

Case Report

Muir-Torre syndrome: the curious case of wobbly microsatellites and their mucosal Lynch

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ABSTRACT

MSH2 mismatch repair gene is commonly associated with Lynch syndrome; however, Lynch syndrome's phenotypic variant, Muir-Torre syndrome is a lesser known entity comprising a spectrum of benign to malignant sebaceous neoplasms and is often the first etiology of a more significant prodromal syndrome. Both syndromes encompass gastrointestinal, genitourinary tract, and prostatic pathologies. We present a 15-year patient progression starting with new sebaceous hyperplasia and congenital melanocytic nevus skin lesions presenting in a 38-year-old caucasian male. After approximately four years additional cutaneous lesions began continuously appearing identified as: ulcerated sebaceoma, basal cell carcinoma, sebaceous hyperplasia, sebaceous adenoma, and hidradenoma. The patient went on to develop prostate adenocarcinoma and tubular adenoma of the ascending colon and rectum. Immunohistochemical staining demonstrated MSH2 and MSH6 instability and patient was recommended for Lynch Syndrome genetic testing. Later genetic analysis showed pathologic variant of MSH2 confirming Muir-Torre Syndrome. When multiple pathologies are involved that affect ectoderm differentiation, a diagnostic workup for microsatellite instability is recommended in association with a genetic counselor consultation. When a familial defect in a DNA repair enzyme (MSH1, MSH2, etc.) is known, we recommend PCR amplification for microsatellite instability in offspring between ages 5-15 to reduce morbidity and mortality in this population.

Keywords: Lynch syndrome, Muir-Torre syndrome, Microsatellite, MSH2

INTRODUCTION

Sebaceous glands are a normal part of our skin mucosa with an average of 2-5 million found throughout the body, except on the palms and soles of the feet, and are primarily associated with hair follicles. Males and females have the same number of glands; they differ in the amount of sebum produced, a lipid-rich secretion for cooling the body, with males producing five times more than females.¹ Multiple pre-neoplastic sebaceous gland entities have been documented in the literature: sebaceous nevus (Figure 1A), sebaceous hyperplasia

(Figure 1B), sebaceous adenoma (Figure 1C), and sebaceoma (Figure 1D). These benign entities are associated with fair skinned individuals characteristically above 40 years of age with the exception of sebaceous nevus which is a congenital anomaly.

Sebaceous nevus is seen in infancy as a skin-colored, hairless, warty plaque associated with the scalp. A unique microscopic pattern of verrucous epidermal hyperplasia overlying abundant sebaceous glands erroneously positioned in the superficial layer of the dermis, with glands touching the rete pegs at times.²

Sebaceous hyperplasia presents most commonly on the face and is grossly identified by a small, yellowish, discrete papule that is histologically identified by abundant, prominent sebaceous glands involving a dilated folliculosebaceous duct. No nuclear pleomorphism or mitotic activity is associated with this pathology.^{1,3}

Sebaceous adenoma may clinically mimic a basal cell carcinoma with a flesh-colored to yellow domed appearance located, stereotypically, on the head or neck of older adults. Microscopically these lesions are noted for their lobular histology, eye-liner peripheral basaloid architecture, and increased mitotic activity.^{3,4}

Sebaceoma may be identified grossly due to its reddish-yellow, nodular, smooth features and identified morphologically on glass slide by a disordered basaloid proliferative growth (>50%) with nests of sebocytes and conspicuous ducts and cysts; mitotic figures are typically evident, but pleomorphism is absent.^{2,3}

Sebaceous carcinoma is the malignant variant and may imitate chalazion. They are typically associated with the periorbital region of the face and are reddish-yellow, papular, and may have areas of ulceration. Under the microscope, infiltrative, haphazardly arranged tumor cells with variable differentiation, pleomorphic nuclei and hyperchromasia may be seen beneath an epidermis with scant, atypical sebocytes.^{2,5}

Hidradenoma (Figure 1E) are ectoderm derived from the same pluripotent stem cells as benign and malignant sebaceous neoplasms. Hidradenomas classically present as a solitary, skin-colored to reddish, smooth lesion. Histologically these entities are distinct for their fusiform cells with abundant eosinophilic or clear cytoplasm. The presence of focal squamous differentiation is typical as well as areas of ductal differentiation.²

In the clinical context of multiple sebaceous pathologies, the workup for Muir-Torre syndrome (phenotypic variant present in up to 9% of Lynch syndrome patients) is merited, especially in the case of sebaceous tumors appearing in other locations outside of the head and neck due to multiple studies associating this finding with Muir-Torre syndrome.⁶ We propose adding ectodermal derived hidradenomas as an independent variable for Muir-Torre surveillance when presented with a sebaceous neoplasm. An investigation of internal malignancy via colonoscopy should be explored, as colonic neoplasms are common. Both Lynch syndrome and Muir-Torre syndrome are associated with DNA mismatch repair gene defects, inherited in an autosomal dominant fashion. Diagnosis can be established by immunohistochemical mismatch repair protein expression, microsatellite instability testing via PCR, and DNA gene sequencing – systematically listed by increasing cost to the healthcare system.

