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Ira F. Braun

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Prolactin-Secreting Pituitary Microadenomas: Inaccuracy of High-Resolution CT Imaging

Patricia C. Davis¹
James C. Hoffman, Jr.¹
George T. Tindall²
Ira F. Braun¹

Computed tomographic (CT) and surgical findings were correlated retrospectively in 51 patients with preoperative diagnoses of prolactin-secreting pituitary microadenomas. Twenty-four had microadenomas at surgery. Twenty-eight had identifiable discrete lesions. Of these, 18 had microadenomas and 10 did not; these two groups could not be distinguished reliably. Six patients with proven microadenomas had normal CT scans. Focal hypodense lesions, sellar floor erosion, infundibulum displacement, gland height greater than 8 mm, and an abnormal diaphragma sellae configuration are neither sensitive nor specific findings of microadenoma. A significant number of patients with proven microadenomas had few or none of these abnormalities. Thus, recognition of prolactin microadenoma is seldom possible by CT alone, even with high-resolution direct coronal imaging.

Computed tomography (CT) has replaced pluridirectional tomography, pneumoencephalography, and most angiographic studies in the neurodiagnostic examination of patients suspected of harboring a pituitary adenoma. CT is useful in localizing the lesion and in evaluating suprasellar or parasellar extent [1-7]. CT criteria suggestive of prolactin microadenoma include focal hypo- or hyperdense lesions, elevated diaphragma sellae, abnormal gland height, infundibulum displacement, and sellar floor erosion [1, 2, 4, 7-14]. Relatively few large series of CT findings in pituitary prolactin-secreting microadenomas with surgical correlation have been reported [1, 2, 8, 9]. In an effort to evaluate the diagnostic accuracy of high-resolution CT in this disorder, we retrospectively determined the accuracy of CT in diagnosing and localizing pituitary microadenomas in 51 patients who underwent transsphenoidal surgery.

Materials and Methods

From May 1980 to July 1983, 51 patients had direct coronal CT scans of the sella and transsphenoidal surgery for suspected prolactin-secreting pituitary microadenoma. All patients had clinical symptoms attributed to hyperprolactinemia (amenorrhea, galactorrhea, infertility and/or decreased libido), and elevated prolactin levels (greater than or equal to 25 ng/ml). Patients with nondiagnostic scans; axial CT images only; evidence of a nonfunctioning or nonprolactin, hormonally active lesion; and patients with prior sellar surgery were excluded. Microadenomas were defined as being less than or equal to 10 mm in size. Macroadenomas, greater than 1 cm in size, were excluded (one patient with maximum height of intrasellar contents on CT of 10 mm and estimated surgical size of 11 mm was included). Patients were offered surgical intervention primarily on the basis of clinical and laboratory determinations, with CT used to exclude macroadenomas and other masses. All patients meeting these criteria were offered surgery. No other factors were identified that precluded surgery, although some patients elected nonsurgical therapy. Patient age, preoperative symptoms, laboratory values, surgical size and location, and histologic diagnoses were correlated with CT findings.

All patients had preoperative direct coronal CT scans of the sella turcica (GE CT/T 8800). After a lateral scout view, contiguous images with 1.5 mm collimation were completed immediately after a 100 ml bolus of 60% intravenous contrast material (28.2 g I/ml) followed

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¹ Department of Radiology, Emory University School of Medicine and Emory Clinic, 1365 Clifton Rd., N.E., Atlanta, GA 30322. Address reprint requests to P. C. Davis.

² Department of Neurosurgery, Emory University School of Medicine and Emory Clinic, Atlanta, GA 30322.

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by a drip infusion of 30% (42.3 g l/ml) contrast material during the rest of the study. Images were retrospectively interpreted blindly without knowledge of laboratory, surgical, or histologic diagnosis. CT criteria evaluated included height of intrasellar contents [15]; gland homogeneity; infundibulum position; diaphragma sellae configuration; presence, location, and size of focal lesions; and sellar floor erosion. Statistical analysis was completed using Fisher exact test.

All of the transsphenoidal surgical procedures were performed by the same neurosurgeon (G. T. T.). Particular note was made of the size and exact location (i.e., anterior, posterior, right, or left) of the microadenoma in the sella. For purposes of CT correlation, these were grouped only as right, midline, or left.

Histologic examination was performed on all specimens. An excessive proliferation of one benign cell type with disruption of the normal acinar pattern of the pituitary gland and surgical size estimate less than or equal to 10 mm was identified as a microadenoma [16–18]. An increase in the number of cells without disruption of the normal acinar pattern was identified as focal hyperplasia. The significance of focal hyperplasia is controversial; some evidence suggests that it may be a precursor to microadenoma formation [16, 19–23].

