

Pituitary Adenoma in Pediatric and Adolescent Populations

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Abstract

Pituitary adenomas are rare in children and adolescents and although mostly benign, they can sometimes be challenging to manage due to their locally invasive nature. In this study, we examined the clinicopathologic features of 42 pituitary adenomas in patients ≤ 21 years of age. The youngest patient was 8 years old (median age: 18 years), and the female-to-male ratio was 1.8:1. Five patients had recurrence after resection. There was no obvious difference between the recurrent rates in the typical (11.7%) and atypical adenomas (12.5%) based on the 2004 WHO classification. However, the recurrence rate was much higher in adenomas with an elevated proliferation index of $\geq 3\%$ (20.8%) or with evidence of local invasion (18.2%). Adenomas with combination of an elevated proliferation index of $\geq 3\%$ and imaging evidence of local invasion had the highest recurrence rate of 25%. In summary, pituitary adenomas are more frequent in adolescents as compared with children and are more common in girls. An elevated proliferation index of $\geq 3\%$ and evidence of local invasion on imaging seem to correlate with a high probability of recurrence. Furthermore, we observe rarity of α -thalassemia/mental retardation syndrome X-linked (ATRX) protein loss (surrogate to ATRX mutation) in these tumors without any connotation on prognosis.

Key Words: ATRX, atypical, clinicopathologic features, invasive, pediatric, pituitary neuroendocrine neoplasm, prognosis, WHO classification.

INTRODUCTION

Pituitary adenomas are neoplasms predominantly arising in the adenohypophysis. They represent 10%–25% of all intracranial neoplasms and the estimated prevalence rate in the general population is $\sim 17\%$ (1–3). Most pituitary adenomas are benign. However, there are some aggressive adenomas that grow rapidly, tend to recur or progress, and are resistant to currently available treatment options including sur-

gery and radiation (4). Pituitary adenomas are, however, rare in children and adolescents constituting only about 3% or less of all diagnosed intracranial tumors and 5% of all pituitary adenomas (5–9). When compared with the adult tumors, pituitary adenomas in children are predominantly comprised of secreting tumors, with prolactin, adrenocorticotropic hormone (ACTH), and growth hormone (GH) secreting tumors being the most frequent (7, 8), and in turn related to substantial morbidity. Due to its rarity and complexity, pediatric pituitary adenoma has been relatively infrequently studied, and recommendations regarding its optimal management are debated. In this study, we examined the overall clinicopathologic features of pituitary adenomas in pediatric and adolescent populations.

The 2004 WHO classification categorizes pituitary adenomas as typical adenomas, atypical adenomas, and pituitary carcinomas, the latter are diagnosed only by craniospinal and/or systemic metastases (10). The majority of pituitary adenomas are typical adenomas with a Ki-67 proliferation index $< 3\%$ and infrequent mitotic figures. Atypical adenomas were defined as adenomas with increased proliferation index ($\geq 3\%$), excessive p53 immunoreactivity, and increased mitotic activity. However, a clear cutoff of “excessive” p53 immunoreactivity and “increased” mitotic activity was not provided. This caused substantial interobserver variability with variable incidence of atypical adenomas in different studies. For instance, in the German Pituitary Tumor Registry, 2.7% of the adenomas were classified as atypical (11). Others groups, however, reported $\sim 15\%$ atypical adenomas in their cohort (12). Multiple groups have proposed several different diagnostic criteria for pituitary adenomas. For example, Tortosa and Webb (13) proposed a diagnostic strategy for atypical pituitary adenomas using a scoring system based on 5 clinical and histopathological parameters. Due to lack of clinical validation, the new 2017 WHO classification disparages the use of the 3 subcategories based on Ki-67, mitotic index, and p53 protein expression (14). Instead, it encourages taking into account tumor invasion (evaluated by magnetic resonance imaging [MRI] and/or histology) in addition to the histopathological parameters. More recently, a new common classification framework for neuroendocrine neoplasms across different organ systems has been proposed by the International Agency for Research on Cancer and WHO expert consensus (15). This consensus has recommended the use of term “pituitary neuroendocrine tumor” rather than adenoma or carcinoma (Table 1). Most research about pituitary adenomas has been performed on general population and only a few studies were directed

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TABLE 1. Three Classification Systems of Pituitary Tumors

