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CASE REPORTS

Cutaneous Follicular Center B-Cell Lymphoma Treated With Intralesional Rituximab

R. Gamo,[a] L. Calzado,[a] F. Pinedo,[b] and J. L. López-Estebaranz[a]

[a]Servicio de Dermatología and [b]Servicio de Anatomía Patológica, Hospital Fundación Alcorcón, Alcorcón, Madrid, Spain

Abstract. Cutaneous follicular center B-cell lymphomas are indolent tumors characterized by the presence of neoplastic follicular center cells. They contain a mixture of centrocytes with a variable number of centroblasts. The tumor is usually treated by surgery or radiotherapy, although other treatments may be used such as interferon-α, chemotherapy, and biological agents (rituximab). Rituximab is a chimeric monoclonal anti-CD20 antibody that can be administered intravenously or intralesionally. We report the case of a 41-year-old man who consulted for violaceous nodular lesions in the left scapular region and who was diagnosed with cutaneous follicular center B-cell lymphoma after biopsy, laboratory tests, thoracic-abdominal-pelvic computed tomography, abdominal ultrasound, and bone marrow biopsy. It was decided to treat him with 30 mg of intralesional rituximab administered for 1 week (3 times) every month for 4 months. Complete response was obtained. We also review the published cases of cutaneous B-cell lymphoma treated with intralesional rituximab.

Key words: B-cell lymphoma, follicular center B-cell lymphoma, rituximab, intralesional.

LINFOMA CUTÁNEO DE CÉLULAS B DEL CENTRO FOLICULAR TRATADO CON RITUXIMAB INTRALESIONAL

Resumen. Los linfomas cutáneos de células B del centro folicular son tumores indolentes compuestos por células neoplásicas del centro folicular. Están constituidos por una mezcla de centrocitos con un número variable de centroblastos. Los tratamientos habitualmente utilizados son la cirugía y la radioterapia, aunque se utilizan otros como el interferón-α (IFN-α), la quimioterapia y tratamientos biológicos (rituximab). El rituximab es un anticuerpo monoclonal quimérico anti-CD20. Puede utilizarse por vía intravenosa o intralesional. Presentamos el caso de un paciente varón de 41 años que consultó por lesiones nodulares violáceas en el área escapular izquierda y que, tras la realización de una biopsia, analítica, tomografía axial computarizada (TAC) toracoabdominopélvica, ecografía abdominal y biopsia de médula ósea fue diagnosticado de linfoma cutáneo de células B del centro folicular. Se decidió tratamiento con 30 mg de rituximab intralesional, tres veces a la semana, una vez al mes, durante 4 meses, con respuesta completa. Realizamos una revisión de los casos de linfoma cutáneo de células B tratados con rituximab intralesional.

Palabras clave: linfoma cutáneo de células B, linfoma B del centro folicular, rituximab, intralesional.

Introduction

Cutaneous follicular center B-cell lymphomas are a heterogeneous group of lymphoproliferative diseases that affect the skin. The classification of the World Health Organization and European Organization for Research and Treatment of Cancer (WHO-EORTC) groups them as follows: primary cutaneous marginal zone B-cell lymphoma; primary cutaneous follicular center B-cell lymphoma; primary cutaneous diffuse large B-cell lymphoma, leg type; and primary cutaneous diffuse large B-cell lymphoma, other.

Cutaneous B-cell lymphoma is usually treated with surgery, radiotherapy, or both, and less frequently with interferon alfa, chemotherapy, or more recently, rituximab, a chimeric monoclonal anti-CD20 antibody (CD20 is expressed in 95% of cases of cutaneous B-cell lymphoma). Rituximab has been used successfully against systemic non-

Correspondence:
Reyes Gamo
Departamento de Dermatología
Hospital Fundación Alcorcón
Avda Budapest, 1
28922 Alcorcón, Madrid, Spain
reyesgamo@vodafone.es
rgamo@fhalcorcon.es

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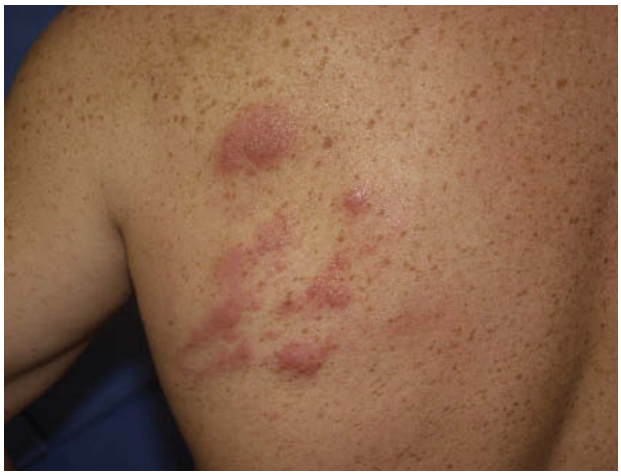

Figure 1. Violaceous nodular lesions grouped together on the left scapular area.

