Primary cutaneous B-cell lymphoma

Report of a case and review of the English-language literature[1]

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B-cell lymphomas may involve the skin late in the course of the disease, but only infrequently have primary presentation in the skin. The cutaneous lesions are red-to-violaceous nodules, most often located on the head and neck. Most patients have been treated with radiation alone or combined with surgical excision of the tumors or systemic chemotherapy. In general, patient survival has been poor. The authors report a case of B-cell lymphoma initially confined to the skin and review the clinical characteristics of these lymphomas as reported in the English-language literature.

Index terms: Dermatology features • Lymphoma

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Malignant lymphoma of the skin may be of T-cell or B-cell origin.[1] Cutaneous T-cell lymphomas (CTCL) are more common and include mycosis fungoides and its leukemic variant, Sezary syndrome. These T-cell lymphomas are epidermotropic and present first in the skin and only later involve lymphatic and visceral tissue. CTCL is immunologically defined by monoclonal antibodies to T_{11}, T_3, and T_4 differentiation antigens. Cutaneous B-cell lymphomas (CBCL) are less commonly reported,[1–5] although a recent series found a 32% frequency of malignant lymphoma of the skin to be of B-cell origin.[6] Primary presentation of CBCL in the skin is less common than CTCL. CBCL is defined immunologically by polyclonal antibodies to immunoglobulin heavy and light chains and monoclonal antibodies to B_1 antigen.

We report a case of CBCL with initial presentation only in the skin.

Case report

A 66-year-old white man presented to the Cleveland Clinic's Department of Dermatology with a six-month history of pruritic and slightly tender nodules on the scalp, abdomen, and extremities. Previous treatment with topical and systemic corticosteroids had been unsuccessful. The patient reported no fevers, night sweats, or weight loss, and the medical history was otherwise noncontributory.

On physical examination, there were numerous violaceous and hyperpigmented, indurated nodules and plaques on the head, chest, back, and extremities (*Fig. 1*). Shotty left axillary adenopathy was present, but otherwise the remainder of the physical examination was normal.

Results of laboratory studies, including a complete blood cell count, SMA-18, Westergren sedimentation rate, rapid plasma reagin, antinuclear antibody, serum protein electrophoresis, acid phosphatase, and buffy coat for Sezary cells, were normal or negative with the exception of random glucose (260 mg/dL [normal, 70–110 mg/dL]). Other results were: triglycerides, 455 mg/dL (normal, 35–135 mg/dL); lipoprotein electrophoresis, consistent with a type IV pattern; circulating T cells, 82.4% (normal, 75.2 ± 5.3%); and circulating B cells, 14.8% (normal, 21.8 ± 6.1%). Delayed hypersensitivity reaction to purified protein derivative was negative, whereas reactions to *Trichophyton* and

