EJGO European Journal of Gynaecological Oncology

Adenocarcinoma of the cervix associated with a neuroendocrine small cell carcinoma of the cervix in the spectrum of Muir-Torre syndrome

P. Donati[1], G. Paolino[2], M. Donati[1], C. Panetta[1]

[1]Dermatopathological Laboratory "San Gallicano Institute of Rome", Rome
[2]Clinica Dermatologica, La Sapienza University of Rome, Rome (Italy)

Summary

Muir-Torre syndrome (MTS) is an autosomal genodermatosis that is diagnosed by the presence of at least one sebaceous gland tumor and at least one visceral malignancy. The most frequent visceral malignancies reported in literature are low-grade colon-rectal and genitourinary cancers, with prolonged survival. The authors report the case of a 52-year-old female, with a positive familial history for MTS, who developed a cutaneous sebaceous carcinoma, a synchronous colon-rectal adenocarcinoma, and a metachronous endocervical adenocarcinoma associated with a neuroendocrine small cell carcinoma of the cervix (SCNC), with lymph node metastasis. The rare occurrence in literature of the cervical SCNC and the rarest occurrence of a neuroendocrine carcinoma in the context of a MTS deviate from the usual and low-grade types of cancers normally described with MTS. It should be always appropriate to assess any symptoms that might reveal an underlying malignancy, although not within the spectrum of neoplasms most associated with this rare syndrome

Key words: Muir-Torre syndrome; Sebaceous carcinoma; Adenocarcinoma; Neuroendocrine small cell carcinoma of the cervix.

Introduction

Muir-Torre syndrome (MTS) is an autosomal genodermatosis that is diagnosed by the presence of one sebaceous gland tumor and at least one visceral malignancy [1]. Cutaneous neoplasms diagnostic for MTS include sebaceous adenomas, sebaceous epitheliomas, sebaceous carcinomas, and keratocanthoma; these tumors, develop often after an internal malignancy presentation [2]. While, the most frequent visceral malignancies, reported in literature, are low-grade colon-rectal and genitourinary cancers [1].

Neuroendocrine small cell carcinoma of the cervix (SCNC) is a rare subtype of cervical cancer with an aggressive behavior, that deviate from the usual low-grade types of cancers normally associated with MTS [1-2].

The authors report the case of a 52-year-old female, with a positive familial history of MTS, who progressively developed synchronous and metachronous malignancies.

Case Report

A 52-year-old Caucasian female, presented to the present Department with a three-month history of a nodule arising in the left nipple; the lesion (1.2 x 1 cm) was firm and showed a central portion slightly ulcerated and did not produce secretions. (Figure 1A)

At the general clinical examination, the patient did not have any other cutaneous lesions, which could require further investigations. Three years prior the patient had removed, in another Institute, a sebaceous adenoma on the frontal region. In the family history, the patient presented two brothers with a positive history of Muir-Torre syndrome (MTS), diagnosed two years prior.

A surgical excision of the cutaneous lesion of the nipple was performed. Histologic examination of the skin biopsy showed a poorly circumscribed epidermoid-follicular proliferation (Figures 1A-C); the keratinocytes showed variably sebaceous differentiation, characterized by remarkably vacuolated neoplastic cells. The nuclei were large with visible nucleoli and scattered mitoses. (Figure 1D) Based on these histopathological findings, a final diagnosis of sebaceous carcinoma was made.

One month after, during a colonoscopy, an asymptomatic polypoid lesion of the transverse colon was removed. At the histological examination, the lesion was compatible with an adenocarcinoma (Figure 2A) with focal aspects of mucinosis (G2). The lesion infiltrated the muscle layer thickness, with a little desmoplastic reaction and a poor inflammatory infiltrate (pT2N0). For this reason, a partial colectomy was performed.

According to the patient's history and to the familial history, the authors decided to perform a molecular evaluation, which showed a mutation in the eson7- gene MSH2; this mutation, was the same detected also in her two brothers. A final diagnosis of MTS was made.

