Cystic Sebaceous Neoplasms in Muir-Torre Syndrome

Jared J. Abbott, AB; Pablo Hernandez-Rios, MD; Robin H. Amirkhan, MD; Mai P. Hoang, MD

• Cystic sebaceous neoplasms have been seen only in patients with Muir-Torre syndrome (MTS) and have recently been characterized as marker lesions of MTS. Histologically, these lesions form a spectrum of tumors ranging from benign cystic adenomas to proliferative cystic sebaceous tumors. We describe 2 proliferative cystic sebaceous tumors in a 53-year-old man whose workup revealed colonic adenocarcinoma and other sebaceous tumors consistent with MTS. Both the chest wall and the left thigh masses were grossly cystic, measuring 1.0 and 1.5 cm, respectively. Histologic sections demonstrated well-circumscribed cystic neoplasms located in the deep dermis and subcutaneous tissue. Each had a focally infolded cyst wall composed of immature basaloid cells with prominent nucleoli and mitoses, consistent with a proliferative cystic sebaceous tumor. Recognition of cystic sebaceous neoplasm by pathologists and communication to clinicians of its strong association with MTS is of diagnostic importance.

(*Arch Pathol Lab Med.* 2003;127:614–617)

Muir-Torre syndrome (MTS) is an autosomal dominant syndrome defined by the presence of at least 1 sebaceous gland tumor and the presence of an internal malignancy.[1] Colorectal carcinoma is the most common form of internal malignancy in these patients.[1] The sebaceous neoplasms are typically adenomas, sebaceomas/sebaceous epitheliomas, or carcinomas. Cystic sebaceous neoplasms are seen only in patients with MTS and have recently been characterized as marker lesions of MTS.[2,3] We present 2 cystic sebaceous neoplasms in a patient whose workup revealed colonic adenocarcinoma and other sebaceous tumors consistent with MTS. Recognition of cystic sebaceous neoplasm by pathologists and communication to clinicians of its strong association with MTS are of diagnostic importance.

REPORT OF A CASE

A 53-year-old man presented with a cystic chest wall mass and shoulder nodules. These lesions were excised. The chest wall mass was a proliferative cystic sebaceous tumor, and the shoulder lesions were sebaceous epitheliomas. The possibility of MTS was raised. Subsequent colonoscopy and biopsy 6 months later revealed an invasive adenocarcinoma in the cecum, with metastatic carcinoma in 1 of 6 mesenteric lymph nodes. The patient underwent a right hemicolectomy without adjuvant chemotherapy. Therefore, the clinical diagnosis of MTS was confirmed by the presence of sebaceous neoplasms and colonic adenocarcinoma. Since that time, he has had sebaceous adenomas, sebaceous carcinomas, and actinic keratoses removed from his nose and cheek. Four years after excision of the proliferative cystic sebaceous tumor of the chest wall, he presented with a left thigh mass that had been present for 1.5 years. The clinical impression was an epidermal inclusion cyst. The mass was excised and was characterized histologically as another proliferative cystic sebaceous tumor. The patient's family history is significant for colonic adenocarcinoma in his father.

MATERIALS AND METHODS

Four-micrometer-thick sections were cut from paraffin blocks and stained with hematoxylin-eosin. Additional sections of a selected block were obtained for immunohistochemical study, which was performed on an automated immunostainer (Biotek System, Ventana Medical Systems Inc, Tucson, Ariz) using the standard avidin-biotin-peroxidase technique, the heat-induced epitope retrieval buffer, and primary antibody to epithelial membrane antigen (clone E29, dilution 1:200, Dako Corporation, Carpinteria, Calif).

PATHOLOGIC FINDINGS

The gross appearance of both the chest wall mass and the left thigh mass was cystic. The tumors measured 1.0 and 1.5 cm in diameter, respectively. Histologic sections demonstrated well-circumscribed cystic neoplasms located in the deep dermis and subcutaneous tissue. They were surrounded by thick fibrous capsule and filled with homogeneous eosinophilic material, most likely products of holocrine secretion (Figure, A). A flattened layer of epithelium was seen lining the cyst in certain areas. There was regular differentiation of the basaloid cells into sebaceous cells toward the center (Figure, B). In other areas, there was convoluted and infolded epithelium composed of approximately equal proportions of immature basaloid cells and sebaceous cells (Figure, C). Within this proliferative area, cytologic atypia and scattered mitoses were identified (Figure, D). The mature sebaceous cells were immunoreactive for epithelial membrane antigen (Figure, E).

