

REVIEW

Cutaneous MALT-lymphoma: from cutaneous immunocytoma and pseudolymphoma to the current (and future) conceptions

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Abstract

The current report examines the evolution of the concepts of immunocytoma and pseudolymphoma in a historical perspective, paying special attention to their evolution into the groups of marginal-zone lymphoma and cutaneous MALT-lymphoma. It also examines the current conception of the existence of at least two types of cutaneous MALT-lymphomas and their relation to the duality immunocytoma/pseudolymphoma from the old literature.

Keywords: cutaneous MALT-lymphoma, immunocytoma, *Borrelia burgdorferi*, marginal zone lymphoma.

☐ Immunocytoma and cutaneous MALT-lymphoma: historical perspective

Primary cutaneous lymphomas with plasmacytoid differentiation were rarities practically until the 70s, and they were mainly referred to as plasmacytomas [1–6]. In the late 70s, the discovery of the plasma-cell precursors led to the concept that lymphomas with plasmacytoid differentiation were not rare, but rather, that they could show varied cytomorphology [7, 8].

In the early 80s, immunohistochemistry became available for the study of lymphomas, and in Western Europe, cutaneous lymphomas were mainly classified according to the criteria of the Kiel classification [9]. The term “immunocytoma” was introduced in the Kiel classification as well as in the *European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Project Group* classification [9, 10]; the term referred to cases with a predominance of cells having plasmacytic features [11]. Also, in the early 80s, Isaacson P and Wright DH presented the idea of the malignant lymphoma of mucosa-associated lymphoid tissue (MALT) [12]. It was also suggested that similar to MALT, there was a skin-associated lymphoid tissue (SALT) [13, 14].

In 1991, Garbe C *et al.* published an interesting report on four low-grade malignant B-cell lymphomas associated with *Borrelia burgdorferi* infection [15]. They had difficulties in naming these lymphomas under the Kiel classification, but they made a very curious remark: “possibly a specific differentiation of B-lymphocytes may occur under some circumstances in human mucosa and also in human skin” [15].

Almost from the introduction of the *immunocytoma* concept in literature, researchers claimed a close relation between this entity and marginal-zone lymphoma, and some teams even proposed that immunocytoma was a variant of MALT-lymphoma involving the skin, similar

to MALT-lymphomas involving other organs [16–20]. In 1991, Santucci M *et al.* emphasized the similarities between primary cutaneous B-cell lymphoma and MALT-lymphomas from other organs [21]. Researchers also postulated that most primary cutaneous B-cell lymphomas were of marginal type [22]. Experts emphasized, however, the histological similarities between primary cutaneous immunocytomas and marginal-zone lymphomas [23]. The term immunocytoma co-existed in literature with cutaneous marginal-zone lymphoma for many years. In 1993, Rijlaarsdam JU *et al.*, for instance, published their series of 26 cases of cutaneous immunocytomas [24], which seemed to show distinctive clinical and histological features.

In the late 90s, however, several publications emphasized the criteria to define cutaneous marginal zone lymphoma as an entity [10, 25]. In spite of this, the EORTC classification of lymphomas did not include marginal zone lymphoma until 1997 [10].

In a report by Cerroni L *et al.*, in 1997 [25], the authors supported the concept that cutaneous marginal lymphoma was a distinct entity, different from immunocytoma, at least in clinical terms [25]. However, according to Cerroni L *et al.*, the morphologic differences between immunocytoma and marginal-zone lymphoma were very subtle. The monotypic plasma cells, for instance, were evident in both disorders [25]. Some authors reserved the term immunocytoma only for patients with paraproteinemia [26, 27], but that was, obviously, not a morphologic criterion. The main morphologic clue claimed in literature as useful in distinguishing immunocytoma from marginal-zone lymphoma was a more monomorphous lymphocytic infiltrate in immunocytoma than the one seen in marginal-zone lymphoma, with small lymphocytes and lymphoplasmacytoid cells (instead of monocytoid or centrocytoid cells) and the lack of accompanying reactive

germinal centers. These criteria did not represent consensus; some researchers thought that immunocytoma and marginal-zone lymphoma might be the poles of a common spectrum [28]. For example, Duncan LM *et al.* claimed that the density of monocytoid cells, centrocyte-like cells, and plasma cells varied from case to case, and even in different areas of one certain case of immunocytoma [20]. The debate about whether marginal-zone lymphoma and immunocytoma were the same entity continued for a long time [29].

In the EORTC classification for primary cutaneous lymphomas, published in 1997, the term primary cutaneous immunocytoma appeared as a synonym for marginal zone B-cell lymphoma [10]. In their comments, the authors emphasized that there was no consensus on the terminology of these lymphomas and that they were designated under several terms, including “*primary cutaneous immunocytoma*”, “*low-grade malignant B-cell lymphoma of SALT*”, “*primary cutaneous marginal-zone B-cell lymphoma*” or “*MALT type lymphoma*” [10].

