




Silent Corticotroph and Somatotroph Double Pituitary Adenoma: A Case Report and Review of Literature

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Abstract

Clinically silent double pituitary adenomas consisting of corticotroph and somatotroph cells are an exceedingly rare clinical finding. In this report, we present the case of a 28-year-old man with a 1-year history of recurrent headaches. Imaging revealed a 2.1 (anterior-posterior) × 2.2 (transverse) × 1.3 (craniocaudal) cm pituitary adenoma invading into the left cavernous sinus and encasing the left internal carotid artery. Endoscopic transnasal resection was performed without complications. Immunohistochemical staining revealed a double adenoma consisting of distinct sparsely granulated somatotroph and densely granulated corticotroph cells that were positive for growth hormone and adrenocorticotrophic hormone, respectively. Ki-67 index labeling revealed a level of 6% within the corticotroph adenoma. No increase in serum growth hormone or adrenocorticotrophic hormone was found, indicating a clinically silent double adenoma. While transsphenoidal surgery remains a first-line approach for silent adenomas presenting with mass effects, increased rates of proliferative markers, such as the Ki-67 index, provide useful insight into the clinical course of such tumors. Determining the Ki-67 index of silent pituitary adenomas could be valuable in predicting recurrence after initial surgical resection and identifying tumors that are at an increased risk of needing additional therapeutic interventions or more frequent surveillance imaging.

Keywords

- ▶ double pituitary adenoma
- ▶ somatotroph
- ▶ corticotroph
- ▶ Ki-67

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Introduction

Silent pituitary adenomas (SPAs) are a clinically asymptomatic subtype of pituitary neuroendocrine tumors, classified based upon transcription factor and pituitary hormone immunohistochemistry.¹ While all SPAs stain positive for their respective hormone based on the cell type from which they originate, they can be categorized as either “clinically silent” if they secrete that hormone at a normal biochemical level or “totally silent” if they fail to cause an increase in serum hormone levels.² This is in contrast to null cell adenomas which are asymptomatic and stain negatively for both pituitary-specific hormones and transcription factors. In addition to being classified as either clinically or totally silent, SPAs can be further categorized as sparsely or densely granulated based on histology, with the densely granulated subtype expressing higher levels of cell-specific hormone than the sparsely granulated variant, which exhibits a weaker and more focally distributed pattern of hormone immunoreactivity.³ Since SPAs usually remain undiagnosed due to their lack of hormonal effects, they often present as incidental macroadenomas causing mass effects. These include visual field disturbances, headaches, dizziness, and subsequent hormonal alterations, such as hypothyroidism, hypopituitarism, or hyperprolactinemia, the latter of which is due to the stalk effect resulting from infundibular compression.^{4,5}

Out of all pituitary adenomas, somatotroph adenomas comprise approximately 10% of cases and roughly one-third of these are considered to be clinically silent.^{3,6} Silent somatotroph adenomas (SSAs) are characterized based on positive growth hormone (GH) immunohistochemical staining without clinical signs of GH hypersecretion, namely acromegaly. Along with GH positivity, staining for pituitary-specific transcription factor-1 (Pit-1) serves as a useful marker for SSAs since expression of this transcription factor drives the differentiation of the somatotroph cell lineage.⁷ In general, SSAs have a propensity for being sparsely granulated and behaving more aggressively than clinically functioning somatotroph adenomas.⁸ Additionally, they are reported to arise more commonly in women than in men and to present at a younger age than patients with certain types of other silent pituitary tumors, such as silent gonadotroph adenomas.^{9,10}

Compared with SSAs, silent corticotroph adenomas (SCAs) have been found to be more common, comprising up to 20% of all corticotroph adenomas and 10 to 20% of nonfunctioning pituitary adenomas (NFPAs).^{11,12} These tumors have been classified as high risk by the World Health Organization in 2017 due to their aggressive nature and high risk of recurrence.¹³ Since SCAs lack the clinical presentation of Cushing syndrome, as seen in non-SCAs, positive immunostaining for adrenocorticotrophic hormone (ACTH) and T-box transcription factor 19 (Tpit) is needed for a definitive diagnosis. Similar to SSAs, sparsely granulated SCAs seem to occur more frequently than their densely granulated counterpart and to demonstrate a more aggressive and invasive phenotype.^{14,15} Furthermore, SCAs have been found to ex-

