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What is the predominant etiological factor for Merkel cell carcinoma in Turkey: viral infection or sun exposure?

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Abstract

Background Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine skin carcinoma. The pathogenesis involves Merkel cell polyomavirus (MCPyV) and ultraviolet radiation exposure. Studies on MCC in Turkey are scarce, with essential data on local etiopathogenic and prognostic factors still lacking. We aimed to analyze the clinical and histopathologic features, biomarkers, and to evaluate these findings alongside Turkish literature to infer the etiopathogenesis, prognosis, and possible treatment options for the disease.

Methods We analyzed the clinicopathologic features of 7 MCC patients diagnosed at the Pathology Department of Pamukkale University between 2003 and 2024 in this retrospective study. Clinical data was retrieved from the hospital's electronic records. Formalin-fixed, paraffin-embedded tumor specimens stained with hematoxylin-eosin were examined microscopically. MCPyV, Retinoblastoma 1 (RB1), p53, PRAME, PD-L1, and MMR proteins were evaluated immunohistochemically. Research on MCC from Turkey was sourced from Turkish databases (ULAKBIM, Turkiye Atif Dizini, DergiPark, Turk Medline) and international databases (Pubmed, Google Scholar, Scopus, Embase). The literature review identified original research, case reports, theses, and conference presentations.

Results The patients in our series, all aged over 50 (mean age 76.1 ± 14.8), with a slight predominance of one gender (F: M = 1.33:1). During a mean follow-up of 16.1 months, 42.9% (3/7) had lymph node metastases, and 57.1% (4/7) showed distant metastases. PRAME was positive in 42.9% of the cases (3/7). The total number of MCC cases reported from Turkey was estimated at 227 ± 46, with MCPyV status available in a subset, showing a positivity rate of 70.3%. PD-L1 expression was observed in the tumor microenvironment in 55% of virus-positive MCC cases from Turkey.

Conclusions The 9% incidence of gluteal localization in Turkish MCC cases, considering its geographical significance, is noteworthy. Notably, all MCC cases from Turkey in which microsatellite instability status has been assessed were found to be microsatellite stable. PRAME should be investigated in larger series for its potential role in the shared oncogenic pathways of MCC.

Keywords Merkel cell carcinoma, Merkel cell polyomavirus, Neuroendocrine carcinoma, Skin neoplasms, Geographical features, Histopathology, Immunohistochemistry, Microsatellite instability, PRAME

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Background

Merkel cell carcinoma (MCC) is an extremely rare neuroendocrine carcinoma of the skin with an aggressive clinical course. Despite its rarity, it is noteworthy that an epidemiologic study found a 95% increase in incidence between 2000 and 2013 [1]. MCC was first described as "trabecular carcinoma" by Toker et al. in 1972 [2]. Subsequently, in later years, the nomenclature was revised to MCC due to the observed convergence between the structural features and immunohistochemical profile of these tumors and Merkel cells, renowned as cutaneous mechanoreceptors [3, 4]. MCC occurs mostly in the later years of life (usually in the 7th and 8th decades) and is more common in males [5]. Head and neck constitute the most prevalent sites of localization, succeeded by the extremities and trunk [6]. Involvement of other sites, such as the oral mucosa, oesophagus, stomach, parotid gland, submandibular gland, nasal cavity, vulva, or vagina, is exceedingly uncommon [7–12]. Risk factors include older age, immunosuppression (patients with chronic lymphocytic leukemia (CLL), HIV/AIDS, or solid organ transplantation), pale skin and ultraviolet (UV) exposure [1, 13]. The pathogenesis of MCC involves Merkel cell polyomavirus (MCPyV) and exposure to UV radiation. Notably, in the northern hemisphere, approximately 80% of cases are linked to MCPyV. MCPyV integrates into host cell DNA and plays a role in oncogenesis by inactivating the tumor suppressor gene Retinoblastoma [14, 15]. In contrast, within a notable proportion of cases in the southern hemisphere, UV-induced progressive DNA damage assumes a significant role, resulting in a higher mutation burden compared to virus-positive MCC [16].

Immunotherapy agents targeting programmed cell death protein 1 (PD-1), and programmed cell death ligand-1 (PD-L1) have become an important option, especially in the treatment of metastatic MCC [6].

There is considerably limited data on this rare type of cancer, and most of the available information is derived from studies based on Western countries or large-scale epidemiologic research. Research on MCC in Turkey is even more limited, with fundamental data on local etiopathogenic and prognostic factors remaining incomplete.

