CASE REPORT

Looking beyond the surface: Muir Torre syndrome

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ABSTRACT

Muir-Torre Syndrome (MTS) is associated with multiple visceral malignancies. Initial presentation may be a benign skin tumor mimicking a sebaceous cyst. This case report highlights the importance of early diagnosis, genetic testing, and multidisciplinary screening. A 67-year-old man was diagnosed with MTS following excision of a skin lesion (sebaceoma). He was declined both screening colonoscopy and genetic testing. Subsequently, advanced colon cancer was found following presentation with iron deficiency anemia, which ultimately led to palliation despite successful surgery. MTS can present insidiously with skin lesions clinically diagnosed as sebaceous cysts. Once MTS is suspected on histology, genetic testing and screening for MTS-related cancers is warranted. Better understanding of the genetic variants for MTS can aid in earlier diagnosis thus not dismissing the need for screening for MTS-related cancers.

KEYWORDS: Muir-Torre Syndrome; Lynch Syndrome; Colorectal Cancer; Sebaceoma

INTRODUCTION

Sebaceomas can be sporadic or associated with MTS. Upon histological diagnosis, nuclear staining for *MSH2 and MSH6* is required to assess microsatellite instability. MTS is considered a phenotypic variant of hereditary nonpolyposis colorectal carcinoma syndrome (HNPCC or Lynch syndrome) and is caused by germline mutations in one allele of the DNA mismatch repair (MMR) genes [7]. We discuss the essence of vigilance by a pathologist with a case and subsequent diagnosis of colon cancer.

CASE PRESENTATION

A 67-year-old Caucasian man presented to his general practitioner in June 2020 with a long-standing skin lesion on his right upper back (Figure 1). He had a history of melanoma and prostate cancer years prior. The patient was referred in for removal as it has been bothering him. Both his GP and skin specialist documented that the lesion was clinically a sebaceous cyst. The lesion was excised in October 2020, within a timeframe of a routine referral, and sent for histology.

Histology came back conclusive of a sebaceoma: smaller lobules of basaloid cells admixed with cells showing sebaceous differentiation. Immunochemistry for Mismatch Repair (MMR) proteins showed a loss of MSH2 and MSH6, consistent of an allelic variant of Lynch Syndrome (Figure 2). In the context of a sebaceoma, MTS was suspected. The patient was referred for genetic counselling. However, given lack of family history of colorectal cancer, he was not recommended surveillance colonoscopy or further genetic investigations.

In December 2020, the patient presented with iron deficiency anemia: ferritin and hemoglobin was 5ng/mL and 115g/L respectively. He was referred in for a gastroscopy and colonoscopy. A hepatic flexure adenocarcinoma was identified (Figure 3). Subsequent staging computed tomography (CT) scan showed no metastasis.

The patient was an alcoholic on Methotrexate and steroids for rheumatoid arthritis. He took Dabigatran, atorvastatin and Metoprolol for recurrent deep vein thrombosis, atrial fibrillation, and ischemic heart & cerebral disease.

The patient underwent laparoscopic complete mesocolic right hemicolectomy with an ileostomy. His risk of an anastomotic leak was so high owing to his immunosuppressants, co-morbidities and alcoholism. Histology showed low-grade adenocarcinoma T4aN1a R0. Absence of BRAF mutations, hypermethylation of MLH1 and loss of nuclear expression of MMR proteins were noted suggestive of Lynch Syndrome.

The patient was medically deemed unsuitable for adjuvant chemotherapy. The 1-year surveillance scan unfortunately demonstrated lung, liver, and bony metastasis. He was palliated.

