Cutaneous B-Cell Neoplasms Mimicking Granulomatous Rosacea or Rhinophyma

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Background: Unlike T-cell neoplasms, B-cell lymphoproliferative disorders have a limited clinical spectrum of skin involvement. Cutaneous B-cell neoplasms mimicking rosacea or rhinophyma are rare.

Observations: We described 12 patients with B-cell lymphoproliferative neoplasms presenting with a facial eruption clinically mimicking rosacea or rhinophyma. Eleven patients were women; ages ranged from 36 to 81 years. The clinical presentation included small papules on the nose and cheeks, and around the eyes mimicking granulomatous rosacea; nodules on the nose, cheeks, chin, or forehead mimicking phymatous rosacea; or a combination of both. Three patients had preexisting erythematotelangiectatic rosacea and 1 had rhinophyma. Based on a clinicopathologic correlation and B-cell clonality analysis, the diagnosis was primary cutaneous follicular center B-cell lymphoma in 4 cases, primary cutaneous marginal zone lymphoma in 6, and skin involvement of chronic lymphocytic leukemia in 2. All patients had an indolent course as expected for their disease.

Conclusions: Cutaneous involvement of B-cell neoplasms may mimic granulomatous rosacea or rhinophyma. This unusual clinical presentation is more common in women and appears in the setting of preexisting rosacea or as a new eruption. Proliferative B-cell disorders should be added to the differential diagnosis of symmetric papular or papulonodular eruptions of the face.


METHODS

We performed a retrospective case analysis of 12 patients with cutaneous B-cell neoplasms who were referred to our tertiary dermatology clinics from January 1, 1996, through December 31, 2010, for a persistent facial rash. The differential diagnoses included rosacea and rhinophyma. We retrieved clinical history, clinical findings, laboratory results, and follow-up data from the medical files and reviewed the biopsy specimens. Final diagnosis was made according to the criteria of the World Health Organization or the European Organization for Research and Treatment of Cancer. The study was approved by the local ethics committees.

RESULTS

The patients' clinical data and final diagnoses are described in Table 1. The study group included 11 women and 1 man with a mean age of 57 (range, 36-81) years. The time elapsed from the initial presentation to the final diagnosis varied from a few months to 10 years (mean time, 23 months). The distinguishing features of the clinical presentation included nonpustular granuloma-
tous rosacea-like lesions and rhinophyma/phymatous plaques (Table 1, Figure 1, and Figure 2). Four patients (patients 1-3 and 10) had a history of preexisting rosacea manifesting as erythematotelangiectatic rosacea (in 3 patients) and rhinophyma (in 1 patient) (Figure 3). Two of these patients developed rhinophymalike lymphoma on the nose. Half the patients were treated for rosacea with topical or systemic antibiotics or both, without any benefit (Table 1).

The histological and immunophenotypical features of the cases and the results of molecular studies are described in Table 2. Four cases revealed superficial and deep nodular aggregates of centrocytes and centroblasts, features of follicular-center cell lymphoma (Figure 4). Six cases showed superficial and deep nodular aggregates of small irregular B lymphocytes, some with a monocytoid or plasmacytoid appearance.
and residual fragmented germinal centers, features of marginal cell lymphoma (Figure 5). Two cases had diffuse dermal infiltrates of mostly small regular B cells (Figure 6), consistent with skin involvement by chronic lymphocytic leukemia (CLL). Furthermore, in patient 4, results of an IgH rearrangement study showed an identical clone in the blood and skin (Figure 6), establishing the diagnosis of leukemia cutis. Demodex folliculorum was not present in any of the biopsy specimens.

Based on a full workup including clinico-pathologic correlation and analysis of B-cell clonality, the diagnosis retained was primary cutaneous follicular center B-cell lymphoma in 4 of 12 cases (33%), primary cutaneous marginal zone lymphoma in 6 (50%), and skin involvement of CLL in 2 (17%) (Table 2). All the patients had an indolent course as expected for their disease. Initial therapy, which included radiotherapy and/or excisions for 8 patients with primary cutaneous B-cell lymphoma (PCBCL), led to complete remission. However, in patients 3 and 8, new lesions developed at sites not previously treated. Intralesional or potent topical corticosteroids applied to these

