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Tumor shrinkage in a tamoxifen-treated non-functioning pituitary neuroendocrine tumor with positive estrogen receptor-beta (ERβ): A case report and review of the literature

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ABSTRACT

Administration of selective estrogen receptor modulators (SERMs) and anti-estrogens has been shown to reduce the size of pituitary tumors. However, previous studies were performed on animal pituitary tumors or tissue cultures. We administered oral tamoxifen to a postoperative patient with a nonfunctioning pituitary neuroendocrine tumor (NF-PitNET) to investigate its potential effect on tumor volume. This case report presents the case of a 47-year-old female patient with a null cell adenoma who had undergone surgical resection as primary treatment and was left with a residual tumor that grew significantly. She was treated with tamoxifen 20–40 mg daily for one year. She was followed up to assess tamoxifen adherence, tolerability, and adverse events. The resected pituitary tumor was stained with estrogen receptor alpha (ERα) and beta (ERβ), proliferation markers (ki-67 and p53), and H&E staining for mitotic count. MRI of the pituitary gland was performed before starting treatment, after 6 months, and after 1 year of tamoxifen therapy. Her resected tumor showed high-intensity ERβ staining in the absence of ERα expression. She was able to tolerate oral tamoxifen therapy without side effects. Tamoxifen therapy resulted in a remarkable reduction in residual tumor volume of up to 87 % in this patient. Tamoxifen has a potential therapeutic effect in treating patients with residual NF-PitNET tumors that have regrown after primary resection. This finding may provide an alternative treatment modality for recurrent NF-PitNET. ERβ expression may predict response to tamoxifen in this subset of patients.

1. Introduction

Nonfunctioning pituitary neuroendocrine tumors (NF-PitNET) are pituitary tumors characterized by the absence of hormone hypersecretion. Patients may become symptomatic due to hypopituitarism or compression symptoms in large tumors. Although considered benign tumors, patients with NF-PitNET have increased morbidity and slightly increased mortality, mainly due to circulatory, respiratory, and infectious diseases [1,2]. Surgical removal of the tumor is the first-line treatment in most cases. However, complete removal of very large tumors can be difficult, and these adenomas have a high residual tumor rate [3]. For these residual tumors, radiotherapy is an effective treatment option with tumor control of up to 90 % over 10 years [4,5]. However, this high efficacy is offset by a high incidence of complications

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such as hypopituitarism, cognitive impairment, and stroke risk [6]. The stereotactic modality is considered safer, but the incidence of hypopituitarism was 72 % over 10 years, which was comparable to conventional radiotherapy [7]. Another option is clinical observation (wait and see), but the incidence of recurrence is very high (67.9 % over 15 years), and an increased standardized mortality rate of 1.65 has been reported [3,8].

The best identified predictive clinical factor for tumor recurrence is the presence of residual postoperative tumor. Chen et al. [9] evaluated published data from a total of 371 patients without detectable residual postoperative tumor and 600 patients with residual tumor. The recurrence rate for tumors without postoperative residual tumor was 12 % versus 46 % in the presence of residual tumor. Tumor-free survival was also significantly different in patients without residual tumor compared with patients with residual tumor (96 vs. 56 % at 5 years and 82 vs. 40 % at 10 years).

In patients unable or unwilling to undergo surgery, or in whom repeated surgeries failed to completely remove residual tumor or the tumor grew again, medical therapies were used to stabilize or shrink the tumor. Dopamine agonists such as cabergoline have been shown to be effective in 30%–40 % of patients, especially in patients with only small residual tumors, and cabergoline improves symptoms in 30 % of cases [10]. Somatostatin analogs (SA) such as octreotide and temozolamide have been used to target aggressive pituitary tumors including NF-PitNET. However, all previously used agents are considered expensive drugs. Therefore, there is a need for alternative pharmacological approaches for the treatment of significant NF-PitNET remnants after surgical resection.