In the 1997, *Revised European-American Classification of Lymphoid neoplasm (REAL)*, Sander CA *et al.*, when referring to marginal-zone B-cell lymphomas, commented that “*in the skin, these features are exemplified by what has been termed ‘cutaneous immunocytoma’ by some investigators*” [30]. These same authors interchanged both terms, saying for instance: “*cutaneous immunocytoma, or more properly marginal-zone B-cell lymphoma of the skin...*” [30]. They also emphasized how “*cutaneous immunocytoma*” was different from lymphoplasmacytoid lymphoma (immunocytoma) “*as it is considered in the REAL classification, which is usually a systemic disease, showing Waldenström’s macroglobulinemia, and bone marrow, spleen and lymph node involvement*” [30].

The term cutaneous immunocytoma persisted, even at the beginning of the 21st century. In a report on immunocytoma, by Magro CM *et al.*, in 2004, the authors distinguished three subgroups: (1) T-cell rich plasmacytic marginal-zone lymphoma; (2) plasmacytic marginal-zone lymphoma with reactive germinal centers, and a background population of small marginal-zone neoplastic B-lymphocytes; and (3) plasmacytic marginal-zone lymphoma unaccompanied by a significant small lymphocytic infiltrate [11]. Interestingly, in Magro’s series, although most patients clinically did very well (sometimes even with no treatment), there was no extracutaneous involvement apart from two patients who presented paraproteinemia of IgM type [11].

It was not until the middle of the first decade of the current century that the term “*primary cutaneous marginal-zone lymphoma*” encompassed primary cutaneous immunocytoma and primary cutaneous plasmacytoma [31–33]. The *World Health Organization (WHO)-EORTC classification of 2005* pointed out that the term “*primary cutaneous marginal-zone B-cell lymphoma ... includes cases previously designated as primary cutaneous immunocytoma, and cases of cutaneous follicular lymphoid hyperplasia with monotypic plasma cells*” [31].

In the 2008 WHO lymphomas classification, cutaneous marginal-zone lymphomas were included

among the extranodal MALT-lymphomas [34], therefore, assuming that they were similar to MALT-lymphomas from any other organ.

☞ **Pseudolymphoma: historical perspective**

Cutaneous pseudolymphomas were defined in literature as “*benign hyperplastic lymphoproliferative reactions that simulate cutaneous malignant lymphomas clinically and/or histologically*” [35]. Therefore, they represented a heterogeneous group of entities, known by several denominations through history, such as “*lymphadenosis benigna cutis*”, “*Spiegler-Fendt sarcoid*”, “*lymphocytoma cutis*”, “*cutaneous lymphoplasia*”, and “*cutaneous lymphoid hyperplasia*” [36]. It was known that they could be secondary to many conditions, such as insect bites [37], or injections [38]. Curiously, *Borrelia* infection was a known source of pseudolymphomas (*Borrelia lymphocytoma*) [39].

In the early 80s, Burg G and Braun-Falco O proposed a classification of cutaneous pseudolymphomas based on the architectural pattern of the cutaneous infiltrates [40, 41]. However, the morphologic criteria traditionally used in textbooks to distinguish pseudolymphomas from true lymphomas (“top-heavy” vs. “bottom-heavy” pattern, mixed vs. monotonous infiltrate, evidence of other accompanying inflammatory cells, wedge shape, symmetry, absence of follicles, presence of blast-like cells in the follicular structures) were eventually proved not to be reliable [20, 42, 43]. This made the demonstration of clonality crucial in the differential diagnosis between benign and malignant lymphoid infiltrates. Some authors even established at a point that “*the demonstration of the monotypic character (kappa or lambda) of the light chain expression has become the decisive (golden standard) criterion to distinguish the benign from the malignant lymphocytic populations*” [44]. However, some of the cases previously considered pseudolymphomas were actually monoclonal [21, 24, 35, 45–48]. In their study, in 1992, for instance, Rijlaarsdam U *et al.* demonstrated clonal Ig rearrangements in four of seven pseudolymphomas [49]. Some experts even claimed that “*the division between reactive and malignant B-cell proliferations is not absolute, but that these conditions are part of a spectrum of B-cell neoplasia ranging from polyclonal pseudolymphomas, via oligoclonal and monoclonal pseudo-B cell lymphomas, to malignant B-cell lymphomas*” [35]. In the opinion of these same authors, it was not justified to reclassify the clonal pseudolymphomas as malignant lymphomas [35].