We aimed to reveal the clinical and histopathologic features, biomarkers such as MCPyV, p53, RB1, and preferentially expressed antigen in melanoma (PRAME), as well as PD-L1 and MMR proteins of our 7 MCC cases, and to evaluate these findings together with the data in Turkey by reviewing both English and Turkish literature, and to make inferences about the etiopathogenesis, prognosis, and potentially the treatment of the disease in this population.

Methods

Sample selection

We performed a retrospective study of 7 patients diagnosed with MCC between 2003 and 2024, revealing their clinicopathologic features. Essential clinical data, involving age, sex, tumor site, tumor diameter, disease stage, presence of distant or lymph node metastasis, and clinical history, were collected from the computerized medical records of our hospital. Follow-up information was acquired through routine outpatient visits or by telephone.

Formalin-fixed, paraffin-embedded tumor specimens stained with hematoxylin-eosin (H&E) were examined microscopically. Histopathological features, including the status of surgical margins, tumor thickness, Clark level, lymphovascular invasion (LVI), perineural invasion (PNI), tumor growth pattern (TGP), presence of ulceration, tumor-infiltrating lymphocytes (TILs), presence of necrosis, and mitotic index, were systematically assessed.

Immunohistochemical staining

The immunohistochemical stains, including chromogranin, Pan-cytokeratin (AE1/AE3), TTF-1, Vimentin, and melanoma markers (S100, Melan-A, and HMB-45), were administered in the majority of cases and subsequently re-evaluated under the microscope.

Paraffin blocks containing a rich volume of tumor were selected for IHC staining. Selected formalin-fixed paraffin-embedded tissues were sectioned at 5 μm thickness and stained with Cytokeratin 20 (CK20) (Cell Marque, clone Ks20. 8, dilution 1: 200), MCPyV Large T-Antigen (Vitro Master Diagnostica, clone CM2B4, ready-to-use), RB1 (Vitro Master Diagnostica, clone 1F8, ready-to-use), p53 (Cell Marque, clone SP5, ready-to-use), PRAME (Abcam, clone EPR20330, ready-to-use), MutL homolog 1 (MLH-1) (Ventana, clone M1, ready-to-use), MutS homolog 2 (MSH-2) (Ventana, clone G219-1129, ready-to-use), MutS homolog 6 (MSH-6) (Ventana, clone SP93, ready-to-use), Postmeiotic segregation increased 2 (PMS-2) (Ventana, clone A16-4, ready-to-use), PD-L1 (Ventana, clone SP263, ready-to-use) antibodies using a closed automated IHC stainer (Ventana Benchmark XT).

Assessment of immunohistochemistry (IHC)

CK20 expression was classified into perinuclear dot-like and other staining patterns (cytoplasmic, membranous or mixed). MCPyV nuclear expression was evaluated using a 10% threshold value in accordance with a previous publication, and cases exceeding this value were considered positive [17]. RB1 expression was evaluated as strong nuclear staining in tumor cells, and cases with a loss of nuclear expression were classified as negative. p53 expression was assessed as wild type or mutant. Mutant status was defined as complete loss of expression

in tumor cells (null) or abnormal diffuse strong staining in more than 90% of cells. PRAME was evaluated based on the percentage of tumor cells showing nuclear expression, with scores defined as 1 + for 1–25%, 2 + for 26–50%, 3 + for 51–75%, and 4 + for 76–100%, while staining intensity was graded on a scale from 0 + to 3+, as defined by Lezcano [18], followed by Miller et al. [19]. PRAME expression was classified as (+) if the staining percentage was 3 + or 4 + and the staining intensity was 2 + or 3+. Mismatch repair (MMR) proteins (MLH1, MSH2, MSH6, and PMS2) were evaluated as 'intact nuclear expression' or 'loss of nuclear expression' in tumor cells with non-neoplastic cells in the surrounding tissue as internal control. PD-L1 expression was assessed as membranous staining for tumor cells and membranous and/or cytoplasmic staining for immune cells, and samples with at least 100 viable tumor cells and without necrosis were selected. Tumor proportion score (TPS) was calculated by dividing the number of PD-L1 (+) tumor cells by the total number of tumor cells, expressed as percentage. Combined positive score (CPS) was calculated by adding the number of PD-L1 (+) immune cells and tumor cells, then dividing by the total number of tumor cells, and multiplying by 100. A CPS score greater than 1 or a TPS percentage greater than 1% was considered positive.

