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Original research article

FREQUENCY OF LOSS OF MISMATCH REPAIR PROTEINS' IMMUNOHISTOCHEMICAL EXPRESSION IN SEBACEOUS NEOPLASMS, POTENTIAL MARKERS/TOOLS INDICATING THE POSSIBILITY OF MUIR-TORRE SYNDROME

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Abstract: *Screening for Muir-Torre Syndrome (MTS) using Mismatch Repair (MMR) gene immunohistochemistry (IHC) on sebaceous neoplasms (SNs) is technically feasible. Research for this indication is limited, especially in Asia. To address this knowledge gap, we examined the frequency of loss of IHC staining of MMR proteins in SNs.* ***Methods:*** *We conducted a cross-sectional study including 98 patients (120 SNs). Eleven out of 98 patients had concurrent or subsequent SNs.* ***Results:*** *The size and type of tumor showed a significant association with MMR loss. Fifteen (12.5%) sebaceous adenomas, 12 (10.0%) sebaceous, and 93 (77.5%) sebaceous carcinomas were included in the study—sixty-one (50.83 %) SNs presented with loss of one or more MMR proteins. Isolated loss of MSH2 was the most common IHC pattern (27.8%). Fifty cases (29.58%) showed a combined loss of MSH2 and MSH6, and 40 (23.66%) showed a combined loss of MLH1 and PMS2. Most SAs showed isolated loss of MLH1 and PMS2 (7, 26.9% each). Sebaceomas showed isolated loss of MSH2 and MSH6 as the most common (4, 33.3%) pattern. Isolated loss of MSH2 only (37, 28.2%) was the predominant pattern of IHC loss in SCs. Weak to fragile associations between MMR protein status and histopathological findings were observed, with the most notable association being between MLH1 and ulceration on the surface. The models have an accuracy of around 50%, indicating moderate prediction capability. In our cohort, personal and family history was available in 33 cases (25 out of 98 patients).* ***Conclusion:*** *We recommend that MMR IHC be performed routinely on all SNs, considering clinicopathological factors of the lesions, mainly the anatomic site and tumor type. The panel should include antibodies against all four MMR proteins.*

Keywords: Sebaceous Adenoma, Sebaceoma, Sebaceous Carcinoma, Sebaceous Neoplasms, MMR, MSH2, MSH6, MLH1, PMS2, Muir Torre Syndrome.

Introduction

Muir-Torre Syndrome (MTS) is a phenotypic variant of Hereditary Non-Polyposis Colorectal Carcinoma (HNPCC) or Lynch Syndrome (LS) (1, 2). Both syndromes share similar pathogenesis (mismatch repair/MMR genes' mutation) [1] involving MSH6 and MSH2 genes located on chromosome 2 and the MLH1 gene located on chromosome 3(3). The PMS2 gene has been related to MTS less frequently (3). These mutations lead to microsatellite instability (MSI) (4). MTS consists of skin lesions with at least one visceral malignancy (5). Skin lesions that are rare in the general population frequently occur in MTS and include mostly sebaceous neoplasms (SNs) like sebaceous adenoma (SA), sebaceous epithelioma or sebaceous, and sebaceous carcinoma (SC) with or without benign skin lesions such as keratoacanthoma (1, 6). Skin lesions may be the initial sign, or commonly, they follow the diagnosis of visceral malignancies (1). SNs can develop sporadically without any association with MTS, so differentiation between patients with MTS and sporadic SNs has been a vital debate (7). SNs that are multiple, recurrent, and with an early onset (before the age of 50 years) may show an association with MTS (3, 8, 9). Even solitary lesions mandate a correlation with MTS (6). The diagnosis of an SN should always give rise to the suspicion of an inherited MMR gene defect because they are rare, and a detailed clinical history might not always be available to the pathologist (6). A local study by N. Yaqoob et al. described only the frequency of adnexal neoplasms, including tumors with pilosebaceous differentiation, which showed an overall frequency of 69 (41.56%) (10). The visceral malignancies include those of the large bowel, endometrium, genitourinary tract, breast, ovary, small bowel, stomach, hepatobiliary tract, head and neck, brain, and hematolymphoid system, including Mycosis Fungoides (1, 5, 7, 11, 12). Colonic adenomatous polyps may also occur (1). A case of parotid gland SC has been reported in association with MTS by Neelakantan et al. (13). Cutaneous and visceral neoplasms in MTS behave less aggressively than their sporadic counterparts (14). A clinical scoring system and algorithm for MTS have also been suggested in the literature (15).

