. Her past medical history showed no abnormality from 11 years old when menarche occurred until the age of 23 when pituitary function test results revealed elevated PRL levels, then gynecologist treated with oral contraceptives. Despite the treatment, she continued experiencing irregular menstrual cycles during the four upcoming years. After, she was consulted by an endocrinologist and head Magnetic Resonance Image (MRI) revealed a solid sellar lesion, 8 mm, suggesting a micro PitNET (Figure 1), and Chiari type I with syringomyelia from C2 to T5 (Figure 2). Treatment with Cabergoline 0.5 mg/week was started resulting in regular menstrual cycles with first pregnancy at the age of 31. After 9 months of lactation postpartum she was normal. Two years following, bilateral galactorrhea reappeared. PRL was 175 μg/L. In the MRI the tumor size was unchanged. Cabergoline was raised up to 2mg/week since the endocrinologist considered it resistant to the drug (PRL remained high: 210 μg/L). Resistance to Dopamine Agonists (DAs) was concluded and surgery was suggested. Endoscopic transsphenoidal surgery (ETSS) was performed and gross total resection (GTR) resulted. The tumor cells were positive for PRL in immunohistochemistry testing. Histological diagnosis confirmed the diagnosis PitNET. Immediately after surgery the PRL levels returned to normal range. A second PRL three months after was 11 μg/L.

Discussion

Prolactinomas which belong to PitNET1 lineage, originate from pituitary lactotrophs monoclonal expansion and mostly are benign growths with clear demarcated borders. Based on tumor size, PitNETs are classified into small (micro <10 mm), large (macro ≥10 mm) and giant (≥40 mm).[8] Diagnosis of microprolactinomas should be considered in patients exhibiting symptoms of prolactin excess such as galactorrhea and amenorrhea in females or hypogonadism in males. PRL levels above 200 μg/L in women and over 100 μg/L in men are strongly indicative of prolactinomas, however, PRL levels are significantly correlated with prolactinoma size; for microadenomas, PRL usually ranges from 94 to 188 μg/L (2000 to 4000 mU/L).[9,10] Further diagnostic process consists of MRI of the sellar region including T1-weighted and T2-weighted coronal sections before and after gadolinium enhancement, as this is condiederd the gold standard radiological method for detecting prolactinomas.[11]

Regarding medical therapy, DAs are the treatment of choice for prolactinomas. Binding Dopamine (D2) receptors, they inhibit PRL synthesis and tumor growth. Between the three available drugs bromocriptine, quinagolide and cabergoline, the latest has become the most widely used DA worldwide because of its superior

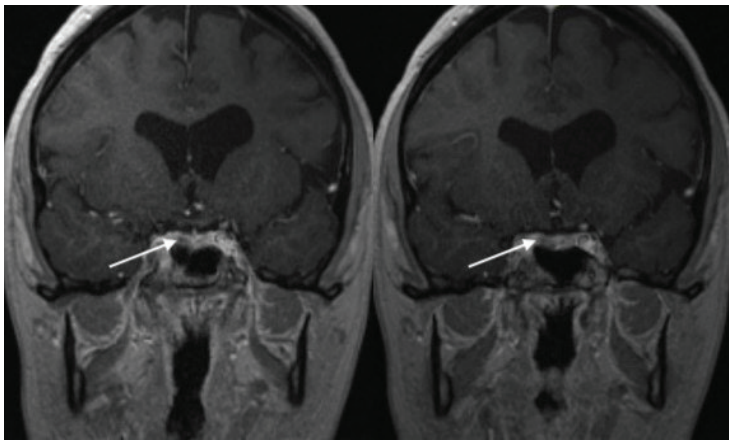


Figure 1. T1-weighted coronal brain MRI showing a micro-PitNET (white arrow) with homogenous enhancement on post gadolinium images.

