

California Tumor Tissue Registry  
98th Semi-Annual Cancer Seminar

on

Lymphoproliferative Disorders

Dedicated to the Memory of  
Robert J. Lukes, M.D.  
(1922-1994)

Syllabus

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## DEDICATION

It is appropriate that with the ninety-eighth California Tissue Tumor Registry Seminar, we pay tribute to Robert Lukes, a bold and original thinker, who brought recognition to California for almost three decades as a vanguard in hematopathology. Today these cases are presented and discussed in the perspective of combined microscopic-immunologic phenotypes. Dr. Lukes, together with his colleague Dr. Robert Collins of Vanderbilt University and his colleague-in-concepts Professor Karl Lennert in Kiel, Germany, was a pioneer in proposing this combined approach to understanding lymphomas. In December of 1976, this same theme was presented in this same forum by Dr. Lukes. For certain entities and cases in today's seminar, it is instructive to analyze again particular cases from the earlier presentation, as they are represented in the original glass slide sets and in the corresponding monograph published in 1979. In some instances, considerable progress has been achieved over the intervening 18 years in our understanding of lymphomatous processes. In others, either our earlier insights were keen or our abilities to advance beyond those original understandings have been unsuccessful. The distinction is sometimes a fine one!

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### Proposed Diagnoses

1. Benign lymphadenitis, syphilitic (secondary stage).
2. Castleman's disease (localized angiofollicular lymph node hyperplasia).
3. Benign lymphadenitis, suppurative granulomatous type (early), indicative of infectious etiology.
4. Mantle cell lymphoma, involving gastrointestinal tract as "multiple lymphomatous polyposis."
5. Malignant lymphoma, unclassifiable, of intermediate grade (?higher grade progression of plasmacytoid small lymphocytic lymphoma).
6. Small lymphocytic lymphoma, pleomorphic variant, with Hodgkin's disease-like features.
7. Low-grade B-cell lymphoma of MALT type, involving jejunum and ileum (B-marginal zone lymphoma, primary extranodal).
8. Low-grade B-cell lymphoma of MALT type, involving parotid gland (B-marginal zone lymphoma, primary extranodal).
9. Low-grade B-cell lymphoma of MALT type, involving tonsil, submandibular gland, and regional lymph node (B-marginal zone lymphoma, primary extranodal).
10. Follicular small cleaved cell lymphoma, with areas of diffuse growth pattern.
11. Diffuse large cell lymphoma (large cleaved cell variant), representing progression from follicular mixed type lymphoma.
12. Small noncleaved cell lymphoma, pleomorphic variant (Burkitt-like lymphoma).
13. Anaplastic plasmacytoma, arising in cecum.
14. Anaplastic large cell lymphoma, of (unusual) B-cell phenotype.
15. Alveolar rhabdomyosarcoma, cervical lymph nodes.
16. Hodgkin's disease, mixed cellularity type, simulating non-Hodgkin's immunoblastic lymphoma.
17. Hodgkin's disease, mixed cellularity type, epithelioid cell-rich variant.
18. Hodgkin's disease, nodular sclerosis type, aggressive histologic variant, simulating (non-Hodgkin's) large cell lymphoma.
19. Hodgkin's disease, lymphocyte predominance type (nodular variant, B-cell phenotype), involving nasopharynx and cervical lymph node.
20. Hodgkin's disease, lymphocyte predominance type (nodular variant, B-cell phenotype), showing focal progression to large cell lymphoma.

## OUTLINE FOR CASE DISCUSSIONS

Lymph Node Hyperplasia	Cases 1-3
Low-Grade B-cell Lymphomas	Cases 4-10
High-Grade B-cell Lymphomas	Cases 11-15
Hodgkin's Disease	Cases 16-20

### LYMPH NODE HYPERPLASIA

Although issues regarding classification of malignant lymphomas are much more strongly represented in publications, the topic of benign lymph node hyperplasia is of great practical diagnostic importance. First, because the immune system is capable of intense cellular proliferation in response to a host of stimuli, such proliferations are sometimes good microscopic simulators of malignancy. It is critical that the pathologist be familiar with such pitfalls, such as acute Epstein-Barr virus infection, anticonvulsant drug reaction, etc. (1,2). Such morphologic simulation is probably more than coincidence, since we now know that in some cases there is actual progression from such atypical hyperplasia to true lymphoma, either Hodgkin's disease or non-Hodgkin's type (3). (\*Case 22 from 1976 Seminar--suggests development of AIL-like peripheral T-cell lymphoma in the setting of Dilantin exposure).

