

# Cutaneous Lymphomatoid Granulomatosis

## Correlation of Clinical and Biologic Features

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Lymphomatoid granulomatosis (LYG) is a rare angiocentric and angiodestructive Epstein–Barr virus-associated B-cell lymphoproliferative disorder (EBV-BLPD), varying widely from an indolent process to an aggressive large cell lymphoma. The skin is the extrapulmonary organ most commonly involved in LYG. We studied 32 skin lesions from 20 patients with known pulmonary LYG, using immunohistochemistry, in situ hybridization for EBV, and polymerase chain reaction for the presence of antigen receptor gene rearrangements (IgH and TCR) to better define both the clinicopathologic spectrum and pathogenesis of the cutaneous lesions. We describe two distinct patterns of cutaneous involvement. Multiple erythematous dermal papules and/or subcutaneous nodules, with or without ulceration, were present in 17 patients (85%). These lesions demonstrate a marked angiocentric lymphohistiocytic infiltrate, composed predominantly of CD4-positive T-cells, with a high propensity for involving the subcutaneous tissues, and exhibiting angiodestruction, necrosis, and cytologic atypia. EBV-positive B-cells were detected in the nodules from five patients; clonal immunoglobulin heavy chain gene (IgH) rearrangements were detected by polymerase chain reaction in two patients. Multiple indurated, erythematous to white plaques were present in three patients (15%). The plaque lesions were negative for EBV and clonal IgH gene rearrangements in all cases studied. The clinical course of overall disease was variable, ranging from spontaneous regression without treatment (1 of 13; 7%), resolution with chemo/immunomodulatory therapy (8 of 13; 62%), and progression (4 of 13; 31%). The clinical and histopathologic features of cutaneous LYG are extremely diverse. However, the majority (85%) of the cutaneous lesions mirrors to some extent LYG in the lung, although EBV+ cells are less frequently identified. This subset of cases shows the histopathologic triad of angiodestruction with associated necrosis, panniculitis, and in some cases atypical lymphoid cells. The commonality of the histologic features in this group suggests a common pathophysiologic basis, possibly mediated by cytokines and chemokines induced by EBV. A small percentage of

the lesions (15%) presented as indurated and atrophic plaques, and EBV was not identified in the small number of cases studied. The relationship of the plaque-like lesions to LYG remains uncertain. Whereas some cases of LYG regress spontaneously, most require therapy.

**Key Words:** Lymphomatoid granulomatosis—Cutaneous—Histopathology—Dermatologic features—Molecular analysis—Epstein–Barr virus.

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Lymphomatoid granulomatosis (LYG) was first described by Liebow et al., who characterized a rare and unique angiocentric and angiodestructive lymphoproliferative process in the lungs.<sup>23</sup> LYG affects patients of all ages, although most cases occur between the 4th and 6th decades of life, with a slight male predilection (male to female ratio 2.5:1).<sup>18</sup> Although the lung is the most frequently involved organ and virtually all patients will have pulmonary disease at some point during the course of their illness, LYG is a multisystem disease. Other organs involved in LYG include skin, kidneys, central nervous system, upper respiratory tract, and gastrointestinal tract, with a striking sparing of lymphoid tissues.<sup>14,18</sup> The clinical behavior of LYG varies widely from an indolent process to an aggressive large cell lymphoma. In cases complicated by constitutional symptoms or with multiple organ involvement, the prognosis is generally poor, with approximately two thirds of patients dying within a year of diagnosis, usually of extensive pulmonary disease complicated by secondary infection.<sup>14</sup>

Since its description nearly 30 years ago, LYG had been somewhat of an enigma, its etiology elusive. An exuberant reactive T-cell infiltrate, which generally accompanies the angiitic lesions, had led to the supposition that LYG might be a T-cell lymphoproliferative disorder.<sup>14,24,29</sup> However, the nature of LYG has been largely

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resolved in more recent years. Recent studies characterize LYG as a type of Epstein–Barr virus (EBV)-positive B-cell lymphoproliferative disease with many similarities to post-transplant lymphoproliferative disorder.<sup>10,13,17,27</sup> EBV RNA has been localized to small numbers of B-cells in the pulmonary lesions, and clonal rearrangements of the immunoglobulin heavy chain (IgH) gene also have been detected, especially in more high-grade lesions.<sup>10</sup> LYG has been clearly distinguished from extranodal natural killer (NK)/T-cell lymphoma, and nasal-type, another EBV-associated angiocentric lymphoproliferative disorder with which it shares pathologic similarities.<sup>12</sup>

The skin is the extrapulmonary organ most commonly involved in LYG, occurring in 40–50% of patients.<sup>18</sup> As a result of this, the cutaneous lesions are easily and readily biopsied for histopathologic diagnosis. Indeed, numerous reports describing the histopathology of cutaneous lesions of LYG appeared shortly after its first description. However, apart from a single report,<sup>26</sup> most of them predate our modern understanding of LYG.<sup>1,3,5,6,11,16,19,28,30,40</sup> Based on our current knowledge of LYG,<sup>9,10</sup> we decided to look anew at the clinical and histopathologic features of 20 cases of LYG with cutaneous manifestations, using immunohistochemical and molecular techniques to investigate the pathogenesis of the cutaneous infiltrates within the spectrum of LYG.

## MATERIALS AND METHODS

### Case Selection

Twenty patients with known pulmonary LYG and cutaneous lesions were selected from the archive files of the Hematopathology Section, Laboratory of Pathology, National Cancer Institute, from 1970 to 2000. Clinical criteria included the presence of skin lesions, with or without renal, central nervous system, or other organ involvement.

In all cases hematoxylin and eosin-stained glass slides of either formalin or B5 fixed tissues were available, of both the lung and skin lesions. All cases met the histologic and clinical criteria for the diagnosis of pulmonary LYG.<sup>15</sup> The histologic criteria for the primary pulmonary diagnosis included the following: 1) a polymorphous cellular infiltrate containing lymphocytes, histiocytes, plasma cells, and varying numbers of atypical cells; 2) evidence of angioinvasion and/or angiodestruction, with or without associated necrosis. The pulmonary lesions were graded by a previously reported scheme,<sup>24</sup> with minor modifications. Briefly, grade 1 lesions were comprised of a polymorphous angiocentric infiltrate without cellular atypia and with minimal to absent necrosis. EBV+ cells were infrequent (<5/high power field [HPF]) or absent. Grade 2 lesions contained scattered

large and sometimes hyperchromatic lymphoid cells with <20 EBV+ cells/HPF in the background of a polymorphous angiocentric and angiodestructive lymphoid infiltrate. Necrosis was nearly always present but was not extensive. Grade 3 lesions contained frequent large atypical lymphoid cells (usually >20 EBV+ cells/HPF) in a polymorphous background. Large confluent areas of coagulative necrosis were often seen. Rare cases diagnosed as grade 3 contained foci that fulfilled criteria for a diagnosis of diffuse large B-cell lymphoma, although such foci were usually small.