Several studies have shown the efficacy of immunohistochemical (IHC) testing for the identification of MMR gene mutations in SNs in patients with MTS and the usefulness of this technique for screening purposes (1, 5, 6, 16, 17). The available literature also shows studies that have reported concordance between MMR proteins' IHC and MSI testing by Polymerase Chain Reaction (PCR) (6, 17, 18). A previous study by Machin et al. described 100% concordance between MSI testing and IHC results (5). Most studies available in the literature have utilized MSH2 and MLH1 antibodies only (6, 16, 17). A few have added MSH6 to the panel (1, 19), and some have studied the utility of all four antibodies (11, 20-22). The commercially available

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antibodies were not widely available before 2000; almost all studies before this year did not mention MMR-IHC (23).
IHC analysis for MTS is being performed internationally, but we lack the availability and resources in Pakistan. Asian research on this topic is scarce. The data on cutaneous SNs in MTS is almost nonexistent in the local literature. Genetic screening is limited in our country, and SNs have not been investigated before for potential MTS associations. We aim to report loss of MMR protein by IHC in this group of patients to caution the physicians and then investigate further and, if possible, order MSI by molecular testing. This will reduce the burden of high-cost molecular tests. This is the first study to examine the IHC patterns between the SNs in Asia, especially the South Asian population, indicating the possibility of MTS.
Our study aims to determine the frequency of loss of immunohistochemical staining of MMR proteins in sebaceous neoplasms presenting at a tertiary care hospital in Karachi, Pakistan.

Methodology

The study was approved by the hospital's Ethical Review Board (2020-5318-14604). We collected sebaceous neoplasms through non-probability and convenience sampling from the archives of the histopathology department. Clinical information and pathology reports were available for review in all cases. Informed verbal consent was obtained by telephone. Hematoxylin and eosin (H&E)-stained slides were reviewed. The paraffin blocks were retrieved for all tumors that showed proper fixation, contained adequate tumor content, and had normal skin tissue. One hundred and twenty skin lesions from 98 patients were selected and included sebaceous adenomas, sebaceous, and sebaceous carcinomas. Eleven out of 98 patients had concurrent or subsequent SNs. None of these patients had been previously analyzed for microsatellite instability by molecular testing or had germline genetic testing done for the MMR genes or other mutations.
The exclusion criteria included all autolyzed or poorly fixed specimens, scanty biopsy specimens with a small amount of tumor, sebaceous hyperplasia, and keratoacanthoma cases.
Immunohistochemistry (IHC) for the MMR gene products MSH2, MSH6, MLH1, and PMS2 was performed according to the manufacturer's (DAKO) protocol using formalin-fixed paraffin-embedded tissue sections. The stained slides were seen for IHC expression by the authors according to the CAP protocol for MMR biomarker reporting. Positive nuclear expression in benign native structures such as endothelial cells, stromal cells, epithelial cells, hair follicles, sweat glands, sebaceous glands, and lymphocytes was considered a positive internal control. Loss of nuclear expression was labeled if tumor cells demonstrated negative results in one or more MMR proteins with positive internal control cells. Intact nuclear expression was labeled if the tumor cells showed positive atomic expression for all 4 MMR proteins, irrespective of the proportion of positive tumor cells. The results and the interpretation were recorded on the predesigned proforma.
The data was saved on a spreadsheet (Microsoft Excel version 2406). The data was analyzed using the software SPSS version 26.0. Descriptive statistics were computed. The mean ± standard deviation (SD) and range were calculated for all the quantitative variables, including patients' age and tumor size. Frequency and percentage were calculated for all the categorical variables, including gender, tumor type, and frequency of loss of IHC expression for all 4 MMR proteins. The significance of MMR expression was assessed in all SNs. Tables were generated to relate qualitative variables, including MMR protein expression, patient characteristics, histopathological findings, and SNs, using the Mann-Whitney U test and Cramér's V test. A p-value of <0.05 was considered statistically significant in the Mann-Whitney U test. Cramér's V test values vary from 0 (corresponding to no association between variables) to 1 (complete association).