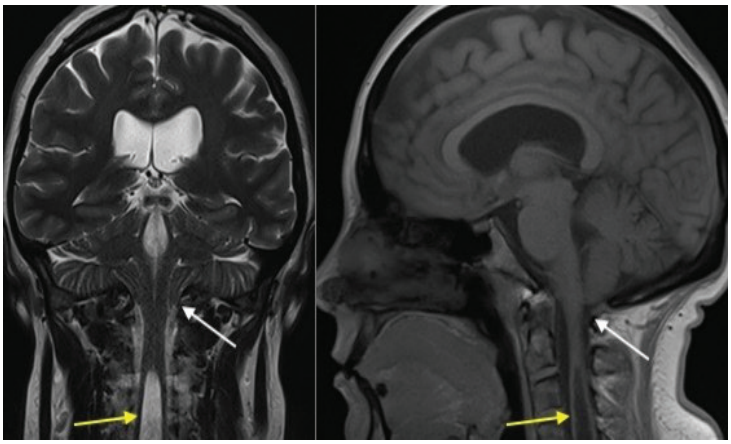


Figure 2. MRI showing tonsillar herniation (white arrow) and syringomyelia (yellow arow) on T2-weighted coronal sequence (left) and on T1-weighted sagittal sequence (right).

efficacy, safety profile and good patient compliance in long term treatment regimens.[1]

Resistance to DAs has been reported in 20% to 30% of patients treated with bromocriptine, and in approximately 10% of those treated with cabergoline.[12] It is defined as failure to achieve normal PRL levels and/or failure to reduce the tumor size more than 50% with a standard daily dose of 10 mg bromocriptine or 2 mg/week of cabergoline for a period of six months.[13] DAs resistance pathophysiology still remains unclear, but mechanisms related to D2 receptors` abnormality both quantitative expression and ligand affinity, as well as down-regulation of the transforming growth factor β (TGF β)/Smad signaling cascade are described. In addition, reduction of filamin-A, somatic mutations in the POU6F2 gene and inhibition of POU6F2 gene, low estrogen receptors (ER α) expression activity and the direct interaction between the ER α and PRL/PRLR pathways may also contribute to DAs resistance of prolactinomas.[14,15]

In such refractory prolactinomas, considering DA switch or increasing DA dose is the next therapeutic approach and in case of repeated failure, surgery is the next therapeutic step, as in our patient. The current neurosurgical technique is through transsphenoidal route, using microsurgery or endoscopy.[16,17] The high remission rates, which are overall 67% and up to 90% for microprolactinomas, along with low recurrence rates of 5–20%, suggest that surgery could serve as a viable second-line treatment option.[18] Research indicates that pituitary surgery can be more cost-effective than long-term medication for patients with a long life expectancy exceeding 10 years. Recent classifications from the WHO have improved the diagnostic assessment of pituitary tumors, but to reach a definitive diagnosis there are still challenges and limitations for both clinicians and pathologists in their management.[19]

Conclusion

This case highlights the importance of early identification of DAs resistant prolactinomas in order to prompt to surgery as the next treatment option. It easily leads to GTR of microprolactinoma in almost all cases and gives satisfactory outcomes with normalization of PRL levels and improvement of clinical symptoms accordingly.

Authors contribution:

Conception and design: Mentor Petrela. Writing original manuscript: Stela Dodaj, Mentor Petrela. Formal analysis: Stela Dodaj, Mentor Petrela. Methodology: Mentor Petrela, Mirel Grada, Mirjeta Guni. Review and editing: Mirel Grada, Artemis Ibra, Mentor Petrela, Vojsava Leka. Data curation: Artemis Ibra, Mirel Grada. Supervision: Mentor Petrela

Data Availability Statement

Data of this case report will be made available from the corresponding author upon reasonable request. Video of the surgery is available on request of Dr. Mirel Grada (mirel_gr@hotmail.com)

Disclosures

The authors declare no conflict of interest.

Informed consent

Informed consent was obtained from the patient for this publication.

Funding

No grants nor funding is received.

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