Seven months later, the patient experienced metrorrhagia; during the gynecological visit, a biopsy of a friable mass in the proximal endocervical canal was performed. Histological examination revealed a poorly differentiated endocervical adenocarcinoma (Figure 2B). However, at higher magnification, in the lower limit of the adenocarcinomatous tumor, there was an atypical bluish epithelioid small cell population, arranged as cords, with trabecular pattern (Figure 2C). Cytologically, these cells were oval to polygonal with iperchromatic nuclei (Figure 2C). This cell pop-

Revised manuscript accepted for publication December 30, 2013

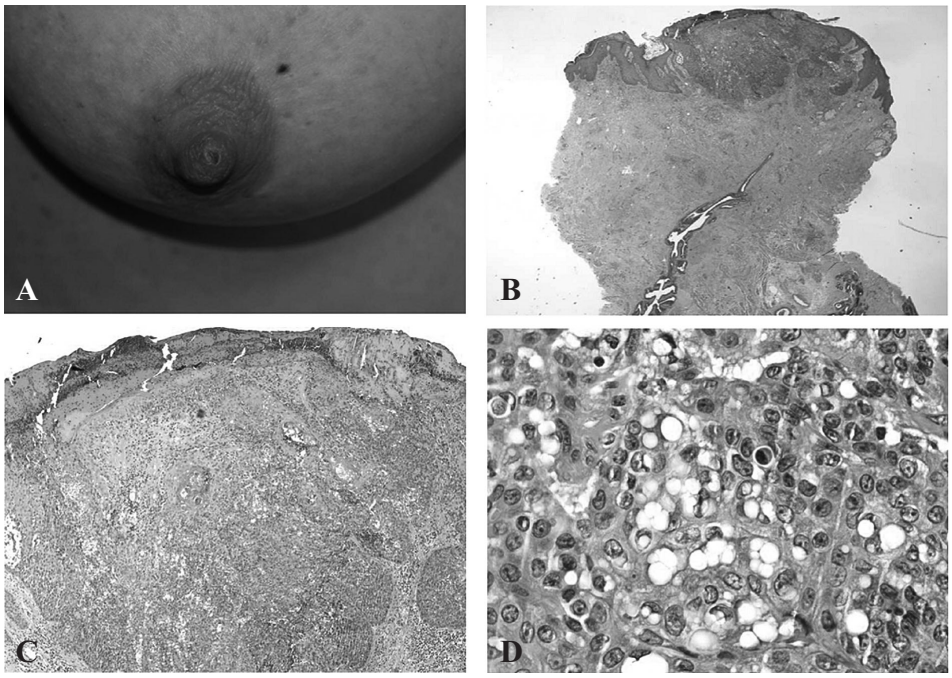

Figure 1. — A) A firm ulcerated nodule of the nipple; B) epidermoid and follicular proliferation, poorly circumscribed and asymmetrical (H-E x2.5); C) ulcerated nodule, consisting of epithelial cellular elements, in part keratinizing and in part of clear cells. (H-E x10); D) atypical epithelial elements associated with numerous vacuolated cells (H-E x40).