hibit a decreased event-free survival after surgery compared with other NFPAs.¹⁶

Compared with single silent adenomas, double pituitary adenomas, which are defined as two synchronous tumors arising from distinct cell lineages, are an even rarer occurrence and appear in approximately 1% of surgically resected pituitary adenomas.^{17–19} GH and ACTH are found to be the most frequently expressed pituitary hormones in double adenomas, with the predominant clinical presentation being acromegaly followed by Cushing's disease.¹⁶ In addition to these hormones, the most common hormone that is concomitantly expressed with either ACTH or GH secreting adenomas is prolactin (PRL).²⁰ However, compared with ACTH-PRL and GH-PRL double adenomas, those that stain positively for both ACTH and GH are infrequent.^{21,22} Furthermore, double adenomas consisting of both silent corticotroph and silent somatotroph cells are exceedingly rare.²³

For clinicians treating patients with pituitary adenomas, being aware of the variability in the aggressive nature of different adenoma subtypes is critical. The use of prognostic markers, such as the Ki-67 index, has proven to be valuable in determining these differences and lending insight into the clinical course of such tumors. Ki-67 is a protein found in the nucleus of cycling cells and is used to determine the mitotic rate of tumor cells.²⁴ Previous studies have reported that tumor aggressiveness can be linked to higher levels of the Ki-67 index due to its association with greater rates of proliferation, larger tumor size, and increased sinus invasiveness.²⁵ Additionally, studies have reported that among NFPAs, Ki-67 levels are greater in invasive rather than noninvasive adenomas and serve as a useful predictor of regrowth among invasive NFPAs when complete surgical resection may not be possible.^{26,27} While the reliability of using the Ki-67 index as a predictor of tumor behavior has been debated, physicians should be aware of its value in patients' diagnosis and treatment.

Case Presentation

A 28-year-old man presented to the endocrinology clinic with an incidental mass of the pituitary gland that was discovered on magnetic resonance imaging (MRI) 1 year prior. The patient had been experiencing recurrent headaches and was evaluated by his primary care physician, during which time imaging analysis revealed a 1.2-cm lesion on the left side of his pituitary. The patient had no significant past medical history, but reported having sharp headaches that occurred four times per week, which lasted approximately 15 seconds and resolved spontaneously. He mentioned that his headaches were triggered upon bending over, but identified no modifying factors that relieved his symptoms. The patient denied peripheral vision loss, galactorrhea, breast growth, heat/cold intolerance, palpitations, fatigue, fractures, polyuria, polydipsia, or proximal muscle weakness. He experienced no decrease in pubic hair or increase in abdominal girth, hat, or shoe size. Furthermore, he reported having normal libido and spontaneous erections.

The patient denied tobacco use, alcohol consumption, and substance use.

On physical exam, the patients' pupils were equal and reactive to light, and he had normal confrontational visual fields. His visual fields were intact and extraocular movements were all normal. He was hemodynamically stable and no striae or bruises were noted. Additionally, the patients' motor strength, reflexes, coordination, gait, and sensory were all found to be unremarkable. Aside from an elevated prolactin level of 53.1 ng/ml (reference <15 ng/ml), laboratory results did not demonstrate any additional hormonal hypersecretion with reported levels of IGF-1 of 308 ng/ml (reference 63-373 ng/ml), ACTH of 19 pg/ml (reference 6-72 pg/ml), hemoglobin A1C (Hgb A1C) of 5.3%, and morning cortisol of 15.2 ug/dl (reference 4-20 ug/dl). These findings are consistent with a NFPA with mild PRL elevation likely due to stalk deviation. A repeat MRI in March 2021 revealed a 2.1 (anterior-posterior) \times 2.2 (transverse) \times 1.3 (craniocaudal) cm pituitary macroadenoma in the left side of the sella invading into the cavernous sinus where it encased the left internal carotid artery (**Fig. 1**). There was no impingement on the optic apparatus and the pituitary stalk was of normal thickness, however, it was deviated to the right. The patient was subsequently scheduled for transsphenoidal surgery.