Results

The group consisted of 50 women (18–36 years old) and one man (50 years old). Symptoms included amenorrhea, galactorrhea, infertility, and decreased libido. As charted in table 1, patients with tumors could not be differentiated from

TABLE 1: Clinical Symptoms Correlated with Histologic Diagnosis in Suspected Microadenomas

Clinical Symptom	Histologic Diagnosis	
	Microadenoma (n = 39)	Nonmicroadenoma (n = 12)
Amenorrhea	34	8
Galactorrhea	32	10
Infertility	1	0
Decreased libido	1	0

Note.—Nonmicroadenoma patients include those with normal histology, benign cysts, and focal hyperplasia.

those without tumors on the basis of clinical findings alone.

All patients had hyperprolactinemia (normal less than 25 ng/ml) with levels of 25–700 ng/ml. The mean prolactin level in patients with microadenoma (39 patients) was 147 ng/ml (range, 34–700 ng/ml), while patients without tumor (12 patients) had a mean prolactin level of 88 ng/ml (range, 25–363 ng/ml). Only one nontumor patient had a preoperative prolactin level greater than 125 ng/ml; in this case, focal prolactin cell hyperplasia was identified histologically. Prolactin levels less than 125 ng/ml were found in patients with microadenomas, focal pituitary hyperplasia, cysts, and normal glands. Histologically, 39 of 51 patients had microadenomas; thus no tumor was identified in 12 patients with hyperprolactinemia. Of these 12 patients, nine had focal hyperplasia, two were histologically normal, and one had a benign cyst. CT and histologic findings are charted in table 2. Microadenoma sizes at surgery were 4–11 mm (one patient was included with maximum height of intrasellar contents of 10 mm on CT and surgical size estimate of 11 mm). Seventeen microadenomas were on the right, 19 were on the left, two were midline, and one was unrecorded in location. All microadenoma patients with prolactin levels greater than 125 ng/ml had lesions greater than 5 mm in diameter at surgery (13 patients).

CT findings in microadenoma patients are correlated with surgical findings in table 2. A laterally displaced pituitary infundibulum was present only in patients with microadenoma (five of 39); all other criteria evaluated were present in patients with microadenomas and those in whom no tumor was found. No infundibulum displacement was present in 14 right- and 17 left-sided microadenomas.

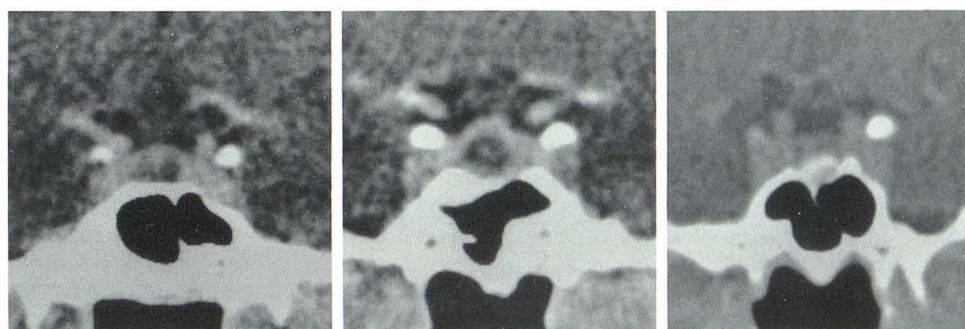
The presence of a focal lesion was a statistically significant indicator for microadenoma ($p = 0.0485$, Fisher exact test). No other CT criteria were statistically significant in distinguishing the microadenoma patients. Nineteen of 39 focal lesions identified with CT were hypodense areas discrete enough to be measured in maximum diameter. Only two nonmicroadenoma patients had measurable hypodense lesions on CT (fig. 1). One was a 9 mm midline benign cyst; the other was a

TABLE 2: Correlation of CT Findings with Histology in Detection of Microadenomas

CT Criteria	No. (%) of Microadenomas (n = 39)		No. (%) of Nonmicroadenomas (n = 12)
	CT Findings	Surgical Agreement	CT Findings
Displaced infundibulum	5 (28)	5 (100)	0
Focal lesion:			
Hypodense	19 (49)	17 (89)	2 (16)
Hyperdense	2 (5)	2 (100)	0
Size of lesion (± 2 mm)	...	10* (48)	...
Total	21 (54)	...	2 (16)
Sellar floor erosion	20 (51)	13 (65)	3 (25)
Abnormal diaphragma sellae:			
Generalized convexity	12 (31)	1 (8)	6 (50)
Focal convexity	11 (28)	10 (91)	2 (16)
Total	23 (59)	...	8 (66)
Gland height >8 mm	5 (13)	...	1 (8)

* Of 21 focal lesions.

