Muir-Torre syndrome – an uncommon localization of sebaceous carcinomas following irradiation

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To the Editor,

Muir Torre syndrome (MTS) represents a rare genodermatosis characterized by cutaneous sebaceous tumors and/or keratoakanthomas preceding or existing coincidently with one or more visceral malignancies [1,2]. Colorectal (47%) and urogenital (21%) malignancies predominate, and nearly half of the patients have two or more solid cancers [3]. It is an autosomal dominant disorder with variable penetrance, which is moleculargenetically characterized by mutations of DNA mismatch repair genes. Up to now germline mutations in MLH1, MSH 2, MSH 6 and PMS 2 have shown to be associated with MTS [4]. Mutations in MSH 2 and MLH 1 genes lead to microsatellite instability (MSI) within DNA promoting further tumor development. Typically, visceral malignancies are accompanied by sebaceous lesion located most commonly in the head and neck region [5]. Up to now the role of further predisposing factors in tumor development is still being discussed [4]. Several reports demonstrated that deterioration of immune system factors may be associated with the number of sebaceous tumors in MTS patients [6]. We report about a patient presenting with a single, uncommon localization of sebaceous carcinoma. The history of radiotherapy possibly did promote the expression of MTS in this patient with tumor formation inside the irradiation field.

Case presentation

A 45-year-old woman presented for the evaluation of a 15 mm-diameter cutaneous nodule at the right lower pelvic wall, which was observed for several months. The patient complained about local pruritus but did not report any further symptoms.

The patient had undergone hysterectomy for moderately differentiated endometrial carcinoma

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(Received 6 June 2011; accepted 28 June 2011)

ISSN 0284-186X print/ISSN 1651-226X online © 2012 Informa Healthcare
DOI: 10.3109/0284186X.2011.602644

(stage IIB) eight years before. Additionally adjuvant irradiation of the pelvic lymph node regions had been administered. A total dose of 50.4 Gy plus intravaginal brachytherapy (3 × 5 Gy) had been applied. Irradiation had been tolerated without any complaints, especially no cutaneous side effects did occur. She had been doing well with no evidence of metastatic disease for the eight following years.

A significant family history of cancer was identified. Specifically, a sister had been diagnosed with endometrial cancer and her mother with both endometrial cancer and colon cancer. Her mother died several years ago due to progressive brain tumor of unknown histology. Additionally, her maternal uncle was diagnosed with kidney cancer in his late forties.

On physical examination no further skin lesions were observed. The subdermal nodule was resected completely. The histopathologist confirmed the diagnosis of sebaceous carcinoma. The tumor was covered by normal epidermis.

Despite complete resection 12 weeks later a small (7 mm) subdermal lesion was excised as local recurrence, which was histopathologically proven to be a metastasis of the known sebaceous carcinoma. A staging CT-scan did not show evidence of further tumor manifestations and the tumor markers (CA125; CA 19-9 and CEA) were normal. Colonoscopy and gastroscopy revealed no further lesions.

Based on both, her individual and family history immunohistochemical and moleculargenetic testings were performed. MSI was determined by PCR-based analysis of dinucleotide repeat polymorphisms. DNA was extracted from paraffin embedded tissue as described previously [4]. Microsatellite markers used were BAT-25, BAT-26, D2S123, D17S250 and D5S346. All PCR's were performed on a MJ PTC200 Thermocycler (Biometra, Göttingen, Germany), PCR products were analysed on an API Prism 3130 genetic analyzer (Applied Biosystems, Darmstadt, Germany). This DNA-based test uses polymerase chain reaction amplification of specific loci with chromatographic determination of amplicon sizes to detect alterations in the length of the tested microsatellite.

On immunohistochemistry the primary uterine carcinoma and the sebaceous carcinomas showed loss of nuclear expression in MSH2 and MSH6. All tumor samples enrolled in this evaluation confirmed MSI of at least two markers (BAT-25 and BAT-26). A genetic shift with increased variability for the loci BAT-25 and BAT-26 could be observed between the primary uterine tumor and the sebaceous carcinomas from the same patient (Figure 1). Moleculargenetic analysis of the endometrioid carcinoma revealed MSI for all loci analyzed. Complete data of MSI by molecular markers and immunohistochemical methods are described in Table I.