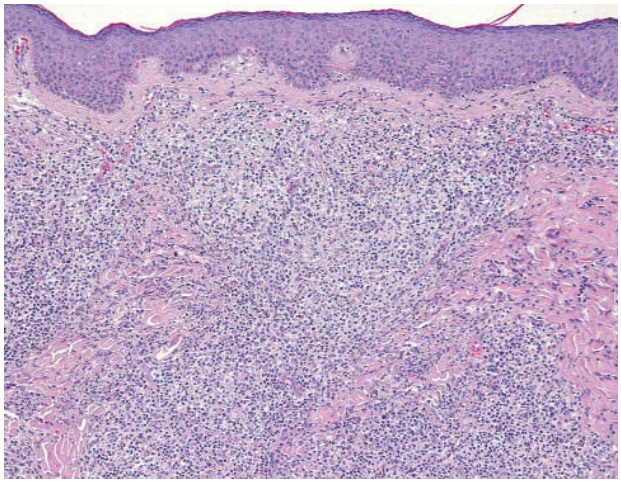

Figure 2. Cellular infiltrate that is polymorphous in size—intermediate and large—and in shape—cleaved cells and large noncleaved cells. Hematoxylin-eosin ×100.

Hodgkin B-cell lymphoma since 1997. In cutaneous B-cell lymphoma, it is administered intravenously and intralesionally. Intralesional administration is very well tolerated, effective, and much more economical than intravenous administration.

Case Description

The patient was a 41-year-old man with no clinical history of interest who consulted because of lesions on the left scapular area that had developed over a 5-month period with no accompanying symptoms.

Physical examination revealed infiltrated erythematous-violaceous papules measuring 1 cm to 3 cm in diameter grouped together in an area of approximately 9 cm on the left scapular area (Figure 1). There were no enlarged lymph nodes.

A biopsy revealed a dermal infiltrate suggestive of a lymphoproliferative process with a variable growth pattern and discrete nodular areas interspersed with other areas that were diffuse in appearance, mainly in the superficial dermis. The lesion was composed of an infiltrate that was polymorphous both in size (intermediate and large) and in shape (many cleaved cells and large noncleaved cells). The cells were intermingled with abundant mature lymphocytes and histiocyte-like cells. The overlying epidermis was normal (Figure 2).

The immunohistochemical study showed that intermediate and large proliferating cells expressed CD20, BCL6, and occasionally, CD10, but not CD3, BCL2, cyclin D-1, or kappa and lambda light chains. Large proliferating cells expressed MIB-1 and, occasionally, CD30. The small lymphocytes, which were mature in appearance, expressed CD3, CD43, and occasionally, BCL2.

A systematic workup including complete blood count, complete urinalysis, biochemistry, and coagulation was performed. All parameters were within the normal range. Serology for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus was negative. Abdominal ultrasound and thoracic-abdominal-pelvic computed tomography were normal, and a bone marrow biopsy did not reveal evidence of neoplastic infiltration.

The patient was diagnosed with cutaneous follicular center B-cell lymphoma. After a request for compassionate use, therapy was started with intralesional rituximab at 30 mg (distributed between the different lesions) for 3 days, 1 week of every month for 4 months. All the lesions were treated. After the second cycle, most of the lesions responded to treatment, with the exception of 1 lesion that resolved after 2 additional cycles of treatment. A biopsy of this lesion performed 1 month after finishing treatment did not reveal neoplastic infiltration (Figures 3 and 4). The patient tolerated the treatment well, complaining of mild injection site pain, and the laboratory workup was normal. After 6 months' follow-up, there have been no recurrences of the lesions.

