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Expression of Pancytokeratin in Meningioma in Correlation with Ki67 Proliferative Index

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Abstract: Background: Meningioma is the most common primary central nervous system tumor. However, its cellular origin remains unclear. While keratin expression is noted in some variants, PanCK expression in grade I and II meningiomas is poorly characterized.

Objective: To assess PanCK expression across meningioma grades and variants and correlate it with mitotic count and Ki67 index.

Methods: A cross-sectional study was conducted at Gazi Al-Hariri Hospital (2022–2023) including 28 grade I–III meningiomas. Clinical data were collected, and immunohistochemistry for PanCK and Ki67 was performed.

Results: The mean patient age was 49.7 years (range 30–75), with a female predominance (1:8.3). Grade II tumors were most common (60%). All anaplastic meningiomas expressed PanCK strongly. Meningothelial variants were PanCK-negative in 57.1% of cases, whereas transitional and chordoid types showed moderate expression. Atypical variants showed variable expression. Expression differed significantly by variant (P=0.007) and grade. All grade III tumors showed strong PanCK expression; 50% of grade I and 52.9% of grade II lacked expression. PanCK score correlated moderately with Ki67 (r=0.504), mitotic count (r=0.433), and grade (r=0.411).

Conclusion: PanCK expression spans all meningioma grades, limiting the diagnosing specificity; its linear correlation with Ki67 suggests involvement in tumor proliferation.

Keywords: meningioma, pan cytokeratin, proliferation index

Introduction

Meningioma is the most prevalent primary central nervous system tumor, contributing to approximately 37.6% of all cases. Fortunately, half of all meningiomas are benign (1, 2).

Meningiomas originate from the meningeal layers of the brain or spinal cord (3). These tumors are classified into three grades according to the World Health Organization (WHO) (3). The majority of meningiomas are benign and considered grade 1. Approximately 1–3% of meningiomas can transform into malignant tumors, with a 5-year survival rate of 32–64%. Several predisposing factors increase the risk of occurrence, including genetic disorders such as neurofibromatosis type 2, exposure to radiation, hormonal therapy, and a family history of the disease (2).

The precise histogenesis of meningioma cells has not yet been determined. It is hypothesized that they possess both mesenchymal and epithelial potential (4). Recent studies investigating the molecular pathogenesis of meningiomas have identified keratins as biomechanically responsive genes in meningiomas that could play a role in the structural integrity and resilience of meningioma cells (5) (6). In the clinical setting, immunohistochemical studies for cytokeratin are applied in high

-grade meningiomas to confirm or exclude metastatic carcinoma (7), however, its expression in lower grades and histopathological variants is limited (4). AE1/ AE3 cocktail used in the current study was reactive to both keratin 6 and keratin 16. AE1 recognizes acidic type I keratins, including keratin 16, while AE3 recognizes basic type II keratins, including keratin 6. This makes the AE1/AE3 cocktail useful for identifying cells of epithelial origin because it detects a broad spectrum of keratins.

This study aimed to evaluate the expression of PanCK in different variants and grades of meningioma and correlate the expression of PanCK with the mitotic count and Ki67 proliferative index.

Patients and Methods

This cross-sectional observational research was carried out at Gazi Al-Hariri Hospital for Surgical Specialties in Medical City, Baghdad, from January 1, 2022, to December 31, 2023.

The study protocol was approved by the Scientific Council of Pathology of the Iraqi Board of Medical Specializations.

The pathology department and private laboratory archives were reviewed to identify reports of cases with GI-III meningioma from 2022 to 2023. All cases were considered without age or sex restrictions, including cases of recurrence. A total of 28 meningioma cases were identified. Paraffin-embedded blocks from these patients were accessible and obtained for further sectioning and staining.

Data collection: Data on patient age, sex, and tumor site were collected from patient notes. Hematoxylin and Eosin (H&E) sections were freshly prepared for each case and reviewed to confirm the histological subtype, morphology, grade, and brain tissue invasion, and to report the presence or absence of unfavorable features (prominent nucleoli, sheets of cells, small cells, and necrosis). Additionally, the number of mitoses per 10 high -power fields (HPF) was counted for each case.

