BRIEF ARTICLES

An Interesting Case of Muir-Torre Syndrome

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ABSTRACT

Muir-Torre syndrome is a rare autosomal dominant syndrome that is believed to be a variant of hereditary nonpolyposis colorectal cancer (HNPCC, or "Lynch syndrome"), both of which are caused by inherited mutations that impair DNA mismatch repair. However, in comparison to Lynch syndrome, Muir-Torre syndrome can be diagnosed in the absence of a family history of malignancies and requires only the presence of a sebaceous tumor and internal malignancy alone. Individuals with Muir-Torre syndrome are prone to colon, breast, and genitourinary tract cancers, as well as cutaneous manifestations such as numerous keratoacanthomas and sebaceous neoplasms.

In patients with sebaceous tumors, routine immunohistochemical detection of loss of DNA mismatch repair proteins helps to identify hereditary DNA mismatch repair deficiency. When the diagnosis of Muir-Torre syndrome is established, it is advised that both patients and their first-degree relatives follow the same screening criteria for colon cancer and other malignancies as those with Lynch syndrome. Since sebaceous neoplasms can precede, coincide with, or follow internal manifestations of disease, early identification of Muir-Torre syndrome is valuable to increase detection of any associated malignancies, and it is also useful to provide counseling for family members at risk for premature malignancies.

CASE PRESENTATION

R.S. is an 83 year old male with a history of multiple non-melanoma skin cancers and a sebaceous adenoma in 2006 who presented with an 8 millimeter, erythematous, hyperkeratotic papule in the medial right eyebrow that was suspicious for a superficial squamous cell carcinoma. However, biopsy revealed sebaceous lobules with a slight increase in thickness of the immature layer of the periphery of the lobule, and the lesion was characterized as a sebaceous adenoma. Clinical correlation for Muir-Torre syndrome was advised, and the patient admitted to a personal history of colon cancer as well as a family history of colon cancer in his father. Furthermore, immunoperoxidase stains revealed preservation of staining with MSH-2 and MSH-6, along with partial loss of staining for MLH-1 and PMS-2. Given the patient's history of multiple sebaceous neoplasms, personal and family history of colon cancer, and loss of staining with MLH-1 and PMS-2, the patient was diagnosed with Muir-Torre syndrome. His family members were advised to undergo early routine detection for skin and internal cancers given the autosomal dominant

nature of the syndrome along with its associated increase in risk for internal and cutaneous cancers.

DISCUSSION

Muir-Torre syndrome is a rare autosomal dominant syndrome that is believed to be a variant of hereditary nonpolyposis colorectal cancer ("Lynch syndrome"). Lynch syndrome is characterized by a high risk of colon cancer along with endometrial, ovarian, stomach, and other cancers, and it is caused by inherited mutations that impair DNA mismatch repair. Muir-Torre syndrome has been identified in 28% of family members and 9% of individuals with Lynch syndrome[1]. However, in comparison to Lynch syndrome, specific neoplasms in Muir-Torre syndrome may lead to the correct diagnosis even when an obvious family history is not present, as diagnosis requires only the presence of at least one sebaceous gland tumor (either an adenoma, epithelioma, or carcinoma) and one or more internal malignancies[2].

Individuals with Muir-Torre syndrome are prone to numerous keratoacanthomas and sebaceous tumors[3], and the most commonly associated malignancies include colorectal (56%), urogenital (22%), small intestine (4%), and breast cancers (4%)[4]. These colorectal cancers tend to develop 15 to 20 years earlier than normal, with a median age of onset of 50. Additionally, one study found that Fordyce spots (ectopic sebaceous glands) were found in all patients with confirmed Muir-Torre syndrome, but only 6.4% of controls[5].

Since many patients with sebaceous neoplasms do not have Muir-Torre syndrome, the Mayo Muir-Torre risk score was designed to clinically identify patients at greater risk for the syndrome[6]. A score of 2 or greater indicates a high positive predictive value, while the syndrome is less likely with a score of 1 or fewer. These criteria include early age of onset of first sebaceous neoplasm (younger than 60), increased number of sebaceous neoplasms (2 or more), personal history of Lynch-related cancer, and family history of Lynch-related cancer.

The genes involved in Muir-Torre syndrome include MLH-1, MSH-2, and MSH-6, all of which are involved in DNA mismatch repair. The loss of mismatch repair proteins leads to microsatellite instability, which results in short, repetitive DNA sequences that are susceptible to mutation during DNA replication. By staining for the MSH-2, MLH-1, MSH-6, and PMS-2 proteins, sensitivity for detecting loss of expression of mismatch repair proteins approaches 90%[7]. Furthermore, lack of expression of MLH-1 or MSH-2 has been associated with microsatellite instability in all reported cases, and mutations in these genes are believed to produce the most profound effects[8]. For these reasons and due to the infrequency of sebaceous neoplasms, researchers have recommended the use of routine immunohistochemistry for all patients with sebaceous growths[9]. Furthermore, patients with abnormal mismatch repair protein staining and/or microsatellite instability are advised to undergo germline mutational analysis to confirm or rule out the diagnosis.

It is suggested that Muir-Torre syndrome patients be treated with oral isotretinoin, which has been discovered to stall tumor growth[10]. It is also advised that these patients follow the same screening criteria for colon cancer and other malignancies as those with Lynch Syndrome. These screening guidelines include that patients with Muir-Torre syndrome and their first-degree relatives undergo annual skin exam for lesions suspicious of sebaceous carcinoma or keratoacanthoma, annual colonoscopy starting at the ages of 20-25, annual screening for endometrial and ovarian cancer, endometrial biopsy and transvaginal ultrasound beginning at 30-35 years, upper endoscopy with biopsy of the gastric antrum beginning at 30-35 years, and annual urinalysis and cytologic

exam beginning at 30-35 years[11]. Since sebaceous neoplasms can precede, coincide with, or follow internal manifestations of disease, early identification of Muir-Torre syndrome is valuable to increase detection of any associated malignancies, and it is also useful to provide counseling for family members at risk of premature malignancies.

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