Second, even when a process can be confidently recognized as a benign hyperplasia, it is important to the patient that pathologists pursue the question of etiology. If you yourself had undergone the rigors of nodal biopsy you would be more than mildly curious as to what had caused such worrisome nodal enlargement. In some cases, special stains for microorganisms or even immunostains for immunologic compartmental patterns are useful in suggesting a particular pathogenesis or specific causation. However, based on more than a century of cumulative experience, detailed conventional microscopic morphology, combined with clinical findings, will often provide an answer (4,5).

## CASE 1

**Contributor:** J. R. Phillips, M.D.  
Fresno, CA

**Tissue From:** Inguinal lymph nodes

**ACCESSION #**19923

**Clinical Abstract:** This 21-year-old male presented with bilateral masses in the groin, present for five to six weeks. He also had been experiencing lower anterior chest pain for one month and had a recent diffuse skin eruption which was fading. He felt well, and denied weight loss, chills or fever. There was no noted exposure to mononucleosis. Physical examination revealed a 3.0 cm fixed, tender, firm node in the medial inguinal crease on the left side and a 2.5 cm firm, fixed, tender node in the right inguinal area. One week later, the nodes were slightly smaller but still very firm and relatively nontender. Right axillary firm, discrete lymph nodes were also present on the second examination one week later. Cervical lymph nodes were not palpable.

**Gross Pathology:** The 1.8 x 1.5 x 1.2 cm right inguinal lymph node and the 3.0 x 5.0 x 2.0 cm left inguinal lymph node were oval, encapsulated masses with moist, gray-tan, soft cut surfaces.

**Discussion:** In the microscope one sees striking expansion of the lymph node capsule by a cellular fibrous proliferation. There is good preservation of functional immune compartments, most strikingly the follicles. There are some abnormal, poorly defined compartments between follicles, which consist of epithelioid histiocytes, plasma cells, and plump fibroblasts. These can be considered organizing granulomas. Higher magnification examination of the capsule reveals dense plasma cellular infiltrate, together with endothelial and fibroblastic proliferation.

In combination with the clinical history, the features are suggestive of a generalized inflammatory process, and with the inguinal nodal predominance the possibility of sexually transmitted disease must be entertained. A Warthin-Starry silver stain demonstrates abundant long spirochete organisms, concentrated in the areas of the organizing granulomas.

Both clinical and microscopic features are classic for the secondary phase of syphilis, a disease which the pathologist is in danger of overlooking nowadays. The patient's recent episode of generalized rash supports this interpretation, and the progression of lymphadenopathy from tender to non-tender goes along with a subsiding phase of cellular reaction to a systemic infectious process. An excellent description of the various phases of luetic lymphadenitis can be found in the section on lymphadenopathies by William St. Clare Symmers (6).

**Diagnosis:** Benign lymphadenitis, syphilitic (secondary stage).

## CASE 2

**Contributor:** John Waken, M.D.  
San Gabriel, CA

**Tissue From:** Anterior mediastinum

**ACCESSION #**19726

**Clinical Abstract:** This 42-year-old Caucasian female had a three week history of right shoulder and arm swelling. Radiographs revealed a right paratracheal mass in the mediastinum. Blood count was normal, and VDRL was negative.

**Gross Pathology:** The 29 gram specimen consisted of a 4.5 x 4.0 x 4.0 cm multinodular, firm, rubbery, encapsulated mass with a solid, yellow-tan parenchyma separated by delicate gray-white bands of interlacing fibrous septa. There were no areas of hemorrhage or cyst formation.