Results

Overall, the age of the patients ranged from 15 to 91 years old, with a mean age of 60.40 years old. Patients were stratified into two groups based on age, with more patients in the >50-year-old group (90, 75%). Males were more commonly affected, with a male-to-female ratio of 1.1:1. The most common location was orbit (including eyelids, canthus, and conjunctiva). Laterality was not mentioned in 38 cases; however, 43 (52.4%) cases were on the right side, and 39 (47.6%) were on the left. Table 1 summarizes the clinical features of SNs. Table 2 shows selected significant results for MMR proteins across various tumor locations.
The biopsy type was unavailable in 81 (67.50%) cases. The remaining specimens comprise 35 (29.17%) excisions, 1 (0.83%) incision, 2 (1.67%) wedges, and 1 (0.83%) punch biopsy specimen. The minimum size of lesions was 0.88, and the maximum length was 1.73. Table 3 summarizes the histopathological findings of SNs. Table 4 depicts selected results showing the association of MMR proteins with histopathological findings. The pathological diagnoses and their frequencies are presented in Figure 1. The frequency of MMR proteins' expression is shown in Figure 2. MMR loss was seen in 61 (50.83%) cases, and MMR was intact in 59 (49.16%) cases. H&E and IHC stains of SNs are shown in Pictures 1, 2, and 3.
Table 5 summarizes the frequency of MMR loss in all SNs and individually in SA, sebaceous, and SC. The p-values indicate significant differences in the distribution of MMR protein loss across different types of SNs. Isolated loss of MSH2 is the most common (47, 27.8%) pattern of overall MMR loss. The combined loss of MSH2 and MSH6 was observed in 50 (29.58%) cases. Most SAs showed isolated losses of MLH1 and PMS2 (7, 26.9% each). Sebaceomas showed isolated loss of MSH2 and MSH6 as the most common (4, 33.3% each) pattern. Isolated loss of MSH2 only (37, 28.2%) was the predominant pattern in SCs.
Figure 3 shows the heatmap that visualizes the Cramér's V values, representing the strength of the association between MMR protein loss and tumor types. The heatmap shows moderate to strong associations between MMR protein loss and SNs. The strongest association observed is between MSH2 and SA (Cramér's V = 0.45). Other notable associations include MSH6 with sebaceous (Cramér's V = 0.44) and PMS2 with SA (Cramér's V = 0.43). Table 6 depicts the logistic regression models showing a moderate prediction accuracy (around 50%) for the loss of MMR proteins.
Personal and family histories were available for 25 out of 98 patients. Nineteen patients were alive, six patients were deceased, and three of them died due to SC (Died of

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Disease/DOD). Recurrences were reported in eight cases. No internal malignancy was reported in any of the patients with SNs; however, a family history of visceral malignancies was present in 3 out of 25 patients. One patient had a family history of colon cancer in the paternal uncle at the age of 81 years. Two patients were given chemotherapy, and two patients received radiotherapy; however, none of the patients were on immunosuppressive drugs.

Table 1: Descriptive characteristics of patients with sebaceous neoplasms

Characteristics	Total (n=120)
Age at diagnosis (years)	
Mean (+/- SD*), Range	60.40 (+/- 14.36), 15-91
Age <= 50, n (%)	30 (25)
Age >50, n (%)	90 (75)
Gender, n (%)	
Male	63 (52.5)
Female	57 (47.5)
Location, n (%)	
Scalp	9 (7.5)
Orbit (including eyelids, canthus, conjunctiva)	52 (43.3)
Face (other than orbital area)	42 (35)
Neck	1 (0.83)
Chest & Back	6 (5)
Extremities	7 (5.83)
Groin	3 (2.50)
Laterality, n (%)	
Right	43 (52.4)
Left	39 (47.6)
Symptoms, n (%)	
Swelling/Lesion/Growth/Mass/Nodule	57 (47.5)
Ulcer	5 (4.17)
Bleeding, Discharge & Itching	7 (5.82)
Recurrent (lesion/swelling)	8 (6.66)
Cyst	4 (3.4)
Duration of symptoms (months)	
Average (Range)	19.9 (2-120)
**SD: Standard deviation.*	

Table 2: Mann-Whitney U test results for MMR proteins vs. tumor locations**

MMR** proteins	Tumor location	Other location	Mann-Whitney U statistic	P-value
MSH2	Scalp	Face	82.0	0.0306*
MSH6	Eyelid	Scalp	48.5	0.0173*
MLH1	Face	Neck	26.0	0.0312*
MLH1	Eyelid	Canthus	97.5	0.0402*
PMS2	Eyelid	Neck	25.5	0.0250*