Discussion

MTS is an autosomal dominant disorder with variable penetrance. It is defined by the occurrence of at least one sebaceous gland tumor and one visceral malignancy. Association of sebaceous carcinomas with other malignancies was first described in 1967 by Muir et al. [1] and Torre [2].

Due to the rarity of this tumor there is a lack of information about epidemiologic factors. Akthar et al. [7] identified 205 cases of MTS in the literature

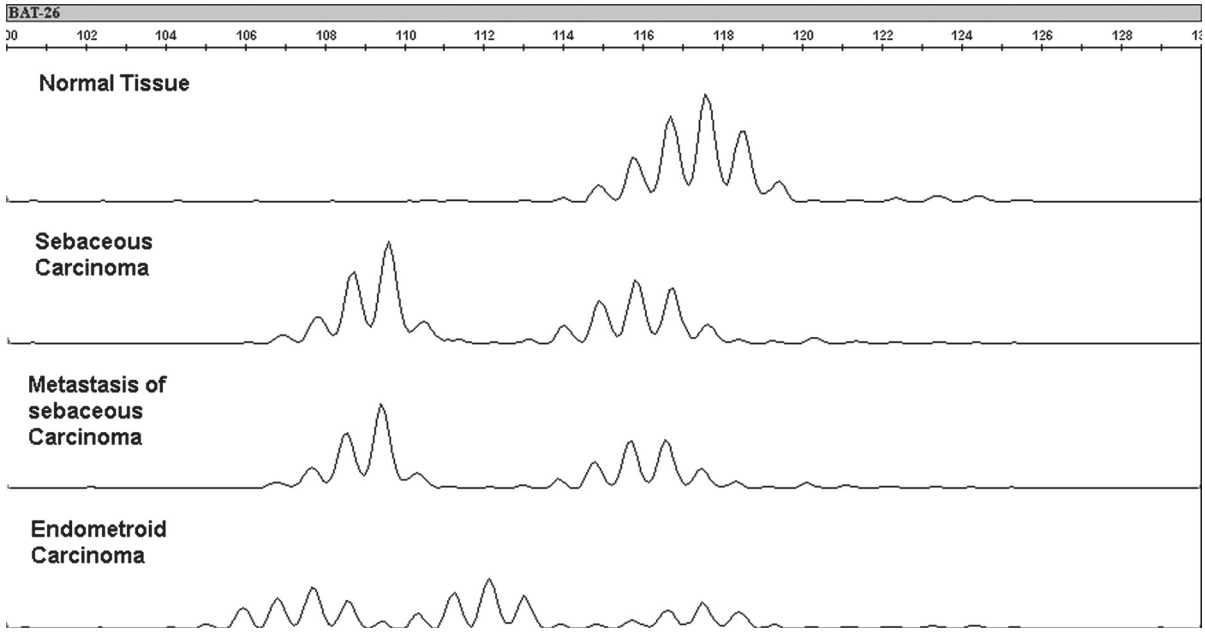

Figure 1. Microsatellite instability results confirming a genetic shift between the primary uterine cancer and the sebaceous carcinomas.

Table I. Moleculargenetic characterization: Result of microsatellite instability by molecular and immunohistochemical methods.

	Normal Tissue	Endometrioid Carcinoma	Sebaceous carcinoma	Metastasis of the sebaceous carcinoma
BAT-25	Stable	Instable*	Instable	Instable
BAT-26	Stable	Instable*	Instable	Instable
D2S123	Stable	Instable	Stable	Stable
D17S250	Stable	Instable	Stable	Stable
D5S346	Stable	Instable	Stable	Stable
MLH1	positive	positive	positive	positive
MSH2	positive	negative	negative	negative
MSH6	positive	negative	negative	negative
PMS2	positive	positive	positive	positive

*Not identical instability with sebaceous carcinoma and the metastasis of the sebaceous carcinoma.