The patient underwent a transsphenoidal pituitary tumor resection without any intraoperative complications. There were no significant postoperative events and the patient had an unremarkable hospital stay and was discharged without needing any new medication.

Histopathological examination of surgically resected tissue demonstrated two different adenomas with discrete

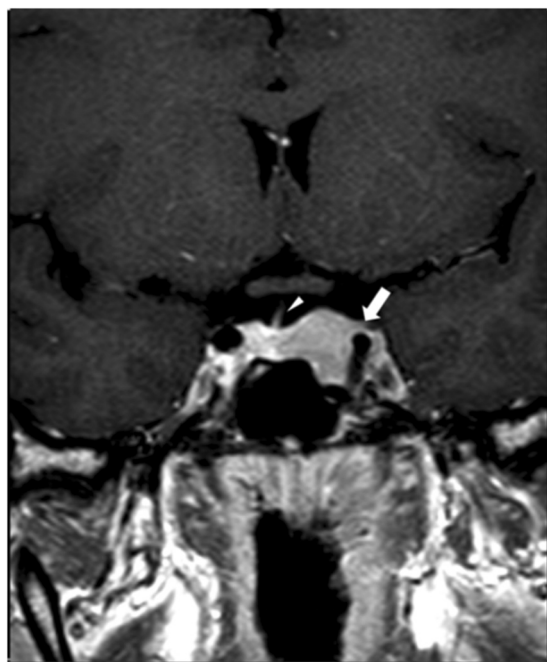


Fig. 1 Coronal T2-weighted contrast-enhanced magnetic resonance imaging (MRI) showing pituitary gland enlargement with resultant stalk deviation (arrowhead) and encasement of the internal carotid artery (arrow).

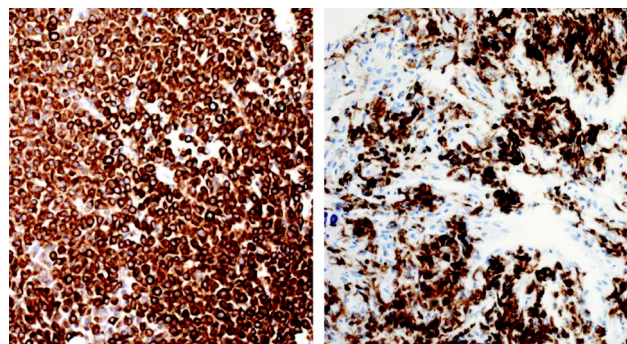


Fig. 2 The corticotroph adenoma (left) shows diffuse cytoplasmic staining with CAM5.2 while the somatotroph tumor (right) shows distinctive fibrous body type staining.

staining patterns. The first adenoma identified was reported to have histopathological features consistent with a sparsely granulated somatotroph adenoma, with distinctive fibrous body type staining with the low molecular weight keratin stain (CAM5.2). Immunohistochemistry revealed weakly positive and spotty staining for GH with a Ki-67 proliferation index of approximately 1%. The second distinct adenoma was a densely granulated corticotroph adenoma with a diffuse cytoplasmic staining pattern, which had negative staining for GH and an elevated Ki-67 proliferation index of approximately 6% (**Fig. 2** and **3**).

One month following resection, the patient reported resolution of his headaches and laboratory results showed normal endocrine hormones, including an improved level of PRL at 17 ng/mL. Gross neurological and musculoskeletal exams remained normal. Plan is to closely follow-up with the patient and repeat MRI in 3 months due to elevated Ki-67 proliferation index.

Discussion

Patients with SPAs fail to experience the hormonal effects of their tumor and often present with signs of mass effects due to the growth of a macroadenoma. Some of the most prevalent symptoms include visual loss and headaches, the latter of which was seen in our patient.²⁸ While the majority of double adenomas stain positive for either ACTH or GH, double adenomas of silent corticotroph and silent somatotroph cells are uncommon. In our report, histological analysis confirmed the

