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Prospective evaluation of the characteristics and incidence of adenoma-associated dural invasion in Cushing disease

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Abstract

Object—Dural invasion by adrenocorticotropic hormone (ACTH)-secreting adenomas is a significant risk factor for incomplete resection and recurrence in Cushing disease (CD). Since ACTH-producing adenomas are often the smallest of the various types of pituitary tumors at the time of resection, examining their invasion provides the best opportunity to identify the precise sites of early dural invasion by pituitary adenomas. To characterize the incidence and anatomical distribution of dural invasion by ACTH-secreting adenomas, the authors prospectively and systematically analyzed features of dural invasion in patients with CD.

Methods—The authors prospectively studied consecutive patients with CD undergoing the systematic removal of ACTH-secreting adenoma and histological analysis of the anterior sella dura as well as other sites of dural invasion that were evident at surgery. Clinical, imaging, histological, and operative findings were analyzed.

Results—Eighty-seven patients with CD (58 females and 29 males) were included in the study. Overall, dural invasion by an ACTH-positive adenoma was histologically confirmed in 30 patients (34%). Eighteen patients (60% of dural invasion cases, 21% of all patients) had evidence of cavernous sinus wall invasion (4 of these patients also had other contiguous sites of invasion), and 12 patients (40% of dural invasion cases) had invasion of the sella dura excluding the cavernous sinus wall. Eleven patients (13% all patients) had invasion of the routinely procured anterior sella dura specimen. Preoperative MR imaging revealed an adenoma in 64 patients (74%) but accurately predicted dural invasion in only 4 patients (22%) with cavernous sinus invasion and none of the patients with non–cavernous sinus invasion. Adenomas associated with dural invasion

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(mean ± SD, 10.9 ± 7.8 mm, range 2–37 mm) were significantly larger than those not associated with dural invasion (5.7 ± 2.1 mm, range 2.5–12 mm; p = 0.0006, Mann-Whitney test).

Conclusions—Dural invasion by ACTH-producing adenomas preferentially occurs laterally into the wall of the cavernous sinus. Preoperative MR imaging infrequently detects dural invasion, including cavernous sinus invasion. Invasion is directly associated with tumor size. To provide a biochemical cure and avoid recurrence after resection, identification and removal of invaded sella dura, including the medial cavernous sinus wall, are necessary.

Keywords

adenoma; cavernous sinus; Cushing disease; dura; invasion; pituitary surgery

Cushing disease is the result of an ACTH-secreting pituitary adenoma that causes prolonged, excessive cortisol secretion by the adrenal glands. The ensuing supraphysiological levels of serum cortisol lead to significant clinical effects, including hypertension, skin atrophy/bruising, diabetes, hirsutism, and obesity as well as a significantly shortened life span if CD is not effectively treated.[3,11,13] Because successful selective resection of an ACTH-secreting adenoma in CD effects immediate remission with the maintenance of pituitary function, it is the treatment of choice for this disorder.[8] Consequently, a complete understanding of the factors associated with the success and, as important, the failure of surgical treatment in patients with CD is critical.

Previous reports based on retrospective case analyses have documented that gross or microscopic dural invasion can be associated with treatment failure in CD as well as in other pituitary tumors.[6,12] While it is apparent that the complete removal of other types of pituitary adenomas is associated with clinical remission and reduced recurrence, the removal of all microscopic tumor involvement is particularly important in CD, as even microscopic residual tumor inhibits biochemical remission or promotes recurrence and thus necessitates further treatment.[6,12] Knowledge of the characteristics and incidence of parasellar dural invasion in CD is incomplete. To characterize the incidence of dural invasion by ACTH-secreting tumors, we prospectively analyzed the features of dural invasion in consecutive patients with CD.

Methods

Patient Population

Consecutive pediatric (21 years of age or younger at surgery) and adult patients with CD who underwent initial resection of an ACTH-secreting pituitary adenoma between July 2000 and December 2004 at the National Institutes of Health were included in this study. At surgery, an anterior dural specimen was taken in all cases to prospectively assess for invasion, and the medial wall of the cavernous sinus and/or other sella dura was either partially or completely removed if it was considered, by direct visual inspection at surgery, to be invaded by tumor. All patients or their legal guardians signed informed consent for evaluation and treatment.

