# Patients with a new-onset cutaneous sebaceous neoplasm following immunosuppression should be evaluated for Muir-Torre syndrome with germline mismatch repair gene mutation analysis: case reports

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## Abstract

Patients with Muir-Torre syndrome may have a systemic malignancy and a sebaceous neoplasm such as an adenoma, epithelioma, and/or carcinoma. The syndrome usually results from a germline mutation in one or more mismatch repair genes. Iatrogenic or acquired immunosuppression can promote the appearance of sebaceous tumors, either as an isolated event or as a feature of Muir-Torre syndrome and may unmask individuals genetically predisposed to the syndrome. Two iatrogenically immunosuppressed men with Muir-Torre syndrome features are described. Similar to these immunocompromised men, Muir-Torre syndrome-associated sebaceous neoplasms have occurred in solid organ transplant recipients, human immunodeficiency virus-infected individuals, and patients with chronic diseases who are treated with immunosuppressive agents. Muir-Torre syndrome-associated sebaceous neoplasms occur more frequently and earlier in kidney recipients, who are receiving more post-transplant immunosuppressive agents, than in liver recipients. The development of sebaceous neoplasms is decreased by replacing cyclosporine or tacrolimus with sirolimus or everolimus. Specific anti-cancer vaccines or checkpoint blockade immunotherapy may merit exploration for immune-interception of Muir-Torre syndrome-associated sebaceous neoplasms and syndrome-related visceral cancers. We suggest germline testing for genomic aberrations of mismatch repair genes should routinely be performed in all patients—both immunocompetent and immunosuppressed—who develop a Muir-Torre syndrome-associated sebaceous neoplasm.

*Keywords: adenoma, carcinoma, epithelioma, germline, microsatellite instability, mismatch repair, Muir-Torre syndrome, neoplasm, sebaceous, somatic*

## Introduction

Muir-Torre syndrome is an autosomal dominant genodermatosis associated with a mutation of one or more mismatch repair genes, which include MutL Homolog 1 (*MLH1*), MutS Homolog 2 (*MSH2*), MutS Homolog 6 (*MSH6*), and/or PMS1 Homolog 2, mismatch repair system component (*PMS2*). These mutations result in the development of defects in mismatch DNA repair and microsatellite instability. The condition is a variant of Lynch syndrome, which is also referred to as hereditary nonpolyposis colorectal cancer. Muir-Torre syndrome is defined clinically by the presence of both a visceral malignancy (usually colorectal cancer or a genitourinary cancer) and a sebaceous neoplasm (either benign or malignant) including a sebaceous adenoma, sebaceous epithelioma, or sebaceous carcinoma [1-8].

Sebaceous adenoma, sebaceous epithelioma, or sebaceous carcinoma occur in three clinical settings. They can be either idiopathic, associated with Muir-Torre syndrome, or related to iatrogenic or acquired immunosuppression. However, the latter two circumstances are not mutually exclusive; indeed, the new appearance of a sebaceous neoplasm following immunosuppression does not eliminate the possibility that the patient also has a mismatch repair gene mutation and therefore fulfills or will subsequently develop the diagnostic clinical criteria of Muir-Torre syndrome [1,9-40].

Two iatrogenically immunosuppressed men who each developed a sebaceous adenoma are described; immunohistochemistry analysis demonstrated that the sebaceous neoplasm from one man had loss of MSH2 and MSH6 expression while maintaining MLH1 and PMS2 expression whereas the other patient's sebaceous neoplasm showed expression of all four mismatch repair genes. Both men had a history of cancer prior to beginning their immunosuppressive therapy, thereby establishing a diagnosis with clinical features of Muir-Torre syndrome. However, the absence of germline testing prevented establishing whether their immunosuppression resulted in idiopathic development of the sebaceous neoplasms or unmasked a hereditary Muir Torre syndrome. We propose that germline testing for mismatch repair gene defects be performed as part of the initial evaluation of all immunosuppressed individuals who develop a Muir-Torre syndrome-associated sebaceous neoplasm, especially if they have had another malignancy because the presence of Muir-Torre syndrome necessitates further screening and follow up for internal malignancy.

## Case Synopsis

### Case 1

A 58-year-old man presented with a new lesion on his forehead; he had a prior history of actinic keratoses. His past medical history was significant for not only chronic lymphocytic leukemia diagnosed nine years earlier but also chronic inflammatory demyelinating polyneuropathy and Addison disease both diagnosed 19 years earlier. The former had not yet needed to be treated and he daily received oral chronic immunosuppressive treatment, azathioprine and prednisone for the latter conditions, respectively. In addition, he received human immunoglobulin G immune globulin intravenously each week. He also had received oral amlodipine for hypertension and levothyroxine for hypothyroidism. His family history was significant for cancer including chronic lymphocytic leukemia (father), liver cancer (paternal uncle), lung cancer (paternal grandfather), and melanoma (maternal aunt).

Cutaneous examination showed a 5mm×4mm flesh-colored papule with a superficial central erosion on the left side of his forehead (**Figure 1**). A shave biopsy was performed.

Microscopic examination showed an ulcerated basaloid neoplasm with neutrophilic crust (**Figure 2**). The benign tumor consists of enlarged cells with sebaceous differentiation. Clear cells outnumbered

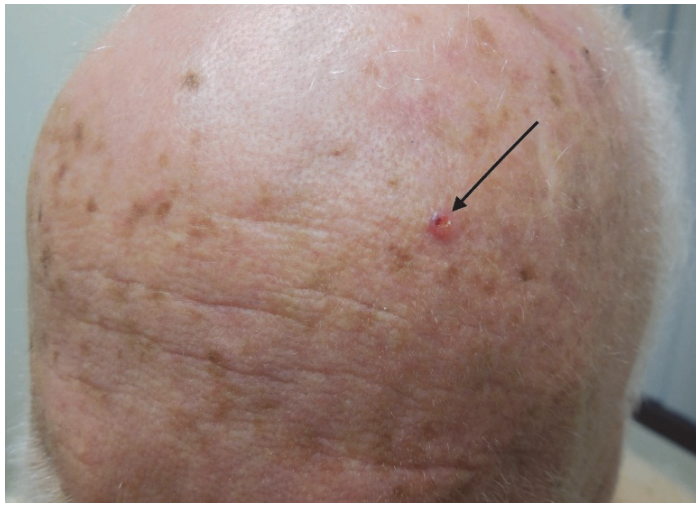

**Figure 1**. *Clinical presentation of a sebaceous adenoma on the forehead of a 58-year-old man with Muir-Torre syndrome appearing as a 5mm×4mm flesh-colored papule with a superficial central erosion on the left side of his forehead. He had chronic lymphocytic leukemia (for nine years and not yet requiring treatment), Addison disease (being treated with daily prednisone), hypertension (treated with amlodipine) and hypothyroidism (treated with levothyroxine); he received human immunoglobulin G immune globulin intravenously each week. He also has chronic inflammatory demyelinating polyneuropathy and for 19 years has receives daily immunosuppressive therapy; currently he is treated with daily azathioprine. His family history was significant for chronic lymphocytic leukemia, liver cancer, lung cancer, and melanoma.*

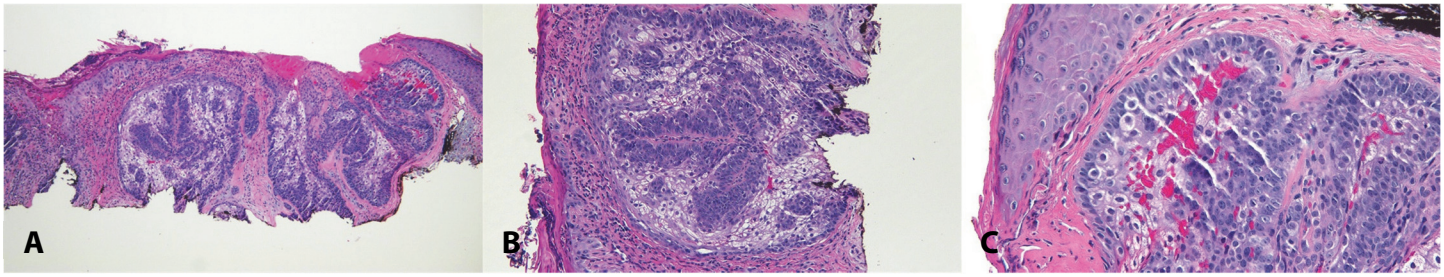


**Figure 2**. *Microscopic examination of sebaceous adenoma on the forehead.* ***A)*** *Low, and* ***B, C)*** *higher magnification views show ulceration and crust overlying a sebaceous neoplasm consisting of clear cells that outnumber the accompanying basaloid cells. Lymphocytic inflammation is present in the fibrotic stroma surrounding the tumor. H&E,* ***A)*** *4×;* ***B)*** *10×;* ***C)*** *20×.*

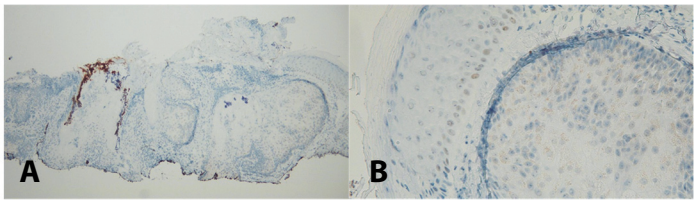


**Figure 3**. *Immunohistochemistry analysis demonstrates loss of MutS Homolog 2 (MSH2) expression. Microscopic examination of* ***A)*** *low, and* ***B)*** *high magnification views of the sebaceous adenoma show very faint staining, being decreased by more than 50 percent, indicating an absence of MSH2 expression within the sebaceous neoplasm. MHS2 immunoperoxidase stain:* ***A)*** *4×;* ***B)*** *20×.*

the basaloid layer by greater than 50 percent. There was associated fibrotic stoma and lymphocytic inflammation around the tumor. The pathologic features showed an eroded and inflamed sebaceous adenoma.

The possibility of Muir-Torre syndrome was considered. Immunohistochemistry analysis was performed to assess for mismatch repair gene expression. Staining for MLH1, MSH2, MSH6, and PMS2 expression was done. MSH2 and MSH6 staining was very faint, being decreased by more than 50 percent (**Figures 3, 4**). MLH1 and PMS2 staining within the tumor, demonstrating intact protein expression, was maintained (**Figures 5, 6**).

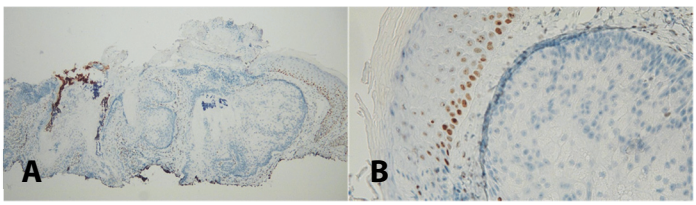


**Figure 4**. *Immunohistochemistry analysis demonstrates loss of MutS Homolog 6 (MSH6) expression. Microscopic examination of* ***A)*** *low, and* ***B)*** *high magnification views of the sebaceous adenoma show very faint staining, being decreased by more than 50 percent, indicating an absence of MSH6 expression within the sebaceous neoplasm. MHS6 immunoperoxidase stain:* ***A)*** *4×;* ***B)*** *20×.*

Correlation of the patient's prior history of chronic lymphocytic leukemia and recent diagnosis of a sebaceous adenoma established clinical features compatible with the diagnosis of Muir-Torre syndrome. Although his immunohistochemistry analysis showed a loss of MSH2 and MSH6 mismatch repair gene expression, his Mayo Muir-Torre syndrome risk score was only 1 (based on his age at diagnosis of the sebaceous neoplasm being less than 60 years; no patients with a score of 0 or 1 were diagnosed with Muir-Torre syndrome in the

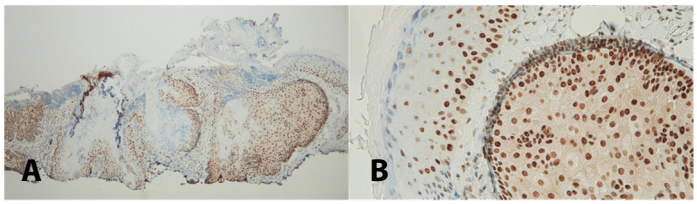


**Figure 5**. *Immunohistochemistry analysis shows preservation of MutL Homolog 1 (MLH1) expression. Microscopic examination of low* ***A)*** *and high* ***B)*** *magnification views of the sebaceous adenoma show strongly positive staining of MLH1, consistent with expression of the mismatch repair gene. MLH1 immunoperoxidase stain:* ***A)*** *4×;* ***B)*** *20×.*

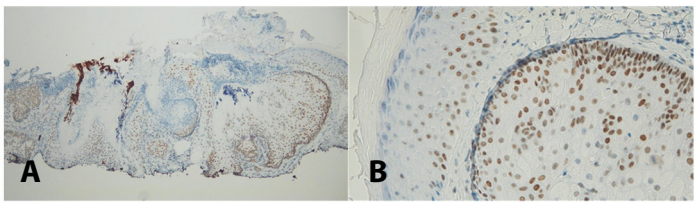


**Figure 6**. *Immunohistochemistry analysis shows preservation of PMS1 Homolog 2, mismatch repair system component (PMS2) expression. Microscopic examination of* ***A)*** *low, and high* ***B)*** *magnification views of the sebaceous adenoma show strongly positive staining of PMS2, consistent with expression of the mismatch repair gene. PMS2 immunoperoxidase stain:* ***A)*** *4×;* ***B)*** *20×.*

investigator's study), [37]. The patient declined germline testing. Hence, evaluation for an inherited mismatch repair gene mutation was not performed. In summary, it is possible that his immunosuppressive therapy for the management of chronic inflammatory demyelinating polyneuropathy resulted in the development of his sebaceous adenoma, but an inherited Muir Torre syndrome could not be ruled out.

He was evaluated for cancer. His chest roentgenogram and colonoscopy were normal; his urine cytology was negative for tumor cells. His physicians decided to change his immunosuppressive treatment; they discontinued the azathioprine and commenced treatment with mycophenylate mofetil and tacrolimus. He did not develop another sebaceous neoplasm in four years of follow-up.

**Case 2**

An 81-year-old man presented for evaluation of a new lesion on his nose. He had previously had nonmelanoma skin cancers that were excised. His past medical history was significant for a kidney transplant and daily oral medication to prevent rejection. He also a prior history of bladder carcinoma that was treated without recurrence.