Immunohistochemistry procedure (IHC): H&E slides were screened to select a representative tissue block. Sections (4 µm thick) were mounted on positively charged slides, deparaffinized, and rehydrated. IHC was conducted according to the manufacturer's protocol. Briefly, antigen retrieval was performed using heat-induced epitope retrieval at 97 °C for 20 min. Endogenous peroxidase activity was blocked, followed by incubation with blocking buffer. Primary monoclonal mouse antibodies, PanCK (AE1/AE3) and Ki67 (MIB-1), both from BioSB, were applied at a 1:50 dilution and incubated at room temperature for 30 min. The slides were then incubated with a rabbit anti-mouse secondary antibody. Visualization was achieved using DAB+ chromogen. The sections were counterstained with Mayer's hematoxylin, dehydrated in ascending ethanol concentrations, cleared with xylene, and mounted. The positive control sections included breast carcinoma for PanCK and small cell lung carcinoma for Ki67.

Evaluation of immunohistochemical staining and scoring: Immunoreactivity of Panck was considered when cytoplasmic and membranous brown staining was observed**.** A semi-quantitative score was employed by taking both the staining intensity score (IS) and proportion score (PS) of positive cells into account according to the method described by previous studies with slight modification of the proportions (8).

Intensity score (IS)

1. No staining (score = 0)
2. Weak intensity (score = 1)
3. Moderate intensity (score = 2)
4. Strong intensity (score = 3)

Proportion score (PS)

1. No staining (score = 0)
2. 1-25% positive cells (score = 1)
3. 26-50% positive cells (score = 2)
4. >50% positive cells (score = 3)

The total score was the summation of intensity and proportion scores with a minimum of 2 and maximum of 6. A score of 0 was deemed negative, 2 was classified as weak, 3-4 as moderate, and 5-6 as strong.

The proliferation index Ki67 was estimated in the entire section by eyeballing. The proportion of the positively stained nuclei of any intensity was considered. A cutoff value of 9% was used based on the median expression in the examined section and supported by previous studies (9).

Statistical analysis

All statistical analyses were carried out using Statistical Package for Social Sciences (IBM SPSS) software version 26. Continuous variables are expressed as mean ± standard deviation or median and range according to the data distribution.

Mann Whitney and Kruskal Wallis tests were used to compare groups. The Bonferroni test was used for post-hoc analysis. The chi-square test was used to compare categorical groups. Bivariate correlation using the Spearman test was applied to examine the association between different variables. *Statistical significance was set at P* < 0.05.

Results

Patients and tumors characteristics

A total of 28 cases of meningioma were identified, with a mean age of 49.7± 13.699 years ranged from 30-75 to years, half of them were between 40-60 years. Females constituted the majority (25 cases), accounting for 89.3% of all cases, with a male -to -female ratio of 1:8.3. Grade II was the most frequent, representing 17 (60%) of the cases; 16 (57.1%) were atypical variants, one chordoid. Grade I was the second most common; seven (25%) were meningothelial, and one was transitional. All grade III were anaplastic 3 (10.7%). tumor’s location varied, as illustrated in Table1, the most common site was the cerebral convexity, precisely the frontal lobe 8 (28.6%).

Table 1. Patients and tumor characteristics

characteristics		*No*	*%*
Age	<40	7	25.0%
	40-60	14	50.0%
	>60	7	25.0%
Gender	Female	25	89.3%
	Male	3	10.7%
Histo-type	Meningothelial	7	25.0%
	Transitional	1	3.6%
	chordoid	1	3.6%
	Atypical	16	57.1%
	Anaplastic	3	10.7%
Grade	I	8	28.6%
	II	17	60.7%
	III	3	10.7%
Site	Cerebral Convexity	14	50.0%
	Parietal	1	3.6%

	Temporal	2	7.1%
	Frontal	8	28.6%
	Not specified	3	10.7%
	Sagittal	1	3.6%
	Parasagittal	1	3.6%
	Posterior fossa -infratentorial	3	10.7%
	Anterior fossa base	6	28.4%
	Olfactory	2	7.1%
	Not specified	2	7.1%
	Sphenoid wing/ planum	2	7.1%
	Suprasellar	3	10.7%

As shown in Table 2, all atypical, anaplastic, and transitional types were female patients, while the only chordoid type was male (P=0.036). The age of the patients and site of the tumor did not show significant association with histopathology variants.