Next-generation sequencing (NGS)

NGS was performed in only one case. The exonic regions and exon-intron junctions of a total 87 genes, including TP53 and RB1, were covered in formalin-fixed, paraffine-embedded (FFPE) tissue samples. The workflow covered sample extraction, library prep, sequencing and bioinformatics steps. DNA was extracted using the QIAamp DNA FFPE Advanced UNG Kit (Qiagen), and concentration measured with the QubitTM dsDNA HS kit (Thermo). Libraries were prepared with the QIAseq Custom Panel (Qiagen), barcoded, amplified, and purified, then diluted to 4nM. Sequencing was performed on the AVITI System (Element Biosciences). Secondary analysis and clinical interpretation used Qiagen Clinical Insight-Analyse Universal and Interpret tools.

Microsatellite instability (MSI) status was determined by examining regions corresponding to the loci BAT40(T)37, MONO-27(T)27, BAT26(A)27, NR24(T)23, BAT25(T)25, NR22(T)21, HSP110-T17(T)17, NR21(A)21, and BAT34C4(A)18. The analyses were conducted using the QIAGEN CLC Genomic Workbench software. The MSI evaluation criteria were as follows: MSI-high indicated cases with more than 40% instability; MSI-low referred to cases with 15–40% instability; MSI-stable represented cases with less than 15% instability.

Literature search for MCC Data from Turkey

Research on MCC from Turkey was sourced by searching ULAKBIM, Turkiye Atif Dizini, DergiPark, and Turk Medline for Turkish literature, while Pubmed, Google Scholar, Scopus, and Embase were used for English literature, with data recorded up until September 2024. The literature review identified not only original research and case reports but also theses and case presentations from conferences. Cases that were repetitive or lacked any clinicopathological information other than the diagnosis were not included in the further analysis. After the literature review, some authors were contacted by e-mail or telephone for additional information: One author was asked about the number of cases from each center in their multicenter study to avoid possible duplications and to clarify the total number of MCC cases in Turkey. Another author was asked whether they had evaluated the CK20 staining pattern, as its potential significance for the prognosis of the disease is being explored. Following the identification of all reported MCC cases in Turkey, a statistical analysis was performed on 91 cases with known MCPyV status.

Statistical analysis

IBM SPSS Statistics (version 29.0) was used for statistical analysis. Studies involving MCC cases with known MCPyV status from Turkey [20–22], including our own, were analysed statistically using Pearson's chi-square for categorical variables and Mann-Whitney U for comparing age distribution. p values < 0.05 were considered statistically significant.

Results

The patients in our series had a mean age of 76.1 ± 14.8 years. The cohort exhibited a slight predominance of one gender (F: M = 1.33:1). In addition to advanced age being a risk factor in all patients, one case had a previous diagnosis of CLL. The mean tumor diameter was 4.1 ± 3.5 cm (1.1–10 cm). Four patients were diagnosed with stage IV disease at the time of their initial diagnosis. Lymph node metastasis was seen in 42.9% (3/7) and distant metastasis in 57.1% (4/7) of cases. One patient, in their 50s, passed away due to metastatic disease involving lymph nodes and bone marrow within a period of 2 months. A different patient, who had metastases to the pelvic region, died from sepsis and cardiac arrest 20 days after the biopsy of the primary tumor. One patient, who had metastases to the lymph nodes and abdominal region, died of a stroke associated with COVID-19 several months after the diagnosis of MCC. Another patient, who had both lymph node and bone metastasis, underwent re-excision along with inguinal lymph node dissection due to positive surgical margins after tumor excision. Subsequently, the patient was scheduled to undergo immunotherapy. The

mean follow-up period for the six available patients was 16.1 months (1–66 months).

Histopathological examination revealed pure neuroendocrine morphology in all cases (7/7, 100%). Subcutaneous adipose tissue invasion was evident in 71.4% of cases (5/7). PNI was observed in 57.1% (4/7). TILs were evident in all cases, with 5 being non-brisk and 2 brisk. Only three cases exhibited a mitotic rate of ≤ 10, while the mean mitotic rate across all cases was 19 mitoses per mm^2. Ulceration was observed in 57.1% (4/7). Necrosis was present in 28.6% (2/7). The mean tumor thickness was 11 ± 5.1 cm (5–18 cm). The tumor was present at the surgical margin in 42.9% (3/7).