Cutaneous examination showed a 4mm×4mm flesh-colored papule with central ulceration on the left side of the nasal tip (**Figure 7**). A shave biopsy was performed. Microscopic examination showed crust overlying the epidermis. There was a benign tumor consisting of basaloid keratinocytes that mature to form mature sebocytes with indented nuclei and vacuolated cytoplasm; atypia was absent. The pathologic changes showed a sebaceous adenoma.

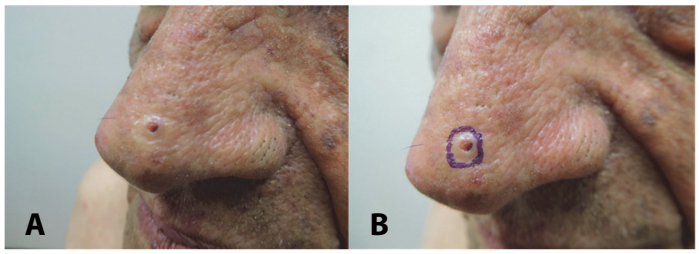


**Figure 7**. *Muir-Torre syndrome-associated sebaceous adenoma on the nose of an 81-year-old man who was a recipient of a solid organ (kidney) transplant on immunosuppressive therapy and a history of bladder cancer. The sebaceous neoplasm presented as a centrally ulcerated, flesh-colored 4mm×4mm papule **A)** on the left side of the nasal tip; **B)** the purple-inked oval outlines the lesion.*

The possibility of Muir-Torre syndrome was considered. Immunohistochemistry analysis was performed to assess for mismatch repair gene expression. Staining for MLH1, MSH2, MSH6, and PMS2 expression was done. Positive staining within the tumor, demonstrating intact protein expression, was present for all four gene products.

Correlation of the patient's prior history of bladder cancer and recent diagnosis of a sebaceous adenoma established clinical features compatible with the diagnosis of Muir-Torre syndrome. However, his Mayo Muir-Torre syndrome risk score was zero (no patients with a score of 0 or 1 were diagnosed with Muir-Torre syndrome in the investigator's study), [37] and his immunohistochemistry analysis did not show any loss of mismatch repair gene expression (though false negatives for immunohistochemistry are known to occur). The patient declined germline testing. Hence, evaluation for an inherited mismatch repair gene mutation was not performed. In summary, it is possible that his solid organ transplant immunosuppressive therapy resulted in the development of his sebaceous adenoma, but a diagnosis of hereditary Muir Torre syndrome could not be ruled out. He did not develop another sebaceous neoplasm in one year of follow-up.

## Case Discussion

**Lynch syndrome-associated cancers**

Hematologic malignancies and solid tumors can be observed in patients with Lynch syndrome. However, the visceral malignancies most commonly associated with Lynch syndrome include colorectal, endometrial, ovarian, small bowel, urinary tract (renal pelvis and ureter), and biliary tract (gallbladder and bile duct) cancers. Indeed, in the United States of America and the United Kingdom, pathology laboratories routinely evaluate colorectal cancers and endometrial carcinomas for mismatch repair gene mutations by performing immunohistochemistry analysis or microsatellite instability testing or both [1-6,41-44].

**Evaluation of Muir-Torre syndrome-associated sebaceous neoplasms**

Sebaceous neoplasms in Muir-Torre syndrome appear before, concurrent with, or after the diagnosis of the associated visceral malignancy. The presence of even a single Muir-Torre syndrome-associated sebaceous neoplasm can be the cutaneous harbinger of a mismatch repair gene mutation. Therefore, in a cancer-free individual, the development of a sebaceous neoplasm potentially related to Muir-Torre syndrome warrants additional evaluation [1-6,39,45-47].

To date, sebaceous neoplasms associated with Muir-Torre syndrome have most frequently been studied with immunohistochemistry analysis. Unfortunately, immunohistochemistry analysis and microsatellite instability testing of sebaceous neoplasms associated with Muir-Torre syndrome and solid tumors related to Lynch syndrome are not the optimal evaluations for diagnosing a mismatch repair gene mutation. Discordant results from immunohistochemistry analysis and microsatellite instability testing have been observed. Also, false negative results have been detected. For example, preservation of mismatch repair gene expression in Muir-Torre syndrome-associated sebaceous neoplasm has been demonstrated by positive staining of the tumor after performing immunohistochemistry analysis in patients with germline-confirmed Muir-Torre syndrome [2,10,39,41,48-52].

**Mayo Muir-Torre syndrome risk score**

In 2014, a group of investigators presented an algorithm to determine which patients with at least one cutaneous Muir-Torre syndrome-associated sebaceous neoplasm should have germline testing for mismatch repair gene mutations. The Mayo Muir-Torre syndrome risk score algorithm was based on four variables: age at presentation of initial sebaceous neoplasm (60 years or older = 0; less than 60 years = 1), total number of sebaceous neoplasms (one = 0; two or more = 2), personal history of Lynch syndrome-related cancer (no = 0; yes = 1), and family history of Lynch syndrome-related cancer (no = 0; yes = 1). A sensitivity of 100 percent and a specificity of 81 percent for predicting a Lynch syndrome mismatch repair gene germline mutation was observed by the investigators for patients with a score of two or more. However, false negative Mayo Muir-Torre syndrome risk score results have been observed in patients with a score of zero or one for whom genetic testing would not be recommended. Indeed, they were found to have a mismatch repair gene mutation when germline testing was subsequently performed. In addition, the investigators emphasized that the risk score algorithm needed to be validated by other researchers [37].

**Muir-Torre syndrome-associated sebaceous neoplasms in immunosuppressed patients**

In addition to being the skin stigmata of an acquired sporadic or an inherited germline syndrome, Muir-Torre syndrome-associated sebaceous neoplasm can occur as either an idiopathic neoplasm or secondary to immunosuppression-related microsatellite instability. These sebaceous neoplasms have been observed in patients with acquired immunodeficiency such as human immunodeficiency virus infection [19-21]. They have also been noted in patients either with systemic diseases or following solid organ transplant who receive chronic immunosuppressant treatment [13-33,35,36,38,39]. Retrospective studies of sebaceous carcinoma in solid organ transplant recipients and published case reports of immunosuppressed individuals with Muir-Torre syndrome-associated sebaceous neoplasm but without documented Muir-Torre syndrome are summarized.

**Sebaceous carcinoma in solid organ transplant recipients—retrospective studies**

Several retrospective studies of solid organ transplant recipients have observed not only virus-associated cancers-such as Kaposi sarcoma and Merkel cell carcinoma, but also sebaceous carcinoma to develop in these individuals [53]. In addition to immunosuppression that occurs in human immunodeficiency virus-infected patients and solid organ transplant recipients, ultraviolet radiation and inherited or acquired mismatch repair gene mutations that occur as either an idiopathic event, iatrogenic sequalae, or associated with Muir-Torre syndrome are risk factors for the development of

sebaceous carcinoma [33,54]. Indeed, one group of investigators noted a 25-fold increased incidence of sebaceous carcinoma in solid organ transplant recipients; the researchers also observed that strong risk factors for developing sebaceous carcinoma were lung transplant and the occurrence of a cutaneous squamous cell carcinoma following the transplant [33].

The investigators noted that sebaceous carcinoma occurred most often in lung transplant recipients. They were patients who had received the more intense post-transplant immunosuppression treatment. In contrast, liver transplant recipients had the lowest incidence of sebaceous carcinoma and had received the least immunosuppression following their transplant [33].

Also, an increased number of sebaceous carcinomas were observed in the solid organ transplant recipients who were treated with thymoglobulin induction prior to transplant. The agent causes a depletion of T cells, similar to the immune deficits observed in patients with acquired immunodeficiency syndrome. Therefore, the thymoglobulin therapy was associated with immunosuppression immediately after the transplant [33].

The researchers also noted that cancers associated with Muir-Torre syndrome were rare in their solid organ transplant recipients who had sebaceous carcinoma. Therefore, they hypothesized that most of the sebaceous carcinomas that occurred in these recipients were not caused by an inherited mismatch repair gene mutation. However, the researchers commented that none of their patients had germline testing data available to be evaluated [33].

A subsequent study by some of the same researchers confirmed their earlier observations. They again noted an elevated risk for sebaceous carcinoma in solid organ transplant recipients. There was 7.1 percent (170 sebaceous carcinomas in a group of 2380 nonkeratinocyte skin cancers) from a group of 444,497 solid organ transplant recipients [54].

Another study observed sebaceous carcinomas in 145 patients from 1996 to 2016. Specifically, 6.2 percent (9 of 145) of these individuals were solid organ transplant recipients. During that 20-year period, 9981 solid organ transplant recipients were seen. Therefore, the prevalence of sebaceous carcinoma in individuals following solid organ transplantation was 0.09 percent [38].

Also, a single center retrospective investigation of immunohistochemistry analysis of cutaneous sebaceous neoplasms from 447 patients during a 10-year period included 32 solid organ transplant recipients with 33 sebaceous neoplasms: sebaceous adenoma (20 patients with 21 tumors), sebaceous carcinoma (8 patients with 8 tumors), and sebaceous neoplasms-not otherwise specified (4 patients with four tumors). Immunohistochemistry analysis was performed on tumors from 16 of the patients (showing abnormal gene expression in 11 patients and normal gene expression in 5 patients). However, there were no patients diagnosed with Muir-Torre syndrome since the investigators did not provide any additional information regarding whether the patients had an internal malignancy [39].

In summary, multiple investigators have established that sebaceous neoplasms, particularly sebaceous carcinoma, have an increased prevalence in immunosuppressed individuals such as solid organ transplant recipients. However, most of these larger retrospective studies did not perform additional studies on the tumor for mismatch repair gene immunohistochemistry analysis or microsatellite instability testing. In addition, an assessment of the individuals with sebaceous neoplasms for Muir-Torre syndrome was not conducted by many of the researchers since they neither evaluated the patients with germline testing for mismatch repair genes nor acquired additional information regarding whether they had a personal history of internal malignancy.

**Muir-Torre syndrome-associated sebaceous neoplasms in solid organ transplant recipients without Muir-Torre syndrome-type internal malignacies—case reports and retrospective study**

Twenty immunosuppressed renal transplant recipients without Muir-Torre syndrome have been observed who developed Muir-Torre syndrome-associated sebaceous neoplasms (**Table 1**),

**Table 2**. *Muir-Torre syndrome-type sebaceous neoplasms in immunosuppressed non-renal transplant recipients without internal malignancy.*

| C | DxA SN<br>Gdr | SN: # | Site<br>of SN | Ti: IS<br>to SN | IS Tx | NMSC | IHC An<br>MSI | GlM+ | Ref |
|---|---|---|---|---|---|---|---|---|---|
| 1[a,b] | 45<br>M | SA:>3 | Back<br>Face | 0.58 | CyA,Pr | KA:2 | ND<br>ND | ND | 16 |
| 2[a] | 64<br>M | SA | Cheek | 1 | CyA | BCC | -MSH2, -MSH6<br>High | ND | 28, C3 |
| 3[a,c] | NS<br>NS | SC | Forehead | NS | NS | NS | NS | NS | 55, C3 |
| 4[d] | 67<br>M | SC | Cheek | 11.6 | Tac | BCC:1<br>SCC:3 | -2[e]<br>ND | ND | 38, C9 |
| 5[d] | 73<br>M | SC | Forehead | 17.7 | Tac | BCC:3<br>SCC:1 | Negative<br>ND | ND | 38, C5 |
| 6-21[f] | NS | NS | NS | 8 | Dif | NS | 12/16<br>ND | None | 26 |

BCC, basal cell carcinoma; C, case; CyA, cyclosporine A; Dif, different; DxA, diagnosis age (years); Gdr, gender; GlM, germline mutation; IHC, immunohistochemistry; IHC An, immunohistochemistry analysis showing loss of gene expression; IS, immunosuppressant; KA, keratoacanthoma; M, man; MLH1, MutL Homolog 1; MSH2, MutS Homolog 2; MSH6, MutS Homolog 6; MSI, microsatellite instability test; MTS, Muir-Torre syndrome; ND, not done; NMSC, nonmelanoma skin cancer; NS, not stated; PMS2, PMS1 Homolog 2, mismatch repair system component; Pr, prednisone; Ref, reference; SA, sebaceous adenoma; SC, sebaceous carcinoma; SCC, squamous cell carcinoma; SE, sebaceous epithelioma; Sir, Sirolimus; SN, sebaceous neoplasm; Tac, tacrolimus; Ti, time (in years); Tx, treatment; W, woman; ≥, greater than; #, number (if greater than one); :, equals; -, absence of gene expression; +, present.

[a]Cardiac transplant recipient.

[b]The patient had a family history of colon and breast cancer. The investigators reported the patient as having MTS; however, he did not have any systemic malignancy.

[c]The information regarding this patient was derived from the legend of a figure in the article.

[d]Liver transplant recipient.

[e]IHC analysis of MLH1, MSH2, MSH6, and PMS2 was performed; the expression of two of the mismatch repair genes were not preserved.

[f]The 16 patients had been a recipient of either a heart, liver, lung, or kidney; however, the specific age of SN diagnosis, type of transplant, time duration from onset of IS Tx to appearance of SN, IHC analysis results, and IS Tx were not described. The time from initiation of IS to the appearance of a SN ranged from 0.6 to 18 years (median, 8 years). IHC analysis showed loss of gene expression in both MSH2 and MSH6 for 7 patients; other loss of mismatch gene expression was observed in 5 patients. No loss of mismatch gene expression occurred in 4 patients.

[13,14,23,25,28,29,31,38,55,56]. In addition, three cardiac transplant recipients who developed Muir-Torre syndrome-associated sebaceous neoplasms but did not have Muir-Torre syndrome have been reported (**Table 2**), [16,26,28,38,55]. Also, Muir-Torre syndrome-associated sebaceous neoplasms were described in two liver transplant recipients who did not have Muir-Torre syndrome (**Table 2**), [16,26,28, 38,55]. A retrospective study also summarized the features of 16 non-Muir-Torre syndrome solid organ transplant recipients who had received various solid organ transplants and subsequently developed Muir-Torre syndrome-associated sebaceous neoplasms (**Table 2**), [26].

**Muir-Torre syndrome-associated sebaceous neoplasms in renal transplant recipients without internal malignacy**

The renal transplant patients without Muir-Torre syndrome internal malignancies but with Muir-Torre syndrome-associated sebaceous neoplasms included three women (ranging in age from 48 years to 82 years, median 62 years), when their sebaceous neoplasm occurred and 18 men (ranging in age from 50 years to 87 years, median 66 years) when their sebaceous neoplasm occurred (Table 1), [13,14,23,25,28,29,31,38,55,56]. They either had one type (19 patients) or three types (1 patient) of sebaceous neoplasms. The number of sebaceous neoplasms was either one (15 patients), two (2 patients), three (1 patient), 5 (1 patient) or more than 41 (1 patient).

