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HISTORY AND HUMANITIES IN DERMATOLOGY

Cutaneous Lymphoma in *Actas Dermo-Sifiliográficas*: A Historical Perspective

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Abstract
This article reviews the history of cutaneous lymphomas through the articles published on this subject in the journal *Actas Dermo-Sifiliográficas*. Approximately 100 years after Alibert published the first description of a patient with mycosis fungoides in 1806, reports of cutaneous lymphoma cases began to appear in *Actas*. These articles reflect how the definition, classification, and treatment of this disease, which continues to pose a challenge for dermatology, have evolved over the 100-year lifespan of the journal.

PALABRAS CLAVE
Actas Dermo-Sifiliográficas;
Linfoma cutáneo;
Historia

Perspectiva histórica de los linfomas cutáneos a través de *Actas Dermo-Sifiliográficas*

Resumen
En este artículo repasamos la historia de los linfomas cutáneos a través de los artículos referidos al tema en la revista *Actas Dermo-Sifiliográficas*. Aproximadamente 100 años después de que Alibert describiera el primer paciente con micosis fungoide en 1806, comienzan a aparecer casos sobre el tema en *Actas*. Veremos cómo a lo largo del siglo que lleva publicándose la revista ha ido cambiando el concepto, la clasificación y el tratamiento de esta enfermedad, que aún hoy en día sigue siendo un reto para el dermatólogo.

A literature search in *Actas Dermo-Sifiliográficas* from its first issue to the present using *cutaneous lymphoma* as a key word turns up more than 250 articles on this subject. Analysis of the results of this search makes 2 things apparent. First, many of the articles, especially those from the first half of the twentieth century, have nothing to do with the subject of the search. Second, the number and quality of the articles increases progressively with time, especially over the past 10 years.

A century after Alibert[1] first described a patient with mycosis fungoides, *Actas* published its first issue. The first article located by the search was written by Covisa[2] in 1911 under the title "Submaxillary viscous lymphoma." In reality, this was a case of syphilis, and a number of similar articles were found in subsequent issues of the journal. Alibert himself contributed to the confusion, since one of the

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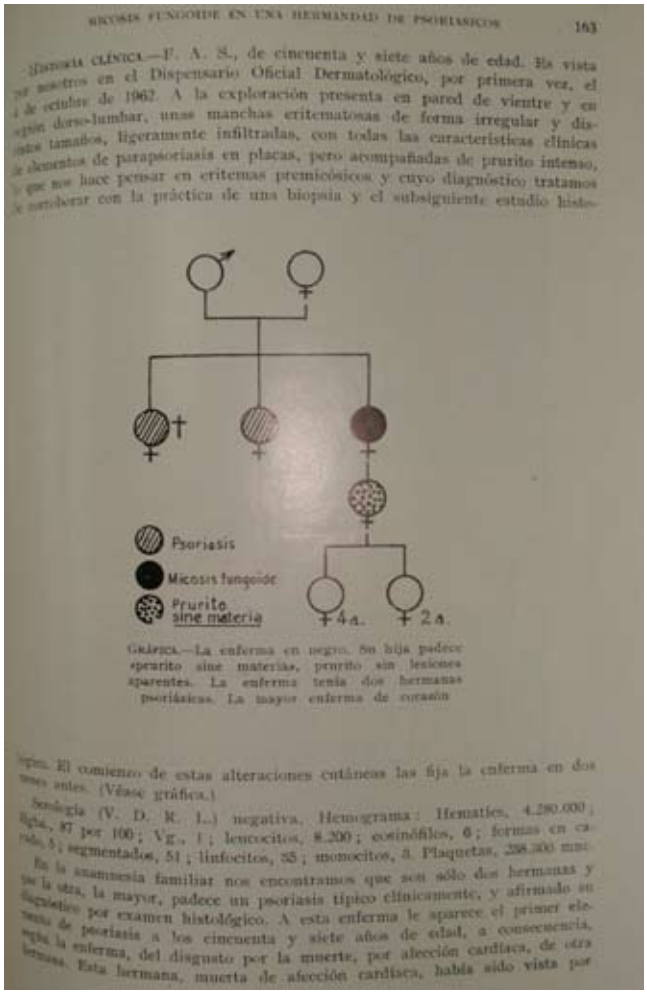
12 branches of his famous "tree of dermatoses" diagram grouped syphilis and what he called mycosis fungoides (tumor lesions that reminded him of a kind of mushroom) as "virulent dermatoses." This was a purely descriptive term since fungal infections were not associated with human diseases until the end of the nineteenth century. Something similar occurred in the case of lymph node involvement in syphilis, which was called viscous lymphoma but had nothing to do with lymphoproliferative processes. Further exploration reveals that in 1915 Covisa,[3] the same author, published "A case of mycosis fungoides," and that 2 more articles on mycosis fungoides were published in 1919.[4,5] At that time, authors used the term *mycosis fungoides*, with the second word in the plural, following the usage of the English-language journals, while more recent articles published in Spanish generally use the singular form. Until a 1942 article[6] there is nothing specifically on cutaneous lymphoma, but titles come up in this search because of the confusion that existed at that time.

