Cutaneous Lymphoid Hyperplasia and Other Lymphoid Infiltrates of the Breast Nipple

A Retrospective Clinicopathologic Study of Fifty-Six Patients

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Abstract: This study characterizes the clinicopathological spectrum of lymphoproliferations involving the breast nipple and/or areola. Morphologic, immunohistochemical, molecular-genetic, and clinical features of 58 specimens from 56 patients were analyzed. They were re-diagnosed as cutaneous lymphoid hyperplasia (CLH, n = 44); other benign lymphoid infiltrates (OBLI, n = 8); peripheral T-cell lymphoma, not otherwise specified (n = 1); cases with overlapping features of CLH and B-cell lymphoma (n = 3), one of them composed of spindle cells. Cutaneous lymphoid hyperplasia infiltrates were dense, composed mainly of B cells forming follicles with germinal centers (GC). Cutaneous lymphoid hyperplasia frequently showed features suggesting a malignancy as coalescing follicles with non-polarized germinal centers lacking mantle zones, and smudged infiltrates of lymphoid cells spreading into collagen (often as "Indian files"), smooth muscle, vessel walls, and nerve sheaths. Only two cutaneous lymphoid hyperplasias recurred; otherwise all patients are without disease (mean follow-up 62 months). Monoclonal rearrangement of immunoglobulin heavy chain gene was detected in five, and of T-cell receptor γ gene in two cutaneous lymphoid hyperplasias using polymerase chain reaction (PCR), but the patients fared well too. In 47% of cases *Borrelia burgdorferi* was detected by polymerase chain reaction and/or serology, of which one was monoclonal. We conclude that cutaneous lymphoid hyperplasia is the most common lymphoproliferation of the breast nipple, rarely recognized clinically, and often overdiagnosed histologically as lymphoma.

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The breast nipple with the areola is a predilection site for cutaneous lymphoid hyperplasia (CLH, synonyms: lymphocytoma cutis, pseudolymphoma, lymphadenosis benigna cutis), together with the face, especially ear lobes and nose, scrotum, and extremities.[1–3] Rarely, a true B-cell or T-cell lymphoma occurs here, either as a spread from a tumor deep in the breast, as a part of a systemic disease, or as a primary lesion in the nipple and areola.[4–8]

In our practice, we encountered several challenging lymphoproliferations involving the breast nipple and areola in which the differential diagnosis between B-cell lymphoma and CLH was difficult. The histopathological features causing difficulties included dense, mainly diffuse and often smudged infiltrates of lymphoid cells spilling into collagen and smooth muscle bundles, resembling infiltration with leukemia in regions devoid of lymphoid follicles. Areas of large cells simulated diffuse large B-cell lymphoma (DLBCL). Further problems were atypical lymphoid follicles raising a consideration of follicular lymphoma (FL) or marginal zone B-cell lymphoma (MZL). In addition, rare cases revealed clonal rearrangement of immunoglobulin heavy chain (IgH) or T-cell receptor (TCR) γ gene of unknown significance. Thus we collected a series of lymphoproliferative diseases affecting the nipple and areola of the breast to analyze their clinical, morphologic, immunohistochemical, and molecular-genetic features and correlated them with follow-up. The aim of this retrospective study is to characterize the clinicopathological spectrum of lymphoproliferative disorders involving the nipple and areola of the breast and to discuss criteria of their differential diagnosis.

MATERIALS AND METHODS

Case Selection

One hundred and twenty cases were retrieved using a computer database search for lymphoma, pseudolymphoma, lymphocytoma cutis, cutaneous lymphoid hyperplasia, and atypical lymphoid infiltrate of the nipple, areola, or deeper tissues of the

breast. Of these, 56 cases (58 specimens) of lymphoid proliferations of the breast nipple and areola were obtained in the files of the Department of Pathology, the Medical Faculty, Charles University in Pilsen, the Czech Republic (23 cases); the Department of Pathology of the Norwegian Radium Hospital in Oslo, Norway (13 cases); the Department of Pathology, the Institute of Oncology in Ljubljana, Slovenia (8 cases); the Dermatopathologic Practice in Friedrichshafen, Germany (7 cases); and the Department of Pathology of the University of Komensky in Martin, Slovakia (5 cases). The search period differed at our institutions, from 1983 to 2003 at the most. There were 4 core needle biopsies and 8 probatory excisions of a similarly small size, a mastectomy, and the remaining specimens varied from 1 to 5 cm in the greatest diameter.

Histology and Immunohistochemistry

In all cases hematoxylin-eosin (H&E)- and Giemsa-stained sections were examined. In 15 cases elastic fibers were visualized using the resorcin-fuchsin method. Immunohistochemical staining was performed on 2-μm-thick sections cut from paraffin-embedded, formalin-fixed tissue blocks according to standard protocols using an alkaline phosphatase-anti-alkaline phosphatase method or avidin-biotin complex labeled with peroxidase or alkaline phosphatase. Antibodies against following antigens were used: monoclonal—CD3 (PS1, 1:50, Novocastra, Newcastle upon Tyne, the United Kingdom), CD5 (4C7, 1:100, Novocastra), CD8 (C8/144B, 1:50, DakoCytomation), CD10 (56C6, 1:100, Novocastra), CD15 (Leu-M1, Becton Dickinson, Erembodegem-Aalst, Belgium), CD20 (L26, 1:500, NeoMarkers, Fremont, CA), CD21 (2G9, 1:30, Novocastra), CD23 (1B12, 1:100, Novocastra), CD35 (RLB25, 1:100, Novocastra), CD30 (BerH2, 1:400, DakoCytomation, Glostrup, Denmark), CD45RO (UCHL1, 1:1000, NeoMarkers), CD68 (PG-M1, 1:200, DakoCytomation), CD79a (JCB 117, 1:100, NeoMarkers), CD138 (MI15, 1:500, DakoCytomation), bcl-2 (124, 1:1000, DakoCytomation), bcl-6 (PG-B6p, 1:20, DakoCytomation), Ki-67 (MIB1, 1:1000, DakoCytomation), cytokeratins (AE1-3, 1:1000, Neo Markers; CAM5.2, 1:200, Becton Dickinson), smooth muscle actin (1A4, 1:1000, DakoCytomation), muscle actin (HHF35, 1:500, NeoMarkers), vimentin (V9, 1:1000, NeoMarkers), TIA-1 (2G9, 1:200, Immunotech, Marseille, France), Epstein-Barr virus (EBV, latent membrane protein, CS1-4, 1:50, DakoCytomation); polyclonal—immunoglobulin light chains (IgL)(kappa, lambda, 1:200, NeoMarkers).

All cases were reviewed by 3 pathologists (LB, DVK, MM). The diagnosis was based on morphologic and immunohistochemical features correlated with clinical data. The diagnostic histologic criteria were used as published previously.[9–11] The following features were assessed: infiltrate density and distribution, Grenz zone, lymphoid follicles, and several features of germinal centers (GC) including size, shape, cytologic composition, polarization, and the presence of tingible-body macrophages. Furthermore, also analyzed were mantle zones, follicular dendritic cell (FDC) meshworks and their size, density, and shape, CD10 immunoreactivity of lymphoid cells inside and outside GC, proliferative activity (as measured by Ki-67 immunoreactivity), the presence of monocytoid B cells, follicular colonization, plasma cells, eosinophils, the ratio of B cells to T cells, and smudging of lymphocytes. In addition, relationship of lymphoid infiltrate toward constituents of the nipple and areola was recorded: smooth muscle infiltration, "Indian file" pattern of spread between collagen and smooth muscle bundles, state of periductal elastic fibers, necrosis, angiocentric arrangement, epidermotropism, infiltration of mammary ducts, lobules, and of skin adnexa.