**P-value <0.05 was considered statistically significant.*
*** MMR: Mismatch repair.*

Table 3: Histopathological findings of sebaceous neoplasms

Variables	Criteria	n (%)
Ulceration on the surface	Present	40/46* (86.96)
	Absent	6/46* (13.04)
Edges	Circumscribed	19/70* (27.14)
	Infiltrating	51/70* (73)
Necrosis	Present	28/56* (50)
	Absent	28/56* (50)
Mitosis	Present	80/95* (84.21)
	Absent	15/95* (15.79)

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Margins status	Involved	26/75* (34.7)
	Tumor free	49/75* (65.3)
In-situ component	Present	6/11* (54.55)
	Absent	5/11* (45.45)
**Denominator denotes sebaceous neoplasms in which respective histopathological findings were reported.*		

Table 4: Cramér's V results for MMR** proteins with Histopathological findings**

MMR**** protein	Histopathological findings	Cramér's V
MSH6	Mitosis	0.116*
MSH6	Necrosis	0.058**
MSH6	Ulceration-surface	0.061**
MLH1	Mitosis	0.077**
MLH1	Necrosis	0.000***
MLH1	Ulceration-surface	0.151*
PMS2	Mitosis	0.134*
PMS2	Necrosis	0.010**
PMS2	Ulceration-surface	0.109*
MSH2	Mitosis	0.120*
MSH2	Necrosis	0.045**
MSH2	Ulceration-surface	0.085**

**Weak association, **very weak association, ***no association.*
*****MMR: Mismatch repair.*

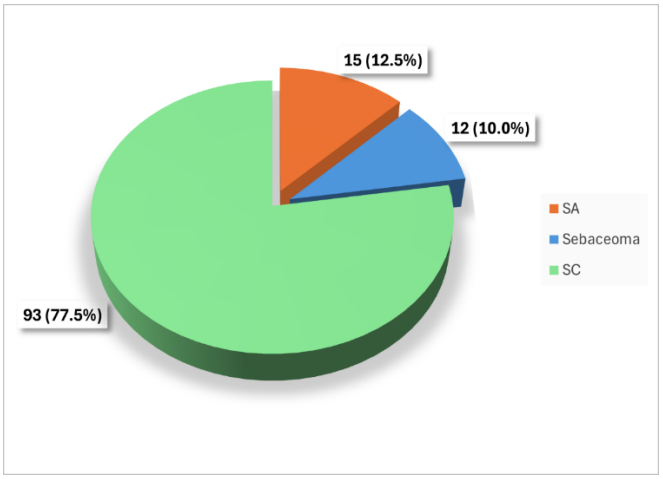

Figure 1: Frequency of sebaceous neoplasms. (SA: Sebaceous adenoma, SC: Sebaceous carcinoma)

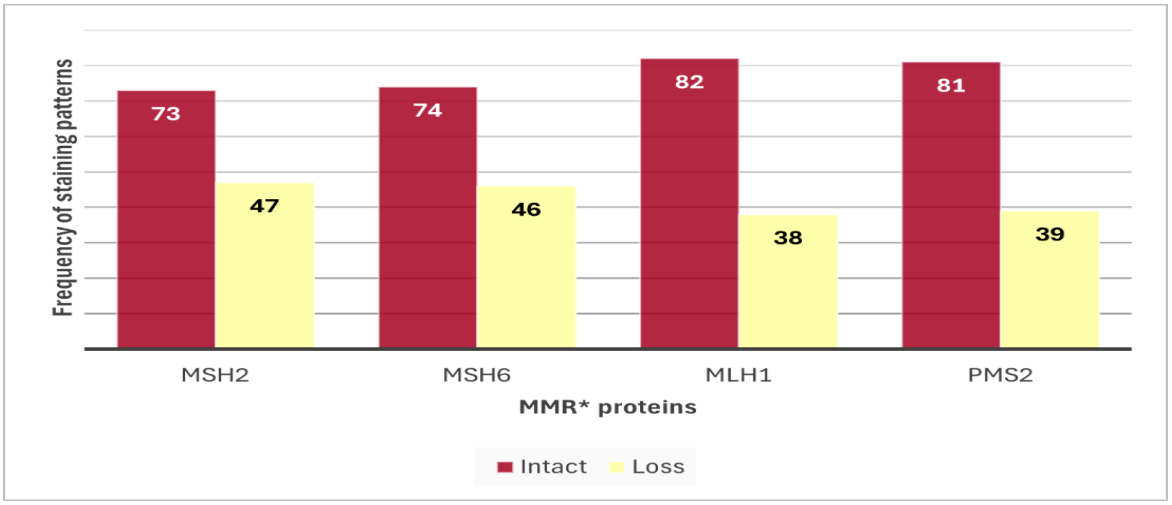

Figure 2: Frequency of MMR* proteins' IHC staining pattern. (*Mismatch repair)