2004 WHO	Pituitary adenoma: infrequent mitotic figures and Ki-67 index <3% Atypical pituitary adenoma: increased proliferation index (≥3%), excessive p53 immunoreactivity, and increased mitotic activity Pituitary carcinoma: craniospinal or systemic metastasis
2017 WHO	Pituitary adenoma: no craniospinal or systemic metastasis Pituitary carcinoma: craniospinal or systemic metastasis
New 2018 WHO proposal	Pituitary neuroendocrine tumor

towards pituitary adenomas in younger population (5–9, 16–20). A better classification system is therefore needed to guide treatment in this particular age group. Thus, in our study, we also compared the recurrence rates between typical and atypical pituitary adenomas using the 2004 WHO classification.

Although the majority of pituitary adenomas are sporadic, ~5% of all cases occur in a familial setting and over half of these are due to multiple endocrine neoplasia type 1 (MEN-1) and Carney’s complex disorders (1). Recently, mutations in α -thalassemia/mental retardation syndrome X-linked (ATRX) have been demonstrated in ~40% of the pancreatic neuroendocrine tumors (a tumor type that shares familial association with MEN-1) and appear to predict metastatic disease and poor survival (21). ATRX is a DNA helicase and chromatin remodeling protein that belongs to the SWItch/Sucrose Nonfermentable family (22). Germline mutations in ATRX are associated with ATRX syndrome (23). ATRX mutations have also been reported in sporadic adult and pediatric astrocytic gliomas (24–26) and neuroblastomas (27). Furthermore, aberrant ATRX protein expression has been identified in 58% of malignant peripheral nerve sheath tumors (MPNSTs) and are found to be associated with poor overall survival in neurofibromatosis type 1-associated MPNSTs (28). Since both pituitary adenomas and pancreatic neuroendocrine tumors share their clinical association with MEN-1, we were intrigued to see if ATRX also plays a role in the pathogenesis and/or prognostication of pituitary adenomas.

MATERIALS AND METHODS

A retrospective clinical and histopathological review of pituitary adenomas, diagnosed at Washington University School of Medicine from 1989 to 2016, in patients ≤21 years of age was performed. Patients’ age, gender, tumor size, clinical hormone production, histopathologic parameters, including mitotic activity, immunohistochemical hormone expression, Ki-67 index, and p53 nuclear expression, were analyzed.

Five- μ m thick formalin-fixed, paraffin-embedded sections of the pituitary adenomas were used for ancillary studies (wherever applicable). Immunohistochemistry for pituitary hormones ACTH (polyclonal, Cell Marque, Rocklin, CA),

follicle-stimulating hormone (polyclonal, Cell Marque), GH (polyclonal, Cell Marque), luteinizing hormone (polyclonal, Cell Marque), prolactin (polyclonal, Cell Marque), thyroid stimulating hormone (polyclonal, Cell Marque), Ki-67 (30-9, Ventana, Oro Valley, AZ), and p53 (DO-7, Ventana) were performed according to the manufacturers’ recommendations. Immunohistochemistry for ATRX (HPA001906, polyclonal, Sigma, St Louis, MO) was performed at a dilution of 1:300. All positive and negative controls stained appropriately.

Atypical pituitary adenomas were defined as adenomas with increased proliferation index (≥3%), excessive p53 immunoreactivity, and increased mitotic activity, based on the 2004 WHO classification. We specifically used a cutoff of ≥2% for excessive p53 immunoreactivity (3, 13). Statistical analysis was performed using GraphPad Prism 7.03 (GraphPad Software, Inc., La Jolla, CA). Statistical significance was defined as $p < 0.05$.

RESULTS

Clinical Features of Pediatric Pituitary Adenomas

Pituitary adenomas from 42 patients were identified. Among them, 41 patients presented as primary tumors, and 1 as a residual tumor status postresection at an outside hospital. Of the 42 patients, the youngest was an 8-year-old girl, and the median age was 18 years, with a predilection for older children (Fig. 1A). There were 27 (64%) female and 15 (36%) male patients, with a female-to-male ratio of ~1.8:1 (Fig. 1B). No statistical significance was observed between the median ages in females and males (18 and 19 years, respectively; $p = 0.7$ by Student t-test).

