

Anetodermic Primary Cutaneous B-Cell Lymphoma

A Unique Clinicopathological Presentation of Lymphoma Possibly Associated With Antiphospholipid Antibodies

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Background: Primary cutaneous B-cell lymphoma manifested by anetoderma has been reported in 7 cases. In all, the secondary anetoderma developed in lesions of marginal-zone lymphoma or posttransplant lymphoproliferative disorder resembling marginal-zone lymphoma. The mechanisms underlying the destruction of elastic tissue in anetoderma are unclear. However, there is growing evidence linking primary anetoderma with a wide range of immunologic abnormalities, the most common being the presence of antiphospholipid antibodies.

Observations: We analyzed data from 5 patients (3 male, 2 female) with clinical and histopathological features of anetodermic primary cutaneous B-cell lymphoma. Three had marginal-zone lymphoma and 2 had follicle-center cell lymphoma. In all, secondary anetoderma developed in self-regressing nodules/plaques of

the lymphoma. Two patients also had lesions clinically and histopathologically compatible with primary anetoderma. Associated immunologic diseases were systemic lupus erythematosus–like disease and rheumatoid arthritis (1 patient each; not in patients with primary anetoderma). Antiphospholipid antibodies were found in 4 patients.

Conclusions: Anetodermic primary cutaneous B-cell lymphoma is a rare and unique clinicopathological manifestation not only of marginal-zone lymphoma, as previously described, but also of follicle-center cell lymphoma. This type of secondary anetoderma, like primary anetoderma, might be associated with immunologic disorders, particularly antiphospholipid antibodies.

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ANETODERMA, DERIVED FROM the Greek word *anetos*, meaning slack, is a rare elastolytic disorder characterized by a limited area of slack skin associated with loss of substance on palpation and a histologic finding of loss of elastic tissue. It is classically divided into 2 forms. Primary, or idiopathic, anetoderma develops in clinically normal skin or following a nonspecific inflammatory process. Secondary anetoderma arises at the site of certain well-defined skin diseases, such as cutaneous infections, inflammatory disorders, and tumors.¹

The etiopathogenesis of anetoderma is unclear. Several studies suggested that the destruction of the elastic tissue is mediated by the release of elastase, metalloproteinases, cytokines, or still-undefined substances by the inflammatory or tumoral cells.¹⁻⁴ A growing body of evidence in recent years has linked primary anetoderma to a wide range of immunologic abnormalities, the most common being the presence of antiphospholipid antibodies (aPLs).⁵⁻⁷

In 1993, Jubert et al⁸ described a patient in whom primary cutaneous B-cell lymphoma (PCBCL) manifested as infiltrated plaques as well as anetodermic lesions.⁸ Since then, reports of an additional 6 cases of anetodermic manifestation of PCBCL have been published.⁹⁻¹²

To shed further light on the characteristics of this rare presentation, we analyzed data from a series of 5 patients with anetodermic PCBCL with emphasis on the clinicopathological findings, associated diseases, and autoimmune laboratory findings. The pertinent literature is reviewed as well.

METHODS

The study group consisted of 5 patients with a diagnosis of PCBCL and anetoderma who were followed up at the Department of Dermatology of Rabin Medical Center from 1994 to 2008. Primary cutaneous B-cell lymphoma was defined as cutaneous lymphoma without nodal and/or visceral involvement.¹³ The diagnosis of anetoderma was based on the typical clinical features combined with histologic

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Table 1. Clinical Presentation of Patients With Anetodermic Primary Cutaneous B-Cell Lymphoma

Patient No./ Sex/Age, y	Relevant Medical History	Clinical Presentation	Time to Diagnosis	Diagnosis
1/F/70	Clinical primary anetoderma	Multiple erythematous nodules on trunk, some surrounded by anetodermic skin	6 y	PCMZL (multifocal), secondary anetoderma
2/M/56	None	Symmetric anetodermic lesions on back; few nodules on trunk and extremities regressing later to anetoderma	3 y	Primary anetoderma, PCFCL (multifocal), secondary anetoderma
3/F/42	SLE-like disease	Large tumor on scalp, small nodules on face and chest; 2 small lesions regressed to anetoderma	1 y	PCFCL (multifocal), secondary anetoderma
4/M/39	Clinical primary anetoderma	Large infiltrated plaque on left calf surrounded by anetodermic skin; symmetric anetodermic lesions on lower back	8 y	PCMZL, secondary anetoderma, primary anetoderma
5/M/68	None	Small nodule surrounded by anetodermic skin over upper arm	6 mo	PCMZL, secondary anetoderma

Abbreviations: PCFCL, primary cutaneous follicle-center cell lymphoma; PCMZL, primary cutaneous marginal-zone B-cell lymphoma; SLE, systemic lupus erythematosus.