Clinical Evaluation

Patients underwent routine histories and physical examinations at their initial clinic visit and/or hospital admission. Preoperative and postoperative clinical and/or laboratory evaluations to confirm the diagnosis of CD and biochemical remission after resection were performed during inpatient hospitalizations and outpatient clinical visits.[2,7,13,14,18] Telephone, mail, and email contact was used to supplement and update clinical information.

Imaging Evaluation

All patients underwent high-resolution MR imaging with and without contrast enhancement using standard T1- and T2-weighted spin echo sequences, as well as spoiled gradient recalled acquisition sequences for optimal imaging evaluation of an adenoma (slice thickness 1 mm).[1,17] For adenomas that were visible on MR imaging, the largest diameter (mm) in any plane was used to determine the tumor size for analysis and was recorded. The presence or absence of sella dura invasion, including cavernous sinus invasion, was determined by a neuroradiologist and was recorded.

Surgical Procedure

Patients underwent a transsphenoidal approach to the sella and microsurgical removal of the adenoma using the histological pseudocapsule as a surgical capsule, as previously described.[8,15] The anterior and inferior bony faces of the sella were removed to expose the entire anterior sella dura, the medial half of the cavernous sinuses bilaterally, and the anterior half of the inferior sella dura, which allowed exposure of the entire anterior pituitary gland to directly view and systematically assess the anterior dura for invasion. A 4 × 5–mm or larger rectangular piece of anterior sella dura was incised to the level of the capsule of the pituitary gland but not into it by using the bevel of a #15 scalpel. Care was routinely taken not to enter the anterior surface of the pituitary gland. To preserve the distinct tissue plane between the inner surface of the dura and the capsule of the pituitary gland, the anterior dural specimen was carefully dissected free from the anterior pituitary capsule by using a disc dissector and was sent for pathological examination. For patients with obvious invasion of the anterior dura, the dura in the region of invasion was removed. Coagulation was avoided during the exposure as well as during the dural incisions and removal of the anterior dura and other dural specimens. Adenomas that were visible upon opening the anterior sella dura were removed via circumferential dissection using the tumor histological pseudocapsule.[15] Adenomas that were not visible upon opening the anterior sella dura were identified through serial inspections of the lateral surfaces of the pituitary gland and then via vertical incisions made at 1.5- to 2-mm intervals in the anterior pituitary gland. Once an adenoma was identified during inspection of the gland, it was removed using circumferential dissection around its histological pseudocapsule. During dissection of the tissue capsule enveloping the tumor, specific attention was directed at identifying any transgression of the pituitary gland capsule by tumor and/or dural invasion. A partial hypophysectomy was performed in cases in which no discrete adenoma was identified. All dura invaded by tumor (including cavernous sinus wall dura) was removed and sent for histological analysis. Operative findings, including tumor size, tumor location, and the presence and site of dural invasion, were recorded.

Histological Analysis

Serial systematic histological and immunohistochemical analyses of the anterior sella dura specimens and resected pituitary adenomas were performed using routine H & E histological stains and immunohistochemical tests for reticulin and ACTH. Intraoperatively presumed invaded portions of the cavernous sinus wall and/or sella dura (aside from the anterior sella dura specimen) were systematically analyzed using routine H & E, cytokeratin immunohistochemistry, and immunohistochemical staining for reticulin and ACTH. The presence of an ACTH-positive adenoma and dural invasion was recorded.

Classification of Dural Invasion

Dural invasion was classified into 2 major categories based on whether the dural specimen 1) was from the routinely procured anterior dura (regardless of adenoma location) or 2) was excised from a site that was invaded according to intraoperative observations.

Statistical Analysis

Specific statistical analyses as defined in the text were performed using Microsoft Excel (Microsoft Corp.) and GraphPad Prism (GraphPad Software) software. For all statistical tests, a p value < 0.05 was considered significant.

Results

Patient Characteristics

Eighty-seven consecutive patients with CD (58 females and 29 males) were included in the study. The mean age at surgery was 31.7 ± 16.7 years (range 7–67 years). There were 32 pediatric (37%) and 55 adult (63%) patients. The mean follow-up after resection was 1.7 ± 2.0 years. Five patients (6%) had evidence of early persistent hypercortisolism after initial surgery and underwent early reoperation (4 patients) or radiation therapy (1 patient).