Of the 27 female patients, 21 (77.8%) patients had macroadenomas and 6 (22.2%) had microadenomas. The median size of adenoma in girls was 2 cm with 23 (85.2%) being functional and 4 (14.8%) nonfunctional. Of the 23 functional adenomas in girls, prolactin-secreting tumors predominated at 12 (52.2%) followed by 8 (34.8%) ACTH-secreting, and 3 (13.0%) GH-secreting ones. The majority (16; 59.3%) had an elevated proliferation index ≥3%, 5 (18.5%) adenomas showed local invasion on imaging and 4 (14.8%) adenomas recurred.

Of the 15 male patients, 7 (46.7%) patients had macroadenomas and 8 (53.3%) had microadenomas. The median size of adenoma in boys was slightly larger than girls at 2.4 cm ($p = 0.17$). Ten (66.7%) patients had functional and 5 (33.3%) had nonfunctional adenomas. Of the 10 functional adenomas, most (6; 60.0%) were prolactin-secreting followed by 3 (30.0%) that were GH-secreting and 1 (10.0%) that was ACTH-secreting. Nine (60.0%) adenomas had an elevated proliferation index ≥3%. Six (40.0%) adenomas showed local invasion on imaging and 1 (6.7%) recurred.

Of the 42 adenomas, 9 (21%) were microadenomas and 33 (79%) were macroadenomas. Exact sizes of 6 microadenomas and 28 macroadenomas were identified from imaging studies and the median size was 2.0 cm. The median age of the patients with microadenomas was 20 years old. Of the 9 microadenomas, 6 (66.7%) were female and 3 (33.3%) were

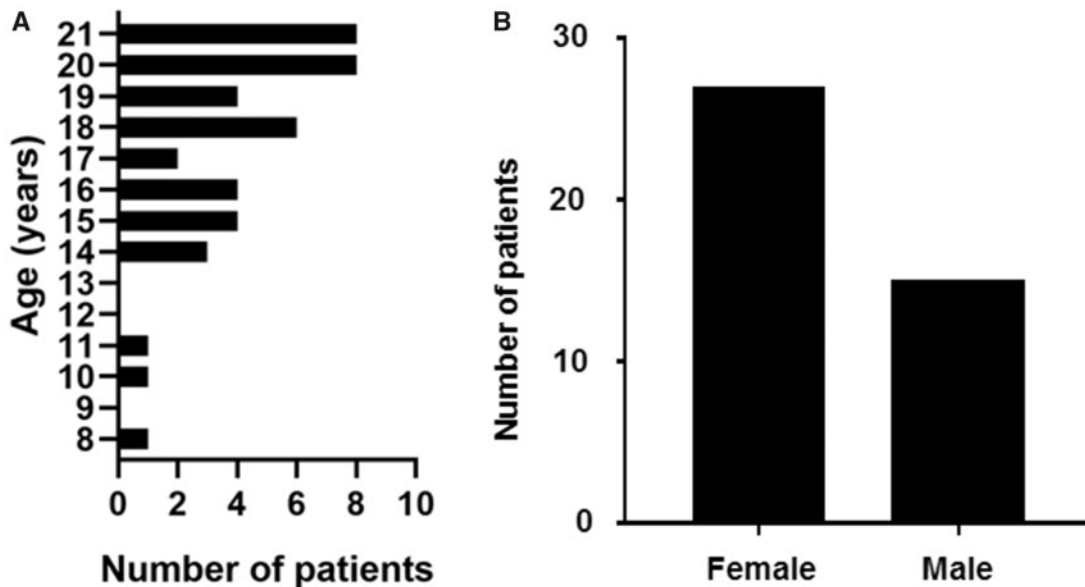


FIGURE 1. Age and gender distribution. The youngest and oldest patients were 8 and 21 years, respectively, with the median age being 18 years (**A**). There were 27 female and 15 male patients with a female-to-male ratio of ~1.8:1 (**B**).

male. None of them showed local invasion or recurrence. Four of the 9 microadenomas were prolactin-secreting, 2 were ACTH-secreting, 1 was GH-secreting, and the remaining 2 were nonfunctional. Six (66.7%) of the 9 microadenomas had an elevated proliferation index $\geq 3\%$. Of the 33 macroadenomas, 21 were female and 12 were male. Eleven showed local invasion and 5 recurred. Nineteen of 33 macroadenomas had an elevated proliferation index $\geq 3\%$. Fourteen were prolactin-secreting, 7 were ACTH-secreting, 5 were GH-secreting, and the remaining 7 were nonfunctional.