Thirty-two separate skin lesions were studied from the 20 selected patients. Three pathologists (M.W.B., E.S.J., and J.B.S.) reviewed all the cutaneous lesions. Routine hematoxylin and eosin-stained slides were examined for the pattern, depth, and cellular composition of the infiltrates, e.g., angiocentric and/or periadnexal infiltrate, including hair, peripheral nerves, eccrine glands, and sebaceous glands. Angiodestruction was considered present when a mononuclear infiltrate was seen within the walls of vessels with associated fibrinoid change. Minimal atypia was noted when the background lymphocytes were enlarged or showed irregularities. Marked atypia was noted in cases with larger cells having pleomorphic nuclei, prominent nucleoli, and/or Reed–Sternberg-like appearance.

### Immunohistochemistry

Immunohistochemical studies were performed on 21 skin biopsies having sufficient paraffin material for analysis. An antigen retrieval method was used before an avidin-biotin complex immunoperoxidase technique on an automated immunostainer (Ventana Medical System, Tucson, AZ, USA), according to the manufacturer's instructions, as previously described.<sup>31</sup> Appropriate positive and negative controls were run for each antibody. The primary antibody panel consisted of CD20 (L26, dilution 1:200; Dako, Carpinteria, CA, USA), CD3 (1:25; Dako), CD8 (1:40 clone 144B; Dako), CD4 (1:40, Novacastra, Vector Laboratories Inc., Burlingame, CA, USA), and CD30 (1:20, Novacastra).

### In Situ Hybridization

In situ hybridization for EBV was performed on the primary pulmonary lesions from eight patients and the cutaneous lesions from 13 patients (22 skin lesions total) as previously described in detail.<sup>20</sup> A Ventana Gen 2 automated in situ hybridization instrument (Ventana Medical System, Tucson, AZ, USA) was used to perform the hybridization. EBER-1, an EBV-encoded digoxigenin-labeled RNA riboprobe, was diluted in a 50% formamide-containing buffer and applied manually to the tissue sections. Sections from a metastatic naso-

pharyngeal carcinoma served as both positive (carcinoma cells) and negative (lymphoid cells) controls. An antisense riboprobe directed against a small nuclear ribonucleoprotein, U6snRNP, was used to confirm RNA integrity of the tissue sections. Hybridization runs using buffer containing sense probe, antisense probe, and absence of probe were performed separately to confirm proper transcription of the riboprobes.

### PCR Antigen Receptor Gene Rearrangement Analysis

Fifteen separate skin lesions from 10 patients were analyzed. DNA was purified from the formalin-fixed paraffin-embedded tissue by standard phenol/chloroform methods and the concentrations were quantitated by optical density at 260/280 nm.<sup>34</sup>

Clonality of the IgH gene was determined by polymerase chain reaction (PCR) assays performed using the JH and VH framework 3 consensus primers and conditions previously described.<sup>35</sup> Briefly, 1 µg of DNA template was mixed with 1× PCR buffer containing 2.5 mM MgCl<sub>2</sub>, 0.2 mM dNTP, 0.5 mM of each primer, and LD AmpliTaq (PE Applied Biosystems, Foster City, CA, USA) previously treated with Taq Start Antibody (Clontech, Palo Alto, CA, USA). The DNA was amplified in a thermocycler (PE Applied Biosystems, model 480) for 35 cycles (94°C, 1 minute; 56°C, 1 minute; 74°C, 1 minute) with a final extension cycle of 7 minutes at 74°C. The products were separated by 16% nondenaturing polyacrylamide gel electrophoresis (PAGE) and visualized with ethidium bromide staining. The expected molecular weight of the appropriate PCR products ranged in size from 70 to 120 bp. Semi-nested PCR amplifications were performed using primers to the framework 2 region of the IgH gene as previously described.<sup>32</sup> The products were analyzed as outlined above, and the expected molecular weight of the appropriate PCR products ranged in size from 220 to about 260 bp.

For the determination of clonal rearrangements in the T-cell receptor (TCR) gamma gene, PCR amplification was performed according to the method of McCarthy et al.<sup>25</sup> Briefly, consensus primers directed to the gamma gene variable (V) and joining (J) regions were used in two separate reactions to amplify genomic DNA; 1 µg of DNA template was mixed with PCR buffer and the reaction was initiated as described above. The reaction continued for 34 cycles (94°C, 1 minute; 60°C, 1 minute; 72°C, 1 min) with a final extension cycle of 7 minutes at 72°C. The resulting PCR products were separated by 16% nondenaturing PAGE and visualized with ethidium bromide staining. The expected molecular weight of the appropriate PCR products ranged in size from 70 to 85 bp.

To control for the amplification ability of each sample, PCR was performed using primers to a housekeeping gene, glyceraldehyde phosphate dehydrogenase, and the products were separated by a 2% agarose gel electrophoresis and visualized by ethidium bromide staining.

## RESULTS

### Clinical Features

Most of the patients initially presented with symptoms related to respiratory tract disease, including cough (60%), dyspnea (45%), chronic sinusitis (20%), and/or chest pain (10%) (Table 1). Constitutional symptoms, including fever, weight loss, fatigue, and/or night sweats, were also very common complaints (80% of cases). Neurologic involvement (35%) was manifested by peripheral neuropathy (20%), weakness (15%), and/or seizures (10%). Other systemic manifestations included arthralgias/arthritis (5%) and anemia (5%). Most of the patients had associated disease in other organs, including central nervous system, kidney, liver, and nasopharynx. One patient was diagnosed with X-linked agammaglobulinemia and suffered from recurrent pneumonias (case no. 18). One patient had rheumatoid arthritis (case no. 15); one patient was diagnosed and treated for classic Hodgkin's lymphoma 6 years before the onset of LYG disease (case no. 20). The remaining patients had no known predisposing immunodeficiencies or autoimmune syndromes.

In three patients (16%) the skin lesions preceded the diagnostic pulmonary lesions by less than 3 months, seven patients had skin lesions at the time of diagnosis, and nine developed cutaneous lesions 3 months to 4 years (mean 11 months) after the primary pulmonary diagnosis. The timing of cutaneous lesions was unknown in one patient (case no. 12). The skin lesions resolved spontaneously in one patient (case no. 7) without treatment; another patient's skin lesions responded initially to prednisone but then recurred with progressive systemic disease, requiring more aggressive chemotherapy, including cyclophosphamide, daunorubicin, vincristine, and prednisone (CHOP) etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) and interferon α-2b (IFN), and a subsequent bone marrow transplant (case no. 8). An additional five patients achieved long-term remissions after therapy with cytoxan (case no. 3), prednisone (case no. 10), IFN (case no. 4) cyclophosphamide, vincristine, prednisone, procarbazine (C-MOPP) (case no. 13), and EPOCH and IFN (case no. 12). Four patients suffered from progressive systemic disease despite aggressive chemotherapy or immunomodulatory therapy (case nos. 5, 9, 16, and 19); two of these patients died of their disease (case nos. 9 and 16). One patient demonstrated progressive disease