findings of partial or complete loss of elastic tissue in the dermis. The staging procedure included physical examination; standard blood tests; computed tomography of the chest, abdomen, and pelvis (and, in some patients, also the neck); and bone marrow biopsy. Punch and/or incisional skin biopsy specimens were obtained from typical lesions of lymphoma, typical lesions of anetoderma, and lesions clinically demonstrating the coexistence of both processes, on an as-needed, case-by-case basis. Biopsy specimens were fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin-eosin and Verhoeff-van Gieson elastic stain. Immunohistochemical studies were carried out on the paraffin-embedded sections with an avidin-biotin complex immunoperoxidase technique (ABC Vectastain Kit; Vector Laboratories Inc, Burlingame, California) with the use of a panel of monoclonal antibodies that included CD20, CD3, LCA, Bcl-2, CD68, and CD79a (Dako A/S, Glostrup, Denmark); Bcl-6 and CD21 (Ventana, Tucson, Arizona); CD10 (Novocastra, Newcastle Upon Tyne, England); Ki67 (Lab Vision, Fremont California); LN-1 (BioGenex, San Ramon, California); MUM-1 (Diagnostic BioSystems, Pleasanton, California); and κ and λ light chains (Pierce-Endogen, Rockford, Illinois). DNA extracted from paraffin-embedded or frozen tissue was analyzed by polymerase chain reaction (PCR) to determine the gene rearrangement of the immunoglobulin heavy chain, as previously described.¹⁴

Additional investigations at the time of diagnosis of anetodermic PCBCL included serologic testing for *Borrelia burgdorferi* and tests for aPLs, including anticardiolipin antibodies (IgG, IgM, and IgA) and anti- β_2 -glycoprotein 1 (IgG, IgM, and IgA). Lupus anticoagulant, VDRL test, *Treponema pallidum* hemagglutination, prothrombin time, and partial thromboplastin time were measured when indicated. Other tests performed in each patient included immunoelectrophoresis, determination of antinuclear antibody, and tests for antithyroid, antiparietal, and anti-smooth muscle antibodies. One patient underwent PCR analysis for the detection *B burgdorferi* in skin lesions. The local Helsinki Committee approved the study.

RESULTS

CLINICAL AND LABORATORY FINDINGS

The study group consisted of 3 male and 2 female patients with a mean age of 55 years at diagnosis of PCBCL (range, 39-70 years) (**Table 1**). In all cases, the eruption at onset was characterized by asymptomatic nodules or infiltrated plaques. Some of the nodules and plaques regressed to anetodermic lesions over time (6 months to 8 years).

Evaluation at presentation yielded multifocal asymmetric nodular disease in 3 patients (patients 1-3) and a single infiltrated plaque in 2 patients (patients 4 and 5). Anetodermic skin was observed at the sites of the partially or completely disappearing preexistent erythematous nodules or plaques.

Three patients (patients 1, 4, and 5) were diagnosed as having primary cutaneous marginal-zone B-cell lymphoma (PCMZL); 1 of them presented with multifocal lesions. The other 2 patients (patients 2 and 3) were diagnosed as having multifocal primary cutaneous follicle-center cell lymphoma (PCFCL), including 1 (patient 3) with diffuse large-type lymphoma. All 5 patients had histopathological findings of anetoderma that developed secondary to the self-regressing lesions (**Figure 1** and **Figure 2**).

Further examination disclosed that, in 2 patients (patients 1 and 4), asymptomatic anetodermic skin lesions had appeared years before the typical nodular erythematous eruption, without any precedent inflammatory phase. Patient 1 had multiple oval skin-colored protrusions measuring 1 to 3 cm in diameter, located symmetrically on the sides of the back and extensor aspects of both arms. The lesions had wrinkled overlying skin and a feeling of tissue loss on palpation (**Figure 3**). The lesions in patient 4 were located symmetrically on the lower part of the back. The clinical appearance in conjunction with the histopathological findings was compatible with primary anetoderma.

Associated autoimmune diseases were diagnosed in 2 patients (patients 2 and 3) (**Table 2**). Patient 3 was known to have a systemic lupus erythematosus-like disease manifested by polyarthralgia, a sustained elevated erythrocyte sedimentation rate, and high titers of antinuclear antibody before diagnosis of the lymphoma. In patient 2, a form of rheumatoid arthritis developed during the course of follow-up of the lymphoma, characterized by fatigue, fever, morning stiffness accompanied by seronegative symmetric polyarthritis of the proximal interphalangeal and metacarpophalangeal joints, and evidence of synovitis of the wrist joints.