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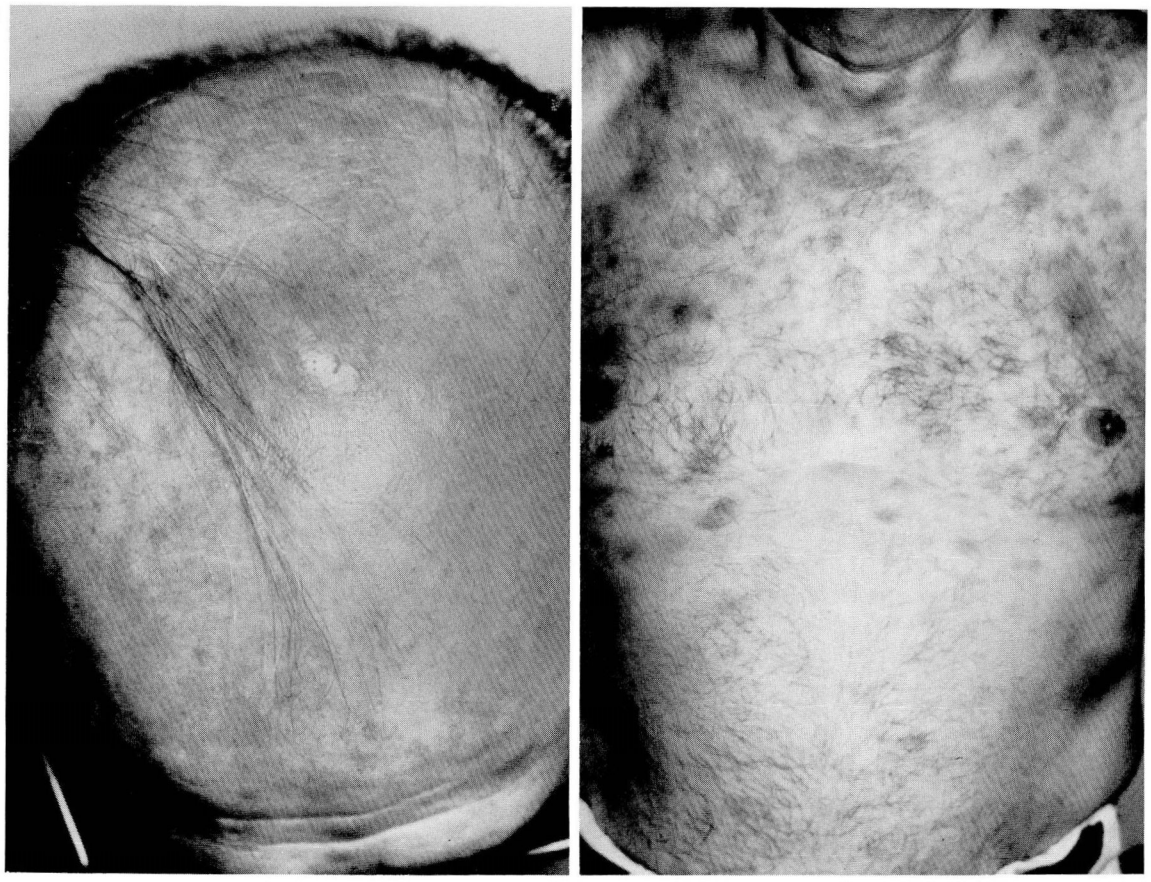

Fig. 1. A. Large nodule on frontal scalp.
B. Pigmented 1- to 4-cm nodules on the chest and abdomen.

Monilia were positive. Results of radiographic studies, including chest roentgenography, upper and lower gastrointestinal series, bone scan, lymphangiography, intravenous pyelography, and computed tomography of the abdomen and pelvis, were normal. Bone marrow biopsy findings revealed mild hypercellularity with erythroid predominance.

Results of a skin biopsy of a nodule on the extremity showed malignant lymphoma (*Figs. 2* and *3*) classified as intermediate grade, large noncleaved cell by the International Working Formulation (Rappaport equivalent, histiocytic lymphoma; Luke's-Collins equivalent, large noncleaved follicular center cell lymphoma).[7] Immunohistology (*Table 1*) documented an immunophenotype consistent with a monoclonal B-cell proliferation ($\gamma-\alpha-\mu+\delta+\epsilon-\kappa-\lambda+B_1+J5-I2+LN1+LN2+T11-T3-$).[7] Direct immunofluorescence of skin biopsy specimen was negative for extra-cellular immune complexes.

A diagnosis of primary CBCL was made because there was no clinical evidence of extracutaneous involvement. Treatment with systemic chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) was given. The nodules resolved, but recurred three months later; the patient was re-treated with CHOP-bleomycin regimen. Six months after initial treatment, high fevers developed and lymphomatous involvement of the bone marrow was found. A partial remission of the lymphoma occurred after a two-month hospitalization and treatment with cytosine arabinoside, cisdiaminedichloroplatinum, and etoposide.