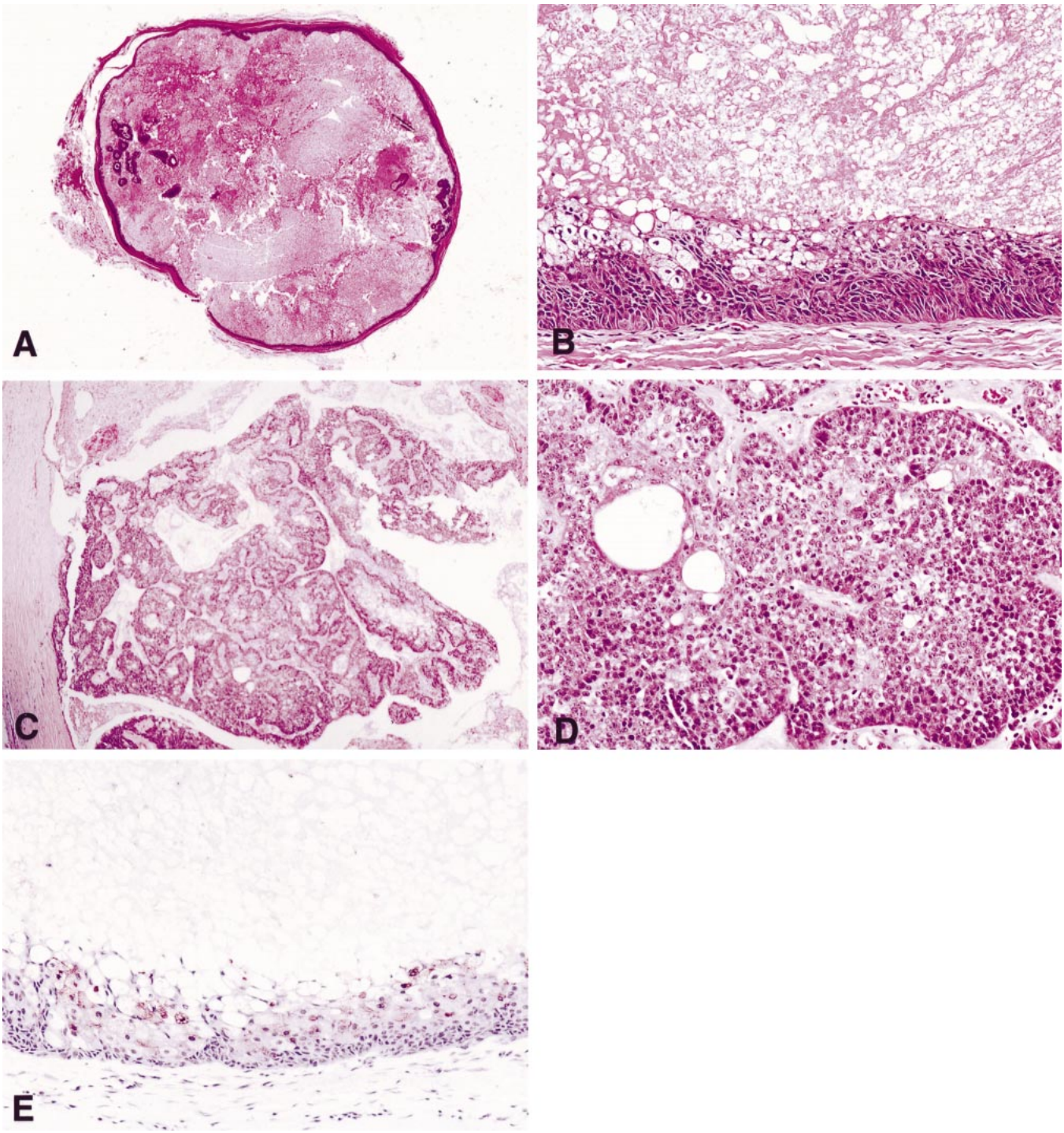
COMMENT

The diagnosis of MTS requires the presence of a sebaceous neoplasm in combination with at least 1 internal malignancy.[1] The skin lesions are most commonly sebaceous adenomas, but sebaceous epitheliomas and carcinomas also occur in MTS. Other common sebaceous neoplasms, such as sebaceous hyperplasia and steatocystoma, are not associated with MTS.[1] Keratoacanthomas are seen

Accepted for publication December 6, 2002.

From the Medical Scientist Training Program (Mr Abbott) and the Department of Pathology (Drs Hernandez-Rios, Amirkhan, and Hoang), the University of Texas Southwestern Medical Center, Dallas; and the VA North Texas Health Care System, Dallas (Dr Amirkhan).

Reprints: Mai P. Hoang, MD, Department of Pathology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9073 (e-mail: mai.hoang@utsouthwestern.edu).



A, A well-circumscribed cystic neoplasm in the deep dermis and subcutaneous tissue (hematoxylin-eosin, original magnification ×5). B, Differentiation of basaloid cells into sebaceous cells toward the center of the cyst (hematoxylin-eosin, original magnification ×200). C, Complex architecture of convoluting epithelium (hematoxylin-eosin, original magnification ×100). D, Cytologic atypia and mitotic figures were noted (hematoxylin-eosin, original magnification ×200). E, Epithelial membrane antigen expression by the sebaceous cells (epithelial membrane antigen immunoperoxidase, original magnification ×200).

in approximately 20% of patients with MTS, but do not define the clinical syndrome. Even the keratoacanthomas in MTS often have sebaceous differentiation, contrary to conventional keratoacanthomas.[4] The second key feature of MTS is internal malignancy. While most patients have only 1 malignancy, 2 or 3 different malignancies can be seen in 37% of the cases. The most common visceral neoplasm is colorectal carcinoma (51%). Of interest, most patients have colonic tumors proximal to the splenic flexure.