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# Mycosis fungoides: creation of a prospective, interdisciplinary and multicenter study in central Italy

Mycosis fungoides (MF) accounts for 55% of all primary cutaneous T-cell lymphoma (CTCL), which are characterized by skin infiltration of malignant T-lymphocytes.[1] MF is most frequently observed in adult patients, >60 years old with a predominance among males. The pathogenesis and disease progression of MF is still unclear, but recent studies have underlined the important role of genetic and epigenetic abnormalities and the environment.[2] New diagnostic and prognostic biomarkers have been identified by molecular studies and new pharmaceuticals have been approved.[3] There are known diagnostic difficulties for MF as differential diagnosis is complex. Early-stage clinical appearance can simulate common inflammatory dermatoses, such as eczema and psoriasis. Early diagnosis remains imperative to reduce treatment toxicity and obtain a fast response; life expectancy associated with early disease stages is similar to the general population, but 5-year survival estimates are as low as 27% in the most advanced MF stage.[4] However, a multicenter, international registry of early-stage MF patients estimated that 85% have a delayed diagnosis of an average of 36 months.[5] MF is typically characterized by localized and then diffuse patches and/or plaques which can slowly progress into tumors or generalized erythroderma over many years. Diagnosis, primarily performed by dermatologists in Italy, therefore requires the integration of clinical, histological, immunophenotypic and molecular data, rendering the dermatologist a reference point for MF patients and multidisciplinary teams of medical professional, as well as being responsible for MF therapeutic management.[2] There are numerous therapeutic options for MF, ranging from topical steroids for early disease to chemotherapy for advanced disease, and molecular targeted approaches have most recently been introduced into the therapeutic pallet of options with promising results. However, as most therapies are unable to assure long term remission, multiple therapies are usually prescribed throughout a patient's therapeutical pathway. However, current guidelines do not specify a sequencing schedule for these disease stages. Therefore, therapeutic choices are often dependent upon institutional experience and pharmaceutical availability. These diverse therapeutic approaches, along with the enrolment of heterogeneous patients in mostly retrospective analyses, make studies of comparative therapeutic efficacy difficult to interpret. Recently, the current state of epidemiological impact and diagnostic-therapeutic pathway of MF patients in Italy was published in the *Italian Journal of Dermatology and Venerology*.[2] The consensus project, made up of Italian MF experts, provided updated information on national MF epidemiology from surveys and a review of studies in literature. The authors highlighted the paucity of data and poor quality of available evidence, lacking uniform diagnostic and therapeutic pathways. The authors called for standardization of care on both regional and national scales to: 1) improve the quality of evidence available; 2) prepare for effective evaluation of upcoming innovative MF therapies; 3) create multidisciplinary collaborations with pathologists, molecular biologists, radiation oncologists and hematologists; and 4) define a unified and homogeneous therapeutic sequence under a combined diagnostic-therapeutic protocol. In central Italy, a concrete response to this request was made with the formation of a Working Group for diagnosis and treatment of MF (Central Italy MF Working Group), aimed to share a common protocol for the prospective registration of all new MF patients, centralized to diagnostic-therapeutic evaluation at reference centers with expert dermatologists, necessary histopathological equipment and expertise, radiation oncologists and hematologists. The working group will develop and disseminate educational material for the classification of suspect cases and in case of biopsy, the type, number and location of optimal sites. Reference centers will follow shared histopathological criteria for MF diagnosis and disease staging with routine use of patient clinical photos and full medical history made available to the pathologist. A shared follow-up and therapeutic schedule will be created, based on disease stage. Information regarding prescribed medical therapy and the general clinical state of the patient will be registered. The Central Italian MF Working Group will endeavor to assist in obtaining accurate, prospective information regarding the epidemiological impact of MF in central Italy, providing a strong base on which standardized care can be monitored and evaluated, and eventually compared with much anticipated, innovative MF therapies. This letter is an invitation to all associated specialists in the area to adhere to this working group.

Marco ARDIGÒ [1] *, Luca BIANCHI [2], Carmen CANTISANI [3], Carlo COTA [4], Cosimo DI RAIMONDO [2], Alessandro DI STEFANI [5], Maria C. FARGNOLI [6], Chiara FRANCESCHINI [1], Giovanni PELLACANI [3], Ketty PERIS [5], Severino PERSECHINO [7], Sara PLEBANI [8], Concetta POTENZA [9], Ilaria PROIETTI [9], Laura QUATTRINI [5], Maria CANTONETTI [10]

[1]Porphyrias and Rare Diseases, San Gallicano Dermatological Institute IRCCS, Rome, Italy; [2]Dermatology, Tor Vergata University, Rome, Italy; [3]Dermatology, Sapienza University, Rome, Italy; [4]Dermatopathology, San Gallicano Dermatological Institute IRCCS, Rome, Italy; [5]Dermatology, Sacred Heart Catholic University, Rome, Italy; [6]Dermatology, University of L'Aquila, L'Aquila, Italy; [7]Dermatology, Sant'Andrea Hospital, Sapienza University, Rome, Italy; [8]Hematology, San Salvatore Hospital, L'Aquila, Italy; [9]Dermatology, Polo Pontino, Sapienza University, Latina, Italy; [10]Lymphoproliferative Diseases Unit, Tor Vergata University, Rome, Italy

*Corresponding author: Marco Ardigò, Porphyrias and Rare Diseases, San Gallicano Dermatological Institute IRCCS, Via Elio Chianesi 53, 00144 Rome, Italy. E-mail: ardigo.marco@gmail.com

## References

**1.** Trautinger F, Eder J, Assaf C, Bagot M, Cozzio A, Dummer R, *et al.* European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2017. Eur J Cancer 2017;77:57–74.