and describe predominance in men. The age at presentation of the first malignant disease ranges from 21 to 88 years. The appearance of sebaceous tumors often is followed by further visceral malignancies [8]. In such cases, cutaneous neoplasm may serve as visible markers of subsequent tumor development. As shown in our case, the diagnosis of MTS is usually based on the association of sebaceous tumors with cancer history and/or family history of malignant diseases. Colden et al. [9] reported that 40% to 50% of MTS patients suffered from two or more malignant tumors, 10% had more than four in their history. Of the documented cases colorectal cancer is the most common type of neoplasia and the most frequent initial cancer [10]. Endometrial tumors are described in 15% of female MTS patients, as also seen in our case. In general, tumors of the genitourinary tract (endometrium, ovary, bladder, ureter and kidney) represent approximately 25% to 30% of MTS malignancies [4,10].

Sebaceous gland tumors have the potential to arise from any sebaceous gland of the body. Tumors present as painless, slowly growing intraepidermal mass, usually located at the face on the eyelid or head and neck region [11]. Interestingly in our case sebaceous carcinomas were located at the pelvic region. Review of the literature did not reveal any report about MTS sebaceous carcinomas originating from glands at the lower abdominal or pelvic wall [8,12,13]. Re-evaluation of the irradiation fields calculated a mean total dose of 31 Gy on body surface in this area, applied eight years before. Ultraviolet radiation and immune suppression are known cofactors for the development of sebaceous gland hyperplasias [14]. Several investigators report, that the development of new sebaceous tumors may increase in parallel with the deterioration of the immune system. Immunsuppression either as a part of disease or of treatment may evoke clinical features of MTS [6,14]. The very untypical localization of sebaceous tumors described in our case support the hypothesis, that the radiotherapy of the uterine cancer applied eight years before may have induced the skin tumor growth and initiated expression of a latent MTS phenotype. Furthermore irradiation does interfere with the DNA mismatch repair system, which is typically involved in tumorigenesis in MTS patients. Molecular genetic investigations have demonstrated an association with germ-line mutations in one of the DNA mismatch repair genes MLH1 and MSH 2 in about 90% of MTS cases. Recently patients have been reported with mutations in MSH 6 [4,15]. Less commonly DNA mismatch repair proteins MSH3, MLH 3, PMS1 and PMS 2 are involved [4]. These proteins identify and repair errors in base pairing occurring during DNA replication. Furthermore pathogenic mutations of MSH2 may be linked to other subsequent moleculargenetic changes that might be involved in skin carcinogenesis [16].

Immunhistochemical analysis with antibodies against the lost mismatch proteins [5,13] and testing for MSI are the main moleculargenetic methods for diagnosis of MTS. Immunohistochemically, genetic involvement of MSH 2 and MSH 6 was confirmed for our patient in all tumor samples examined (uterine cancer and sebaceous cancers) (Table I). A lack of immunoreactivity within tumor cells is indicative for a mutation in the gene and has been shown to correlate significantly with high levels of MSI. Microsatellites are especially prone to replication errors and have been described in MTS patients in up to 90% of cases [17]. Interestingly, we could confirm in our case a genetic shift in MSI with increased variability for the loci BAT-25 and BAT-26 comparing the genetic pattern of the primary uterine tumor with the sebaceous carcinomas from the same patient (Figure 1). Especially in our patient initial irradiation of the uterine carcinoma may have induced the shifting of the MSI pattern. Radiation exposure is known to trigger allelic loss, which promotes the inability to arrest the cell cycle or to induce apoptosis [16].

In conclusion, tumorigenic factors for the expression of a latent MTS phenotype are still under investigation. Early identification of sebaceous lesions in cancer patients is important to identify the Muir Torre syndrome. Microsatellite instability analysis and immunohistochemistry should be used to evaluate the status of DNA mismatch repair proteins in diagnostic work-up. Up to now several reports suggest, that immunsuppression may promote expression of MTS phenotype.

We demonstrate in our case that prior radiation exposure may play a role in the development and localization of skin lesions in MTS.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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