ERα expression has been found to be higher in NF-PitNET than in functioning adenomas in patients younger than 50 years [11]. Null cell adenomas and gonadotroph adenomas were among the most reactive for ERα [12]. The expression pattern of silent corticotroph adenomas (silent subtypes I, II) and subtype III suggest that these adenomas are least reactive for ERα and ERβ, with silent corticotroph adenomas having the lowest percent immunopositivity value for ERα expression. Similarly, gonadotrophic and null cell adenomas had some of the strongest immunoreactivity for ERβ [12]. These results may suggest that estrogen plays a possible role in the stimulation and growth of these tumors.

Many years ago, it was shown that administration of tamoxifen and anti-estrogen can reduce the size of pituitary tumors in rodents [13]. In addition, tamoxifen was found to decrease and normalize IGF-I levels in patients with active acromegaly [14]. In fact, its efficacy in patients with this disease was similar or even better than that of cabergoline [15]. According to a recent study by Hannen et al. [16], SERMs and anti-estrogens such as bazedoxifene, clomiphene, raloxifene, and fulvestrant decreased pituitary adenoma cell survival by inducing apoptosis and reducing migration and invasion potential. Similarly, a recent study demonstrated the effect of fulvestrant and a new anti-estrogen (AZD9496) on the proliferation of estrogen receptor-1 (ESR1)-positive pituitary adenomas, which effectively suppressed the growth of pituitary adenomas in GT1-1 and GH-3 cells and human primary gonadotroph adenomas, with the rate of tumor growth inhibition reaching up to 75 % [17]. Tamoxifen can penetrate the blood-brain barrier and was found to inhibit pituitary adenoma progression by inducing apoptosis and expression changes of apoptosis-related proteins, and reprogramming tumor-associated macrophages [18]. In addition, tamoxifen is inexpensive and readily available.

Here, we present data demonstrating the clinical feasibility of tamoxifen in NF-PitNET patient, with particular attention to its effects on residual tumor volume and association with clinicopathologic features.

2. Materials and method

Data reported in this case report were part of ongoing clinical trial conducted at the Neurosurgery Clinic, Hospital Kuala Lumpur (HKL), Malaysia. The patient signed an informed consent before entering the study. The intervention was designed to evaluate the potential efficacy of tamoxifen in NF-PitNET patients with residual tumor after primary neurosurgery. The diagnosis of NF-PitNET was based on the following criteria: (1) evidence of pituitary tumor by MRI, with or without local tumor signs such as headache and visual acuity/field defects; (2) absence of clinical features of hypersecretion of anterior pituitary hormones; (3) Presence of normal or low circulating levels of growth hormone (GH), insulin-like growth factor 1 (IGF-1), thyroid-stimulating hormone (TSH), thyroid hormone, adrenocorticotropic hormone (ACTH), or 24-h urinary cortisol levels; and (4) Evidence of pituitary adenoma on postoperative histopathologic examination. A thorough history of previous carcinoma or family history of carcinoma was obtained before treatment.

A 47-year-old woman was initially diagnosed with NF-PitNET visual disturbances and multiple hormonal deficiencies including hypogonadism, hypothyroidism, and hypocortisolism. She received 10 mg of oral hydrocortisone and 50 mcg of oral levothyroxine daily. Her serial hormone profiles were relatively stable throughout the intervention period. She has a pituitary macroadenoma with an original tumor volume of 9.89 cm^3 before resection. Residual tumor volume was measured at 0.643 cm^3 6 months after resection. At 26 months after resection, the tumor had doubled in volume to 1.41 cm^3, so tamoxifen treatment was initiated. For the first month, she received tamoxifen at a dose of 20 mg daily. The dose was then increased to 40 mg daily for the following eleven months [19]. She was followed up every 3 months. An investigator (A.H.A.T.) performed the clinical and physical examinations at all time points. The target dose of 40 mg daily was reached within 30 days and maintained until the end of the intervention.