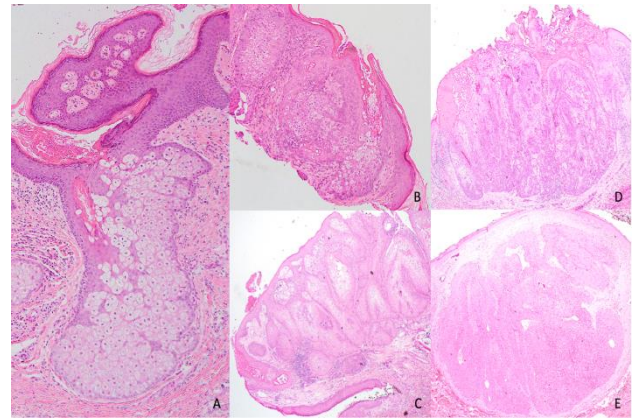


Figure 1 (A-E): Histologic examination of skin lesions in 38-year-old patient with Muir-Torre syndrome. Hematoxylin and eosin stain at 10x magnification. (A) Sebaceous nevus: sebocyte lobule juxtaposed on hyperplastic epidermis. (B) Sebaceous hyperplasia: hair follicle with lobules of sebocytes and epidermal invagination. (C) Sebaceous adenoma: mature sebaceous cells (>50%) within central portion of lobules and peripheral basaloid cells. (D) Sebaceoma: nodular tumor composed primarily of basaloid cells with a scattered area of clear mature sebocytes. (E) Hidradenoma: dermal nodule with stroma around solid areas of poroid cells.

CASE REPORT

Our patient, A 38 year-old caucasian male, became known to our clinic in February of 1998. He presented with new onset skin lesions on his forehead and nose. Biopsies were taken, and a diagnosis of sebaceous hyperplasia and congenital melanocytic nevus were given. His past medical history was notable only for positivity to environmental allergens. He became lost to follow-up over four years. In 2002 he presented again to our clinic; this time with a lobulated, hemorrhagic left upper back lesion measuring 0.4 × 0.3 cm. A diagnosis of ulcerated sebaceoma was rendered. Over subsequent years, numerous skin cancers were identified: basal cell carcinoma with sebaceous differentiation, sebaceous hyperplasia, sebaceous adenoma, and hidradenoma. (Hidradenoma is relevant due to its ectodermal derivation; they have the same derivation as sebaceous glands).

In 2009, prostate adenocarcinoma was diagnosed in two small foci of both the left and right prostate status-post radical prostatectomy. Later, our patient had his first colonoscopy. Biopsies were taken from two polypoid lesions microscopically demonstrating focal areas of basophilic colonic mucosa with heaped pencillate nuclei. The pathologist reported tubular adenoma of the ascending colon and rectum.

The following year an excisional biopsy of an irregular shaped tan-yellow soft tissue mass was removed from the

right hip; it was identified as sebaceoma with focal necrosis and a comment regarding Muir-Torre syndrome. He was closely followed by his PCP who identified more lesions: invasive squamous cell carcinoma, sebaceous hyperplasia, and sebaceous nevus. Increased colonic surveillance was ordered which identified additional tubular adenomas of the ascending and distal transverse colon, and anorectal dysplasia. Immunohistochemical staining demonstrated MSH2 and MSH6 instability. Our institution's genetic counselor was conferred; and a recommendation for Lynch syndrome genetic testing was made in light of the patient's father having pathologies concerning for Lynch syndrome – colon, prostate, and genitourinary cancers– the patient declined more advanced studies.

Three years later the patient agreed to genetic analysis; a pathologic variant of MSH2 was identified and the patient was definitively confirmed to have Muir-Torre/Lynch syndrome.

DISCUSSION

Further investigation of the correlation between hidradenomas and sebaceous entities is justified as they share a common embryologic derivation; they may share the same apocrine pluripotent germinative cells.⁷ Even in the absence of GI and GU abnormalities, when multiple cutaneous entities share a common ectodermal derivation– for example: epidermis, nails, hair follicles, anus, apocrine, sebaceous, and eccrine glands– a primary preventive strategy should be implemented to identify syndromic Lynch syndrome.⁸ This may be executed through microsatellite instability screening, colonoscopy and/or prostate biopsy. In our patient, a diagnosis of Muir-Torre/Lynch syndrome would have occurred earlier had the patient undergone genetic testing at the time of his hidradenoma presentation; his GI tubular adenomas may have been detected earlier; prostate cancer in his son could have been surveilled sooner; and both offspring could have been screened for genitourinary pathologies at a younger age.

We propose MSH2 instability screening as the new standard of care in the setting of multiple ectodermal pathologies. Moreover, we propose screening at risk patients with a known familial defect between ages 5-15 for DNA mismatch repair by microsatellite instability testing via PCR to determine genetic susceptibility to Muir-Torre/Lynch syndrome as germline mutations may be recognized within this age range. Though this case report is of the presentation of a single individual with Muir-Torre syndrome, it is our belief that early detection and surveillance may decrease morbidity and mortality in this cohort.

CONCLUSION

In summary, based on the evidence, clinicians should be vigilant when multiple cutaneous ectodermal differentiated lesions are present in a person. Further workup is necessary, especially genetic testing to identify Muir-Torre/Lynch syndrome, and to closely observe family members; it is important to remember this pathology is transmitted in an autosomal dominant fashion and offspring are susceptible. Prudent management involves colonoscopies, cystoscopy, ureteroscopy, prostate biopsies, and skin surveillance. Further study to timely identify Muir-Torre/Lynch syndrome in adolescence is warranted.

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