Thirty-three (78.6%) patients had functional pituitary adenomas with a female predominance (F:M = 2.3:1). Eighteen of the 33 adenomas were prolactin-secreting, 9 were ACTH-secreting, and 6 were GH-secreting. Twenty-one (63.6%) of the functional adenomas had an elevated proliferation index $\geq 3\%$ (10 prolactin-secreting, 7 ACTH-secreting, 4 GH-secreting). The remaining 9 (24%) were nonfunctional tumors with nearly equal distribution between girls and boys. Four (44.4%) of the nonfunctional adenomas had an elevated proliferation index $\geq 3\%$.

Of the 42 cases, 40 (95%) were sporadic and 2 cases (5%) were familial in association with MEN-1. Both of these occurred in girls and were prolactin-secreting macroadenomas, with a pathology diagnosis of adenoma made at ages 16 and 18. Neither patient suffered a recurrence.

Clinicopathological Features of 5 Cases With Recurrence

Of the 42 patients, 5 (12%) patients had recurrences with 4 of these occurring in girls and 1 in a boy (Table 2). All 5 of these cases were macroadenomas (median size 2.6 cm). Two were ACTH-secreting tumors, 1 was prolactin-secreting, 1 was GH-secreting, and 1 was nonfunctional. Of the 5 cases, the preoperative imaging data of 4 cases was available for

analysis. Two adenomas had evidence of local invasion on imaging, whereas 2 others did not. All 5 cases nevertheless had an elevated proliferation index ($\geq 3\%$). Four cases had a low p53 expression ($\leq 0.5\%$), and 1 had an elevated p53 immuno-expression ($\sim 7.5\%$). Interestingly, 2 cases had a relatively low mitotic count ($< 3/10$ high-power fields), while 3 patients had an elevated mitotic count ($\geq 3/10$ high-power fields). Based on the 2004 WHO classification, of the 5 cases with recurrence, 4 (80%) were typical adenomas, and only 1 (20%) qualified for an atypical designation.

2004 WHO Classification and Tumor Recurrence

Based on the 2004 WHO classification, of the 42 cases there were 34 (81%) typical adenomas and 8 (19%) atypical adenomas (Fig. 2). Four of 34 (11.7%) typical adenomas had recurrences, and 1 of 8 (12.5%) atypical adenomas had recurrence (Table 3) so the recurrence rates in the typical and atypical adenomas are very similar in our cohort.

If adenomas with increased proliferation index as stand-alone criteria are considered as a distinct group, of the 42 cases there were 17 (40.5%) typical adenomas, 17 (40.5%) adenomas with increased proliferation index, and 8 (19%) atypical adenomas. The recurrence rate was 1 of 17 (5.9%) in typical adenomas, 3 of 17 (17.6%) in adenomas with increased proliferation indices, and 1 of 8 (12.5%) in atypical pituitary adenomas (Table 3).

Thus, Ki-67 proliferation index seems to better relate with the recurrence rate. In our cohort of 42 adenomas there were 18 adenomas with low proliferation index ($< 3\%$), and 24 adenomas with elevated proliferation index ($\geq 3\%$). The recurrence rates then become 0 of 18 (0%) for adenomas with low proliferation indices, and 5 of 24 (20.8%) for adenomas with elevated proliferation indices (Table 3).

TABLE 2. Clinicopathological Features of 5 Cases With Recurrence

Case No.	Age (in years)	Gender	Size (cm)	Invasion on Imaging	Hormone Type	Ki-67 (%)	p53 (%)	Mitoses (10 HPF)
WU-1	8	F	1	N	ACTH-S+I	7.4	<1	1
WU-5	14	F	3.1	Y	Nonfunctional	3.0	<1	2
WU-9	15	M	3.6	Y	Prolactin-S	4.3	<1	3
WU-22	18	F	macro	N/A	GH-S	14.6	7.5	3
WU-36	21	F	2.1	N	ACTH-S+I	14.0	<1	6

HPF, high-power fields; F, female; M, male; macro, macroadenoma; Y, yes; N, no; ACTH, adrenocorticotropic hormone; GH, growth hormone; S, serum; I, immunohistochemistry; N/A, not available.