**Discussion:** Low magnification microscopy is essential for correct diagnosis in this case. One recognizes sharply circumscribed regressively transformed germinal centers surrounded by rather abundant mantle compartments of the follicles. Between the follicles are expanses of a complex proliferation involving small caliber blood vessels, lymphocytes, plasma cells, and scattered delicate stromal cells, follicular dendritic reticular cells. At low power one recognizes foci of dense hyaline fibrosis along nodal trabecula. There is total ablation of nodal sinuses, a striking and unusual feature of localized angiofollicular lymph node hyperplasia (true "Castleman's disease").

The term "Castleman's disease" is best reserved for localized angiofollicular lymph node hyperplasia, as in this case. Castleman originally described this syndrome as simulating malignancy, i.e., thymoma, when sharply circumscribed nodal enlargement of the mediastinum simulated thymoma clinically and radiologically, and the regressively transformed follicles simulated Hassall's corpuscles microscopically (7). Subsequently, the plasma cell variant was recognized as capable of producing a peculiar paraneoplastic syndrome (8). Most importantly, whether of classic hyaline-vascular type, as is seen here, or of plasma cell type, the process is effectively cured by nodal excision.

When applied to multicentric lymph node enlargement, the term angiofollicular lymph node hyperplasia has less specificity (9). In cases of this disorder nodal sinuses are typically preserved and even hyperplastic. The proliferation of plasma cells with regression of germinal centers is a somewhat nonspecific combination of microscopic findings, and may be identified in patients with underlying autoimmune disease, intermediate phase HIV infection, and other disorders. When no etiologic explanation for such lymphadenopathy can be found, the case can be thrown into the grouping of "systemic AFLH." Such patients often do well with corticosteroid therapy (10).

Finally, Takatsuki's syndrome, featuring peripheral neuropathy, endocrinopathy, and other lesions of the "POEMS" complex is sometimes associated with this lymph nodal histology. This is the most unfavorable of all the clinical-pathologic groupings of

angiofollicular lymph node hyperplasia (10). Recently, detailed immunophenotypic studies have suggested a pathogenetic role of the mantle cell compartment of follicles for the entire grouping of AFLH (11).

**Diagnosis:** Castleman's disease (localized angiofollicular lymph node hyperplasia).

### CASE 3

**Contributor:** William Saukel, M.D.  
Loma Linda, CA

**Tissue From:** Right inguinal lymph node                      **ACCESSION #27621**

**Clinical Abstract:** This 23-year-old male presented with a four-day history of right groin pain after a fall at work. The clinical impression was that of an incarcerated femoral hernia. The surgical finding was that of tender lymph nodes in the femoral canal.

**Gross Pathology:** Three red-tan, fleshy lymph nodes together weighed 15.3 grams, and ranged from 4.5 to 1.5 cm in greatest length. Their cut surfaces showed a white-tan, finely granular parenchyma.

**Discussion:** There is striking preservation of functional compartments, most notably follicles and the "parafollicular" or monocytoid B-cell or B-marginal zones. Some of the latter compartments attain significant size and contain central foci of suppurative necrosis. This places this lymph node in the grouping of suppurative granulomatous lymphadenitis, one which is effectively specific for an infectious etiology (12). The likelihood of one infectious agent rather than another relates primarily to location and clinical history. For example, if this were an axillary or cervical lymph node from a child the most likely etiology would be cat-scratch agent. In the mesentery *Yersinia* would be more likely. In this inguinal site in a young adult male the most likely causative agent is chlamydia (lymphogranuloma venereum).

The monocytoid B-cell, alternatively named "perisinusoidal cell", "parafollicular cell", or "immature sinus histiocyte" has become a subject of intense study over the past decade, in relation to both reactive and neoplastic conditions. When suppurative necrosis occurs within this compartment it indicates bacterial or chlamydial etiology. By contrast, this compartment can be expanded in the face of other infectious agents such as viruses, without associated neutrophils. (\*Case 24 from the 1976 Seminar--hyperplasia of monocytoid B-cell compartment, ?viral etiology).

A final point is that isolated inguinal lymph node enlargement can be clinically misinterpreted as incarcerated hernia (13). Probably at least once a month on average I receive a consultation case in which either reactive lymphadenitis or malignant lymphoma

has initially been sampled in the expectation of reducing a hernia! (see also cases 10 and 11).