A deliberate laboratory investigation at the diagnosis of PCBCL disclosed the presence of aPLs in 4 of the 5 patients, but without lupus anticoagulant or prolonged partial thromboplastin time. None of the patients had a history of a thromboembolic event. We failed to detect any of the other autoantibodies tested, except for an abnormal ti-



Figure 1. Multifocal presentation of anetodermic primary cutaneous marginal-zone B-cell lymphoma in patient 1. A, Several erythematous nodules located over the back and buttocks, some of which are embedded in circumscribed areas of slack skin. B, Close-up view of the left buttock showing 2 erythematous nodules with wrinkled overlying skin, surrounded by an area of slack skin.

ter of antinuclear antibody in patient 3. Results of serologic testing for *B burgdorferi* were negative in all 3 patients tested (patients 1-3). Patient 1 was tested for this spirochete by PCR, and the findings were negative in both the erythematous nodule and the lesion of primary anetoderma. Patients 1, 2, 3, and 5 were tested for the presence of Epstein-Barr virus (EBV) infection in the lymphoma biopsy specimens by means of EBV-encoded RNA in situ hybridization; the findings were negative in all of these cases.

Two of the patients with localized PCMZL (patients 4 and 5) were treated with electron beam radiation, and 1



Figure 2. Anetodermic primary cutaneous follicle-center cell lymphoma in patient 3. Erythematous tumor located over the left frontoparietal scalp and soft hanging nodule with wrinkled overlying skin, representing partially regressing tumor on the left eyebrow (arrow).



Figure 3. Lesions characteristic of primary anetoderma in patient 1. Small oval skin-colored monomorphic outpouching flaccid lesions are seen on the left upper part of the back and over the extensor aspect of the left arm near the axilla.

patient with multifocal PCFCL (patient 3) was treated by her hematologist with the CHOP regimen (cyclophosphamide, doxorubicin hydrochloride/hydroxydoxorubicin, vincristine sulfate, and prednisone). All 3 had a complete response. Two patients (patients 1 and 2) refused therapy. Both showed a relapsing course on follow-up, with regression of some of the nodules, leaving secondary anetoderma (**Figure 4**). Patient 2 was in a sustained remission for the last 3 years of follow-up. It is noteworthy that in patient 1 the lesions diagnosed as primary anetoderma remained stable throughout follow-up, whereas patient 4 showed outpouching of atrophic lesions with wrinkled overlying skin, located on the popliteal fossa and on the previously affected shin. Repeated biopsy specimens yielded a diagnosis of primary anetoderma.

LIGHT MICROSCOPIC AND IMMUNOHISTOCHEMICAL FINDINGS

Table 3 shows the histopathological findings of the different lesions observed in our patients with anetodermic PCBCL. The spectrum of lesions included nodular

Table 2. Laboratory Abnormalities, Treatment, and Follow-up of Patients With Anetodermic Primary Cutaneous B-Cell Lymphoma

Patient No.	Laboratory Immunologic Abnormalities	Initial Treatment and Course	Development of Other Disorders	Duration of Follow-up and Last Known Status
1	ACL: IgA, 35 APL (ref, ≤ 22 APL); total IgA, 444 mg/dL (ref, 190-310 mg/dL); <i>Borrelia burgdorferi</i> , negative	Refused treatment; chronic relapsing, leaving anetodermic lesions	None	Lost to follow-up after 3 y
2	β_2 GP: IgA, 150 SAU (ref, ≤ 20 SAU); <i>B burgdorferi</i> , negative	Refused treatment; chronic relapsing, leaving anetodermic lesions	Rheumatoid arthritis	10 y, A- with anetoderma
3	β_2 GP: IgM, 29 SMU (ref, ≤ 20 SMU); ANA, 1:160; <i>B burgdorferi</i> , negative	CHOP polychemotherapy	ND	Lost to follow-up
4	ACL: IgG, 26 GPL (ref, ≤ 18 GPL); <i>B burgdorferi</i> , ND	EB, CR; 1 year later, new anetodermic lesions adjacent to irradiated field and popliteal fossa; biopsy specimen showed primary anetoderma	None	3 y, A- with anetoderma
5	<i>B burgdorferi</i> , ND	EB	None	2.5 y, A- with anetoderma

Abbreviations: A-, alive without disease; ACL, anticardiolipin; ANA, antinuclear antibody; APL, antiphospholipid units; β_2 GP, β_2 -glycoprotein; CHOP, cyclophosphamide, doxorubicin hydrochloride/hydroxydoxorubicin, vincristine sulfate, and prednisone; CR, complete response; EB, electron beam; GPL, IgG phospholipid units; ND, not determined; ref, reference cutoff or range; SAU, standard IgA units; SMU, standard IgM units. SI conversion factor: To convert total IgA to grams per liter, multiply by 10.