Table 2. Patients and tumor characteristics in association with histological types

Characteristics		*Meningothelial*		*Transitional*		*chordoid*		*Atypical*		*Anaplastic*		
		No	%	No	%	No	%	No	%	No	%	P value
Age	<40	1	14.3	0	0	0	0	5	31.3	1	33.3	0.864
	40-60	4	57.1	1	100	0	0	7	43.7	2	66.7	
	>60	2	28.6	0	0	1	100	4	25	0	0	
Gender	Female	5	71.4	2	100	0	0	16	100	3	100	0.042
	Male	2	28.6	0	0	1	100	0	0	0	0	
Site	Convexity	1	14.3	2	100	1	100	10	62.5	1	33.3	0.242
	Sagittal	0	0.0	0	0	0	0	0	0	1	33.3	
	parasagittal	1	14.3	0	0	0	0	0	0	0	0	
	PF-IT	1	14.3	0	0	0	0	1	6.2	1	33.3	
	Anterior fossa base	3	42.9	0	0	0	0	3	18.8	0	0	
	Suprasellar	1	14.3	0	0	0	0	2	12.5	0	0	

Panck expression score

PanCk was absolutely absent in 13 (46.4%), weak in 2 (7.1%), moderate in 8 (28.6%) and strong in 5 (17.9%) of all cases, as illustrated in Figure 1.

While weak expression represented PS score 1 and IS score of 1, the median PS and IS in moderate expression were 2, ranging between 1 and 3.

On the other hand, IS in strong expression was always strong (score 3) with a median PS of 2 ranging between 2 and 3) as shown in Table 3.

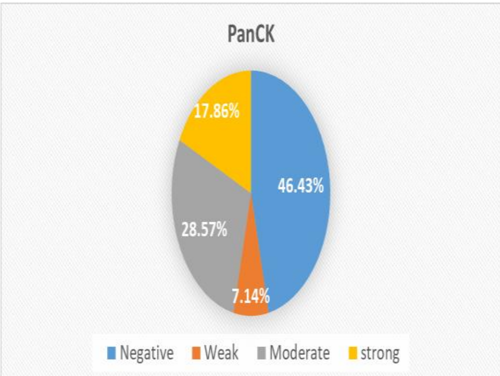

Figure 1. PanCK expression groups in all meningioma cases

Table 3. Description of PanCK expression groups

Semi-quantitative score	***Negative (n=13)*** *median (range)*	***Weak (n=2)*** *median (range)*	***Moderate (n=8)*** *median (range)*	***Strong (n=5)*** *median (range)*
Proportion scores	0	1 (1-1)	2 (1-3)	2 (2-3)
Intensity scores	0	1 (1-1)	2 (1-3)	3 (3-3)
Total score *(PS+IS)*	0	2 (2-2)	4 (3-4)	5 (5-6)

There was a strong and significant linear correlation between IS and PS in the semi -quantitative score (r=0.914, P<0.001). As shown in Figure 2, when the proportion of cells expressing PanCK increased, the intensity of staining also increased.

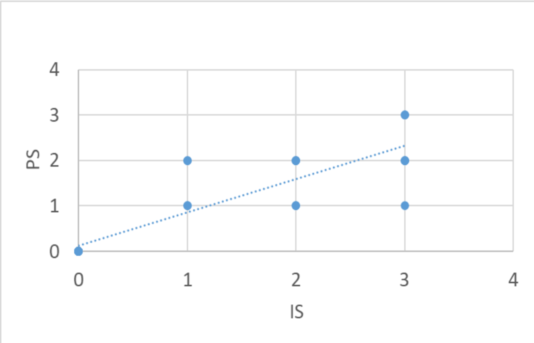

Figure 2. Linear correlation of proportion score (PS) and intensity score (IS) of the semiquantitative score

The association between PanCK semiquantitative expression and meningioma features

PanCK was strongly expressed in all anaplastic meningioma (Figure 3) while it was negative in 4 (57.1%) of meningothelial variant. Interestingly, mild to moderate (Figure 4) expression was observed in two (28.6%) and one (14.3%) patient with this variant. The transitional and chordoid variants showed moderate PanCK expression. The atypical variant was not reactive to PanCK in 9 (56.2%) of the cases, while 5 (31.3%) showed moderate expression, and 2 (12.5%) exhibited strong expression. The difference in expression was significant among the histopathological variants (P = 0.007), as shown in Table 4.