Discussion

Primary cutaneous B-cell lymphomas are a heterogeneous group of lymphoproliferative processes that are characterized by cutaneous monoclonal infiltration of B cells with no extracutaneous involvement after complete staging. Histology by immunotyping with monoclonal antibodies in frozen or paraffin-embedded tissue is necessary for diagnosis. Clinicopathologic suspicion of this condition alerts to the need for computed tomography of the abdomen and pelvis to rule out lymph node involvement, an abdominal

ultrasound to rule out visceral involvement, bone marrow biopsy and aspirate, cell counts, and analysis of lactate dehydrogenase.[1] The WHO-EORTC classification groups primary cutaneous B-cell lymphomas as marginal zone, follicular center, diffuse large (leg type), and diffuse large (other types).

Cutaneous follicular center B-cell lymphoma is an indolent tumor composed of neoplastic follicular center cells comprising a mixture of centrocytes (small or large, cleaved) and a variable number of centroblasts (large, noncleaved and with a prominent nucleolus). Its growth pattern may be diffuse, follicular, or mixed, and it mainly affects the back and head, although it can appear at other sites, or even at several sites without the prognosis being necessarily worse.

Immunophenotyping reveals restriction to 1 immunoglobulin light chain or loss of both, in addition to expression of the pan-B markers CD20 and CD79A. Expression of BCL6 is usually positive, that of CD10 variable, and BCL2 negative or weakly positive. Immunogenotyping reveals rearrangement of the heavy chain and absence of the t(14;18) translocation.

Current treatment of cutaneous B-cell lymphoma involves surgical resection and/or radiotherapy, intralesional or systemic interferon alfa, chemotherapy, or rituximab.[2]

Surgical resection is a good option in the case of an isolated lesion or a small number of lesions grouped together in one area, and it can be combined with radiotherapy.

Radiotherapy is effective against the lesions caused by primary cutaneous B-cell lymphoma and doses generally range from 20 Gy to 30 Gy. Treatment is well tolerated, and several authors consider it the first choice for localized lesions.

Interferon alfa has immunomodulatory and antitumor properties and is used less commonly in cutaneous B-cell lymphoma than in cutaneous T-cell lymphoma. The standard dose ranges from 3 to 9 million units subcutaneously per week. Interferon alfa can also be administered intralesionally. The most common side effects are asthenia, fever, and nausea.

Chemotherapy is not the treatment of choice for cutaneous B-cell lymphoma and is reserved for the more aggressive forms, such as large-cell lymphoma, leg type. The CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) is the most widely used.

Rituximab is a chimeric monoclonal anti-CD20 antibody. CD20 is a membrane phosphoprotein expressed only in B lymphocytes and is present in 95% of B-cell lymphomas. Since 1997, rituximab has been used in the treatment of non-Hodgkin B-cell lymphoma and has proven effective in cutaneous B-cell lymphoma. It can be administered intravenously[3] or intralesionally.

The standard intravenous dose is 375 mg/m^2 weekly for between 4 and 8 weeks, giving a total dose of 1500 mg/m^2 to 3000 mg/m^2. It leads to transitory depletion of B lymphocytes without associated immunodeficiency and the B cells are regenerated after a period of between 6 and 12 months. The adverse events reported after systemic administration of rituximab include fever, headache, hypotension, dyspnea, bronchospasm, urticaria, angioedema, thrombocytopenia, and lymphopenia. However, these systemic reactions are uncommon, observed mainly during the first infusion, and diminish with subsequent doses. Oral analgesics and hydroxyzine dihydrochloride are usually administered before and after the infusion. Intravenous rituximab is not associated with a significant risk of systemic toxicity or opportunistic infections.

Intralesional rituximab is very well tolerated, the only complaint being pain at the injection site. The dose usually ranges from 10 mg to 40 mg administered 3 times during

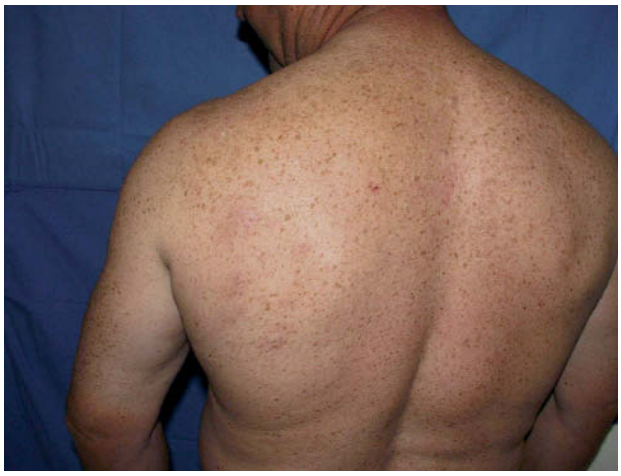

Figure 3. Scapular area with complete response after 4 cycles of intralesional rituximab.