The immunoprofile was determined by automated immunostaining with antibodies to adrenocorticotropic hormone, growth hormone, prolactin, follicle-stimulating hormone, luteinizing hormone, and thyroid-stimulating hormone. IHC for anterior pituitary hormones was performed in the Histopathology Unit, Hospital Kuala Lumpur (HKL). Additional immunostaining for detection of estrogen receptors and proliferation markers (ki-67 and p53) was performed at the UKM Medical Center Histopathology Laboratory. Formalin-fixed tumor tissue embedded in kerosene was analyzed in whole section. Slides were deparaffinized with xylene and rehydrated through a series of graded alcohols. Antigen retrieval was performed with citrate buffer (10 mM, pH 6.0), and endogenous peroxidase activity was blocked with a 6 % hydrogen peroxide solution. A commercially available ERα-rabbit monoclonal antibody (ready-to-use antibody, clone EP1, Dako Autostainer/Autostainer Plus) was used for immunostaining for ERα. For ERβ detection, a commercially available mouse ERβ monoclonal antibody was used (1:300; Abcam). For secondary antibody, the Max Polymer Detection System (Novo Link Kit, Novocastra, UK) was used according to the manufacturer's instructions. Formalin-fixed, paraffin-embedded breast and prostate carcinoma tissues, respectively, were used as positive controls for ERα and ERβ immunoreactivity. All immunostained slides were scored by a single experienced neuropathologist using the Histo (H) score method. For ERα and ERβ, the H-score algorithm [12] consists of the sum of the percentage of stained tumor cells multiplied by an ordinal value corresponding to the intensity grade (0 = none, 1 = weak, 2 = moderate, and 3 = strong), thereby assigning a score on a continuous scale from 0 (no staining) to 300 (diffuse intense staining).

MRI of the pituitary gland was performed twice, at baseline (T0) and 6 months (T1) after the start of the intervention, to determine the remaining tumor volume. Gadolinium-contrasted MRI of the pituitary gland was performed with a 1.5-T scanner (Philips Ingenia) in the MRI department of the Department of Radiology at HKL. Images were acquired in the sagittal and coronal planes. Tumor residual volume (in cm^3) was calculated using 3D volume analysis in Horos on coronal slices of T1-weighted MRI images with contrast agent. The edges of the tumor (region of interest) were manually delineated in each 3-mm image without gaps between slices using Horos software [20]. All

measurements were performed by a single HKL neuroradiologist who specializes in the interpretation of pituitary images.

3. Results

Radiologic and IHC examination in this patient revealed a grade 2a with invasion of the sphenoid sinus [21], has high intensity for ERβ (H score = 240) in the absence of ERα expression and all anterior pituitary hormones (null cell adenoma), a ki-67 index of 0.6 %, and no p53 positivity. Mitoses were not detected. Tamoxifen therapy had no major side effects. The patient was able to tolerate a tamoxifen dose of 20–40 mg until the end of treatment. 6 months after starting tamoxifen treatment, her residual tumor volume shrank from 1.41 cm^3 to 0.66 cm^3. A subsequent MRI scan after one year of tamoxifen therapy showed a further decrease in volume to 0.18 cm^3, resulting in an overall 87 % shrinkage of the tumor under tamoxifen therapy. There was no evidence of pituitary infarction in any MRI images. Fig. 1 shows serial MRI images demonstrating marked tumor shrinkage after tamoxifen therapy. Fig. 2 shows strong immunoexpression for ERβ and negative ERα.

4. Discussion

Considering the high prevalence of residual tumors in patients with NF-PitNET after transsphenoidal surgery, the frequency of side effects with radiotherapy, and the high risk of tumor regrowth with a wait-and-see approach, additional therapies are essential for the treatment of residual tumors in NF-PitNET. To date, this is the first case in which significant tumor shrinkage was observed after tamoxifen therapy in estrogen receptor-beta-positive NF-PitNETS. In this case report, tamoxifen was well tolerated and was feasible in a patient who had residual tumor on radiograph after surgical resection. This case demonstrates that tamoxifen is able to significantly reduce residual tumor volume in estrogen receptor beta-positive tumors (>25 % tumor shrinkage) [22].