The numbers of cases of each diagnostic group (depicted in the Results section) studied with a particular immunomarker appear in the following consequence in the brackets: cutaneous lymphoid hyperplasia; other benign lymphoid infiltrates; peripheral T-cell lymphoma, not otherwise specified; cases with overlapping features of cutaneous lymphoid hyperplasia and B-cell lymphoma. CD3 (30; 7; 1; 3), CD5 (28; 5; 1; 3), CD8 (0; 0; 1; 0), CD10 (35; 5; 0; 3), CD15 (0; 0; 1; 0), CD20 (40; 8; 1; 3), CD21 (28; 8; 1; 3), CD23 (29; 8; 1; 3), CD30 (0; 0; 1; 0), CD35 (20; 2; 0; 3), CD68 (41; 7; 0; 3), CD79a (28; 8; 1; 3), CD138 (35; 8; 0; 3), bcl-2 (35; 7; 0; 3), bcl-6 (10; 2; 0; 1), Ki-67 (43; 8; 1; 3), cytokeratins (15; 7; 0; 3); smooth muscle actin (8; 2; 0; 1), muscle actin (0; 0; 0; 1), vimentin (0; 0; 0; 1), Epstein-Barr virus (0; 0; 1; 0), TIA-1 (0; 0; 1; 0), immunoglobulin light chains (33; 6; 0; 3).

Molecular Genetics

DNA was extracted from several 10-μm-thick sections cut from formalin-fixed, paraffin-embedded tissue blocks of 51 samples from 49 patients using DNeasy Tissue Kit (QIAgen, Hilden, Germany). In 15 cases, the original amount of the extracted DNA was low, requiring microconcentration with Microcon 100 (Millipore, Billerica, MA). The quality of the DNA templates was assessed by PCR amplification of a 268 bp fragment of the β-globin gene.[12] Ten samples that failed to amplify were excluded from further molecular-genetic studies. In the remaining 41 samples from 39 patients (including 2 patients with 2 biopsies) the presence of *B. burgdorferi* DNA and clonality of B and T cells were analyzed.

The detection of *B. burgdorferi* DNA was performed by a nested PCR using primers amplifying a 222 bp fragment of the gene encoding 23S rRNA.[13]

The IgH gene rearrangements were evaluated using a seminested PCR with FR2A/LJH and VLJH primers[14,15] and a single round PCR with FR3A/VLJH primers.[15] Amplification products were examined by fragment analysis on 8% denaturing acrylamide gel (ReproGel High Resolution) (AP Biotech, Upsalla, Sweden) using ALFexpress automated sequencer and fragment analyzer (AP Biotech).

The TCRγ gene was amplified using a mix of primers J1, J3, J4, V2, V3, V4, V8, and V9.[16] Amplification products were analyzed by heteroduplex analysis on temperature gradient gel electrophoresis (Biometra, Goettingen, Germany) in 8% denaturing acrylamide gel (AA:bis-AA [37,5:1], 4M Urea, 1x MOPS, 2% glycerol) with a temperature gradient from 20 to 55°C.[17] The gels were silver stained. Samples with unclear results were additionally analyzed using ALFexpress as mentioned above.

Clinical Data

Referring pathologists and physicians treating the patients were specifically questioned about the patients' age and

sex, lesion size, localization, and clinical appearance, duration, suspected clinical diagnosis, insect or tick bite, other clinical symptoms, staging investigations, *B. burgdorferi* serology, clinical signs suspicious of *B. burgdorferi* infection, clinical and laboratory signs of immune deficiency, therapy for the nipple/areolar lesion, recurrence, other diseases and medication of the patient, follow-up, and cause of death.

RESULTS

The retrospective analysis of clinicopathological data allowed a subdivision of the 56 cases into 4 groups (Table 1): (1) cutaneous lymphoid hyperplasia (CLH) (n = 44); (2) other benign lymphoid infiltrates (OBLI) (n = 8); (3) peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) (n = 1); (4) cases with overlapping features of CLH and B-cell lymphoma (n = 3).

Group 1: Cutaneous Lymphoid Hyperplasia

The main clinical data are summarized in Table 1. CLH presented as a solitary pale or erythematous, circumscribed, nodule or plaque confined to the breast nipple and/or areola (Fig. 1). Ulceration was reported only in 1, concomitant erythema chronicum migrans in 2 patients. The preoperative diagnoses included Paget carcinoma (n = 13), lymphoid tumor (n = 8), tumor, NOS (n = 8), inflammation or abscess (n = 6), gynecomastia or fibroadenoma (n = 4), atheroma (n = 2), injury (n = 1), foreign body (n = 1); no clinical diagnosis was made in 1 case. Originally CLH were diagnosed histopathologically as pseudolymphomas (n = 27), malignant lymphomas (n = 12), and unspecified inflammation (n = 1). The diagnosis was unresolved between a high-grade lymphoma and a pseudolymphoma in 3 cases and it was not known in 1 case. Surgery was the only mode of treatment in 28 cases (26 excisions, 1 excision of the breast lesion and axillary lymphadenectomy, 1 lumpectomy). Excision together with antibiotics (mainly doxycycline) was provided to 12 patients. Radiotherapy alone was given to 1 patient. One man was administered chemotherapy and one combined radio- and chemotherapy, both after the diagnosis of a malignant lymphoma in a core needle biopsy. Staging examinations were performed in 15 patients, with negative results. Only 2 cases recurred, but were cured by re-excision, as described in detail further. No dissemination occurred at a follow-up of 5 to 240 months (mean 62, median 29 months); data are available for 35 patients (3 were lost and 6 are new cases).

Histopathological Findings of Cutaneous Lymphoid Hyperplasia

A vaguely nodular or diffuse dense lymphoid infiltrate extended throughout the whole dermis and sometimes into the underlying breast parenchyma (Figs. 2A, 2B). The four smallest lesions were patchy, composed of several lymphoid follicles only (Fig. 2C). The Grenz zone between the uninvolved epidermis and the infiltrate was preserved in most cases, and was partially effaced only in 5 of 41 biopsies (12%). Epidermotropism was not noted. Major parts of the infiltrates were formed by lymphoid follicles with germinal centers (GC), which were identified in 38 biopsies in H&E sections, and in an additional 6 lesions by immunohistochemistry (44 of 46, 95%). Only 2 infiltrates showed no follicles (Fig. 3). The

TABLE 1. Summarized Clinical Data

Diagnosis N (%)	Age (years) Median Mean (range)	Sex F:M	Duration (months) Median Mean (range)	Size (cm) Median Mean (range)	Side L:R	Therapy	Follow-up (months)* Median Mean (range)
CLH	n = 44	n = 44	n = 37	n = 37	n = 38	n = 43	n = 35
44 (77%)	58	27:17	2	1, 5	17:21	S: 28	29
	56 (17–76)		4 (0.5–12)	4 (0.5–3.5)		S+AB: 12	62 (5–240)
						S+RT: 1	
						RT+CHT: 1	2 recur.
						CHT: 1	CR
						Unknown: 1	
OBLI	n = 8	n = 8	n = 6	n = 7	n = 8	n = 8	n = 6
8 (14%)	51	7:1	7 (2–12)	2	6:2	S:6	41
	52 (40–82)			2 (1–2.5)		S+AB: 2	44 (12–96)
							CR
PTCL NOS	n = 1	n = 1	n = 1	n = 1	n = 1	n = 1	n = 1
1 (2%)	77	1:0	presentation	1.5	1:0	PUVA, rePUVA	32
						UVB	CR
Unclass.	n = 3	n = 3	n = 2	n = 2	n = 3	n = 3	n = 2
3 (5%)	67	2:1	3.5 (1–6)	3 (3–5)	1:2	S: 2	79 (57–100)
	63 (46–77)					S+RT:1	CR

N, number of patients; n, in respective columns indicate data given for a subset of patients of each diagnostic group; F, female; M, male; L, left; R, right; CLH, cutaneous lymphoid hyperplasia; OBLI, other benign lymphoid infiltrates; PTCL, NOS, peripheral T-cell lymphoma, not otherwise specified; Unclass, unclassifiable cases; CR, complete remission; recur, recurrence; S, surgery; AB, antibiotics; RT, radiotherapy; CHT, chemotherapy; rePUVA, retinoids, psoralens, ultraviolet radiation A; UVB, ultraviolet radiation B.