**Diagnosis:** Benign lymphadenitis, suppurative granulomatous type (early), indicative of infectious etiology.

## MALIGNANT LYMPHOMAS (NON-HODGKIN'S)

Dr. Lukes was one of the first proponents of the concept of lymphomas as solid neoplasms of the immune system (14). Lennert had closely preceded him with the earliest evidence of a lymphoid (B-cell) origin of "reticulum cell sarcoma", in the form of whole tumor tissue homogenates demonstrating immunoglobulin monoclonality, by quantitative analysis of heavy and light chain types. The first case in the monograph for the 1976 Seminar was actually an avian bursa of Fabricius, chosen to emphasize the importance of modern immunology to the understanding of lymphomas (\*Case 25--1976 Seminar).

Immunologic characterization of malignant lymphomas has allowed their classification based largely on normal cell counterparts within the reactive immune system. Although the Working Formulation of 1982 was hailed by clinicians as a practical, prognostically relevant system for lymphoma classification, both Lukes and Lennert were unenthusiastic contributors to the final published work (15). They pointed out that this system was profoundly limited to conventional microscopic resolution in distinguishing various lymphomas.

The recently proposed Revised European American Lymphoma (REAL) Classification System is a current attempt to incorporate data regarding newly recognized types of lymphoma from diverse authors over the intervening 12 years since publication of the Working Formulation (16). This classification is not intended to be an original work. Rather it represents an eclectic effort by specialists diverse in background and experience to agree upon distinct lymphomatous entities. Important advantages of the REAL classification include a broad base of scientific data to characterize the various entities (a single practical reference source for many lymphoma types!), and its inclusion of the categories of the European Kiel classification system, allowing prospective joint studies between European and American clinical groups. Disadvantages include its emphasis on immunologic identity of lymphomas and its large number of lymphoma types, making it difficult to learn (particularly for clinicians!).

However, in most instances terminology is borrowed from one existing classification system or another, so that the diagnoses are already usually understood, even by pathologists unfamiliar with this particular classification. Lymphoma diagnoses in this Seminar are listed in the form of REAL classification terminology.

Low-Grade B-cell Lymphomas

The vast majority of lymphoid neoplasms in the West are of B-cell differentiation. Those which behave in an indolent fashion are almost exclusively B-cell tumors (the only exception is the rare large granular lymphocytosis of T-cell or NK cell type). The few biologically pure lymphoma types of the Working Formulation corresponded in large part to the follicular lymphomas, neoplastic counterparts of the germinal center. These have been carried over intact into the REAL classification as "follicular center lymphomas." Other types of low-grade B-cell lymphoma include CLL/small lymphocytic, lymphoplasmacytoid, mantle cell, marginal zone, and hairy cell disease. Although these types are closely related, there are subtle phenotypic, morphologic, and clinical distinctions (17).

**LOW GRADE B-CELL LEUKEMIA/LYMPHOMA**

	Plasmacytoid	CLL	Hairy Cell	Mantle	B-marginal (MBC)
Leukemia	-/+	+/-	-/+	-/+	-/+
Lymphoma	+/-	-/+	+/-	+/-	+
Surface Ig	-/+	+/-	+	+	+
Cytoplasm Ig	+	-	-	-/+	+/-
B-cell CD's	-/+	+	+	+	+
CD5	-/+	+	-	+	-
CD11c	-/+	-/+	+	-/+	-/+
CD25	-	-/+	+	-	-
TRAP	+/-	-	+	-	-/+

#### CASE 4

**Contributor:** Peter M. Banks, M.D.  
San Antonio, TX

**Tissue From:** Cecum & Ascending colon

**ACCESSION #**27713

**Clinical Abstract:** This 56 year old man suffered progressive diarrhea over the recent 6 months. Barium enema revealed innumerable polyps throughout the large bowel. Obstructive symptoms led to resection of the cecum and ascending colon. There was no family history of colon cancer.

**Gross Pathology:** The specimen consisted of 20 cm of distal ileum, 50 cm of cecum-ascending colon, and appendix. Innumerable polyps ranging from imperceptible to 3 cm in size were present throughout the entire specimen, the largest concentrated around the ileocecal valve.