[1] Other major internal neoplasms in MTS are carcinomas of the genitourinary tract (including bladder, renal pelvis, ovary, and uterus), breast carcinomas, and hematologic, head and neck, and small intestinal malignancies.[1]

The sebaceous neoplasms in MTS are unique and have

Clinicopathologic Features of Cystic Sebaceous Tumors in Muir-Torre Syndrome

Patient No.	Source	Age, y/Sex	Size, cm*	Location	Histopathology	Internal Malignancy
1	Rutten et al,[2] 1999; Kruse et al,[9] 1998; Kruse et al,[12] 2001	68/M	ND	Upper back	Cystic sebaceous adenoma	Colorectal and renal cancer
				Lower back	Proliferating cystic sebaceous tumor	
2	Rutten et al,[2] 1999; Kruse et al,[9] 1998	72/M	ND	Groin	Cystic sebaceous adenoma	Colorectal cancer
3	Rutten et al,[2] 1999; Kruse et al,[9] 1998; Kruse et al,[12] 2001	48/M	ND	Upper back	Proliferating cystic sebaceous tumor	Colorectal cancer
4	Rutten et al,[2] 1999	69/M	ND	Trunk	Proliferating cystic sebaceous tumor	Colorectal cancer
5	Rutten et al,[2] 1999	54/M	ND	Abdomen	Cystic sebaceous adenoma	Colorectal cancer
6	Rutten et al,[2] 1999	45/M	ND	Cheek	Cystic sebaceous adenoma	Colorectal and endometrial cancer
				Trunk	Cystic sebaceous adenoma	
7	Rutten et al,[2] 1999	58/M	ND	Elbow	Proliferating cystic sebaceous tumor	Renal cancer
				Trunk	Cystic sebaceous adenoma	
				Trunk	Proliferating cystic sebaceous tumor	
8	Rutten et al,[2] 1999	66/F	ND	Upper back	Proliferating cystic sebaceous tumor	Colon, breast, and endometrial cancer
9	Misago and Narisawa,[3] 2000	59/F	2.0	Chest wall	Proliferaing cystic sebaceous tumor	Colon cancer
	Current case	53/M	1.0	Chest wall	Proliferating cystic sebaceous tumor	Colon cancer
			1.5	Thigh	Proliferating cystic sebaceous tumor	