*Only patients with a follow-up of 5 months and more are counted.

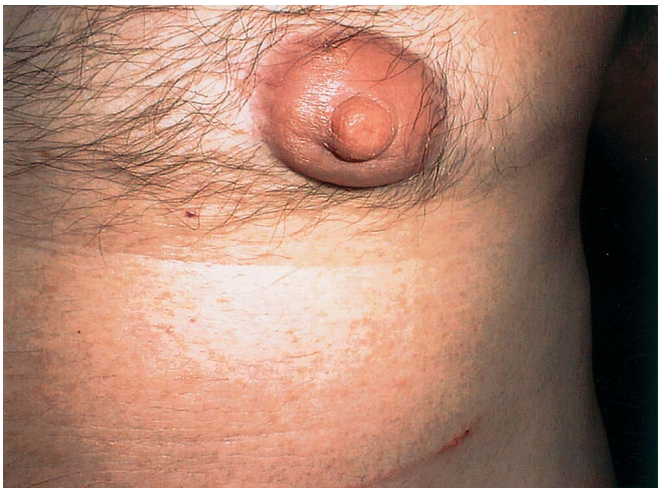

FIGURE 1. Cutaneous lymphoid hyperplasia presenting as a circumscribed erythematous nodule of the nipple and areola of the left breast in a male patient.

GC consisted predominantly of centroblasts and immunoblasts. In H&E sections, the GC showed various sizes and shapes in 35 of 38 (92%) assessable specimens (Fig. 4A), but were markedly small in 2 biopsies. In 33 of 39 (82%) lesions GC polarization was not observed in H&E; it was present in some follicles in 7 biopsies, and merely in 1 infiltrate prominent. Using Ki-67 reaction, GC polarization was detected in a minority of follicles in an additional 10 biopsies. Tingible-body macrophages were seen in GC in 38 of 41 (93%) specimens, and of these were prominent in 10 (24%) biopsies. GC B-cells were bcl-2 negative in all 35 cases tested. Mantle zones were typically absent, leaving GC naked (28 of 41 lesions, 68%), or narrow and irregular (11 specimens, 27%). The closely packed follicles often coalesced (28 of 41 lesions, 68%) (Fig. 4B), and in 5 specimens (12%) vast areas of confluent GC composed of large blasts resembled diffuse large B-cell lymphoma (DLBCL).

As estimated in immunostains, in 31 of 42 lesions (74%) B cells predominated, T cells in 4 cases (10%), and in 7 cases their proportions equaled. In the 31 B-cell predominant CLH the B cells formed 70% (median), and in 8 of these lesions they represented 75% or more of lymphoid cells. The proliferative activity was 75% to 90% in the GC, yet very low outside them (<5%). CD10 decorated GC cells in the follicles, but a small number of single scattered CD10-positive lymphoid cells were also in the interfollicular areas in 18 of 35 biopsies (51%). In 21 of 32 biopsies (66%) FDC meshworks (visualized using CD21, CD23, or CD35) were irregular and loose at least in several follicles, reflecting irregular shapes of follicles with expanding GC. The interfollicular areas contained a mix of B cells and T cells, polyclonal plasma cells (present in 43 specimens, 100%, prominent in 17 cases, 40%), which were often conspicuous at the periphery of the infiltrate but never formed large sheets, and a variable admixture of histiocytes, eosinophils (numerous in 2 specimens), and mast cells (increased in 1 lesion). Granulomas were not seen. Monocytoid B cells never formed prominent areas, but in 11 of 45 biopsies

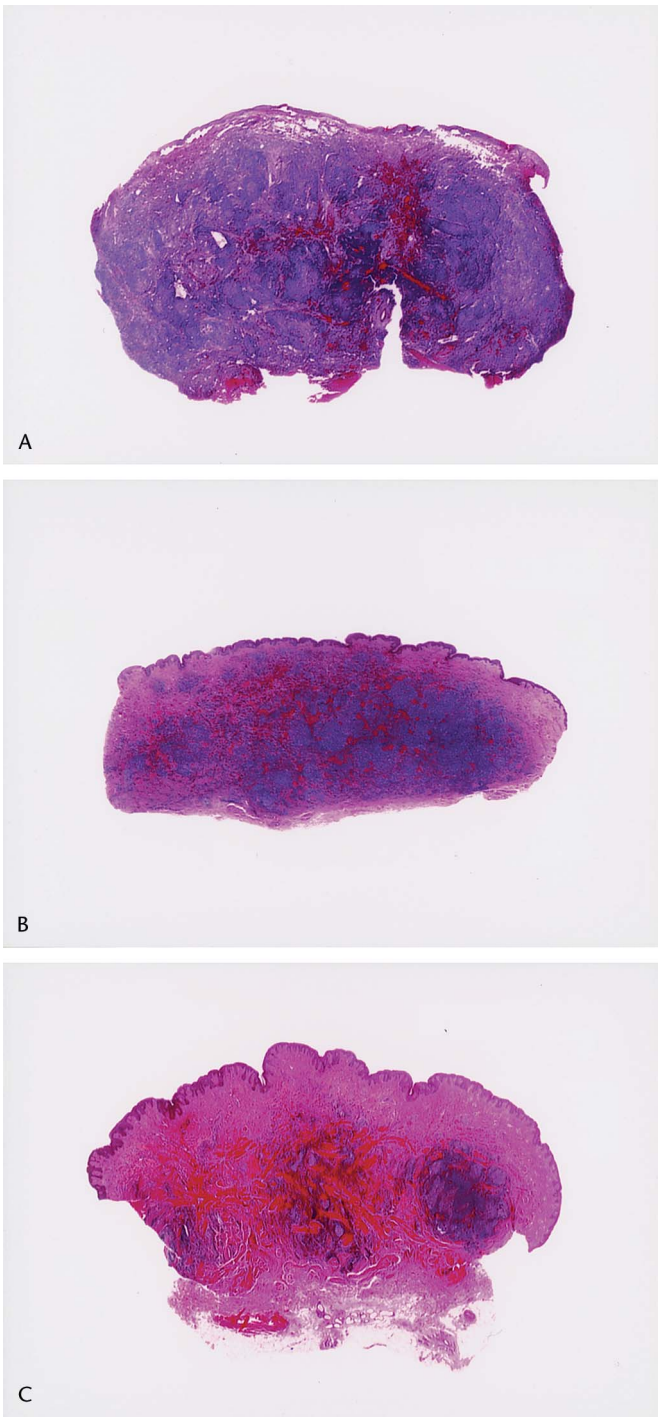

FIGURE 2. A, Vaguely nodular cutaneous lymphoid hyperplasia composed of lymphoid follicles extending throughout the whole dermis (hematoxylin-eosin, H&E). B, A dense diffuse lymphoid infiltrate of cutaneous lymphoid hyperplasia. C, A small, patchy infiltrate of cutaneous lymphoid hyperplasia is formed by several nodules consisting of coalescing follicles with germinal centers.