Imaging Characteristics

Before the initial operation, MR imaging was performed in 84 patients (97%). Three patients (3%) did not undergo MR imaging because of a contraindication (1 patient) or because they exceeded the size permissible for imaging (2 patients). A pituitary adenoma was identified on preoperative MR imaging in 64 patients (74% of patients with imaging), who had a mean tumor size of 6.8 ± 5.7 mm (range 2–37 mm). While 6 tumors (7%) demonstrated cavernous sinus invasion on preoperative MR imaging, no other tumors were identified as involving the sella dura other than the cavernous sinus. The mean adenoma size (15.1 ± 12.5 mm, range 5–37 mm) associated with imaging evidence of cavernous sinus invasion was significantly ($p < 0.05$, Mann-Whitney test) larger than the mean size of adenomas not associated with imaging evidence of invasion (5.6 ± 2.7 mm, range 2–15 mm).

Operative Findings

General Features—After the initial operation, 82 patients (94%) had early biochemical evidence of remission and 5 (6%) had continued hypercortisolism. Four of these latter patients (5%) underwent early reoperation (mean time from initial operation to reoperation

25.5 ± 23.4 days, range 8–58 days), and of these patients, 1 had evidence of dural invasion with carotid artery involvement. One (1%) of the 5 patients with continued hypercortisolism after the initial surgery underwent radiation therapy for residual tumor in the cavernous sinus along the carotid artery. Overall, 85 patients (98%) had biochemical remission after the initial operation or early reoperation, and none had a recurrence at the last follow-up.

Adenoma Location—An ACTH-positive adenoma was histologically confirmed in 86 patients (99%) at the initial surgery or early reoperation (1 tumor was aspirated during dissection in a patient who proceeded to biochemical remission with profound and sustained hypocortisolism postoperatively). A discrete ACTH-positive adenoma was identified during surgery in 80 patients (92%) or was discovered in tissue from a partial hypophysectomy in 6 patients (7%). Specifically, histological evidence of an adenoma was found at the initial operation in 82 patients (94%), early reoperation in 1 patient (1%), or at both times in 3 patients (3%).

Eighty-five adenomas (98%) were surgically identified within the sella, and 2 (2%) were ectopically located either within the sphenoid sinus (1 adenoma) or entirely within the cavernous sinus (1 adenoma). Aside from the 2 ectopic extrasellar adenomas (2%), tumors were found in the anterior pituitary gland in 81 patients (93%), between the anterior and posterior pituitary gland in 2 patients (2%), or in the posterior pituitary gland[22] in 2 patients (2%). Adenomas in the anterior pituitary lobe had an epicenter in the right third of the gland (31 tumors [38% of anterior pituitary adenomas]), the central third (16 tumors [20%]), or the left third (32 tumors [40%]). Two patients (2%) had large adenomas occupying most of the sella. Overall, 30 adenomas (37%) were located in the far lateral aspect of the anterior pituitary lobe.

Dural Invasion—Overall, dural invasion was histologically confirmed in 30 patients (34%), which composed 81% of the cases with presumed intraoperative evidence of dural invasion (Figs. 1–3). Eighteen patients (60% of dural invasion cases, 21% of all patients) had surgical and histological evidence of cavernous sinus wall invasion, and 12 patients (40% of dural invasion cases) had surgical and histological evidence of invasion of the sella dura other than the cavernous sinus, including the anterior, inferior, and/or posterior sella dura (Table 1). Four patients (22% of those with cavernous sinus wall invasion) with cavernous sinus invasion also had other contiguous sites of dural invasion.

Among the 30 adenomas located in the far lateral portion (tumors that had their lateral surface at the level of the lateral pituitary capsule) of the anterior lobe, 13 (43%) had cavernous sinus invasion, despite being very small in some cases (2 mm). Overall, the mean size of tumors in the far lateral portion of the anterior lobe was 7.4 ± 3.5 mm (range 2–16 mm). There was no significant difference between tumors arising in the far lateral aspect of the anterior pituitary gland and invading the cavernous sinus (8.5 ± 4.3 mm, range 2–16 mm), and those that did not invade the cavernous sinus (6.5 ± 2.8 mm, range 2–15 mm; $p = 0.3$, Mann-Whitney test).

Histological analysis of the routinely procured anterior sella dura specimens revealed invasion by an ACTH-positive adenoma in 11 (13%) of the 87 patients (Table 2 and Fig. 2).

Five of these patients (45% of patients with anterior dural invasion) had gross invasion evident on exposure of the anterior dura that was resected; three of these patients (60%) had other contiguous sites of dural invasion (all in the cavernous sinus). The remaining 6 patients (55% of those with anterior dural invasion, 7% of all patients) did not have gross evidence of anterior dural invasion, although histological analysis did reveal invasion. Two of these patients (33%) had other sites of dural invasion (1 cavernous sinus wall and 1 inferior sella dura).