* ND indicates not documented.

unusual architectural patterns, such as cystic structures, solid basaloid sheets, mucinous areas, and convoluted glands.[5] Cystic sebaceous neoplasms have been seen so far only in patients with MTS and recently have been characterized as marker lesions of MTS.[2,3] A total of 9 patients with cystic sebaceous neoplasms associated with MTS have been described in the literature to date. The clinicopathologic data for these 9 patients, together with the data for our patient, are summarized in the Table. The ages of the patients ranged from 45 to 72 years (median, 58 years). Most cystic sebaceous neoplasms tend to occur on the trunk and are cystic dermal structures with no epidermal connection. In contrast, conventional sebaceous neoplasms tend to be located on the head and neck area, and are superficially located with connections to the epidermis.

Histologically, cystic sebaceous neoplasms associated with MTS constitute a spectrum of tumors ranging from benign cystic adenomas to proliferative cystic sebaceous tumors. Cystic sebaceous adenomas have a thin cyst wall lined with basaloid cells exhibiting regular maturation into sebaceous cells toward the center.[2] There are no or few mitotic figures. On the other hand, proliferative cystic sebaceous tumors have a lobulated growth pattern in addition to the cystic pattern. Basaloid cells, cytologic atypia, and mitoses are prominent features.[2] Our patient's tumors demonstrated a focally infolded cyst wall composed of immature basaloid cells with prominent nucleoli and mitoses. Their sebaceous differentiation is confirmed by epithelial membrane antigen expression. These features are consistent with proliferative cystic sebaceous tumors.

Because of their large size, deep location, and cytologic atypia, cystic sebaceous neoplasms could represent well-differentiated sebaceous carcinomas. The biologic behavior of cystic sebaceous neoplasms is not known. There have been no reported recurrences or metastases in cystic sebaceous neoplasms.[2] In the setting of multiple lesions, they can be diagnosed as metastatic sebaceous carcinomas. This possibility is unlikely in our case, since the cystic sebaceous tumor on the chest presented 3 years prior to the diagnosis of sebaceous carcinoma of the nose. The differential diagnosis of our tumors also includes basal cell carcinoma with sebaceous differentiation, intradermal sebocrine adenoma with cystic degeneration and hemorrhage, and conventional sebaceous neoplasms with cystic degeneration. Although basal cell carcinoma can be cystic, it would be predominantly nodular and exhibit peripheral palisading and clefting from the adjacent stroma. Our tumors do not have either apocrine differentiation or intraepidermal pagetoid spread, as seen in intradermal sebocrine adenoma with cystic degeneration and hemorrhage.[6] Lastly, other sebaceous neoplasms in the context of MTS can undergo cystic degeneration.[5] However, those tumors are predominantly solid with only focal cystic changes due to degeneration. In addition, they lack the overall cystic architecture and the surrounding thick fibrous capsule.

While MTS is defined by clinical presentation, molecular pathology has brought a new understanding of its genetic origin. First understood as an autosomal dominant syndrome with high penetrance and variable expression,[4] clues concerning the molecular origin of MTS are emerging. Similarity between MTS and hereditary nonpolyposis colorectal cancer was noticed years ago, and MTS was postulated to be the full phenotypic expression of hereditary nonpolyposis colorectal cancer.[7] This relationship was solidified when 69% of tumors from MTS patients were found to exhibit microsatellite instability in a minimum of 40% of markers tested.[8–10] The vast majority of mutations (usually truncated mutants) occurred on the *MSH2* or *MLH1* genes, which are involved in DNA mismatch repair.[11] During replication, the mismatch repair