Discussion

Extranodal non-Hodgkin's lymphoma may arise in the skin,[1-6,8-12] orbit,[13] salivary glands,[14,15] gonad,[16] thyroid,[17] breast,[18] lung,[19] and gastrointestinal tract.[20] Clinical course and survival rates vary widely from each site of origin.[21] One large series of 1,467 patients found five-year relative survival rates of approximately 60% for lymphomas arising in the skin, salivary gland, connective tissue, and lung, but less than half of that for small intestine, adenoid, and testis.[21]

From 1972 to 1983, there have been several reports of cutaneous non-Hodgkin's lymphoma in the English-language literature (*Table 2*). A total of 196 patients was described (mean age, 56.2 years; slight male predominance). Most nodules were red-to-purple or violaceous and most

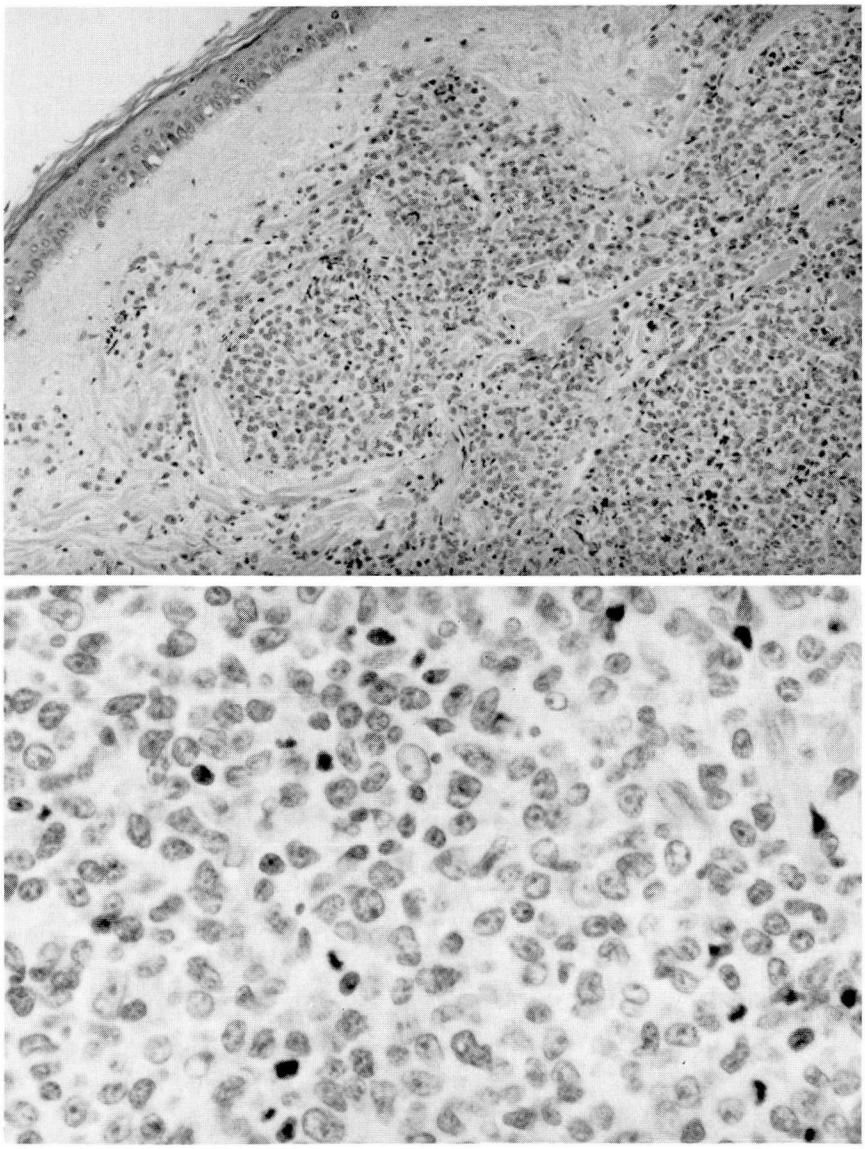

Fig. 2. A. Photomicrograph shows dense collection of atypical mononuclear cells in the dermis which spare the epidermis (hematoxylin-eosin, ×160).

B. On higher magnification, large noncleaved cells with small nucleoli, some in apposition to the nuclear membrane, are the predominant cell type (hematoxylin-eosin, ×400).

were solitary (from 16% in one series to 84% in another). The head and neck were the most common sites of skin nodules in six of the eight series. Most patients were treated with radiation therapy alone or combined with surgical excision of the tumors or systemic chemotherapy. Patient survival was generally poor.

