Opinion Paper

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Role of microsatellite instability, immunohistochemistry and mismatch repair germline aberrations in immunosuppressed transplant patients: a phenocopy dilemma in Muir-Torre syndrome

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Abstract: Sebaceous tumours and keratoacanthomas are uncommon neoplasms that constitute important clinical criteria for Muir-Torre syndrome (MTS) diagnosis. In MTS patients, the increased risk of developing synchronous or metachronous visceral malignancies is characterised by autosomal dominant inheritance. However, there are further conditions, other than MTS, that increase the risk of sebaceous neoplasms, e.g. iatrogenic immunosuppression. In this latter scenario, the sebaceous tumours can present microsatellite instability (MSI) and loss of mismatch repair (MMR) proteins, characteristic of hereditary syndromes, even in the absence of MMR germline mutations. In this article, we examine transplant probands in which the immunosuppressive therapies unmask the MTS cutaneous phenotypes, showing MSI and loss of MMR protein expression, as demonstrated by immunohistochemistry (IHC). Furthermore, MMR genes sequencing analysis identified the presence of germline mutations in MTS-suspected individuals, in the absence of a visceral MTS phenotype. It is well known that immunosuppression plays a central role in the development of sebaceous tumours in both MTS and in non-syndromic settings. Sebaceous skin tumours' MSI status and IHC profiles can be influenced by epigenetic or iatrogenic factors; however, they constitute valuable tools and a cost-effective approach to screen individuals who otherways should undergo MMR genes direct sequencing in the context of immunosuppression. In this complex setting, the choice of the immunosuppressive drug becomes a critical decision for the management of both MTS and sporadic transplant patients, which may benefit from the administration of immunosuppressive drugs, resulting in a low impact on skin cancerogenesis.

Keywords: immunohistochemistry; immunosuppressed transplant patients; microsatellite instability; mismatch repair germline aberrations; Muir-Torre syndrome phenocopy.

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Introduction

Immunosuppressed organ transplant recipients have an increased risk of malignancies [1]. Generally, the non-melanoma skin cancers (NMSCs) are the most frequently reported tumours affecting this population; in fact, cohort studies of recipients of organ transplants demonstrate a 50- to 100-fold increased risk of squamous cell carcinoma (SCC) and a 5- to 10-fold increased risk of basal cell carcinoma (BCC) compared with the general population [2]. It has been demonstrated that the cumulative risk of NMSC in transplant recipients may be as high as 40% by 20 years after transplantation [1]. Among NMSCs, evidence of an increased incidence of sebaceous tumours arises in transplant recipients [3–5], even though the sebaceous appendageal tumours are uncommon, difficult to diagnose before excision and pathological analysis, and usually associated to hereditary cancer syndromes [6–8]. In fact, the presence of early-onset sebaceous tumours and keratoacanthomas associated to visceral malignancies is distinctive of the so-called Muir-Torre syndrome (MTS), a variant of Lynch syndrome (LS) [9, 10]. MTS or LS associated tumours are featured by the presence of a typical microsatellite loci instability (MSI), which is caused by mismatch repair (MMR) germline mutations responsible of the loss of MMR protein expression, as evidenced by immunohistochemistry (IHC) analysis [11–13].

Although detailed reports of appendageal tumours have been reported developing in the context of transplant-related primary immunosuppression [1, 14–16], this clinical-pathologic relationship has not been fully explained. The literature reports that sebaceous tumours and keratoacanthomas occurring during immunosuppression show MSI and loss of IHC expression of MMR proteins, even in the absence of documented MMR germline mutations [17, 18]. Along the same lines, it is also known that the occurrence of sebaceous tumours is modulated by specific type of immunosuppressive drugs [19, 20], and some primary and secondary immunodepressive conditions are associated to an increased incidence of rare sebaceous tumours [21], showing MSI and IHC aberrations. In this regard, beyond the direct pathogenic effect of oncogenic viruses [13], a role for immunosuppressive therapies [18, 22–24], genetic aberrations [22, 25] and *MLH1* hypermethylation [26] have been hypothesised. Regarding this latter phenomenon, it is known that some MSI-high cancers are due to aberrant *MLH1* gene promoter methylation, a somatic event leading to LS/MTS phenocopies [26, 27]. Interestingly, recent in vitro evidence show that some immunosuppressive drugs (i.e. tacrolimus) can condition the DNA methylation status inducing specific epigenetic modifications, in particular hypermethylation, of some genes [28]; these preliminary laboratory evidence shed some light on the intriguing relationship between immunosuppression and hypermethylation.

