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Mycosis fungoides (CTCL) associated with colorectal adenocarcinoma. A rare case of combined response to neoadjuvant therapy.

Mycosis fungoides (MF) is a well-known and common form of cutaneous T-cell lymphoma (CTCL), composed of malignant proliferation of CD4+CD45Ro+helper memory T cells. In the patient with MF, the incidence of secondary malignancies is higher than general population but very few cases with both MF and colorectal adenocarcinoma have been reported.
Herein we describe a case of MF occurring in a 64-year-old man and followed, five months later, by a diagnosis of colorectal adenocarcinoma. Of notice, simultaneous regression of both rectal mass and cutaneous MF manifestations was observed after administration of chemioradiation therapy prior to rectal surgery. The patient is alive and in stable clinical remission at eight years from the diagnosis.

KEY WORDS: CTCL, Colorectal adenocarcinoma, Mycosis fungoides, PUVA

Introduction

Mycosis fungoides (MF) is a well-known and common form of cutaneous T-cell lymphoma (CTCL), which consists of malignant proliferation of CD4+ CD45Ro+ helper memory T cells. Clinical onset is insidious [1]. At earlier stages it is usually confined to the skin, starting as small patches and plaques, and finally progresses to systemic involvement. The aetiology is still unknown. Patients with MF show higher incidence of secondary malignancies than general population but very few cases with both MF and colorectal adenocarcinoma have been described. Herein we report a case of a 64-year-old man who firstly had a diagnosis of MF followed, 5 months later, by a diagnosis of colorectal adenocarcinoma. The patient is alive and maintains stable remission at four years from the diagnosis. This peculiar, almost unique case in literature confirms the correlation between MF and secondary neoplasms, arguably based on the carcinogenic effects of the therapies received, immunosuppression connected with MF and treatments administered, and, furthermore, underlying genetic alterations in the mechanisms of tumour suppression.

Case Report

In July 2012, a 64-year-old man was admitted at the Surgery Rehabilitation Department of University Federico II of Naples, Italy, for evaluation of atypical, pruritic, persistent cutaneous plaques appeared approximately five years before. At clinical examination they

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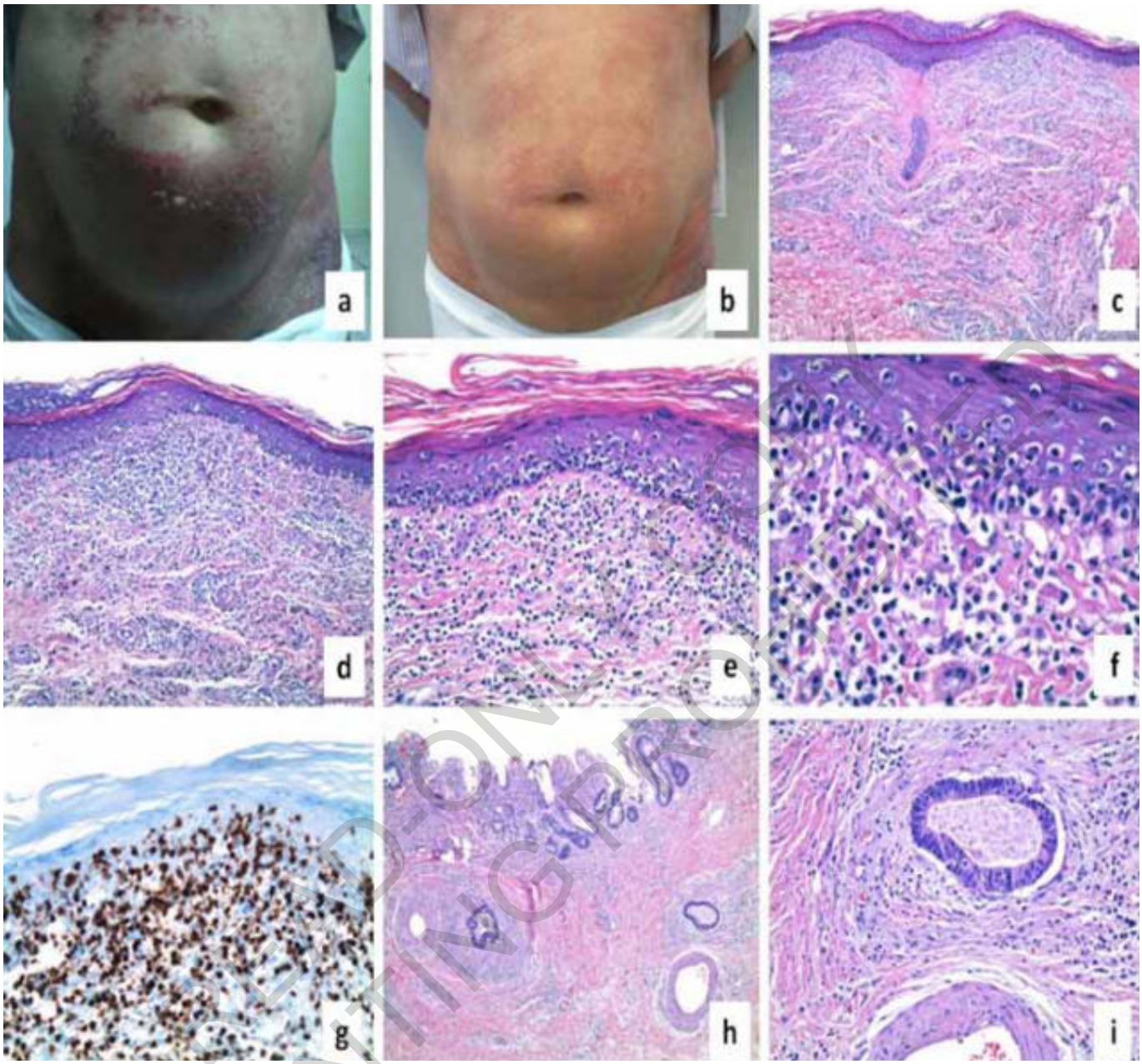