DISCUSSION

MTS was first described by Muir & Torre (1968) associating sebaceous skin lesions with malignancy. It is caused by a mutation in DNA mismatch repair (MMR) genes, resulting in

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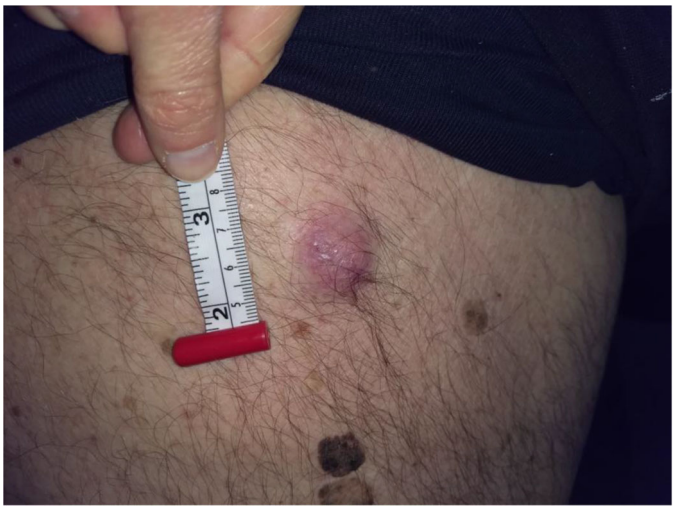

Fig. 1. Initial presentation of a sebaceous cyst like sebaceoma.

