Primary cutaneous marginal zone B-cell lymphoma represents a low grade B-cell lymphoma that originates in the skin with no evidence of extracutaneous disease at the time of diagnosis. The diagnosis of this type of lymphoma can be very difficult especially when presenting with unusual features. Clinically, the lesions may simulate inflammatory processes or benign conditions. Histologically, the reactive T-cell infiltrate can be so abundant that the true neoplastic B-cell infiltrate is overlooked. Hence, integration of all clinical, histological, immunohistochemical and molecular data is critical in establishing the correct diagnosis and initiation of appropriate treatment. We present the case of a primary cutaneous marginal zone B-cell lymphoma with multifocal lesions, spontaneous resolution and formation of anetodermic scars that was misinterpreted as lupus erythematosus tumidus, Jessner-Kanof infiltrate, or benign lymphoid hyperplasia for 7 years. We emphasize the difficulties encountered in the diagnosis of this particular type of cutaneous lymphoma.

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Abstract

Primary cutaneous marginal zone B-cell lymphoma represents a low grade B-cell lymphoma that originates in the skin with no evidence of extracutaneous disease at the time of diagnosis. The diagnosis of this type of lymphoma can be very difficult especially when presenting with unusual features. Clinically, the lesions may simulate inflammatory processes or benign conditions. Histologically, the reactive T-cell infiltrate can be so abundant that the true neoplastic B-cell infiltrate is overlooked. Hence, integration of all clinical, histological, immunohistochemical and molecular data is critical in establishing the correct diagnosis and initiation of appropriate treatment. We present the case of a primary cutaneous marginal zone B-cell lymphoma with multifocal lesions, spontaneous resolution and formation of anetodermic scars that was misinterpreted as lupus erythematosus tumidus, Jessner-Kanof infiltrate, or benign lymphoid hyperplasia for 7 years. We emphasize the difficulties encountered in the diagnosis of this particular type of cutaneous lymphoma.

Keywords:
cutaneous T-cell lymphoma, primary cutaneous marginal zone B-cell lymphoma, lupus erythematosus
Introduction

Primary cutaneous marginal zone B-cell lymphoma (PCMZL) represents a low grade B-cell lymphoma that originates in the skin with no evidence of extracutaneous disease at the time of diagnosis (1). Patients are usually males in their 4th and 5th decades of life (2-5), who present with asymptomatic solitary lesions localized especially on the upper trunk or upper extremities. Multicentric or generalized eruptions are encountered less often and they are associated with frequent recurrences after various treatment modalities. Spontaneous resolution with development of anetoderma is an unusual feature that has very rarely been described (7). This peculiar phenomenon may be a potential pitfall in the diagnosis of PCMZL especially when it presents with papules and small nodules only, without obvious tumoral lesions. These types of lesions can be easily misinterpreted as inflammatory or benign processes, both clinically and histopathologically. Hence, the correct diagnosis can be delayed for a long period of time, sometimes for decades (4).

We present a case of PCMZL with multifocal lesions, spontaneous resolution and formation of anetodermic scars that was misinterpreted as lupus erythematosus tumidus, Jessner-Kanof infiltrate, borrelian lymphocytoma cutis or benign lymphoid hyperplasia for 7 years. We emphasize the difficulties encountered in the diagnosis of this particular cutaneous lymphoma.

Patient, Methods and Results

A 25 years-old man presented with a 7 year history of erythematous papules and nodules located on the upper back and upper arms. Over these 7 years the lesions were interpreted as either lupus erythematosus tumidus, Jessner-Kanof infiltrate, borrelian lymphocytoma cutis or benign lymphoid hyperplasia, based on clinical features and/or histological aspects revealed by three consecutive biopsies. Close-up clinical examination revealed lesions in various stages of evolution, namely: perifollicular papules, infiltrated plaques, indurated nodules, nodules with anetodermic surface, and anetodermic scars.

All three biopsies were available for evaluation. First biopsy performed at the onset of the disease showed a moderate superficial perivascular and interstitial infiltrate (Figure 2A) composed mainly of small lymphocytes with a variable number of plasmacytoid cells and mature plasma cells (Figure 2B). Second biopsy (not shown) performed several years later revealed similar histological findings. The last biopsy performed 7 years after the onset of the dis-
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The disease showed a dense nodular and diffuse infiltrate sparing the epidermis and the papillary dermis and occupying the whole reticular dermis with involvement of the superficial part of the subcutaneous fat (Figure 3A). The infiltrate showed a remarkable vertical orientation with perifollicular involvement (Figure 3B) and destruction of the adnexa (Figure 3C). Various reactive germinal centers were apparent. A population of small-medium cells with indented nuclei, non-prominent nucleoli, and abundant pale cytoplasm (centrocytes-like cells) accompanied by plasma cells, lympho-plasmacytoid cells, a few immunoblasts, and many reactive small lymphocytes occupied the perifollicular and interfollicular spaces (Figure 3D). The histological findings of the 3rd biopsy were highly suggestive of cutaneous marginal zone B-cell lymphoma.