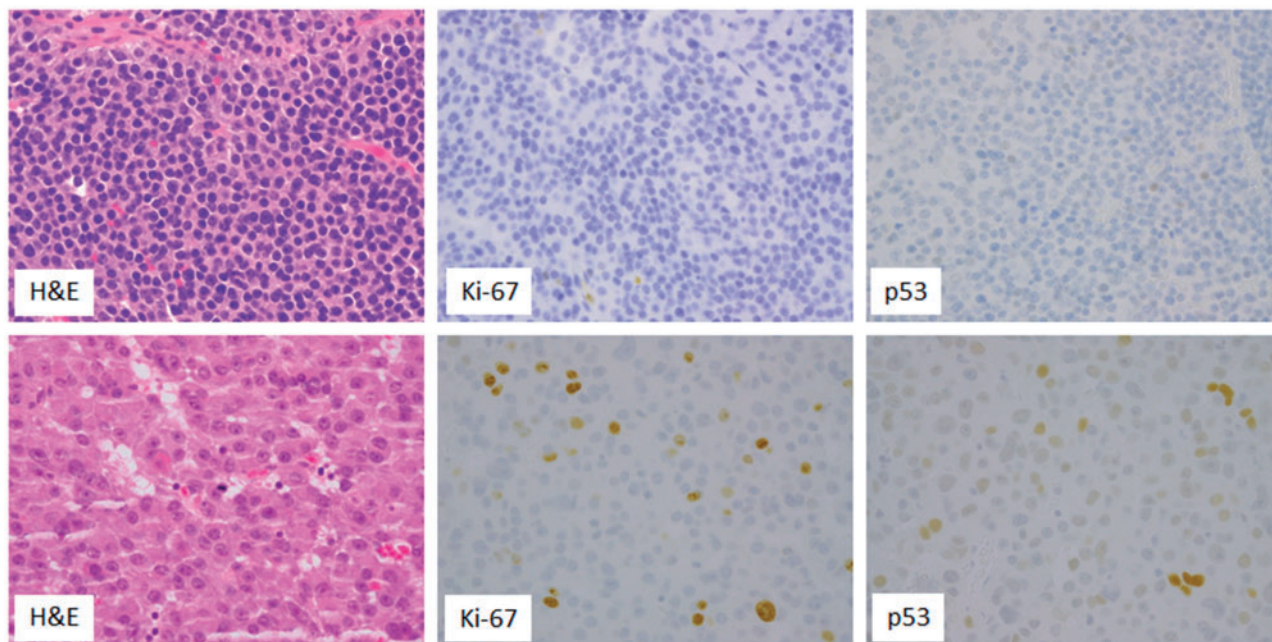


FIGURE 2. Histopathologic images of pituitary adenomas. Representative images demonstrating negligible Ki-67 and p53 protein expression in a “typical” adenoma as compared with “atypical” adenoma.

TABLE 3. Recurrence Rates of Adenomas With Elevated Proliferation Index and/or Local Invasion

	Typical	Atypical	Typical	Increased Proliferation Index	Atypical	Ki67 < 3%	Ki67 ≥ 3%	With Invasion	Without Invasion	Ki67 ≥ 3% and Invasion
Total number of cases	34	8	17	17	8	18	24	11	23	8
Number of recurrence	4	1	1	3	1	0	5	2	2	2
Recurrence rates	11.8%	12.5%	5.9%	17.6%	12.5%	0%	20.8%	18.2%	8.7%	25%

Local Invasion and Tumor Recurrence

Of the 42 cases, 35 cases had preoperative imaging available. Of those, 23 (65.7%) adenomas showed no evidence of local invasion on preoperative imaging, 1 (2.9%) case showed questionable invasion into the cavernous sinus, and 11 (31.4%) cases showed definitive evidence of local invasion (Fig. 3). Five patients with invasive adenomas were girls and 6 were boys (F:M = 1:1.2). All invasive adenomas were macroadenomas with a median size of 3 cm. Seven were

prolactin-secreting tumors, 1 was ACTH-secreting, 1 was GH-secreting, and the remaining 2 were nonfunctional.

The recurrence rate was 2 of 23 (8.7%) in noninvasive adenomas, and 2 of 11 (18.2%) in locally invasive adenomas in our cohort (Table 3). This result indicates that locally invasive adenomas are more than twice as likely to recur as noninvasive ones.