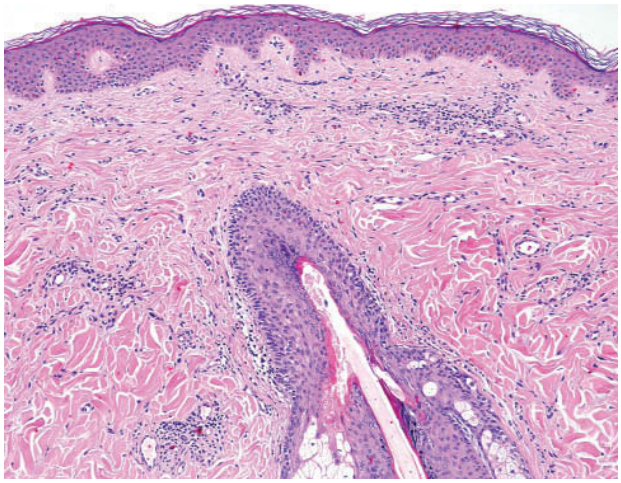

Figure 4. Biopsy after treatment with no evidence of lymphoma. Hematoxylin-eosin ×100.

Table. Patients With Cutaneous B-cell Lymphoma Treated With Intralesional Rituximab

Reference/y		*Sex/Age, y*	*Diagnosis*	*Symptoms*	*Previous Treatment*
Heinzerling et al[4]	2000	1 F/62	LCL	Scalp	Topical corticosteroids, PDT, PUVA, topical carmustine, injected cisplatin
		2 M/35	FCL	Thorax, UE, abdomen, right thigh	Surgery
Paul et al[5]	2001	3 F/65	FCL	Parietal area	None
		4 F/42	FCL	UE and left leg	Surgery
		5 F/41	FCL	UE	Surgery
Roguedas et al[6]	2005	6 M/40	FCL	Back and UE	Cyclophosphamide, vindesine, prednisolone Interferon alfa
Fink-Puches et al[7]	2005	7 F/48	MZL	Face and forehead, 2 lesions	Antibiotics
		8 F/78	FCL	Back and forehead, 4 lesions	Surgery
		9 F/58	FCL	Head, 1 lesion	Radiotherapy
		10 M/50	MZL	Thighs, knee, UE, 4 lesions	Resection, interferon alfa
		11 M/74	MZL	Arm, 1 lesion	None
		12 F/82	MZL	Back, 3 lesions	None
		13 M/34	FCL	Nose, 3 lesions	None
Kyrtsonis et al[8]	2006	14 F/67	MZL	Both shoulders, right thigh, arm	None
		15 M/54	MZL	Shoulder, back	None
Kerl et al[9]	2006	16 M/57	MZL	Trunk, 4 lesions	None
		17 M/65	MZL	Back, arm, 2 lesions	None
		18 M/38	MZL	Trunk, 6 lesions	Liquid nitrogen
		19 M/54	FCL	Face, 9 lesions	Radiotherapy
		20 F/64	FCL	Scalp, 3 lesions	Corticosteroids
		21 M/40	FCL	Face, 3 lesions	Antibiotics
This study		22 M/41	FCL	Back, 6 lesions	None

Abbreviations: BL, B-cell lymphoma; CR, complete response; F, female; FCL, follicular center lymphoma; LCL, large-cell lymphoma; M, male;