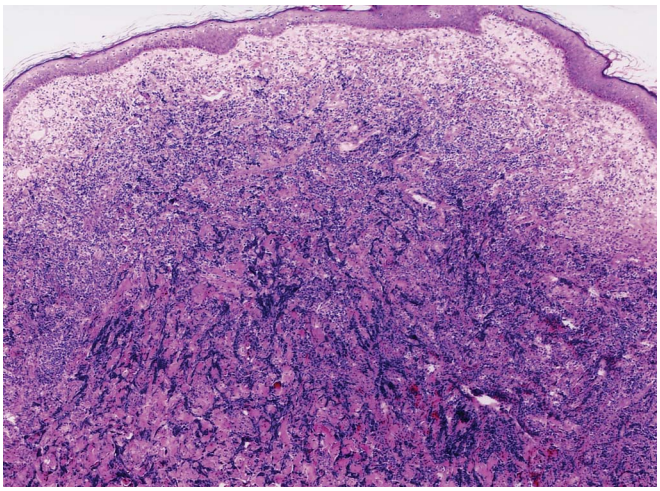

FIGURE 3. No follicles are seen in this diffuse infiltrate of cutaneous lymphoid hyperplasia with conspicuous smudging (H&E).

(24%) created small foci and in 4 of 45 lesions (9%) colonized some follicles. Dutcher bodies were not seen.

The lymphoid cells spread in linear arrays as "Indian files" between collagen fascicles at least in some areas in all but 1 specimen (43 of 44 biopsies; 98%) (Fig. 5). Lymphoid elements infiltrated smooth muscle bundles in 42 of 45 lesions (93%), causing virtually muscle fragmentation in 13 specimens (29%) (Fig. 6A). Naked GC were often seen in an intimate proximity to smooth muscle bundles, blood vessels, nerves, skin adnexa, or mammary ducts. Sometimes such GC were encased in smooth muscle bundles (Fig. 6B), or pierced by smooth muscle or collagen fascicles. Some GC adhered to blood vessels or encircled them (Fig. 7A). Smooth muscle and fibrous tissue necrosis occurred in 3 of 45 lesions (7%). Angiocentric arrangement of lymphoid cells around and within blood vessel walls was seen in 31 cases and prominent in 9 of 45 biopsies (20%), but complete vessel wall destruction or zonal necrosis were not noted. Interestingly, this infiltrative behavior of lymphoid cells towards nipple and areola constituents was markedly pronounced in bigger infiltrates. Sheaths of elastic fibers around mammary ducts were usually slightly disrupted in 10 of 15 cases studied, and ductal elastosis was never seen. In practically all CLH (40 of 42; 95%) there were remarkable areas of smudged lymphoid infiltrates (Figs. 3, 7B) in different parts of excised tissues, not only near margins. Thus they seem not a mere surgical artifact, but rather a result of compression of an abundant dense infiltrate by the connective and muscle tissues of the nipple and areola.

Lymphocytes infiltrating epithelium of mammary ducts or skin adnexa were noted in 11 of 30 specimens (37%) in which these structures were present. However, they were mainly T cells, and true lymphoepithelial lesions (LEL) formed by a group of at least 3 marginal zone cells in the epithelium, as defined in other sites,[18] were seen exceptionally (in 3 of 30 biopsies, 10%).

Features of CLH of the breast nipple that may cause diagnostic difficulties are summarized in Table 2.

Molecular Genetics

Thirty-one specimens of 29 patients were analyzed, of which 26 lesions showed a polyclonal IgH rearrangement. Five women (aged 55–70 years) had CLH with monoclonal IgH rearrangement, which was detected using FR2A/LJH and VLJH primers in 4 patients and using FR3A/VLJH primers in 1 patient. The lesions lasted 2 weeks to 1 year (size 1.5–3.5 cm). All patients were well and without disease 6 to 216 months after the excision (median 24, mean 63). One monoclonal CLH was a recurrence of the first polyclonal lesion appearing several months after the excision; it was re-excised, and the woman remained in complete remission for

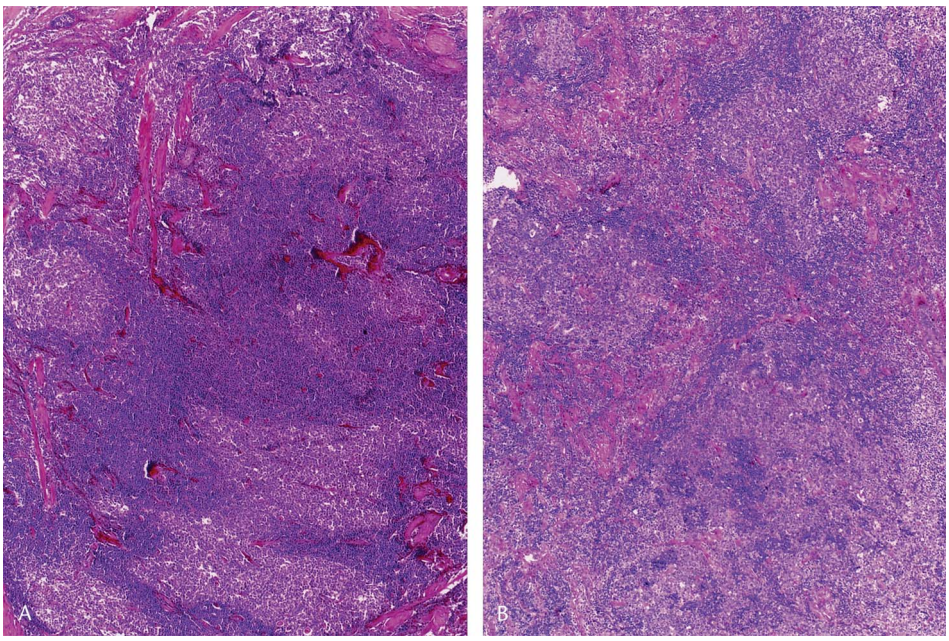

FIGURE 4. A, Lymphoid follicles of cutaneous lymphoid hyperplasia with reactive germinal centers of various sizes and shapes (H&E). B, Lymphoid follicles in cutaneous lymphoid hyperplasia are closely packed and may coalesce (H&E). Mantle zones are markedly irregular and reduced.

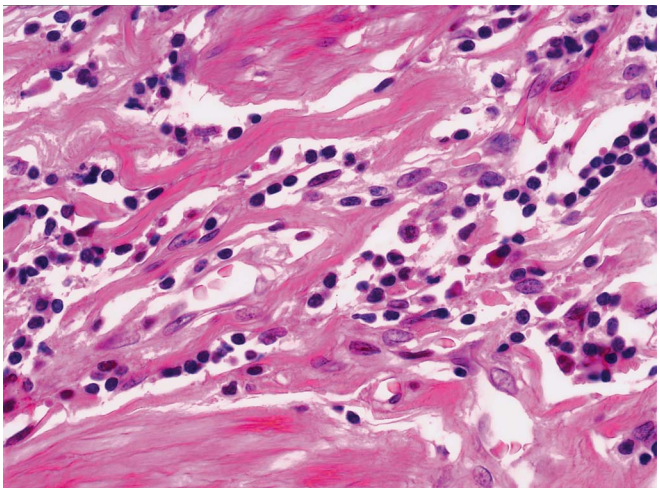

FIGURE 5. Lymphoid cells of cutaneous lymphoid hyperplasia spread in ''Indian files'' between fascicles of collagen (H&E).

the next 60 months. One monoclonal lesion contained *B. burgdorferi* DNA.

TCR γ gene clonal rearrangement was detected in 2 cases: one was a 17-year-old man with a 3-month history of the nipple lesion that exhibited microscopically a dense infiltrate composed of an equal number of B cells and T cells without any lymphoid follicles. As there had been no improvement after 6 weeks of antibiotic therapy, excision was performed and antibiotic therapy was continued; the patient was free of disease 7 months after the diagnosis. The other patient was a 71-year-old woman with a typical histopathological appearance of CLH with B cells (80%) forming confluent follicles with prominent GC and DLBCL-like areas. Staging procedures were not performed, and she died of another cause.