The most common sebaceous neoplasm was sebaceous carcinoma (15 patients); one patient had a borderline sebaceous tumor which appeared to be a sebaceous carcinoma arising from a sebaceous adenoma. Three patients had a sebaceous adenoma and one patient had multiple sebaceous tumor types: carcinoma, adenoma, and epithelioma.

The sebaceous neoplasms were located on one (16 patients) or two (4 patients) sites. They most commonly occurred on the head and neck (15 neoplasms). The torso (8 neoplasms) and thigh (1 neoplasm) were other locations.

Post renal transplant immunosuppression agents included azathioprine, cyclosporin A, mycophenolate mofetil, prednisone, and tacrolimus. Patients were either receiving two (5 patients), three (14 patients), or 5 (one patient) drugs. The duration of time from starting immunosuppressive therapy to the development of a sebaceous neoplasm ranged from 2.3 years to 28 years; the median was 7 years.

Post-transplant nonmelanoma skin cancers were observed in 13 patients; three of the individuals had two types of tumors. Squamous cell carcinoma and/or keratoacanthoma was noted in 10 patients and basal cell carcinoma was noted in four patients. One patient had not only multiple squamous cell carcinomas and a basal cell carcinoma, but also an eccrine carcinoma.

Immunohistochemistry analysis was performed on the sebaceous neoplasms from 10 renal transplant patients. Loss of gene expression was observed for MSH2 (3 tumors), MSH2 and MSH6 (2 tumors), MHL1 (1 tumor) and not specified (1 tumor). The analysis showed preservation of the gene expression for mismatch repair genes in three of the tumors.

Microsatellite instability testing was conducted on 8 sebaceous neoplasms. It was negative for four of the tumors. It showed high instability for four of the sebaceous tumors.

Germline testing was performed for four of the patients; it was negative in one of the patients. *MSH2* mutation and *MSH6* mutation were noted in two patients and one patient, respectively. Both patients with *MHS2* germline mutation had family history of Lynch syndrome-related cancers [23,28]. Indeed, the investigators claimed that one of the patients had Muir-Torre syndrome [23]; however, neither of these patients had an internal malignancy at the time when their cases were published [23,28].

**Muir-Torre syndrome-associated sebaceous neoplasms in cardiac transplant recipients without Muir-Torre syndrome-type internal malignacies**

The cardiac transplant patients without Muir-Torre syndrome internal malignancy but with Muir-Torre syndrome-associated sebaceous neoplasms included three patients (**Table 2**), [16,28,55]. The two men were 45 years old and 64 years old when their sebaceous neoplasm occurred. The gender and age of the third patient were not provided. They each had one type of sebaceous neoplasm. The number of sebaceous neoplasms was either one (2 patients) or more than three (1 patient).

The most common sebaceous neoplasm was sebaceous adenoma (2 patients). One patient had a sebaceous carcinoma.

The sebaceous neoplasms were located on one (2 patients) or two (1 patient) sites. They most commonly occurred on the head and neck (at least three neoplasms). The back (at least one neoplasm) was the other location.

Post cardiac transplant immunosuppression agents included prednisone and/or cyclosporine A. Patients were either receiving one (1 patient) or two (1 patient) drugs; the immunosuppressive treatment for one patient was not described. The duration of time from starting immunosuppressive therapy to the development of a sebaceous neoplasm was provided for two patients and it ranged from 7 months to one year with a median of 10 months.

Post-transplant nonmelanoma skin cancers were described in two patients; one individual had two types of tumors. A basal cell carcinoma was noted in one patient and two keratoacanthomas were noted in another patient.

Immunohistochemistry analysis was performed on the sebaceous adenoma from one cardiac transplant patient; loss of gene expression was observed for MSH2 and MSH6. Microsatellite instability testing was conducted on the same sebaceous adenoma and it showed high instability for the sebaceous tumor. Germline testing was not performed.

The 45-year-old man with more than three sebaceous adenomas that were located either on his back or face had a family history of not only breast

**Table 3**. *Muir-Torre syndrome-type sebaceous neoplasms in immunosuppressed HIV-infected patients without internal malignancy.*

| C | DxA SN Gdr | SN: # | Site of SN | Ti: IS to SN | IS Tx | NMSC | IHC An MSI | GlM+ | Ref |
|---|---|---|---|---|---|---|---|---|---|
| 1[a] | 34 M | SC | Caruncle | NS | None | None | ND ND | ND | [57], C2 |
| 2[b] | 36 W | SC | Eyelid | NS | None | None | ND ND | ND | [57], C1 |
| 3 | 39 M | SA | Nose | 2 | None | KS | ND ND | ND | [19] |
| 4[c] | 42 M | SC | Jaw | 1 | None | None | ND ND | ND | [58] |
| 5 | 45 M | SC | Chest | NS | None | None | ND ND | ND | [59] |
| 6[d] | 62 M | SA | Back | 14 | None | None | ND ND | ND | [20] |

*C, case; DxA, diagnosis age (years); Gdr, gender; GlM, germline mutation; IHC An, immunohistochemistry analysis showing loss of gene expression; IS, immunosuppressant; KS, Kaposi sarcoma; M, man; MSI, microsatellite instability test; ND, not done; NMSC, nonmelanoma skin cancer; NS, not stated; Ref, reference; SA, sebaceous adenoma; SC, sebaceous carcinoma; SN, sebaceous neoplasm; Ti, time (in years); Tx, treatment; #, number (if greater than one); :, equals; +, present.*
*[a]One year after exenteration of his right eye, he developed metastases to his preauricular nodes.*
*[b]Deoxyribonucleic acid insitu hybridization testing of the tumor for both human papillomavirus and p53 protein were negative.*
*[c]The patient died after 70 days in the hospital.*
*[d]The patient had congenital hemophilia A.*

cancer but also a Lynch syndrome-associated cancer (colon carcinoma). Indeed, he was described to have Muir-Torre syndrome by the researchers who reported him. However, he did not have an internal malignancy [16].

**Muir-Torre syndrome-associated sebaceous neoplasms in liver transplant recipients without Muir-Torre syndrome associated internal malignancy**

The liver transplant patients without Muir-Torre syndrome-type internal malignancy but with Muir-Torre syndrome-associated sebaceous neoplasms included two men who were 67 years old and 73 years old when their sebaceous neoplasm occurred (**Table 2**), [38]. They each had a single sebaceous carcinoma located on the forehead or cheek.

Post liver transplant immunosuppression only included tacrolimus. The duration of time from starting immunosuppressive therapy to the development of a sebaceous neoplasm ranged from 11.6 years to 17.7 years with a median of 14.6 years.

Post-transplant nonmelanoma skin cancers were observed in both patients. One man had a basal cell carcinoma and three squamous cell carcinomas. The other man had three basal cell carcinomas and one squamous cell carcinoma.

Immunohistochemistry analysis was performed on the sebaceous carcinoma from both patients. Loss of gene expression was observed for two mismatch repair genes in two of the tumors. Analysis of the other sebaceous carcinoma showed preservation of the gene expression for mismatch repair genes. Microsatellite instability testing and germline testing were not conducted.

**Muir-Torre syndrome-associated sebaceous neoplasms in recipients of various solid organ transplants without Muir-Torre syndrome-type internal malignancy**

In addition to the individual reports of Muir-Torre syndrome-associated sebaceous neoplasms in solid organ transplant recipients without Muir-Torre syndrome-type internal malignancy, an immunohistochemistry analysis study of 90 patients with Muir-Torre syndrome-type sebaceous neoplasms included 16 solid organ transplant recipients who had a variety of solid organ transplants (including kidney, liver, lung, and heart) and post-transplant treatment with different immunosuppressive regimens (**Table 2**), [26]. The

duration of time from starting immunosuppressive therapy to the development of a sebaceous neoplasm ranged from 0.6 years to 18 years; the median was 8 years. Immunohistochemistry analysis showed loss of gene expression of at least one mismatch repair gene in 75 percent (12 of 16) of these individuals. Microsatellite instability testing was not performed and none of the 16 patients had either germline testing that documented a mismatch repair gene mutation or fulfilled the researcher's criteria for Muir-Torre syndrome [26].

**Muir-Torre syndrome-associated sebaceous neoplasms in human immunodeficiency virus-infected patients without Muir-Torre syndrome-type internal malignancy—case reports**

Human immunodeficiency virus-infected patients without Muir-Torre syndrome-type internal malignancy but with Muir-Torre syndrome-type sebaceous neoplasms included one woman who was 36 years old when her sebaceous neoplasm occurred, and 5 men ranging in age from 34 years to 62 years (median 42 years) when their sebaceous neoplasm occurred (**Table 3**), [19,20,57-59]. Each patient either had a sebaceous carcinoma (4 patients) or a sebaceous adenoma (2 patients). The sebaceous neoplasms were located on the head and neck (3 sebaceous carcinomas, and one sebaceous adenoma) on the torso (one sebaceous carcinomas and one sebaceous adenoma). The onset of immunosuppression was designated by the diagnosis of human immunodeficiency virus infection. The duration of time from immunosuppression to the development of a sebaceous neoplasm was provided for three of the men. It ranged from one year to 14 years with a median of two years.

A nonmelanoma skin cancer, Kaposi sarcoma, was observed in only one man. None of the sebaceous tumors had immunohistochemistry analysis or microsatellite instability testing. None of the patients had germline testing.

**Muir-Torre syndrome-type sebaceous neoplasms in chronic disease-related immunosuppressed patients without Muir-Torre syndrome-type internal malignancy—case reports**

The chronic disease-related immunosuppressed patients without Muir-Torre syndrome-type internal malignancy but with Muir-Torre syndrome-associated sebaceous neoplasms included two individuals (**Table 4**), [13,40]. One patient was a man who was 62 years old when their sebaceous neoplasm occurred. Very few details regarding the second patient were provided by the investigators.

The man had psoriasis and had previously been treated with cyclosporin A. A solid-cystic sebaceous neoplasm developed on his back 16 years later. He did not have any nonmelanoma skin cancers. Neither immunohistochemistry analysis nor microsatellite instability testing was performed on the sebaceous tumor. However, germline testing demonstrated a *MSH2* gene mutation.

**Table 4**. *Muir-Torre syndrome-type sebaceous neoplasms in immunosuppressed patients with chronic diseases without internal malignancy.*

| C | DxA SN Gdr | SN: # | Site of SN | Ti: IS to SN | IS Tx | NMSC | IHC An MSI | GlM+ | Ref |
|---|---|---|---|---|---|---|---|---|---|
| 1[a] | 62 M | SC-SN | Back | 16 | CyA | None | ND ND | MSH2 | [40] |
| 2[b] | NS NS | SC | NS | NS | NS | NS | ND ND | ND | [13] |

C, case; CyA, cyclosporine A; DxA, diagnosis age (years); Gdr, gender; GlM, germline mutation; IHC An, immunohistochemistry analysis showing loss of gene expression; IS, immunosuppressant; M, man; MSH2, MutS Homolog 2; MSI, microsatellite instability test; ND, not done; NMSC, nonmelanoma skin cancer; NS, not stated; Ref, reference; SC, sebaceous carcinoma; SC-SN, solid-cystic sebaceous neoplasm; SN, sebaceous neoplasm; Ti, time (in years); Tx, treatment; #, number (if greater than one); :, equals; +, present.

[a]The man had psoriasis.

[b]The specific chronic disease was not stated for this patient. The study included appendageal tumors in 10 individuals potentially immunocompromised by 1 or more of the following medical conditions: hemodialysis for end-stage renal disease (2), chronic renal failure secondary to insulin-dependent diabetes (1), chronic lymphocytie leukemia (1), primary transitional cell carcinoma of the bladder (1), colonic carcinoma (1, celiac disease with idiopathic thrombocytopenic purpura (1), hemophilia with hepatitis (2), and Down syndrome (1).

The second patient had a sebaceous carcinoma. The patient had been included in a study of appendageal neoplasms in 10 individuals who were immunocompromised by one or more medical conditions. However, the investigators only provided a list of the conditions without identifying which disease each patient had (**Table 4**), [13].

**Muir-Torre syndrome features in immunosuppressed patients: solid organ transplant recipients**, **human immunodeficiency virus-infected individuals**, **and patients with immunosuppression-associated chronic diseases**

Muir-Torre syndrome-type sebaceous neoplasms have been observed in immunosuppressed patients who do not have Muir-Torre syndrome-type internal malignancy and/or germline mismatch repair alterations. However, there are a substantial number of individuals whose previously unsuspected diagnosis of Muir-Torre syndrome is discovered after their immune system has been compromised and they subsequently develop a Muir-Torre syndrome-associated sebaceous neoplasm. These patients either have a preexisting internal malignancy or they develop a visceral cancer. Similar to immunosuppressed patients who do not have Muir-Torre syndrome, Muir-Torre syndrome-associated sebaceous neoplasm have been noted in immunosuppressed individuals who have undergone solid organ transplant, have human immunodeficiency virus, or have immunosuppression-associated chronic diseases. Indeed, for some of these individuals, the immunosuppressive treatment or immunocompromising condition unmasks their germline testing-confirmed mismatch repair gene mutation.

**Muir-Torre syndrome-associated sebaceous neoplasms in renal transplant recipients accompanied by Muir-Torre syndrome-type cancers—case reports**

Muir-Torre syndrome-associated sebaceous neoplasms have been described in 11 immunosuppressed renal transplant patients with Muir-Torre syndrome (Table 5), [13-15,24,32,35,36, 38]. This includes one woman who was 43 years old when her sebaceous carcinoma occurred, and 8 men (ranging in age from 37 years to 81 years—median 47 years) when their sebaceous neoplasm occurred). The additional two renal transplant recipients with Muir-Torre syndrome were two of three patients reported by investigators who with multiple sebaceous adenomas, colorectal cancer, and a family history of colorectal cancer (Table 5), [13]. Hence, most of the specific information regarding renal transplant recipients with Muir-Torre syndrome are only available for the other 9 patients.

The woman was 43 years old when her colon cancer was diagnosed. The men ranged in age from 30 years to 80 years (median, 41 years) when their visceral malignancy was discovered. The relationship between the post transplantation occurrence of a sebaceous neoplasm and the diagnosis of the initial systemic cancer was provided for 8 of the patients; cancer preceded the detection of the sebaceous neoplasm in four patients by one to 21 years (median, four years), occurred concurrently in two patients, and followed the appearance of the sebaceous neoplasm in two patients by two to four years (median, three years).

The renal transplant patients with Muir-Torre syndrome either had one type (8 patients), two types (2 patients) or three types (1 patient) of sebaceous neoplasms. The number of sebaceous neoplasms was either one (7 patients), two (2 patients), three (1 patient), 33 (1 patient) or 85 (1 patient).