Fig. 1:
a) before neoadjuvant therapy: reddish plaques on the abdomen;
b) after neoadjuvant therapy: clinical remission;
c) histology of skin biopsies: dense lymphoid infiltrate within a thickened fibrotic papillary dermis (hematoxylin and eosin, x5)
d) higher magnification of lymphoid infiltrate (hematoxylin and eosin, x10);
e) note prominent epidermotropism of lymphocytes (hematoxylin and eosin, x20)
f) higher magnification showing epidermotropism (hematoxylin and eosin, x40);
g) diffuse positivity for CD3 (immunostaining for CD3, x20);
h) histology of rectal cancer: small nests of residual well differentiated tumour (hematoxylin and eosin, x5);
i) higher magnification of residual rectal tumour (hematoxylin and eosin, x20).

were irregularly round-shaped, scaly, slightly raised, and disseminated on the whole body (Fig. 1a). Biopsies for histopathological analysis were performed on the left thigh, left side and right paraumbilical region.
Microscopic examination showed an atypical lymphoid proliferation, consisting of small - and medium - sized elements, diffusely infiltrating the superficial dermis with only focal involvement of middle dermis and hypodermis (Fig. 1c-d). Multifocal alignment along the baseline of the epidermis and epidermotropic lymphocytes were observed, with formation of several nests (Fig. 1e-f). At immunohistochemical analysis, lymphoid elements

showed positive for CD3, CD4, CD8; expression of CD5 was partially reduced (Fig. 1g). These aspects were more pronounced in those biopsies taken from the left thigh and the right paraumbilical region. A diagnosis of MF was made. The patient underwent the standard first-line treatment with photochemotherapy (PUVA) and follow-up procedure for MF. About six months later, the patient came back to the surgeons' attention for rectal bleeding; a diagnosis of rectal carcinoma was made on endoscopic biopsy. After the administration of neoadjuvant radio-chemo-therapy (RT/capecitabine) a segmental colorectal resection with total mesorectal excision was performed. Macroscopic examination of the surgical specimen revealed an ulcerated lesion of 3x2 cm with corresponding histology of granulation tissue, chronic inflammation and fibrosis entrapping small nests of residual well differentiated tumour, with perivisceral fat infiltration, free resection margins and lymph nodes (Fig. 1h-i). Staging was ypT3G1N0; TRG=2. Concurrently, MF plaques showed unexpected, striking clinical benefit from the chemoradiation therapy carried out before colorectal surgery (Fig. 1b)