Fig. 1.—Focal hypodense lesions not caused by microadenoma. **A**, 25-year-old woman with bilateral focal hypodense lesions (4 mm each), prolactin level of 73 ng/ml, and normal gland histologically. **B**, 21-year-old woman with 9 mm midline focal hypodense lesion, prolactin level of 60 ng/ml, and benign cyst histologically.



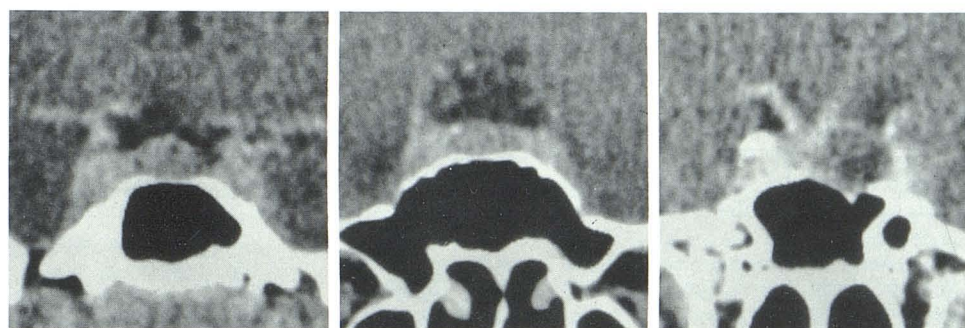
1A

1B

2

Fig. 2.—21-year-old woman with focal calcified lesion (298 H) on CT, prolactin level of 237 ng/ml, and microadenoma containing calcospherites at surgery.

Fig. 3.—Diaphragma sellae abnormalities. **A**, Generalized convexity of diaphragma sellae in 23-year-old woman with 7 mm right-sided microadenoma at surgery. No focal hypo- or hyperdense lesion identified by CT. **B**, Focal convexity of diaphragma sellae on left correlated with 8 mm left-sided microadenoma at surgery. No focal hypo- or hyperdense lesion identified by CT. **C**, More marked focal convexity of diaphragma sellae on right with infundibulum displacement in patient with right-sided hypodense lesion, prolactin level of 550 ng/ml, and 9 mm right-sided microadenoma at surgery.



A

B

C

patient with normal histology who had two 4 mm nonmidline focal lucencies. This was the only patient in our series with multiple focal hypodense lesions. In microadenoma patients, focal hypodense lesions were located on the right in 11 and on the left in eight. No midline focal hypodense lesions were present in patients with microadenomas. Two patients had well defined hyperdense lesions that were calcified by CT criteria (about 300 H) and that consisted of microadenomas containing calcospherites (fig. 2). No other hyperdense or enhancing masses were encountered.

Focal lesions were 2–9 mm in size on CT. Surgical findings matched the location of focal lesions on CT in 19 of 21 cases; in two patients, nonmidline focal hypodense lesions were opposite the microadenoma at surgery. In 10 of 21 microadenomas, the size estimate at surgery was within ± 2 mm of the lesion size as determined by CT.

The sellar floor was evaluated by CT for focal ballooning, erosion, or thinning unrelated to the sphenoidal septum insertions. We were conservative in describing sellar floor thinning without ballooning, because marked variations have been reported for sellar floor thickness in normal patients [24–27]. Twenty microadenoma patients had abnormalities of the sellar floor; the site of sellar floor erosion failed to correlate with surgical tumor site in seven of 20 patients. Three patients without microadenomas had sellar floor abnormalities; two of these three had no lesion at surgery to account for the bony changes.

Diaphragma sellae configuration was classified as generally convex, focally convex, flat, or concave (fig. 3). In microadenoma patients, 12 of 39 had generalized convexity and 11 of 39 had focal convexity of the diaphragma sellae. The site of focal convexity correlated with surgical tumor locus in 10 of 11 patients. In microadenoma patients with generalized convexity, only one of 12 harbored a midline lesion.

Maximum height of intrasellar contents ("gland height") by CT was 4–10 mm. Only five patients with proven microadenomas and one patient with a benign cyst had gland heights greater than 8 mm; thus, 34 patients with proven microadenomas had gland heights less than or equal to 8 mm.