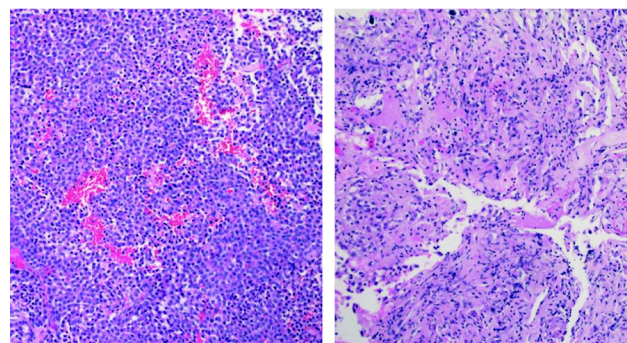


Fig. 3 Ki-67 proliferative index is elevated in the corticotroph adenoma (~6%; left) and lower in the somatotroph adenoma (~1%; right).

diagnosis through positive immunohistochemical staining of both densely granulated corticotroph and sparsely granulated somatotroph cells. Furthermore, staining for K_i-67 revealed an index > 6% for the corticotroph cell lineage, indicating a highly aggressive tumor.

SPAs are a distinct form of neuroendocrine tumors that positively stain for hormones of the anterior pituitary without exhibiting an elevation in serum hormone levels. Despite the failure of these tumors to induce clinical effects due to their lack of hormonal hypersecretion, these adenomas tend to behave more aggressively than other pituitary adenoma variants with regards to tumor invasion and postsurgical recurrence. In one study by Jahangiri et al, investigators compared characteristics of tumor aggressiveness among hormone negative adenomas ($n = 1,726$) and SCAs ($n = 75$) and discovered that cavernous sinus invasion occurred in 18 and 30% of cases, respectively.²⁹ Other studies have cited even higher rates, with one report by Yamada et al observing an 85% cavernous sinus invasion rate among SCAs.³⁰ In addition to cavernous sinus invasion, SCAs have been shown to exhibit greater rates of postsurgical recurrence compared with other nonfunctional pituitary tumors. Pawlikowski et al observed that 35% of SCAs experienced tumor recurrence, a rate more than double of that observed among non-ACTH positive NFPAs.³¹ Similar postresection recurrence rates have been observed by Langlois et al, with 36% of SCAs ($n = 39$) and only 10% of silent gonadotroph adenomas ($n = 70$) exhibiting recurrence.³² Furthermore, silent adenomas of the corticotroph lineage have been noted to demonstrate earlier regrowth after surgery as well as a higher likelihood of multiple recurrences compared with other NFPAs. Cooper et al conducted a cohort study and found that SCAs recurred, on average, 5 years earlier than other silent adenomas.³³ Additionally, Cho et al observed that 57% of SCAs ($n = 28$) experienced more than two recurrences compared with only 2.8% of NFPAs ($n = 134$).³⁴ Similar to SCAs, SSAs have also been found to exhibit a high rate of postsurgical recurrence, with studies reporting rates close to those of SCAs.⁹ Studies have found that in contrast to functional somatotroph adenomas, SSAs tend to occur at a younger age and to be more invasive and recur more frequently.³⁵ Furthermore, previous case reports have documented the potential for SSAs to become clinically active and to develop signs of acromegaly after initial presentation.³⁶ The transformation of adenomas from silent to functional forms has also been reported among SCAs.³⁷ These characteristics demonstrate the need for appropriate clinical management of such adenomas and the challenges they pose in developing effective therapies.

In predicting the clinical course of pituitary adenomas, proliferative markers, such as the K_i-67 index, have proven to be useful. Previous reports have suggested that a labeling index of 3% could be used to distinguish invasive versus noninvasive adenomas with over 97% specificity and 72% sensitivity.³⁸ While high levels of K_i-67 are indicative of increased mitotic rates, it has also been found to correlate with tumor aggressiveness and progression after surgical intervention.³⁹ In one study analyzing 29 patients with

NFPAs, a K_i-67 index > 3% was found to correlate with increased rates of tumor regrowth after surgery with 67% of patients experiencing regrowth postadenectomy compared with only 17% of those patients with K_i-67 < 3%.⁴⁰ Another study of 35 NFPAs found that early postsurgical recurrence was associated with higher K_i-67 index levels and that these levels progressively increased between nonrecurrent (0.42 ± 0.45), late recurrent (> 4 years) (0.86 ± 0.62), and early recurrent (< 4 years) (2.11 ± 1.18) adenomas.⁴¹ In addition to recurrence, K_i-67 levels have also been found to correlate with tumor invasiveness. Liu et al analyzed 45 somatotroph and 61 corticotroph adenomas and found that the K_i-67 levels among invasive somatotrophs (6.2 ± 3.4) and invasive corticotrophs (3.6 ± 1.5) were much greater than those that were noninvasive (2.7 ± 1.1 and 2.7 ± 1.1 , respectively).⁴²