In this article, we have reviewed the literature with the aim to explain the clinical history of patients with numerous familial visceral malignancies, experiencing the onset of several sebaceous adenomas after receiving immunosuppressive therapy with tacrolimus (Prograf©), administered to prevent kidney transplant rejection.

Cyclosporin A (CsA) and tacrolimus are the most commonly used immunosuppressive drugs to prevent rejection in transplant patients. Tacrolimus is the generic name for the macrolide immunosuppressant previously known as FK506 [29] and is produced by *Streptomyces tsukabaensis*, a bacterium found in the soil near Tsukuba, Japan. The mechanism of action of tacrolimus is closely related to that of cyclosporine. However, while tacrolimus binds tightly to the cellular protein named FK506-binding protein 12 (FKBP12), cyclosporine binds cyclophilin. The target of either drugs or intracellular receptor complex is a calcium-activated phosphatase, calcineurin, required for many functions in a variety of tissues. The immune response suppression leads to therapeutic efficacy in transplantation, but it also leads to an increased risk of tumours [1]. In addition to the immunosuppressive activity, tacrolimus affects tumour development and growth via different molecular mechanisms, such as the over-expression of VEGF-C, inhibiting apoptosis in non-lymphoid tissues and influencing crucial cancer signalling pathways (e.g. Erk and p53) [30, 31].

The impact of immunosuppression on *MMR* genes deficiency and sebaceous carcinogenesis: our clinical and laboratory experience

Our experience is based on the retrospective assessment of a cohort of immunosuppressed transplant patients that assumed anti-rejection therapies and developed multiple eruptive sebaceous neoplasms and keratoacanthomas. The lesions always occurred suddenly as firm, fast growing, flesh coloured papules and nodules of the face and had translucent, telangiectasia-like surface, often associated with central erosion/ulceration [32]. The main clinical and dermoscopic differential diagnosis included other sebaceous tumours, BCC, adnexal tumours and keratoacanthomas [32]. The skin neoplasms were surgically excised and the pathologist observed well defined, enlarged, sebaceous lobules with fully mature sebocytes, frequently demonstrating an attachment to the epidermis with epidermal thinning, as it occurs in sebaceous adenomas. A detailed family history was collected for each patient by conducting interviews of the patients and/or of their relatives. Verification of cancer occurrence among family members was obtained in the majority of patients through clinical and pathological records, or death certificates. Our approach was based on the assessment of biomolecular (MSI) and IHC characteristics of the sebaceous neoplasms, leading to the identification of a high MSI and a loss of expression of the *MMR* proteins (IHC) in sebaceous tumour and KA excised from the immunosuppressed patient even in the absence of visceral neoplasm and clear MTS clinical diagnosis (Figure 1).

In this clinical scenario, it is important to pursue the concept that immunosuppressed patients with multiple sebaceous neoplasms and keratoacanthomas are often affected by MTS; therefore, the clinician has a clear indication to perform endoscopy in order to screen these patients, for an increased risk of visceral neoplasms [22, 25]. For the molecular diagnostic confirmation of MTS, taking into account the high concordance, near to 100%, between MSI and IHC, whenever one of these two tests result in changes compatible with MTS, the presence of germline mutations should also be investigated by the direct sequencing of *MMR* genes, when at least one of the preliminary molecular and/or IHC tests is suggestive of a hereditary setting.