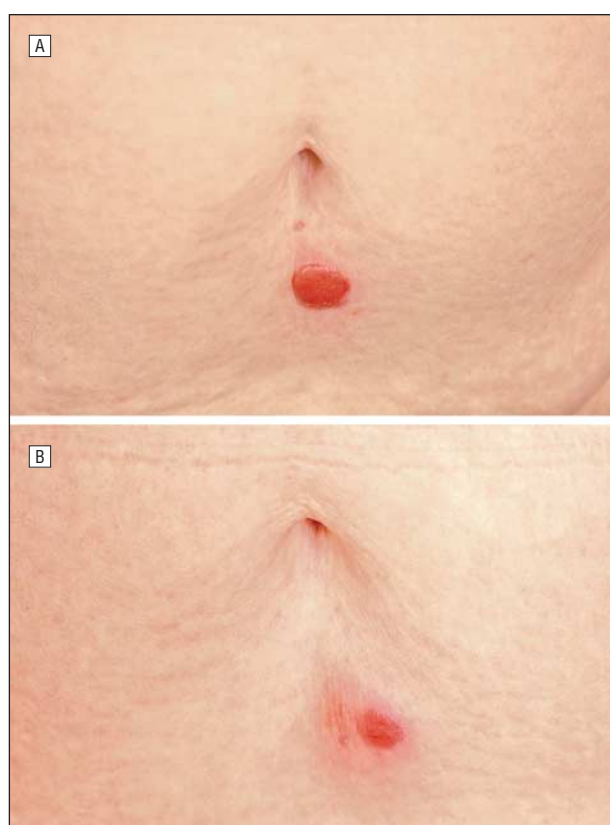


Figure 4. Nodular lesion on the abdomen of patient 1 (A); after several months, the nodule showed spontaneous partial regression (B), leaving combined features of lymphoma and secondary anetoderma.

lesion of lymphoma, partially regressing nodular lesion, completely regressing lesion, and primary anetoderma.

Three patients presented with erythematous nodular lesions without clinical evidence of regression as well as with lesions showing partial regression (patients 1-3). However, 2 patients presented with nodular lesions that were already partially regressing (patients 4 and 5). In 3 patients (patients 2-4), we detected nodular lesions that had regressed completely. In those cases, we also documented the histopatho-

logical findings. Two patients (patients 1 and 4) also exhibited lesions of what seemed to be primary anetoderma.

Three patients had hematoxylin-eosin and immunohistochemical findings of PCMZL: 2 with typical findings (patients 1 and 5) and 1 with findings of immunocytoma, currently classified as part of PCMZL (patient 4).

The histopathological findings of the lymphoma and the anetoderma secondary to the partially regressing lymphoma of patient 1 are shown in **Figure 5** and **Figure 6**.

Two patients had diagnostic findings of PCFCL (patients 2 and 3), one of which was diffuse large type. The histopathological findings of the lymphoma and the anetoderma secondary to the partially regressing lymphoma of patient 2 are shown in **Figure 7** and **Figure 8**.

COMMENT

The association between hematologic malignant neoplasms and cutaneous elastolysis, although rare, is well recognized. The literature includes descriptions of granulomatous slack skin,¹⁵ anetodermic mycosis fungoides (a recently described unusual variant of mycosis fungoides),¹⁶ acquired cutis laxa in association with multiple myeloma,¹⁷ heavy-chain deposition disease,¹⁸ and cutaneous angiocentric T-cell lymphoma.¹⁹

In the present study, we evaluated 5 cases of PCBCL with a unique clinicopathologic presentation, for which we suggest the term *anetodermic PCBCL*. Our review of the literature yielded 7 similar cases, which are summarized in **Table 4**. The patients were diagnosed as having PCMZL, plasmacytoma without underlying multiple myeloma or immunocytoma (the latter two are currently classified as PCMZL¹³), or posttransplant lymphoproliferative disorder in the skin resembling PCMZL. In all, the elastolytic skin lesions were a manifestation of the cutaneous lymphoma, which showed spontaneous partial regression in the form of anetoderma. The authors of a report of 2 cases⁹ specifically classified the anetoderma as secondary. In the other case reports, the authors did not use this term, but the available data indicate that they also represented secondary anetoderma, namely, anetoderma that arises at the

Table 3. Histopathological, Immunohistochemical, and Genotypic Findings in Patients With Anetodermic Primary Cutaneous B-Cell Lymphoma