Our finding of increased ERβ immunoexpression in a null cell adenoma is consistent with results from a previous study [12]. The differential expression patterns of ERα and ERβ in pituitary adenomas may suggest that estrogen plays a possible role in the stimulation and growth of these tumors. The relative levels of ERα and ERβ are an important determinant of the pharmacology of antiestrogens. Previous results suggest that the tissue-specific agonist activity of anti-estrogens may be determined by the relative expression of ERα and ERβ in a tissue [23]. Tamoxifen acted as an agonist when only ERα was expressed in the cell and showed no agonist activity when only ERβ was expressed [23]. The response of tumor volume shrinkage to tamoxifen therapy may correlate with the intensity of ERβ immunoexpression, which is consistent with our result showing a significant response to treatment in a patient who had a high intensity of ERβ expression. The observation that tamoxifen is a stronger competitive antagonist of ERβ [24–26] and lacks agonistic activity at the receptor raises the possibility that tamoxifen may be more responsive in ERβ-positive tumors. Nevertheless, post-menopausal women and men might respond differently to anti-estrogens.

We had sought to further investigate the possibility of concomitant apoptosis-induced tumor shrinkage in the female patient. Pituitary tumor apoptosis has been associated with pituitary tumor disappearance [27]. Other proposed possible mechanisms for the substantial shrinkage include postoperative changes such as resorption of hemorrhagic changes within the tumor remnant, intratumoral ischemia and consecutive tumor necrosis caused by surgical disruption of blood vessels, and formation of intratumoral fibrosis [28]. She never showed clinical signs of apoplexy such as sudden or severe headache or recurrent hypocortisol symptoms that required an increase in hydrocortisone dose. Otherwise, her serial hormone profiles were relatively stable throughout the study period. Her serial preoperative and postoperative MRI scans did not show any of these potential changes that could cause shrinkage. No