Treatment	*Response*	*Follow-up*
30 mg, 3 times/wk, 1 wk/mo TD: 18 injections (540 mg)	PR Biopsy: BL	12 mo
30 mg, 3 times/wk, 1 wk/mo TD: 6 injections (180 mg)	PR No biopsy performed	No data
10-30 mg, 2-3 times/wk TD: 23 doses (400 mg)	CR Biopsy: no evidence of BL	12 mo
1 mL (10 mg) per lesion, 2-3 times/wk TD: 210 mg	CR Biopsy: no evidence of BL	12 mo
10 mg, 2 or 3 times/wk TD: 6 cycles (60 mg)	CR Biopsy: no evidence of BL	6 mo
10 mg 3 times/wk 1 wk/mo 6 mo TD: 180 mg New similar 9-mo cycle (all lesions but 1 disappear)	PR No biopsy performed	Relapse at 6 mo after the first injection
20 mg 3 times/wk 1 wk/mo TD: 12 cycles (240 mg)	PR	Relapse Rituximab 27 mo
40 mg 3 times/wk, 1 wk/mo TD: 6 cycles (240 mg)	CR	16 mo
10 mg 3 times/wk 1 wk/mo TD: 24 cycles (240 mg)	CR	Relapse Systemic rituximab 27 mo
40 mg 3 times/wk, 1 wk/mo TD: 24 cycles (720 mg)	CR	Relapse at other sites 12 mo
10 mg 3 times/wk 1 wk/mo TD: 1 cycle (30 mg)	CR	26 mo
30 mg 3 times/wk 1 wk/mo TD: 3 cycles (180 mg)	CR Relapse other site	Relapse with surgery 14 mo
30 mg 3 times/wk 1 wk/mo TD: 1 cycle (90 mg)	CR	12 mo
5-15 mg depending on the size of the lesion. Initially twice/wk for the first 15 d and afterwards once/wk for 18 wk	CR	Relapse at 22 mo treated with rituximab for 6 wk
5-15 mg depending on the size of the lesion. Initially twice/wk for the first 15 d and afterwards once/wk for 18 wk	CR	36 mo
Between 10 mg and 30 mg 3 times/wk. 1 wk/mo TD: 1 cycle	CR No subsequent biopsy reported	4 mo 1 relapse
Between 10 mg and 30 mg 3 times/wk. 1 wk/mo TD: 2 cycles	CR No subsequent biopsy reported	3 mo
Between 10 mg and 30 mg 3 times/wk. 1 wk/mo TD: 2 cycles	CR No subsequent biopsy reported	6 mo 1 relapse
Between 10 mg and 30 mg 3 times/wk. 1 wk/mo TD: 1 cycle	CR No subsequent biopsy reported	8 mo 2 relapses
Between 10 mg and 30 mg 3 times/wk. 1 wk/mo TD: 1 cycle	CR No subsequent biopsy reported	6 mo 2 relapses
Between 10 mg and 30 mg 3 times/wk. 1 wk/mo TD: 1 cycle	CR No subsequent biopsy reported	14 mo
30 mg, 3 times/wk, 1 wk/mo TD: 360 mg	CR Biopsy. No evidence of BL	5 mo

MZL, marginal zone lymphoma; PDT, photodynamic therapy; PR, partial response; TD, total dose; UE, upper extremities.

a single week every month until a complete response is achieved.

There have been reports of 21 patients with primary cutaneous B-cell lymphoma treated with intralesional rituximab.[4-9] When our patient is included in the data presented below, the age of the studied patients ranges from 34 to 82 years of age, with a mean age of 54 years. Nine of the patients reported were women and 13 men; 12 cases were of primary cutaneous follicular center B-cell lymphoma, 9 marginal zone B-cell lymphoma, and 1 diffuse large-cell, other.

Total intralesional dose varied from 30 mg to 720 mg with an estimated mean of 187 mg. Most patients received treatment in the form of 3 doses provided in a single week once a month. The daily dose ranged from 1 mL to 4 mL of rituximab solution (10 mg and 40 mg).

Some patients had already received treatment, including surgery, radiotherapy, interferon, CHOP, and psoralen–UV-A, although others received intralesional rituximab as their first treatment (Table).

A complete response was observed in 18 of the 22 cases, and in some this was confirmed by histology. Of the 18 cases with a complete response, 10 were cutaneous follicular center B-cell lymphomas and 8 cutaneous marginal zone B-cell lymphomas.

Ten of the 18 complete responders had not had a relapse after a follow-up ranging from 3 months to 36 months (mean, 14.2 months). The total cumulative dose in patients with a complete response and no relapses was similar to that of patients who had a complete response and relapses.

Treatment with intralesional rituximab is very well tolerated, effective, and much more economical than intravenous rituximab.

Studies comparing intralesional and intravenous rituximab are necessary to evaluate the response, adverse effects, and percentage of recurrence with each route of administration. Similarly, dosage must be standardized and the dose associated with the lowest relapse rates must be established.

Conflict of Interests

The authors declare no conflicts of interest.

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