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**Table 2. Histological, Immunophenotypical, and Molecular Characteristics of Cases of B-Cell Neoplasms Mimicking Rosacea and Rhinophyma**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Architecture</th>
<th>Cells</th>
<th>Immunophenotype</th>
<th>IgH Gene Rearrangement</th>
<th>Final Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Superficial and deep nodular</td>
<td>Small and large (centrocytes, centroblasts)</td>
<td>Positive for CD20 and CD10 in germinal center–like structures; negative for bcl-2</td>
<td>ND</td>
<td>PCFCL</td>
</tr>
<tr>
<td>2</td>
<td>Superficial and deep, nodular and diffuse</td>
<td>Small and large, regular and irregular</td>
<td>Positive for CD20, bcl-6, and CD10 in follicular center cells; CD23 in nonfollicular center cells; and CD3 small cells between aggregates</td>
<td>Monoclonal</td>
<td>PCFCL</td>
</tr>
<tr>
<td>3</td>
<td>Superficial and deep, nodular and diffuse, follicular colonization, prominent marginal zone</td>
<td>Small irregular and monocytoid in marginal areas and between germinal centers</td>
<td>Positive for CD20 and bcl-2 in T cells and marginal areas, bcl-6 and CD10 in germinal centers, and CD3 in small cells</td>
<td>Monoclonal</td>
<td>PCMZL</td>
</tr>
<tr>
<td>4</td>
<td>Diffuse infiltrate involving the whole dermis, with areas of proliferation centers</td>
<td>Small regular and slightly irregular, prolymphocytes and paraimmunoblasts in proliferation centers</td>
<td>Positive for CD20 and CD23; negative for CD5</td>
<td>Same clone in the skin and peripheral blood</td>
<td>Cutaneous localization of B-CLL</td>
</tr>
<tr>
<td>5</td>
<td>Superficial and deep nodular, small remnants of germinal centers</td>
<td>Irregular small lymphocytes, also at the periphery of the nodules, few plasma cells</td>
<td>Positive for CD20 and bcl-2 in the small irregular lymphocytes, bcl-6 in remnants of germinal centers, and CD3 in T cells at the periphery of the nodules; some plasma cells, lambda predominates</td>
<td>Monoclonal</td>
<td>PCMZL</td>
</tr>
<tr>
<td>6</td>
<td>Superficial and deep nodular aggregates, few small germinal centers</td>
<td>Small irregular, some monocytoid</td>
<td>Positive for CD20(+) and CD3(+) at the periphery, bcl-2 in small B and T cells, and CD10 in germinal centers</td>
<td>Monoclonal</td>
<td>PCMZL</td>
</tr>
<tr>
<td>7</td>
<td>Superficial and deep nodular, residual germinal centers</td>
<td>Small irregular cells, plasma cells</td>
<td>Positive for CD20 and bcl-2 in most of the cells, bcl-6 and CD10 in residual germinal centers, and CD3 in small T cells</td>
<td>Polyclonal</td>
<td>PCMZL</td>
</tr>
<tr>
<td>8</td>
<td>Superficial and deep nodular aggregates, focally fragmented germinal centers</td>
<td>Small and large, regular and irregular</td>
<td>Positive for CD20, CD45RA, bcl-6, and CD10 in follicle center cells; bcl-2 in some of the B cells and in T cells; and CD3</td>
<td>Monoclonal</td>
<td>PCFCL</td>
</tr>
<tr>
<td>9</td>
<td>Diffuse infiltrate involving the whole dermis</td>
<td>Small irregular lymphocytes, plasmacytoid and plasma cells</td>
<td>Positive for CD20 (approximately 50%) and bcl-2 in B and T cells; negative for bcl-6; many plasma cells, lambda predominates</td>
<td>Polyclonal</td>
<td>PCMZL</td>
</tr>
<tr>
<td>10</td>
<td>Diffuse infiltrate involving the deep dermis and subcutaneous tissue</td>
<td>Small and medium lymphoid cells, reactive T lymphocytes, few histiocytes</td>
<td>Positive for CD5, CD20, and bcl-2; negative for bcl-6; clonal expression of k light chain</td>
<td>Monoclonal</td>
<td>Cutaneous localization of B-CLL</td>
</tr>
<tr>
<td>11</td>
<td>Nodular infiltrate involving the whole dermis with a grenz zone toward the epidermis</td>
<td>Small lymphocytes, reactive T cells, some histiocytes</td>
<td>Negative for CD10; positive for CD20 and bcl-2; a few bcl-6–positive follicle center cells; no light chain restrictions</td>
<td>Monoclonal</td>
<td>PCMZL</td>
</tr>
<tr>
<td>12</td>
<td>Nodular infiltrate involving the whole dermis with a grenz zone toward the epidermis, focally germinal centers</td>
<td>Small and medium lymphoid cells, reactive T cells, few histiocytes and plasmocytes</td>
<td>Positive for CD20 and bcl-6; negative for CD10; no light chain restriction</td>
<td>Polyclonal</td>
<td>PCFCL</td>
</tr>
</tbody>
</table>

Abbreviations: B-CLL, B-cell chronic lymphocytic leukemia; ND, testing not performed; PCFCL, primary cutaneous follicular center cell lymphoma; PCMZL, primary cutaneous marginal zone lymphoma.
small lesions led to complete remission. The cutaneous lesions of CLL resolved completely after a course of prednisone and chlorambucil therapy in patient 4 and rituximab and radiotherapy in patient 10. Two patients had only received the diagnosis at the time of this report, and follow-up was not available.