The most common sebaceous neoplasm was sebaceous carcinoma (5 patients). Three patients had a sebaceous adenoma, and two patients had a sebaceous carcinoma, and either one or 32 sebaceous adenomas. One patient had 70 sebaceous adenomas, 10 sebaceous carcinomas, and 5 sebaceous epitheliomas.

The sebaceous neoplasms were located on one (5 patients) or two (3 patients) sites; the location was not provided for one patient. At least 6 neoplasms occurred on the torso and at least 5 neoplasms occurred on the head and neck.

Post renal transplant immunosuppression agents included azathioprine, cyclosporin A, everolimus, mycophenolate mofetil, prednisone, sirolimus, tacrolimus, and Wuzhi capsule (which was being

used to reduce serum glutamic-pyruvic transaminase). Patients were either receiving two (2 patients), three (4 patients), or four (1 patient) drugs; the post-transplant treatment was not described for one patient. One patient's sebaceous neoplasm appeared four years prior to his renal transplant; the duration of time from starting immunosuppressive therapy to the development of a sebaceous neoplasm was provided for 6 other patients and ranged from three months to 16 years (median, 2.6 years).

However, three of the patients changed the post-transplant immunosuppressive agent tacrolimus after the diagnosis of their sebaceous neoplasm. Two men stopped the tacrolimus and substituted sirolimus after the diagnosis of the sebaceous tumor. One woman stopped tacrolimus and began everolimus after the diagnosis of her sebaceous carcinoma.

Ten of the renal transplant patients had a total of 14 cancers. The patients had either one cancer (7 patients), two cancers (two patients), or three cancers (one patient). The malignancy was not described for the final patient.

Ten malignancies involved organs of the gastrointestinal tract. The cancers involved either the colon (4 tumors), colon and rectum (two tumors), esophagus (one tumor), rectum (one cancer), small bowel (one tumor), or stomach (one tumor). Three of the cancers involved urologic organs: bladder (two tumors) or renal pelvis (one tumor). One patient also had a liposarcoma.

Post-transplant nonmelanoma skin cancers were described in 5 patients. Four of the individuals had two types of tumors. Squamous cell carcinoma and/or keratoacanthoma was noted in 5 patients and basal cell carcinoma was noted in four patients.

The Mayo Muir-Torre syndrome risk score was assessed for 9 patients and ranged from 0 to 5: 0 (one patient), 1 (one patient), 2 (two patients), 3 (two patients), 4 (two patients) and 5 (one patient). Eight patients were less than 60 years old when their sebaceous neoplasm was diagnosed. Four patients had two or more sebaceous neoplasms. A personal history (two patients) or family history (two patients) or both a personal and family history (two patients) of Lynch syndrome-related malignancies was also noted for 6 patients.

Immunohistochemistry analysis was performed on the sebaceous neoplasms from 7 renal transplant patients. Loss of gene expression was observed for either MSH2 and MSH6 (three tumors) or MSH2 (one tumor). Indeed, the loss of expression of both MSH2 and MSH6 were also observed in the visceral malignancies from these three patients. One patient's sebaceous carcinoma had loss of expression of two mismatch repair genes but the specific genes were not described. Immunohistochemistry analysis was negative for loss of gene expression in two patient's tumors. One of the patients only had his sebaceous neoplasm evaluated for MHL1 and MSH2.

Microsatellite instability testing was conducted on three sebaceous neoplasms; it showed high instability for all three of the sebaceous tumors. Germline testing was performed for four of the patients. *MSH2* mutation was noted in all four patients.

**Muir-Torre syndrome-associated sebaceous neoplasms in cardiac transplant recipients with Muir-Torre syndrome type internal cancers—case reports**

Muir-Torre syndrome-associated sebaceous neoplasms have been described in two immunosuppressed cardiac transplant patients with accompanying cancers (**Table 6**), [17,18,30,60]. The men were 51 years old and 65 years old when their initial sebaceous neoplasm occurred. One man was 54 years old when his colon cancer was diagnosed. The other man was 71 years old when his lung cancer and multiple myeloma were discovered.

The relationship between the post transplantation occurrence of a sebaceous neoplasm and the diagnosis of the initial systemic cancer was provided for both patients. The cancer followed the appearance of the sebaceous neoplasm in both men by three to 6 years (median, 4.5 years).

The cardiac transplant patients with Muir-Torre syndrome type cancers both had three types of sebaceous neoplasms. The number of sebaceous

neoplasms was either 7 or 13. One man had three sebaceous epitheliomas, two sebaceous carcinomas, one sebaceous adenoma and one sebaceous neoplasm that was not otherwise defined. The other man had 5 sebaceous adenomas, 5 sebaceous epitheliomas, and three sebaceous carcinomas. The sebaceous neoplasms were located on face (at least three tumors) or torso (at least three tumors).

Post cardiac transplant immunosuppression agents included azathioprine, cyclosporin A, mycophenolate mofetil, prednisone, and tacrolimus. The patients were either receiving two (one patient) or three (one patient) drugs. The duration of time from starting immunosuppressive therapy to the development of a sebaceous neoplasm ranged from one year to 16 years (median, 8.5 years).

The two cardiac transplant patients had a total of three cancers. One man had adenocarcinoma of the colon. The other man had not only non-small cell lung cancer, but also multiple myeloma.

Post-transplant nonmelanoma skin cancers were described in both patients. One man had two keratoacanthomas. The other man had three squamous cell carcinomas.

The Mayo Muir-Torre syndrome risk score was assessed for both patients and ranged from three to 5: three (one patients) and 5 (one patient). One patient was less than 60 years old when his sebaceous neoplasm was diagnosed. Both patients had two or more sebaceous neoplasms. A family history (one patient) or both a personal and family history (one patient) of Lynch syndrome-related malignancies was also noted for the patients.

Immunohistochemistry analysis was performed on the sebaceous neoplasm from one cardiac transplant patient. Loss of gene expression was observed for MSH6.

Microsatellite instability testing was not conducted. Germline testing was performed for both patients; one man had an *MSH2* gene mutation and the other man had an *MSH6* gene mutation.

**Muir-Torre syndrome-associated sebaceous neoplasms in a liver transplant recipient with internal malignancy—case report**

A Muir-Torre syndrome-associated sebaceous neoplasm has been described in an immunosuppressed liver transplant patients with Muir-Torre syndrome (**Table 7**), [27]. The man was 67 when his sebaceous neoplasm occurred. He was younger than 61 years old when his hepatocellular carcinoma was diagnosed.

The relationship between the post transplantation occurrence of a sebaceous neoplasm and the diagnosis of the initial systemic cancer was provided. The cancer preceded the appearance of the sebaceous neoplasm by more than 6 years.

The liver transplant patient with Muir-Torre syndrome had a single sebaceous neoplasm. The researchers evaluating his tumor considered it to be a sebaceous epithelioma that had progressed into a sebaceous carcinoma. It was located on his suprapubic region.

His post liver transplant immunosuppression agent only included tacrolimus. The duration of time from starting immunosuppressive therapy to the development of a sebaceous neoplasm was 6 years. Post-transplant nonmelanoma skin cancer was not described.

The Mayo Muir-Torre syndrome risk score for the patient was 0. He was older than 60 years old when his sebaceous neoplasm was diagnosed. He only had one sebaceous neoplasm. There was neither a personal nor family history of Lynch syndrome-related malignancies.

Immunohistochemistry analysis and microsatellite instability testing had not been performed on the sebaceous neoplasm. In addition, germline testing had not been done.

**Muir-Torre syndrome-associated sebaceous neoplasms in human immunodeficiency virus-infected patients with Muir-Torre-type visceral maligancy—case reports**

Muir-Torre syndrome-associated sebaceous neoplasms have been described in three human immunodeficiency virus-infected men with Muir-Torre syndrome type internal malignancy (**Table 8**), [21,22,61]. They ranged in age from 43 years to 53 years (median 48 years) when their sebaceous neoplasm occurred.

They ranged in age from 28 years to 50 years (median, 39 years) when their visceral malignancy was discovered. The relationship between the occurrence of a sebaceous neoplasm post-human immunodeficiency virus infection detection and the diagnosis of the initial systemic cancer was provided for all patients. The cancer preceded the detection of the sebaceous neoplasm in all three patients by three to 20 years (median, 5 years.

Each of the human immunodeficiency virus-infected patients with Muir-Torre syndrome only had one type of sebaceous neoplasm. The number of sebaceous neoplasms was either one (one patient), 10 (one patient), three or more than 23 (one patient). The most common sebaceous neoplasm was sebaceous adenoma (two patients); the other man had a sebaceous carcinoma.

The sebaceous carcinoma was located on the back. One man's 10 sebaceous adenomas were all located on his forehead. Some of the other man's sebaceous adenomas were located on his face (9 tumors), trunk (8 tumors), extremities (two tumors) or scrotum (one tumor).

None of the patients were receiving immunosuppressive agents. The duration of time from establishing the diagnosis of human immunodeficiency virus infection to the development of a sebaceous neoplasm ranged from 10 months to 7 years (median, four years) for two of the patients. The diagnosis of human immunodeficiency virus infection occurred concurrently with the appearance of his sebaceous adenoma in the third patient.

Each of the human immunodeficiency virus-infected patients had a cancer. Two of the men had colon cancer. The other patient had bilateral urinary tract transitional cell carcinoma.

Two human immunodeficiency virus-infected men had nonmelanoma skin cancers. One man had a keratoacanthoma. The other man had also had a keratoacanthoma, two basal cell carcinomas, and a cutaneous metastatic adenocarcinoma.

The Mayo Muir-Torre syndrome risk score was assessed for all three patients and ranged from two to 5: two (one patient) and 5 (two patients). All patients were less than 60 years old when their sebaceous neoplasm was diagnosed. Two patients had two or more sebaceous neoplasms; the other man only had one sebaceous tumor. A personal history (one patients) or both a personal and family history (two patients) of Lynch syndrome-related malignancies was noted the patients.

Immunohistochemistry analysis was not performed on any of the sebaceous neoplasms. Microsatellite instability testing was conducted on the sebaceous adenoma from one man; it showed high microsatellite instability. Germline testing was not performed for any of the patients.

**Muir-Torre syndrome-associated sebaceous neoplasms in chronic disease-related immunosuppressed patients with Muir-Torre syndrome-type cancers—case reports**

Muir-Torre syndrome-associated sebaceous neoplasms have been described in four chronic disease-related immunosuppressed patients with Muir-Torre syndrome-type cancers (**Table 9**), [28,34]. This includes two women (ranging in age from 50 years to 59 years, median 55 years) when their sebaceous neoplasm occurred. It also includes two men (ranging in age from 58 years to 68 years, median 63 years) when their sebaceous adenoma occurred.

The women ranged in age from 50 years to 61 years (median, 56 years) when their first visceral malignancy was discovered. The men ranged in age from 49 years to 55 years (median, 52 years) when their visceral malignancy was discovered. The relationship between the occurrence of a sebaceous neoplasm and the diagnosis of the initial systemic cancer was provided for all patients. The cancer preceded the detection of the sebaceous adenoma in two patients by 9 to 13 years (median, 11 years), occurred concurrently in one patient, and followed the appearance of the sebaceous carcinoma in one patient by two years.

The chronic disease-related immunosuppressed patients with Muir-Torre syndrome-type cancers each had only one sebaceous neoplasm. The most common sebaceous neoplasm was sebaceous

adenoma (three patients); one patient had a sebaceous carcinoma. The sebaceous neoplasms were located on either the head (two patients) or the torso (two patients).

The patients were receiving immunosuppression agents. These included anti-interleukin-12 antibody, azathioprine, combination chemotherapy (consisting of R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovine, and prednisone), interferon beta 1a, methimazole, ocrelizumab (which depletes B cells), prednisone, radioactive iodine. Patients were either receiving individual immunosuppressants sequentially (two patients), or two or more agents together (two patients). The duration of time from starting immunosuppressive therapy to the development of a sebaceous neoplasm ranged from one year to 29 years (median, 11 years).

The chronic disease-related immunosuppressed patients with Muir-Torre syndrome-type cancers had a total of 6 malignancies. The patients had either one cancer (two patients) or two cancers (two patients).

Two cancers involved organs of the gastrointestinal tract; the cancers involved either the cecum (one tumor) or the colon (one tumor). Two patients had hematopoietic malignancies: chronic lymphocytic leukemia or non-Hodgkin lymphoma. The other tumors included endometrial adenocarcinoma or prostate cancer.

A nonmelanoma skin cancer was described in one patient. Two of the other individuals did not have any skin cancer but one of these men had a history of actinic keratoses. Information regarding nonmelanoma skin cancer was not provided for the last patient.

The Mayo Muir-Torre syndrome risk score was assessed for all patients and ranged from 0 to 3: no (one patient), one (two patients), and three (one patient). Three of the patients were less than 60 years old when their sebaceous neoplasm was diagnosed. None of the patients had two or more sebaceous neoplasms. Only one patient had both a personal and family history of Lynch syndrome-related malignancies was also noted for 6 patients.

Immunohistochemistry analysis was performed on the sebaceous neoplasms from three chronic disease-related immunosuppressed patients with Muir-Torre syndrome. Loss of gene expression was observed for either MSH2 and MSH6 (2 sebaceous adenomas) or MLH1 (1 sebaceous carcinomas). Microsatellite instability testing was conducted on two sebaceous neoplasms and showed high instability for both tumors.

Germline testing was performed for three patients. *MSH2* mutation was noted in one individual. Mutation of a mismatch repair gene was absent for the other two patients; however, they were only tested for *MLH1*, *MSH2*, and *MSH6*.

**Salient observations regarding Muir-Torre syndrome-associated sebaceous neoplasms in immunosuppressed patients**

There have been several individual case reports of Muir-Torre syndrome-associated sebaceous neoplasms in immunosuppressed patients. Most of these individuals have been solid organ transplant recipients. However, they also include human immunodeficiency virus-infected patients and patients with chronic diseases requiring immunosuppressive agents for management. Many of the immunosuppressed patients do not have Muir-Torre syndrome but a substantial number of these individuals previously, concurrently, or subsequently developed a solid malignancy and thereby fulfill the diagnostic criteria for Muir-Torre syndrome. Indeed, at least two patients who did not have a visceral cancer were erroneously reported as Muir-Torre syndrome since their other personal features and family history were so suggestive of the condition [16,23]. Several other salient observations regarding Muir-Torre syndrome-associated sebaceous neoplasms in immunosuppressed patients have also been noted.