Recurrent Cases

Only 2 CLH recurred: in one patient a recurrence with a clonal IgH rearrangement followed several months after the first polyclonal infiltrate. In the other patient both the first lesion and the recurrence following after 4 months were polyclonal. All had a typical histologic appearance of CLH, and were cured by re-excision. Staging examinations were negative and the follow-up uneventful (lasting 60 and 108 months, respectively).

Association with *B. burgdorferi* Infection

Association with *B. burgdorferi* was documented by PCR and/or serology in 14 of 30 CLH with known laboratory data. In 10 patients, *B. burgdorferi* DNA was detected by PCR: in 3 of them *B. burgdorferi* serology was positive too; for the 7 others serology data are not known. In an additional 4 patients (3 of them with a tick bite), *B. burgdorferi* serology was positive, whereas the PCR results were negative. One lesion with PCR-proved *B. burgdorferi* association showed clonal IgH rearrangement. Six cases with a laboratory-proven *B. burgdorferi* association were from the Czech Republic, 6 from Germany, 1 from Slovenia, and 1 from Slovakia. Two patients had concomitant erythema chronicum migrans, suggesting an early manifestation of *B. burgdorferi* infection.[19] Other symptoms of *B. burgdorferi* infection were not reported, except for arthralgias in one patient.

Other stimuli as vaccinations, drug injections, medication known to cause lymphoid infiltrates, acupuncture, piercing, tattoos were noted neither at the clinical examination at the time of the diagnosis, nor anamnestically. Immune deficiencies were not diagnosed.

Group 2: Other Benign Lymphoid Infiltrates of the Nipple and Areola

Distinct features of all cases led to correct primary diagnoses, namely chronic mastitis (n = 4), retromammillar

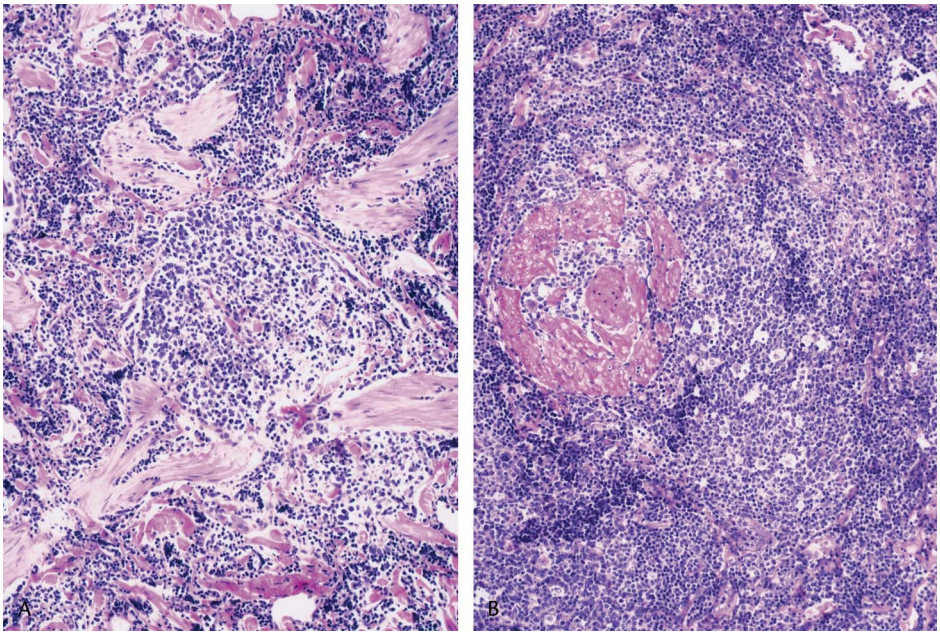

FIGURE 6. A, Smooth muscle bundles are heavily infiltrated and fragmented by lymphoid cells of cutaneous lymphoid hyperplasia (H&E). B, A smooth muscle bundle is embedded within and partially fragmented by germinal center in cutaneous lymphoid hyperplasia (H&E).

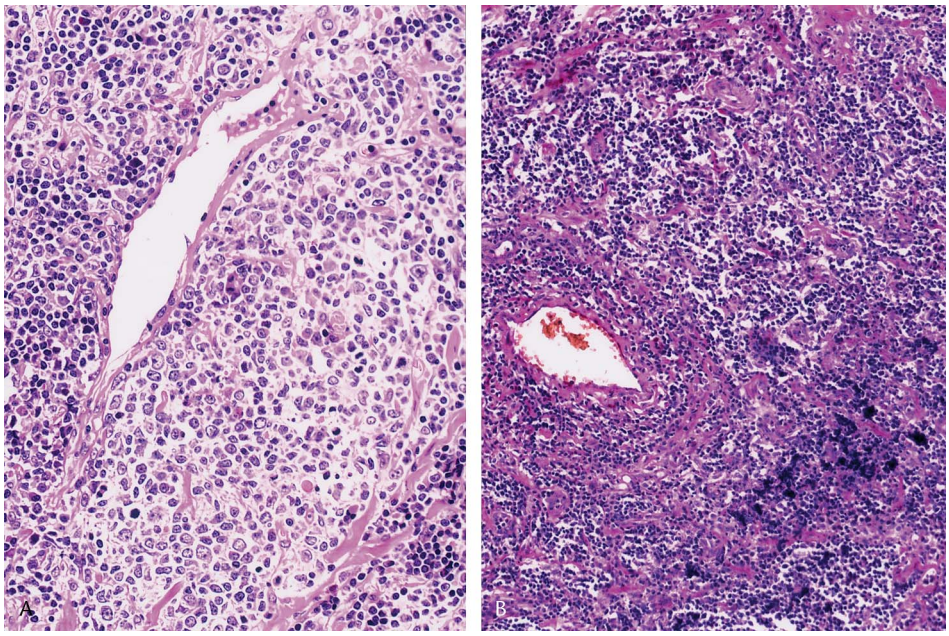

FIGURE 7. Cutaneous lymphoid hyperplasia. A, A germinal center adheres intimately to a vein (H&E). B, Lymphoid cells are tightly arranged around and infiltrate into the wall of a vein. An area of a smudged lymphoid infiltrate is seen at lower right (H&E).

abscess (n = 2), herpes zoster ulceration (n = 1), and nonspecific chronic nipple ulceration (n = 1). Treatment included a simple excision in 5 cases, subcutaneous mastectomy in 1, and excision and antibiotics in 2 patients. Staging procedures, performed in 1 patient only, were negative. Follow-up is available for 6 patients who are well and without disease 12 to 96 months after the diagnosis.

In addition to the clinical and histopathological features characteristic of these diseases, all cases displayed a marked lymphoid infiltration in the nipple and/or areola with lymphoid follicles. At low magnification other benign lymphoid infiltrates (OBLI) differed clearly from CLH in that they were notably less dense, contained markedly fewer follicles, and GC were small, polarized, and never confluent. FDC meshworks were regular, small, and dense. PCR detected neither monoclonal IgH gene rearrangement nor *B. burgdorferi* DNA in any of 7 cases studied. Monoclonal TCRγ gene rearrangement was found in 1 patient with an abscess with predominant B cells (70%) among the accompanying lymphoid population; the patient is alive and well 48 months after the excision.

Group 3: Peripheral T-Cell Lymphoma, Not Otherwise Specified

Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) presented as a single red 1.5-cm induration of the areola. In several weeks, numerous non-ulcerating 2- to 2.5-cm nodules appeared on the chest and on the forehead. The woman was treated with PUVA (psoralens and ultraviolet radiation A), then with rePUVA (retinoids and PUVA), and further with phototherapy with prevailing UVB radiation (300–320 nm). At the point of 32 months after the presentation, she has been in complete remission for 6 months.