Immunologic analysis of our patient's lymphoma was compatible with B-cell origin. We found four other reports in the English-language literature of patients with CBCL.[2–5] Knowles et al[2] described 1 patient with CBCL which presented three years after nodal lymphoma was diagnosed. Willemze et al[3] described 3 patients with CBCL. Lymphatic or visceral disease subsequently developed in these patients and they died. In the largest series, Wood et al[4] described 10 patients with CBCL, 5 of whom had primary CBCL. Two of the 5 patients died with visceral disease. Goldberg et al[5] reported a case of lymphoma cutis of B-cell origin that also involved the lymph nodes and spleen. Their patient was

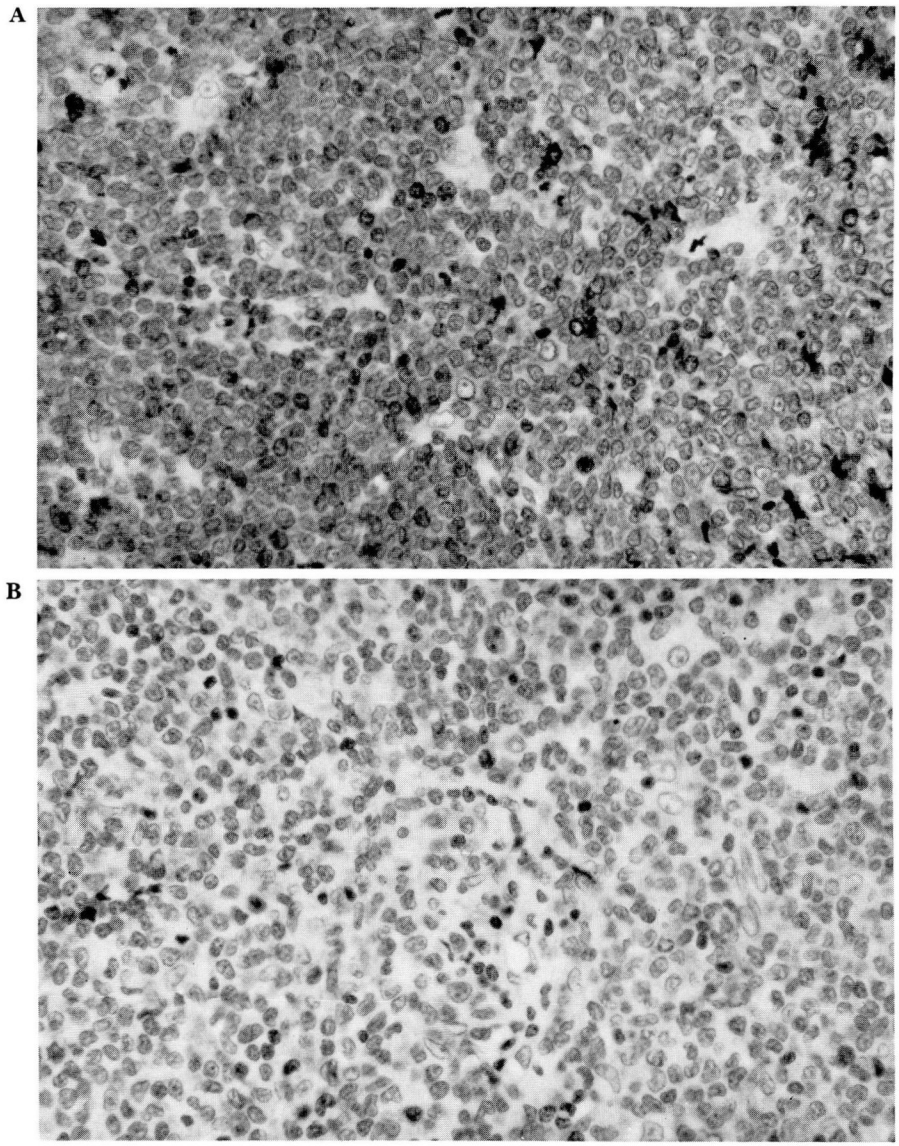

Fig. 3. A. Photomicrograph shows lymphoma cells which express LN2, a marker for B cells using the avidin-biotinylated peroxidase technique.