**Incidence of Muir-Torre syndrome in solid organ transplant recipients with Muir-Torre syndrome-associated sebaceous neoplasms**

The observed incidence of Muir-Torre syndrome may be low in transplant patients since a previous history of most internal malignancies is a contraindication to transplantation [38]. Hence, many of the solid organ

transplant recipients who subsequently develop Muir-Torre syndrome were patients who had no history of a visceral cancer at the time of transplant. Subsequently, after transplant, they developed a sebaceous neoplasm and a systemic malignancy. However, many of the reports published in solid organ transplant recipients were done after a Muir-Torre syndrome-associated sebaceous neoplasms had been observed but perhaps prior to the patient developing cancer. Therefore, in these individuals, the potential diagnosis of Muir-Torre syndrome would have been missed by the investigators since additional studies such as immunohistochemistry analysis or microsatellite instability testing or the sebaceous neoplasm or germline testing of the patient had not been performed.

**Progression of a benign sebaceous neoplasm to a malignant sebaceous carcinoma in immunosuppressed solid organ transplant recipients with or without Muir-Torre syndrome or Muir-Torre syndrome-type cancers**

Unusual sebaceous neoplasms have been observed in immunosuppressed patients. A borderline sebaceous neoplasm was described in a renal transplant patient without Muir-Torre syndrome and the investigators suggested the possibility of an oncogenic sequence from sebaceous adenoma to sebaceous carcinoma [25]. Another group of researchers also described a unique sebaceous neoplasm in a liver transplant recipient whose initially biopsy was interpreted as a sebaceous epithelioma. However, microscopic evaluation after complete excision of the tumor demonstrated a sebaceous carcinoma [27].

**Variables associated with post-transplant development of a sebaceous neoplasm**

Previous studies have shown that the incidence of sebaceous neoplasm may be based on the organ of transplant. For example, sebaceous neoplasms are most frequently in lung recipients, followed by kidney recipients, and then liver recipients. The researchers postulated that this may occur since lung patients have the most intensive post-transplant immunosuppression treatment [33,38].

Specifically, the intensiveness of the post-transplant immunosuppression treatment correlates directly with the number of concurrent immunosuppressants. In addition to the incidence of sebaceous neoplasm post-transplant, the number of concurrent immunosuppressants may also influence how rapidly sebaceous neoplasm appear following transplantation. Previous investigators noted the post-transplant duration prior to the onset of sebaceous neoplasm in liver transplant recipients was longer than that observed in renal transplant patients. They speculated that this related to liver transplant patients only receiving one immunosuppressant (tacrolimus) as compared to renal transplant recipients who receive at least two immunosuppressants and that the dose of tacrolimus was lower in patients who had received a liver as compared to patients who had received a kidney [38].

We noted the same observation in solid organ transplant recipients with or without Muir-Torre syndrome who developed Muir-Torre syndrome-associated sebaceous neoplasm (**Table 10**). Liver transplant patients only received tacrolimus as an immunosuppressant, whereas renal transplant patients most commonly received either two or three immunosuppressive agents. In solid organ transplant recipients patients without Muir-Torre syndrome, the initial sebaceous neoplasm was observed after a median of 14.6 years in liver transplant recipients compared to a median of 7 years in kidney transplant recipients. Similarly, in solid organ transplant recipients with Muir-Torre syndrome, the initial sebaceous neoplasm was observed after 6 years in the liver transplant recipient compared to a median of 2.6 years in kidney transplant recipients.

**Mechanism of action of immunosuppressant agents with regard to promoting the development of sebaceous neoplasms**

Several of the medications used to prevent rejection in the transplant patients have been observed to promote the development of sebaceous neoplasms, particularly sebaceous carcinoma. These predominantly include azathioprine and the calcineurin inhibitors cyclosporin A and tacrolimus. Induction therapy with thymoglobulin also increases the risk of sebaceous carcinoma. In addition to

enabling the occurrence of sebaceous neoplasm, many investigators have suggested that the immunosuppressant agents received by solid organ transplant recipients may unmask the patient's expression of either latent Muir-Torre syndrome phenotype or actual innate Muir-Torre syndrome genotype [14,16,23,35,36,38].

Azathioprine allows for the proliferation of cells with mismatch repair abnormalities that subsequently promote the development of sebaceous neoplasms. Specifically, the cytotoxic effects of azathioprine are not effective against cells with deoxyribonucleic acid mismatch repairs. Therefore, the cells with these genomic aberrations persist. Subsequently, patients receiving azathioprine are predisposed to develop sebaceous neoplasm since the drug results in the emergence of an iatrogenically-induced mutator phenotype [14,25,35].

The multifunctional cytokine transforming growth factor-beta is related to tumor invasiveness and metastatic potential. The calcineurin inhibitors, cyclosporin A and tacrolimus, promote the progression of tumors such as sebaceous neoplasms by not only elevating the levels of transforming growth factor-beta and interleukin-6, but also causing overexpression of vascular endothelial growth factor. The latter subsequently results in accelerating angiogenesis. In addition, cyclosporin A and tacrolimus result in cutaneous carcinogenesis by inhibiting another deoxyribonucleic acid repair mechanism: nucleotide excision repair [25,27,32,35].

Thymoglobulin is a potent T cell inhibitor. When thymoglobulin is used as part of the induction treatment prior to a solid organ transplant, immediately post-transplant the recipient experiences a severe, yet short-term, immunosuppression. An analogous situation characterized by T cell depletion that promotes sebaceous carcinoma tumorigenesis has been observed in acquired immunodeficiency syndrome patients who have low CD4 T cell counts. Indeed, the standardized incidence ratio of developing sebaceous carcinoma in individuals with acquired immunodeficiency syndrome is 8.1 [33,48].

**Reduction of sebaceous neoplasms after changing post-transplant immunosuppressants**

The mammalian target of rapamycin (mTOR) participates in several signaling pathways of the

**Table 10.** *Relationship between number of immunosuppressant agents and the duration of time between the onset of immunosuppression and the development of the initial sebaceous neoplasm in immunosuppressed patients.*

| **Immunosuppressed patients without Muir-Torres syndrome** | | | | | |
|---|---|---|---|---|---|
| Feature | Renal transplant patients | Cardiac transplant patients | Liver transplant patients | HIV-infected patients | Chronic disease patients |
| Number of IA | 2: 15 pts<br>3: 14 pts<br>5: 1 pt | 1: 1 pt<br>2: 1 pt | 1: 2 pts[a] | None: 6 pts | 1: 1 pt |
| Duration[b] | Range: 2.3 yr-28 yr<br>Median: 7 yr | Range: 7 mo-1 yr<br>Median: 10 mo | Range: 11.6yr-17.7yr<br>Median: 14.6 yr | Range: 1 yr-14 yr<br>Median: 2 yr | Range: 16 yr<br>Median: 16 yr |
| | | | | | |
| **Immunosuppressed patients with Muir-Torres syndrome** | | | | | |
| Feature | Renal transplant patients | Cardiac transplant patients | Liver transplant patients | HIV-infected patients | Chronic disease patients |
| Number of IA | 2: 2 pts<br>3: 4 pts<br>4: 1 pt | 2: 1 pt<br>3: 1 pt | 1: 1 pt[a] | None: 3 pts | 1: 2 pts<br>≥2: 2 pts |
| Duration[b] | Range:[c] 3 mo-16 yr<br>Median: 2.6 yr | Range: 1 yr-16 yr<br>Median: 8.5 yr | Range: 6 yr<br>Median: 6 yr | Range:[d] 10 mo-7 yr<br>Median: 4 yr | Range: 1 yr-29 yr<br>Median: 11 yr |

HIV, human immunodeficiency virus; IA, immunosuppressant agents; mo, months; pt, patient; pts, patients; yr, years; ≥, greater than or equal to.
[a]The patients were only receiving tacrolimus.
[b]This is the duration of time between the onset of immunosuppression and the development of the initial sebaceous neoplasm
[c]The development of the initial sebaceous neoplasm occurred 4 years prior to the renal transplant and onset of immunosuppression in 1 patient.
[d]The development of the initial sebaceous neoplasm concurrently occurred with the diagnosis of HIV infection in 1 patient.

body including those associated with cancer. Apoptosis, autophagy, and cell proliferation are regulated by the mTOR. In contrast to azathioprine, cyclosporin A, tacrolimus, and thymoglobulin, mTOR inhibitors (such as sirolimus and everolimus) decrease the incidence of skin cancers such as sebaceous neoplasms. Some antitumor mechanisms of mTOR inhibitors include blocking the expression of cell cycle-controlling cyclin inhibitors, decreasing endothelial cell responsiveness to stimuli thorough vascular endothelial growth factor receptors, inducing G1 arrest, inhibiting transforming growth factor-beta, inducing vascular endothelial growth factor-related antiangiogenesis activity, and interfering with cell proliferation by suppressing mTOR. Therefore, some investigators have initially or subsequently used mTOR inhibitors as an immunosuppressant agent in solid organ transplant recipients [32,35].

There are several individual reports which demonstrate a reduction of sebaceous neoplasms after changing or decreasing one of the immunosuppressants that a solid transplant organ recipient is receiving. This includes changing either tacrolimus or cyclosporin A to sirolimus [15,24,36]. It also includes either changing tacrolimus to everolimus or decreasing the daily dose of tacrolimus and adding everolimus [29,32,49].

**Changing the post-transplant immuno-suppressant to sirolimus**

Changing the post-transplant immunosuppressant to sirolimus has been successfully observed to halt or diminish the new occurrence of sebaceous neoplasms in three men with Muir-Torre syndrome. Two men were initially receiving tacrolimus [15,36]. The third man was initially being treated with cyclosporin A [20].

A 51-year-old man, previously on hemodialysis for 7 years, was the recipient of a kidney. His past medical history was significant for resection of a sigmoid colon cancer at age 39 years and right nephrectomy and ureterectomy to treat transitional cell carcinoma of the right renal pelvis at age 44 years; the latter surgery was followed by deterioration of the man's renal function and initiation of hemodialysis. His post-transplant daily medication included mycophenolate mofetil, prednisone, and tacrolimus. Within 5 months, he began to develop numerous skin lesions which continue to appear on his face, chest wall, and trunk during the next two years. In addition, he developed 6 adenomatous colon polyps. The skin lesions included 32 sebaceous adenomas, one sebaceous carcinoma, one keratoacanthoma, and one basal cell carcinoma. Germline testing showed an R680X mutation in *MSH2*, thereby establishing the diagnosis of Muir-Torre syndrome [15].

The tacrolimus was stopped and sirolimus was substituted. New skin lesions did not appear during the next 5 weeks but he experienced several sirolimus-associated adverse effects. Therefore, the sirolimus was discontinued and tacrolimus restarted. Within two months, numerous new sebaceous neoplasms appeared. Hence, the tacrolimus was again discontinued and sirolimus was again started. He was now able to tolerate the drug and no new skin lesion appeared during 11 weeks of follow-up [15].

A 22-year-old man received a kidney transplant; daily post-transplant treatment included tacrolimus and prednisone. At age 38 years, he developed a sebaceous carcinoma on his left shoulder and 9 months later, a second sebaceous carcinoma appeared on his left cheek. Immunohistochemical analysis of both sebaceous neoplasms showed loss of expression of MSH2 and MSH6 [36].

Adenocarcinoma of the esophagus with pulmonary and infra-diaphragmatic lymph node metastases was diagnosed 16 months later, at age 40 years. In addition, a primary adenocarcinoma of the colon was also discovered. His CA19-9 was markedly elevated at 9889U/ml (normal, <37U/ml). Immunohisto-chemical analysis of both tumors also showed loss of expression of MSH2 and MSH6. In addition, next generation sequencing of genomic deoxyribonucleic acid demonstrated a heterozygous pathogenic c.(366+1_367-1)_(1276+1_1277-1) deletion variant in *MSH2*. The diagnosis of Muir-Torre syndrome was established [36].

Sirolimus was used to replace tacrolimus. Palliative FOLFOX (oxyplatin, leucovorin, and 5-fluouracil) chemotherapy was initiated. After receiving 12

cycles of treatment, he not only had good clinical and radiological responses but also a normal CA19-9 level [36].

A 63-year-old man with Muir-Torre syndrome had a kidney transplant. His post-transplant daily treatment included cyclosporin A, mycophenolate mofetil, and prednisone. During the 16 years prior to receiving the kidney, from age 47 to 63 years, he had developed 38 sebaceous neoplasms including 32 adenomas, 5 epitheliomas, and one carcinoma [20].

A dramatic increase in the number of new sebaceous neoplasms on his face occurred within months after starting the cyclosporin A. Indeed, during the 18 months following the transplant, he developed 45 sebaceous neoplasms. They included 38 adenomas and 9 carcinomas [20].

The cyclosporin A was discontinued. Sirolimus was added. During the next 18 months, he only developed 5 sebaceous adenomas and no sebaceous carcinomas [20].

**Changing the post-transplant immuno-suppressant to or adding everolimus**

The introduction of everolimus in calcineurin inhibitor-treated heart transplant recipients has been demonstrated to result in a decreased incidence of non-melanoma skin cancer. An observation study included 10 heart transplant patients who were evaluable with regard to skin cancers; their post-transplant treatment included cyclosporin A [62]. After introducing everolimus, cyclosporin A was either stopped (four patients) or decreased (6 patients). Also, azathioprine was discontinued in two patients: one whose cyclosporin A had been stopped and one whose cyclosporin A had been decreased. Either systemic corticosteroids (5 patients) or mycophenolate mofetil (two patients) were continued in those individuals who were receiving these immunosuppressants [62].

During the 'before' period of 28 months prior to introducing everolimus, the 10 men had a total of 33 non-melanoma skin cancers. These included 28 squamous cell carcinomas (of which 20 were invasive and 8 were in situ) and 5 basal cell carcinomas. During the 'follow-up' period of 28 months after initiating treatment with everolimus, the 10 men had a total of 12 non-melanoma skin cancers. These included 8 invasive squamous cell carcinomas and four basal cell carcinomas. The study showed that the number of squamous cell carcinomas was significantly lower after discontinuing or decreasing the cyclosporin A and adding everolimus [62].

Altering the post-transplant immunosuppressant and adding everolimus has been done to either prevent new Muir-Torre syndrome-associated neoplasms (one woman) or to halt and resolve sebaceous neoplasms (one woman). Both women were receiving tacrolimus prior to adding everolimus. After adding everolimus, the tacrolimus dose was decreased (one woman) or discontinued (one woman), [29,32].

A 32-year-old woman required hemodialysis to treat IgA nephropathy-associated end-stage kidney disease. A year later, at age 33 years, she received a kidney; post-transplant daily treatment included methylprednisolone, mycophenolate mofetil, and tacrolimus. Ten years later, at age 43 years, a sebaceous carcinoma was excised from the back of her head. A screening for visceral tumors was performed and an early-stage adenocarcinoma in the transverse colon was discovered and treated with endoscopic mucosal resection [32].