Table 4. Association between Panck semiquantitative expression and tumor type, grade and unfavorable morphological features

		PanCK semiquantitative expression								
		Negative		Weak		Moderate		strong		P value
Tumor features		No	%	No	%	No	%	No	%	
Type	Meningothelial	4	57.1	2	28.6	1	14.3	0	0	0.007
	Transitional	0	0	0	0	1	100	0	0	
	chordoid	0	0	0	0	1	100	0	0	
	Atypical	9	56.2	0	0	5	31.3	2	12.5	
	Anaplastic	0	0	0	0	0	0	3	100	
Grade	I	4	50	2	25	2	25	0	0	0.008
	II	9	52.9	0	0	6	35.3	2	11.8	
	III	0	0	0	0	0	0	3	100	
Macro nucleoli	Absent	9	50	2	11.1	7	38.9	0	0	0.157
	Present	4	57.1	0	0	1	14.3	2	28.6	
Increased cellularity	Absent	10	52.6	2	10.5	5	26.3	2	10.5	0.887
	Present	3	50	0	0	3	50	0	0	
Sheets	Absent	11	50	2	9.1	7	31.8	2	9.1	1
	Present	2	66.7	0	0	1	33.3	0	0	

Small cells	Absent	12	52.2	2	8.7	7	30.4	2	8.7	0.5
	Present	0	0	0	0	1	100	0	0	
Necrosis	Absent	11	55	2	10	6	30	1	5	0.569
	Present	2	40	0	0	2	40	1	20	
brain invasion	No invasion	9	45	2	10	6	30	3	15	1.000
	Invasion	4	50	0	0	2	25	2	25	

Similarly, all grade III tumors showed strong PanCK expression, whereas four (50%) grade I and nine (52.9%) grade II tumors did not show any PanCK expression. The difference was statistically significant. However, weak to moderate expression was observed in 4 (50%) grade I tumors, and moderate to strong expression was observed in 6 (35.3%) and 2 (11.8%) grade II tumors, respectively.

Although none of the unfavorable morphological features exhibited significant association with PanCK expression, the single case that had small cells expressed moderate PanCK expression, three (50%) of the cases with increased cellularity showed moderated expression, three (42.9%) of cases with macro nucleoli expressed moderate to strong expression, and three (60%) of those with tumors expressed moderate to strong expression. Brain invasion was not significantly associated with PanCK expression.

The association between Ki67 proliferation index and meningioma features

The median Ki67 expression in all meningioma cases was 8.50%, ranging between 1% and 90%. When cases were categorized according to the 9% proliferation index, all anaplastic, chordoid, and 9 (60%) atypical cases exhibited >9% Ki67 expression. In contrast, 7(100%) of the meningothelial variants showed Ki67 expression of ≤9%. The difference was statistically significant (P=0.002). This was further confirmed in tumor grades, where three (100%) of grade III and 11 (64.7%) of grade II exhibited Ki67> 9%, while eight (100%) of grade I had ≤9% ki67 expression. The difference was statistically significant (P=0.001). Interestingly, all cases with necrosis had Ki67 expression > 9%, compared to 14 (70%) of those without necrosis, which expressed lower ki67 expression ≤9% (P=0.009). Furthermore, five (83.3%) tumors with increased cellularity had ki67>9%, while 13 (68.4%) of those without this feature had lower Ki67 expression; however, the P value was marginal (0.056). Further features and details are listed in Table 5.

Table 5. The association between Ki67 index and tumor type, grade and unfavorable morphological features

		<=9 (N=14)		*>9 (n=14)*		*P value*
Tumor features		No	%	No	%	
Type	Meningothelial	7	100.0%	0	0.0%	0.002
	Transitional	1	50.0%	0	0	
	chordoid	0	0.0%	1	100.0%	
	Atypical	6	37.5%	10	62.5%	
	Anaplastic	0	0.0%	3	100.0%	
Grade	I	8	100.0%	0	0.0%	0.001
	II	6	35.3%	11	64.7%	
	III	0	0.0%	3	100.0%	
Macro nucleoli	Absent	12	66.7%	6	33.3%	0.177
	Present	2	28.6%	5	71.4%	
Increased cellularity	Absent	13	68.4%	6	31.6%	0.056
	Present	1	16.7%	5	83.3%	
Sheets	Absent	13	59.1%	9	40.9%	0.565
	Present	1	33.3%	2	66.7%	
Small cells	Absent	14	60.9%	9	39.1%	0.417

	Present	0	0.0%	1	100.0%	
Necrosis	Absent	14	70.0%	6	30.0%	0.009
	Present	0	0.0%	5	100.0%	
Brain invasion	No invasion	10	50.0%	10	50.0%	1
	Invasion	4	50.0%	4	50.0%	

The correlation of PanCK and proliferation markers and tumor grade

The total PanCK score showed a significant moderate linear correlation with the Ki67 rate (r=0.504, P=0.006), mitotic count (r=0.433, P=0.021), and tumor grade (r=0.411, P=0.03).