Of the 11 cases that showed definitive evidence of local invasion, 8 cases also had an elevated proliferation index

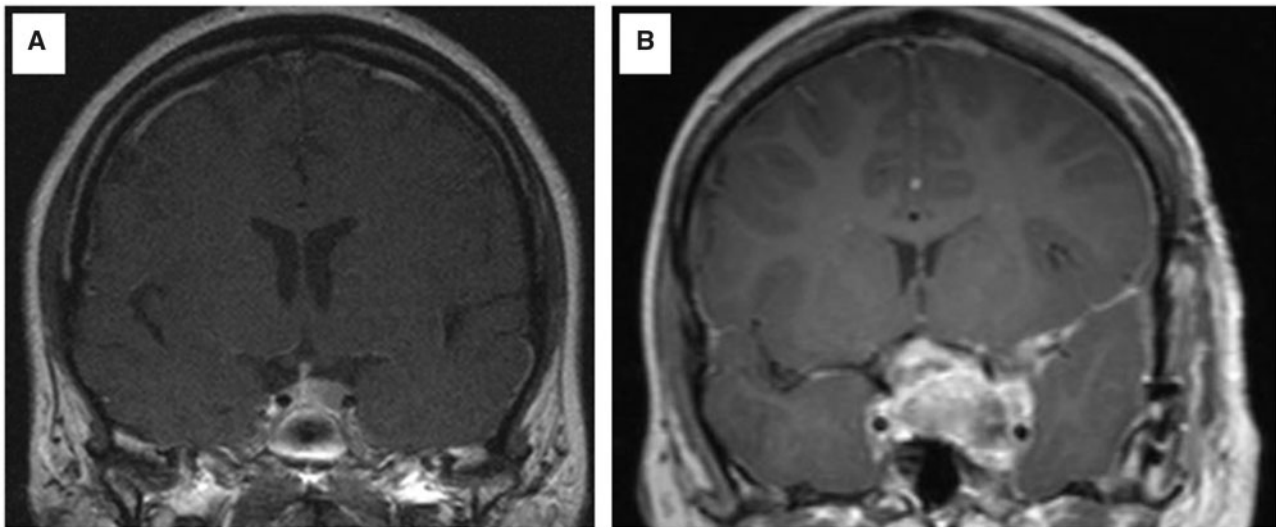


FIGURE 3. Magnetic resonance imaging. Representative T1-postcontrast image of a pituitary adenoma without (**A**) and with invasion of bilateral cavernous sinuses (**B**).

$\geq 3\%$. Of those 8 cases, 2 (25%) cases recurred. In other words, adenomas with both an elevated proliferation index of $\geq 3\%$ and imaging evidence of local invasion have the highest recurrence rate of 25%, compared with adenomas with only an elevated proliferation index (20.8%) or imaging evidence of local invasion (18.2%).

ATRX Protein Expression

Nuclear reactivity for ATRX was retained in 39 (92.9%) of 42 cases (Fig. 4), and was consistent with “wild-type” staining pattern. Of the 3 cases that showed loss of ATRX immunoreactivity, 2 were girls and 1 was a boy. Specifically, loss of nuclear staining was seen in $>80\%$ tumor cells in 2 cases and the remaining one had lack of $>50\%$ immuno-expression in a background of marked cautery artifacts. Two were typical adenomas and 1 was an adenoma with an increased proliferation index $\geq 3\%$. All 3 were functional macroadenomas (prolactinomas) with a median size of 2.1 cm. Preoperative imaging data was available for 1 adenoma, which showed local invasion. No recurrence occurred during the follow-up (2–24 years). However, this data is insufficient to draw any substantial conclusions regarding ATRX expression in pituitary adenoma, particularly in younger patients, and requires larger studies to corroborate the stated findings mainly due to the lack of concomitant genomic studies.

DISCUSSION

Our cohort of 42 pituitary adenomas is the largest cohort of pituitary adenomas in pediatric and adolescent populations to investigate the prognostic role (if any) of proliferation indices, p53 protein expression, and local invasion in the published literature thus far (5–9, 16–20).

The percentage of atypical adenomas in the general population varies among different study groups (2.7%–15%;

12, 29). Within our series, atypical pituitary adenomas accounted for $\sim 19\%$ of total adenomas, which is higher than those reported in the general population. It could be reflective of the physiological differences across the age groups, being higher in the growing age of young children and adolescents. This could also be partially due to a selection bias because our hospital is a large tertiary referral center where patients come from the nearby regions for management of their challenging pituitary adenomas.