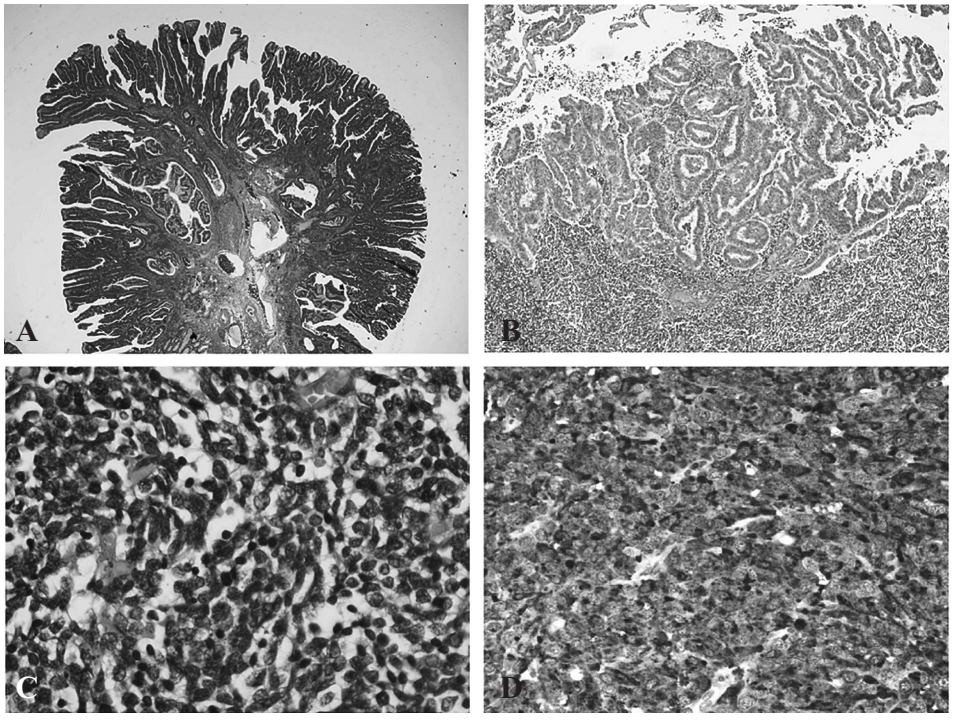

Figure 2. — A) Adenocarcinomatous polyp of the transverse colon (H-E x2.5); B) adenocarcinoma of the endocervix with underlying an atypical bluish epithelioid small cell population (H-E, x10); C) neuroendocrine small cell cancer of the endocervix (H-E x20); D) tumor cells positive for chromogranin (x20).

ulation was positive for chromogranin (Figure 2D), synaptophysins, CD10 and CD56; while it was negative to cytokeratin 20 (CK 20) and TTF-1. A final diagnosis of an adenocarcinoma associated with a neuroendocrine small cell carcinoma (SCNC) of the endocervix was made.

A total hysterectomy associated with a lymphadenectomy of left and right pelvic lymph nodes and of the lumbar-aortic lymph nodes was performed; one lymph node was found to be metastatic by SCNC component (pT1b1, pN1; FIGO Stage IIIB).

Currently the patient is carrying out chemotherapy treatments with periodic imaging studies.

Discussion

MTS is a dominant condition characterized by the simultaneous presence of visceral malignancies and skin tumors (particularly sebaceous gland tumors). The principal muta-

tions involved in this uncommon syndrome interest genes encoding DNA mismatch repair proteins as hMLH1 or hMSH2 and, less commonly, MSH6, MSH3, MLH3, PMS1, and PMS2 [3-7]. An association with the mutation in MuY homolog (MYH), a base excision repair gene, was found in MTS patients without mismatch repair deletions [8].

MTS is actually considered to be a clinical variant of the non-polyposis colon rectal cancer syndrome (HNPCC, Lynch syndrome) since approximately 30 to 70 percent of patients with HNPCC present a germ-line mutation in the hMLH1 or hMSH2 gene [6].

In the general population with MTS, the cutaneous neoplasms appear often after the presentation of a visceral cancer; however there are rare cases, where the cutaneous cancers develop before the internal malignancies or where they are synchronous [2-4]. The absence of preceding clinical and instrumental controls, may have caused the contemporary diagnosis in our patient of the sebaceous carcinoma and adenocarcinoma of the transverse colon.

Although initially the colon-rectal carcinoma was believed to be the only and principal type of cancer in association with MTS, it was observed that MTS patients show an increased risk to develop various malignancies [5]. In fact, from when MTS was discovered in 1967 [9], several types of cancers have been found associated with this uncommon syndrome; among these malignancies, cases of neuroendocrine tumors have not been reported.

Neuroendocrine SCNC is a rare subtype of cervical cancer with an aggressive behavior (with lymph nodal tropism), which accounts for only 1% of uterine cervical cancers [10, 11]. The present cervical tumor was constituted by an adenocarcinomatous component and by a SCNC component. In literature, only one other case of SCNC of the cervix associated with an endocervical adenocarcinoma has been described in 2007 by Alphandery *et al.*, but the patient did not present a MTS [11]. Patients, with apparent Lynch syndrome, that had an adenocarcinoma and a neuroendocrine tumor or an adenocarcinoma with neuroendocrine features, have been reported in literature [12-15]. However, until now, have not been reported in association with MTS.

Summarizing, the rare occurrence of the cervical SCNC and the rarest occurrence of a neuroendocrine carcinoma in the context of a MTS, deviate from the usual and low-grade types of cancers normally described with MTS [1-2].