Imaging Correlation—While invasion of the cavernous sinus wall was predicted by preoperative MR imaging in 6 patients (7% of all patients), it was confirmed in only 4 (22% of the 18 patients with cavernous sinus invasion) based on surgical and histological findings. Preoperative MR imaging indicated cavernous sinus invasion in the remaining 2 patients, but they did not have evidence of invasion at surgery or histological analysis. The sensitivity of MR imaging for cavernous sinus invasion was 22% and the specificity was 97%. Preoperative MR imaging did not demonstrate dural invasion at sites other than the cavernous sinus in any patient (Figs. 1 and 2).

Size of Tumor—Overall, the mean adenoma size measured at surgery was 7.5 ± 5.7 mm (range 1.5–37 mm). The mean size of adenomas associated with dural invasion (10.9 ± 7.8 mm, range 2–37 mm) was significantly larger than the size of those not associated with dural invasion (5.7 ± 2.1 mm, range 2.5–12 mm; $p = 0.0006$, Mann-Whitney test). The tumors in all 6 patients who underwent partial hypophysectomy were microadenomas. There was a direct correlation between adenoma size and the incidence of cavernous sinus and/or sella dura invasion (Tables 1 and 2 and Fig. 3), including the presence of dural invasion associated with all adenomas > 15 mm in diameter.

Effect of Age on Dural Invasion—There was no significant difference in the incidence or distribution of dural invasion between the 9 pediatric (28% of 32 pediatric patients) and 21 adult patients (38% of 55 adult patients; $p = 0.4$, chi-square test) with invasion. Overall, the mean age of patients with adenoma-associated dural invasion was 32.9 ± 15.9 years (range 10–63 years), which was not significantly ($p = 0.6$, unpaired t-test) different from the mean age of patients without such invasion (31.1 ± 17.1 years, range 7–67 years).

Discussion

Methodological Differences Compared with Previous Studies

Previous studies have examined the characteristics and incidence of pituitary adenoma-associated dural invasion for differing pituitary tumor subtypes, including ACTH-positive adenomas.[5,12,19–21] Data from these studies demonstrated that extrapituitary tumor invasion of surrounding sella dura could be frequent (24%–94%) and that increasing tumor size as well as age is directly associated with the incidence of invasion.[5,12,19,21] Further, the data showed that dural invasion was associated with incomplete tumor removal and recurrence.[12] While these studies provided important information about the incidence of adenoma-associated dural invasion, they were limited by several methodological factors that have

made it difficult to draw direct conclusions related to the precise origin and incidence of this pathological feature in CD.

Specific methodological limitations of previous studies have been multifactorial.[5,12,19–21] First, all previous reports of pituitary adenoma–associated dural invasion were based on retrospective case series, and most examined nonconsecutive specimens.[5,12,19–21] This resulted in a selection bias in which only patients with sites of apparent invasion during surgery[12,21] and/or primarily macroadenomas (most ACTH-positive adenomas are microadenomas) were included in the analysis.[5,12,20,21] Second, in previous studies of anterior dura samples,[12] the sample was coagulated. This can cause tissue distortion and alter dural histology, leading to a misdiagnosis of invasion as a result of adherence of the underlying surface of the pituitary to the inner layer of dura. Third, although immunohistochemical analysis of the tumor was commonly performed, it was not done for the dural specimen.[5,12,19,21] Fourth, no correlation between adenoma location and dural invasion location was established, including situations in which the anterior dura was sampled.[12,19,21]

To overcome these methodological limitations, we prospectively examined the characteristics and incidence of dural invasion in a large series of consecutive patients with CD. Specifically, we systematically examined the sella dura by routinely removing a large section of the anterior sella dura (the anatomical region with the largest surface area exposed to the anterior pituitary gland). The anterior dura and other dural sites of presumed invasion identified at surgery were removed without coagulation, including the medial wall of the cavernous sinus. Immunohistochemical analysis of all dural specimens was performed to confirm or refute adenoma-associated dural invasion and to differentiate invasion from tissue procurement–related histological artifact. Finally, tumor location and dural invasion location correlations were analyzed.