	Findings, Patient No.				
	1	2	3	4	5
Type of lymphoma	PCMZL	PCFCL	PCFCL, diffuse large type	PCMZL (immunocytoma)	PCMZL
Erythematous nodular lesion on HE staining	Heavy diffuse and nodular dermal lymphocytic infiltrates with monocytoid and plasma cells; subcutaneous involvement	Heavy diffuse and nodular dermal lymphocytic infiltrates with small and large cleaved cells	Heavy diffuse and nodular dermal lymphocytic infiltrates with predominantly large noncleaved cells; subcutaneous involvement	Not present	Not present
Partially regressing nodular lesion/elastic staining	Patchy nodular, perivascular, and interstitial infiltrates with similar cytologic findings; pale and focally hyalinized dermis/decreased elastica	Perivascular and interstitial infiltrates with similar cytologic findings; pale and focally hyalinized dermis/decreased elastica	ND	Heavy nodular plasmacytoid infiltrate; subcutaneous involvement/decreased elastica	Heavy perivascular monocytoid lymphocytic infiltrate with many plasma cells; pale and focally hyalinized dermis/decreased elastica
Immunoperoxidase/IgH gene rearrangement	CD20+, Bcl-2+, Bcl-6-, CD10-, LN1-, λ+/monoclonal band	CD20+, Bcl-2+, Bcl-6+, CD10+, MUM-1-/monoclonal band	CD20+, Bcl-2-, Bcl-6+, CD10-, MUM-1-/ND	CD20-, CD79a+, Bcl-2-, Bcl-6-, CD10-, CD138+, κ+/polyclonal band	CD20+, Bcl-2+, Bcl-6-, CD10-, λ+/monoclonal band
Completely regressing nodular lesion/elastic staining	Not present	Very mild perivascular CD3+, CD20- lymphocytic infiltrates/decreased elastica in reticular dermis	Mild perivascular and periadnexal CD3+, CD20- lymphocytic infiltrates/decreased elastica in papillary and reticular dermis	Very mild perivascular CD3+, CD20- lymphocytic infiltrate/decreased elastica in reticular dermis	Not present
Lesion of apparent PA/elastic staining	Normal-looking skin/complete absence of elastica in papillary and reticular dermis	Not present	Not present	Normal-looking skin/decreased elastica in reticular dermis	Not present

Abbreviations: HE, hematoxylin-eosin; IgH, immunoglobulin heavy chain; LN1, monoclonal antibody to B lymphocytes (CDw75); MUM-1, myeloma-associated antigen 1; PA, primary anetoderma; PCFCL, primary cutaneous follicle-center cell lymphoma; PCMZL, primary cutaneous marginal-zone B-cell lymphoma; ND, not determined.

site of a well-defined skin disease—specifically, in these cases, regressing lymphomatous infiltrates. In addition, colocalization of elastolysis and lymphoproliferative disorder was reported in 1 patient with benign cutaneous lymphoid hyperplasia and secondary anetoderma²⁰ and another with localized acquired cutis laxa and primary cutaneous lymphoplasmacytoid lymphoma (immunocytoma).²¹

In line with the literature, 3 of our 5 patients had anetodermic PCMZL. The other 2 constitute the first reported cases of anetodermic PCFCL, to our knowledge. This diagnosis is unexpected given the rarity of self-regression in PCFCL. Multifocality is also a rare occurrence in PCFCL, with a rate of 8% (of 101 patients) reported in a recent Dutch series.²² Because 1 of these patients (patient 2) refused therapy, we were able to observe the natural course of his malignant neoplasm. We found that it was typified by chronic relapse/self-regression during a period of many years. This finding suggests that anetodermic PCFCL may have different biological characteristics from classic PCFCL. By contrast, a multifocal presentation is not rare in PCMZL, and it was observed in most of the previously described patients with anetodermic PCBCL.^{8-10,12} According to the Dutch Cutaneous Lymphoma Working Group, multifocality occurs in 44% to 72% of cases,^{22,23} and sometimes the skin lesions resolve spontaneously.¹³

Interestingly, 2 of our patients, both with PCMZL, also had skin lesions with clinical and histopathological char-

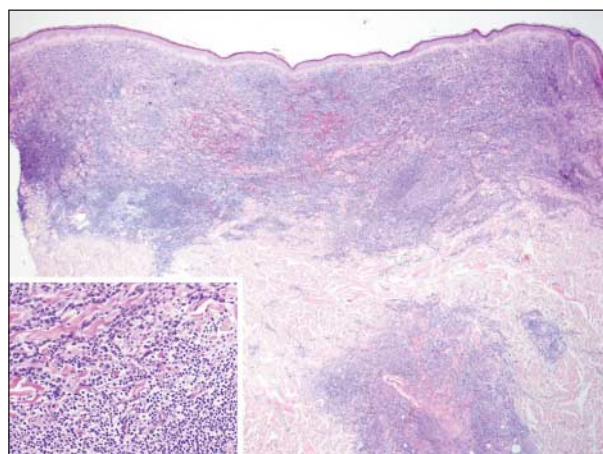


Figure 5. Histopathological findings of a nodule on the abdomen of patient 1 showing features of primary cutaneous marginal-zone B-cell lymphoma. Heavy diffuse and nodular lymphocytic infiltrates are seen in the dermis (hematoxylin-eosin, original magnification ×20). Inset, Higher-power view showing aggregates of monocytoid B lymphocytes and plasma cells (hematoxylin-eosin, original magnification ×200).

acteristics of primary anetoderma. It is unlikely that a preceding lymphoma at the sites of the anetoderma was overlooked owing to the symmetric distribution of monomorphic anetodermic skin lesions and the absence of inflammatory or tumoral infiltrates on biopsy study. Fur-