**Discussion:** Microscopically, one sees uniform lymphoid expanses distending zones of mucosa by virtue of growth within the lamina propria. There is no involvement of overlying flat or glandular epithelium. At high power, one sees a relatively monotonous population of small cleaved cells without associated basophilic large transformed cells. The only larger cells present have delicate nuclei and scant cytoplasm, corresponding to follicular dendritic cells. In regional lymph nodes (not included in seminar slides) a definite faint follicular growth pattern attended neoplastic replacement of normal architecture.

Paraffin immunostains show strong co-expression of both B-cell marker CD20 and T-cell marker CD43 by the neoplastic cells, a common finding among mantle cell lymphomas.

The specific term mantle cell lymphoma was historically preceded by less specific terms such as "intermediately differentiated lymphocytic lymphoma" and "mantle zone lymphoma." Lennert's centrocytic type lymphoma was essentially identical to mantle cell type (18). Although the clinical manifestations of so-called multiple lymphomatous polyposis had been described much earlier, Triozzi et al. in 1986 first recognized the association of the mantle cell type with this phenomenon (19).

Mantle cell lymphoma is strongly associated with a specific genetic marker, specifically bcl-1 oncogene activation, often on the basis of an 11;14 chromosomal translocation. The disease shows a strong predilection for middle aged and elderly males. Prognostically, there is considerable range, from the low grade end to the high grade end of the intermediate grade grouping. Favorable histologic findings include follicular growth pattern, small cell size, and low mitotic rate. The blastic variant of mantle cell lymphoma can be difficult or impossible to distinguish from lymphoblastic lymphoma on morphologic criteria alone.

In many patients this type of lymphoma represents the worst of both worlds, specifically the incurability of low grade lymphoma with the relatively rapid course of high grade lymphomas (17).

**Diagnosis:** Mantle cell lymphoma, involving gastrointestinal tract as "multiple lymphomatous polyposis."

## CASE 5

**Contributor:** Stanley Hino, M.D.  
Hemet, CA

**Tissue From:** Spleen

**ACCESSION #**26486

**Clinical Abstract:** This 67-year-old Caucasian female presented with a one-week history of left-sided pleuritic chest pain. She also complained of sweating and shortness of breath, as well as upper abdominal pain without nausea or vomiting. CT-scan of the abdomen revealed huge splenomegaly. Patient's past medical history included an abdominal hysterectomy for adenocarcinoma of the uterus.

**Gross Pathology:** The massively enlarged spleen measured 37 x 14 x 13 cm and weighed 2400 grams. The cut surface of the spleen revealed multiple subcapsular hematomas but otherwise showed a fairly uniform diffuse appearance without accentuation of the follicular pattern.

**Discussion:** In a small minority of lymphoma cases, one can be very confident as to the diagnosis of lymphoma, without any confidence whatsoever in classifying the process. When features of a lymphoma are atypical, it is important not to jam the case into one category or another. In the first place, this creates "unclean" data, contaminating precisely defined lymphoma categories with outliers. In the second place, such efforts carry prognostic and therapeutic implications which have not been established for the particular patient.

Lymphomas are often difficult to classify, or even to recognize confidently, in the spleen. In this case there is both enlargement of lymphoid pulp and infiltration of sinus pulp by a neoplastic process composed of slightly pleomorphic, medium sized lymphoid cells. These feature one or two small nucleoli and moderately abundant, slightly basophilic cytoplasm. In some blocks from this case there is a suggestion of plasmacytoid differentiation within the lymphomatous population, and the sinus pulp distribution goes along with an immunosecretory neoplasm. However, paraffin immunostaining failed to demonstrate immunoglobulin light chain restriction. The tumor cells did react strongly for B-cell antigen CD20, and coexpressed CD43.

I suspect this may represent a progression of earlier low grade lymphoplasmacytic lymphoma into a more aggressive form of malignancy, without the classic features of immunoblastic lymphoma per se. Intermediate grade lymphoplasmacytic lymphomas are essentially unrecognized as such in any classification system. I have occasionally encountered such processes, particularly in the Waldeyer's ring area, and diagnose these descriptively.