Relevance of Dural Invasion Incidence in Cushing Disease to Other Adenoma Types

Histological evidence of dural invasion in the current series occurred in 30 (34%) of 87 patients with CD. Meij and colleagues[12] detected dural invasion in 18 (45%) of 40 patients with CD, an incidence that was identical to the overall incidence of dural invasion by all pituitary adenoma subtypes in their study. Although they reported a higher incidence (45% versus 34%) than we did, their value may reflect the nonconsecutive retrospective nature of their study. Specifically, the dura was not sampled in 35% of the surgical patients with pituitary adenomas over the same interval, and patients with microadenomas were less likely to have sampling of the dura.[12] This selection bias could have produced an artificially high incidence of dural invasion in their study. Since previous studies have demonstrated no difference in the incidence of dural invasion by the various types of pituitary adenomas, it is likely that the results of our study are also applicable to other tumor types of various sizes.[12,19,21]

Pattern of Dural Invasion by Adenomas

While previous studies have suggested that the lateral medial cavernous sinus wall is the least common site of invasion by pituitary adenomas,[20] data in the current study indicate

that it is the most common site of invasion by ACTH-secreting adenomas. Overall, because the CD-associated tumors were generally small when treated, the precise region of preferential dural invasion could be captured with an accuracy that is impossible with larger adenomas that have progressed well beyond the stage at which the site of initial invasion is apparent. Previous studies have failed to document a correlation between the location of the adenoma (including microadenomas) and the likelihood of the anatomical site of invasion, perhaps because of the predominance of large tumors in those studies. Further, authors of previous studies did not remove the medial wall of the cavernous sinus for analysis in cases of dural invasion identified at the time of surgery. The lack of a precise correlation with tumor location and the failure to remove the medial cavernous sinus wall when invaded probably led to an underestimation of cavernous sinus wall invasion in these prior studies.

Although nearly all (98%) ACTH-positive adenomas were located in the anterior lobe of the pituitary gland in the current study, 60% (Table 1) of dural invasions involved the medial wall of the cavernous sinus and only 37% involved the anterior dura (13% of all cases, 7% of cases if grossly evident anterior sella dura invasion was excluded). Based on epidemiological, physiological, and anatomical findings, there are several explanations for the preferential invasion of the medial wall of the cavernous sinus by these adenomas. Because most of these lesions arise in the lateral aspect of the anterior pituitary gland (78% in the current study), the medial walls of the cavernous sinuses are immediately adjacent to the region of tumor origin and thus susceptible to invasion. Further, venous drainage of the pituitary gland occurs through venous channels that direct pituitary venous blood on each side into the cavernous sinus through the medial dural wall.[16,23] These lateral sites are also the regions of penetration of the pituitary capsule, a dense multilayered reticulin structure, by the veins, and they are at the same location as the site of penetration of the dura of the cavernous sinus wall. The sites of contiguous penetration of the pituitary capsule and dura provide lower resistance corridors for tumor invasion, as compared with other regions of the sella dura, including the immediately adjacent anterior sella dura (Fig. 4 and Table 2).[15]

The critical impact that this anatomical conduit, which is formed by the penetration of the pituitary capsule and medial cavernous sinus wall by draining veins, has for dural invasion is underscored by the high frequency of invasion by tumors arising in the far lateral aspect of the anterior pituitary gland (including very small tumors in this location of the pituitary gland). In the current study, 43% of the adenomas located at the lateral edge of the anterior lobe had invasion of the medial wall of the cavernous sinus. Further, there was no significant difference in the size of tumors arising in this region between those that invaded the cavernous sinus and those that did not. These findings indicate that adenomas in the far lateral regions of the pituitary gland can easily grow into the cavernous sinus wall and cavernous sinus.

Imaging Detection of Invasion

Magnetic resonance imaging correctly identified only 4 (22%) of the 18 patients (78% false negatives) with cavernous sinus invasion and did not accurately predict invasion of other sites of sella dura invasion in any patient. Further, MR imaging inaccurately (false positive) predicted cavernous sinus invasion in 2 patients (33% of the 6 patients in whom this imaging

modality predicted cavernous sinus invasion) who did not have cavernous sinus invasion at surgery. These findings are consistent with previous imaging and clinical reports,[4,9,10] including the study by Dickerman and Oldfield[6] that described features associated with cases of persistent and recurrent CD. At repeat surgery for CD, they found that residual tumor was always at sites immediately contiguous with the original tumor site. Furthermore, most patients (62%) had dural invasion (95% in the medial cavernous sinus wall) but none had MR imaging evidence of invasion. Given the low sensitivity of MR imaging (22%), these findings underscore the importance of systematic and careful exploration of the sella and adenoma-associated dura to assess for the presence of invasion (particularly cavernous sinus invasion) in CD cases, as preoperative MR imaging may not predict the absence of cavernous sinus or other sella dura invasion. On the other hand, if cavernous sinus invasion is seen on MR imaging (specificity 97%), it is likely that it exists and is important to identify surgically.