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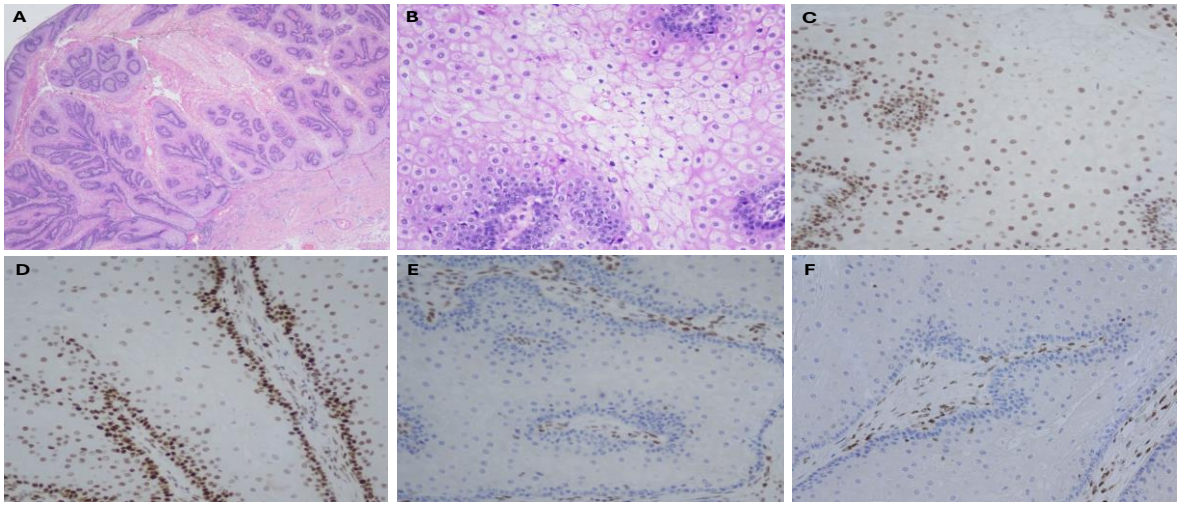
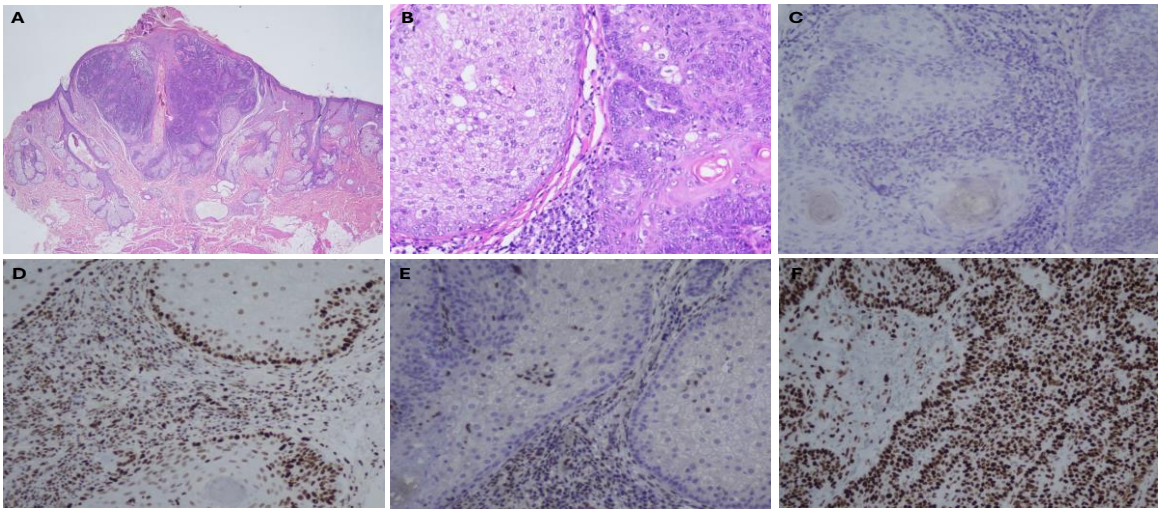
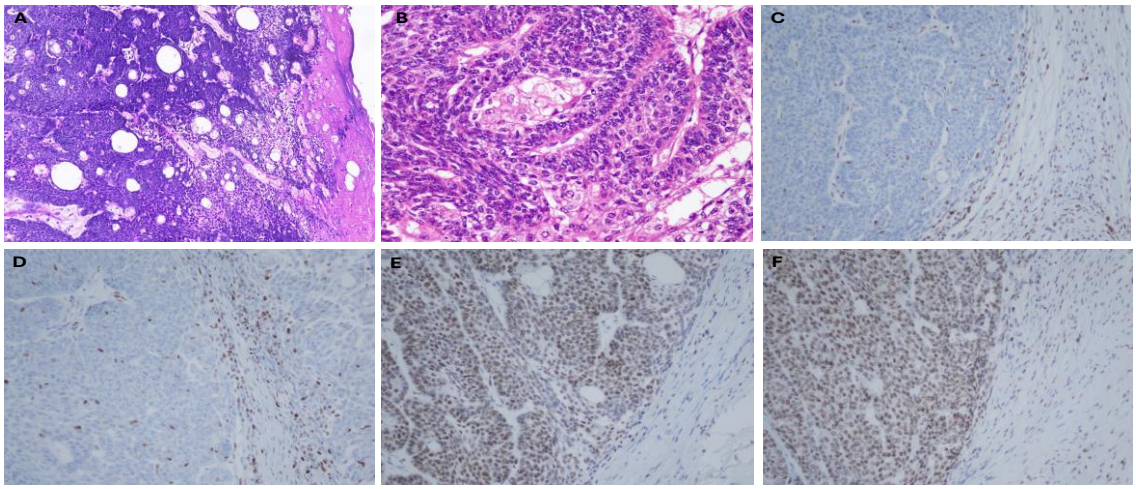