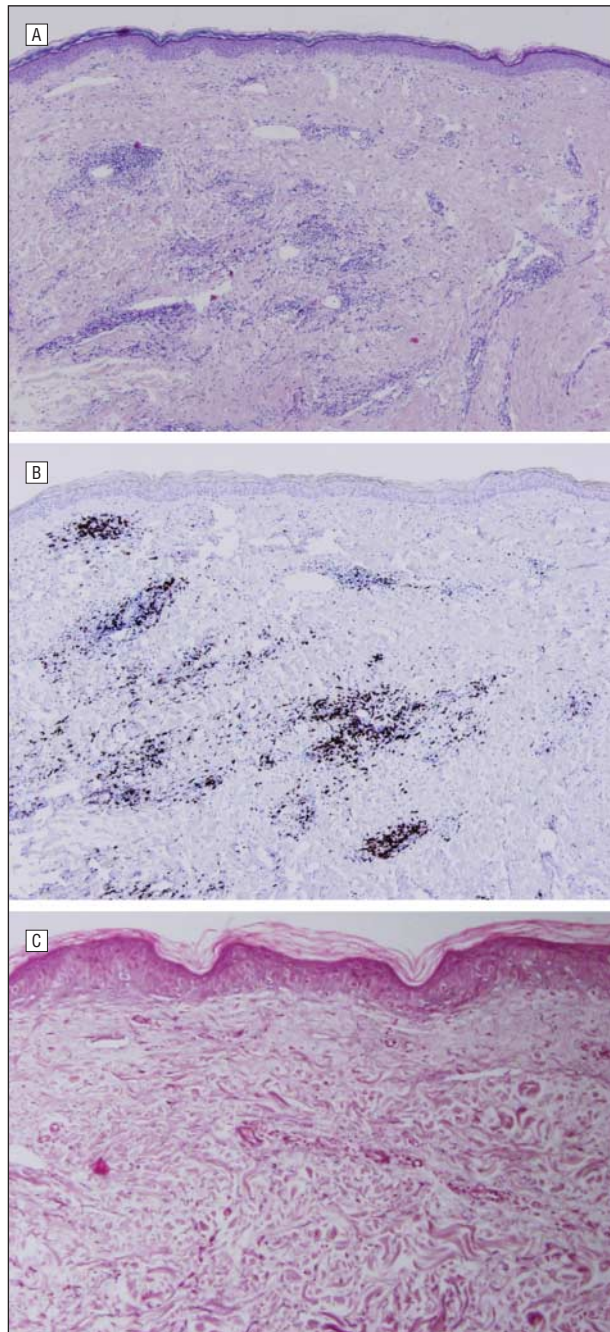


Figure 6. Histopathological findings of a partially regressing nodule on the abdomen of patient 1 showing anetoderma secondary to lymphoma. A, Residual perivascular and interstitial lymphocytic infiltrates in the dermis (hematoxylin-eosin, original magnification $\times 40$). B, CD20 immunopositivity of the infiltrates (original magnification $\times 40$). C, Elastic stain demonstrating a marked reduction in elastic fibers (original magnification $\times 100$).

thermore, in 1 of these patients (patient 4) during follow-up we were able to detect the appearance of new anetodermic lesions that showed typical clinical and histopathological findings of primary anetoderma.

Primary anetoderma in conjunction with anetodermic PCBCL has not been previously described, to our knowledge.⁸⁻¹² However, in 1 case,¹² the available data were not sufficient to reach a definite conclusion regarding the nature of the additional anetodermic lesions that appeared in conjunction with the anetodermic lymphoma lesion.