In our study population, the recurrence rate was 5.9% in typical adenomas, 17.6% in adenomas with increased proliferation indices, and 12.5% in atypical pituitary adenomas. Although the recurrence rate in the atypical adenomas was almost double that of the recurrence rate in typical adenomas, adenomas with increased proliferation indices also seem to have a high recurrence rate. This means that at least for adenomas in pediatric and adolescent populations, combined p53 immunoreactivity and mitotic activity do not appear to correlate with recurrence. Instead, proliferation index indicated by Ki-67 immunostaining is a more important prognostic factor. Indeed, in our cohort, adenomas with an elevated proliferation index ($\geq 3\%$) had a recurrence rate of 20.8%, whereas in adenomas with a low proliferation index ($<3\%$), the recurrence rate is 0%. But the caveat with regards to diverse range of antibodies, staining techniques, and Ki-67 interpretation cannot be overlooked to use this parameter for comparison with other studies in the future.

Similar to an increased proliferation index, presence of local invasion on imaging also seems to correlate with a high recurrence rate. In our cohort, the recurrence rate for local invasive adenomas was 18.2%, which was much higher than the recurrence rate for the noninvasive adenomas at 8.7%. In other words, locally invasive adenomas are twice as likely to recur than noninvasive ones. Comparable findings have also been reported in studies involving the adult pituitary adenomas. In a cohort of 121 consecutive patients with pituitary adenomas,

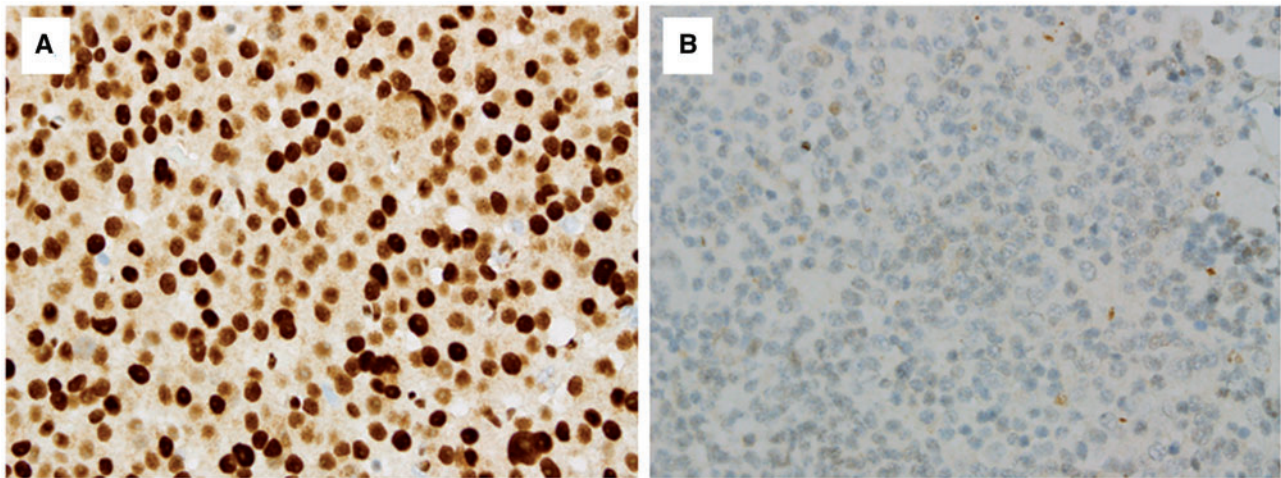


FIGURE 4. Representative images of pituitary adenomas with retained (**A**) and lost (**B**) ATRX immunoreactivity, surrogate for “wildtype” and “mutant” ATRX staining patterns, respectively. Immunoreactivity for ATRX was retained in 39 pituitary adenomas, and loss of nuclear reactivity was observed in 3 pituitary adenomas (400 \times).

Zada et al reported that the only preoperative factor that correlated with atypical adenomas was evidence of surrounding invasion on imaging studies (29). In their study, 85% of atypical adenomas showed invasion on imaging studies while only 45% of typical adenomas did. Miermeister et al reported that 58 of 64 (91%) atypical adenomas showed radiological invasion, compared with 68 of 145 (47%) typical adenomas (3). In 2013, Trouillas et al suggested a new prognostic clinicopathological classification of pituitary adenomas based on a multicentric case-control study of 410 patients with 8 years postoperative follow-up (30). They reported that invasive (defined as histological and/or radiological signs of cavernous or sphenoid sinus invasion) and proliferative tumors had a poor prognosis with an increased probability of tumor persistence or progression of 25- or 12-fold, respectively, as compared with noninvasive tumors. The most recent 2017 WHO classification duly takes into account the presence of tumor invasion (evaluated by MRI and/or histology) in addition to the other histopathological parameters discussed in the 2004 classification (14).