Table 1 Clinicopathological and immunohistochemical characteristics of our MCC cases ($n = 7$)

Features	Frequency (%)
Mean age, SD	76.1 ± 14.8
Sex	
Female	4 (57.1%)
Male	3 (42.9%)
Tumor Localization	
Head and Neck	3 (42.9%)
Upper ext	2 (28.6%)
Trunk	1 (14.3%)
Lower ext	1 (14.3%)
LVI	
Present	4 (57.1%)
Absent	3 (42.9%)
TGP	
Nodular	3 (42.9%)
Infiltrative	4 (57.1%)
MCPyV	
Positive	4 (57.1%)
Negative	3 (42.9%)
P53	
WT	5 (71.4%)
N	2 (28.6%)
RB1	
Loss of expression	3 (42.9%)
No loss	4 (57.1%)
PD-L1 (SP263)	
CPS	
< 1	3 (42.9%)
≥ 1	4 (57.1%)
TPS	
< 1%	3 (42.9%)
≥ 1%	4 (57.1%)
MSI (by IHC)	
MSS	6 (85.7%)
d-MMR	1 (14.3%)
PRAME	
Positive	3 (42.9%)
Negative	4 (57.1%)

Abbreviations, CPS: Combined positive score, d-MMR: Deficient mismatch repair, LVI: Lymphovascular invasion, MCPyV: Merkel cell polyomavirus, MSI: Microsatellite instability, N: Null, IHC: Immunohistochemistry, PD-L1: Programmed death-ligand 1, PRAME: Preferentially expressed antigen in melanoma, RB1: Retinoblastoma 1, SD: Standard deviation, TGP: Tumor growth pattern, TPS: Tumor proportion score, WT: Wild-type

Immunohistochemical examination revealed CK20, AE1/AE3, and chromogranin positivity in all cases (7/7, 100%), while TTF-1, Vimentin, S100, Melan A, and HMB-45 were negative, supporting the differential diagnosis of metastatic neuroendocrine carcinoma, melanoma and sarcoma. CK20 showed the classic perinuclear dot-like pattern in 57.1% (4/7), whereas membranous, cytoplasmic, or mixed patterns were observed in the remaining cases (3/7). Key clinicopathological features, together with MCPyV, p53, RB1, PD-L1, MSI (MLH1, MSH2, MSH6, and PMS2), and PRAME IHC results, were presented in the table (Table 1). NGS was performed in only one of our cases (1/7, 14.3%), and no mutations were detected, including in TP53 and RB1.

Including our cases, the MCPyV status was available in approximately 40.1% (91/227) of MCC cases reported from Turkey in the literature, with an MCPyV positivity rate of 70.3% (64/91). The clinicopathological features according to MCPyV status in Turkey were presented in the table (Table 2). Detailed information about MCC cases in the Turkish literature is provided in the discussion section.

Discussion

The median age was 72, and the most common site was head and neck (3/7, 42.9%), consistent with the literature [23]. However, females (4/7, 57.1%) slightly outnumbered males (3/7, 42.9%), contrary to the literature [24], which may be due to the limited number of our cases.

Our results showed that 57.1% (4/7) of cases were positive for MCPyV by IHC, matching the literature which reports rates of 46–90% [25, 26].

PD-L1 was evaluated as positive in 50% (2/4) of MCPyV (+) cases and 57.1% (4/7) of the total cases in our series. MCPyV (+) tumors tend to respond better to PD-L1 inhibitors [27] and more frequently express PD-L1 [28]. While MCPyV or PD-L1 status of the tumor does not directly influence treatment decisions under existing protocols [6, 29], larger cohorts and further studies are needed in this area.

The role of MSI in MCC is less defined than in colorectal cancer, but the growing importance of immunotherapy has brought MMR proteins and PD-L1 forward as potential biomarkers for research. Gambichler et al. found that 16% (9/56) of the patients in their series had a loss of MMR proteins. Among the five cases that underwent MSI testing, four were found to be MSS (microsatellite stable), while one was classified as MSI-H (microsatellite instability-high). The MSI-H case was a patient with loss of MLH-1 and PMS-2 expression [30].