**TABLE 1.** Clinical and dermatologic features of 19 patients with lymphomatoid granulomatosis

Case no.	Age (yr)	Sex	Involvement (grade)	Systemic manifestations	Skin findings (distribution)	Treatment	Status
1	59	F	Lung (2), CNS, skin	Fatigue, peripheral neuropathy	Multiple nodules (SNS)	N/A	N/A
2	54	F	Lung (3), nasopharynx, skin	Fever, chronic sinusitis	Multiple nodules (lower extremities)	N/A	N/A
3	24	M	Lung (2), skin, testes	Fever, night sweats, weight loss, dyspnea, chest pain, paresthesias, peripheral neuropathy	Multiple ulcerated nodules/tumors, subcutaneous nodules (lower extremities)	Cytoxan (100 mg)	NED 53-mo f/u
4	28	M	Lung (3), CNS, skin	Fever, fatigue, weakness, peripheral neuropathy, night sweats	Multiple erythematous papules, subcutaneous nodules (lower extremities)	Interferon $\alpha$ -2b (20 mu/3 $\times$ wk/ $\times$ 3 yrs)	NED 89-mo f/u
5	49	M	Lung (2-3), kidney, skin	Fever, fatigue, weakness, peripheral neuropathy	Multiple ulcerated nodules erythematous papules, subcutaneous nodules (trunk, extremities)	Cytoxan (150 mg/d); Prednisone (60 mg/qod)	PD 49-mo f/u
6	67	M	Lung (1-2), skin	Fever, cough, dyspnea	Multiple nodules, erythematous plaques (trunk, extremities)	Prednisone	N/A
7	77	M	Lung (2-3), bone marrow, skin	Fever, cough, anemia	Multiple nodules (lwere extremities)	None	NED 12-mo f/u
8	24	M	Lung (3), CNS, skin	Fever, cough, chronic sinusitis	Multiple oval erythematous nodules (trunk, extremities)	CHOP $\times$ 3 cycles; EPOCH; Interferon $\alpha$ -2b; BMT	NED 63-mo f/u
9	18	M	Lung (2), CNS, skin	Cough, weight loss, seizures	Multiple oval, indurated white plaques w/ violaceous border (trunk)	Interferon $\alpha$ -2b (10 mu/3 $\times$ wk/ $\times$ 1 yr)	PD (DOD) 22-mo f/u
10	41	M	Lung (1), nasopharynx, skin	Fever, chronic sinusitis, cough, dyspnea, night sweats	Multiple indurated white plaques (axilla, antecubital fossa)	Prednisone	NED 34-mo f/u
11	29	M	Lung (3), CNS, liver, kidney, skin	Fever, fatigue, night sweats, dyspnea, cough	Multiple nodules (scalp, neck, trunk, extremities)	N/A	N/A
12	44	F	Lung (1), skin	Cough	Multiple nodules subcutaneous nodules (trunk)	EPOCH $\times$ 6 cycles; Interferon $\alpha$ -2b	NED
13	39	F	Lung (3), CNS, skin	Cough, dyspnea, disseminated erythema nodosum	Erythematous and violaceous papules/nodules (trunk, extremities)	C-MOPP $\times$ 9 cycles	NED 272-mo f/u
14	26	M	Lung (2), skin	Fever, dyspnea, cough	Multiple tan nodules (SNS)	N/A	N/A
15	39	M	Lung (2), skin	Fever, fatigue, arthritis, dyspnea, cough	Multiple plaques associated with alopecia (scalp)	Prednisone (60 mg/d)	N/A
16	27	M	Lung (3), skin, CNS, kidneys, heart	Fever, fatigue, cough, dyspnea, weight loss, seizures	Erythematous and necrodes (trunk, extremities)	Cytoxan, vincristine, prednisone, procarbazine, bleomycin	PD (DOD) 10-mo f/u
17	37	M	Lung (1), skin, liver	None reported	Subcutaneous nodules (lower extremities)	N/A	N/A
18	35	M	Lung (2), nasopharynx, skin	Chronic sinusitis, recurrent pneumonias, XLA	Subcutaneous nodules (cheek)	N/A	N/A
19	44	F	Lung (1), liver, spleen, skin	Fever, night sweats, dyspnea, cough, arthralgias, chest pain	Multiple erythematous papules/nodules (face, neck, trunk)	Prednisone; ProMACE; cytoBOM	PD
20	44	M	Lung (2-3), liver, kidney, CNS, skin	Night sweats, leg weakness, incontinence	Multiple erythematous papules (trunk, extremities)	Hx of CHL, treated w/MOPPABV $\times$ 8 cycles; cranial-spinal XRT; MIME $\times$ 8 cycles; Receiving Interferon $\alpha$ -2b	Early/initial response to Interferon

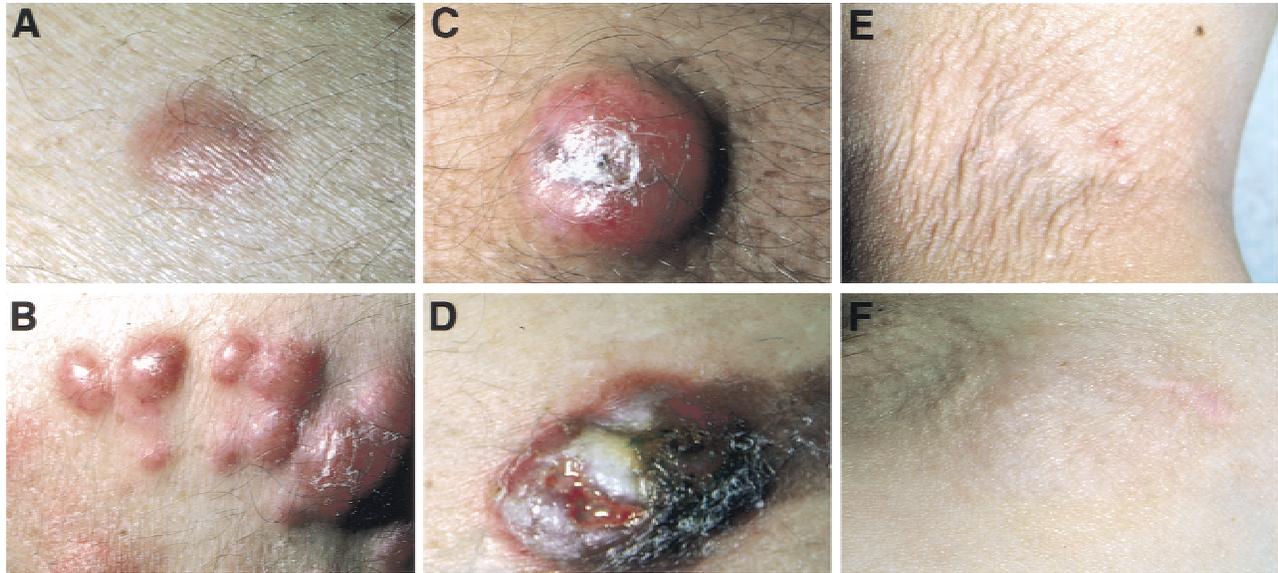
SNS, site not specified; PD, progressive disease; DOD, died of disease; NED, no evidence of disease; XLA, X-Linked agammaglobulinemia; N/A, not available; f/u, follow-up; HX, history; CHL, classic Hodgkin's lymphoma; XRT, radiotherapy; CNS, central nervous system. Histologic grade of pulmonary lesions within parentheses - (1, 2, or 3).

after treatment with methyl-GAG, ifosfamide, mitoxantrone, etoposide (MIME) chemotherapy, although the patient has subsequently shown an early initial response to IFN (case no. 20).

