Secondary lymphomas of the skin

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Abstract

Infection of the skin may be the result of an underlying disease, or lymphoma may be the primary cause. As a result, it is possible to differentiate between two types of lymphomas: primary cutaneous lymphoma and secondary cutaneous lymphoma (SCL), which is a type of systemic lymphoma that also affects the skin. The objective of the current review is to examine what is currently known about this neglected subject. Following this, SCL was examined from a clinical, histological, and survival perspective.

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Key words: secondary cutaneous lymphoma; T/NK cell lymphoma; B-cell lymphoma.

Contributions: AP, SC, LS, MM, performed the research; AP, SC, MM, SL, designed the research study; SC, AP, analyzed the data; SC, AP, wrote the paper. All the authors approved the final version to be published.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Availability of data and material: data and materials are available by the authors.

Informed consent: the manuscript does not contain any individual person's data in any form.

Received: 5 May 2023.
Accepted: 1 July 2023.
Early view: 24 August 2023.

Dermatology Reports 2024; 16;(s2):9743
doi:10.4081/dr.2023.9743

Introduction

Skin can be primarily involved by a lymphoma or can be colonised by a systemic disease. Hence, two categories of lymphoma can be distinguished: the primary cutaneous lymphoma (PCL) and the systemic lymphoma that secondarily involves the skin, also known as secondary cutaneous lymphoma (SCL).[1] PCLs encompass a group of lymphoid neoplasms characterized by heterogeneous clinical, histologic, immunohistochemical, and molecular characteristics. PCLs are estimated to represent 19% of all non-Hodgkin lymphomas and are currently the object of several studies on the epidemiology, clinical features and treatment options.[2-4] On the other hand, SCL have been poorly analyzed both from clinical, epidemiologic and survival perspective and to the state of the art only a few studies have been performed.[5-12] The aim of the present review is to analyze the current knowledge of such neglected topic. SCL were then analyzed from a clinical, histological and survival ground.

Epidemiologic and clinical features

The studies available in the literature report a frequency of SCL ranging from 20 to 50% of the reported cases.[5-9] Such impressive data may be explained to the retrospective nature of the studies as well as to the super selected cohort of patients due to the presence of a third referral centre in all the studies. Concerning Hodgkin lymphoma (HL) range of skin involvement varies from 0.5 to 7%.[11,12]

The largest study has been provided in 2015 by Lee *et al.* who analyzed the clinical presentation of 106 SCL.[6-9] Interestingly in the South Korean series only one case of HL involving the skin was reported. The authors distinguished B-cell from natural killer T- (T/NK) cell lineage SCL. The former showed an older age when compared to the latter (52.5 *vs*. 49.7 years, respectively), while no gender predilection nor difference in the primary tumor site were observed, being lymph node the most common site of involvement at diagnosis. However, extra-nodal involvement was more common in T/NK lymphoma than in B-ones. In terms of lactate dehydrogenase levels, the presence of lymphadenopathy, visceral involvement or advanced stage B and T/NK cell SCL showed the same features, albeit in bone marrow infiltration, an event more commonly observed in T/NK SCL. In a recent paper,[12] HL featuring skin dissemination have been described as affecting mostly male (M:F ratio 2.66:1) in their 5th decade.

Concerning the anatomic site of SCL involvement, the extremities were more likely to be affected by T/NK SCL, while B-cell lineage SCL mostly involved the trunk.[9] In contrast, HL have been commonly observed in the head and neck area, as well as in axillary and inguinal folds; in general, it has been reported that the drainage area of lymph nodes affected by HL could all be possible sites of skin lesions (sometimes, there could even be a direct extension from an underlying lymph node).[11,12]

The clinical presentation of SCL is quite heterogeneous and

papules, plaques, tumors and even erythroderma have been observed in the literature.[6-13] However, Lee *et al.* observed that T/NK SCL were more likely to present as maculo-papular eruption, while B-cell SCL with plaques or nodules. Some cases of angioimmunoblastic lymphoma (AIL) or peripheral T-cell lymphoma not otherwise specified (PTNL) not otherwise specified have been described as mimicking reactive dermatoses or erythroderma.[13,15] HL are commonly present as reddish-brown papules, patches or even nodules, sometimes with ulceration.[11,12,16] For what concerns the T-/NK-cell lineage, the most common lymphomas associated with skin manifestations were PTNL, NK/T-cell lymphoma, anaplastic large-cell lymphoma (ALCL), AIL and adult T-cell lymphoma/leukaemia (ATLL). Finally, among the aforementioned T-/NK-cell lymphomas, several can spread to the subcutaneous tissues and therefore, they should be differentiated from the primary subcutaneous T-cell lymphoma; this term indicates a homogeneous group of cases characterized morphologically by an exclusive involvement of subcutaneous tissues, immunohistochemically by a T-cytotoxic alpha/beta phenotype, and biologically by a relatively good prognosis.[17]