B. A negative control section shows no immunostaining when nonimmune mouse plasmacytoma supernatant is substituted for primary mouse monoclonal antibody. (× 240)

treated with systemic chemotherapy and the disease regressed. Other authors have not classified cutaneous non-Hodgkin's lymphoma into immunologic types. It appears from the cited reports that primary CBCL is uncommon.

A recently published series of 736 patients from Germany and Austria with "cutaneous lymphomas primarily showing skin manifestations" showed that 32% were of B-cell type.[6] The authors differentiated CBCL from CTCL based on clinical, morphologic, and functional criteria. The clinical characteristics of CBCL and CTCL are well-known and helpful discriminating criteria. A morphologic diagnosis of CBCL, however, is often difficult and not as straightforward as these authors imply. In fact, prediction of immunologic phenotype using light microscopy alone is successful in approximately 61%–81% of cases of histiocytic lymphoma involving lymph nodes.[22,23] Epidermotropism may rarely be found

Table 1. Specificity of antibodies used in this study

Monoclonal Antibody	Source	Primary Specificity
T_{11}	Coulter	T cells (sheep erythrocyte receptor positive)
T_3	Coulter	T cells
B_1	Coulter	B cells
J_5	Coulter	Early B cells
I_2	Coulter	Ia-like antigens (B cells, some activated T cells, macrophages)
LN1	Techniclone	Follicular center B cells, macrophages
LN2	Techniclone	B cells, dendritic reticulum cells

Polyclonal Antibody	Primary Specificity
PO goat antihuman IgG (Fc specific)	γ (IgG) heavy chains
PO goat antihuman IgA (Fc specific)	α (IgA) heavy chains
PO goat antihuman IgM (Fc specific)	μ (IgM) heavy chains
PO goat antihuman IgD (Fc specific)	δ (IgD) heavy chains
PO goat antihuman K	κ light chains
PO goat antihuman λ	λ light chains

PO = Peroxidase enzyme conjugated to antibody.

in B-cell neoplasms,[24] and some of the CTCLs may be nonepidermotropic.[25] Therefore, diagnosis of CBCL by morphology is not error-free. Surface markers for B cells used in the German and Austrian series include HLA-DR/Ia, Ig, and C_3. It is well known, however, that macrophages, histiocytes, and Langerhan's cells are also identified by the HLA-DR/Ia antigens. Lastly, the authors used only monoclonal intracytoplasmic immunoglobulins in some cases to diagnose CBCL.

We used both monoclonal and polyclonal antibodies to diagnose CBCL in our patient (*Table 1*). Monoclonal antibodies are more specific than surface markers for detecting cell surface antigens.[26] In addition, cytochemistry or immunohistochemistry is necessary to make a reliable discrimination between small T and B lymphocytes as compared to light microscopy.[24] Therefore, we are confident of the diagnosis of CBCL in our patient.

The discrepancy in the prevalence of primary CBCL as reported by Burg et al[6] compared to previous reports[1–4,8–12] is disconcerting. Burg et al made the diagnosis of primary CBCL using "routine and special staging procedures." These procedures, however, are not defined; therefore, it is impossible to compare their data with those of previous reports. In addition, a "relatively good prognosis" of primary CBCL is reported by Burg et al, which is contrary to our literature review and our experience. The reasons for the different prevalence and prognosis of primary CBCL reported by Burg et al and our review of the English-language literature are unclear. One possible explanation is that a different patient population was seen by these authors. Secondly, we believe our method of identifying B- and T-cell populations is more specific than that used by Burg et al. Therefore, they may be including other non-B-cell lymphomas (i.e., histiocytic) in their decription of CBCLs. Lastly, although treatment is not defined by these authors, their therapy must differ from ours and from that in previous reports[1–4,8–12] to affect a significant change in prognosis of patients with these tumors.