The immunohistochemical analysis was accomplished on 5-μm-thick sections, on poly-L-Lysine coated slides. The immunohistochemical technique used was an indirect biotinial one, based on polymerized Dextran conjugated with secondary antibody and horseradish peroxidase (DAKO, EnVision), using overnight primary antibodies incubation and DAB saline solution with 0.03% hydrogen peroxide as substrate. Both positive and negative controls were used. The following antibodies were used: CD3 (monoclonal mouse anti-human CD3, clone F7.2.38, dilution 1:50; Dako), CD20 (monoclonal mouse anti-human CD20c, Clone L26, dilution 1:200, Dako), CD30 (monoclonal mouse anti-human CD30, clone Ber-H2, dilution 1:20, Dako), CD10 (monoclonal mouse anti-human CD10, clone 56C6, dilution 1:40; Dako), CD79 (monoclonal mouse anti-human CD79a, dilution 1:25; Dako), bcl2 (monoclonal mouse anti-human bcl2 oncoprotein, clone 124, dilution 1:50; Dako), bcl6 (monoclonal mouse anti-human bcl6 protein, clone PG-B6F, dilution 1:10; Dako), κ (polyclonal rabbit anti-human kappa light chains, dilution 1.80000, Dako), λ (polyclonal rabbit anti-human lambda light chains, dilution 1.80000, Dako). Histopathological and immunohistochemical evaluation was performed with Leica DM2500 microscope and images were acquired using Leica DFC490 camera.

Immunohistochemically, numerous cells disposed in nodular aggregates outside reactive follicular centers stained with CD20 (Figure 4A), CD79 (Figure 4B), bcl2 (Figure 4C) and CD43, and were negative for bcl6 and CD10. A prominent reactive T-cell infiltrate (Figure 4D) that obscured the neoplastic B-cell population was apparent. Plasma cells were monotypic, with the restriction of the Ig light chain kappa (κ:λ ratio > 5:1) (Figures 4E, F).

Molecular genetic studies using polymerase chain reaction-based methods demonstrated a monoclonal population for the FR2-JH region of the immunoglobuline heavy chains, indicating the presence of a monoclonal B-cell population. Four reactions without amplifications at the level of the V and J regions of γ T cell receptor chains (TCR) were conducted.

Clinical, histological, and immunohistochemical findings coupled with paraclinical and molecular genetic studies established the final diagnosis of primary cutaneous marginal zone B-cell lymphoma.

The patient underwent various treatments such as systemic corticosteroids, topical corticosteroids, intralesional steroid injections, cryotherapy, and surgical excisions with limited effects. Two years after diagnosis of lymphoma was established and nine years from the onset of the disease the patient is in good health with disease limited to the skin.

Discussion

PCMZL represents a low grade B-cell lymphoma that originates in the skin with no evidence of extra-
cutaneous disease at the time of diagnosis (1). Most patients are in the 4th and 5th decades of life but the age at presentation ranges from 12 to 80 years (2-4). The disease mainly affects males (61% males vs 49% females) (5). The usual presentation of PCMZL is with asymptomatic solitary lesions (6). Patients may also present with clusters of erythematous papules, plaques or nodules involving one or more anatomical sites. Generalized eruption was classically considered to be rare. However, a recent study (8) conducted on 137 patients with PCMZL showed that generalized skin lesions affected an important number (20%) of patients. Upper trunk and upper arms are particularly affected but any other body site may be involved (1, 9, 10). Spontaneous resolution with development of anetoderma, as in our case, has rarely been observed (7). This peculiar phenomenon may be a potential pitfall in the diagnosis of PCMZL as one usually do not expect a neoplastic lymphoid infiltrate (except for lymphomatoid papulosis cases and some cases of primary cutaneous anaplastic large T-cell lymphoma) to completely disappear without therapeutic inter-

Another diagnostic difficulty may arise when presentation is with papules and small nodules only, without obvious tumoral lesions. These lesions can be easily mistaken for inflammatory or benign processes like lupus erythematosus tumidus, Jessner-Kanof infiltrate, or benign lymphoid hyperplasia. Hence, the correct diagnosis can be delayed. Our case illustrates very well these diagnostic challenges. The lesions started as erythematous perifollicular papules with progressive enlargement and confluence into slightly elevated and infiltrated plaques and small indurated nodules and never progressed to large tumors. In time, some lesions developed an atrophic surface and few others spontaneously disappeared leaving anetodermic scars.