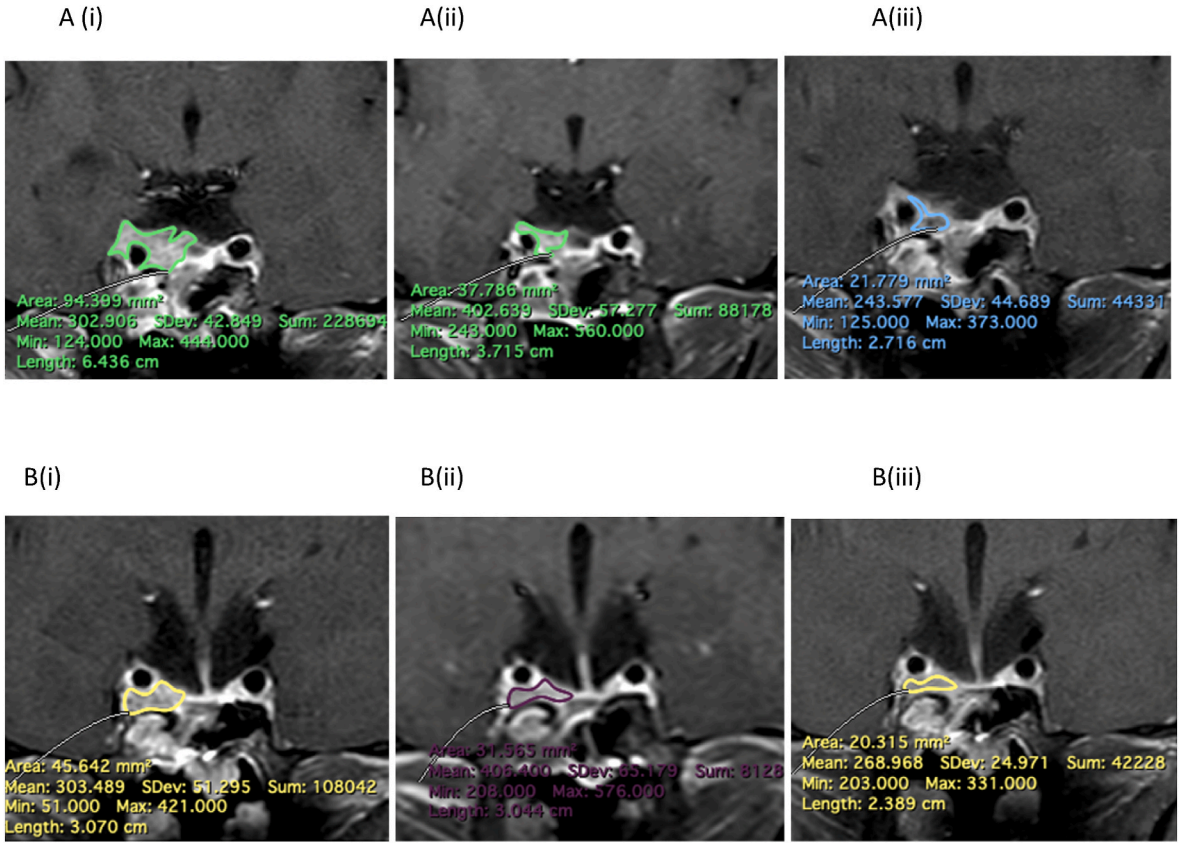

Fig. 1. Representative MRI images showing the most shrinkage (A) Coronal contrasted T1-weighted MR images obtained at baseline (i) at 6-month (ii) & at 1-year of tamoxifen therapy (iii) (B) Coronal contrasted T1-weighted MR images obtained at baseline (i) at 6-month (ii) & at 1-year of tamoxifen therapy (iii).

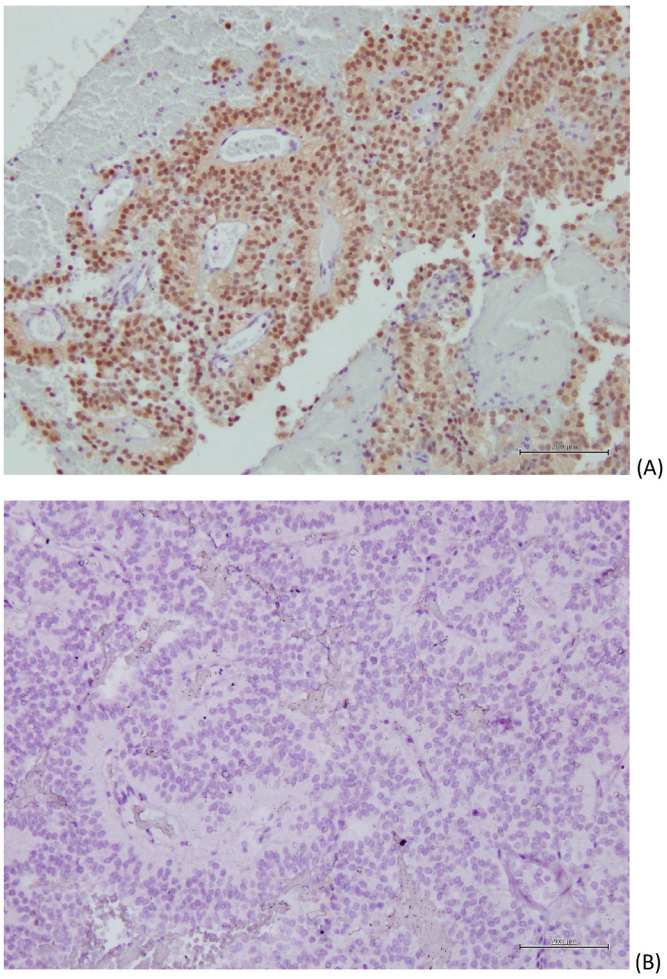

Fig. 2. Pattern of nuclear ERα and ERβ expression. High immunohistochemical staining of ERβ (A). Absent ERα (B).

apoplectic area was detected in the histopathologic specimen.