### Dermatologic Features

The dermatologic manifestations of LYG lesions were variable, and in some patients more than one type of lesion was seen. Fifty-five percent (11 of 20 patients) exhibited tan to plum colored dermal and/or subcutaneous nodules, with 27% (3 of 11) also having ulcerations

(Fig. 1). Three patients with subcutaneous nodules were initially diagnosed with erythema nodosum; 20% (4 of 20 patients) clinically had both dermal nodules and multiple erythematous papules, and one patient (5%) had papular lesions solely (case no. 20). In addition, one patient was described as having both multiple nodules and plaque lesions (case no. 6). Fifteen percent of the patients (3 of 20) had multiple, well-demarcated indurated plaques, in the absence of both nodules and papules; two patients (10%) had plaques that resembled lichen sclerosus et atrophicus (atrophic white, oval



**FIG. 1.** Clinical spectrum of cutaneous lesions in LYG. **(A)** An erythematous papule. **(B)** Multiple dermal nodules. **(C)** Plum-colored dermal/subcutaneous tumor. **(D)** Indurated subcutaneous nodule with necrosis and central ulceration. **(E)** Atrophic-appearing plaque with prominent skin folds. **(F)** A lichen sclerosus-like lesion showing hypopigmentation and a shiny texture.

plaques with violaceous borders). In one patient the plaques were associated with patches of alopecia on the scalp (case no. 15). Overall, the cutaneous lesions were disseminated, i.e., located on both extremities and trunk ± head/neck (40%), solely on the extremities (30%), the trunk (10%), and head and neck (10%). The clinical and dermatologic features are summarized in Table 2.

**Histopathology**

We examined 32 separate skin lesions from the 20 patients; multiple skin lesions were obtained in six patients (Table 3). In patients with multiple skin biopsies, the histopathologic features among the lesions were remarkably similar, except in case no. 4 in which a single

**TABLE 2.** Summary of clinical and dermatologic features in 20 patients with lymphomatoid granulomatosis

Clinical features	Patients (%)	Dermatologic features	Patients (%)
Age (range 18–77 yr)	Mean 39 yr	Temporal appearance	
Sex		Pre-Dx	3 (15%)
Female	5 (25%)	Simultaneous	7 (35%)
Male	15 (75%)	Post-Dx	9 (45%)
Organ involvement		Not specified	1 (5%)
Lung/skin	20/20 (100%)	Distribution	
Central nervous system	8 (40%)	Disseminated	8 (40%)
Liver	4 (20%)	Extremities	6 (30%)
Kidney	4 (20%)	Truncal	2 (10%)
Nasopharyngeal	3 (15%)	Head/neck	2 (10%)
Other	4 (20%)	Not specified	2 (10%)
Systemic manifestations		Lesion type	
Constitutional symptoms	16 (80%)	Nodules	8 (40%)
Respiratory symptoms	13 (65%)	Nodules + ulcerations	3 (15%)
Neurologic symptoms	7 (35%)	Nodules + papules	4 (20%)
Sinusitis	4 (20%)	Nodules + plaques	1 (5%)
Anemia	1 (5%)	Papules	1 (5%)
Therapy		Plaques	3 (15%)
None	1 (5%)	Follow-up	
Corticosteroids	3 (15%)	Spontaneous resolution	1 (5%)
Chemotherapy	1 (10%)	Regressed	7 (35%)
Combined	4 (35%)	Progressive disease	2 (10%)
Combined + interferon	3 (15%)	Died of disease	2 (10%)
Interferon	2 (10%)	Unknown/lost to follow-up	8 (40%)
Unknown	6 (30%)		

TABLE 3. Histopathologic features of cutaneous lymphomatoid granulomatosis lesions

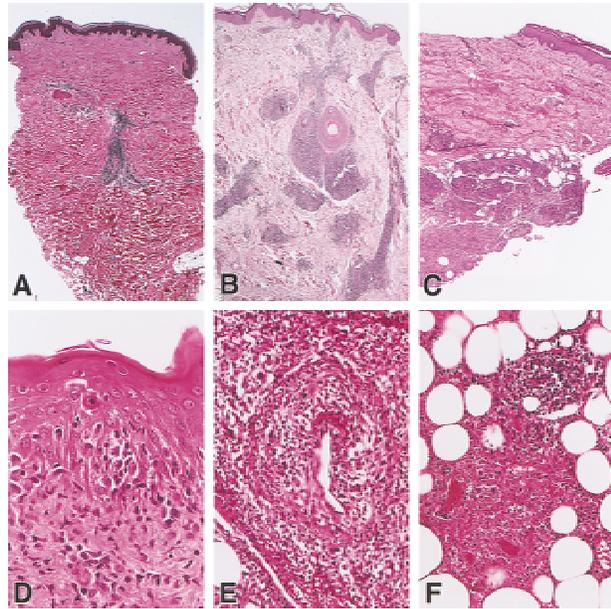
Case no.	Histologic feature						Involvement			Infiltrate		Atypia		Ancillary studies							
	Clinical picture	Angiocentricity	Periadnexal	Angiodestruction	Fat Necrosis	Coagulative necrosis	Panniculitis	Epidermis	Superficial dermal	Deep dermal	Pannus	Lymphoid	Lymphohistiocytic	Minimal	Marked	EBV (Skin)	EBV (lung)	T-cell (CD3)	B-cell (CD20)	IgH (PCR)	TCR (PCR)
1	C	+	+	+	NA	-	NA	-	+	+	NA	-	+	-	+	NA	NA	NA	NA	NA	NA
2	C	+	-	+	+	+	+	NA	-	-	+	-	+	-	+	1-5/hpf	NA	RX +	Atyp+	UNSAT	UNSAT
3	C	+	+	+	-	-	-	-	+	+	-	+	-	+	-	NA	NA	NA	NA	NA	NA
4a	B	+	+	-	-	-	-	-	+	+	+	+	-	+	-	Neg		RX+	Scatt+	Pol	NA
4b	B	-	-	+	+	+	NA	+	+	+	NA	+	-	+	-	Neg		Rx+	Scatt+	NA	NA
4c	B	+	+	-	-	-	NA	+	+	+	NA	+	-	+	-	Neg		Rx+	Scatt+	NA	NA
4d	C	+	-	+	-	+	+	NA	NA	NA	+	-	+	-	+	5-20/hpf	>50/hpf	Rx+	Atyp+	Clo	Neg
5a	C	+	+	+	+	+	+	+	+	+	+	+	-	+	-	NA	NA	NA	NA	NA	NA
5b	C	+	+	+	+	+	+	-	+	+	+	-	+	+	-	NA		NA	NA	NA	NA
6	C	+	+	+	+	+	+	-	+	+	+	-	+	+	-	NA	NA	NA	NA	NA	NA
7	C	+	+	-	-	-	+	-	+	+	+	-	-	+	1-5/hpf	5-20/hpf	Rx+	Atyp+	NA	NA	
8	C	+	+	-	-	-	-	-	+	+	+	-	+	+	Neg	>50/hpf	Rx+	Scatt+	Pol	Clon	
9	A	-	+	-	-	-	-	-	+	+	-	+	-	+	Unsat	Neg	Rx+	Scatt+	Pol	Neg	
10a	A	-	+	-	-	-	-	-	+	-	-	+	+	-	Neg	1-5/hpf	Rx+	Rare+	Pol	Neg	
10b	A	-	+	-	-	-	-	-	+	-	-	+	+	-	Neg		Rx+	Rare+	NA	NA	
10c	A	-	+	-	-	-	-	-	+	-	-	+	+	-	NA		Rx+	Rare+	NA	NA	
10d	A	-	+	-	-	-	-	-	+	-	-	+	+	-	Neg		Rx+	Rare+	Pol	Neg	
10e	A	-	+	-	-	-	-	-	+	-	-	+	+	-	Neg		Rx+	Rare+	Pol	Neg	
11a	C	+	+	+	+	+	+	-	+	+	+	+	-	+	>50/hpf	NA	Rx+	Atyp+	Clo	NA	
11b	C	+	+	+	+	+	+	-	+	+	+	+	-	+	>50/hpf		Rx+	Atyp+	Clo	NA	
12	C	+	N	+	+	+	+	NA	NA	+	+	-	+	+	Neg	NA	Rx+	Scatt+	Pol	Neg	
13a	B	+	+	-	-	-	+	-	+	+	+	-	+	+	NA	NA	NA	NA	NA	NA	NA
13b	B	+	+	-	-	-	+	-	+	+	+	-	+	+	NA		NA	NA	NA	NA	NA
14	C	+	+	-	-	-	+	+	+	+	+	-	+	+	NA	NA	NA	NA	NA	NA	NA
15	A	-	+	-	-	-	-	-	+	+	-	+	-	+	Neg	NA	NA	NA	NA	NA	NA
16	C	+	N	+	+	+	+	-	-	-	+	-	+	+	NA	NA	NA	NA	NA	NA	NA
17	C	-	+	-	-	-	+	-	-	+	+	+	+	+	Neg	NA	NA	NA	NA	NA	NA
18	C	+	-	-	-	-	+	-	-	+	+	-	+	+	Neg	5-20/hpf	Rx+	Scatt+	Pol	Neg	
19a	B	-	+	-	-	-	NA	+	+	+	NA	-	+	-	Neg	Neg	Rx+	Scatt+	Pol	Neg	
19b	B	-	+	-	-	-	NA	+	+	-	NA	-	+	-	Neg		Rx+	Scatt+	Pol	Neg	
20a	B	+	+	-	-	-	+	-	+	+	+	-	+	+	1-5/hpf	5-50/hpf	Rx+	Rare+	unsat	unsat	
20b	B	+	-	-	-	-	NA	-	+	-	NA	+	-	+	Neg	NA	Rx+	Scatt+	Pol	-	