The first article on treatment, "Observations on radiotherapy in a case of mycosis fungoides," by JS Gallardo,[7] discusses a treatment still in use today for localized tumors. In 1958, N Gollnick[8] published "Mycosis fungoides and vitamin B12," a curious article not only because of its subject, but because the author is by all indications a German dermatologist who, a year earlier, published an article on new possibilities in the treatment of mycosis fungoides[9] in the journal *Zeitschrift für Haut- und Geschlechtskrankheiten (Journal of Skin Disorders and Venereal Diseases)*. In 1961 two young doctors, Vilanova and De Moragas,[10] published "Topical nitrogen mustard in the treatment of mycosis fungoides." It is regrettable that this highly effective and inexpensive treatment, which produces almost no side effects, is now so difficult to obtain.

In 1965 we find an article by C. Aguilera Maruri[11] with the startling title of "Mycosis fungoides in siblings with psoriasis [in Spanish, *hermandad de psoriásicos*]." This title caught my attention not only because it was published in the same year I was born, but also because the use of *hermandad* suggested the existence of some sort of "brotherhood" or club of patients with psoriasis. Reading the article, however, one sees that this is, in fact, a case in which several members of the same family had psoriasis, and one of them had mycosis fungoides as well (Figure). The article explores the question of whether psoriasis could be a precursor of mycosis fungoides, as parapsoriasis is known to be. The illustrious doctors Gómez Orbaneja, Iglesias Díez, and Sánchez Yus[12] published an article in 1967 on the same subject entitled "Mycosis fungoides with initial clinical presentation as plaque parapsoriasis." At present, thanks to genetic reordering techniques, practically all cases that would have been identified in years past as large plaque parapsoriasis are classified today as mycosis fungoides.

After the 1960s it became possible to identify T and B lymphocytes, and on this subject there are 2 interesting articles by Dr Carapeto published in 1978: "Distribution of T and B lymphocytes in peripheral blood in some forms of cutaneous lymhoma"[13] and "An indication of the thymus-dependent nature of cellular proliferation in 7 patients with Sézary syndrome."[14] These publications represented a year of hard work for our colleague and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Psoriasis
Micosis fungoide
Prurito sine materia
+4a. +2a.

Figure Detail, family tree of the "siblings with psoriasis." Source: Aguilera Maruri.[11]

an example of how, up to that time, articles were almost always published by single authors, in contrast to current publications for which the teams of authors can even be a little too large. Nearly 40 years after Sézary described the syndrome that bears his name, the research group headed by Dr Sotillo Gago published "Sézary syndrome,"[15] and in 1978 Drs Crespo, Ramirez, and Lendoyro[16] published another review article on this subject focusing on the clinical manifestations, hematological characteristics, and course of the disease.

From the 1980s onward, case reports published on mycosis fungoides begin to increase in number. In 1987 *Actas* published the abstracts of papers presented at the XI Iberian and Latin American Conference on Dermatology (CILAD) held in Madrid from May 17 to May 21, 1987.[17] Among the many symposia was one organized by Dr Ledo Pozueta, entitled "Mycosis Fungoides." The papers, presented by a roster of distinguished speakers, are closer to current research on the subject (Table). Especially noteworthy is the presence of Edelson,[18] who was the first to introduce the term *cutaneous T-cell lymphoma* in 1970. In addition to "Classification of cutaneous lymphomas," the subject of his paper, Edelson also discussed the value of clonal reordering in the diagnosis

Table Contents, *Actas Dermo-Sifiliográficas* 1987, issue 78 (Suppl 1): Papers presented at the Symposium on Mycosis Fungoides, XI CILAD Conference, Madrid, Spain

Abbreviations: CTCL, cutaneous T-cell lymphoma; PUVA, psoralen plus ultraviolet A therapy.