Of note, shrinkage of the pituitary tumor could be detected on MRI up to one year after surgery [29]. The fact that this patient had undergone transsphenoidal surgery more than 24 months before tamoxifen therapy may mean that significant shrinkage of the tumor due to postoperative changes is unlikely. We used 3D volume assessment to estimate the remaining tumor volume and consequently to assess the efficacy of tamoxifen. The edges of the tumor were manually delineated in each 3-mm image with no gap between slices to increase the precision of the volume measurements. The Di Chiro equation has been used for years in most pituitary surgery studies, but a strong correlation between volume measurements with 3D reconstructed tumors and values determined by the equation has been previously demonstrated in NF-PitNET [30]. Due to surgical manipulation, many adenomas have irregular shapes. Depending on the tumor shape, volume measurements may be underestimated or overestimated. In addition, because tumor shrinkage from tamoxifen treatment is not necessarily homogeneous throughout the adenoma, measurement in only three axes may not reflect the true effect of treatment on the tumor. Small changes in tumor diameter in one or all three axes may be reflected in obvious volumetric changes that may have been missed when estimating total volume using tumor diameters in three axes.

Alternatively, tamoxifen also inhibits protein kinase C [31], and this pathway may contribute. While induction of apoptosis has been proposed as a mechanism for the effect of tamoxifen on prolactinomas, few studies have attempted to elucidate the molecular cascade leading to destruction of lactotrophic cells [32]. Some in vitro studies have shown that tamoxifen has both antiestrogenic and direct toxic effects on pituitary tumor cells [33]. ERβ has been shown to bind tamoxifen [34], and it has been suggested that low ERβ levels are associated with tamoxifen resistance in breast carcinomas [35]. Conversely, Hopp et al. [36] showed that ERβ expression in a group of 186 tamoxifen-treated tumors had a beneficial effect on disease-free and overall survival, which may suggest a role for ERβ as a predictive marker of tamoxifen sensitivity. Clinical trial studies could demonstrate the potential efficacy of tamoxifen as a therapeutic agent in residual NF-PitNET and investigate the role of ERβ as a predictive marker for response.

In conclusion, SERM appears to be a promising alternative for the treatment of postoperative NF-PitNET patients with residual tumors, especially those with high estrogen receptor immunoexpression. ERβ expression may predict response to tamoxifen. Further studies are warranted to search for reliable clinical, laboratory, or immunohistochemical markers that predict patient response to SERMs.

Declarations

4.1. Ethics approval and consent

This study was approved and registered by Medical Review and Ethics Committee (MREC), Ministry of Health Malaysia. The patient signed an informed consent to participate.

4.2. Consent for publication

The patient signed an informed consent for publication.

4.3. Availability of data and material

All data analyzed are included in this published article or in the data repositories listed in References.

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CRediT authorship contribution statement

Haydar Ali Tajuddin Amalina: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization, Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Sukor Norlela:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Azizan Elena Aisha:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Kamaruddin Nor Azmi:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Omar Ahmad Marzuki:** Funding acquisition. **Geok Chin Tan:** Validation, Investigation, Formal analysis, Conceptualization. **Mustangin Muaatamarulain:** Validation, Investigation, Formal analysis. **Mohamed Mukari Shahizon Azura:** Investigation, Formal analysis. **Alias Azmi:** Supervision, Project administration, Conceptualization. **Abd Latif Kartikasalwah:** Validation, Investigation, Formal analysis, Conceptualization. **Poh Sen Tay:** Validation, Investigation, Formal analysis. **Idris Nurdillah:** Validation, Investigation, Formal analysis. **Kasim Fauziah:** Validation, Investigation, Formal analysis. **Wan Ismail Wan Ruza Iswati:** Validation, Investigation, Formal analysis.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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