Table 2 Comparison of clinicopathological features of MCC cases with known MCPyV status in Turkey, including our cases [20–22]

	MCPyV (+) (*n* = 64)	MCPyV (-) (*n* = 27)	*P* value
	n (%)	*n* (%)	
Sex			
Female	36 (66.7)	10 (37)	0.15
Male	28 (33.3)	17 (63)	
Age, median (range) *	71 (35–91)	70 (54–95)	0.84
Anatomical localization**			
Head and Neck	12 (24)	14 (56)	**0.005**
Upper ext	19 (38)	2 (8)	
Trunk	10 (20)	2 (8)	
Lower ext	9 (18)	7 (28)	
CK20 expression***			
Positive	53 (100)	19 (90.5)	0.14
Negative	0 (0)	2 (9.5)	
CK20 staining pattern***			
Perinuclear	21 (39.6)	7 (41.2)	1.0
Other	32 (60.4)	12 (58.8)	
TILs			
Present	30 (57.7)	19 (79.2)	0.07
Absent	22 (42.3)	5 (20.8)	
PD-L1 (SP263) *			
CPS			0.81
< 1	9 (45.0)	7 (41.2)	
≥ 1	11 (55.0)	10 (58.8)	
TPS			0.054
< 1%	12 (60.0)	15 (89.2)	
≥ 1%	8 (40.0)	2 (11.8)	
LVI***			
Present	28 (50.9)	11 (47.8)	1.0
Absent	27 (49.1)	12 (52.2)	
TGP***			
Nodular	16 (30.8)	5 (22.7)	0.67
Infiltrative	36 (69.2)	17 (77.3)	
Follow-up*			
Ex	11 (57.9)	11 (64.7)	0.94
Alive	8 (42.1)	6 (35.3)	
Lymph node and/or distant metastasis****			
Present	29 (52.7)	11 (61.1)	0.73
Absent	26 (47.3)	7 (38.9)	
p53***			
Mutant	6 (10.5)	10 (47.6)	**0.001**
WT	51 (89.5)	11 (52.4)	
RB1***			
Loss of expression	11 (20.3)	12 (66.7)	**0.001**
No loss	43 (79.7)	6 (33.3)	

*In the study by Erdem et al. (20), age, follow-up and PD-L1 expression status details for MCPyV positive and negative groups were unavailable, and thus it was excluded from the analysis of these parameters. **In the study by Erdem et al. (20), 12 cases showed primary lymph node localization, while in the study by Ogut et al. (21), 3 cases were from lymph node metastases and 1 case was from brain metastasis; however, these cases were not included in the analysis of anatomical localization.***The study by Acikalin et al. (22) did not contain data on CK20 expression, CK20 staining pattern, LVI, TGP, p53, and RB1 expression, therefore, it was excluded from the analysis of these parameters.**** Metastasis data were not available in the study by Ogut et al. (21), and thus it was not included in the analysis of this parameter. Abbreviations, CPS: Combined positive score, LVI: Lymphovascular invasion, MCPyV: Merkel cell polyomavirus, RB1: Retinoblastoma 1, TGP: Tumor growth pattern, TPS: Tumor proportion score, WT: Wild-type

Recently, Kestel et al. studied 12 patients with MCC in Turkey and found that expression was intact in all cases [31]. Our one case (1/7, 14.3%) showed loss of nuclear expression with MLH-1 and was subsequently identified as MSS through NGS analysis.

PRAME was positive in 42.9% of the cases (3/7), with two showing diffuse and strong positivity and one showing heterogenous weak staining. PRAME is not only a diagnostic marker for melanoma but has also recently emerged as an immunotherapy target in uveal melanoma [32]. Elsensohn et al. detected PRAME positivity in 57% of 23 MCC cases, with 9% showing strong positivity, while Miller et al. observed strong positivity in 27% of 39 cases [19, 33]. Our series presents the first results on PRAME expression in MCC from Turkey, and the discussion, including the topic of shared oncogenic pathways, is provided towards the end of this section.

Given the rarity of MCC, the unknown dominance of either sun exposure or MCPyV in its pathogenesis locally, the limited number of studies, and the advances in immunotherapy, we decided to conduct a comprehensive literature review to provide a detailed overview of MCC studies in Turkey. The largest cohort was from a multicenter study [34], but despite contacting the corresponding author, we were unable to determine the exact number of patients contributed each center. After excluding confirmed duplications from this study, the total number of MCC cases reported from Turkey, including our own, was estimated at 227 ± 46. To prevent duplication and conflicting data, this study was excluded from further analysis, and all subsequent evaluations for MCC in Turkey were based on 227 cases. The mean age was 64 ± 18.3 years (range: 8–94) in the Turkish population. Among the 216 cases with reported gender, there was a slight male predominance (50.9%), with a male-to-female ratio of 1.04:1, consistent with the literature [35]. In 198 cases, tumor