Histologically, PCMZL can also pose diagnostic problems. Biopsies from early lesions only show a sparse to moderate superficial perivascular and interstitial lymphoid infiltrate composed of predominantly small lymphocytes, a few plasmacytid cells and mature plasma cells (Figure 2). Also, established lesions can sometimes show a top-heavy infiltrate (Figure 3).
more in keeping with a pseudolymphomatous process. Moreover, many reactive germinal centers are usually observed. However, there are certain important clues that point to the real nature of the neoplastic infiltrate. At scanning power, the infiltrate shows a biphasic or triphasic appearance, with areas of pale cells located outside dark lymphoid nodules or reactive germinal centers. The density of the infiltrate is also of concern. The nodular to diffuse infiltrate involves the whole reticular dermis and sometimes the superficial part of the subcutaneous fat and spares the epidermis and papillary dermis. The infiltrate shows a characteristic vertical orientation along adnexa that can be both a clue and a pitfall in the diagnosis. Adnexal involvement is a usual feature in lupus erythematosus that can also rarely present with reactive germinal centers. However, in PCMZL the neoplastic infiltrate usually destroys the hair follicles, arrector pili muscles, and eccrine glands with accompanying necrosis. At higher power, the peri- and interfollicular pale areas are shown to be composed of small- to medium-sized cells with irregular nuclei, inconspicuous nucleoli, and abundant pale cytoplasm (centrocyte-like cells), i.e. marginal zone B cells, lymphoplasmacytoid cells, plasma cells, a few centroblast- or immunoblast-like cells, and many reactive T cells. An important aid to the diagnosis is the identification of plasma cells at the periphery of the infiltrates and in the superficial dermis beneath the epidermis. One of the major histologic pitfalls is the presence of many

Figure 4. Immunohistochemically, numerous cells disposed in nodular aggregates outside reactive follicular centers stained with (A) CD20, (B) CD79, and (C) bcl2. A prominent reactive T-cell infiltrate, stained with (D) CD3, obscured the neoplastic B-cell infiltrate. Plasma cells were monotypic, (E) κ: (F) λ ratio > 5:1 (cd20 stain, 25x; cd79 stain, 25x; bcl2 stain, 25x; cd3 stain, 25x; κ stain, 200x; λ stain, 200x)
reactive small lymphocytes that can be so abundant as to obscure the neoplastic infiltrate (T-cell rich B-cell lymphoma) (8, 11).

Apart from this conventional variant of PCMZL there are cases characterized by a predominance of lymphoplasmacytoid lymphocytes, small lymphocytes and plasma cells (lymphoplasmacytic variant of PCMZL), and cases characterized by a predominance of plasma cells (plasmacytic variant of PCMZL) (10). Also, there are rare reported cases with predominance of blasts.

Given the clinical and histologic diagnostic difficulties, immunohistochemistry and molecular studies are crucial to arriving at the correct diagnosis. Immunohistochemically, the tumour cells forming nodules outside lymphoid follicles express CD20, CD79a and CD138. The neoplastic infiltrate usually shows either κ or λ light chain restriction. Reactive follicles are positive for Bcl-2 and CD10 and negative for Bcl-2/A monoclonal rearrangement of the immunoglobulin heavy chain (Jh) gene can be detected in most cases (11).

Translocation t(14;18)(q32;q21)/IgH-malt1, t(3;14) (p14;q32) involving IgH and FoxP1 genes has been reported in a minority of cases (16).

The association of PCMZL with *B. burgdorferi* has been observed in some European cases, especially in the lymphoplasmacytic variant of it (17, 18). In general, patients with PCMZL have an excellent prognosis with an estimated 5 year survival of almost 100% (19). Dissemination to extracutaneous sites is exceedingly rare. However, cases with multiple lesions have a tendency to recur in the skin after treatment, regardless of the method used (8). This was also the case with our patient. For solitary lesions or localized disease, the recommended treatment is surgical excision, radiotherapy or combination of these methods. No significant differences were observed between surgery and radiotherapy, but surgery alone was associated with more frequent recurrences at the initial site (8). Antibiotherapy is the treatment of choice for cases associated with *B. burgdorferi* infection and for cases with lymphoplasmacytic predominance. Other treatment modalities such as IFNα, rituximab, chlorambucil, and corticosteroids may be of benefit in cases with multifocal skin lesions.

**Conclusions**

The diagnosis of PCMZL can be very difficult especially when presenting with unusual features like spontaneous resolution and formation of anetodermic scars. In the absence of large tumors, presentation with papular and small nodular lesions can be misleading as these lesions may simulate inflammatory processes or benign conditions. Histologically, the reactive T-cell infiltrate can be so abundant that the true neoplastic B-cell infiltrate can be overlooked. Hence, integration of all clinical, histological, immunohistochemical and molecular data is critical in establishing the correct diagnosis and initiation of appropriate treatment.

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**Bibliography**