The frequency of mitotic figures is an old fashioned but dependable criterion for assessing aggressiveness of lymphoma. As

a final check before diagnosing any case as low grade lymphoma, I always scan several fields for mitotic figures. If I encounter more than a few, I call off the diagnosis and reassess the case in detail. In this case the mitotic rate is moderate (about 1 per high power field on average). This effectively excludes any low grade lymphoma.

It is interesting that the lymphomatous process was in this patient's bone marrow aspirate smear, but there also in a subtle and unclassifiable form. Dr. Hino indicates that the patient survived about 20 months without intensive therapy. Thus, despite initial manifestations suggesting an aggressive course, the process behaved more in an intermediate grade fashion.

**Diagnosis:** Malignant lymphoma, unclassifiable, of intermediate grade (?higher grade progression of plasmacytoid small lymphocytic lymphoma).

## CASE 6

**Contributor:** Mark DeMeo, M.D.  
Santa Rosa, CA

**Tissue From:** Axillary lymph node

**ACCESSION #**23178

**Clinical Abstract:** This 73-year-old Caucasian male presented with recent onset of right axillary lymphadenopathy. This was approximately 7 cm in size. No other lymph nodes were found at the time of surgical dissection and physical examination. His lung fields were clear and his peripheral smear was within normal limits.

**Gross Pathology:** A 60 gram, 9 x 3 x 4 cm lymph node showed gray-tan, minimally nodular parenchyma without fibrosis. There was no obvious hemorrhage.

**Discussion:** This large lymph node shows obvious diffuse replacement by a lymphomatous process which is cytologically very heterogeneous. The mitotic rate is low to moderate. There is a subtle nodularity related to proliferation centers in which delicate prolymphocytes and paraimmunoblasts exhibit pale cytoplasm and delicate vesicular nuclei with distinct small nucleoli. Interestingly, occasional bizarre multilobated nuclei are present, some approaching diagnostic Reed-Sternberg cells in atypia. Although these are accompanied by occasional eosinophils, the sharp "hiatus" between large tumor cells and benign-appearing small lymphocytes necessary for diagnosing Hodgkin's disease is not to be found.

This represents an extremely pleomorphic variant of small lymphocytic lymphoma. Peripheral blood examination failed to reveal any evidence of chronic lymphocytic leukemia.

Small lymphocytic lymphoma/CLL has a distinctive marker recognizable by low power microscopy: proliferation centers (20). These do not occur in the other forms of low grade B-cell lymphoma, such as mantle cell lymphoma, B-marginal zone lymphoma,

etc. Rarely, such proliferation centers do accompany lymphoplasmacytic lymphoma. Even when a relatively high percentage of prolymphocytes is present, this disease is usually relatively indolent (21).

In recent years, attention has been paid to the rare phenomenon of the Hodgkin's disease variant of Richter's syndrome (22). When Hodgkin's disease does arise within pre-existent CLL/small lymphocytic lymphoma, a background of reactive T-cells accompanies the neoplastic tumor giant cells. This feature is useful in distinguishing Hodgkin's disease-like pleomorphic variants of CLL/small lymphocytic lymphoma from a true Hodgkin's disease transformation. EBV may be involved in such true disease transformation (23).

**Diagnosis:** Small lymphocytic lymphoma, pleomorphic variant, with Hodgkin's disease-like features.

#### CASE 7

**Contributor:** Wen Chuan, M.D.  
Reno, NV

**Tissue From:** Small intestine

**ACCESSION #**27514

**Clinical Abstract:** This 50-year-old male presented with an acute abdomen. During surgery for appendicitis, the surgeon found some serosal flattening, and since the patient had been complaining of abdominal pain for many years, these lesions were resected for pathologic examination.

**Gross Pathology:** The mucosal surface of the ileum showed two flattened areas which on sectioning revealed a submucosal infiltrate with a fishflesh appearance. The proximal jejunum had six similar areas of mucosal flattening.