location was known and distributed as follows: head and neck (29.8%) [20–22, 36–47], lower extremities (22.7%) [20–22, 36–38, 48–58], trunk (21.2%) [20–22, 36–38, 48, 49, 59–67], upper extremities (18.7%) [20–22, 36–38, 48, 68–71], and other sites (7.6%). In the other sites, 13 cases had primary nodal involvement [20, 72], 1 was in the oral cavity [73], 1 was paravertebral [74], and 1 was in the parotid gland [75]. We noted that 40% of the cases located on the trunk (and 9% of the total), including one of our cases, were in the gluteal region [22, 36, 37, 48, 49, 59, 60, 62, 65, 66]. Among the MCC cases, one (1/227, 0.44%) showed features of SCC [59], one (1/227, 0.44%) had squamous cell carcinoma in situ (CIS) [20], and one (1/227, 0.44%) was associated with actinic keratosis [46], displaying characteristics of a mixed tumor, with in situ case being MCPyV (-), consistent with findings in the literature that associate MCPyV negativity more frequently with mixed tumors [76]. There were synchronous tumors in two cases (2/227, 0.88%), one being pulmonary small cell carcinoma [63] and the other both SCC and basal cell carcinoma (BCC) [46]. As a risk factor for MCC, 7.5% of the cases (17/227) had a history of secondary malignancy [20, 22, 36, 63, 77], with the major being CLL [22, 36, 77]. Other etiologies included renal transplantation in four cases (4/227, 1.76%) [55, 56, 62, 78], liver transplantation in one case (1/227, 0.44%) [79], chronic renal failure in one case (1/227, 0.44%) [57], chronic venous insufficiency in one case (1/227, 0.44%) [80], and rheumatoid arthritis in one case (1/227, 0.44%) [42]. The tumor size was known for 128 cases, with a mean tumor diameter of 3.75 cm (range: 0.5–20 cm). Lymph node metastasis was present in 24.7% of the cases (56/227) [20–22, 36, 38, 44, 48–51, 53, 55–59, 62, 64, 68, 73, 75, 80, 81], and distant metastasis in also 24.7% (56/227) [20, 22, 31, 38, 39, 48, 51–53, 55–57, 62, 65–68, 70, 73, 80, 83, 84]. Seventy-two (51.1%) of the 141 patients with known survival status were alive, and 69 (49.9%) were deceased. One hundred and thirty-one patients with available follow-up data had a mean follow-up period of 36.2 months. Wide excision was performed in 127 cases, and chemotherapy and/or radiotherapy was given in 89 cases. There was no infoation on whether the cases received immunotherapy, possibly because it is a more recent treatment option. In one of our cases, immunotherapy was planned in addition to radiotherapy due to the presence of distant metastasis.

Histopathological examination revealed that infiltrative growth pattern (69.7%) was more common that nodular pattern (30.3%) among 76 cases with known TGP [20, 21, 54, 69]. LVI was evident in 45.7% of 105 cases [20, 21, 37, 42, 51, 62]. TILs were present in 65.8% of 76 cases [20–22]. CK20 was positive in 95.4% (21,22,36,37,39,43,45,46,50,54,57,62,63,65,66,68,69,71,72,74,75,81,82) of 132 cases, and negative in only 6 patients [20, 36, 59, 73]. CK20 staining pattern was known in 95 patients, with 48.4% showing positivity in the classic perinuclear dot-like pattern (20,21,39,45,49,50,52,55,57,62,71,74,75,81,82), while the remaining cases exhibited cytoplasmic, membranous, or mixed patterns [20, 21, 46, 63, 65, 68, 72]. MMR proteins were investigated only in two studies on MCC, including ours, where no loss of expression in 21 cases (21/22, 95.4%), while MLH-1 loss was observed in only one of our cases 1/22 (4.6%), which was further classified as MSS through NGS analysis [31].