A, plaques; B, papules; C, nodules; +, described feature present; -, described feature not present (absent); NA, not available; Poly, polyclonal rearrangements; Clon, clonal gene rearrangement; UNSAT, unsatisfactory for PCR amplification; Neg, negative; Rx, reactive cells; Scatt, scattered cells; Num, numerous cells.

nodular biopsy specimen showed significant clinical and pathologic differences from the other papular lesions. In general, a lymphocytic or lymphohistiocytic infiltrate, with or without multinucleated giant cells, was the dominant cellular composition in every case. The infiltrates had a periadnexal and/or perivascular-angiocentric distribution. The subcutaneous tissue showed a lymphohistiocytic panniculitis, often with poorly formed granulomas, but well-formed sarcoid-like granulomas or necrotizing granulomas were not seen (Fig. 2). A mild exocytosis of lymphocytes was present in five papular or nodular lesions. In case no. 19 the presence of atypical small lymphocytes in the epidermis prompted an initial diagnosis of mycosis fungoides. The background lymphocytes (CD3-positive cells) often showed mild atypia, with irregular or slightly enlarged nuclei. However, hyperchromasia or cytologically malignant features were

not seen. One skin lesion also contained eosinophils, plasma cells, and neutrophils.

The 16 nodular lesions biopsied from 14 patients exhibited a moderate to marked periadnexal and angiocentric, lymphocytic to lymphohistiocytic infiltrate, involving the superficial and deep dermis. Most of the lesions had subcutaneous fat tissue involvement, in a primarily lobular distribution, and in two cases it was the only feature. Angiodestruction, necrosis, and some cytologic atypia were also consistent features in these nodular lesions. Notably, large hyperchromatic lymphoid cells with pleomorphic nuclei were noted in some nodules and closely correlated with the presence of EBV-positive cells (Fig. 3). The nine papular lesions (from four patients) had mild to moderate dermal infiltrates, and panniculitis was present in three of the lesions; six biopsy specimens did not include the underlying subcutaneous



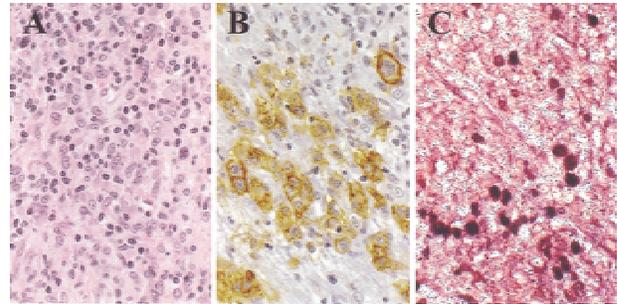
**FIG. 2.** Cutaneous manifestations of LYG, histologic spectrum. **(A)** Low-power view of an indurated, well-demarcated plaque with a sparse angiocentric, lymphocytic infiltrate involving the upper dermis and sparing the deeper dermis and adipose tissue (case no. 10d). **(B)** An erythematous papule containing a moderate angiocentric and periadnexal lymphocytic infiltrate involving the superficial and deep dermis but sparing the subcutis (case no. 4a). **(C)** A nodular lesion exhibiting a lobular panniculitis (case no. 12). **(D)** A papular lesion containing a superficial dermal infiltrate with exocytosis of lymphocytes into the epidermis. This case also manifested a marked deep dermal and subcutaneous lymphohistiocytic infiltrate. EBV was identified in scattered cells (case no. 20a). **(E and F)** A nodular lesion (in case no. 2) with lymphohistiocytic panniculitis, vasculitis **(E)**, and focal necrosis **(F)**.

tissue. Angiodestruction and necrosis were not present in the papular lesions.

The plaque lesions from three patients exhibited a sparse periadnexal lymphocytic infiltrate involving the papillary and reticular dermis. Three lesions also had a thin, atrophic epidermis. Panniculitis, angiodestruction, necrosis, and cytologic atypia were uncommon features in the plaque lesions. The histopathologic features are summarized in Table 4.