In an interesting 1995 report on 18 cases of cutaneous follicular lymphoid hyperplasia with monotypic plasma cells [50], the authors concluded that, in spite of monoclonality, marginal-zone cells and a marginal-zone pattern of growth were missing in their cases, therefore allowing the differential diagnosis of MALT-lymphoma. As mentioned above, the WHO-EORTC classification of 2005 subsequently considered such cases part of the primary cutaneous marginal-zone B-cell lymphoma spectrum.

☞ Status of cutaneous MALT-lymphomas

Two subsets of marginal-zone lymphomas

Recent years have defined at least two subsets of cutaneous MALT-lymphomas [51, 52].

One type is composed of non-switched tumoral cells. These cells mainly express IgM and they are commonly positive for CXCR3. Moreover, this subset of cutaneous MALT-lymphoma commonly develops in a predominant B-cell reactive environment [51, 52], with an associate dominant Th-1 response. They have been associated with the infection by *B. burgdorferi* [53–55] (Figure 1).

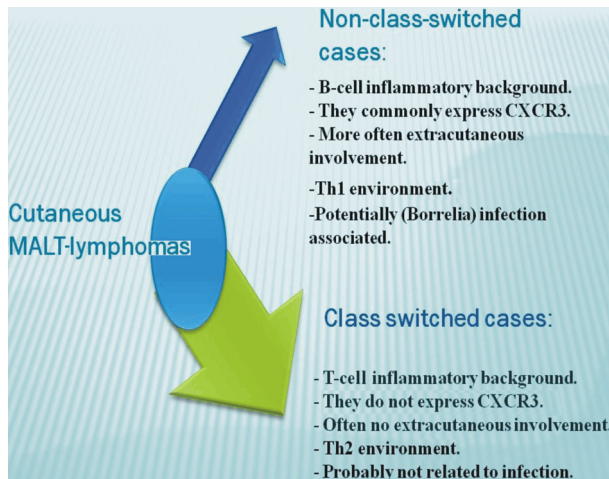


Figure 1 – Scheme on the two main types of cutaneous MALT-lymphomas and their main features. The green thick arrow is meant to indicate that class-switched cases are far more numerous than non-switched ones.

The second subset of cutaneous MALT-lymphomas is made of tumoral switched B-cells, expressing either γ - , α - or ϵ -Ig heavy chains. They commonly do not express CXCR3, and they develop in a predominant reactive T-cell environment [51, 52], with a dominant Th-2 response [56]. Unlike the first subset, this variant has not been associated with the infection caused by *B. burgdorferi* [56] (Figure 1).

Distinguishing between these two subsets has clinical relevance. While class-switched cases commonly lack extra-cutaneous involvement, the IgM+ cases show extra-cutaneous spreading in up to 50% of the cases [52]. Fortunately, the switched-cases represent the majority of cutaneous MALT-lymphomas [56]. Additionally, some have even suggested that the malignant character of switched-cases should be reassessed [52].

In this sense, there seems to be parallelism with the historic evolution of the concept of immunocytoma, marginal-zone lymphoma, and pseudolymphoma, briefly explained at the beginning of this report. The approach suggests a return to the past in conceptions of the low-grade B-cell cutaneous infiltrates, with a non-switched-type MALT-lymphoma, close to the concept of immunocytoma (a low-grade B-cell lymphoma, capable of disseminate to other organs), and a switched-type cutaneous MALT-lymphoma, close to the concept of pseudolymphoma (Figure 2).

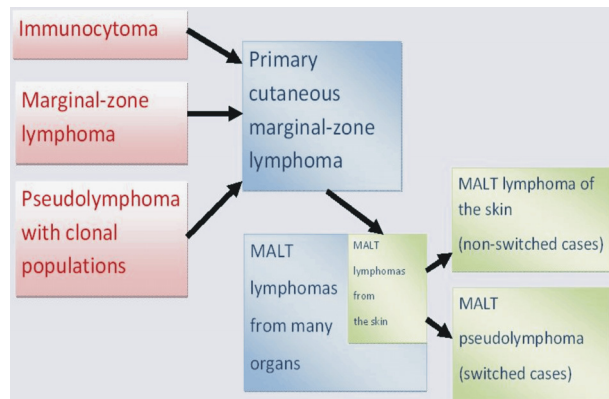


Figure 2 – Scheme on the conceptual evolution of immunocytoma, pseudolymphoma and marginal-zone lymphoma into cutaneous MALT-lymphoma first, and currently into two entities, one of them close to the pseudolymphomas, and the other one close to the MALT-lymphomas from other organs.

Similarities with marginal-zone lymphomas from other organs

The WHO 2008 classification encompasses cutaneous marginal-zone lymphoma as part of the extranodal MALT-lymphomas [34]. Under the epigraph of “sites of involvement”, they recognize that “other common sites include..., skin (11%)”, implying that cutaneous MALT-lymphomas are simply a subgroup among MALT-lymphomas.