This study is the first to provide insights into the rate of MCPyV-positive cases among MCCs in Turkey to date. MCPyV positivity rates show significant geographical variation, with 25–30% in Australia [84], 60% in Japan [85], 80% in North America [15], and 85% in Germany [86]. The MCPyV status was available in approximately 40.1% (91/227) of MCC cases reported from Turkey, with an MCPyV positivity rate of 70.3% (64/91). Although this appears lower than the rates reported in European and North American countries, the MCPyV positivity rate of 70.3% in Turkey is slightly higher than the countries in Asia, such as Japan. There was a female predominance in the MCPyV (+) group (36/64, 56.2%), while males predominated in the MCPyV (-) group (17/27, 63%), consistent with the literature [87, 88]. Although age differences by virus status had been reported in various studies from Turkey [20–22], overall, the ages in both groups were similar. However, in the broader literature, virus-negative patients tend to be older than virus-positive patients, although the age difference appears to have a limited impact on MCC pathogenesis [87, 88]. MCPyV (+) MCCs were more commonly localized in the upper extremities (19/50, 38%) and trunk (10/50, 20%), while head and neck localization (14/25, 56%) were more prominent in the MCPyV (-) group in Turkey ($p = 0.007$), in line with the literature [88, 89]. It can be concluded that MCPyV plays a more significant role in tumor development in regions less exposed to sunlight, such as the trunk and upper extremities, while the oncogenic effect of sun exposure becomes more prominent in the head and neck region, for the MCC population in Turkey. The gluteal location of MCC was reported rarely in the English literature [51]. It is noteworthy that 9% (17/227) of MCC cases in Turkey were localized to the gluteal region. The mean age of these patients was 63.1 ± 13.6, with a male-to-female ratio of 1.5:1. In our series, the case located on the gluteal region was a patient in their late 60s. While UV radiation plays a significant role in the pathogenesis of MCC, in gluteal cases, factors such as MCPyV, environmental influences, genetic predisposition, and skin type are expected to be more prominent. Notably, only one case (1/17, 5.9%) was presented with immunosuppression due

to kidney transplantation [62], while the remaining cases (16/17, 94.1%) had no identifiable etiologic risk factors, including our case. Moreover, lymph node metastasis was found in 24% (4/17) cases and distant metastasis in 35% (6/17), suggesting that gluteal MCCs are aggressive in nature and may be associated with poor prognosis. In conclusion, considering MCC in the differential diagnosis of patients presenting with a gluteal lesion, along with a multidisciplinary approach, may lead to earlier diagnosis and more effective treatment.

Immunohistochemistry revealed a mutant p53 pattern (10/21, 47.7%) and loss of Rb expression (12/18, 66.7%) more frequently in MCPyV (-) tumors, whereas MCPyV (+) group showed more wild-type p53 (51/57, 89.5%) and intact Rb expression (43/54, 79.6) in MCCs cases reported from Turkey ($p < 0.01$). MCPyV (-) MCCs commonly show TP53 mutations resulting in dysfunctional p53 protein, and the RB1 gene is frequently inactivated through mutations or deletions, causing uncontrolled cell cycle progression. Conversely, in MCPyV (+) tumors, wild type p53 and RB1 are typically retained, as viral proteins such as large T (LT) antigen inactivate Rb protein, driving tumorigenesis without the need for mutations in tumor suppressor genes [87, 88, 90]. There was no difference between virus-positive and negative groups regarding TGP ($n = 74$), LVI ($n = 78$), TIL ($n = 76$), PD-L1 expression ($n = 37$), and metastasis ($n = 73$) in MCC cases with known virus status reported from Turkey ($n = 91$, $p > 0.05$). However, MCPyV (-) MCCs are more likely to exhibit frequent LVI, an infiltrative growth pattern, lower levels of TILs, and a higher likelihood of metastasis, whereas the opposite is expected for MCPyV (+) tumors according to the literature [91, 92].

The composition and distribution patterns of TILs can provide deeper insights beyond simply noting their presence, offering valuable information about the tumor microenvironment, immune response, and prognosis in MCC. Nakamura et al. suggested that the presence of tertiary lymphoid structures around the tumor in virus-negative cases may indicate a favorable prognosis [93]. Feldmeyer et al., in their study of 62 MCC cases, examined TIL density and distribution within the tumor center and periphery, finding that PD-L1-positive cells were particularly concentrated in the tumor periphery of virus-positive patients [94]. Ricci et al. evaluated CD3, CD8, FoxP3, and PD-L1 expression in TILs to develop an "immunoscore" model, reporting that virus-positive cases with a high immune score were associated with improved survival [87]. Turkish data showed that PD-L1 expression was observed in the tumor microenvironment in 55% of virus-positive MCC cases [20–22]. However, larger cohort studies that comprehensively investigate the composition of TILs in MCC are still needed.