Incidence of Invasion is Related to Adenoma Size

Adrenocorticotropic hormone–secreting adenoma invasion of the cavernous sinus wall and/or sella dura is directly linked to tumor size (Table 1). While microadenomas (≤ 10 mm in diameter) were associated with cavernous sinus and/or sella dura invasion in 26% of cases, macroadenomas (> 10 mm in diameter) were associated with invasion in 86% of cases. The not infrequent incidence of dural invasion associated with ACTH-secreting microadenomas underlines the fact that a small, entirely intrasellar adenoma (even those ≤ 5 mm in diameter) can be associated with invasion of the immediately adjacent dura (93% of tumors were located in the anterior pituitary gland). Further, the presence of an adenoma contained completely within the cavernous sinus indicates the potential for varying presentations of these tumors with respect to the sella and surrounding dural structures.

Effect of Age on Incidence of Dural Invasion

Patient age at surgery did not have an association with the incidence of dural invasion. The incidence of dural invasion in pediatric patients with CD was 28%, which was similar to the incidence in adults with CD (38%; $p = 0.4$, chi-square test). Meij and colleagues[12] previously reported that the incidence of pituitary adenoma invasion increased with age: the mean age of patients with noninvasive adenomas was 43 years, whereas the mean age of those harboring invasive adenomas was 50 years. Meij and colleagues attributed the increased incidence of dural invasion to the possibility that older patients may have larger tumors at the time of diagnosis and treatment. Because ACTH-secreting adenomas associated with CD often have a profound clinical effect even when they are small, they may frequently be detected before they become large, which might explain why the previously described association between age and adenoma invasion was not found in ACTH-secreting adenomas.

Surgical Implications

Taken together, findings in the current study have several direct implications for the surgical management of CD-associated pituitary adenomas. First, wide exposure of the anterior and inferior sella dura, including the medial dural wall of the cavernous sinuses, is critical to accurately assess for sites of dural invasion. Most ACTH-secreting adenomas (78% of those

in this series) arise in the lateral thirds of the pituitary gland and could subsequently involve the medial wall of the cavernous sinuses. Close inspection of these structures through wide exposure is needed. Second, the identification and use of the adenoma histological pseudocapsule to circumferentially remove the tumor can assist in recognizing sites of dural attachment or invasion during lesion removal.[8] Third, dural sites with suspected or gross invasion should be completely resected when possible to maximize the opportunity for lasting therapeutic benefit. Ninety-eight percent of this series of patients had a biochemical cure and no recurrence at the last follow-up. The 2 patients whose conditions were not cured because of extensive cavernous sinus invasion with carotid artery involvement underwent radiation therapy. Fourth, late recurrence after evidence of early biochemical remission likely represents the intradural recurrence of microscopic disease near or at the site prior to adenoma removal.[6]

Conclusions

Overall, although the incidence of dural invasion in the current study of consecutive patients with CD is, in general, consistent with the results of other studies, the distribution of invasion preferentially into the cavernous sinus, the low incidence of histological invasion in the absence of invasion visible at surgery, and the correlation between the site of the adenoma and the site of dural invasion differ considerably.

Abbreviations used in this paper

ACTH	adrenocorticotropic hormone
CD	Cushing disease

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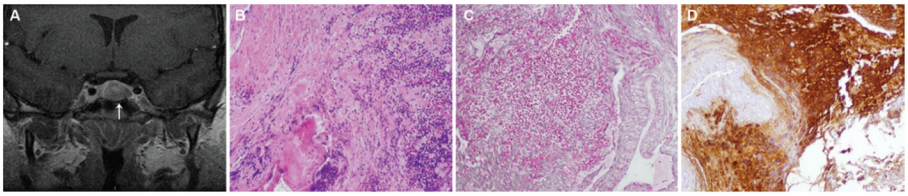

Fig. 1.