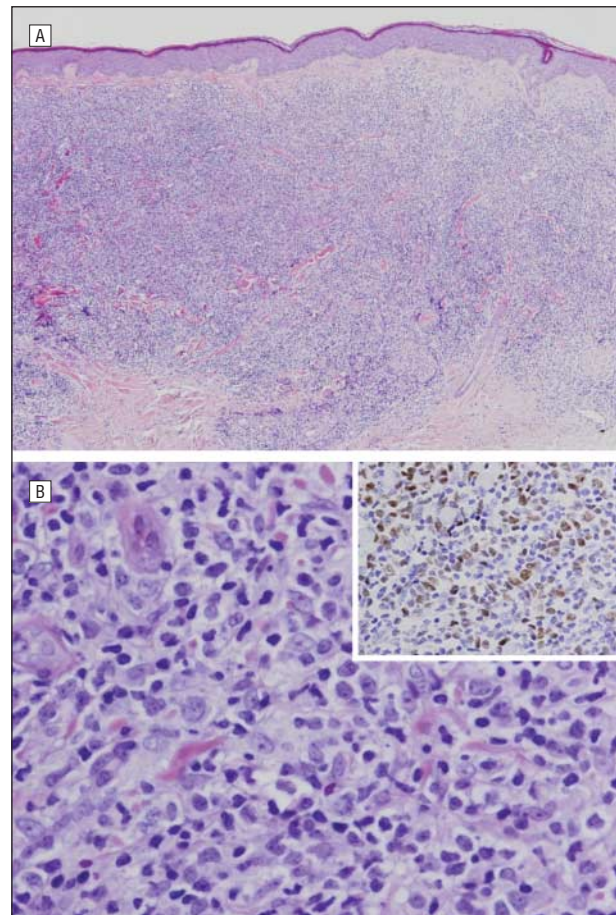


Figure 7. Histopathological findings of a representative nodule in patient 2 showing features of primary cutaneous follicle-center cell lymphoma. A, Diffuse and dense infiltrates are seen involving the dermis and are separated from the epidermis by a grenz zone (hematoxylin-eosin, original magnification $\times 40$). B, Higher-power view. The infiltrate is composed of small and large cells, many with cleaved nuclei (hematoxylin-eosin, original magnification $\times 200$). Inset, BCL-6 immunopositivity in the small and large atypical cells (original magnification $\times 400$).

Prompted by earlier reports of an association of primary anetoderma with autoimmune disorders,¹ followed by studies in the 1990s²⁴⁻²⁷ and a later one from our center⁵ that focused specifically on aPLs, we conducted a thorough investigation of autoantibodies in all of our patients. Four of them, including the 2 with primary anetoderma, were found to have aPLs without evidence of antiphospholipid syndrome. Lymphoproliferative malignant neoplasms have been reported to be related to the generation of aPLs,²⁸ although this seems to occur rarely in PCBCL (our unpublished data, 2007). Therefore, we postulate that immunologic mechanisms, possibly mediated by aPLs, may be involved not only in primary anetoderma but also in anetodermic PCBCL. Likewise, there are other rare examples of an association of secondary anetoderma with increased aPLs in patients with human immunodeficiency virus/infection.²⁹ Anetoderma, mostly secondary to resolving lesions, has been described in other infections such as borreliosis,³⁰ which also might be associated with aPLs.³¹ *Borrelia burgdorferi* has been isolated from the DNA of patients with PCBCL, specifically PCMZL.³² In our 3 patients who underwent serologic testing, 2 with PCFCL and 1 with PCMZL, no evidence of *B burgdorferi* infection was found. Lesions from the latter pa-

tient were also tested by PCR. Nevertheless, the infection cannot be definitively ruled out.³³

An immunologic nature of anetodermic PCPBL was further suggested by the various autoimmune diseases diagnosed in 2 of our 5 patients and in 3 of the 7 previously described patients.⁸⁻¹⁰ These include primary Sjögren syndrome (1 patient), rheumatoid arthritis (2 patients), urticarial vasculitis (1 patient), and systemic lupus erythematosus–like disease (1 patient). This observation is in keeping

with the known higher risk of non-Hodgkin lymphoma among patients with such chronic inflammatory diseases.³⁴ Sjögren syndrome was found to be associated with PCMZL in extranodal locations including the skin, as well as in the nodes.³⁵ Primary Sjögren syndrome has also been reported in association with primary anetoderma.³⁶

Studies have shown that aPLs may be detected in a significant proportion of patients with primary Sjögren syndrome or rheumatoid arthritis.^{37,38} However, data on the aPL status are lacking in the previous reports.^{8,36} Two additional patients were renal transplant recipients who had posttransplant lymphoproliferative disorder associated with EBV infection.^{10,11} Although the cause of the renal disease was not provided in these reports, EBV infection has been found to be associated with aPLs.³¹

How aPLs affect the elastic fibers remains to be clarified. It has been suggested that aPLs bind directly to the elastic fibers because of the presence of an antigenic epitope that is phospholipid related, possibly apolipoprotein H.³⁹

Salmon et al⁴⁰ demonstrated that activation of complement is a central mechanism in aPL-induced pregnancy loss in a murine model of antiphospholipid syndrome, and they suggested that this mechanism might be involved in the tissue injury in systemic lupus erythematosus. Because C3 deposits on remaining elastic fibers have been detected in primary anetoderma, we have previously suggested that the same mechanism might play a role in the destruction of elastic tissue in patients with aPLs who have primary and/or secondary anetoderma.⁶

Others have hypothesized that the elastolytic process may be induced by local inflammatory factors directly secondary to the lymphoma or reactive infiltrates.⁹ Cytokines, and particularly interleukin 6, the central plasma growth factor involved in the final maturation of activated B cells into immunoglobulin-producing cells, might serve as mediators of this process.²⁰ Findings that myeloma cells in culture could produce aspartic acid proteases⁴¹ suggest that these elastolytic enzymes might play a role in the development of anetoderma in cutaneous lymphoproliferative nodules and plaques rich in plasma cells. Alternatively, given that elastases are also produced by mac-