Picture 1: A, B: Sebaceous adenoma (H&Ex2, 20). Immunohistochemical stains; C: MSH2 intact nuclear expression (x20), D: MSH6 intact nuclear expression (x20), E: MLH1 loss of atomic expression (x20), F: PMS2 loss of nuclear expression (x20).



Picture 2: A, B: Sebaceoma (H&Ex2, 20). Immunohistochemical stains; C: MSH2 loss of nuclear expression (x20), D: MSH6 intact nuclear expression (x20), E: MLH1 loss of atomic expression (x20), F: PMS2 intact nuclear expression (x20).



Picture 3:
A, B: Sebaceous carcinoma (H&Ex10, 20). Immunohistochemical stains; C: MSH2 loss of nuclear expression (x20), D: MSH6 loss of atomic expression (x20), E: MLH1 intact nuclear expression (x20), F: PMS2 intact nuclear expression (x20).

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Table 5: Comparison of sebaceous neoplasms by the patterns of MMR IHC loss**

MMR** IHC patterns	All lesions, n (%)	Sebaceous adenoma, n (%)	Sebaceoma, n (%)	Sebaceous carcinoma, n (%)	P-value
MSH2 loss	47 (27.8%)	6 (23.1%)	4 (33.3%)	37 (28.2%)	0.015*
MSH6 loss	46 (27.2%)	6 (23.1%)	4 (33.3%)	36 (27.5%)	0.020*
MLH1 loss	38 (22.5%)	7 (26.9%)	2 (16.7%)	29 (22.1%)	0.012*
PMS2 loss	38 (22.5%)	7 (26.9%)	2 (16.7%)	29 (22.1%)	0.022*
MSH2/MSH6 loss	50 (29.58%)	6 (46%)	5 (63%)	39 (57%)	0.025*
MLH1/PMS2 loss	40 (23.66%)	7 (54%)	3 (38%)	30 (43%)	0.028*