Ki67 rate showed stronger correlation with tumor grade (r=0.752, P,0.001) and mitotic activity (r=0.689, P<0.001). Mitotic count on the other hand showed the highest correlation with tumor grade (r=0.808, P<0.001

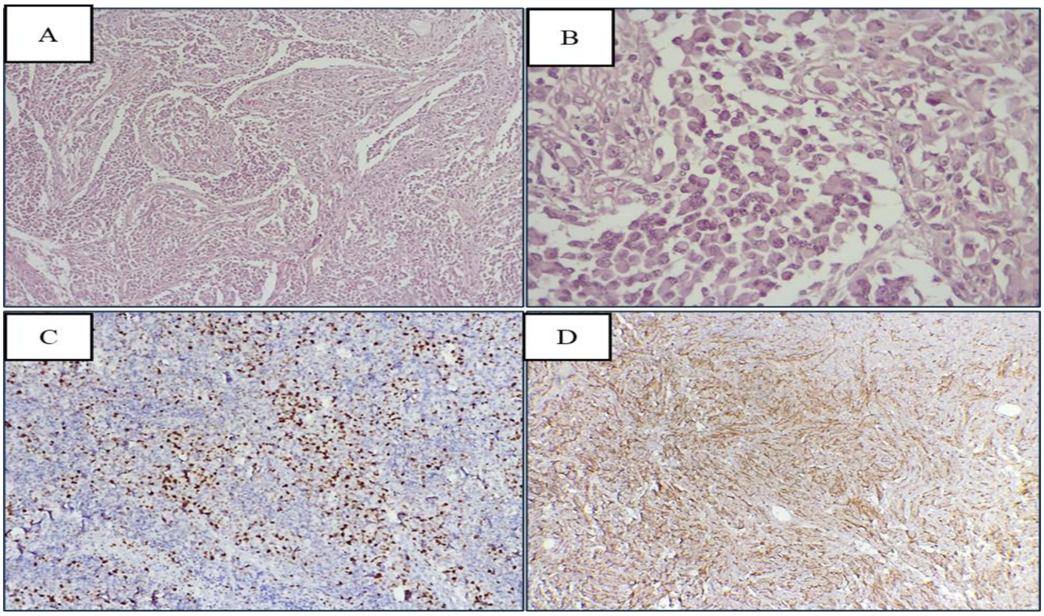

Figure 3. Microphotograph of anaplastic meningioma. A) H&E staining, 100X; B) 400X; C) Ki67 70%, 100X; D) PanCK semiquantitative score 5 (strong expression), 100X.