Gland homogeneity proved difficult to evaluate. An attempt was made to describe each gland as homogeneous or mottled (inhomogeneous), excluding discrete focal lesions when present. Mild inhomogeneity or mottling of the sellar contents was found in seven of 39 microadenoma patients and in three of 12 patients without tumors.

Categorization of each patient by the number of CT abnormalities revealed no clear-cut distinction between microadenoma and nonmicroadenoma patients (table 3), although patients with several CT abnormalities were more likely to harbor microadenomas. The sensitivity (probability of a positive test in a patient with microadenoma) and specificity (probability of a negative test in a patient without microadenoma) of CT abnormalities in diagnosing and localizing pituitary microadenomas are charted in table 4.

TABLE 3: Frequency of Major CT Abnormalities with Microadenomas and Nonmicroadenomas

Diagnosis	No. of Abnormal CT Findings					
	0	1	2	3	4	5
Microadenoma	6	12	8	8	4	1
Nonmicroadenoma	4	4	3	0	1	0

Note.—CT findings considered were gland height >8 mm, abnormal diaphragma sellae, infundibulum displacement, sellar floor erosion, and presence of a focal lesion.

TABLE 4: Sensitivity and Specificity of CT in the Diagnosis and Localization of Prolactin Microadenomas

CT Criteria	No. Positive/ Negative	% Sensitivity/ Specificity
Gland height:		
>8 mm	5/1	...
<8 mm	34/11	13/92
Focal lesion:		
Present	19/2*	...
Absent	20/10	49/83
Sellar floor:		
Eroded	13/3†	...
Not eroded	26/9	33/75
Infundibulum:		
Displaced	5/0	...
Not displaced	34/12	13/100
Diaphragma sellae:		
Normal	23/8	...
Abnormal	16/4	59/33

* Two of 19 had focal lesions that did not correlate with tumor locus.

† Although 20 microadenoma patients had sellar floor erosion, in only 13 did it correlate correctly with surgical tumor site.

Discussion

High-resolution CT has replaced all other radiographic techniques, with the exception of a preoperative lateral skull film, at our institution in the evaluation of patients for pituitary microadenoma. Although CT alone permits visualization of the intrasellar contents, the reliability of high-resolution CT in diagnosing and localizing microadenomas in a large number of surgically proven cases is unclear. In our series, CT abnormalities were not specific indicators for microadenomas; overlap occurred with nonmicroadenoma patients demonstrating similar CT abnormalities. Likewise, many microadenomas resulted in few or no radiographic abnormalities; thus, CT was relatively insensitive in diagnosing and localizing the microadenoma.

Certain CT abnormalities were helpful in identifying the microadenoma patient. The presence of a focal hyper- or hypodense lesion was the only statistically significant indicator for microadenoma in our series. In our series and in others [2, 7, 8, 28], a solitary, focal, nonmidline, hypodense lesion relative to the surrounding pituitary gland discrete enough to be measured was likely to represent a microadenoma. Scanning technique is important in this determination; scanning must be completed immediately after bolus injection of intravenous contrast material. Delayed scanning may result in the conversion of a hypodense lesion to an isodense lesion [9]. In a recently reported series of 25 patients with prolactin

levels greater than 100 ng/ml and surgically proven microadenomas [9], all had focal hypodense lesions by CT.

Two nonmicroadenoma patients in our series had focal hypodense lesions by CT (fig. 1). One patient with a benign cyst histologically had a solitary midline focal hypodense lesion with a convex diaphragma sellae and hyperprolactinemia. Although colloid cysts often occur in the midline [29, 30] and microadenomas tend to occur laterally [31, 32], in this situation a midline microadenoma could not be excluded preoperatively. The other patient had bilateral, nonmidline, focal, hypodense lesions, which were very discrete and lobular, and a convex diaphragma sellae with hyperprolactinemia; this patient had a histologically normal gland. Although small, bilateral, diverging, focal lucencies have been attributed to colloid cysts bilaterally within the pars intermedia [29], because of the size, symptoms, and diaphragma sellae abnormality, the diagnosis of microadenoma could not be excluded preoperatively. Other reported etiologies resulting in focal hypodense intrasellar lesions by CT not found in our series include infarction, metastases, abscess, necrotic or cystic tumor, hematoma, fat, and epidermoid cyst [1, 2, 7, 8, 29, 33, 34]. In our opinion, an atypical location of focal lesion on CT should not be sufficient reason to exclude microadenoma in the appropriate clinical setting.

Syvertsen et al. [2] observed that microadenomas associated with hyperprolactinemia may be isodense with normal pituitary tissue after administration of intravenous contrast material. In our series, 43% of surgically proven microadenomas were isodense with the rest of the pituitary gland. Dynamic and delayed CT images were not evaluated [9, 35]; perhaps an isodense lesion could be identified with these techniques.