**Discussion:** Sections show massive localized infiltration of the mucosal and submucosal tissues by a lymphoid process with sharply defined, benign-appearing germinal centers interspersed within diffuse expanses of B-marginal zone cellularity; small lymphocytes, monocytoïd B-cells, and occasional large transformed cells. Rare lymphoepithelial lesions can be identified in conventional sections, although these are more readily appreciated with cytokeratin immunostains. No Helicobacter type organisms are identified.

In the early 1980's Isaacson in England first noted peculiar clinical and microscopic features among many primary, localized lymphomas of the GI tract (24). Subsequently, his observations have been elaborated into a complex but useful concept of extranodal low grade B-cell lymphomas of "mucosa associated lymphoid tissue" (MALT) type (25). There is recent evidence from fluorescence in situ chromosome studies indicating trisomy 3 as a common finding in these MALT-type tumors (26). Converging from a separate starting point, Sheibani and Nathwani first described lymph nodal lymphomas of monocytoïd B-cell composition, and later

observed neoplasms of similar cellular composition in extranodal sites such as salivary gland (27). Today, in the REAL classification there is an eclectic approach, describing these tumors as low grade neoplasms of B-marginal zone derivation, both extranodal (MALT-type) and nodal (monocytoid B-cell type) (16). It is important to understand that the distinction between these two variants of B-marginal zone lymphoma does not rest upon microscopic criteria, but rather upon distribution. Tumors arising in lymph node tend to be widespread at detection and to behave as systemic low-grade lymphoma (17). Those which arise in extranodal sites usually remain long localized and may be effectively cured with surgical resection, radiation therapy, or even chemotherapy.

In the case of gastric MALT-type lymphoma, Isaacson presents compelling evidence as to a causative role for Helicobacter organisms (28). Together with the implication that early antimicrobial therapy may actually induce regression of such "tumors", this observation raises the possibility of initial "antigen dependence" as an explanation for the long localized behavior of these monoclonal B-cell proliferations.

**Diagnosis:** Low-grade B-cell lymphoma of MALT type, involving jejunum and ileum (B-marginal zone lymphoma, primary extranodal).

## CASE 8

**Contributor:** Willard Worthen  
Inglewood, CA

**Tissue From:** Platysmal and submandibular nodes **ACCESSION #27545**

**Clinical Abstract:** This 76-year-old female presented with a non-tender, firm, slightly movable mass over the right submandibular area. This was associated with a cold, some coughing, and a toothache on the right side. There was no history of fever, chills, loss of appetite or night sweats, and no history of tuberculosis.

**Gross Pathology:** The "lymph nodes" varied from 0.5 to 4.5 cm in greatest diameter. They had a homogeneous tan, fleshy, firm cut surface without suspicious areas of discoloration, softening or unusual induration.

**Discussion:** The representative blocks consist of salivary gland tissue massively infiltrated by lymphoid cellularity to the point that this is easily mistaken for lymph nodal tissue. Together with benign-appearing germinal centers, there are diffuse expanses of heterogeneous cellularity with conspicuous plasmacytic elements, epithelioid histiocytes, and many monocytoid B-cells. This latter cellular compartment is concentrated around lymphoepithelial lesions, a few of which are still recognizable as

intercalated ducts. Paraffin immunostains show conclusive kappa Ig light chain restriction.

Although this neoplasm could be considered low grade lymphoplasmacytic lymphoma with associated epithelioid histiocytes (29), in deference to the extranodal location and the abundant associated lymphoepithelial lesions, this is probably better considered a low-grade B-cell lymphoma of MALT-type.

Isaacson's observations relating to primary extranodal low-grade B-cell lymphomas in the GI tract carried over for lesions in diverse sites, including salivary gland, orbital tissue, skin, breast, and even more exotic sites (25,30). Although these tumors range considerably in proportion of cellular elements, which include small lymphocytes, plasmacytic and plasmacytoid cells, monocytoid B-cells, large transformed cells, and epithelioid histiocytes, these all correspond to the B-marginal zone compartment. Evidence supporting this unifying concept of MALT-type lymphomas comes from the observation that this type of lymphoma may occur in the same patient in two or more separate extranodal sites without evidence of systemic disease (25). Isaacson's theory of "antigen dependence" may relate to parenchymal cells being autoimmune targets of the tumor cells or of the T-cells associated with the tumor (31).

