

Histopathologic Predictors of Malignancy and Long-Term Outcomes in Acromegaly

Arjun Adapa, MD, MS¹; Alex Hernandez, BS¹; Misha Amini, MD¹; Jeffrey Bruce, MD¹; Peter Canoll, MD, PhD²; Pamela Freda, MD³

¹Department of Neurological Surgery, Columbia University Irving Medical Center

²Department of Pathology and Cell Biology, Columbia University Irving Medical Center

³Department of Medicine, Columbia University Irving Medical Center

Introduction

- Acromegaly is caused by functional, growth hormone-secreting pituitary adenomas and is associated with increased long-term morbidity and malignancy risk.
- Chronic excess of growth hormone and insulin-like growth factor-1 has been implicated in tumorigenesis; however, cancer risk among patients with acromegaly is heterogeneous and not fully explained by biochemical disease activity alone.
- Histopathologic features of somatotroph adenomas, including **granulation pattern and proliferative indices**, reflect underlying tumor biology and have been associated with differences in treatment response and outcomes.
- The relationship between adenoma histopathology and malignancy risk in acromegaly remains poorly characterized.
- This study evaluates the association between histopathologic features of GH-secreting pituitary adenomas and malignancy risk in a single-institution cohort of patients with acromegaly.

Methods and Materials

- A retrospective analysis was performed using a prospectively maintained institutional database of patients with acromegaly who underwent transsphenoidal surgery by a single surgeon between 1992 and 2019.
- Acromegaly was diagnosed by elevated age-adjusted IGF-1 levels or failure of growth hormone suppression following oral glucose tolerance testing.
- 134 consecutive acromegaly patients were studied.
- Immunohistochemistry included CAM5.2 staining to classify granulation pattern as densely granulated, sparsely granulated, or mixed, and assessment of MIB-1 labeling index. Clinical, biochemical, and treatment data were collected at diagnosis and during longitudinal follow-up.
- The primary outcome was the presence of any malignancy diagnosed during follow-up. Statistical analyses included pairwise comparisons and univariate and multivariate logistic regression.

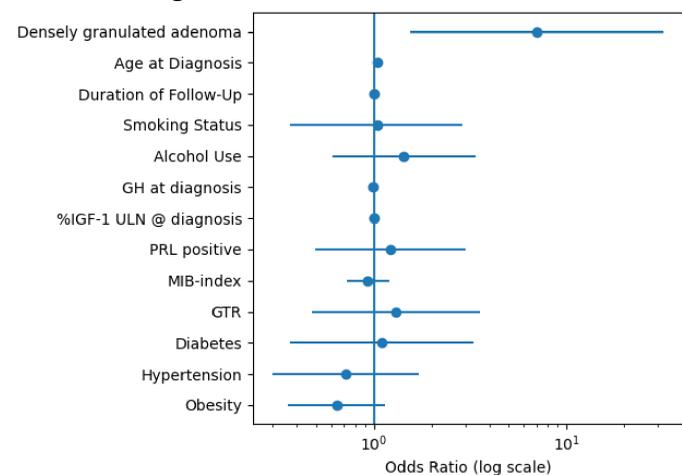
Table 1. Clinical and biochemical characteristics stratified by granulation pattern

Characteristic	Overall (n = 134)	Densely Granulated (n = 77)	Sparsely Granulated (n = 47)	Mixed Granulation (n = 10)	p-value
Age at diagnosis (years)	45.7 ± 14.7	49.4 ± 13.9	41.9 ± 14.6	37.2 ± 16.6	0.049
Follow-up duration (months)	111.9 ± 85.1	114.0 ± 78.6	114.6 ± 95.8	116.5 ± 84.1	0.996
Adenoma size (mm)	16.8 ± 8.9	15.9 ± 8.8	18.4 ± 8.6	14.4 ± 9.0	0.453
Gross total resection N (%)	97 (73)	62 (81)	27 (59)	9 (90)	0.028
%IGF-1 ULN at diagnosis	243.6 ± 17.6	165.7 ± 126.7	227.6 ± 175.7	118.8 ± 99.3	0.127
%IGF-1 ULN at last follow-up	100.5 ± 12.2	87.3 ± 50.6	118.8 ± 100.6	95.3 ± 78.4	0.087
Any malignancy N (%)	27 (20)	18 (25.0)	2 (4.5)	6 (60.0)	0.016

Results

- A total of 134 patients with complete histopathologic data were analyzed, with a mean age at diagnosis of 46 years and a mean follow-up of 112 months.
- Granulation patterns included 77 densely granulated, 47 sparsely granulated, and 10 mixed adenomas; adenoma size and IGF-1 levels were not associated with granulation pattern.
- On univariate analysis, **densely granulated adenomas demonstrated a higher odds of malignancy compared with sparsely granulated adenomas (OR 7.0, p = 0.012)** (Figure 1).
- On multivariate analysis, densely granulated adenomas remained the strongest predictor of malignancy (OR 20.0, p = 0.017), along with age at diagnosis and duration of follow-up.
- Higher MIB-1 labeling index was associated with increased likelihood of requiring adjuvant postoperative somatostatin analog therapy (OR 1.320, 95% CI 1.04-1.67, p=0.022)

Figure 1. Univariate Forest Plot



Discussion

- Densely granulated somatotroph adenomas were strongly associated with malignancy risk, independent of GH and IGF-1 levels, suggesting that cancer risk in acromegaly may not be fully explained by biochemical disease activity alone.
- The lack of association between granulation pattern and IGF-1 levels contrasts with prior reports and indicates that histopathologic features may provide complementary prognostic information beyond hormonal measures.
- The association between higher MIB-1 labeling index and the need for adjuvant postoperative somatostatin analog therapy supports its role as a marker of tumor proliferative behavior and persistent disease.
- These findings highlight the potential clinical value of integrating histopathologic characteristics into long-term risk stratification and surveillance strategies for patients with acromegaly.

Conclusions

- Histopathologic features of GH-secreting pituitary adenomas, particularly granulation pattern, are strongly associated with malignancy risk in patients with acromegaly.
- Densely granulated adenomas confer the highest risk of malignancy, independent of GH and IGF-1 levels at diagnosis or at last follow-up, age at diagnosis, and extent of resection.
- Integrating histopathologic characteristics into long-term surveillance strategies may improve cancer risk stratification and guide understanding of tumor biology in acromegaly.

Contact

Arjun Adapa, MD
Columbia University Department of Neurosurgery
177 Ft. Washington Avenue
New York, NY 10032
Aa5031@cumc.columbia.edu
443-812-8653

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