Clinical evaluation to uncover lymphatic or visceral disease has been described by the Committee on Hodgkin's Disease Staging Procedures (Ann Arbor System).[27] Our patient may exemplify the limitations of present staging and diagnostic procedures. Although it is conceivable that extracutaneous lymphoma was present in our patient at initial evaluation but was undetected, it is doubtful based on our patient's initial good health and lack of symptoms.

Summary

Primary CBCL is an underreported tumor. It presents as solitary or multiple red-to-violaceous nodules usually on the head and neck. The patient prognosis is generally poor with standard treatment regimens, which are usually radiation therapy alone or combined with surgical excision

Table 2. Clinical characteristics of cutaneous non-Hodgkin's lymphoma

Series	No. of Patients	M	F	Age Range (yr)	Mean Age (yr)	Lesion Distribution (%)			% With Single Lesions	Predominant Lesion	Cell of Origin				Primary Cutaneous Disease at Diagnosis (%)
						Head and Neck	Trunk	Extremities			T Cell	B Cell	Histiocyte	Unclassifiable	
Ribeiro[8] (Christie Hospital)	32	18	14	36–86	64.1	50	–	–	–	Red-purple small nodules or single tumor			ND		50
Fisher et al[9] (Shadyside Hospital)	13	–	–	–	57.5	67	–	16	–	–			ND		54
Burke et al[10] (Stanford)	50	33	17	2–93	53.0	65	41	38	78	Red-purple nodules			ND		41
Long et al[11] (Harvard)	25	11	14	48–83	62.0	60	28	12	84	Nodules			ND		100
Evans et al[12] (Mayo)	37	22	15	10–81	52.0	39	35	26	28	Red or erythematous nodules			ND		6
Knowles et al[2] (Columbia)	6	3	3	33–82	56.5	80	40	40	16	Nodules	5	1	0	0	–
Willemze et al[3] (The Netherlands)	12	6	6	22–84	58.8	33	25	42	50	Blue-red tumors	0	3	8	1	100
Wood et al[4] (Stanford)	21	12	9	4–74	45.5	33	48	38	–	Red to violaceous nodules	9	10	0	2	48
Total	196				56.2										

M = male, *F* = female, and *ND* = not done.

or systemic chemotherapy. The skin is a clinically apparent organ of involvement in non-Hodgkin's lymphoma, whereas other extranodal organs, unless symptomatic, are less so. With this in mind, it is hoped that clinicians will recognize and diagnose CBCL with greater frequency early in the course of the disease, and that with early treatment, the prognosis may be improved.