There is growing discussion about the role of virus-independent, shared oncogenic pathways in MCC pathogenesis. One study highlighted that transcription factors NFAT, P-CREB, and P-STAT were active in both virus-positive and virus-negative MCC, with virus-positive cases able to activate these specific pathways and acquire features similar to virus-negative cases despite their low mutation burden [95]. Ricci et al. suggested that DNA methylation in the intron 4–5 region of the hTERT gene could influence MCC prognosis and contribute to shared oncogenic pathways, independent of virus status [96]. Based on another study by Ricci et al., which highlights the prognostic impact of PD-1 promoter methylation in MCC, it can be proposed that immune modulation via epigenetic mechanisms may influence both virus-associated and UV-induced MCC [97]. In Miller et al.'s study, PRAME expression was observed in both virus-positive and virus-negative cases, suggesting PRAME's potential role in a shared oncogenic pathway in MCC [19]. In our cases, however, all three PRAME-expressing cases (3/7, 42.9%) were also MCPyV-positive, which may be attributed to the limited number of cases. PRAME, initially identified in the testis, is a cancer-testis antigen (CTA) known to play a key role in gametogenesis and is also involved in the reprogramming and pluripotency of germ cell tumors [98–101]. These findings lead to interest in the potential influence of PRAME expression on the well-known stem cell reacquisition characteristic of MCC.

Harms et al. reported that CK20-negative MCCs may arise through virus-independent molecular pathways and could harbor distinct mutations [102]. No significant difference in CK20 expression was observed between MCPyV-positive and MCPyV-negative MCC cases from Turkey ($n = 91$, $p > 0.05$). The small number of CK20-negative cases (2/91, 0.2%) in the Turkish cohort with known virus status may explain the lack of significant difference.

The primary limitations of our study were the small sample size, due to rarity of MCC, and its retrospective design. The presence of MCPyV was evaluated only by IHC, and molecular methods such as polymerase chain reaction (PCR) were not utilized. While comparing MCC studies from Turkey, the lack of assessment of standardized parameters in each study was also a limitation.

Conclusions

This study highlights that MCPyV status influences clinical features, such as tumor localization, with upper extremities and trunk more common in virus-positive cases, as well as molecular characteristics like p53 and Rb in MCC cases from Turkey, consistent with global findings. In Turkey, MCPyV appears to play a greater role MCC etiopathogenesis, with a 70.3% positivity rate, compared to UV exposure. Interestingly, 9% of MCC cases in Turkey occur in the gluteal region, suggesting a

geographically significant trend that should be explored further in larger studies. Notably, all MCC cases from Turkey in which MSI status has been assessed were found to be MSS, confirmed by immunohistochemical methods, with NGS performed in only one case.

In summary, this pilot study focused on the epidemiology, histopathological, and immunohistochemical characteristics of MCC, aiming to investigate the potential role of PRAME expression in shared oncogenic pathways and its impact on disease prognosis in a larger series of cases in the near future.

Abbreviations

AE1/AE3	Pan-cytokeratin
BCC	Basal cell carcinoma
CK20	Cytokeratin 20
CIS	Carcinoma in situ
CLL	Chronic lymphocytic leukemia
CPS	Combined positive score
CTA	Cancer-testis antigen
F	Female
H&E	Hematoxylin-eosin
IHC	Immunohistochemistry
LVI	Lymphovascular invasion
M	Male
MCPyV	Merkel cell polyomavirus
MLH-1	MutL homolog 1
MMR	Mismatch repair
MSH-2	MutS homolog 2
MSH-6	MutS homolog 6
MSS	Microsatellite stable
N	Null
N/A	Non-available
NGS	Next-generation sequencing
No.	Number
PNI	Perineural invasion
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PMS-2	Postmeiotic segregation increased 2
PRAME	Preferentially expressed antigen in melanoma
RB1	Retinoblastoma 1
SCC	Squamous cell carcinoma
TGP	Tumor growth pattern
TIL	Tumor-infiltrating lymphocytes
TPS	Tumor proportion score
TTF-1	Thyroid transcription factor-1
UV	Ultraviolet
WT	Wild-type

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Not applicable.

Author contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Erdem Comut and Ozge S. Karstarli Bakay. The first draft of the manuscript was written by Erdem Comut. Nese Calli Demirkan commented on previous versions of the manuscript. All authors read and approved the final version of the manuscript.

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Data availability
The DNA sequencing data for one patient diagnosed with MCC generated and/or analysed during the current study are available in the European Nucleotide Archive (ENA) repository. The data are registered under the project accession number PRJEB82659 and can be accessed at https://www.ebi.ac.uk/ena/browser/view/PRJEB82659.

Declarations

Ethics approval and consent to participate
This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the Local Ethical Committee of Pamukkale University (Ethics Approval Number: E-358452), with a waiver for the requirement of informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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