**2.** Alberti Violetti S, Alaibac M, Ardigò M, Baldo A, DI Meo N, Massone C, *et al.* An expert consensus report on mycosis fungoides in Italy: epidemiological impact and diagnostic-therapeutic pathway. Ital J Dermatol Venereol 2021;156:413–21.

**3.** Wong HK, Mishra A, Hake T, Porcu P. Evolving insights in the pathogenesis and therapy of cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome). Br J Haematol 2011;155:150–66.

**4.** Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. Arch Dermatol 2003;139:857–66.

**5.** Scarisbrick JJ, Quaglino P, Prince HM, Papadavid E, Hodak E, Bagot M, *et al.* The PROCLIPI international registry of early-stage mycosis fungoides identifies substantial diagnostic delay in most patients. Br J Dermatol 2019;181:350–7.

*Conflicts of interest.*—Maria C. Fargnoli has served on advisory boards, received honoraria for lectures and research grants from Amgen, Almirall, Abbvie, BMS, Galderma, Kyowa Kyrin, Leo Pharma, Pierre Fabre, UCB, Lilly, Pfizer, Janssen, MSD, Novartis, Sanofi-Genzyme, Sunpharma; Marco Ardigò has served on advisory boards, received honoraria for lectures from Recordati Rare Diseases, Alnylam, Helsinn, Almirall, Mavig, Kyowa Kirin Pierre Fabre; Maria Cantonetti has participated at conventions, meetings, advisory boards and offered expert consultancy for Takeda, Roche, Kyowa Kirin, Clinigen, Inside, Vifor, Abvvie, Celgene, Novartis, Janssen, Mundipharma and Gentili; Alessandro Di Stefani acted as consultant for Janssen-Cilag, Pierre-Fabre, Sun Pharma.

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# The role of cutaneous human-papillomavirus (HPV) infection in *in situ* squamous cell carcinoma: a pilot study

Among the most debated controversies in dermatology, certainly the naming of keratinocyte skin cancers is among the first. Squamous cell carcinoma (SCC) can be, indeed, classified into *in situ* and invasive forms; the former are named SCC *in situ* (iSCC) and Bowen's disease (BD); invasive ones are referred to as well-differentiated SCC or keratoacanthoma (KA).[1]

A further classification of skin epithelial tumors could be made according to whether they appear on photodamaged skin or not.[1]

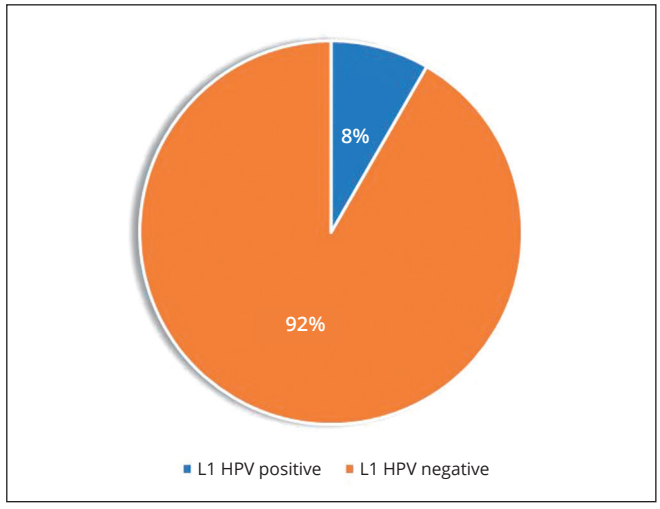


Figure 1.—Samples of *in situ* squamous cell carcinoma analyzed by PCR showing only 8% of L1 HPV positivity.

The authors hypothesized that UV radiation plays a fundamental role in the etiopathogenesis of the *in situ* as well as invasive forms of SCC raised in the context of field cancerization, while less evidences exist about the etiopathogenesis and risk factors in KA and BD, mainly found in absence of field cancerization.

Several studies investigated the presence of HPV-DNA in the aforementioned tumor types and its possible pathogenetic role with conflictual results mainly due to the detection of different HPV genera. Cutaneous HPVs are distributed over all five HPV genera, namely Alpha, Beta, Gamma, Mu and Nu,[2, 3]but only some α-genus HPV types have been associated with human carcinogenesis.[2] Beta genus HPV types have been detected in 84% keratoacanthomas and 50% well-differentiated SCC,[4] but also in healthy skin.[3] Contrarily to alpha types, β HPVs do not seem to be required for the maintenance of the malignant phenotype.[3] Although most diagnostic kits reveal alpha HPV-DNA, it is usually less investigated in cutaneous lesions[3, 5].

Taken into account these evidences, the aim of our pilot study was to evaluate the presence of alpha types HPV-DNA in iSCC. Lesions arisen exclusively on chronically photo-exposed areas, surrounded by signs of photodamage and/or actinic keratosis (AK) with glomerular vessels on dermoscopy were considered iSCC, thus excluding AK, BD or SCC.[3] All lesions were histologically confirmed as iSCC. Thirty iSCC samples from immunocompetent patients (12 women, 18 men, mean age 77±5 year old) were submitted to the detection of alpha HPV DNA by PCR using 200-400 ng of DNA and GP5 and GP6 consensus primers for HPV L1. Two out 30 samples resulted positive to HPV detection. After sequencing, both samples resulted HPV-16 positive (Figure 1).

Therefore, we report the lack of correlation between SCC *in situ* and HPV alpha cutaneous infection. Nevertheless, we acknowledge as a limitation in this study that beta and gamma HPV genera were not investigated.

The finding of variable percentages of beta HPV positivity in well differentiated exophytic lesions (KA and well-differentiated SCC) and the absence of viral infection in flat lesions (BD and SCC *in situ*) suggest that probably HPV plays a role in determin-