Magnetic resonance imaging and histological findings in a patient with evidence of cavernous sinus invasion during both surgery and histological analysis. **A:** Coronal postcontrast T1-weighted MR image showing a hypoenhancing pituitary adenoma (1.1 cm, *arrow*) in the left side of the anterior lobe of the pituitary. **B:** Photomicrograph of dural specimen demonstrating cellular invasion suggestive of adenoma. **C:** Photomicrograph showing fibrous dura and loss of normal lobular pituitary architecture in adjacent tissue consistent with adenoma and invasion. **D:** Photomicrograph confirming invasion of the dura by an ACTH-producing adenoma. H & E **(B)**, reticulin **(C)**, and ACTH immunostaining **(D)**. Original magnification × 10.

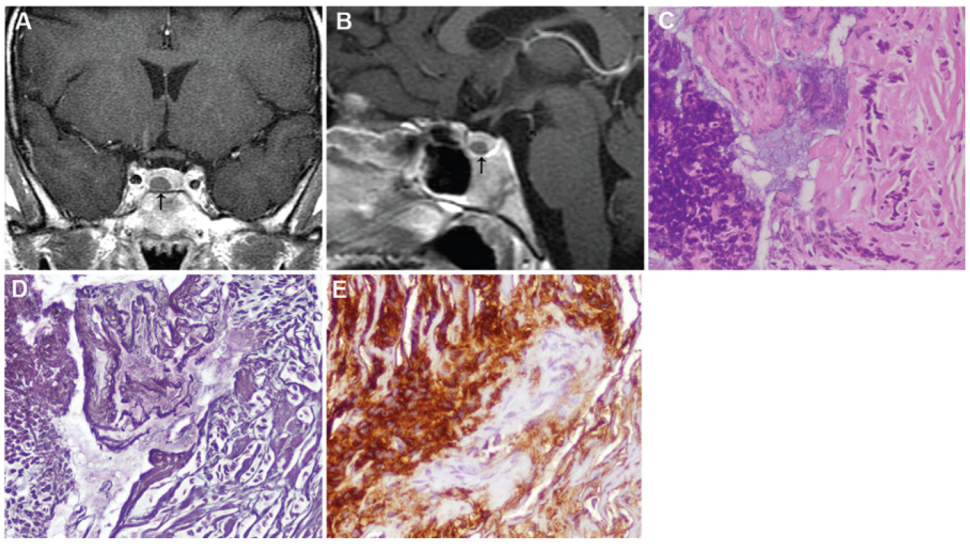

Fig. 2.

Magnetic resonance imaging and histological findings in a patient with evidence of anterior dural invasion during both surgery and histological analysis. **A:** Coronal postcontrast T1-weighted MR image showing a hypoenhancing pituitary adenoma (8 mm, *arrow*) in the right anterior pituitary gland. **B:** Sagittal postcontrast T1-weighted MR image showing a hypoenhancing pituitary adenoma (6 mm, *arrow*) in the anterior pituitary gland, abutting the anterior dura. **C:** Photomicrograph of anterior dural specimen demonstrating cellular invasion by an adenoma. **D:** Photomicrograph showing fibrous anterior dura and loss of normal lobular pituitary architecture in adjacent tissue consistent with adenoma and invasion. **E:** Photomicrograph showing invasion of the anterior dura by an adenoma. H & E **(C)**, reticulin **(D)**, and ACTH immunostaining **(E)**. Original magnification × 20.