Even though it is known that immunosuppression is a risk factor for sebaceous tumours, it is our opinion that whenever an immunosuppressed patient is affected by sudden multiple sebaceous lesions erupted at a relatively young age, with positive MSI and IHC, the clinician should perform the *MMR* genetic sequencing. Therefore, we suggest as a practical workflow for the management of these patients that MSI and IHC should be determined first, and only if they are positive, direct genetic sequencing of *MMR* genes should be performed in order to determine if the patient is affected by MTS.

Some of the patients in our cohort are emblematic of the clinical condition aforementioned, e.g. RTR1 was diagnosed a colonic adenoma at the age of 36. He underwent renal transplant at the age of 49 because of an end-stage renal failure after glomerulonephritis initiating at the age of 35. After the transplant, he developed a BCC on the nose and a keratoacanthoma on the face. At the age of 52, he developed five sebaceous adenomas, four located on the face and one in the lumbar region. All sebaceous

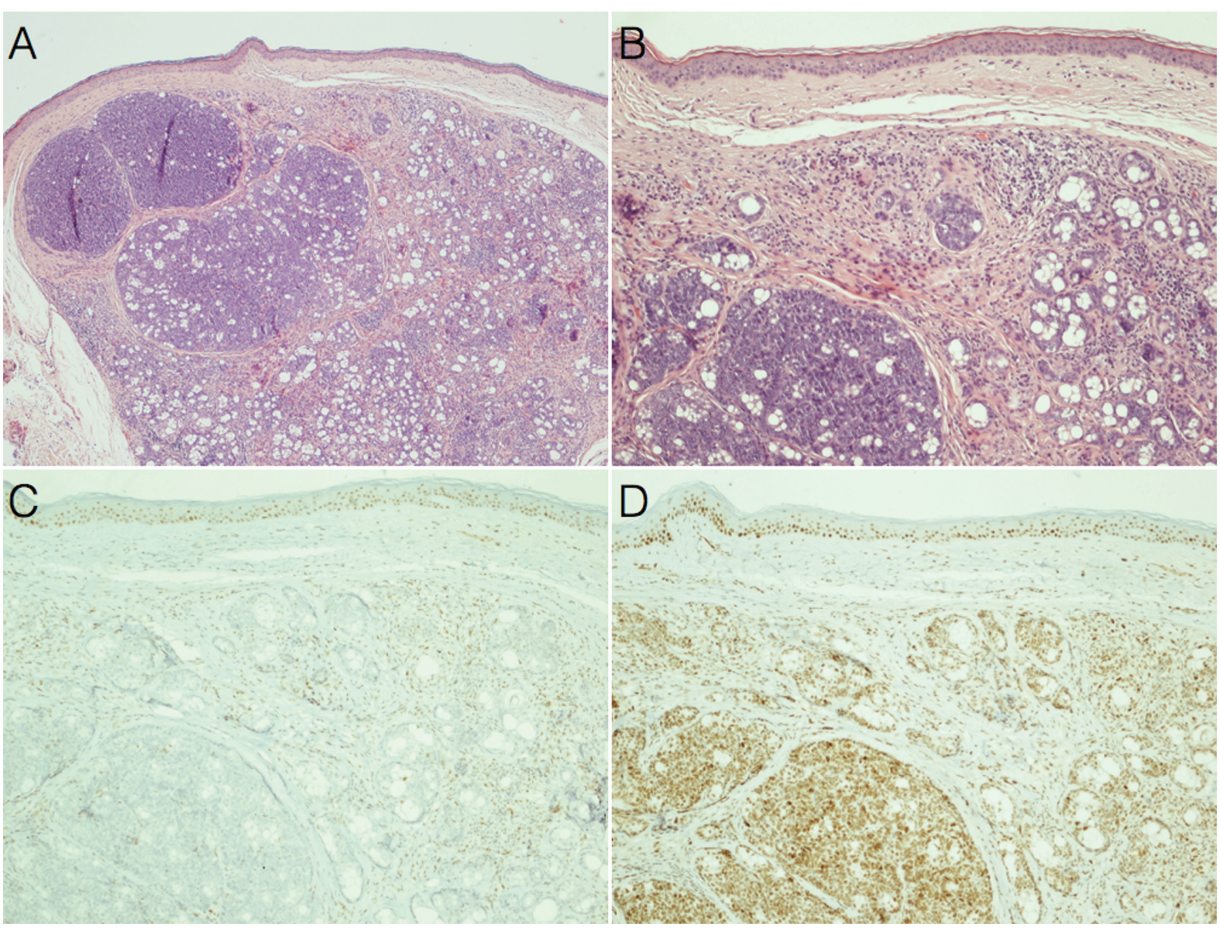

Figure 1: Histological and IHC analysis of a sebaceous adenoma of RTR.
The histological analysis of one of the nodules of the face of RTR1 showed a well-demarcated intradermal mass characterised by discrete lobules formed by a variable number of sebocytes and basaloid cells not arranged around a distended duct, as is found with sebaceous hyperplasia (haematoxylin and eosin stain) (A, B). IHC of the same tumour showing absence of MSH2 protein (C) and presence of MLH1 product (D).

tumours were adenomas and shared the same molecular markers, IHC MMR protein expression, mutation and methylation. The systemic genetic analysis performed on leukocyte blood cells revealed the presence of a germline *MSH2* mutation at codon 406, c.1216C>T (p.Arg406x) corresponding to a stop codon with consequent loss of function of *MSH2*. Among his relatives, his sister had a positive personal history of colon cancer discovered at the age of 65, while another sister and a niece were diagnosed with endometrial cancer at the age of 54 and 50, respectively. The patient was under immunosuppressive treatment with prednisone and tacrolimus (Figure 1). However, cutaneous sebaceous tumours did not affect his family members.

Another patient, RTR2, underwent kidney transplant in 1998 at the age of 45 and developed a sebaceous adenoma of the left lower eyelid at the age of 58. Later on, two more sebaceous adenomas of the face were found. The patient has not been diagnosed of any visceral malignancies so far and he is affected by Berger syndrome. The systemic genetic analysis performed on leukocyte blood cells revealed the presence of a germline *MSH6* mutation at codon 782, c.2345T>C (p.Leu728Pro) that generates a variant of uncertain significance (Class III) [26]. In his family, two sisters had uterine fibromas and one of them also had colon cancer of the sigmoid tract with liver metastasis; moreover, one maternal uncle had colon cancer. The patient was under immunosuppressive treatment with CsA and switched to prednisone and tacrolimus in 2012.