**P-value <0.05 was considered statistically significant.*
***MMR: Mismatch repair.*

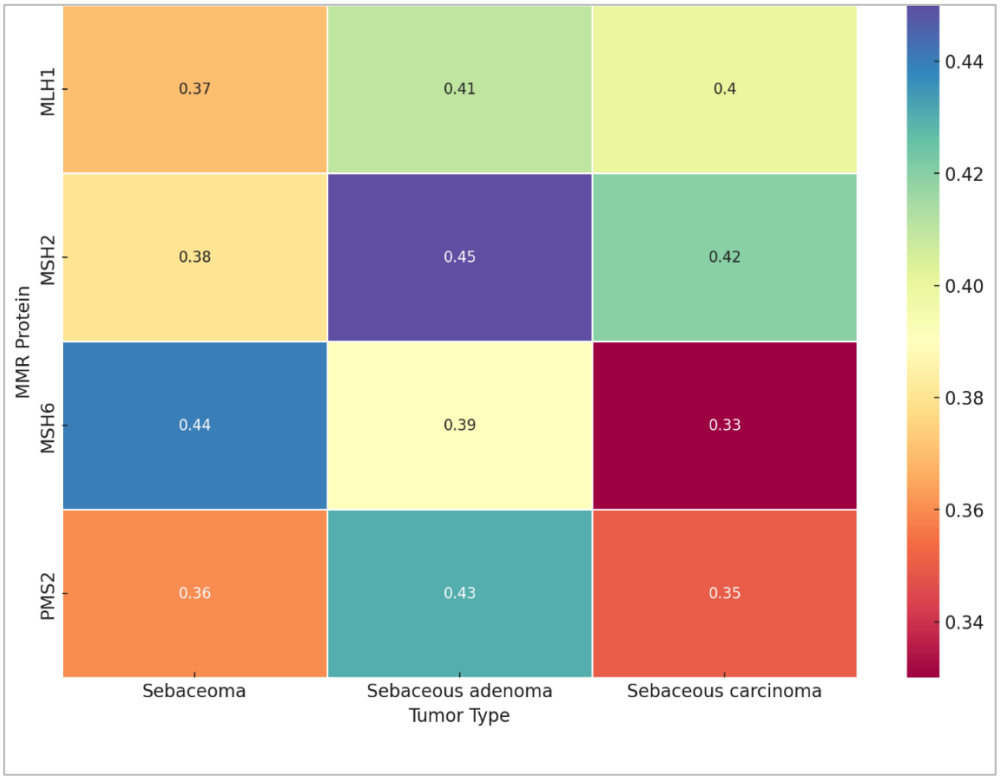

Figure 3: Strength of association between MMR* proteins and tumor types.
(*Mismatch repair)

Table 6: Logistic Regression Results

MMR** protein	Accuracy	AUC-ROC*
MSH2	50%	0.60
MSH6	53%	0.58
MLH1	53%	0.51
PMS2	44%	0.55

**AUC: Area under the curve, ROC: Receiver operating curve.*
***MMR: Mismatch repair.*

Discussion

Our study shows a wide age range (15-91 years) of patients diagnosed as SNs. However, Entius M.M. et al. reported that most individuals were between 60 and 80 years old (7). Gender and MMR protein expression status were significantly correlated by C. J. Jessup et al., who reported that 103/143 (72%) men had lost at least one MMR protein (21). Our study does not report an association between gender and MMR loss. Some studies have reported that most non-head and neck lesions were linked to MMR deficiency (8, 21, 24), while other studies have stated that the most affected skin area is the head and neck (3, 7, 25). Our study has identified the orbit (including the eyelids, canthus, and conjunctiva) as the most common site of SNs. Our results indicate that the distribution of MMR protein loss varies significantly between different tumor locations. The distribution of MSH2 protein loss is significantly different between tumors located on the scalp and those on

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the face. A significant difference in the distribution of MSH6 protein loss between the eyelid and scalp was also noted. MLH1 protein loss distribution varies significantly between the face and neck and between the eyelid and canthus. A significant difference was also observed in PMS2 protein loss distribution between tumors on the eyelid and those on the neck. The considerable p-values highlight the differences in the distribution patterns of MSH2, MSH6, MLH1, and PMS2 proteins across various tumor sites, suggesting that tumor location is an essential factor in the expression of these MMR proteins.

Our results show weak to very weak associations between MMR protein status and histopathological findings, with the most notable association being between MLH1 and ulceration on the surface (Cramér's V = 0.151). Konstantinova et al. reported a strong correlation between MMR loss and epidermal ulceration that was found at least focally in nearly 64% of the lesions with MMR loss (22).