The sebaceous carcinoma and the colon adenocarcinoma were evaluated with immunohistochemistry analysis, microsatellite instability testing, and deoxyribonucleic acid sequencing analysis and both tumors showed the same results. Immunohistochemistry analysis showed a loss of MSH2 and MSH6 mismatch repair genes expression in the cancer cells. There was a high prevalence of microsatellite instability which showed that three of 7 markers were positive in the gene locus assay. Deoxyribonucleic acid sequencing analysis of the tumors showed a germline mutation of c.1226_1227delAG, p.Gln409ArgfsXT in *MSH2* exon 7. These findings established the diagnosis of Muir-Torre syndrome. To prevent the development of subsequent syndrome-associated neoplasms, her daily immunosuppressant treatment was changed by adding everolimus and lowering the dose of tacrolimus [32].

A 39-year-old woman with renal failure had a kidney transplant. Her post-transplant daily treatment, for 13 years until age 52 years, included azathioprine, cortisone, and cyclosporin A. At age 55 years, three years later, she had a second kidney transplant; post-transplant daily treatment included cortisone, mycophenolic acid, and tacrolimus. During the next 7 years, she developed numerous skin lesions on her face, arms, and legs [29].

At age 62 years, a new lesion of three months duration developed on her nose and a biopsy revealed a sebaceous carcinoma. Microscopic evaluation of additional lesions showed a sebaceous carcinoma on her right thigh and a keratoacanthoma with sebaceous differentiation on her upper lip. Her other cutaneous lesions were not biopsied [29].

Additional evaluation of the sebaceous carcinoma was performed. Microsatellite instability testing did not show any abnormalities. However, a mutation in *MSH6* exon 1 (c116G>A) was demonstrated on genetic studies. She did not have any visceral malignancies and did not fulfill the criteria for Muir-Torre syndrome [29].

Concern regarding the occurrence of additional cutaneous neoplasms prompted a change in her immunosuppressive treatment. Tacrolimus was discontinued and everolimus was added. Follow-up two months later not only showed complete disappearance of all previous skin tumors on her face and limbs, but also no new cutaneous lesions. In addition, at subsequent follow-up visits, there have been no systemic malignancies or further Muir-Torre syndrome-associated skin lesions [29].

**Pharmacologic prevention of sebaceous neoplasms**

The potential to decrease the incidence of cutaneous malignancies using pharmacologic agents has been investigated. For example, the incidence of squamous cell carcinoma in heart transplant recipients is dramatically decreased by using everolimus as one of the immunosuppressant agents and decreasing or eliminating cyclosporin A [62]. Also, the initiation of mTOR inhibitors such as sirolimus and everolimus instead of tacrolimus or cyclosporin A has been noted to significantly decrease the development of sebaceous neoplasms in solid organ transplant recipients who have Muir-Torre syndrome, or who have only syndrome-associated cutaneous sebaceous lesions without a visceral malignancy [15,20,29,32,36].

In addition, two patients with Muir-Torre syndrome have demonstrated dramatic prevention of syndrome-associated malignant neoplasms while receiving treatment with either an immune checkpoint inhibitor or an immunoglobulin. Cancer immunoprevention was observed in a man during his treatment with pembrolizumab; during and following treatment, new cutaneous or visceral hyperplastic or neoplastic lesions ceased to appear [63]. Also, a woman did not develop any visceral tumors during the years that her multiple sclerosis was being treated with intravenous immunoglobulin G [34].

A 36-year-old man had a colon cancer resected in 1991. Subsequently, at age 44 years, he developed sebaceous epitheliomas on both his scrotum and groin. Germline testing revealed a splice site mutation (1661+1G>T) in segment 1 of the *MSH2* mismatch repair gene. A diagnosis of Muir-Torre syndrome was established [63].

From age 44 years (1999) to age 63 (2018), he developed 136 cutaneous or visceral hyperplastic or neoplastic lesions over the period of 19 years (mean, 7.5 neoplasms per year with range 2-26 neoplasms per year and median 12 neoplasms per year). These included 9 primary visceral malignancies: small intestine (four cancers), colon (colon cancers), ureter or uretero-vesical junction (two cancers), and prostate (one cancer). They also included 37 sebaceous neoplasms: adenoma (23 tumors), epithelioma (7 tumors), carcinoma (5 tumors), and metastatic carcinoma (two tumors), [63].

At age 62 years, in November 2017, he developed both invasive papillary urothelial carcinoma of the right uretero-vesical junction and prostate adenocarcinoma (Gleason grade 9). He declined surgery and was initially treated, over a period of four months, with chemo-radiotherapy (consisting of weekly intravenous gemcitabine and radiation, delivered in 20 fractions, consisting of either 60 Gray,

50 Gray, or 40 Gray to the prostate, bladder, or pelvic nodes, respectively). Subsequently, beginning in April 2018, he received immune checkpoint blockade therapy with pembrolizumab (200mg intravenous every three weeks) for one year. In addition, for his prostate carcinoma, he also received androgen deprivation therapy [63].

Follow-up evaluation demonstrated absence of any residual urothelial cancer. In addition, there was no detectable prostate cancer and his prostate-specific antigen was 0. However, during the 22 months from April 2018 to March 2020, he did not develop a new cutaneous or visceral cancer or premalignant hyperplastic lesion. Based on these observations, his researchers postulated that immune-interception may be an efficacious strategy to reduce cancer risk in patients with Muir-Torre syndrome (which is typically characterized by having a high mutational burden of greater than 12 mutations per million bases) who have deficits in their mismatch repair genes [63].

A 46-year-old woman was diagnosed with optic neuritis; the following year, at age 47 years, she was diagnosed with relapsing-remitting multiple sclerosis. During the next 18 months, she experienced three relapses of the multiple sclerosis which each required treatment with corticosteroids. In addition, she received a short course of interferon beta 1a that was stopped because of mood changes and severe bruising at the injection sites [34].

At age 50 years, as part of a clinical trial, she began treatment for the multiple sclerosis with an anti-interleukin-12 antibody. Prior to beginning treatment, additional work-up revealed that she had hypermobile Ehlers-Danlos syndrome. Also, her family history was remarkable for both her mother and sister having had endometrial adenocarcinoma [34].

Prior to the end of the trial, she developed a biopsy-confirmed sebaceous adenoma on her left shoulder. Germline testing was performed and the results demonstrated that in the *MSH2* gene she was heterozygous for a constitutional pathogenic nonsense variant: p.Lys537Ter. Evaluation for cancer discovered endometrial carcinoma which was successfully treated surgically with a hysterectomy and bilateral salpingo-oophorectomy. A diagnosis of Muir-Torre syndrome was established [34].

At age 51 years, intravenous immunoglobulin G (once monthly for the first two years and then every two months thereafter) was initiated to treat her multiple sclerosis. Except for a 3-week episode of spontaneously resolving oscillopsia after 3.5 years of treatment, she remained on the immunoglobulin G for 10 years. During this period, there was minimal progression of her multiple sclerosis and she did not develop any new malignancies. Indeed, this prompted her doctors to postulate the possibility of a potential role of immunoglobulin G as an anti-cancer therapy [34].

At age 61 years, a global shortage of immunoglobulin G resulted in the medication being discontinued. Pegylated interferon beta 1a was initiated; however, it was discontinued after 6 months because of drug-related side effects [34].

Two months after stopping the interferon, she experienced a severe relapse of her multiple sclerosis with paraplegia requiring hospitalization and intravenous corticosteroids. Ocrelizumab, a B cell-depleting agent, was started. However, 5 months after the first infusion, a cecal carcinoma treated with colectomy and stoma placement, was discovered during a surveillance colonoscopy. Approval to reinitiate immunoglobulin G was pending when the case report was published [34].

The absence of any new malignancy during the 10-year treatment with immunoglobulin and the discovery of colon cancer 11 months after stopping therapy prompted investigators to propose that there might be a potential role of intravenous immunoglobulin G as an antineoplastic agent [34]. However, long-term treatment with intravenous immunoglobulin G did not prevent the development of either malignancy or sebaceous neoplasm in the man described in this report who developed chronic inflammatory demyelinating polyneuropathy at age 39 years. Furthermore, 10 years later, at age 49 years, he was diagnosed with chronic lymphocytic leukemia and 19 years later, at age 58 years, he developed a sebaceous adenoma. Hence, additional

research may be warranted to further evaluate whether intravenous immunoglobulin G has anti-tumor properties in immunosuppressed patients with chronic diseases.

**Summary: evaluation of Muir Torre syndrome in immunosuppressed patients with Muir Torre syndrome-associated sebaceous neoplasms**

In summary, some patients who develop Muir-Torre syndrome-associated sebaceous neoplasms after starting immunosuppressive therapy do not have, and do not develop Muir-Torre syndrome. Indeed, Gallon et al. recommended that all individuals with extraocular Muir-Torre syndrome-associated sebaceous neoplasm—except solid organ transplant recipients—receive germline testing for mismatch repair genes in order to discover patients at risk for Lynch syndrome [42]. However, lack of insurance coverage, patients declining additional evaluation, and low suspicion of Lynch syndrome based on immunohistochemistry analysis results, a negative personal or family history of Lynch syndrome-associated cancers, and/or a low Mayo Muir-Torre syndrome risk score are some reasons why germline testing is currently not being done in individuals who develop a Muir-Torre syndrome-associated sebaceous neoplasm [26,37,39].

However, many investigators have described patients in whom immunosuppressive treatment has unmasked latent Muir-Torre syndrome. Many of these researchers have affirmed that germline genetic testing is the standard for diagnosing Muir-Torre syndrome [26,35,42]. We concur with these investigators. Therefore, in order to diagnose Muir-Torre syndrome in patients receiving immunosuppressive treatment, we suggest that germline testing be seriously considered in individuals—not only immunocompetent individuals but also immunosuppressed patients—who develop a Muir-Torre syndrome-associated sebaceous neoplasm [64].

## Conclusion

Muir-Torre syndrome is an inherited genodermatosis characterized by the occurrence of both a systemic malignancy and a sebaceous neoplasm, including either a sebaceous adenoma, sebaceous epithelioma, and/or sebaceous carcinoma, which are manifestations of a germline alteration in a mismatch repair gene. The syndrome usually results from an autosomal dominant mutation in one or more mismatch repair genes such as *MLH1*, *MSH2*, *MSH6*, and/or *PMS2*. More recently, some autosomal recessive cases of Muir-Torre syndrome have been described which do not display microsatellite instability and are due to defects in the base excision repair gene *MYH*; these cases account for approximately one-third of Muir-Torre syndrome cases and are designated Muir Torre Syndrome II (MTSII). Muir-Torre syndrome-type sebaceous neoplasms can develop spontaneously. However, they can either help establish the diagnosis of the syndrome in an oncology patient or be the harbinger of the syndrome in a cancer-free individual. In addition, iatrogenic or acquired immunosuppression can promote the appearance of sebaceous tumors as an isolated event or as a feature of Muir-Torre syndrome that unmasks individuals genetically predisposed to the syndrome.

Two iatrogenically immunosuppressed men are herein described. Each had a prior history of cancer and therefore had features of Muir-Torre syndrome when they developed a sebaceous adenoma. Similar to these immunocompromised men, sebaceous neoplasms have occurred in solid organ transplant recipients, individuals infected with human immunodeficiency virus, and patients with chronic diseases who are treated with immunosuppressive agents.

There are several salient observations that have been noted in immunosuppressed patients with Muir-Torre syndrome-associated sebaceous neoplasms. The observation of Muir-Torre syndrome in solid organ transplant patients may be low since visceral cancer is often a contraindication to transplantation and the subsequent Muir-Torre syndrome-associated sebaceous neoplasm was observed post-transplant but perhaps prior to the development of a systemic malignancy. Germline testing was not performed in most of these individuals and therefore neither the potential diagnosis of Muir-Torre syndrome was suspected nor was subsequent monitoring for a visceral cancer done.

Two of the solid organ transplant recipients, a woman with Muir-Torre syndrome type cancer following kidney transplant and a man without Muir-Torre syndrome type cancer after liver transplant, had unusual sebaceous neoplasms that demonstrated progression from a benign adenoma or epithelioma to a malignant sebaceous carcinoma. Similar to previous investigators, we observed that Muir-Torre syndrome-associated sebaceous neoplasms were not only more common but also occurred earlier in solid organ transplant recipients who received a kidney than in those who received a liver. It has been postulated that this may be related to the greater number of post-transplant immunosuppressive agents that renal transplant patients receive each day as compared to only tacrolimus by the liver transplant patients.

Immunosuppressant agents such as azathioprine, the calcineurin inhibitors (such as cyclosporin A and tacrolimus), and thymoglobulin may unmask a patient's expression of either latent Muir-Torre syndrome phenotype or actual innate Muir-Torre syndrome genotype. Yet, when alternatives to these drugs, such as mTOR inhibitors including sirolimus and everolimus, are used to replace or lower the dose of cyclosporin A and/or tacrolimus, a significant decrease in the development of sebaceous neoplasms is observed.

Pharmacologic immunoprevention of not only Muir-Torre syndrome-associated sebaceous neoplasms but also syndrome-related visceral cancers were observed in a man during and following a one-year treatment with the immune checkpoint inhibitor pembrolizumab. Researchers also made an incidental observation that intravenous immunoglobulin G, in a woman with Muir-Torre syndrome, seemed to prevent new Muir-Torre syndrome-associated cutaneous neoplasm and systemic malignancies. However, the potential antineoplastic role of immunoglobulin G in Muir-Torre syndrome patients requires additional investigation.

In summary, many of these individuals with Muir-Torre syndrome-type sebaceous neoplasms do not have and do not develop a visceral malignancy. However, immunohistochemistry analysis or microsatellite instability testing and/or preferably germline testing for mismatch repair gene abnormalities can establish the diagnosis of Muir-Torre syndrome. In contrast to the immunocompromised individuals with Muir-Torre syndrome-associated sebaceous neoplasm who do not have and who do not develop a visceral malignancy, there are a substantial number of immunosuppressed patients following solid organ transplant, human immunodeficiency virus infection or chronic disease treatment who develop a Muir-Torre syndrome-type sebaceous neoplasm and have a history of systemic cancer or subsequently develop an internal malignancy thereby suggesting the presence of a genodermatosis. Indeed, many of these individuals have positive germline testing for a mutation in their deoxyribonucleic acid mismatch repair genes.