**COMMENT**

B-cell lymphoproliferative diseases clinically mimicking rosacea are extremely rare and have been previously reported in only 7 cases detailed in Table 3. The findings of the present case series of 12 patients with B-cell lymphoproliferative diseases simulating granulomatous rosacea, rhinophyma, or both are comparable to those reports. Likewise, most of our patients were women. However, our patients were somewhat younger than those described in the previous reports (mean age, 57 vs 76 years), making the initial diagnosis of rosacea more plausible. Clinically, all our patients presented with phymatous lesions (mostly rhinophyma), granulomatous rosacea-like lesions, or both. In contrast, all previously described patients who had PCBCL had phymatous lesions. Three patients described herein and 1 described previously had preexisting rosacea presenting as facial flushing, erythema, and telangiectasia. Therefore, the development of papules or rhinophyma in these patients was considered part of the preexisting rosacea. Two patients described in the literature also had pustules, and both of them had CLL. In one of those patients, earlier biopsy findings showed polymorphonuclear leukocytes, which probably represented preexisting rosacea. In the other patient, histological features of the pustules were not described. Thus, pustules might have formed secondary to occlusion of the folliculosebaceous unit by the leukemic infiltrate. In contrast, none of the patients described herein had a pustular eruption.

This unique clinical presentation of B-cell neoplasm involving the skin and simulating rosacea led to a diagnosis delay that ranged from months to years. Half the patients in the present series (6 of 12) and most of the patients described in the literature (6 of 7) had been initially treated with topical or systemic antibiotics for at least a few months without any benefit before a biopsy specimen was obtained. Thus, rosacea and rhinophyma should be added to the list of the unusual manifestations of B-cell neoplasms simulating other skin diseases (Table 4). The clinical differential diagnosis of these lesions does not include only rosacea. For the papular/granulomatous rosacea-like lesions, the differential diagnosis would include mostly adnexal tumors, such as basal cell carcinoma, trichoepithelioma, or sebaceous hyperplasia, and cutaneous sarcoidosis. For the phymatous lesions, granulomatous diseases (infectious or noninfectious) and T-cell lymphoma should be considered.

Fifteen of the 19 total patients (10 in the present series and 5 in previously reported cases) had PCBCL, with the marginal zone lymphoma being the most common (10 of 19 patients, including 1 with immunocytoma, currently considered a type of marginal zone lymphoma) followed by follicular center cell lymphoma (5 of 19 patients). In 4 patients, the skin infiltrative lesions represented leukemia cutis of CLL. In general, primary cutaneous marginal zone lymphoma is uncommonly located on the face. One may therefore speculate that chronic antigenic stimulation caused by a resident organism such as *D folliculorum* leads to the development of the lymphoma similar to the relation between *Helicobacter pylori* and gastric lymphoma. Although we did not observe *Demodex* organisms in any of the biopsy specimens, such a mechanism is plausible because it would
account for the lymphoma development and the clinical presentation. Alternatively, similar to descriptions of leukemic infiltrates of CLL localized to the sites of herpes zoster, the lymphomatous/leukemic infiltrates localized to the face may represent the isomorphic phenomenon on the sites of a preexisting rosacea/rhinophyma.

In all 19 reported cases, the diagnosis was based on histological and immunophenotypical characteristics, supported in most of the cases by genotypic findings. Demonstration of a monotypic plasma cell population or IgH gene rearrangement is crucial for the diagnosis of primary cutaneous marginal zone lymphoma in this setting because some cases of rosacea may show dense lymphohistoplasmacytic infiltrate. It is also essential to show the identical clone of B cells in the skin infiltrate and in the blood in cases of CLL, especially if the findings for CD5 are negative (as in patient 4) or when a concomitant B-cell lymphoma has to be excluded.