However, considering the two subsets of cutaneous MALT-lymphomas mentioned above, it is evident that switched cases do not share many features with MALT-lymphomas from other organs (Figure 3): they develop in a T-cell-rich environment, with a dominant Th-2 response; they do not express CXCR3; they behave as a pseudolymphoma; they do not show relationships with any infectious agent. All of these features are, in many ways, quite distant from evidence of MALT-lymphomas from other organs. In contrast, the subset of non-switched cases does actually show many of these similarities with MALT-lymphomas from other organs.

	CXCR3 expression	Th response	Environment	Prognosis
Cutaneous MALT lymphomas (Switched cases)	Less than 15 % of the cases	Th2 predominance	T-cell rich	Their malignancy has been questioned
Other MALT lymphomas (Thyroid, eye...)	More than 80 % of the cases	Th1 predominance	B-cell rich	They behave as low grade lymphomas
Cutaneous MALT lymphomas (Non-switched cases)	Frequently expressed	Th1 predominance	B-cell rich	They behave as low grade lymphomas

Figure 3 – When several features are evaluated in the two subsets of cutaneous MALT-lymphomas (switched and non-switched cases), it is obvious that switched cases seem to be an outstanding group; however, non-switched cases show many similarities with MALT-lymphomas from organs other than the skin.

This paper proposes that there is a strong line dividing switched cases, close to pseudomalignancies from the skin, and non-switched cases, or “real” MALT-lymphomas, with similarities to MALT-lymphomas from organs other than the skin (Figure 3).

There are some additional curiosities regarding this division. For instance, a Th1-type response usually dominates the *Borrelia* infection environment [57, 58]. It is curious that non-switched cases related to *Borrelia* infection also show a Th-1 predominant environment.

In addition, demonstrations of CXCR3 expression in clonal cells of MALT-lymphoma in peripheral blood [59] are interesting, suggesting a role for CXCR3 in the capability of dissemination of these lymphomas. It is difficult not to establish a connection with the expression of CXCR3 in the non-switched cases (the ones that are also able to disseminate from the skin to other organs).

The two subsets of cutaneous marginal-zone lymphomas and the dynamics of the follicle

In a previous letter [60], I rendered the hypothesis that there is a connection between MALT-lymphomas and the dynamics of the follicle. In summary, there are two well-defined areas in the follicle (at least of certain sites): the marginal zone and the germinal center (GC). There is current evidence that the marginal zone cells are derived from the GC, where they suffer their hypermutations, but that they escape before the switching of immunoglobulins has started [61] (Figure 4). On the contrary, the cells staying in the GC would suffer switching of immunoglobulins, producing switched memory B-cells.

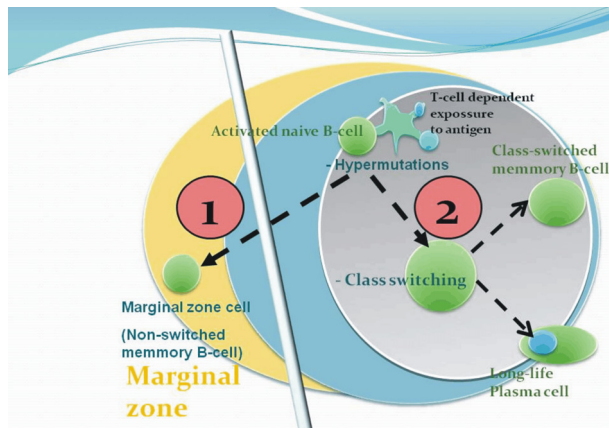


Figure 4 – The two main immunologic areas in the follicle commented on in the report: the GC and the marginal zone. The fact that the two populations of cells from these areas are switched as opposed to non-switched memory cells makes the parallelism with the two types of cutaneous MALT-lymphomas obvious.

It is therefore logical *a priori*, to establish a parallelism between these two well-defined areas in the follicle, and the two types of cutaneous MALT-lymphomas: non-switched cases and switched cases. Non-switched cases originate from marginal-zone cells, which explain their “non-switched” character and their B-cell inflammatory background. Contrary to this, the switched cases would have a direct GC origin. This explains their accompanying inflammatory T-cell

background, their preferentially nodular pattern, and their switched character.

If this is correct, there should be several other morphologic and immunophenotypic clues that are typical of the germinal center of the follicle, which should be found in the switched cases, but not in the non-switched ones. *Vice versa*, the non-switched cases should have some other peculiarities closer to the marginal area. The marginal zone is very different, in immunophenotypic terms, from the GC of the follicle and the cellular accompanying environment is also quite different in both areas.

We are already investigating several of these differences and their parallelism with switched and non-switched cases. It is probable that some aspects of MALT lymphomas, which are apparently discordant between investigating teams, might be easily re-interpreted if this approach is eventually confirmed.

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