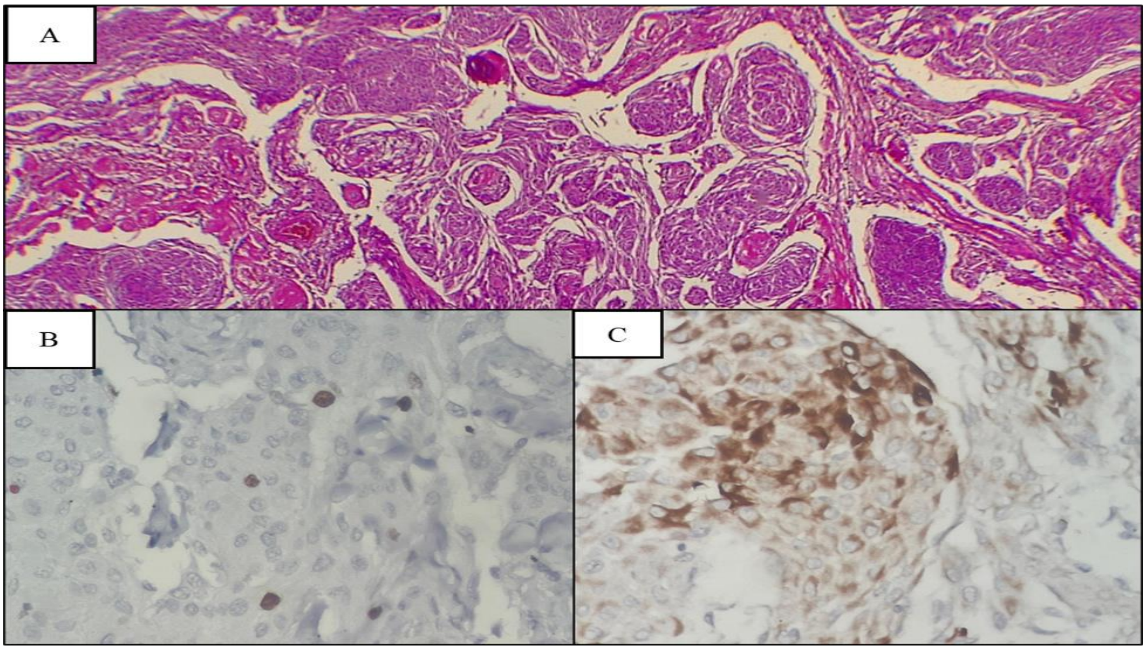

Figure 4. Microphotographs of meningothelial meningioma. A) H&E, 100X staining; B) Ki67 1%, 400X; C) PanCK semiquantitative score 4 (moderate expression), 400X.

Discussion

The current study confirmed the immunoreactivity of meningeal neoplastic cells to PanCK, which was the highest in grade III anaplastic variant (100%) and the lowest in grade I meningothelial variants (42.9 %).

The current study included 25 (89.3%) females with a male -to -female ratio of 1:8.3 and a mean age of 49.7± 13.699 years. Epidemiological studies confirm female predominance, with incidence rates of benign meningioma and malignant tumors (1)with male-to-female ratios of 1:2.33 and 1:1.12, respectively (1), and a median age at diagnosis of 66 years (1). In a local study evaluating 57 cases of surgically excised meningiomas between January 2018 and December 2020, Hussein et al. reported a mean age 48.4 years which agrees with the findings of the current study, however, male to female ration was about the half (1:4) (10). In their series, Hussein et al. reported a higher rate of grade I meningiomas (96.5 %), with meningothelial meningiomas being the most prevalent (71 %). These results differ from those of the current study, where grade I constituted 28% and meningothelial made up 25% of all cases. Nevertheless, this is justified as the objective of the current investigation was to assess the expression of PanCK in all tumor grades and variants, rather than to estimate the prevalence of these entities.

All of the cases included in the current investigation were intracranial meningiomas, with 14 (50%) affecting the cerebral convexity, 3 (10.7%) the posterior fossa, and 3 (10.7%) the suprasellar region. Other studies have reported comparable figures, with 34.4% of intracranial meningiomas occurring in the convexity, 10-15% in the posterior fossa, and 5-10% in the suprasellar region (11). In Iraq, Husain et al. reported that intracranial meningiomas constituted 86% of their series. In agreement with the current study, 53% of their cases were in the cerebral convexity, and 12% were in the posterior fossa (10).

Our results showed a differential expression of Panck in meningioma, being strongly expressed in all anaplastic cases, moderate to strong in 47.1% of atypical variants, and weak to moderate in 50% of benign variants. PanCK was negative in 50% of benign variants and 52.9% of atypical variants.

The value of PanCK in separating malignant meningioma from metastatic carcinoma has been the focus of other studies. Liu et al. concluded that cytokeratin is not a reliable immunohistochemical marker to separate a malignant meningioma from metastatic carcinoma, as it was expressed in 75% of malignant meningiomas and 100% of metastatic carcinomas. However, unlike the results of the current study, they did not observe any expression (0%) in benign meningiomas (7). In contrast, Miettinen et al., who mapped keratin polypeptides in 463 meningiomas of various types, found that K18 was expressed in every meningioma they examined, as well as non-neoplastic leptomeninges, while K7, K8, K19, and AE1 were expressed mostly in secretory variants, very rarely in other benign variants, and were negative in the leptomeninges (12).They concluded that antibodies to AE1, AE3, K19, K8, and K7 were beneficial because these proteins rarely label significant numbers of meningioma cells but are positive in the majority of carcinomas (12). However, the authors acknowledged the potential pitfall in distinguishing anaplastic meningiomas from metastatic carcinomas because of the overlapping patterns of several keratins; yet, they considered CK20 a good marker that was not present in any type of meningioma in their series (12).