The PCBCLs were treated with excision or radiotherapy, as indicated for low-grade PCBCL. In contrast, skin infiltrates of CLL in which most of the cells are small are related to a favorable prognosis and do not require specific therapy. However, in cases in which they pose an aesthetic problem, such as those described in the present series, radiotherapy and even systemic therapy may be indicated. For small papules and nodules that continue to appear, topical corticosteroids may be the treatment of choice for early lesions. This modality may be more practical and accepted from the cosmetic point of view, probably without affecting the course of the disease. Nevertheless, further studies are needed to validate this approach, particularly in cases of follicular center B-cell lymphoma.

In summary, cutaneous involvement by B-cell neoplasms may mimic rosacea or rhinophyma. This unusual clinical presentation is more common in women and appears in the setting of preexisting rosacea or as a new eruption. A B-cell proliferative disorder presenting

Figure 5. Histological features of primary cutaneous marginal zone lymphoma (patient 3). A, Superficial and deep nodular aggregates are seen (hematoxylin-eosin, original magnification ×20). B and C, The aggregates show distended marginal zones of monocytoid B cells (hematoxylin-eosin [B] and CD20 [C], original magnification ×200). C, The residual germinal center reveals positive staining for CD20 and negative staining for bcl-2. D, The marginal B cells are positive for bcl-2 (original magnification ×200).
Table 3. Reports of B-Cell Neoplasms Mimicking Rosacea or Rhinophyma: Review of the Literature

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Clinical Presentation/Initial Diagnosis</th>
<th>Early Therapy</th>
<th>Final Diagnosis</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/69</td>
<td>Erythematous papules and pustules on the cheeks, forehead, and chin/roacea</td>
<td>Tetracycline hydrochloride</td>
<td>CLL</td>
<td>Thomson and Cochran, 1978</td>
</tr>
<tr>
<td>2/F/50</td>
<td>Multiple erythematous infiltrated nodules and plaques over face and ears/granulomatous rosacea</td>
<td>Topical metronidazole, minocycline hydrochloride</td>
<td>PCMZL (immunocytoma)</td>
<td>Colvin et al, 2003</td>
</tr>
<tr>
<td>3/F/86</td>
<td>Indurated, well-demarcated, erythematous to violaceous nodule extending from the midnasal bridge to the nasal tip/rhinophyma</td>
<td>Topical metronidazole</td>
<td>PCFCL</td>
<td>Seward et al, 2004</td>
</tr>
<tr>
<td>4/F/83</td>
<td>Erythema and swelling of the nose/rhinophyma (also nodule on pinna of the ear and nail fold swelling)</td>
<td>Minocycline</td>
<td>PCMZL</td>
<td>Stanway et al, 2004</td>
</tr>
<tr>
<td>5/F/78</td>
<td>Nontender erythematous nodules and plaques at tip of nose/rhinophyma</td>
<td>Erythromycin, acyclovir sodium</td>
<td>PCMZL</td>
<td>Ogden and Coulson, 2008</td>
</tr>
<tr>
<td>6/F/80</td>
<td>Slightly infiltrated painless erythematous plaque localized on tip of nose/rhinophyma</td>
<td>Minocycline</td>
<td>PCMZL</td>
<td>Rosmaninho et al, 2010</td>
</tr>
<tr>
<td>7/F/83</td>
<td>Infiltrated nodules and plaques on nose, cheeks, and periorbitally; papules and pustules; sebaceous hyperplasia; and telangiectasia/rosacea and rhinophyma</td>
<td>None</td>
<td>CLL</td>
<td>Bennett et al, 2010</td>
</tr>
</tbody>
</table>

Abbreviations: CLL, chronic lymphocytic leukemia; PCFCL, primary cutaneous follicular center cell lymphoma; PCMZL, primary cutaneous marginal zone lymphoma.

Figure 6. Leukemia cutis of chronic lymphocytic leukemia mimicking phymatous rosacea (patient 4). A, Erythematous plaques and nodules on the nose, cheeks, and chin. B, Diffuse lymphocytic infiltrate involving the dermis (hematoxylin-eosin, original magnification ×40). C, The infiltrate is composed of small round lymphocytes and larger cells (prolymphocytes and paraimmunoblasts) (hematoxylin-eosin, original magnification ×400). D, Results of the IgH study show identical clones (dark filled peaks marked by arrows at 125 kilobase) in the skin biopsy specimen (top) and in the peripheral blood (bottom). The y-axes show peak intensity, measured in arbitrary units; the x-axes show DNA fragment size, measured in kilobases.
Table 4. Unusual Clinical Manifestations of Cutaneous B-Cell Neoplasms