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References

1. Holbert JM Jr, Chesney TM. Malignant lymphoma of the skin: a review of recent advances in diagnosis and classification. J Cutan Pathol 1982; **9:**133–168.
2. Knowles II DM, Halper JP, Jakobiec FA. The immunologic characterization of 40 extranodal lymphoid infiltrates: usefulness in distinguishing between benign pseudolymphoma and malignant lymphoma. Cancer 1982; **49:**2321–2335.
3. Willemze R, Ruiter DJ, Van Vloten WA, Meijer CJLM. Reticulum cell sarcomas (large cell lymphomas) presenting in the skin: high frequency of true histiocytic lymphoma. Cancer 1982; **50:**1367–1379.
4. Wood GS, Burke JS, Horning S, Doggett RS, Levy R, Warnke RA. The immunologic and clinicopathologic heterogeneity of cutaneous lymphomas other than mycosis fungoides. Blood 1983; **62:**464–472.
5. Goldberg J, Davey FR, Lowenstein F, Gottlieb AJ. Lymphoma cutis of apparent B cell origin. Arch Pathol Lab Med 1978; **102:**15–18.
6. Burg G, Kerl H, Przybilla B, Braun-Falco O. Some statistical data, diagnosis, and staging of cutaneous B-cell lymphomas. J Dermatol Surg Oncol 1984; **10:**256–262.
7. Tubbs RR, Fishleder A, Weiss RA, Savage RA, Sebek BA, Weick JK. Immunohistologic cellular phenotypes of lymphoproliferative disorders: comprehensive evaluation of 564 cases including 257 non-Hodgkin's lymphomas classified by the International Working Formulation. Am J Pathol 1983; **113:**207–221.
8. Ribeiro GG. Primary lymphosarcoma and reticulum cell sarcoma of skin: a review of thirty-two cases. Clin Radiol 1972; **23:**279–285.
9. Fisher ER, Park EJ, Wechsler HL. Histologic identification of malignant lymphoma cutis. Am J Clin Pathol 1976; **65:**149–158.
10. Burke JS, Hoppe RT, Cibull ML, Dorfman RF. Cutaneous malignant lymphoma: pathologic study of 50 cases with clinical analysis of 37. Cancer 1981; **47:**300–310.
11. Long JC, Mihm MC, Qazi R. Malignant lymphoma of the skin: a clinicopathologic study of lymphoma other than mycosis fungoides diagnosed by skin biopsy. Cancer 1976; **38:**1282–1296.
12. Evans HL, Winkelmann RK, Banks PM. Differential diagnosis of malignant and benign cutaneous lymphoid infiltrates: a study of 57 cases in which malignant lymphoma had been diagnosed or suspected in the skin. Cancer 1979; **44:**699–717.
13. Knowles II DM, Jakobiec FA. Orbital lymphoid neoplasms: a clinicopathologic study of 60 patients. Cancer 1980; **46:**576–589.
14. Colby TV, Dorfman RF. Malignant lymphomas involving the salivary glands. Pathol Ann 1979; **14:**307–324.
15. Hyman GA, Wolff M. Malignant lymphomas of the salivary glands, review of the literature and report of 33 new cases, including four cases associated with the lymphoepithelial lesion. Am J Clin Pathol 1976; **65:**421–438.
16. Paladugu RR, Bearman RM, Rappaport H. Malignant lymphoma with primary manifestation in the gonad: a clinicopathologic study of 38 patients. Cancer 1980; **45:**561–571.
17. Burke JS, Butler JJ, Fuller LM. Malignant lymphomas of the thyroid: a clinical pathologic study of 35 patients including ultrastructural observations. Cancer 1977; **39:**1587–1602.
18. Mambo NC, Burke JS, Butler JJ. Primary malignant lymphomas of the breast. Cancer 1977; **39:**2033–2040.
19. Koss MN, Hochholzer L, Nichols PW, Wehunt WD, Lazarus AA. Primary non-Hodgkin's lymphoma and pseudolymphoma of lung: a study of 161 patients. Hum Pathol 1983; **14:**1024–1038.
20. Lewin KJ, Ranchod M, Dorfman RF. Lymphomas of the gastrointestinal tract: a study of 117 cases presenting with gastrointestinal disease. Cancer 1978; **42:**693–707.
21. Freeman C, Berg JW, Cutler SJ. Occurrence and prognosis of extranodal lymphomas. Cancer 1972; **29:**252–260.
22. Frizzera G, Gajl-Peczalska KJ, Bloomfield CD, Kersey JH. Predictability of immunologic phenotype of malignant lymphomas by conventional morphology: a study of 60 cases. Cancer 1979; **43:**1216–1224.
23. Jaffe ES, Strauchen JA, Berard CW. Predictability of immunologic phenotype by morphologic criteria in diffuse aggressive non-Hodgkin's lymphomas. Am J Clin Pathol 1982; **77:**46–49.
24. Kerl H, Burg G. Histomorphology and cytomorphology of cutaneous B-cell lymphomas. J Dermatol Surg Oncol 1984; **10:**266–270.
25. Kerl H, Kresbach H. Germinal center cell-derived lymphomas of the skin. J Dermatol Surg Oncol 1984; **10:**291–295.
26. Burg G, Kerl H, Schmoeckel C. Differentiation between malignant B-cell lymphomas and pseudolymphomas of the skin. J Dermatol Surg Oncol 1984; **10:**271–275.
27. Rosenberg SA, Boiron M, DeVita Jr VT, et al. Report of the Committee on Hodgkin's Disease Staging Procedures. Cancer Res 1971; **31:**1862–1863.