**Immunohistochemistry**

The lymphoid infiltrates were composed predominantly of small- to medium-sized CD3-positive, CD4-positive T-cells. The CD3-positive lymphocytes were sometimes slightly enlarged, or appeared irregular, especially when admixed with histiocytes. CD8-positive T-cells were present in lesser numbers. B-cells were present in much fewer numbers, being either scattered to rare, as demonstrated with L26 (CD20) staining. In cases with



**FIG. 3.** **(A)** Subcutaneous nodule (case no. 4d) showing marked cytologic atypia with large, pleomorphic, and nucleolated cells within a background rich in histiocytes and smaller reactive-appearing lymphocytes (hematoxylin and eosin, original magnification  $\times 630$ ). **(B)** Same case showing the large atypical cells expressing L26 (CD20), indicative of a B-cell phenotype (DAB and hematoxylin counterstain, original magnification  $\times 630$ ). **(C)** In situ hybridization with EBER-1 probe demonstrating strong nuclear signal in the atypical cells (original magnification  $\times 630$ ). PCR for IgH was clonal in this case, consistent with an EBV-associated B-cell lymphoproliferation.

cellular atypia, the atypical lymphoid cells demonstrated expression for CD20, indicative of a B-cell phenotype.

**In Situ Hybridization**

EBV-positive cells were present in 37.5% of the papular/nodular lesions (6 of 16 lesions, from 11 different patients). The number of EBV-positive cells varied: 1–5 cells/HPF (three cases), 5–20 cells/HPF (one case), and >50 cells/HPF (one case). In two cases (case nos. 4 and 20) one biopsy was positive for EBV, whereas other skin biopsies in these patients were negative. The plaque lesions were negative (0 of 5 lesions, from two patients, case nos. 10 and 15) for EBV. Case no. 10 was also examined for EBV by PCR for the LMP-1 and EBNA2 genes<sup>21</sup> and was negative (data not shown).

Eight primary lung lesions were also analyzed for EBV: six lesions contained EBV-positive cells, either

**TABLE 4.** Summary of clinical and histopathologic findings of 31 cutaneous lymphomatoid granulomatosis lesions

Clinical Picture	# Lesions	Perivascular	Angiodestruction	Necrosis	Panniculitis	Atypical Cells	EBV		IgH	
							+	-	+	-
Plaques	7	7	0	0	0	0	5	0	3	
Papules	9	9	0	0	3	1	6	0	3	
Nodules	16	16	11	8	14	7	5	4	3	

EBV, Epstein-Barr virus; IgH, immunoglobulin heavy chain rearrangement.

scattered or numerous in number, and two cases were negative. The number of EBV-infected cells correlated with the grade of the lesions: scattered cells 1–5/HPF, grade 1 (case no. 10); numerous cells 5–20/HPF, grade 2 (case nos. 7, 18, and 20); and >20/HPF, grade 3 (case nos. 4 and 8).

### PCR Antigen Receptor Gene Rearrangement Analysis

A clonal B-cell population was present in the cutaneous papulonodular lesions from 2 of 8 patients (case nos. 4 and 11). One of the two skin lesions from case no. 4 (4d) demonstrated an IgH gene rearrangement. Notably, in case no. 11 two separate skin lesions had distinct and nonrelated IgH clonal populations. Four patients with cutaneous papulonodular lesions had ladder patterns consistent with polyclonal B-cell populations; in one patient (case no. 8) the nodular skin lesion demonstrated a weak clonal band for TCR (case no. 8). In two cases with nodular lesions (case nos. 2 and 20) the PCR assays were technically unsatisfactory, with negative glyceraldehyde phosphate dehydrogenase controls. The skin lesions from two patients with plaques demonstrated polyclonal patterns.

## DISCUSSION

The dermatologic manifestations of LYG are diverse. However, the most common clinical dermatologic pattern (85% of patients) was multiple erythematous, dermal, and subcutaneous papules and nodules on the extremities and/or trunk. In most patients both papules and nodules were seen clinically, suggesting that they represent different phases of the same process. Ulceration was seen in 15%. The histologic appearance of the cutaneous lesions correlated with the clinical pattern. Nodular lesions showed a high propensity for involvement of subcutaneous adipose tissues. Moreover, angiodestruction, necrosis, and cellular atypia were much more common in the deeper subcutaneous nodules. Although papular lesions contained less infiltrate, they appeared as likely to involve the subcutaneous tissue. Therefore, it is important that the skin biopsies contain at least a portion of the subcutaneous tissue in patients with a known or suspected diagnosis of LYG. The presence of large atypical lymphoid cells closely correlated with the presence of EBV in the infiltrate.

Fifteen percent of patients had plaque-like lesions with a sparse superficial dermal periadnexal and perivascular lymphoid infiltrate reminiscent of lichen sclerosus et atrophicus. Thinning and atrophy of the epidermis were seen. The plaques were almost never seen in patients with nodules, and transitional forms were not identified. EBV was absent in all cases studied. These lesions are

histologically and clinically nonspecific, and their relationship to the primary disease process remains uncertain. The remainder of the discussion will deal with the more typical papulonodular lesions seen in the majority of patients.

The cutaneous lesions of LYG may occur at any stage of the disease and have been reported to appear as the initial manifestation in up to one third of patients.<sup>18</sup> However, most of the clinical reports of LYG and its cutaneous manifestations predate modern staging techniques. Therefore, one should be aware of the stage migration that has taken place since these earlier reports because modern staging techniques more readily detect disseminated disease. Sixteen of our patients had disseminated or multiorgan disease, either at the time of the pulmonary diagnosis or shortly thereafter. In three patients the skin lesions appeared from 12 months to 4 years after chemotherapy for LYG. Only three patients (15%) had skin lesions before the appearance of their diagnostic pulmonary disease. Thus, the appearance of skin lesions in LYG is usually associated with disease at other sites. The diagnosis of LYG in the skin in the absence of other evidence should be made with caution.

We and others have noted that EBV is more difficult to identify in skin lesions than in pulmonary lesions.<sup>1</sup> Six of the 20 patients in the series had EBV demonstrable by *in situ* hybridization. In LYG EBV is localized to B-cells both in the lung and skin,<sup>10,26</sup> and it is associated with a marked reactive T-cell response. However, in some cases the number of EBV-infected B-cells is small and undetectable. Previous studies have shown that the number of EBV-positive cells correlates with histologic grade,<sup>9,10</sup> and we observed a similar correlation in this study. EBV-positive lesions contained large cytologically atypical cells and were associated with marked necrosis. However, other histologic features were similar in both EBV-positive and -negative lesions, such as panniculitis with an angiocentric and/or periadnexal T-cell infiltrate. Moreover, in patients with multiple lesions EBV was not consistently present or absent. Therefore, we think that all of the papulonodular lesions are related and are a manifestation of LYG. The absence of EBV-positive cells in some cases may be the result of sampling error in the usually small skin biopsies that are obtained in these patients.