<table>
<thead>
<tr>
<th>B-Cell Neoplasm</th>
<th>Clinical Appearance</th>
<th>Selected Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>Papules in a dermal distribution (after herpes zoster)</td>
<td>Wakelin et al, 1997</td>
</tr>
<tr>
<td>CLL</td>
<td>Fingertip hypertrophy</td>
<td>Feinerman et al, 2003</td>
</tr>
<tr>
<td>MZL/FCC/CLL</td>
<td>Rosacea/rhinophyma</td>
<td>Present series</td>
</tr>
<tr>
<td>FCC/MZL</td>
<td>Anetoderma</td>
<td>Hodak et al, 2010</td>
</tr>
<tr>
<td>MZL</td>
<td>Lipoma (subcutaneous)</td>
<td>Paulli et al, 2010</td>
</tr>
<tr>
<td>Large B-cell lymphoma</td>
<td>Cutaneous horns</td>
<td>Dasgupta et al, 2006</td>
</tr>
<tr>
<td>Large B-cell lymphoma</td>
<td>Chronic venous ulcer</td>
<td>Garbea et al, 2002</td>
</tr>
<tr>
<td>Intraocular lymphoma</td>
<td>Livedo reticularis and livedo vasculitis</td>
<td>Rüglin and Bürger, 2007</td>
</tr>
<tr>
<td>Secondary involvement of the skin by MZL</td>
<td>Mycosis fungoides</td>
<td>Chui et al, 1999</td>
</tr>
</tbody>
</table>

Abbreviations: CLL, chronic lymphocytic leukemia; FCC, follicular center cell; MZL, marginal zone lymphoma.

in the skin should be added to the long list of diseases affecting the face manifested by rhinophyma or papulonodular rosacea-like eruptions.


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Author Contributions: Drs Barzilai, Feuerman, Quaglino, and Hodak had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Barzilai, Feuerman, and Hodak. Acquisition of data: Barzilai, Feuerman, Quaglino, and Hodak. Analysis and interpretation of data: Barzilai, Feuerman, Quaglino, David, Feinmesser, Halpern, Feldberg, Tomasinii, Tabibian-Keissar, Amarilgio, and Hodak. Drafting of the manuscript: Barzilai. Critical revision of the manuscript for important intellectual content: Barzilai, Feuerman, Quaglino, David, and Hodak. Administrative, technical, and material support: Feinmesser, Tabibian-Keissar, and Amarilgio. Study supervision: Barzilai and Hodak.

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REFERENCES

Morbus Europaeus: Europeans Naming Syphilis for Their Enemies

The Spanish physician Rodrigo Ruiz Diaz de Isla attributed the entry of syphilis in Europe to Christopher Columbus, who brought it from the New World (1493). After King Charles VIII conquered the Neapolitan kingdom, the French called syphilis maladie de Naples or mal napolitain. Interestingly, Italians Luca Ghini and Nicola Massa used the name morbus neapolitanus in the titles of their 2 works, respectively. After the battle of Fornovo, with a victory by the Italian League over the French army commanded by Charles VIII, syphilis was called male italiano or morbo italico.

Syphilis became the symbol of shame that was used by people to cast aspersion on their enemies. It was named morbo lusitano by the Castilians and mal castigliano by the Lusitans, showing the ancient acrimony between them. Castilians also called syphilis mal di Galizia, referring to both Catholic kings Isabella of Castile and Ferdinand of Aragon. Turks used the name mal dei cristiani, underscoring the never-ending hostility between Turks and Christians. In the early 16th century, the Dutch and Flemish called syphilis morbo spagnolo, in commemoration of the Spanish invasion. Russians used the synonyms mal dei Polacchi and mal dei Tedeschi.

Morbus europaeus was justified because syphilis spread through all of Europe and beyond. Pietro Rostino used the term male indiano, referring to the New World; Antonio Scnaro used more precisely the term mal d'America; and Francois Xavier Swediaur used mal de la baia di St Paul. Syphilis was named malattia del Portogallo in Italy because of the undesirable presence of the Portuguese Vasco de Gama in 1498 and Pedro Alvarez in 1500 and their men. Firanga was the name used in Calcutta, in remembrance of the Carlovingian empire. The Japanese called syphilis mal portoghese as an affront to the Portuguese and ulcerà della Cina or veleno di susino to offend the Chinese. Finally, the Chinese named syphilis ulcerà di susino or eruzione di Canton, after the first Chinese city where syphilis spread. Chinese poets compared syphilis to the budding of a flower without fear of winter, meaning that the appearance of syphilis is both abrupt and startling.

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5. Swediaur F, ed. Traite complet sur les symptomes, les effets, la nature et le traitement des maladies syphilitiques. Paris, France: Cellot; 1817.

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