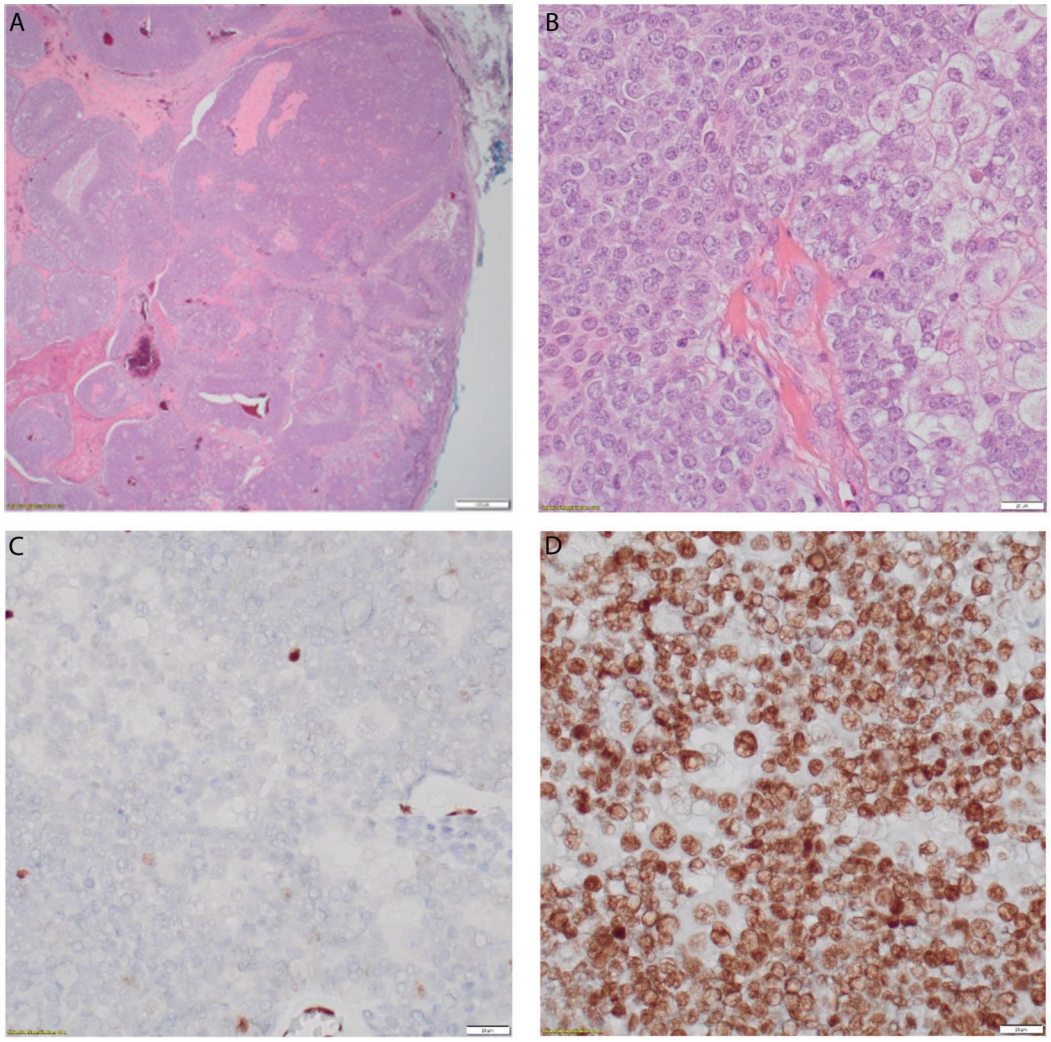

Fig. 2. (A) Dermal nodule (HE, x20); (B) Dermal nodule consisting of >50% basaloid cells (left) and mature sebocytes (right) (HE, x40). (C) Mismatch repair enzymes showing loss of MSH2 (IHC, Anti-MSH2 Ab, x40); (D) Mismatch repair enzymes showing normal staining for MLH1 (IHC, Anti-MLH1 Ab, x40).

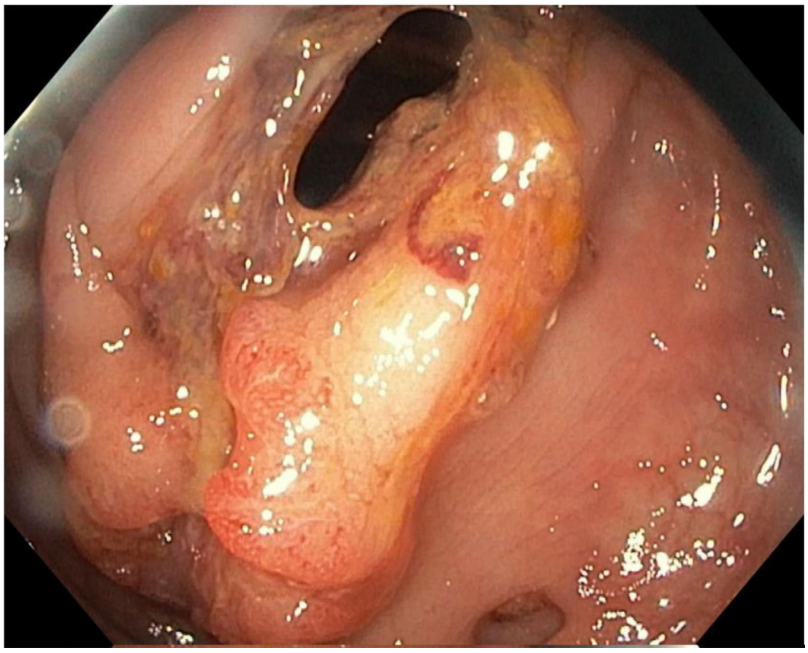

Fig. 3. Hepatic flexure adenocarcinoma during colonoscopy.

loss of MSH2, MLH1, MSH6, EPCAM and PMS2 genes [7]. Skin lesions are usually sebaceous adenoma or carcinomas, but also include basal cell carcinoma and keratoacanthomas with sebaceous differentiation and cystic sebaceous tumors. Colorectal malignancy is the most associated with MTS followed by malignancy of urogenital tract, endometrium, ovary, bladder, and kidney. Other cancers that are linked to MTS include those of prostate, pancreas, brain, lung, and hematological [1].

MTS diagnosis requires a thorough history and physical examination. Our patient had no family history of cancer but had personal history of two malignancies (melanoma and prostate cancer). Both were in locations associated with MTS. Sebaceomas typically present in head and neck regions, in MTS, they are usually found on the trunk [2]. This is consistent with our patient's sebaceoma location. Additional to skin examination, examining the oral mucosa is essential due to association of Fordyce spots (ectopic sebaceous glands).