Histology

Literature data reporting histologic features of SCL are very poor, so we focused on the most reviewed types. PTNL is the most frequent type of lymphoma that showed skin involvement.[9] Its histopathological characteristics are an atypical and dense lymphoid infiltrate, that is usually found in reticular dermis and subcutaneous tissue. Epidermotropism has been reported, just like necrosis, but it is not a peculiar feature like in mycosis fungoides histology. In some cases, epitheloid granulomatous formations have been observed.[18] Immunophenotyping displays a dense monoclonal T-cell population commonly featuring CD30 molecule expression associated with aberrant loss of T-cell markers such as CD5 or CD7. However, cases with skin infiltration have no specific features in immunohistochemistry.

Extra-nodal NK/T-cell lymphoma (ENKTCL) is a malignancy that can be distinguished based upon the first site of involvement: in ENKTCL "nasal-type", a primary cutaneous affection is usually found, whereas the ENKTCL "nasal" variant is commonly associated with a tumor involvement of nasal and/or aerodigestive structures that can later extend to the skin and cause ulceration and cellulitis. Skin histology of ENKTCL (nasal variant) shows pleomorphic lymphoid cells displaying an angiocentric pattern alongside angiodestruction, while an extensive necrosis of connective tissue may be found. The tumor cells are usually positive for CD3 granzyme-B, CD56 by immunohistochemistry and for EBV by in situ hybridization.[19] Again, in systemic cases no peculiar features can be observed in skin dissemination of systemic diseases.

In ALCL, skin histology usually reveals a dense lymphocytic proliferation that extends from the dermis to the subcutaneous tissues; the infiltrate is typically composed of both large and small pleomorphic cells with kidney-shaped nuclei and unevenly distributed chromatin. Immunohistology shows a phenotype positive for CD30, EMA, CD3, CD45RO and ki-67 while ALK may be both positive and negative. ALK-positivity is a crucial element in differential diagnosis between primary cutaneous ALCL (which is ALK-negative) and systemic ones which express ALK molecule. However, some ALK-negative systemic ALCL with skin involvement; MUM-1 and Bcl-6 expression were studied for differential diagnosis in ALK-negative ALCL and primary cutaneous ALCL but with no remarkable outcomes in terms of differential diagnosis.[20-22]

ATLL has different clinical manifestations which impact on the histological picture found in skin specimens. As a matter of fact, we can find diffuse, nodular or superficial banded dermal infiltrate, the latter sometimes with epidermotropism (just like in mycosis fungoides). In cases of erythematous lesions, it is possible to find perivascular or diffuse infiltration of small to medium-sized atypical lymphocytes, while papules and nodules show more frequently a nodular or diffuse infiltration of medium to large-sized lymphocytes, from the dermis to subcutaneous tissues. ATLL may show pleomorphic cells, resembling PTCL unspecified. Angiocentrism, large cell morphologies, as well as large Pautrier-like microabscesses, have been reported. Neoplastic cells are mature, activated, post-thymic CD4+ T-lymphocytes. The malignant cells show a CD3+, CD4+, CD7-, CD8-, CD25+ immunophenotype.[23-26] By contrast, their B-counterparts that were more frequently correlated with skin involvements were diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, LH, extranodal marginal zone mucosa-associated lymphoid tissue, mantle-cell lymphoma and follicular lymphoma (FL).

In DLCBL, skin biopsies generally show an atypical large and transformed B-cells infiltrate, with prominent nucleoli and basophilic cytoplasm, located in the dermis and subcutaneous tissue; small lymphocytes ($CD3^+$) can be found in the specimens. Immunohistology reveals an overall expression of pan B-cell markers (CD19, CD20, CD22, CD79a), CD45, Bcl-2, Bcl-6, CD10 and MUM1 with possible variants such as the polymorphous variant of EBV+DLBCL that shows strong PAX-5 and CD30 expression, CD20 and CD79a positivity with a poor inflammatory background (histopathology helps since it shows a mixture of centroblasts, immunoblasts, Reed-Sternberg-like cells, as well as histiocytes and other pleomorphic cells).[12,27]

In FL, biopsied specimens feature an irregular nodular/follicular lymphoid infiltrate that extends from the dermis to the subcutaneous tissues. A CD20, CD10, Bcl-2 and Bcl-6 positivity confirms the diagnosis of FL in skin lesions.[28] The most important clue to distinguish a nodal form with skin spread of FL and a primary FL is the strong expression of Bcl-2 molecule at immunohistology.[29] However, mounting evidence has highlighted the possibility of a (partial) expression of Bcl-2 even in primary FL.[30] Indeed, the t(14;18) translocation, which involves the IgH/BCL-2 genes, is commonly observed in nodal FLs. However, primary cutaneous FLs have been reported to lack this translocation, suggesting a distinct molecular pathogenesis. Nevertheless, studies using fluorescence *in situ* hybridization analysis have detected the IgH/BCL-2 translocation in primary cutaneous FLs, albeit at a lower frequency compared to secondary cutaneous FLs. The presence of the translocation was more common in grade 1 or 2 primary cutaneous FLs.[31]