Immunohistochemistry is a fast and cost-effective procedure that allows for high-output screening. We report 61/120 (50.83%) cases of SNs cases showing MMR protein loss by IHC. A higher frequency of MMR protein loss (89 SNs, 61.4%) was reported in a study by Konstantinova et al., in which a total of 145 SNs were included (22). Our study reports a predominant loss of MSH2 (47 SNs, 27.8%), as supported by previous studies performed in Europe and the USA (6, 17, 23). We report a higher frequency of combined loss of MSH2 and MSH6 (50 SNs, 29.58%). The combined MSH2 and MSH6 loss was also the most prevalent pattern mentioned in earlier studies. Roberts et al. and MD Walsh et al. reported a combined loss of MSH2 and MSH6 in 24 (47%) and 187 (66.5%) patients, respectively (8, 25). The variations in the rate of aberrant MMR IHC could be due to differences in methodology. Since we have not utilized MSI testing or genetic analysis in our study, we preferred the 4-antibody approach like Konstantinova et al., C. J. Jessup et al., and Roberts et al.(11, 21, 22).

Our results suggest that the patterns of MMR IHC loss are significantly associated with the type of tumor with the highest prevalence of MSH2 loss (37, 28.2%) in SCs, like Popnikolov et al.(16). Our study also reports isolated loss of MLH1 and PMS2 as the most common patterns in SAs (7, 26.9% each), which is comparable to Popnikolov et al., who showed isolated loss of MLH1 and MSH2 in SAs (3, 25.0% each) (16). The moderate to strong associations between MMR protein status and tumor types as shown in the heatmap also suggest that the MMR protein status is significantly related to the type of tumor. This heatmap has a moderate to strong association between MSH2 status and SA, indicating the strongest association (0.45). A moderate to strong association between MSH6 and sebaceoma and between PMS2 and SA is also observed. However, Singh et al. reported SA in the head and neck region only as a tumor type significantly associated with MMR loss (8).

A study performed in Australia reported an AUC (highest value = 0.68) for distinguishing MMR loss from MMR intact in SNs based on the type of lesion and anatomic location subgroups (25). Our study reports an AUC value close to 0.5, which suggests the model cannot distinguish between the classes (with one being perfect and 0.5 being random guessing).

A study by Roberts et al. depicts the diagnostic utility of MMR IHC in conjunction with other variables for MTS, suggesting that a personal and family history is more helpful in diagnosing MTS than aberrant IHC data (11). Another study suggests an alternative molecular genetic pathway involving the germline hMSH-6 mutation that does not show MSI and could also be responsible for the MTS phenotype (7). As a result, family history might not help identify possible MTS patients who solely show MSH6 loss on MMR IHC (11). Since personal and family history was unavailable for most of the patients in our cohort, the findings support previous recommendations for appropriate IHC screening of all SNs, regardless of the strength of personal or family history. The study by Roberts et al. showed kidney transplant recipients had a much higher prevalence of SNs than immunocompetent patients (30% vs. 6%) (11). This study focused solely on immunosuppressive therapy-treated renal transplant patients and included two patients with MTS who had multiple SAs (11). A lack of complete clinical information on the participants again limits our study.

The strengths of our study include the retrospective and prospective designs. Most previous studies had used a retrospective design only, except for A. Mojtahed et al., who included 7 SNs in the prospective cohort out of 49 SNs (18). Limitations of our study include a lack of MSI testing and germline mutation analysis to determine the efficacy of MMR IHC for MTS identification. Because the chosen cases were not drawn from a nationwide database, we cannot extrapolate our prevalence findings to a nationwide prevalence, which is another drawback of our study. Third, most of our patients had no personal or family history. In the cases in which history was available, it was incomplete.

Conclusion

Microsatellite instability testing by PCR is widely used globally for the identification of patients with Muir-Torre syndrome. Immunohistochemistry testing for sebaceous neoplasms may be a more practical screening technique, particularly in low-income countries, that has value for identifying sebaceous neoplasms deficient in MMR. The utility of a larger panel of antibodies, including all four MMR proteins, is more appropriate. This study investigates the relationship among tumor site, histopathology, sebaceous neoplasms, and MMR IHC staining patterns. MMR loss is significantly related to anatomic site and tumor type. Histopathological findings show a weak to very weak relationship with MMR protein loss. These findings can provide valuable insights into the biological behavior of SNs and may have implications for diagnosis and treatment strategies. Our study will encourage other researchers from this region to make further recommendations for these rare neoplasms concerning Muir-Torre syndrome.

Declarations

Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate.

Approved by the department concerned. (IRB-2020-5318-14604)

Consent for publication

Approved

Funding

Not applicable

Conflict of interest

The authors declared an absence of conflict of interest.

Authors Contribution

RABIA QURESHI (Resident, Section of Histopathology)
Study Design & Data Analysis, data collection, Drafting, and Final Approval of version.
SAIRA FATIMA (Associate Professor)
Revisiting Critically, Concept of Study

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