Among pituitary adenomas considered to be of high risk, those composed of silent corticotroph and sparsely granulated somatotroph cells have been found to contain higher levels of the K_i-67 index compared with other adenomas. SCAs are considered to be one of the most aggressive forms of all NFPAs. In one study by Strickland et al comparing 100 SCAs with 841 NFPAs, patients with SCAs were found to demonstrate a K_i-67 index that was significantly higher than other nonfunctioning adenomas (2.88 ± 2.79 vs. 1.94 ± 1.99) and to experience a shorter progression-free survival (24.5 vs. 51.1 months).⁴³ Another study analyzing 101 patients with acromegaly observed that sparsely granulated somatotroph adenomas occurred at a younger age and were associated with a higher MIB-1 index, which stains for the K_i-67 antigen, than densely granulated somatotroph tumors (MIB-1 index $3.6 \pm 1.9\%$ vs. $2.7 \pm 1.8\%$).⁴⁴ While the value of the K_i-67 index to predict tumor behavior and aggressiveness has been debated over the years, especially with regards to the cutoff value of the K_i-67 index used in analysis, it remains an important marker for physicians to be aware of. Further studies must continue to examine the association between K_i-67 and tumor aggression, invasion, and recurrence to more definitively assess its association with these characteristics. Furthermore, additional markers, such as cavernous sinus invasion and tumor diameter, may be utilized concurrently with the K_i-67 index score to more accurately determine long-term event-free survival and to add strength to the prognostic value of this marker.¹⁴

Despite the high rates of recurrence and invasion among SCAs and SSAs, transsphenoidal surgical resection remains a first-line treatment, particularly for macroadenomas presenting with mass effects.⁴⁵ However, disease remission after surgical therapy alone has been found to be variable among different types of pituitary tumors and in those cases where complete surgical resection may not be possible. Previous reports have determined that the presence of postsurgical tumor remnants and length to follow-up are major factors in determining regrowth and recurrence after surgery.⁴⁶ Due to the high risk of sinus invasion and, therefore, increased likelihood of subtotal resection among certain pituitary adenoma variants, surgical monotherapy often remains inadequate. For these cases, radiotherapy has

proven to be an effective adjuvant treatment. SCAs that have undergone subtotal resection have been reported to experience extended rates of event-free survival if they were treated with radiotherapy after surgery compared with those that were not.⁴⁷ Additionally, patients who received radiation after subtotal resection exhibited similar rates of event-free survival to those SCAs that underwent gross total resection. However, the aggressive nature of SCAs has likely contributed to the decreased effectiveness of radiotherapy compared with that among other NFPAs as observed by some investigators. Among patients in one study examining the effectiveness of stereotactic radiosurgery among pituitary adenomas, only 10% of NFPAs ($n = 70$) demonstrated tumor progression after treatment compared with 42% of SCAs ($n = 34$).⁴⁸ At this time, the effectiveness of radiotherapy among SSAs is lacking, however, this is likely due to the rare occurrence of these types of SPAs. Regardless, current results indicate the need for more effective and targeted therapies to be developed for the treatment of such aggressive pituitary adenomas.

Conclusion

While surgery remains a first-line approach in the treatment of pituitary adenomas presenting with mass effects, postsurgical recurrence remains an issue. Radiotherapy has proven to be a useful adjuvant treatment for many invasive adenomas where gross total resection may not be possible; however, recurrence rates remain high for some forms of aggressive adenomas. Furthermore, many studies have failed to demonstrate the efficacy of this treatment modality among SSAs and dual pathology tumors, specifically. Moving forward, the use of proliferative markers, such as the Ki-67 index, could be valuable in identifying tumors that have a more aggressive phenotype with a higher likelihood of recurrence. This information could help physicians in understanding the clinical course of pituitary adenomas, predicting the effectiveness of certain treatments, and modifying the surveillance of such tumors after surgery.

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Conflict of Interest

None declared.

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