system fixes errors in repeat sequences of the DNA (microsatellites). Deficiency in this process results in accumulating mutations of these microsatellites (microsatellite instability). The mechanism of tumorigenesis follows the ''two-hit'' hypothesis, in which one mutant allele is inherited and the other is the result of somatic mutation. The mechanism of this process is being explored, and current research indicates that loss of heterozygosity is not the preferred mode of inactivation.[12] Molecular analysis of 10 cystic sebaceous tumors revealed microsatellite instability in 100% of cases and *MHS2* mutations in 50% of cases.[2] Microsatellite instability is found even in actinic keratoses of MTS patients, while it is rarely seen in skin cancers of non-MTS patients.[13] These advances in understanding the molecular pathogenesis of MTS will allow a combination of immunohistochemical staining and microsatellite instability analysis to impact screening for MTS in individuals with characteristic skin lesions before the development of visceral tumor.[14] Further investigation is needed to explain the predisposition for development of sebaceous neoplasms in MTS and their unique cystic appearance.

References

1. Schwartz RA, Torre DP. The Muir-Torre syndrome: a 25-year retrospect. *J Am Acad Dermatol.* 1995;33:90–104.
2. Rutten A, Burgdorf W, Hugel H, et al. Cystic sebaceous tumors as marker lesions for the Muir-Torre syndrome. *Am J Dermatopathol.* 1999;21:405–413.
3. Misago N, Narisawa Y. Sebaceous neoplasms in Muir-Torre syndrome. *Am J Dermatopathol.* 2000;22:155–161.
4. Schwartz RA, Goldberg DJ, Mahmood F, et al. The Muir-Torre syndrome: a disease of sebaceous and colonic neoplasms. *Dermatologica.* 1989;178:23–28.
5. Burgdorg WHC, Pitha J, Fahmy A. Muir-Torre syndrome: histologic spectrum of sebaceous proliferations. *Am J Dermatopathol.* 1986;8:202–208.
6. Mahalingam M, Byers HR. Intra-epidermal and intra-dermal sebocrine adenoma with cystic degeneration and hemorrhage. *J Cutan Pathol.* 2000;27:472–475.
7. Lynch HT, Lynch PM, Pester J, Fusaro RM. The cancer family syndrome: rare cutaneous phenotypic linkage of Torre's syndrome. *Arch Intern Med.* 1981;141:607–611.
8. Bocker T, Diermann J, Friedl W, et al. Microsatellite instability analysis: a multicenter study for reliability and quality control. *Cancer Res.* 1997;57:4739–4743.
9. Kruse R, Rutten A, Lamberti C, et al. Muir-Torre phenotype has a frequency of DNA mismatch-repair-gene mutations similar to that in hereditary nonpolyposis colorectal cancer families defined by the Amsterdam criteria. *Am J Hum Genet.* 1998;63:63–70.
10. Entius MM, Keller JJ, Drillenburg P, Kuypers KC, Giardiello FM, Offerhaus GJA. Microsatellite instability and expression of hMLH-1 and hMSH-2 in sebaceous gland carcinomas as markers for Muir-Torre syndrome. *Clin Cancer Res.* 2000;6:1784–1789.
11. Kruse R, Lamberti C, Wang Y, et al. Is the mismatch repair deficient type of Muir-Torre syndrome confined to mutations in the hMSH2 gene? *Hum Genet.* 1996;98:747–750.
12. Kruse R, Rutten A, Hosseiny-Malayeri HR, et al. ''Second hit'' in sebaceous tumors from Muir-Torre patients with germline mutations in *MSH2*: allele loss is not the preferred mode of inactivation. *J Invest Dermatol.* 2001;116:463–465.
13. Quin AG, Healy E, Rehman I, Sikkink S, Rees JL. Microsatellite instability in human non-melanoma and melanoma skin cancer. *J Invest Dermatol.* 1995;104:309–312.
14. Southey MC, Young MA, Whitty J, et al. Molecular pathologic analysis enhances the diagnosis and management of Muir-Torre syndrome and gives insight into its underlying molecular pathogenesis. *Am J Surg Pathol.* 2001;25:936–941.