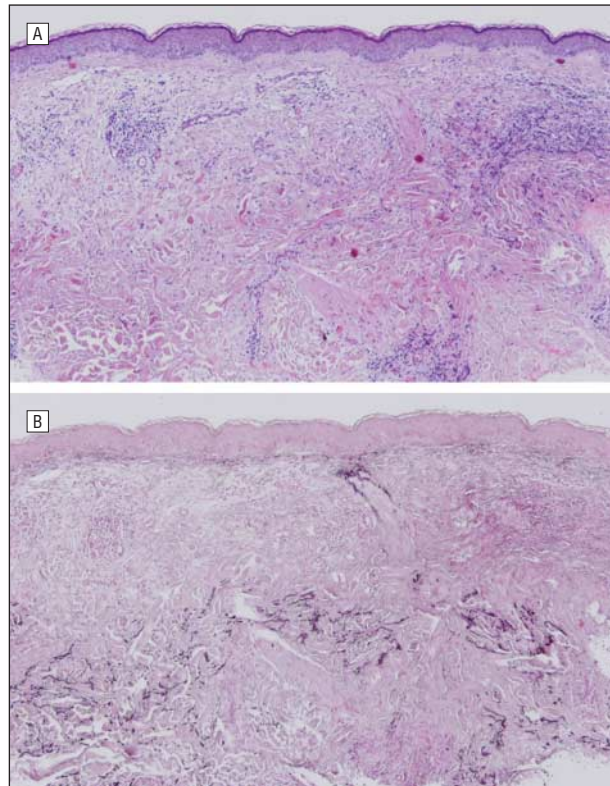


Figure 8. Histopathological findings of a partially regressing nodule in patient 2 showing features of anetoderma secondary to lymphoma. A, Residual perivascular and interstitial lymphocytic infiltrates in the dermis (hematoxylin-eosin, original magnification $\times 40$). B, Elastic stain demonstrating a marked reduction in the elastic tissue (original magnification $\times 40$).

Table 4. Summary of Reported Cases of Primary Cutaneous B-Cell Lymphoma With Anetoderma

Source	Patient No./ Sex/Age, y	Clinical Features	Associated Diseases	Diagnosis
Jubert et al, ⁸ 1993	1/M/64	Small infiltrated plaques and anetodermic skin on trunk and upper arms	Sjögren syndrome; glandular B-cell lymphoma	Plasmacytoma (multifocal) and anetoderma
Child et al, ⁹ 2000	3/M/27	Nodules on trunk and limbs resolving to anetoderma	Urticarial vasculitis	Immunocytoma (multifocal) and secondary anetoderma
	4/M/36	Nodules on trunk and arms resolving to anetoderma	None	Immunocytoma (multifocal) and secondary anetoderma
Kasper et al, ¹⁰ 2001	5/M/39	Erythematous ballotable macules and flaccid nodules resolving to anetoderma	Rheumatoid arthritis	PCMZL (multifocal) and anetoderma
	6/F/26	Erythematous ballotable macules and flaccid nodules resolving to anetoderma	Renal transplant recipient (cause not mentioned)	Posttransplant lymphoproliferative disorder resembling PCMZL (multifocal) associated with EBV and anetoderma
Garcia-Dura et al, ¹¹ 2003	7/M/41	Anetodermal erythematous/purplish nodule on back and several anetodermic lesions	Renal transplant recipient (cause not mentioned)	Posttransplant lymphoproliferative disorder resembling PCMZL associated with EBV and anetoderma
Segurado et al, ¹² 2006	8/M/44	Plaques and nodules progressing to areas of redundant skin	None	PCMZL (multifocal) and anetoderma

Abbreviations: EBV, Epstein-Barr virus; PCMZL, primary cutaneous marginal-zone B-cell lymphoma.

rophages, polymorphonuclear leukocytes, and fibroblasts, elastolysis may be effected by these other inflammatory cells associated with the neoplastic ones.¹⁰ Finally, it is plausible that combined inflammatory and immunologic mechanisms are involved in the pathogenesis of anetodermic PCBCl.

In conclusion, anetodermic PCBCl is a unique clinicopathological manifestation of low-grade B-cell lymphoma. It is a rare variant of PCMZL, as has already been described, and can also be a manifestation of PCFCL. Therefore, PCFCL should be added to the list of diseases causing secondary anetoderma. Primary cutaneous B-cell lymphoma is also sometimes associated with primary anetoderma. The cause of this peculiar clinicopathological manifestation is still unknown. However, our study results and review of the literature suggest that immunological mechanisms, possibly mediated by aPLs, may be involved in at least some cases of anetoderma secondary to PCBCl, as in primary anetoderma. Further studies are needed before a definite conclusion can be reached.

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Author Contributions: Dr Hodak had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Hodak. *Acquisition of data:* Hodak, Feuerman, Barzilai, Cerroni, and Feinmesser. *Analysis and interpretation of data:* Hodak, Feuerman, David, Barzilai, and Feinmesser. *Drafting of the manuscript:* Hodak. *Critical revision of the manuscript for important intellectual content:* Feuerman, Barzilai, David, and Cerroni.

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