Investigations involve biopsy of the skin tumor with immunochemistry (IHC) for MMR proteins, microsatellite instability analysis and genetic testing. Approximately 1/3 of MTS patients will not have any MMR proteins deficiency. In patients with a clinical suspicion of MTS but no variant in the MMR genes detected, testing for MUYTH mutation (base excision repair gene) should be done [2]. Patients with MMR deficiency but MMR and MUTYH genes abnormality should go on to have further analysis for biallelic somatic MMR mutation or hypermethylation of the MLH1 promoter region [3].

Differentiating sporadic colorectal malignancies from Lynch or MTS can also be done. Around 15% of sporadic colorectal malignancies will have loss of MLH1 proteins due to hypermethylation so this is not an accurate method of differentiation [7]. 85% of sporadic malignancies are associated with a mutation in the BRAF pV600E proto-oncogene. This aids in distinguishing diagnosis of a Lynch-related malignancy from sporadic colorectal malignancy. It is very rare for Lynch syndrome with a BRAF mutation [1].

Table 1. Mayo MTS Risk Score [4].

Criteria	Score
Age <60 years at first presentation of sebaceous tumors, including sebaceous adenomas, sebaceous epitheliomas, and sebaceous carcinomas	1
Two or more sebaceous tumors	2
Personal history of any Lynch-related cancers*	1
Family history of any Lynch-related cancers*	1

*Such as colorectal, endometrial, urothelial cancer.

Table 2. Recommendations for follow up strategies for Muir Torre syndrome [7].

Genetic testing of first-degree relatives
Annual skin checks for skin lesions
Surveillance colonoscopy ever 1-2 years, beginning at age 25 or 5 years before the youngest colorectal case in the family
Surveillance endoscopy with gastric antrum biopsy every 2-3 years, beginning at age 35
Annual urinalysis and cytology
Annual screening for endometrial and ovarian cancer

A risk scoring system (Mayo-MTS score, Table 1) was developed, which predicts the likelihood of having MTS [4]. A score > 2 indicates the need for genetic testing of the skin tumor. Furthermore, a retrospective study [5] suggests that genetic testing should be performed in those with a loss of MMR proteins on immunochemistry or in those with normal IHC results but a personal or family history of malignancy. Our patient, however, was declined genetic testing.

22% of MTS skin tumors precede the incidence of visceral malignancy [6], appropriate management of patients

presenting with a skin lesion could aid in earlier detection and prevention of malignancy. Our patient was declined a colonoscopy. On hindsight, our patient had advanced colon cancer. Had MTS been diagnosed months earlier or colonoscopy and genetic testing been offered, a different outcome may have resulted.

Revision of current investigation protocols for MTS is warranted, to extend past only investigating colorectal cancer as a Lynch-related cancer. Lynch syndrome demonstrates the wide array of visceral malignancies and perhaps routine investigation of MTS with urogenital tract cancers and sebaceous tumors should be inclusive to colonoscopy for colorectal cancer.

Specifically, the New Zealand criteria for routine colonoscopy surveillance and genetic testing to patients with loss of MMR proteins and history of malignancy, rather than just limiting to family history of Lynch syndrome, could lead to improved detection rates of MTS malignancies. Furthermore, appropriate follow-up for MTS patients is critical. Follow up strategies are similar to those used for Lynch syndrome monitoring (Table 2) [7].

CONCLUSION

Clinically diagnosed sebaceous cysts are very common and routine referrals remain acceptable. This case highlights the insidious presentation of MTS. Once suspected, clinical and family history must be correlated. Early intervention with multidisciplinary health professionals and geneticists is needed to improve screening for earlier staged cancers. More awareness around the multiple visceral malignancies associated with MTS is needed. Better understanding of the characteristic differences in clinical presentation of sebaceomas and immunohistochemistry can aid in earlier diagnosis of MTS.

Financial Disclosures

None to declare.

Consent

Written informed consent of the patient for the publication of his medical history has been obtained.

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None.

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