of cutaneous lymphomas at this conference. Nearly another decade would pass before this technique, which is extremely valuable in both the differential diagnosis and early diagnosis of the disease, would become routine in Spanish hospitals. Dr Knobler, one of the organizers of the cutaneous lymphoma research group in the European Organization for Research and Treatment of Cancer (EORTC), presented a paper on extracorporeal photopheresis, a treatment he firmly supports although it remains controversial within the EORTC. Dr Díaz Pérez also spoke on the treatment of Sézary syndrome, a subject on which he is a great expert, having made important contributions to the literature on this subject. An example is the article he co-authored following his time at the Mayo Clinic in the 1970s.[19] Dr Díaz Pérez was also one of the organizers of the EORTC, as shown by his participation in the development of both the first classification for cutaneous lymphomas published by EORTC in 1997[20] and the one published in 2005.[21] Until then, cutaneous lymphomas had been partially included in the classification of systemic lymphomas. In the early 1990s there were two lymphoma classifications the 1974 Kiel classification used mainly in Europe and the 1982 Working Formulation used mainly in the United States. These 2 systems were revised by the International Lymphoma Study Group and unified into a single new classification known as REAL (Revised European American Classification of Lymphoid Neoplasms).[22] The new system was more useful for classifying cutaneous lymphomas, but still did not take sufficiently into account the less aggressive behavior of cutaneous lymphomas in comparison with ganglionic lymphomas. For this reason, in 2001 the World Health Organization (WHO) modified the REAL, arriving at a new classification that included the majority of cutaneous lymphomas.[23] Finally, in 2005, the EORTC and WHO classifications were unified into a single system, the one currently in use.[21]

To return to *Actas*, from 1990 onward, publications on this subject gradually increased in number, although many of the titles would now have to be altered to reflect the new classifications. For example, the disease referred to in "Primary cutaneous Ki-1-positive anaplastic large-cell lymphoma: a case report"[24] would now, using the new classification, be called "Cutaneous anaplastic large-cell lymphoma (CALCL)" under the new classification system, as it would fall into the group of CD30-positive cutaneous T-cell lymphomas. It would be possible to retitle many articles published in Actas in this manner.

During this period, the pioneering research group led by Dr Luis Iglesias at Hospital 12 de Octubre was especially prolific. One of its outstanding members, Dr Ortiz Romero, who is an active member of the Spanish Lymphoma Research Group of the EORTC and the group's current secretary, has been interested in this subject since his residency. Two of his publications are especially worthy of note: a study of 15 cases of lymphomatoid papulosis in which the use of genetic reordering techniques is discussed[25]; and an article on the old nomenclature debate over B-cell lymphoma vs pseudolymphoma, a term that has fallen into disuse.[26] Regarding pathology, there is an interesting article by Drs Sangüeza and Requena,[27] "Variation in the clinical pathology of mycosis fungoides."

In the late 1990s, when the core of what is now the Spanish Lymphoma Research Group was beginning to form, 2 extremely important articles on etiopathology were published in Actas by members of this group: "A study of the expression of E7 integrin (CD103) and the antigens CD54 (ICAM-1) and CD11a (LFA-1) in early and late-stage cutaneous T-cell lymphoma (mycosis fungoides/Sézary syndrome)" by Pujol et al[28] and "Etiopathogenesis of cutaneous T-cell lymphoma (mycosis fungoides/Sézary syndrome)" by Gómez de la Fuente et al.[29]

The end of this search brings us to the twenty-first century, and several noteworthy articles. Two publications by Drs Gallardo and Pujol[30,31] were intended for a wider audience: "Diagnosis and treatment of primary cutaneous T-cell lymphomas" and "Diagnosis and treatment of primary cutaneous B-cell lymphomas." Two articles by members of the Hospital 12 de Octubre research group were awarded the Spanish Academy of Dermatology and Venereology prize in successive years, 2002 and 2003: "Clinical and blood profile factors in the progression and survival rates of cutaneous T-cell lymphomas (mycosis fungoides/Sézary syndrome)"[32] and "Possible implications of molecular alterations in the TNF pathway for tumorigenesis of mycosis fungoides: description of a possible molecular diagnosis chip for mycosis fungoides".[33] These publications reflect the high caliber of some of the current members of the Spanish Lymphoma Research Group who have published steadily in *Actas*, while other dermatologists in the group have tended to place their work in other journals.

As the high point of the rising trajectory of *Actas*, at the end of the journals centenary year, the group headed by Dr Sterry, a well-known lymphoma specialist at the Charité medical school in Berlin, published a review article in English entitled "Treatment of cutaneous lymphomas: today and tomorrow,"[34] which was an important update of current knowledge in the field.

It is to be hoped that the Spanish Cutaneous Lymphoma Research Group will continue to write future chapters in the history of this exciting and ever-changing subject.

Conflict of interest

The author declares she has no conflict of interest.

Acknowledgment

I would like to dedicate this article to Dr Díaz Pérez, the man to blame for my interest in cutaneous lymphomas. He was my dermatology professor and the co-director of my doctoral thesis on this subject. I hope that he will enjoy reading this article.

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