

## CLINICAL VIGNETTE

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# Treatment of Muir-Torre Syndrome with Low-Dose Isotretinoin

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### **Background**

Muir-Torre syndrome is an autosomal dominant inherited disorder characterized by the development of both cutaneous and visceral neoplasms that is thought to be a variant of hereditary non-polyposis colon cancer (HNPCC) syndrome.<sup>1</sup> The cutaneous tumors tend to be either sebaceous gland neoplasms (i.e. sebaceous adenomas and carcinomas) or kerato-acanthomas. As in HNPCC, visceral tumors typically involve the large bowel and the genitourinary tract, including the uterus, ovary, bladder, kidney, and ureters. The disease is caused by mutations in mismatch repair enzyme genes, including MLH1, MSH2, MSH6, and PMS2.<sup>2,3</sup> This leads to higher rates of genetic mutation, as evidenced by microsatellite instability, eventually causing malignant transformation. Sebaceous gland tumors are relatively rare neoplasms and their appearance should prompt an evaluation for Muir-Torre syndrome and underlying visceral malignancy.<sup>4</sup>

### **Case Presentation**

A 57-year old male with a past medical history of hypertension, GERD, adenocarcinoma of the ascending colon, and Muir-Torre syndrome presented to the dermatology clinic for second opinion and management of his numerous growing papules on his skin that frequently had been biopsied consistent with numerous sebaceous hyperplasia or neoplasms. Many of these lesions were treated with either shave excision, electrodesiccation or formal excisions.

As a result, the patient would visit dermatology on a nearly monthly basis for evaluation of new lesions, including the rapid recurrence of lesions at previously biopsied sites. Over the past 2 years, he had had 27 biopsies of concerning sebaceous lesions, six of which had pathological diagnosis of sebaceous carcinoma or atypical sebaceous neoplasm, with the remaining 21 lesions diagnosed as sebaceous adenomas – many requiring destruction or excision. DNA analysis of several skin biopsies demonstrated a high frequency of microsatellite instability, with five out of five microsatellite sites showing mutation, and loss of DNA mismatch repair enzymes MLH1 and PMS2. Additionally, the patient's past surgical history was significant for right hemicolectomy at the age of 28 for colon cancer. He has undergone yearly colonoscopies since then, with numerous adenomas removed from the transverse colon.

The patient's physical exam was notable various larger erythematous, umbilicated papules along with numerous scattered

yellowish-pinkish papules with central dells throughout his face and torso. Additional shave biopsies of some of these new lesions revealed additional sebaceous adenomas.

In considering prophylactic or other non-invasive options, the patient was started on a regimen of isotretinoin 20 mg PO daily, which led to a profound response to therapy upon follow up. His chronic facial sebaceous hyperplasia was noticeably reduced, with existing lesions becoming flattened or completely disappearing at his 3-month follow up. Consequently, over the past two years, he has not needed biopsy of any lesions since beginning therapy. He reported mild side effects of skin and eye dryness, treated with topical moisturizers and over the counter eye drops. Laboratory monitoring revealed minimal elevation in total cholesterol, HDL, LDL, and triglycerides over the last eight months, but no other lab abnormalities.

### **Discussion**

Medical therapy for Muir-Torre syndrome with isotretinoin has been reported previously.<sup>5-7</sup> Isotretinoin is a retinoid related to vitamin A that is commonly prescribed to treat severe cystic acne. Additionally, it is effective for some disorders of keratinization such as lamellar ichthyoses, and the neural crest cell derived cancer neuroblastoma. The mechanism of action of isotretinoin is poorly understood, however recent research has suggested that isotretinoin exerts its effects by inducing apoptosis in many cell types, including sebocytes, keratinocytes, and neural crest cells.<sup>8</sup> Apoptosis of sebocytes causes significant reduction in the size of sebaceous glands. This also leads to an up to 90% reduction in sebum production, with consequent effects on the skin microbiome and subsequent inflammatory responses, partially explaining its effectiveness in acne.<sup>9</sup> Common side effects of isotretinoin therapy include dry eyes and skin, transaminitis, anemia, thrombocytopenia, and lipid abnormalities.<sup>10</sup> Isotretinoin is also a potent teratogen in pregnancy category X, requiring registration through the federal iPledge program, with females of reproductive age required to use two forms of contraception and have regular pregnancy tests while using isotretinoin.<sup>11</sup>

Given that sebaceous cells and keratinocytes are the cell types primarily affected in Muir-Torre syndrome, treatment with isotretinoin was proposed with demonstrated effectiveness in several case reports. Both Spielvogel et al. and Marcusson et al. demonstrated that patients exposed to isotretinoin experienced

a reduction in size or disappearance of concerning cutaneous lesions, as well as prophylaxis in the development of new lesions.<sup>5,6</sup> Of note, cessation of isotretinoin therapy led to recurrence of cutaneous lesions, both as new lesions as well as recurrence of previously noted lesions. Graefe et al. used isotretinoin in combination with IFN- $\alpha$  to similar effect.<sup>7</sup> In each of these reports, patients were initially treated with doses of isotretinoin ranging from 40 to 80 mg daily. In some cases, the initial dose was titrated down to a maintenance dose of 10-20 mg daily. The drug was well tolerated, with side effects including mildly elevated transaminases, cholesterol, and triglycerides.

Here we present a case of Muir-Torre syndrome treated with a low-dose of isotretinoin, 20 mg orally daily, as both initial and maintenance management. This is a lower starting dose than heretofore described yet has been similarly effective in treating existing cutaneous lesions and preventing the development of new lesions in our patient. Treating with a lower dose is advantageous by reducing the potentially toxic effects associated with isotretinoin therapy. Our patient has experienced only mild side effects of dry eyes and cheilosis that have been well managed with topical treatments. He has not developed any changes in hepatic enzymes or complete blood counts from his baseline before therapy although he has developed increased cholesterol and triglycerides above the upper limit of normal since starting therapy.

Current standard of care for Muir-Torre syndrome also involves vigilant monitoring for cutaneous and visceral neoplasms. This includes annual colonoscopy, upper GI endoscopy every 2-3 years, and endometrial biopsy every 1-2 years, in accordance with practice guidelines from several agencies including the American College of Gastroenterology and American College of Obstetricians and Gynecologists.<sup>11,12</sup> Annual urinalysis for screening of urothelial cancers can also be considered. Additionally, frequent skin examination for cutaneous malignancy is recommended.<sup>4</sup> Our patient is well monitored by dermatology, gastroenterology, and his primary care physician for cancer screening. Whether treatment with isotretinoin reduces his frequency of colon adenomas remains to be seen but potentially provide additional promise.



**Figure 1.** Before treatment with low dose isotretinoin, the patient had numerous sebaceous hyperplasia as well as lesions biopsied consistent with sebaceous adenomas and concerning for adenocarcinomas.



**Figure 2.** Six months post-treatment initiation with isotretinoin 20 mg PO daily, the patient with complete resolution of cutaneous findings including in other areas of the body not shown.

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