In conclusion, many investigators have indicated that germline genetic testing is the standard for diagnosing Muir-Torre syndrome. We agree with these researchers. Therefore, because of the risk of internal malignancy, we recommend that germline testing for genomic aberrations of mismatch repair genes should be strongly considered in all patients—both immunocompetent and immunosuppressed—who develop a Muir-Torre syndrome-type sebaceous neoplasm.

## Potential conflicts of interest

Dr. Cohen is a consultant for ParaPRO; however, this activity has no influence as a potential conflict of interest with regards to the manuscript. Dr. Kurzrock receives research funding, as well as receiving financial compensation for being a consultant, a speaker and/or an advisory board member, as well as an equity interest, as well as being a board member of two companies and a co-founder of one company; however, these activities have no influence as a potential conflict of interest with regards to the manuscript. Therefore, the authors declare no conflicts of interest.

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**Table 1**. *Muir-Torre syndrome-type sebaceous neoplasms in immunosuppressed renal transplant recipients withut internal malignancy.*

| C[a] | DxA SN<br>Gdr | SN: # | Site<br>of SN | Ti: IS<br>to SN | IS Tx | NMSC | IHC An<br>MSI Test | GIM+ | Ref |
|---|---|---|---|---|---|---|---|---|---|
| 1[a] | 48<br>W | SC | Eyelid | 13 | Aza, CyA | SCC:5 | ND<br>ND | ND | [55], C1 |
| 2[b] | 50<br>M | SC | Ear | 28 | Aza,<br>CyA,Pr | KA:21<br>SCC:20 | Negative<br>Negative | ND | [13], C16<br>[14], C3 |
| 3[c] | 52<br>M | SA:>30<br>SC:8<br>SE:3 | H&N<br>Trunk | 4 | MM,Pr,Tac | SCC:2 | -MSH2<br>ND | MSH2 | [23] |
| 4[d] | 52<br>M | SA:5 | Back:1<br>Face:4 | 3 | Pr,Tac | BCC:1<br>KA:1 | -MSH2<br>-MSH6<br>High | MSH2 | [28], C1 |
| 5 | 54<br>M | SC | Back | 6.9 | MM,Pr | None | -1[e]<br>ND | ND | [38], C7 |
| 6 | 55<br>M | SC | Ear | 11 | CyA,<br>MM,Pr | BCC:1 | ND<br>Negative | ND | [56] |
| 7[f] | 58<br>M | SA:3 | Eyelid:1<br>Face:2 | 13 | CyA, Pr,Tac | None | -MSH2<br>-MSH6<br>High | Neg | [28], C2 |
| 8 | 59<br>M | SC | Back | 6 | Aza,<br>CyA,Pr | None | -MSH2<br>High | ND | [14], C4 |
| 9 | 60<br>M | SA | Abdomen | 11 | Aza,<br>Cya,Pr | BCC:1 | ND<br>ND | ND | [31] |
| 10[g] | 62<br>W | SC:2 | Nose<br>Thigh | 23<br>10 | Aza,<br>CyA,<br>MM,Pr,Tac | KA:1 | ND<br>Negative | MSH6 | [29] |
| 11 | 65<br>M | SC | Scalp | 9.6 | MM,Pr,Tac | SCC:1 | ND<br>ND | ND | [38], C3 |
| 12 | 66<br>M | SC | Flank | 3.3 | MM,Pr,Tac | SCC:1 | ND<br>ND | ND | [38], C8 |
| 13 | 67<br>M | SC | Forehead | 4 | MM,Pr,Tac | None | ND<br>ND | ND | [38], C6 |
| 14 | 70<br>M | SC | Back | 8 | Aza,<br>CyA,Pr | BCC:1<br>SCC:1 | -MSH2<br>High | ND | [14], C10 |
| 15 | 71<br>M | SC | Nose | 2.3 | MM,Pr,Tac | SCC:1 | ND<br>ND | ND | [38], C4 |
| 16 | 73<br>M | SC | Back | 9 | Aza,<br>CyA,Pr | None | ND<br>ND | ND | [13], C13 |
| 17 | 75<br>M | SC:2[h] | Lip | 8 | Aza,<br>CyA,Pr | BCC:1<br>ECC:1<br>SCC:11 | Negative<br>Negative | ND | [13], C17<br>[14], C2 |
| 18 | 75<br>M | SC | Temple | 6 | Aza, Tac | None | Negative<br>ND | ND | [38], C2 |
| 19[i] | 82<br>W | BSN | NLF | 7 | MM,Pr,Tac | NS | -MLH1<br>ND | ND | [25] |
| 20[j] | 87<br>M | SC | Temple | 4 | Aza, CyA | SCC:3 | ND<br>ND | ND | [55], C2 |

Aza, azathioprine; BCC, basal cell carcinoma; BSN, borderline sebaceous neoplasm; C, case; CyA, cyclosporine A; DxA, diagnosis age (years); ECC, eccrine carcinoma; Eve, everolimus; Gdr, gender; GIM, germline mutation; H&N, head and neck (includes eyebrow, lip, neck, and scalp); IHC, immunohistochemistry; IHC An, immunohistochemistry analysis showing loss of gene expression; IS, immunosuppressant; KA, keratoacanthoma; M, man; MLH1, MutL Homolog 1; MM, mycophenylate mofetil; MSH2, MutS Homolog 2; MSH6, MutS Homolog 6; MSI, microsatellite instability test; MTS, Muir-Torre syndrome; ND, not done; Neg, negative; NLF, nasolabial fold; NMSC, nonmelanoma skin cancer; NS, not stated; PMS2, PMS1 Homolog 2, mismatch repair system component; Pr, prednisone; Ref, reference; SA, sebaceous adenoma; SC, sebaceous carcinoma; SCC, squamous cell carcinoma; SE, sebaceous epithelioma; SN, sebaceous neoplasm; Tac, tacrolimus; Ti, time (in years); Tx, treatment; W, woman; ≥, greater than;

#, number (if greater than one); :, equals; -, absence of gene expression; +, present.
[a]She had 3 renal transplants, a history of actinic keratoses, and dysplastic nevus syndrome.
[b]He underwent transplantation on 3 occasions: 1969 to 1981, 1983 to 1987, and 1989 onwards. He received CyA only after the third transplant.
[c]The patient is an African American man with a personal history of hepatitis C and a family history of colon cancer. His SC were on his face (eyelid) and scalp. The investigators presented him as a MTS patient; however, he did not have any systemic cancer.
[d]He had glomerulonephritis; his family history was significant for colon cancer and uterine cancer (2 relatives). His GIM for MSH2 was: [exon 7, c.1216C>T (p.Arg406x) codon 406].
[e]IHC analysis of MLH1, MSH2, MSH6, and PMS2 was performed; the expression of one of the mismatch repair genes was not preserved.
[f]The man had Berger syndrome. Two of his relatives had colon cancer. After the diagnosis of SA, his CyA was changed to Pr. IHC analysis was only performed for MLH1, MSH2, and MSH6; it was not evaluated for PMS2.
[g]The man had 2 renal transplants. His SC appeared 23 years after the first transplant and 10 years after the second transplant. His initial immunosuppression after the first transplant was Aza, CyA, and Pr for 10 years. After his second transplant, it was MM, Pr, and Tac for 10 years; after the diagnosis of the SC, the Tac was changed to Eve and all his skin lesions were gone. The KA had sebaceous differentiation. GIM showed MSH6 mutation: exon 1 (c116G>A).
[h]The patient had a two SC; however, the second SC occurred outside the time frame of the study that was conducted by the investigators.
[i]The patient had a family history of colon cancer. The investigators interpreted his borderline sebaceous neoplasm to possibly be a well-differentiated, low-grade SC within a SA. The investigators also favored his loss of MLH1 expression observed on IHC analysis to be the result of a somatic mutation.
[j]After the diagnosis of SC, the dose of Aza was lowered and CyA was added; 3 years after the diagnosis of SC, he dies of metastatic SC.

**Table 5**. *Muir-Torre syndrome-type sebaceous neoplasms in immunosuppressed renal transplant recipients with internal malignancy.*

| C[a] | DxA SN<br>Ca<br>Gdr | SN<br>(#) | Site<br>of SN | Ti: IS to<br>SN | IS Tx | Systemic Ca | NMSC | ≥2<br>SN | LSM:<br>PHx[b]<br>FHx[b] | MMTS<br>RS[c] | IHC<br>analysis | MSI<br>test | GlM+ | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 37<br>41<br>M | SC | Chest | -4[d] | MM, Pr,<br>Tac, WC | Colon (sigmoid)<br>adenoca | NS | No | No<br>Yes | 2 | -MSH2[e]<br>-MSH6[e] | ND | MSH2[f] | 35 |
| 2 | 38<br>40<br>M | SC<br>(2)[g] | Cheek<br>Shoulder | 16 | Pr, Tac[h]<br>Sir | Colon adenoca<br>Esophagus adenoca | NS | Yes | Yes<br>Ns | ≥4 | -MSH2[i]<br>-MSH6[i] | ND | MSH2[j] | 36 |
| 3 | 41<br>41<br>M | SA[k]<br>SC | Back<br>Back | NS | NS | Small bowel<br>adenoca | SCC:2 | Yes | Yes<br>Yes | 5 | None[l] | High | ND | 14,<br>C9 |
| 4 | 43<br>43<br>W | SC | Head | 10 | MM, Pr,<br>Tac,[m]<br>Eve | Colon adenoca | NS | No | No<br>Yes[n] | 2 | -MSH2[e]<br>-MSH6[e] | High<br>(3/7)[e] | MSH2[o] | 32 |
| 5[p] | 47<br>NS<br>M | SA (70)<br>SC (10)<br>SE (5) | NS<br>NS<br>NS | <0.25 | CyA,Sir | NS | NS | Yes | NS<br>NS | ≥3 | ND | ND | ND | 24 |
| 6 | 51<br>30[q]<br>44[r]<br>M | SA (32)<br>SC | Face<br>Chest | 0.42 | MM, Pr,<br>Tac,[s]<br>Sir | Colon ca<br>Renal pelvis tcc | BCC:1<br>KA:1 | Yes | Yes<br>No | 4 | ND | ND | MSH2[t] | 15 |
| 7 | 56<br><56<br>M | SC | Breast | 2.2 | MM, PR,<br>Tac | Bladder ca<br>Liposarc<br>Rectal ca | BCC:1<br>SCC:1 | No | Yes<br>Yes | 3 | -2[u] | ND | ND | 38,<br>C1 |
| 8 | 58<br>52<br>M | SC | Cheek | 3 | Aza,<br>CyA, Pr | Gastric carcinoid | BCC:8<br>SCC:10 | No | No<br>No | 1 | -MSH2 | High | ND | 13,<br>C14<br>14,<br>C1 |
| 9 | 81<br><81<br>M | SA | Nose | NS | NS | Bladder ca | BCC<br>SCC | No | No<br>NS | 0 | Neg | ND | ND | CR,C<br>2 |

adenoca, adenocarcinoma; Aza, azathioprine; BCC, basal cell carcinoma; C, case; Ca, cancer; CR, current report; CyA, cyclosporine A; DxA, diagnosis age (years); Eve, everolimus; FHx, family history; Gdr, gender; GlM, germline mutation; IHC, immunohistochemistry; IS, immunosuppressant; KA, keratoacanthoma; Liposarc, liposarcoma; LSM, Lynch syndrome-related malignancy; M, man; MLH1, MutL Homolog 1; MM, mycophenylate mofetil; MMTS RS, Mayo Muir-Torre syndrome risk score; MSH2, MutS Homolog 2; MSH6, MutS Homolog 6; MSI, microsatellite instability; ND, not done; NGS, next-generation sequencing; NMSC, nonmelanoma skin cancer; NS, not stated; PHx, personal history; PMS2, PMS1 Homolog 2, mismatch repair system component; Pr, prednisone; Ref, reference; SA, sebaceous adenoma; SC, sebaceous carcinoma; SE, sebaceous epithelioma; SCC, squamous cell carcinoma; Sir, Sirolimus; SN, sebaceous neoplasm; Tac, tacrolimus; tcc, transitional cell carcinoma; Ti, time (in years); Tx, treatment; W, woman; WC, Wuzhi capsule (to reduce serum glutamic-pyruvic transaminase); ≥, greater than or equal to; ?, location not provided; #, number (if greater than one); =, equals; :, equal; <, less than; -, absence of gene expression, +, present.

[a]Cases 10 and 11 include 2 of the 3 following patients with a SA: (1) a 67-year-old man with a BCC and an SA on the back that appeared after 9 years of treatment with Aza, CyA, and Pr [1,C10]; (2)

a 54-year-old woman with a BCC and SCC and an SA on the chin after 14 years of treatment with Aza and Pr [1,C11]; and (3) a 50-year-old man with no NMSC and a SA on the nose after 10 years of treatment with Aza, CyA, and Pr [1,C12]. Both patients had a history of multiple SN and personal and family histories of colorectal ca.

[b]LSM include the following cancers: colorectal, endometrial, ovarian, small bowel, urinary tract (renal pelvis and ureter), and biliary tract (gallbladder and bile ducts).

[c]MMT RS ranges from 0 to 5 based on age at presentation of initial SN (60 years or older = 0; less than 60 years = 1), total number of SN (one = 0; two or more = 2), personal history of LS-related cancer (no = 0; yes = 1), and family history of LS-related cancer (no = 0; yes = 1).

[d]The SC was present, yet undiagnosed, when he received his renal transplant. After 4 years of immunosuppressant treatment, the chest nodule (SC) rapidly increased in size, became painful, and was excised.

[e]IHC analysis and MSI testing were performed in both the SC and the colon adenoca; MLH1 and PMS2 normal expression.

[f]NGS was performed; the mutation location was exon2 c.299_230delAG, p.Ser77fs.

[g]The second SC appeared nine months after the first SC.

[h]The Tac was changed to Sir after the diagnosis of the SC.

[i]Not only the SC but also the esophageal and colon adenocas; MLH1 and PMS2 demonstrated normal expression.

[j]The mutation location was C.(366+1_367-1)_(1276+1_1277-1).

[k]The patient had multiple SA.

[l]Only MLH1 and MSH2 were tested.

[m]The Tac was decreased and Eve was added after the diagnosis of MTS.

[n]Her brother had colon ca.

[o]The location of the c.1226_1227delAG, p.Gln409ArgfsXT germline mutation was in the MSH2 exon 7; it was detected by deoxyribonucleic acid sequencing analysis (real-time polymerase chain reaction/direct) in both the SC and the colon cancer lesions.