Although pituitary adenomas have been described as enhancing lesions relative to the surrounding pituitary gland [1, 8, 10–14, 36], in our series no microadenomas were identified that showed enhancement. Two patients had hyperdense lesions; the CT density (300 H) of these lesions suggested calcification, and both contained calcospherites within microadenomas histologically. Perhaps the contrast-enhanced lesions described in the literature may result from a delay between contrast administration and scanning, larger lesions, volume-averaging with thicker slices or axial scanning, calcification, and/or hyperdensity relative to brain parenchyma rather than to surrounding pituitary tissue.

A laterally displaced infundibulum was encountered only with microadenoma in our series. In anatomic studies [29], however, the infundibulum occasionally may be slightly off midline in histologically normal glands because of eccentric positioning of the posterior lobe of the pituitary.

In our study, sellar floor abnormalities correlated inconsistently with microadenoma location, with 65% agreement of tumor locus with bony changes on CT. Forty-nine percent of patients with proven microadenomas had no sellar floor abnormality. Our data thus agreed with those of other investigators [20, 29, 37, 38] that sellar floor abnormalities are supportive evidence only when clearly associated with a focal lesion in a patient with clinical, endocrinologic, and other CT criteria to support the diagnosis of microadenoma.

The diaphragma sellae configuration was variable in patients with microadenoma. In our series, 31% of microadenoma and 50% of nonmicroadenoma patients had generally convex diaphragma sellae. Focal convexity of the diaphragma sellae correlated well with site of microadenoma (91%); however, this abnormality was also found in two nonmicroadenoma patients. A "normal" diaphragma sellae (concave or flat) was present in 41% of proven microadenoma and 33% of nonmicroadenoma patients.

Height of intrasellar contents ("gland height") did not differentiate microadenoma from nonmicroadenoma patients. Eighty-seven percent of microadenoma patients and 92% of nonmicroadenoma patients had a normal "gland height" (less than or equal to 8 mm). Six patients had gland heights in the 8–10 mm range; of these, one had a benign cyst. A recent report suggests that the maximum height of intrasellar contents in normal adult women may be as great as 9.7 mm [15].

Evaluation of gland homogeneity was not helpful in distinguishing the etiology of hyperprolactinemia. Inhomogeneous glands were found in microadenoma and nonmicroadenoma patients. This criterion was subjective at best and of little value in our series. With 1.5 mm scan collimation, Swartz et al. [15] found tiny focal lucencies resulting in an inhomogeneous appearance in the normal pituitary gland, possibly related to colloid cysts.

Normal CT scans were found in six microadenoma and four nonmicroadenoma patients. Normal CT scans in patients with microadenomas were often noted with earlier-generation scanners [1, 5, 8]; however, it appeared likely that, with high-resolution imaging, small microadenomas in the symptomatic patient could be identified. Our findings did not confirm this; thus, strong reliance should be placed on clinical and endocrinologic abnormalities, even in the setting of a normal CT scan. A recent series [15] suggested that the criteria for normal in a child-bearing-age woman should be expanded to include focal lucencies, gland heights less than or equal to 9.7 mm, and a convex diaphragma sellae. A "certainly abnormal" gland was one with a focal lesion greater than one-third the size of the intrasellar contents. Using these criteria in our series, 20 of 39 microadenoma and 10 of 12 nonmicroadenoma patients would be classified as having normal CT scans.

In our series, all CT abnormalities attributed to microadenomas except infundibulum displacement occurred also in patients in whom microadenomas were not found at surgery. Of these, all patients had hyperprolactinemia, and nine of 12 had focal prolactin cell hyperplasia on histologic examination. The explanation for the CT abnormalities found in this group is unclear; only one patient had a true space-occupying lesion (benign cyst) that could account for the CT findings.

In summary, no absolute CT criteria were identified to differentiate the patient harboring a microadenoma from the patient with hyperprolactinemia from other causes. When the five major criteria for microadenoma are considered (table 3), patients with several abnormalities were more likely to harbor a microadenoma. Many patients with proven microadenomas, however, had few or none of the generally accepted CT criteria for microadenoma. Of interest, many of our patients

would be indistinguishable by CT criteria from normal women of child-bearing age described by Swartz et al. [15]. Thus, despite high-resolution CT imaging, the radiologist cannot exclude by CT examination the presence of a clinically significant functioning pituitary microadenoma. The diagnosis of a prolactin-secreting pituitary microadenoma must be made on this basis of radiographic, endocrinologic, and clinical data.

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