The role of immunosuppressive therapy

Sebaceous tumours are rare, but they are the most common cutaneous appendage tumours in the immunosuppressed transplant recipients [18]. The occurrence of sebaceous tumours was previously related to the iatrogenic immunosuppressive therapies [14–16], to the infection with human immunodeficiency virus [33], to the development of Hodgkin's lymphoma [34] and to the presence of MMR germline mutations in the setting of MTS/HNPCC spectrum [6].

While an inherited MMR defect can always be suspected in the majority of patients with sebaceous gland tumours, it is important to investigate the molecular mechanism underlying the development of these neoplasms in the transplant recipients and their clinical implications in the MTS patients' screening.

Regarding the iatrogenic factors, azathioprine has been postulated to contribute to the selection of cells bearing DNA MMR deficits, evading its cytotoxic effects [35]: in fact, there is evidence suggesting that immunosuppressive drugs, most plausibly azathioprine, could determine the selection of a mutator phenotype predisposing to the development of sebaceous neoplasms [21]. Cyclosporine and tacrolimus are calcineurin inhibitors and have been hypothesised to increase tumour growth through the increase of transforming growth factor (TGF)-β and interleukin-6 [24, 36]. Maluccio et al. found that tacrolimus has a dose-dependent effect on tumour progression and TGF-β1 expression in mice [37]. TGF-β1 is a multifunctional cytokine related to tumour invasiveness and metastatic progression. In addition, tacrolimus may affect tumour growth and development by the overexpression of VEGF-C as it was demonstrated in tacrolimus treated hepatocellular carcinoma-bearing rat. The main target of VEGF is the endothelial cell, where it modulates the angiogenesis and/or lymphangiogenesis mechanism, but it also exerts other effects upon the differentiation and pathophysiology of different cell types including the sebocytes [38]. Several studies have demonstrated the presence of VEGFRs in liquid and solid tumour cells, such as NSCLC, melanoma, prostate cancer, leukaemia, mesothelioma and breast cancer [39], being involved in microvascular permeability, endothelial cell proliferation, migration and invasion [40]. It should be further noted that despite an increase of apoptosis in T-cells, tacrolimus was also shown to inhibit apoptosis in non-lymphoid cells [31, 41]. Moreover, an influence on proteins of some of the most significant cancer signalling pathways (e.g. Erk and p53) has been demonstrated [31]. Consequently, the carcinogenic potential of tacrolimus may be also due to a direct effect, promoting the transformation of initiated cells. A direct link between tacrolimus and Bcl-2 family proteins should also be taken into consideration: the tacrolimus-binding protein FKBP38 blocks apoptosis, binds to Bcl-2 and targets Bcl-2 in mitochondria [41].