Alternatively, the cutaneous manifestations could be related to systemic effects of EBV and its induced cytokine-chemokine cascade. In approximately one third of the lesions, lymphocytes (CD3+) showed direct vascular invasion causing infarct-like tissue necrosis, or angiodestruction, even in the absence of EBV-positive cells within the lesion. The chemokines IP-10 and Mig, which are induced by EBV, have been implicated in mediating the vascular damage in pulmonary LYG and most likely

play a similar role in the skin.<sup>41</sup> These agents inhibit angiogenesis, promote T-cell adhesion to endothelial cells, and directly damage endothelium.<sup>37-39</sup> IP-10 is overexpressed in tissues involved by LYG and is also increased in the serum in patients with LYG, suggesting that it could act at distant sites.<sup>41</sup> Systemic vasculitis is an uncommon but well-recognized manifestation of EBV infection in patients with X-linked lymphoproliferative disorder, and the vasculitic lesions may be negative for EBV by *in situ* hybridization.<sup>8</sup>

LYG is an EBV-positive B-cell lymphoproliferative disorder. However, the ability to demonstrate monoclonality correlates closely with histologic grade and the proportion of EBV-positive cells.<sup>10</sup> The results of our study and a previous one suggest that this statement also applies to cutaneous lesions.<sup>26</sup> We found clonal IgH gene rearrangements in three cutaneous lesions from two of six patients with informative PCR studies (case nos. 4 and 11). All three lesions contained numerous EBV-positive cells, and both patients had grade 3 disease. Notably, two different skin lesions from a single patient had distinct nonrelated IgH clonal populations by PCR (case no. 11). Unfortunately, we were unable to compare either of the two cutaneous clones to the patient's pulmonary lesion. We have encountered other instances of LYG in which distinct B-cell clones have been identified in different sites in the same patient.<sup>43</sup> The finding of different clones arising in different locations in the skin supports the concept that LYG is an EBV-associated B-cell lymphoproliferative process in which clonal expansion of the EBV-infected B-cells takes place at a variety of different sites, analogous to the post-transplant lymphoproliferative disorders.<sup>36</sup>

Analysis of TCR by PCR identified a single case (case no. 8) with a weak clonal banding pattern, whereas the IgH demonstrated a polyclonal pattern. The histologic and clinical features were typical of LYG, and the patient remains in complete remission after therapy. There is precedent for the development of clonal-oligoclonal T-cell proliferations associated with both acute and chronic EBV infections. It has been postulated that this phenomenon may represent an antigen-driven immune response.<sup>4</sup>

The differential diagnosis of cutaneous LYG includes Wegener's granulomatosis (WG). The clinical presentations of LYG and WG can be very similar, in that they both frequently present with constitutional symptoms, pulmonary infiltrates, and renal and skin lesions. The skin lesions in both LYG and WG may both manifest as erythematous plaques, papules, and/or nodules, with or without ulceration. However, in no patient with LYG did we observe either leukocytoclastic small vessel vasculitis or necrotizing granulomatous inflammation, both characteristic histologic features of cutaneous WG.<sup>2</sup> Distinction from extranodal NK/T-cell lymphoma, nasal type is

usually straightforward. This EBV-associated "angiocentric" lymphoma often involves cutaneous sites.<sup>7,12,13</sup> However, the pattern of EBV-positive cells as identified by *in situ* hybridization is extremely helpful in distinguishing these two lesions. In LYG the EBV-positive cells are rare to sparsely scattered, large CD20+ cells, whereas in NK/T-cell lymphoma the majority of the infiltrating cells will be EBV-positive cells with an NK-cell phenotype (CD56+, cytoplasmic CD3ε+).<sup>15</sup> Pulmonary involvement is also uncommon in NK/T-cell lymphoma. Because cutaneous LYG is commonly associated with panniculitis, the differential diagnosis also includes subcutaneous panniculitis-like T-cell lymphoma (SPTCL).<sup>22,33</sup> In contrast to LYG, the infiltrate is more monomorphic, with cytologically atypical cytotoxic T-cells rimming fat spaces or invading blood vessels.<sup>22</sup> Conversely, in LYG although occasional large atypical cells are seen, they are always associated with a marked polymorphous background. Immunohistochemical studies will be helpful in this differential diagnosis because CD8-positive lymphocytes are sparse and scattered in LYG and they usually predominate in SPTCL. Finally, SPTCL is consistently negative for EBV.<sup>22,33</sup>

The clinical behavior of LYG varies widely from an indolent process, sometimes with spontaneous remissions, to an aggressive large cell lymphoma.<sup>14</sup> Six of our patients showed no evidence of disease, including cutaneous lesions, at follow-up after aggressive chemotherapy, whereas four patients had progressive systemic disease. A recent initial clinical trial with IFN-α, which has anti-viral, anti-proliferative, and immunomodulatory effects, showed remissions in the majority of patients with grade 1 or 2 lesions.<sup>42,43</sup> Five of our patients received IFN-α: three remain clinically free of disease without cutaneous lesions (case nos. 4, 8, and 12) after therapy, one has shown initial response to early treatment (case no. 20), and one patient died of progressive disease (case no. 9) after developing a diffuse large B-cell lymphoma (LYG, grade 3). The ability to obtain complete remissions with only immunomodulatory therapy suggests further that LYG is not an autonomous malignant proliferation but rather an EBV-driven lymphoproliferative disorder, at least for patients with grade 1 and 2 disease. We did not observe any correlation between the clinical or histologic features of the skin lesions and disease status at follow-up.

Although the development of cutaneous lesions in the absence of other sites of disease was rare, it nevertheless suggests the presence of unregulated EBV+ B-cells that may progress to disseminated disease. Thus, we generally recommend treatment with IFN-α if isolated skin disease is widespread and/or progressive or if it is a site of recurrence in a patient with a history of disseminated disease. Although patients with localized or waning skin disease could be observed, particularly if there is uncer-

tainty in the diagnosis, we remain concerned that such patients will ultimately progress. Notably, one patient who did develop an isolated cutaneous recurrence had regression of cutaneous lesions after reinstatement of IFN- $\alpha$  therapy, suggesting a benefit of therapy in this instance. □