In secondary cutaneous marginal zone lymphoma, histologically, showed tropism for adnexal structures and had similar immunophenotypes, just like primary cutaneous marginal zone lymphoma. The main histologic difference was the T- to B-cell ratio and the presence of germinal centers, with primary cases showing more T-cell infiltrates and germinal centers. However, histologic differences alone were insufficient to reliably distinguish primary from secondary disease.[32]

In HL, biopsies of cutaneous lesions may not correlate with their nodal counterparts since HL variants (lymphocyte-rich, nodular sclerosis, mixed cellularity and lymphocyte-depleted) do not show up identically in skin lesions.[10] Skin lesions usually show histopathologic features such as Hodgkin cells (HC), Reed-Sternberg cells (RSC), lacunar cells and so-called popcorn cells, scattered in a background of small lymphocytes, plasma cells, neutrophils, eosinophils and histiocytes; the neoplastic infiltrate

always spares the epidermis, whereas it typically involves the dermis (sometimes it may extend to the subcutaneous tissue). However, in more than 40% of skin lesions, classical RSC may be absent but, if there's a lymph node biopsy with histopathologic features of HL, the presence of HC alone within an appropriate cellular background is enough to diagnose cutaneous HL. Reed-Sternberg-like cells are not a specific finding in the diagnosis of cutaneous HL since they can be found in other conditions such as lymphomatoid papulosis and ALCL. Immunohistology shows cytoplasmic positivity of RSC, HC and lacunar cells for Ber-H2/CD30, M1/CD15, while they all result negative for LCA/CD45, just like in nodal samples. However, it has been reported rare cases of $CD30^{+}/CD15^{-}/CD45^{-}$ RSC and HC phenotypes, which may be found in LCAL that needs to be ruled out in these situations. Popcorn cells are strongly positive for CD20, negative for CD15 and sometimes positive for CD30.[33] RSC and HC cytoplasmic positivity for immunoglobulin light chains (both lambda and kappa) can be found.[11] Recently, the presence of mummified cells has been highlighted in literature as another clue for HL diagnosis; these cells manifest features of nonclassical apoptosis (so-called para-apoptosis), with a variable appearance (*e.g.*, multilobate/haloed/binucleated/mononuclear) and a $CD20^{+}/CD30^{+}/CD15^{+}$ phenotype associated with absence of DNA strand breaks. These features suggest that they may be regressing cells of correspondent diagnostic type (*e.g.*, RSC, HC, popcorn cells or lacunar cells) have recently observed that mummified cells (cells with condensed cytoplasm and pyknotic eosinophilic or basophilic nuclei) can be observed in HL cases featuring a skin infiltration, suggesting that such a type of cells may be a diagnostic clue.[10]

Survival

Patients affected by SCL have a poorer prognosis than patients affected by PCL (respectively, they show a 5-year survival rate of 31% *vs*. 87-92.5%). T/NK-cell and B-cell lineage of SCL show no difference in terms of overall survival and survival from the time of cutaneous involvement but, they have different prognostic factors: T/NK-cell lineage seems to be influenced by the primary tumor site with extranodal lymphomas being correlated with a worse outcome than their nodal counterparts, whereas B-cell lineage lymphomas prognosis is affected by elevated LDH levels. More specifically, DLBCL cases negative for bcl-2 were associated with better outcomes, which is something mostly found in primary cutaneous DLBCL. Secondary cutaneous DLBCL had poorer survival rates than their primary counterparts, and skin involvement soon after the initial diagnosis indicated a more aggressive clinical outcome.[34,35] Other conventional prognostic factors such as stage, age, sex and International prognostic index seem to have a minor impact on SCL prognosis.[9]

Conclusions

In contrast to PCL, SCL is a rare occurrence and literature is scarce. The aim of the present paper was to analyze in detail the state of the art on clinical presentation, histologic and immunophenotipic features and clinical outcome. In summary, clinical characteristics are quite heterogeneous and non-specific: papules, plaques, and nodules. Indeed, the same lesions can be related to inflammatory benign skin diseases. However, histology shows the same features of the internal counterpart. Survival rate is very poor because skin lesions are secondary to disease progression; furthermore, it can be the sign of an increased tumor burden and/or the ability of the disease to spread via blood or lymphatic vessels. The take-home message is to perform a biopsy in case of cutaneous lesions in patients affected by a lymphoma.

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