Histologically, there was a diffuse lymphoid infiltrate in the areolar dermis largely sparing the Grenz zone. The infiltrate consisted mainly of small- to medium-sized, moderately pleomorphic CD3+ CD5+ CD45RO+ T cells with an ample clear cytoplasm, and a low proliferative activity (<10%). CD8 as well as TIA-1 labeled only a minority of tumor cells (<10%). There was an admixture of numerous histiocytes and eosinophils, a small number of B cells without follicle formation, and occasional polyclonal plasma cells. CD30 decorated rare large cells, some of them resembling Reed-Sternberg

TABLE 2. Features of Cutaneous Lymphoid Hyperplasia of the Breast Nipple That May Cause Diagnostic Difficulties

Feature	n/N	%
Absence of germinal centre polarization	33/39	82
Absence of mantle zones	28/41	68
Coalescence of lymphoid follicles	28/41	68
DLBCL-like areas	5/41	12
Marked B-cell predominance (B:T ratio ≥3:1)	8/42	19
Follicular colonization by monocytoid B-cells	4/45	9
"Indian files" of lymphoid cells between collagen fascicles	43/44	98
Smooth muscle fragmentation by the lymphoid infiltrate	13/45	29
Smooth muscle and fibrous tissue necrosis	3/45	7
Prominent angiocentric arrangement	9/45	20
Smudged lymphoid infiltrates	40/42	95
Lymphoepithelial lesions	3/30	10
B-cell clonality detected using polymerase chain reaction	5/31	16
T-cell clonality detected using polymerase chain reaction	2/31	6
Local recurrence	2/44	5

n, number of cases displaying a certain feature; N, total number of cases analyzed; DLBCL–like areas, diffuse large B-cell lymphoma-like areas of large blasts of confluent germinal centers.

cells, but these were CD15 and EBV (LMP) negative. Neither clonality nor *B. burgdorferi* DNA were detected using PCR.

Group 4: Cases With Overlapping Features of Cutaneous Lymphoid Hyperplasia and B-Cell Lymphoma

Case 1

A 66-year-old woman had a 1-month history of a 3 × 2-cm, red, hard nodule of the upper part of the right areola. It was excised because of a clinical suspicion of Paget disease. The histologic diagnosis was a low-grade B-cell lymphoma. Staging procedures were negative, and no other treatment was administered. *B. burgdorferi* serology was not examined. Six years later the patient was diagnosed to have rheumatoid arthritis. Eight years and 4 months after the excision, she is still without any recurrence of the breast lesion and any other evidence of lymphoma.

At low power, prevailing spindle cells were arranged in a vaguely nodular pattern. At higher magnification, coalescing lymphoid follicles with small irregular reactive GC were encircled and often colonized by broad sheets of small- to medium-sized spindle cells with regular, ovoid, or round nuclei with a coarse chromatin, very low mitotic activity, and an ample light cytoplasm. They constituted the majority of the predominating B-cell infiltrate (making up over 80%) (Figs. 8A–C). Albeit unusual, they resembled monocytoid B cells. The conspicuous appearance and cohesive growth of the spindle cells in some areas prompted us to test for actin, vimentin, and cytokeratins, of which only vimentin was focally positive. Further, the spindle cells expressed CD20, CD79a, bcl-2, and in a small subset CD21 and CD35 too, yet were CD5, CD23, CD10, and bcl-6 negative. They showed neither IgL expression nor Dutcher bodies. Their proliferation was low (about 5%). In contrast, non-polarized small reactive GC were composed mainly of bcl-2–negative proliferating centroblasts (Ki-67 > 90%) and of a moderate number of tingible-body macrophages. CD21 and CD35 displayed largely expanded FDC meshworks. Polyclonal plasma cell clusters were scattered around the follicles. Mast cells were occasional. No LEL could be identified, as no mammary ducts and only scarce skin adnexa were observed. The lymphoid cells infiltrated smooth muscle bundles resulting in their fragmentation, spread along the nerves, and were focally arranged in an angiocentric pattern. Neither monoclonality nor *B. burgdorferi* DNA were found by PCR.

Diagnosis

In spite of a long, uneventful follow-up and lacking a proof of monoclonality, the prevalence of monocytoid B cells colonizing the follicles suggests the diagnosis of marginal zone B-cell lymphoma of the areola composed of peculiar spindle cells.

Case 2

A 5-cm lesion had been present for 6 months in the right breast of a 46-year-old man. The clinical diagnosis was gynecomastia. Diagnosed originally as MALT lymphoma on histology, radiotherapy was administered. *B. burgdorferi* serology was not tested. Staging investigations were negative and the patient is healthy 57 months after the diagnosis.

Fibromuscular tissues of the areola embedded several mammary ducts and an extremely dense vaguely nodular mainly B-cell infiltrate (constituting of over 80% of the population). The small excision size and absence of epidermis did not allow assessing the architecture reliably. Areas of monocytoid CD20- and CD79a-positive, CD5- and CD23-negative B cells produced focal follicular colonization and exceptionally rare

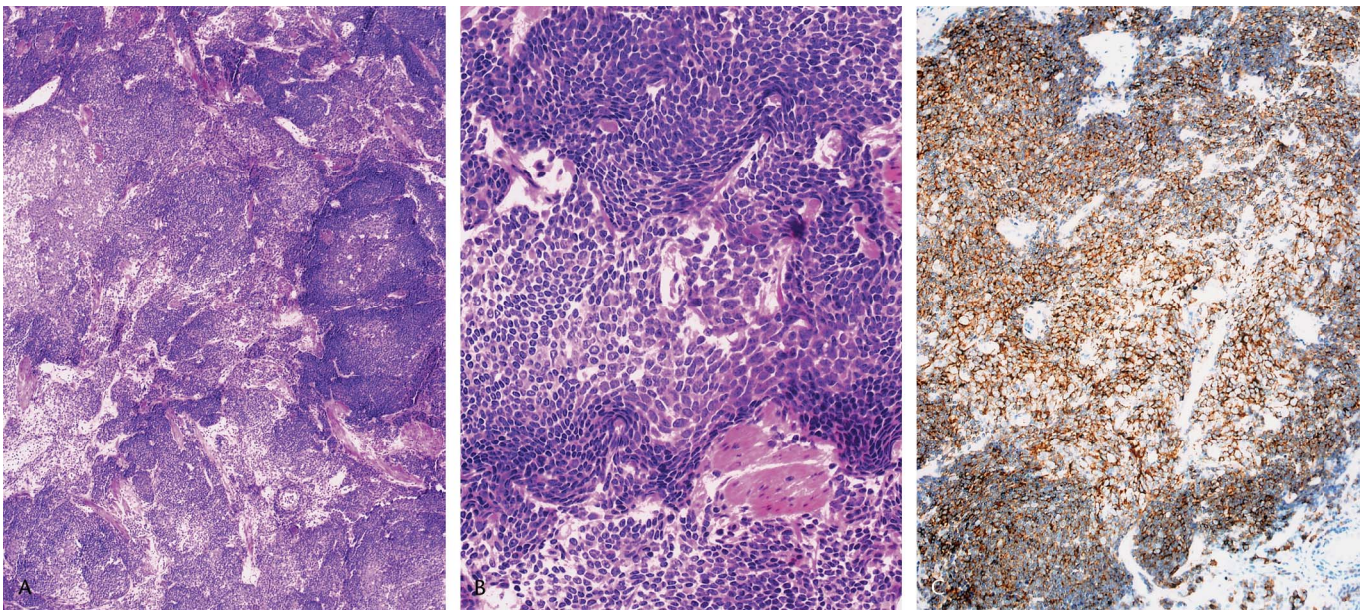

FIGURE 8. Case 1. Suggested diagnosis: marginal zone B-cell lymphoma of the areola composed of peculiar spindle cells. A, A dense vaguely nodular lymphoid infiltrate (H&E). B, Spindle cells encircle a germinal center (H&E). C, The infiltrate consists predominantly of B cells (CD20).