## REFERENCES

- Angel CA, Slater DN, Royds JA, et al. Epstein-Barr virus in cutaneous lymphomatoid granulomatosis. *Histopathology* 1994;25:545-8.
- Barksdale SK, Hallahan CW, Kerr GS, et al. Cutaneous pathology in Wegener's granulomatosis: a clinicopathologic study of 75 biopsies in 46 patients. *Am J Surg Pathol* 1995;19:161-72.
- Brodell RT, Miller CW, Eisen AZ. Cutaneous lesions of lymphomatoid granulomatosis. *Arch Dermatol* 1986;122:303-6.
- Callan MF, Steven N, Krausa P, et al. Large clonal expansions of CD8+ T cells in acute infectious mononucleosis. *Nat Med* 1996;2:906-11.
- Camisa C. Lymphomatoid granulomatosis: two cases with skin involvement. *J Am Acad Dermatol* 1989;20:571-8.
- Carlson KC, Gibson LE. Cutaneous signs of lymphomatoid granulomatosis. *Arch Dermatol* 1991;127:1693-8.
- Chan JKC, Sin VC, Wong KF, et al. Nonnasal lymphoma expressing the natural killer cell marker CD56: a clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. *Blood* 1997;89:4501-13.
- Dutz JP, Benoit L, Wang X, et al. Lymphocytic vasculitis in X-linked lymphoproliferative disease. *Blood* 2001;97:95-100.
- Guinee DG Jr, Perkins SL, Travis WD, et al. Proliferation and cellular phenotype in lymphomatoid granulomatosis: implications of a higher proliferation index in B cells. *Am J Surg Pathol* 1998;22:1093-100.
- Guinee DJ, Jaffe E, Kingma D, et al. Pulmonary lymphomatoid granulomatosis: evidence for a proliferation of Epstein-Barr virus infected B-lymphocytes with a prominent T-cell component and vasculitis. *Am J Surg Pathol* 1994;18:753-64.
- Holden CA, Wells RS, MacDonald DM. Cutaneous lymphomatoid granulomatosis. *Clin Exp Dermatol* 1982;7:449-54.
- Jaffe E. Nasal and nasal-type T/NK cell lymphoma: a unique form of lymphoma associated with the Epstein-Barr virus. *Histopathology* 1995;27:581-3.
- Jaffe ES, Harris NL, Stein H, et al. *Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC Press, 2001.
- Jaffe ES, Lifford EH, Margolick JB, et al. Lymphomatoid granulomatosis and angiocentric lymphoma: a spectrum of postthymic T-cell proliferations. *Semin Respir Med* 1989;10:167-72.
- Jaffe ES, Wilson WH. Lymphomatoid granulomatosis: pathogenesis, pathology, and clinical implications. *Cancer Surv* 1997;30:233-48.
- James WD, Odom RB, Katzenstein AL. Cutaneous manifestations of lymphomatoid granulomatosis: report of 44 cases and a review of the literature. *Arch Dermatol* 1981;117:196-202.
- Katzenstein A-L, Peiper S. Detection of Epstein-Barr genomes in lymphomatoid granulomatosis: analysis of 29 cases by the polymerase chain reaction. *Mod Pathol* 1990;3:435-41.
- Katzenstein AA, Carrington CB, Liebow AA. Lymphomatoid granulomatosis: a clinicopathologic study of 152 cases. *Cancer* 1979;43:360-73.
- Kessler S, Lund HZ, Leonard DD. Cutaneous lesions of lymphomatoid granulomatosis: comparison with lymphomatoid papulosis. *Am J Dermatopathol* 1981;3:115-27.
- Kingma DW, Medeiros LJ, Barletta J, et al. Epstein-Barr virus is infrequently identified in non-Hodgkin's lymphomas associated with Hodgkin's disease. *Am J Surg Pathol* 1994;18:48-61.
- Kingma DW, Weiss WB, Jaffe ES, et al. Epstein-Barr virus latent membrane protein-1 oncogene deletions: correlations with malignancy in Epstein-Barr virus-associated lymphoproliferative disorders and malignant lymphomas. *Blood* 1996;88:242-51.
- Kumar S, Krenacs L, Elenitoba-Johnson K, et al. Subcutaneous panniculitic T-cell lymphoma is a tumor of cytotoxic T-lymphocytes. *Hum Pathol* 1998;29:397-403.
- Liebow AA, Carrington CRB, Friedman PJ. Lymphomatoid granulomatosis. *Hum Pathol* 1972;3:457-558.
- Lipford EH, Margolick JB, Longo DL, et al. Angiocentric immunoproliferative lesions: a clinicopathologic spectrum of postthymic T cell proliferations. *Blood* 1988;5:1674-81.
- McCarthy KP, Sloane JP, Kabarowski JH, et al. A simplified method of detection of clonal rearrangements of the T-cell receptor-gamma chain gene. *Diagn Mol Pathol* 1992;1:173-9.
- McNiff JM, Cooper D, Howe G, et al. Lymphomatoid granulomatosis of the skin and lung: an angiocentric T-cell-rich B-cell lymphoproliferative disorder. *Arch Dermatol* 1996;132:1464-70.
- Medeiros LJ, Jaffe ES, Chen YY, et al. Localization of Epstein-Barr viral genomes in angiocentric immunoproliferative lesions. *Am J Surg Pathol* 1992;16:439-47.
- Minars N, Kay S, Escobar MR. Lymphomatoid granulomatosis of the skin: a new clinicopathologic entity. *Arch Dermatol* 1975;111:493-6.
- Nichols PW, Koss M, Levine AM, et al. Lymphomatoid granulomatosis: a T-cell disorder. *Am J Med* 1982;72:467-71.
- Prenovault JM, Weisbrod GL, Herman SJ. Lymphomatoid granulomatosis: a review of 12 cases. *Can Assoc Radiol J* 1988;39:263-6.
- Quintanilla-Martinez L, Thiebmont C, Fend F, et al. Mantle cell lymphomas lack expression of p27Kip1, a cyclin-dependent kinase inhibitor. *Am J Pathol* 1998;153:175-82.
- Ramasamy I, Brisco M, Morley A. Improved PCR method for detecting monoclonal immunoglobulin heavy chain rearrangement in B cell neoplasms. *J Clin Pathol* 1992;45:770-5.
- Salhany KE, Macon WR, Choi JK, et al. Subcutaneous panniculitis-like T-cell lymphoma: clinicopathologic, immunophenotypic, and genotypic analysis of alpha/beta and gamma/delta subtypes. *Am J Surg Pathol* 1998;22:881-93.
- Sambrook J, Maniatis T. *Molecular Cloning*, 2nd ed. Cold Spring Harbor, NY: Cold Spring Harbor Press, 1989.
- Segal GH, Jorgensen T, Scott M, et al. Optimal primer selection for clonality assessment by polymerase chain reaction analysis. II: follicular lymphomas. *Hum Pathol* 1994;25:1276-82.
- Seiden MV, Sklar J. Molecular genetic analysis of posttransplant lymphoproliferative disorders. *Hematol Oncol Clin North Am* 1993;7:447-65.
- Sgadari C, Angiolillo AL, Cherney BW, et al. Interferon-inducible protein-10 identified as a mediator of tumor necrosis in vivo. *Proc Natl Acad Sci USA* 1996;93:13791-6.
- Sgadari C, Farber JM, Angiolillo AL, et al. Mig, the monokine induced by interferon-gamma, promotes tumor necrosis in vivo. *Blood* 1997;89:2635-43.
- Taub DD, Lloyd AR, Conlon K, et al. Recombinant human interferon-inducible protein 10 is a chemoattractant for human monocytes and T lymphocytes and promotes T cell adhesion to endothelial cells. *J Exp Med* 1993;177:1809-14.
- Tawfik NH, Magro CM, Crowson AN, et al. Lymphomatoid granulomatosis presenting as a solitary cutaneous lesion. *Int J Dermatol* 1994;33:188-9.
- Teruya-Feldstein J, Jaffe ES, Burd PR, et al. The role of Mig, the monokine induced by interferon-gamma, and IP-10, the interferon-gamma-inducible protein-10, in tissue necrosis and vascular damage associated with Epstein-Barr virus-positive lymphoproliferative disease. *Blood* 1997;90:4099-105.
- Wilson WG, Gutierrez M, Raffeld M, et al. Lymphomatoid granulomatosis: phase 2 study of dose-adjusted interferon-alfa or EPOCH chemotherapy. *Blood* 1999;94:599A.
- Wilson WH, Kingma DW, Raffeld M, et al. Association of lymphomatoid granulomatosis with Epstein-Barr viral infection of B lymphocytes and response to interferon-alpha 2b. *Blood* 1996;87:4531-7.