It has been reported that the switching from tacrolimus to sirolimus halts the appearance of new sebaceous neoplasms in MTS patients [19]. Sirolimus was initially discovered as an antifungal metabolite produced by *Streptomyces hygroscopicus*, it forms a gain-of-function complex with the FKBP12; this complex acts as an inhibitor of mammalian TOR (mTOR) complex 1 (mTORC1) [42]. Constitutive hyperactive mTORC1 signalling is directly linked to the unregulated cell growth that drives the clinical manifestations of lymphangioleiomyomatosis (LAM) and tuberous sclerosis (TSC), which is characterised by the development of benign hamartomatous tumours involving multiple organs. Both LAM and TSC are caused by loss-of-function mutations in the *TSC* genes (*TSC1* or *TSC2*), whose protein products function as a complex to inhibit the activity of mTORC1. Sirolimus and rapamycin analogues possess immunosuppressive and antiproliferative properties in mammalian cells, impairing cancer metabolism, suppressing protein synthesis and inducing autophagy. Thus, drugs that selectively target mTORC1, like rapamycin, are expected to impair cancer metabolism and are considered a promising anticancer therapy [42].

In our renal transplant patients (RTR1 and RTR2), the occurrence of sebaceous adenomas during the tacrolimus-based immunosuppressive regimens represented the leading event to investigate MSI and MMR IHC protein status and to analyse the sequence of the MMR genes unveiling, respectively, *MSH2* and *MSH6* germline alterations, compatible with MTS diagnosis (Figure 2). As confirmed by the genetic alterations in *MSH6* gene found in RTR2, it was possible to pose the MTS diagnosis even in the absence of visceral malignancies or the fulfilling of MTS clinical criteria. This evidence has important clinical implications in the management of MTS-suspected patients showing cutaneous MTS stigmata only, which should be screened for MTS visceral tumour spectrum.

The assessment of MSI and MMR through IHC analysis in a sebaceous gland neoplasm is highly relevant for the detection of familial cancer predisposition. However, it is known that sebaceous tumours and KA can display MSI and loss of MMR protein expression even in the absence of MMR germline mutations. The reason underlying this phenomenon is not completely understood; some authors suggested that the mechanisms of development of MSI in sporadic colonic and endometrial carcinomas and also in sebaceous neoplasms [43] are related to the biallelic inactivation of the *hMLH-1* gene either by mutation or by promoter hypermethylation [26, 27, 44].

The high incidence of MSI and the lack of MMR protein expression in sebaceous tumours and KA from RTR suggest either that immunosuppression unmasks a latent MTS phenotype or an interaction between MMR proteins and immunosuppressive drugs eliciting in immune surveillance diminution and, in some cases, exerting a carcinogenic effect associated to MSI and loss of MMR proteins.

The MTS-suspected population could include both the patients harbouring the sebaceous tumours or keratoacanthomas in the absence of visceral neoplasm phenotype, and the immunosuppressed patients, presenting sebaceous gland tumours with MSI and loss of MMR proteins, as evidenced by IHC. In the first case, MMR genes sequencing should be performed in order to define the molecular diagnosis of MTS; concerning the latter, even though the incidence of sebaceous tumours in the immunosuppressed patient is possible, it is important to remember that immunosuppression may “unmask” a MMR gene defect that has to be investigated through direct gene sequencing.