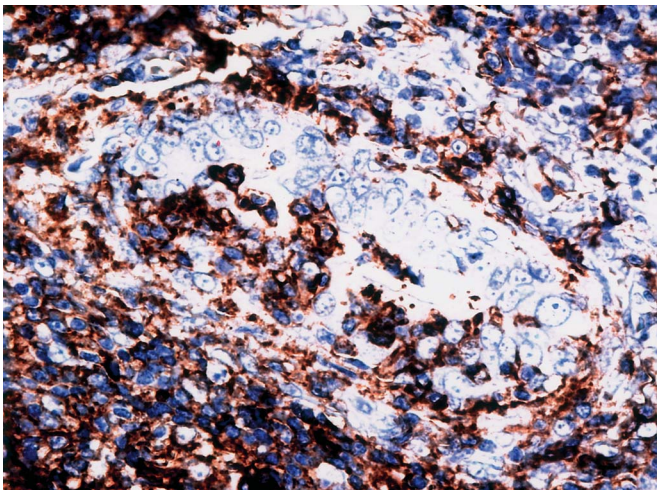

FIGURE 9. Case 2. Diagnosis unresolved: cutaneous lymphoid hyperplasia versus marginal zone B-cell lymphoma. A lymphoepithelial lesion in a mammary duct (CD20).

LEL in the mammary ducts (Fig. 9). They can occur both in MZL and CLH, although we did not encounter monocytoid foci of similar size in our unequivocal cases of CLH. The virtual extent of monocytoid population could not be assessed. Irregular sheets of large B cells resembling DLBCL were identified as confluent GC with few macrophages when using Ki-67 and CD10. However, many proliferating cells, some of large size, were scattered outside GC, too, making the impression of MZL with interspersed large B blasts, or with a large cell transformation. FDC meshworks were conspicuously expanded and irregular. Mast cells and polyclonal plasma cells were occasional. The infiltrative behavior of lymphoid cells, especially toward the smooth muscle, and "Indian files" between collagen fascicles were prominent. IgL restriction was not detected. Neither clonality nor *B. burgdorferi* were evaluated by using PCR.

Diagnosis

Histologic, immunophenotypic, and molecular-genetic features do not allow establishing the diagnosis in a small biopsy. Further, negative staging examinations and uneventful course of 57 months after radiotherapy could be the same both for CLH and MZL.

Case 3

The patient was a 67-year-old woman with clinically suspected Paget disease of the left breast areola, lost to follow-up after the excision. Histologically, a patchy infiltrate in the dermis and adjacent mammary parenchyma consisted of scattered lymphoid follicles (Fig. 10A). Approximately half of them showed GC, which were sometimes confluent and polarized, with tingible-body macrophages and the proliferative activity about 70%. Mantle zones were poorly formed or absent. The other follicles raised a suspicion of FL: they were more regular, smaller, and cytologically uniform, composed mainly of centrocytes with very few centroblasts and macrophages, and narrow mantle zones (Fig. 10B). The GC proliferative activity was markedly low (about 30%). CD10 decorated cells of GC in both types of follicles and single scattered positive lymphoid cells in interfollicular areas. In both types of follicles bcl-2 was negative and no differences in FDC patterns were noted. Bcl-6 could not be evaluated. Neither IgL restriction nor LEL were identified. Neither clonality nor *B. burgdorferi* could be evaluated using PCR.

Diagnosis

Unresolved, cutaneous lymphoid hyperplasia/possibly with developing follicular lymphoma.

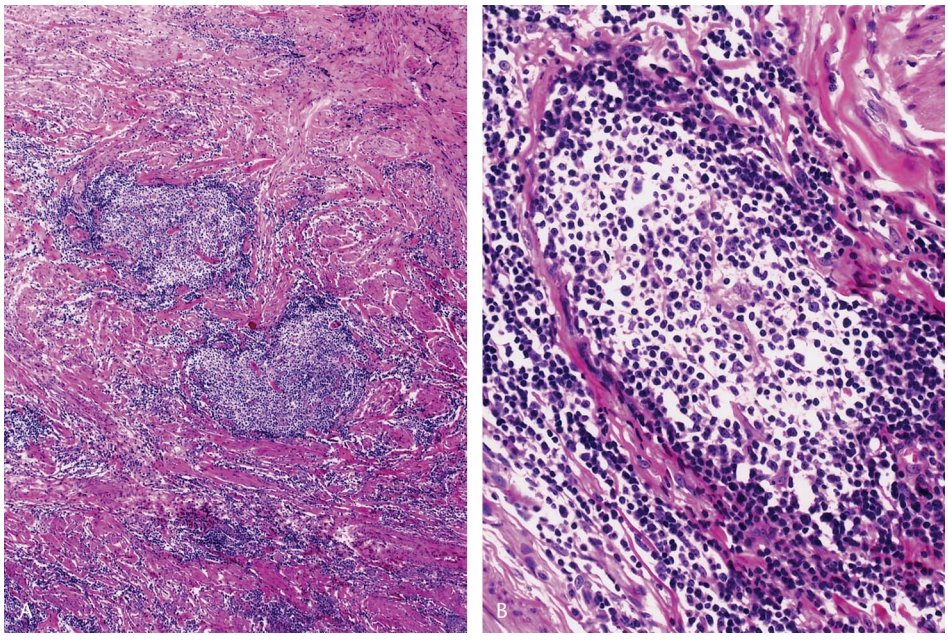

FIGURE 10. Case 3. Diagnosis unresolved: cutaneous lymphoid hyperplasia/ possibly with developing follicular lymphoma. A, A patchy infiltrate in the dermis is composed of relatively uniform follicles with very narrow mantle zones (H&E). B, A monotonous cytologic appearance formed mainly by centrocytes, whereas centroblasts and macrophages are very few (H&E).

DISCUSSION

Our retrospective study of 56 cases demonstrates that a majority of lymphoproliferations of the breast nipple and areola represent CLH. It is typically formed by dense vaguely nodular or diffuse infiltrates containing lymphoid follicles with GC. CLH involves the entire dermis, and sometimes also the adjacent breast parenchyma, whereas the epidermis is spared.

Cutaneous lymphoid hyperplasia in the nipple and areola often shows worrisome histologic features (Table 2) prompting to consider a malignancy, and the most common disorders to differentiate are MZL and FL. In CLH, closely packed, poorly defined lymphoid follicles with non-polarized, naked GC lacking mantle zones and consisting mainly of large blasts[1,10] may resemble FL grade IIIB.[18] Follicle sizes, shapes, and lack of GC polarization are similar in CLH and primary cutaneous FL. Yet typically, a combination of proliferating large blasts and tingible-body macrophages is characteristic for GC in CLH,[1] whereas the predominance of centrocytes and low proliferation are usually found in cutaneous FL.[10] Marginal zone cells are the most significant feature of MZL, whereas they are only rare and inconspicuous in CLH.[20] Further, in contrast to CLH, MZL displays follicular mantle zones, GC polarization, and plasma cell sheets, but its follicles do not coalesce.[10,20] In contrast to criteria used in the past,[21] a bottom-heavy infiltrate is not a distinguishing feature of MZL. Likewise, a Grenz zone, eosinophils, neutrophils, epithelial infiltrating lymphocytes, and the low frequency of LEL is common for both.[20,22,23]

An important source of a diagnostic error is the B-cell predominance in our cases of CLH. In contrast to Baldassano,[20] 7 cases of CLH in our series had the B:T ratio ≥3:1, of which 6 have follow-up (mean 46, median 29, range 6–108 months). As they did not differ from other CLH cases in respect to benign clinical course, a high B:T ratio does not seem a strong indicator of malignancy.