The authors think that this report is further evidence of how more new malignancies can be found to be associated with MTS and how it should be always be appropriate to analyze any symptoms that might reveal an underlying malignancy, although not within the spectrum of neoplasms most associated with this rare syndrome.

References

[1] Landis M.N, Davis C.L., Bellus G.A.: "Immunosuppression and sebaceous tumors: a confirmed diagnosis of Muir-Torre syndrome unmasked by immunosuppressive therapy". *J. Am. Acad. Dermatol.*, 2011, *65*, 1054.

[2] Davis D.A., Cohen P.R.: "Genitourinary tumors in men with the Muir-Torre syndrome". *J. Am. Acad. Dermatol.* 1995, *33*, 909.

[3] Akhtar S., Oza K.K., Khan S.A., Wright J.: "Muir-Torre syndrome case report of a patient with concurrent jejunal and ureteral cancer and a review of the literature. *J. Am. Acad. Dermatol.* 1999, *41*, 797.

[4] Cesinaro A.M., Ubiali A., Sighinofili P., Trentini G.P., Gentili F., Facchetti F.: "Mismatch repair proteins expression and microsatellite instability in skin lesions with sebaceous differentiation: a study in different clinical subgroups with and without extracutaneous cancer". *Am. J. Dermatopathol.*, 2007, *29*, 351.

[5] Shalin S.C., Lyle S., Calonje E., Lazar A.J.: "Sebaceous neoplasia and the Muir-Torre syndrome: important connections with clinical implications". *Histopathology*, 2010, *56*, 133.

[6] Higgins H.J., Voutsalath M., Holland J.M.: "Muir-torre syndrome: a case report". *J. Clin. Aesthet. Dermatol.*, 2009, *2*, 30-2

[7] Schwartz R.A., Torre D.P.: "The Muir-Torre syndrome: a 25-year retrospect". *J. Am. Acad. Dermatol.*, 1995, *33*, 90.

[8] Guillén-Ponce C., Castillejo A., Barberá V.M., Pascual-Ramírez J.C., Andrada E., Castillejo M.I., *et al.*: "Biallelic MYH germline mutations as cause of Muir-Torre syndrome". *Fam. Cancer*, 2010, *9*, 151.

[9] Muir E.G., Bell A.J., Barlow K.A.: "Multiple primary carcinoma of the colon, duodenum, and larynx associated with kerato- acanthomata of the face". *Br. J. Surg.*, 1967, *54*, 191.

[10] Tokunaga H., Nagase S., Yoshinaga K., Tanaka S., Nagai T., Kurosawa H., *et al.*: "Small cell carcinoma of the uterine cervix: clinical outcome of concurrent chemoradiotherapy with a multidrug regimen". *Tohoku J. Exp. Med.*, 2013, *229*, 75.

[11] Alphandery C., Dagrada G., Frattini M., Perrone F., Pilotti S.: "Neuroendocrine small cell carcinoma of the cervix associated with endocervical adenocarcinoma: a case report". *Acta Cytol.,* 2007, *51*, 589.

[12] Sorscher S., Saroya B.: "A molecularly confirmed neuroendocrine tumor resulting from Lynch Syndrome". *J. Gastrointest. Oncol.*, 2013, *4*, 95.

[13] Wagner D.G., Gatalica Z., Lynch H.T., Kohl S., Johansson S.L., Lele S.M.: "Neuroendocrine-type prostatic adenocarcinoma with microsatellite instability in a patient with lynch syndrome". *Int. J. Surg. Pathol.*, 2010, *18*, 550.

[14] Miquel C., Sabourin J.C., Elias D., Grandjouan S., Viguier J., Ducreux M.: "An appendix carcinoid tumor in a patient with hereditary non polyposis colorectal cancer". *Hum. Pathol.*, 2004, *35*, 1564.

[15] Rodriguez-Bigas M.A., Vasen H.F., Lynch H.T., Watson P., Myrhøj T., Järvinen H.J., *et al.*: "Characteristics of small bowel carcinoma in hereditary non-polyposis colorectal carcinoma". International Collaborative Group on HNPCC". *Cancer*, 1998, *83*, 240.

Address reprint requests to:
G. PAOLINO, M.D.
Clinica Dermatologica,
La Sapienza University of Rome,
Viale del Policlinico 15, 00186 Rome (Italy)
e-mail: gio8519@libero.it