Within our series, there were 27 (64%) female and 15 (36%) male patients, with a female-to-male ratio of \sim 1.8:1, which reached 2.3:1 in functional adenomas. A wide range of female-to-male ratio has been reported in pituitary adenomas, from 0.9:1 to 1.5:1 in the general population (30, 31). Nevertheless, female preponderance has been reported in the limited available literature pertaining to younger population with the ratio reaching up to 3.3:1 (17). Interestingly, males tend to present with larger adenomas (median 2.4 vs 2.0 cm; $p = 0.17$) with a higher possibility of local invasion (40% vs 21.7%).

Thirty-three (78.6%) of 42 patients had functional pituitary adenomas. Eighteen (54.5%) of the 33 adenomas were prolactin-secreting, 9 (27.2%) were ACTH-secreting, and 6 (18.2%) were GH-secreting. It has been previously reported that most pediatric adenomas are functioning (80%–97%), with ACTH-secreting adenomas being the most common in early childhood, and prolactinomas predominating in older children and adolescents (9, 19, 32). The results from our co-

hort are very similar to previous reports in older children and adolescents.

In recent years, genetic defects have been identified in the genes regulating pituitary tumor genesis. These genes include *GNAS*, *PRKARIA*, *MEN1*, *AIP*, and others. These defects can affect both sporadic and familial cases, the latter accounting for about 5% of pediatric pituitary adenomas (19, 20, 33). In our cohort, 40 (95%) were sporadic and 2 cases (5%) were familial associated with MEN-1. Both patients with prolactin-secreting macroadenomas were girls. However, since we did not perform next-generation sequencing on our cohort, we are not sure if we are missing some of the other underlying genetic defects in these patients or in additional cases.

In this study, we also looked at the nuclear expression of ATRX in pediatric and adolescent pituitary adenoma because ATRX mutations have been described in pancreatic neuroendocrine tumors, another tumor that is frequently associated with MEN-1 syndrome (28). The majority (92.9%) of adenomas were found to have retained nuclear expression of ATRX. This result is consistent with a recent publication of retained ATRX nuclear expression in 246 pituitary adenomas although the patients' age range of that cohort is not clear (34). Those authors reported that 1 of the 2 corticotroph carcinomas showed loss of ATRX immunolabeling in both the primary and metastatic lesion, suggesting a possible relationship between loss of ATRX expression and the metastatic potential in a subset of pituitary tumors. Of note, ATRX immunostaining in this study was performed on tissue microarrays. In our cohort, all the 3 adenomas with loss of ATRX nuclear expression were prolactinomas. However, no recurrence occurred during a follow-up period of 2–24 years.

In conclusion, we examined the clinicopathologic features of 42 pituitary adenomas in pediatric and adolescent population (age range 8–21 years), which is the largest cohort to investigate the utility of proliferation indices, p53, and invasion in adenoma of this particular age group. Interestingly, pituitary adenomas were more frequent in adolescents as com-

pared with young children, and were more common in girls, comparable to published studies. An elevated proliferation index of $\geq 3\%$ and evidence of local invasion on imaging correlated with a high probability of recurrence, while mitotic activity and p53 expression did not. Therefore, our results argue against the use of 2004 WHO classification scheme of atypical adenomas based on a combination of mitotic activity, p53 expression and proliferation index even in younger patients. On the other hand, incorporation of proliferation index and invasiveness will be helpful in predicting its chance of recurrence. Finally, loss of ATRX protein expression was found to be uncommon in adenomas with no association with recurrence. This finding contends the potential role of ATRX in pathogenesis and/or prognostication in younger patients with pituitary neuroendocrine neoplasms. Nevertheless, lack of pituitary carcinoma patients, and genomic data are some of the limitations of our cohort. Larger studies are essential to support these inceptive findings as well as to better understand the biology of pituitary neuroendocrine tumors in a quest to identify novel molecular markers as prognosticators in this specific group of patients.

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