In the current study, we observed positive focal weak to moderate expression in three out of seven meningothelial variants, with a total score ranging between 0-4. The literature on the expression of CK in meningothelial cells is conflicting. While some studies have confirmed CK expression by meningothelial meningiomas, with a specific pattern of expression seen in the vicinity of hyaline bodies (13), other studies have described the complete absence of this marker in meningothelial meningiomas (4, 7). The expression in the single transitional variant in the current study was moderate, with a total score of 3, in keeping with the findings of Tertishniy et al., who had five cases of transitional variant. They reported that 20% of cases exhibited focal cytoplasmic CK expression with a mean score of 1.5 (4). While many studies in keeping with the current study confirmed the strong expression of PanCK in anaplastic meningiomas (7, 12), there are no data in the specialized literature on CK expression in grade II atypical meningiomas. However, in 52.9% of the samples studied, cytoplasmic PanCK expression was established: 35.3% of grade II meningiomas (5 atypical and 1 chordoid) showed moderate expression was observed, while the remaining 11.8 % atypical tumors were characterized by strong diffuse immunoreactivity.

The correlation between PanCK expression and different atypical features was further investigated in the current study; however, no significant association was observed between the presence of macronucleoli, increased cellularity, sheet pattern, small cells, or necrosis and the positive expression of PanCK.

Based on the aforementioned information, it is evident that PanCK is not exclusively expressed in anaplastic variants; it can also be expressed by grade I and grade II variants, suggesting its potential involvement in tumorigenesis and progression. A recent study assessing the molecular signature of low-grade meningiomas found that the KRT6a and KRT16 genes, which are members of the keratin family, were differentially expressed in these tumors (5). The study demonstrated that the mutation of tumor necrosis factor Receptor-Associated Factor 7 (TRAF7), which is involved in cell signaling and ubiquitination, can disrupt normal cellular processes, including structural integrity through KRT6a and KRT16 (5).

As the expression of PanCK showed a trend of increase with increasing tumor grade, we sought to study the correlation between the PanCK total score and the mitotic activity of the tumors exemplified by the mitotic count and Ki67 index. We observed a significant moderate linear correlation between PanCK and mitotic count (r=0.433) and a higher correlation with Ki67 (r=0.504). We also observed a significant correlation with the tumor grade (r=0.411). No study in the literature directly correlates PanCK with Ki 67 or mitotic count.

Before directly correlating PanCK expression with mitotic activity parameters, we evaluated the proliferative activity of the tumor. In agreement with previous studies, we observed that anaplastic and atypical meningiomas exhibited significantly higher KI-67-PI than WHO grade 1 histological subtypes (14-16). In terms of atypical morphological features, we observed a significant association between a high Ki67 index and the presence of necrosis and a marginal association with increased cellularity. Wagle et al. found that a higher KI67 index was significantly correlated with larger tumor volume, peritumoral edema, and necrosis on preoperative MRI (16). The Ki67 index in atypical tumor ranged between 2%-70% while the mitotic count was between 2-8 per 10HPF, however, there was a significant correlation between the two parameters (r=0.689) which is higher than what has been previously reported in a larger study including 68 patients (r=0.490)(17). Notably, the correlation between tumor grade and mitotic index was higher (r=0.808) than that between tumor grade and Ki67 index (r=0.752); however, both indices still showed a very strong connection with grade.

Study limitations

The study was conducted on a relatively small sample size of 28 patients, which may limit the generalizability of the findings. The study only included patients who underwent neurosurgical operations, which might not represent the entire population of meningioma patients.

Conclusions

PanCK is variably expressed across all grades of meningioma and is not confined to grade III tumors, thereby limiting its diagnostic value in differentiating primary meningiomas from metastatic carcinomas. Its linear correlation with Ki67 indicates a potential role in driving tumor proliferation.

Recommendations

Further studies are recommended to evaluate the prognostic significance of PanCK expression in patients with grade I and II meningiomas, particularly in relation to recurrence risk and disease progression. Additionally, targeted research into the molecular evolution and differential expression of specific keratin subtypes in low-grade meningiomas may provide deeper insights into tumor biology and potential diagnostic markers.

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Ethical clearance: The study protocol was approved by the Scientific Council of pathology of the Iraqi Board of Medical specializations.

Conflict of interest: No conflict of interest.

Acknowledgement: None

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