Discussion

MF is definitely the most common form of cutaneous T cell lymphoma [2]. Several retrospective studies attempted to demonstrated that patients with MF have increased risks of developing a second primary malignancy [3,10,16]. Lymphomas are the most frequently acquired metachronous tumours following MF. Other secondary neoplasms that have been associated with MF include tumours of the lung, colon, urinary system, biliary system, vulva, melanoma, and acute myeloid leukaemia. The first and unique data in the literature regarding the association between CTCL and colorectal carcinomas was in 1989 in a work of Kantor and colleagues [7]. In this study, among 544 patients with a first primary tumour reported as CTCL, a second cancer was developed in 35 (6%), with a significantly elevated relative risk for cancers of the lung and colon and non-Hodgkin's lymphomas. All studies conducted to date have been limited mainly to North America or Europe (Great Britain and Finland). This notion should be taken into account for a correct epidemiological overview of each reported association because an important pathogenic role can be attributed to genetic and environmental factors.

Many authors have found that in MF there is a higher incidence of lymphomas, both B- and T- cell and many possible explanations have been proposed for the coexistence of lymphomas of different lineages (B-cell and T-cell) in the same patient, including a common origin from a cancer stem cell [9]. To a greater extent, various factors could be singled out to disclose the relation, if any, between synchronous and metachronous tumours 15. Evidence exist that cytotoxic anti-tumour treatments may occasionally contribute to the initiation and promotion of another cancer or, in alternative, the immunodeficiency that characterizes

oncologic patients can be regarded as the substrate for the development of a second malignancy [11]. Moreover, exposure to carcinogens or cytokines produced by the first tumour can facilitate or stimulate the development of secondary neoplasms [12].

Regarding early stage MF conventional therapy, studies of large cohorts have failed to demonstrate a link between non-cutaneous diseases and psoralen + ultraviolet A (PUVA) therapy [13]. According to such results, confirmed in a recent study [14], it can be inferred that PUVA does not play an important role in the development of a secondary neoplasm or at least its role is yet to be determined. In contrast, a deregulation in T-cell cytokines' production, similar to imbalance found in AIDS, has been described and proved in patients with cutaneous T-cell lymphoma (CTCL), thus encouraging carcinogenesis [9].

Conclusions

In the presented case, we have confirmed the increased risk of synchronous cancer in patient with CTCL with regards to MF. The purpose of this study was to report a new and more recent example representative of the association between MF and colorectal adenocarcinoma. It is our view that, besides the paucity of MF cases associated with colorectal carcinoma, attention must be focused on the need for special surveillance for early detection of synchronous or metachronous tumors in patients with MF. Careful periodical clinical examination inscribed in strict follow-up programmes is mandatory. In such context, combined treatment strategies may be designed to implement the simultaneous management of MF and concomitant malignancies.

Further data in the literature and population-based studies may improve our understanding of the complex mechanisms implied in the pathogenesis of secondary malignancies associated with MF. Additional studies are expected to clarify the immunologic, genetic, viral, and environmental factors that may contribute to the development of second cancers.

Riassunto

La Micosi Fungoide (MF) è una comune e ben nota forma di linfoma cutaneo a cellule-T (CTCL), costituito da una proliferazione maligna di CD4+CD45Ro+ cellule T-helper della memoria. In un paziente affetto da MF l'incidenza di una seconda neoplasia maligna è più elevata che nella popolazione generale, ma sono molto rari i casi in letteratura di MF associato ad un adenocarcinoma colorettale.

Di qui la presentazione di un caso di MF in un soggetto di 64 anni, cui è stato diagnosticato un adenocarcinoma rettale cinque mesi dopo. Da notare è la regressione simultanea sia della massa rettale che delle manifestazioni cutanee della MF dopo trattamento neoadiuvante radio-chemioterapico prima del trattamento chirurgico della lesione del retto.
Il paziente è attualmente vivo e in remissione clinica stabile ad otto anni dalla diagnosi.

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