The identification of immunosuppressed patients with MMR gene mutations, therefore affected by MTS, is of great relevance, prompting to perform a screening for

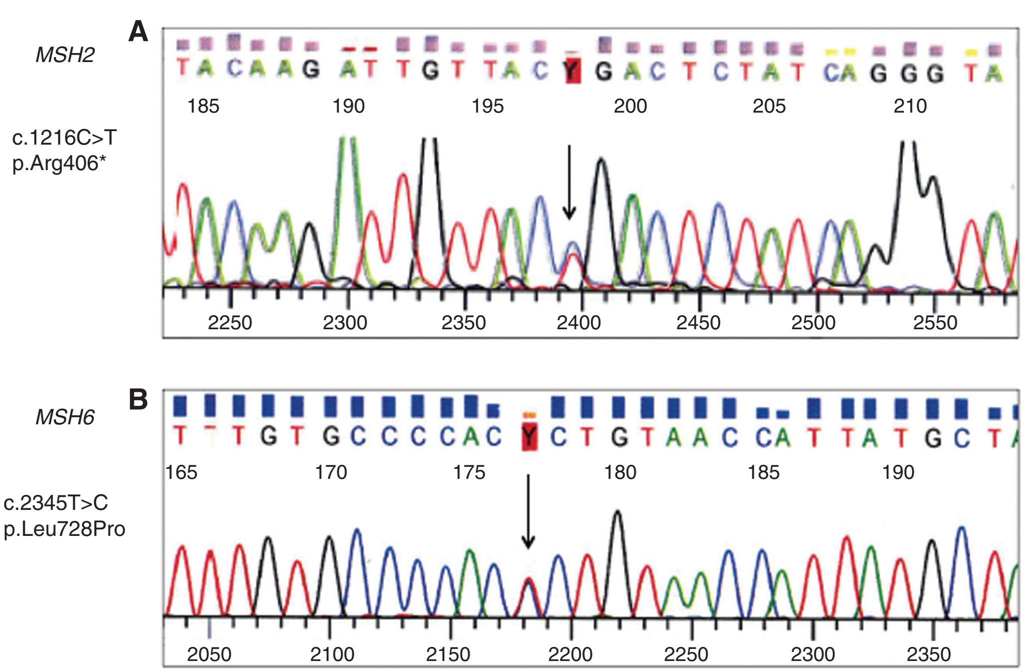

Figure 2: Electropherograms of RTR1 *MSH2* showing the mutation c.1216C>T p.Arg406 (A), and of RTR2 *MSH6* showing the variant of unknown significance c.2345T>C p.Leu728Pro (B), as indicated by arrows.

MTS visceral tumours and a genetic screening addressed to the first- and second-degree relatives of the patients.

In conclusion, although rare sebaceous tumours and keratoacanthomas constitute the clinical criteria for the diagnosis of MTS, the same tumours can also be found within an immunosuppressive context.

The combination of MSI and IHC status can therefore be considered essential for MTS detection, even in case of an incomplete MTS phenotype and/or in immunosuppressed patients, allowing a cost-effective approach in the screening of individuals who are meant to undergo MMR genes direct sequencing. Given the aforementioned molecular and clinical evidence, the administration of some immunosuppressive drugs to MTS patients and to immunosuppressed MTS-suspected patients may have a crucial impact on the cutaneous expressivity of the MTS phenotype. Therefore, the immunosuppressive drug choice should be done taking into consideration that some immunomodulatory molecules (i.e. sirolimus) are able to prevent sebaceous carcinogenesis because of the mechanism of action, an important advantage for the patient that has to be considered whenever starting a life-long immunosuppressive therapy. The best therapeutic choice for MTS patients, both with partial or complete phenotypic expression, needs further study to compare the benefits and side effects that can be attained by adopting different immunosuppressive agents.

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