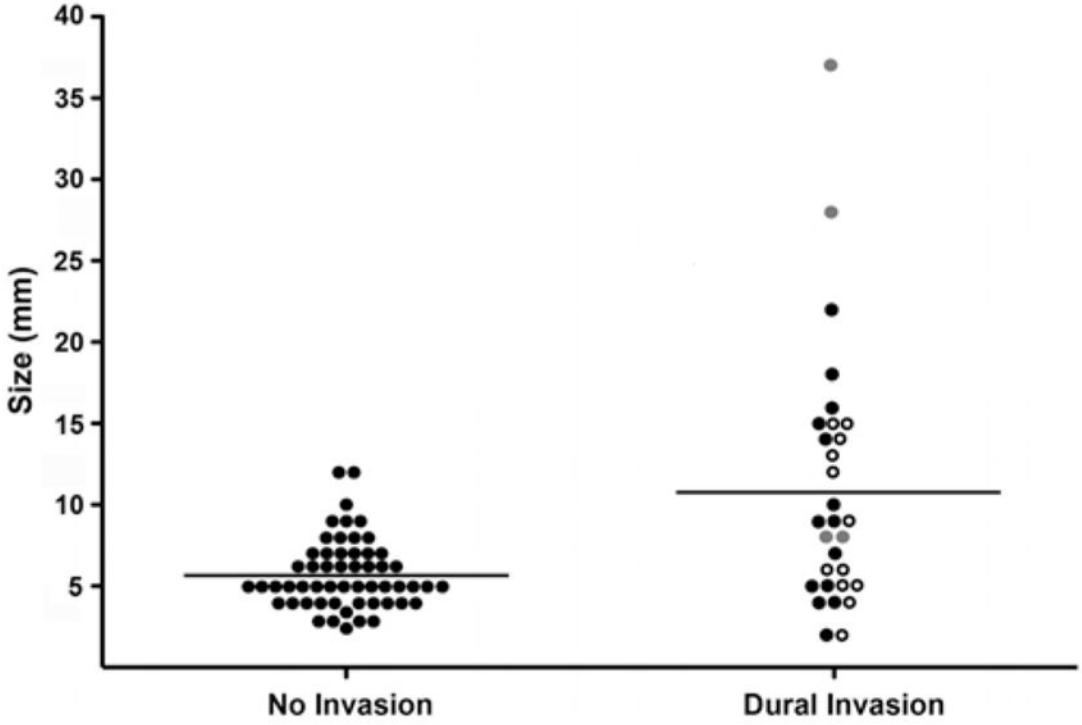

Fig. 3.

Graph showing the correlation among adenoma size, adenoma distribution, and dural invasion. Invasive adenomas are classified as invading the cavernous sinus *(closed circles)*, the sella dura (not including cavernous sinus, *open circles*), and both the cavernous sinus and the sella dura *(gray circles)*. The mean size of adenomas associated with dural invasion *(horizontal line*, mean 10.9 ± 7.8 mm, range 2–37 mm) was significantly larger than the mean size of adenomas not associated with dural invasion *(horizontal line*, mean 5.7 ± 2.1 mm, range 2.5–12 mm; p = 0.0006, Mann-Whitney test).

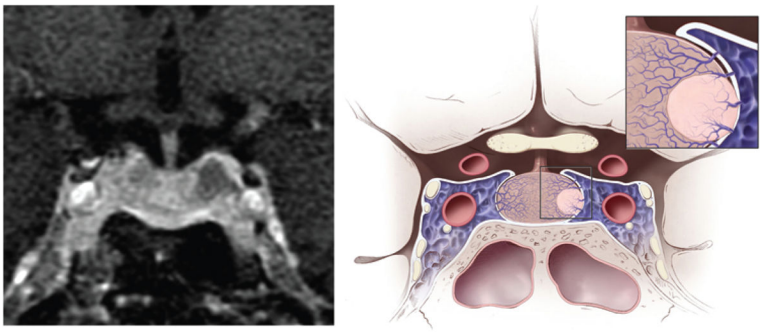

Fig. 4.

Coronal postcontrast MR image **(left)** demonstrating a hypointense adenoma in the far lateral aspect of the pituitary gland. At surgery, the adenoma was found invading the cavernous sinus wall dura. Illustration **(right)** depicting the relationship of the tumor to the venous drainage of the pituitary gland, which courses laterally into the cavernous sinuses. The veins draining the pituitary penetrate the pituitary capsule as well as the dura of the medial cavernous sinus wall. These sites of contiguous pituitary capsule and dura penetration provide low resistance corridors for tumor invasion **(inset)**, compared with other regions of the sella dura, including the immediately adjacent anterior sella dura. This anatomical relationship underlies the preferential invasion of tumors into the medial cavernous sinus wall.

TABLE 1

Histological incidence of dural invasion based on adenoma size*

Size (mm)	Total No. of Tumors (%)	CS Invasion Only (%)	Sella Dura Invasion Only (%)	CS & Sella Dura Invasion (%)	Total No. of Invading Tumors (%)
0–5	40 (47)	5 (13)	4 (10)	0 (0)	9 (23)
6–10	31 (36)	4 (13)	3 (10)	2 (6)	9 (29)
11–15	9 (11)	2 (22)	5 (56)	0 (0)	7 (78)
>15	5 (6)	3 (60)	0 (0)	2 (40)	5 (100)
total	85	14 (16)	12 (14)	4 (5)	30 (35)

* CS = cavernous sinus.

TABLE 2

Histological incidence of anterior dural invasion based on adenoma size

Size (mm)	Anterior Dural Invasion (%)
0–5	2 (5)
6–10	4 (13)
11–15	3 (33)
>15	2 (40)
total	11 (13)