It is of particular note that large sheets of confluent GC without clear-cut mantle zones, occurring in 11% of our CLH specimens, simulate DLBCL, especially in small biopsies.[1,24] In CLH, naked GC composed of large cells were frequently embedded in or pierced by smooth muscle bundles, and occasionally arranged tightly perivascularly and perineurally, which strengthened further the impression of a malignancy. Similar features are found in leukemia cutis.[25] Smooth muscles of the nipple and areola were extremely often infiltrated by lymphoid cells, leading to muscle fragmentation in almost one third of our CLH cases, yet necrosis was rare. Infiltration of blood vessel walls, typical not only for angiocentric lymphoma, but also for leukemia cutis,[18,25] was conspicuous in 20% of our CLH cases, but in contrast to angiocentric lymphoma, complete vessel wall destruction or zonal necroses were not seen. Infiltrating lymphoid cells partially disrupted and reduced elastic fibers, which normally ensheathe smooth muscle bundles and mammary ducts.[26] On the contrary, duct elastosis, prominent in ductal carcinoma, which may be of diagnostic help even in frozen sections as described by Azzopardi,[27] was not encountered in our CLH series. "Indian files" of lymphoid cells between collagen and smooth muscle bundles bore a resemblance to leukemia in the skin,[25] and such a similarity was further enhanced by smudged infiltrating cells, which are a common finding in leukemia cutis (Prof. Dr. Burg, Zűrich, Switzerland, personal communication). So it should be reminded that "Indian files", in the breast prototypical of lobular carcinoma, are also encountered both in CLH and lymphomas of this site as confirmed in the literature.[28]

Thus in our own experience, and as documented by others, CLH in the nipple and also in the scrotum look different histopathologically from lesions in other sites, as they display denser infiltrates and atypical features as mantle zone absence, follicle confluence,[1,10] and conspicuous intimate interactions with other tissues raising a consideration of malignancy. Parenthetically, this offers a similarity to melanocytic nevi, which often simulate melanoma in genital, breast, and other areas.[29] We think that some of the atypical features of nipple and scrotal CLH are due to the histologic constitution of these sites, namely the abundance of smooth muscle. Besides, other researchers state the absence of mantle zones to characterize lymphocytoma cutis induced by *B. burgdorferi,*[1] which is a common causative factor of CLH, especially in endemic regions in Europe.[30,31] This association was proved by PCR and/or serology in 14 of our 30 patients with available laboratory data (47%), all of these living in countries with endemic *B. burgdorferi* infection. This rate is nevertheless lower than in the series of Colli.[1] The number of positive cases may be in reality higher as both methods may yield false-negative results. We have not found any histologic difference between *B. burgdorferi*-associated versus *B. burgdorferi*-non–associated cases. Importantly, atypical microscopic features of CLH of the nipple led to a frequent overdiagnosis of malignancy, occurring in 28% of this series. This is of consequence as 3 of the patients underwent, in our opinion, unnecessary radiotherapy and/or chemotherapy. Further, although in its typical site, CLH in the nipple/areola was also underrecognized clinically; the most common preoperative clinical diagnosis was Paget carcinoma of the breast (in 28%), whereas a lymphoproliferative disorder was considered in only 19%.

Apart from unequivocal CLH depicted so far, 3 additional specimens were difficult to categorize, even retrospectively, as a CLH or a low-grade B-cell lymphoma. All 3 were predominantly B-cell infiltrates with a follicular growth pattern. The first case was completely unusual as cohesive spindle B cells prevailed in a vaguely nodular infiltrate. Sheets of peculiar spindle B cells with a very low proliferative activity encircled and colonized reactive GC. This suggests the diagnosis of a low-grade B-cell lymphoma, namely MZL of the skin composed of unusual spindle cells, but negative staging, lack of a monoclonality proof, and an uneventful follow-up of 8 years are well compatible with a benign diagnosis, too. Cerroni described cutaneous spindle-cell B-cell lymphoma on the head and trunk as a variant of large B-cell lymphoma,[32] yet we are not aware either of any low-grade B-spindle cell lymphoma of the skin, or of any CLH with such a peculiar morphology. In the second case, areas of monocytoid B cells with follicular colonization and rare LEL, together with a large size and a relatively long duration point also to MZL, but no decisive results could be obtained in a small biopsy and the follow-up of 57 months is uneventful. In the third case,

architectural and cytologic uniformity of a part of follicles composed mainly of centrocytes with few macrophages, and with a low proliferative activity, led to a serious consideration of FL grade II.[18]

All in all, a precise diagnostic separation of low-grade B-cell lymphomas as MZL and FL from CLH is not always possible. The number of cases difficult to classify will be certainly higher in a daily practice than in this retrospective study. Even a favorable clinical course and monoclonality are unreliable in separating these conditions. Fortunately, similarly to MALT lesions in the stomach, CLH, cases with overlapping features of CLH and B-cell lymphoma, and a part of cutaneous B-cell lymphoma may be responsive to antibiotic treatment and cured by surgery. However, skin lymphomas should be certainly distinguished from CLH whenever possible, because although a majority of cutaneous B-cell lymphoma run a benign course, they may, albeit rarely, lead to dissemination and the death of patients.[33] Further, skin involvement by a lymphoma should prompt staging examinations, as it often proves to be a part of a systemic disease.[34]

Several links connect cutaneous B-cell lymphoma and CLH, as the association with *B. burgdorferi*[1,22,35–38] or the presence of a monoclonal population in a subset of cases.[1,39,40] Further, there are on record cases of pseudolymphoma that have progressed in time into a B-cell lymphoma,[22,41] suggesting a continuum of lymphoproliferative disorders with CLH at the benign end, clonal CLH as an intermediate condition that may progress into cutaneous lymphoma, representing the malignant extreme.[42–45] The significance of monoclonality has not been settled: according to some authors, patients with CLH with a clonal B-cell or T-cell population should be observed for emergence of a lymphoma,[42,44,46] but others have not proven such a progression.[39,43,47] Only 1 of our 7 clonal CLH recurred, and otherwise all of these patients were well and without any disease at a follow-up of 6 to 216 months (median 24).

Apart from CLH and cases with overlapping features of CLH and B-cell lymphoma, we encountered 1 peripheral T-cell lymphoma arising in the skin of the areola, and several marked inflammatory lymphoid infiltrates containing lymphoid follicles. They differed clearly from CLH by distinct clinicopathological features, posing no diagnostic difficulties. Interestingly, in none of 60 malignant lymphomas involving the breast gland, which we reviewed, was there a nipple specimen excised for a histologic examination because of a conspicuous involvement. Similarly, there are only very few records of the breast nipple and/or areola involvement by a primary or secondary breast lymphoma.[5,6,8] Thus a lymphoproliferation encountered in the nipple is usually not a spread from a deeper tumor.

In summary, most lymphoid infiltrates of the breast nipple and areola represent CLH, often *B. burgdorferi*–associated, which respond well to antibiotic treatment. CLH of the nipple still remains underrecognized clinically, and it tends to be overdiagnosed histopathologically as a lymphoma because it manifests features suggestive of a malignancy. Further diagnostic problems may be caused by a small size of the specimen, recurring lesions, and clonality interpretation. For practical purposes, the nipple/areolar localization itself can be considered as an important feature favoring a benign diagnosis of a lymphoid infiltrate in most cases, although rare malignant lymphomas occur in this site too[4,5,7,8] and the evidence of *B. burgdorferi* association per se does not exclude a diagnosis of malignant lymphoma.[5,22,35,38,48] A minority of lymphoid lesions in this region cannot be reliably categorized as CLH or lymphoma using current histopathologic, molecular-genetic, and clinical approaches. It appears reasonable to view such lesions as benign at the diagnosis and to provide these patients antibiotic therapy for *B. burgdorferi,* and a long follow-up.

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