[p]The patient is described as a man with MTS and end-stage renal disease who underwent kidney transplantation; however, the investigators did not described his MTS-associated systemic cancer. He developed 32 SA, 5 SE, and 1 SC prior to his renal transplant; during the 18 months after his renal transplant her received CyA and developed 38 SA and 9 SC. The CyA was stopped and Sir was started; only 5 SA developed during the next 18 months.

[q]Age at diagnosis of first systemic cancer.

[r]Age at diagnosis of second systemic cancer.

[s]The Tac was changed to Sir.

[t]The mutation location was (R680x).

[u]IHC analysis of MLH1, MSH2, MSH6, and PMS2 was performed; the expression of 2 of the mismatch repair genes were not preserved.

**Table 6**. *Muir-Torre syndrome-associated sebaceous neoplasms in immunosuppressed cardiac transplant recipients and germline mismatch repair alterations.*

| C | DxA SN<br>Ca<br>Gdr | SN<br>(#) | Site<br>of SN | Ti: IS<br>to SN | IS Tx | Systemic Ca | NMSC | ≥2<br>SN | LSM:<br>PHx[a]<br>FHx[a] | MMTS<br>RS[b] | IHC<br>analysis | MSI<br>test | GlM+ | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 51<br>54<br>M | SA (1)<br>SC (2)<br>SE (3)<br>SN[c] (1) | NS<br>Eyelid, Mastoid<br>Cheek, chest, ?<br>NS | 7 | Aza,<br>CyA,<br>Pr | Colon adenoca | KA:2 | Yes | Yes<br>Yes | 5 | ND | ND | MSH2[d,e] | [17], [18], [60] |
| 2 | 65<br>71<br>M | SA (5)<br>SC (3)<br>SE[f] (5) | Shoulder<br>NS<br>Back | 1 | MM, Tac | Lung, non-small cell adenoca<br>Multiple myeloma | SCC:3 | Yes | No<br>Yes[g] | 3 | -MSH6 | ND | MSH6[h] | [30] |

*adenoca, adenocarcinoma; Aza, azathioprine; C, case; Ca, cancer; CyA, cyclosporine A; DxA, diagnosis age (years); FHx, family history; Gdr, gender; GlM, germline mutation; HNPCC,* hereditary nonpolyposis colon cancer; IHC, immunohistochemistry; IS, immunosuppressant; KA, keratoacanthoma; LSM, Lynch syndrome-related malignancy; M, man; MLH1, MutL Homolog 1; MM, mycophenylate mofetil; MMTS RS, Mayo Muir-Torre syndrome risk score; MSH2, MutS Homolog 2; MSH6, MutS Homolog 6; MSI, microsatellite instability; ND, not done; NMSC, nonmelanoma skin cancer; NS, not stated; PHx, personal history; PMS2, PMS1 Homolog 2, mismatch repair system component; Pr, prednisone; Ref, reference; SA, sebaceous adenoma; SC, sebaceous carcinoma; SE, sebaceous epithelioma; SCC, squamous cell carcinoma; Sir, Sirolimus; SN, sebaceous neoplasm; Tac, tacrolimus; Ti, time (in years); Tx, treatment; ≥, greater than or equal to; #, number (if greater than one); =, equals; :, equals; -, absence of gene expression, +, present.

[a]LSM include the following cancers: colorectal, endometrial, ovarian, small bowel, urinary tract (renal pelvis and ureter), and biliary tract (gallbladder and bile ducts).

[b]MMT RS ranges from 0 to 5 based on age at presentation of initial SN (60 years or older = 0; less than 60 years = 1), total number of SN (one = 0; two or more = 2), personal history of LS-related cancer (no = 0; yes = 1), and family history of LS-related cancer (no = 0; yes = 1).

[c]This is a sebaceous neoplasm that is not otherwise specified.

[d]MLH1, MSH6, and PMS2 were not tested.

[e]The patient was a member of the Canadian family 169 with HNPCC; the HNPCC locus had been designated as COCA1.

[f]These sebaceous neoplasms was classified as a SE/sebaceoma

[g]Mother and maternal aunt had colon adenoca.

[h]The mutation location was exon 2 (c.432delC).

**Table 7**. *Muir-Torre syndrome-associated sebaceous neoplasms in an immunosuppressed liver transplant recipient with internal malignancy.*

| C | DxA SN<br>Ca<br>Gdr | SN (#) | Site of SN | Ti: IS to SN | IS Tx | Systemic Ca | NMSC | ≥2 SN | LSM:<br>PHx[a]<br>FHx[a] | MMTS RS[b] | IHC analysis | MSI test | GIM+ | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[c] | 67<br><61<br>M | SE to SC[d] | Spubic | 6 | Tac | HCC[e] | NS | No | No<br>No | 0 | ND | ND | ND | [27] |

C, case; Ca, cancer; DxA, diagnosis age (years); FHx, family history; Gdr, gender; GIM, germline mutation; HCC, hepatocellular carcinoma; IHC, immunohistochemistry; IS, immunosuppressant; LSM, Lynch syndrome-related malignancy; M, man; MLH1, MutL Homolog 1; MM, mycophenylate mofetil; MMTS RS, Mayo Muir-Torre syndrome risk score; MSH2, MutS Homolog 2; MSH6, MutS Homolog 6; MSI, microsatellite instability; MTS, Muir-Torre syndrome; ND, not done; NMSC, nonmelanoma skin cancer; PHx, personal history; PMS2, PMS1 Homolog 2, mismatch repair system component; Ref, reference; SC, sebaceous carcinoma; SE, sebaceous epithelioma; SN, sebaceous neoplasm; Spubic, suprapubic; Tac, tacrolimus; Ti, time (in years); Tx, treatment; ≥, greater than or equal to; <, less than; #, number (if greater than one); =, equals; ;, equals; -, absence of gene expression, +, present.

[a]LSM include the following cancers: colorectal, endometrial, ovarian, small bowel, urinary tract (renal pelvis and ureter), and biliary tract (gallbladder and bile ducts).

[b]MMT RS ranges from 0 to 5 based on age at presentation of initial SN (60 years or older = 0; less than 60 years = 1), total number of SN (one = 0; two or more = 2), personal history of LS-related cancer (no = 0; yes = 1), and family history of LS-related cancer (no = 0; yes = 1).

[c]Although the investigators who described this patient did not report him as a MTS patient, he fulfills the clinical diagnostic criteria of the syndrome.

[d]The investigators considered that the SN had progressed of SE to a SC.

[e]The patient had hepatitis C and developed HCC and liver cirrhosis.

**Table 8**. *Muir-Torre syndrome-type sebaceous neoplasms in HIV-infected individuals with systemic cancer.*

| C | DxA SN Ca Gdr | SN (#) | Site of SN | Ti: IS to SN | IS Tx | Systemic Ca | NMSC | ≥2 SN | LSM: PHx[a] FHx[a] | MMTS RS[b] | IHC analysis | MSI test | GIM+ | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 43<br>38<br>M | SA<br>>23 | Trunk:8<br>Nose:4<br>Neck:3<br>Cheek:2<br>Ext:2<br>Scrtum:1 | 0[c] | None | Colon adenoca | BCC:2<br>CMA: 1[d]<br>KA=1 | Yes | Yes<br>Yes | 5 | ND | High | ND | [22] |
| 2 | 48<br>28<br>M | SC<br>(1) | Back | 7 | None | Colon ca | None | No | Yes<br>No | 2 | ND | ND | ND | [61] |
| 3 | 53<br>50<br>M | SA<br>(10) | Forehead | 0.83[e] | None | Bilateral urinary tract tcc | KA:1 | Yes | Yes<br>Yes | 5 | ND | ND | ND | [21] |

adenoca, adenocarcinoma; BCC, basal cell carcinoma; C, case; Ca, cancer; CMA, cutaneous metastatic adenocarcinoma; DxA, diagnosis age (years); Ext, extremity; FHx, family history; Gdr, gender; GIM, germline mutation; HIV, human immunodeficiency virus; IHC, immunohistochemistry; IS, immunosuppressant; KA, keratoacanthoma; LSM, Lynch syndrome-related malignancy; M, man; MLH1, MutL Homolog 1; MMTS RS, Mayo Muir-Torre syndrome risk score; MSH2, MutS Homolog 2; MSH6, MutS Homolog 6; MSI, microsatellite instability; ND, not done; NMSC, nonmelanoma skin cancer; PHx, personal history; PMS2, PMS1 Homolog 2, mismatch repair system component; Ref, reference; SA, sebaceous adenoma; SC, sebaceous carcinoma; Scrtum, scrotum; SN, sebaceous neoplasm; Spubic, suprapubic; Ti, time (in years); Tx, treatment; ≥, greater than or equal to; >, greater than; #, number (if greater than one); =, equals; :, equals; -, absence of gene expression, +, present.

[a]LSM include the following cancers: colorectal, endometrial, ovarian, small bowel, urinary tract (renal pelvis and ureter), and biliary tract (gallbladder and bile ducts).

[b]MMT RS ranges from 0 to 5 based on age at presentation of initial SN (60 years or older = 0; less than 60 years = 1), total number of SN (one = 0; two or more = 2), personal history of LS-related cancer (no = 0; yes = 1), and family history of LS-related cancer (no = 0; yes = 1).

[c]His HIV infection was diagnosed during a hospital admission for a laminectomy for a herniated disc; his SAs were also diagnosed that admission. Two years earlier, he had a colonoscopy that was complicated by a ruptured colon that required surgery and blood transfusion.

[d]The CMA demonstrated high MSI.

[e]He had bilateral nephrectomy for bilateral urinary tract tcc; two years later he began hemodialysis; lab studies at that time discovered his HIV-infection. The SC on his right forehead appeared 10 months after starting hemodialysis.

**Table 9**. *Muir-Torre syndrome-type sebaceous neoplasms in immunosuppressed patients with a chronic disease requiring immunosuppressant therapy.*

| C | DxA SN<br>Ca<br>Gdr | SN (#) | Site of SN | Ti: IS to SN | IS Tx | Chronic disease | Systemic Ca | NMSC | ≥2 SN | LSM:<br>PHx[a]<br>FHx[a] | MMTS RS[b] | IHC analysis<br>MSI test | GIM+ | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 50<br>50[c]<br>67[d]<br>W[e] | SA | Shoulder | 3 | AIL-12, IFN, Ocrel, Pr | EDS<br>RRMS | Endometrial adenoca<br>Cecal ca | NS | No | Yes<br>Yes[j] | 3 | ND<br>ND | MSH2[f] | [34] |
| 2 | 58<br>49<br>M | SA | Forehead | 19 | Aza,[g] Pr | Addison disease<br>CIDP | Chronic lymphocytic leukemia | None[h] | No | No<br>No | 1 | -MSH2<br>-MSH6<br>ND | ND | CR, C1 |
| 3 | 59<br>61<br>W | SC | Back | 29 | Methim<br>RI | HyperT | Colon[i] | None | No | No<br>No | 1 | -MLH1<br>High | Neg[j] | [28], C5 |
| 4 | 68<br>55[c]<br>67[d]<br>M | SA | Cheek | 1 | R-CHOP | NHL | Prostate ca<br>NHL | BCC | No | No<br>No | 0 | -MSH2<br>-MSH6<br>High | Neg[j] | [28], C4 |

adenoca, adenocarcinoma; AIL-12, antileukin-12 antibody; Aza, azathioprine; BCC, basal cell carcinoma; C, case; Ca, cancer; CIDP, chronic inflammatory demyelinating polyneuropathy; CMA, cutaneous metastatic adenocarcinoma; CR, current report; DxA, diagnosis age (years); EDS, Ehlers Danlos syndrome; FHx, family history; Gdr, gender; GIM, germline mutation; HyperT, hyperthyroidism; IFN, interferon beta 1a; IHC, immunohistochemistry; IS, immunosuppressant; IVIg, intravenous immunoglobulin; LSM, Lynch syndrome-related malignancy; M, man; Methim, methimazole; MLH1, MutL Homolog 1; MM, mycophenylate mofetil; MMTS RS, Mayo Muir-Torre syndrome risk score; MSH2, MutS Homolog 2; MSH6, MutS Homolog 6; MSI, microsatellite instability; ND, not done; Neg, negative; NHL, Non Hodgkin lymphoma; NMSC, nonmelanoma skin cancer; Ocrel, ocrelizumab; PHx, personal history; PMS2, PMS1 Homolog 2, mismatch repair system component; Ref, reference; R-CHOP, rituximab, cyclophosphamide, hydroxydaunorubicin (doxorubicin hydrochloride), oncovine (vincristine sulfate) and prednisone; RI, radioactive iodide; RRMS, relapsing-remitting multiple sclerosis; SA, sebaceous adenoma; SC, sebaceous carcinoma; SN, sebaceous neoplasm; Ti, time (in years); Tx, treatment; W, woman; ≥, greater than or equal to; #, number (if greater than one); =, equals; :, equals; -, absence of gene expression, +, present.

[a]LSM include the following cancers: colorectal, endometrial, ovarian, small bowel, urinary tract (renal pelvis and ureter), and biliary tract (gallbladder and bile ducts).

[b]MMT RS ranges from 0 to 5 based on age at presentation of initial SN (60 years or older = 0; less than 60 years = 1), total number of SN (one = 0; two or more = 2), personal history of LS-related cancer (no = 0; yes = 1), and family history of LS-related cancer (no = 0; yes = 1).

[c]Age at diagnosis of first systemic cancer.

[d]Age at diagnosis of second systemic cancer.

[e]She developed optic neuritis at age 46 years; RRMS was diagnosed at age 47 years. During the next 18 months, she received 3 courses of prednisone and a short course of INF. At age 50 years, after 3 years of intermittent immunosuppressive treatment, EDS was also diagnosed and her RRMS was treated with AIL-12 on a clinical trial; toward the end of the trial, her SA was diagnosed. A MSH2 gene mutation was diagnosed; cancer screening discovered endometrial carcinoma, establishing the diagnosis of MTS. She had a hysterectomy and bilateral salpingo-oophorectoy. Beginning at age 51 years her RRMS was treated with monthly (for 2 years) and every 2 months (for 8 years) IVIg. After 10 years, the IVIg was stopped; she received pegylated INF for 6 months, followed by intravenous corticosteroids for a severe flare of her RRMS. Thereafter, Ocrel (an agent that depletes B-cells) was started; within 5 months, cecal carcinoma was diagnosed. She had a colectomy with stoma placement; at the time of publication of her report, reinstitution of IVIg was being contemplated.

[f]The mutation location was p.(Lys537Ter).

[g]The AZA was changed to MM and Tac after the diagnosis is MTS was established.

[h]The patient had a history of actinic keratoses.

[i]This was a tubule-villus adenoma with high grade dysplasia.

[j]The patients were only tested for MLH1, MSH2, and MSH6; testing for PMS2 was not performed.