These extranodal MALT-type lymphomas are microscopically extremely diverse and can be mistaken for a variety of other processes: benign "pseudolymphoma", benign autoimmune inflammatory processes, and higher grade lymphomas. The benign germinal centers associated with these tumors may process tumor cells, a phenomenon Isaacson has described as "follicular colonization" (32). Sometimes the colonized follicles resemble neoplastic follicles, leading to the false interpretation of follicular lymphoma. In other cases, the follicles contain many large transformed cells, imparting the incorrect impression of high grade lymphoma (\*Case 6--1976 Seminar). See also the pulmonary MALT-type lymphoma, originally described as "diffuse small cleaved cell lymphoma of lung" (\*Case 26--1976 Seminar).

**Diagnosis:** Low-grade B-cell lymphoma of MALT type, involving parotid gland (B-marginal zone lymphoma, primary extranodal).

## **CASE 9**

**Contributor:** D. R. Dickson, M.D.  
Santa Barbara, CA

**Tissue From:** Tonsil, Submaxillary lymph node

**ACCESSION #21283**

**Clinical Abstract:** This 49-year-old male presented with recurrent tonsillitis for which a tonsillectomy was performed. Eight months later he noted nontender masses in the submental region while shaving. These were not associated with any inflammatory process in the upper respiratory passages. They were excised.

**Gross Pathology:** The tonsils were 4.0 x 2.5 x 2.0 cm and 5.0 x 3.0 x 2.8 cm. The three submaxillary lymph nodes were soft, rubbery, smoothly encapsulated, and varied from 1.8 to 2.4 cm in greatest diameter.

**Discussion:** This case is an extreme example of the difficulty in making the distinction between chronic hyperplasia and early partial involvement of lymph node by a low grade lymphoma. In favor of low grade malignancy is the uniform expansion of the B-marginal zone (monocytoid B-cells) and extension of the process into perinodal fat. It is interesting to contrast this case with Case #24 from the 1976 Seminar, an example of benign B-marginal zone (monocytoid B-cell) hyperplasia. In that case one sees intense follicular hyperplasia associated with focal expanses of marginal zone enlargement.

In retrospect, it is interesting to study the tonsillar tissues from this patient, removed eight months previously. Although the appearances suggest a benign, orderly immune response, there is considerable expansion of the B-marginal zone. Immunostaining for bcl-2 protein shows an inverted pattern among some of the follicles, suggesting that these were involved by a neoplastic B-marginal zone process, as "colonized" follicles, rather than by a benign reactive state. Interestingly, MALT-type lymphomas are relatively uncommon in the Waldeyer ring area, despite the fact that lymphoepithelial lesions are normally abundant there, representing exchange of activated lymphoid cells with the epithelial surfaces.

Unfortunately, Dr. Dickson was unable to obtain long-term clinical follow-up on this patient. In a recently published retrospective study, it was found that nodal B-marginal zone lymphomas are relatively indolent, but behave as typical low grade lymphomas with continued fall in survival over many years (17).

**Diagnosis:** Low-grade B-cell lymphoma of MALT type, involving tonsil, submandibular gland, and regional lymph node (B-marginal zone lymphoma, primary extranodal).

## CASE 10

**Contributor:** Weldon K. Bullock, M.D.  
Los Angeles, CA

**Tissue From:** Inguinal lymph nodes

**ACCESSION #24671**

**Clinical Abstract:** This 70-year-old male had a month history of pain and swelling of his left groin. He denied chills, fever, night sweats, weight loss, change in bowel habits, or back pain. Physical examination revealed enlarged left inguinal lymph nodes.

**Gross Pathology:** A 50 gram oval mass was 8.0 x 4.0 cm. Cut sections revealed a lymph node partially replaced by pink-tan tissue. There were no areas of necrosis or hemorrhage.

**Discussion:** Sections vary somewhat among the several blocks used, however all contain some areas of diffuse growth by a monotonous lymphoid cell population. Additionally, in some blocks there is a definite follicular growth pattern, and abundant proliferative fibrosis is present, as is often the case in the retroperitoneum. At high magnification one appreciates occasional large transformed basophilic lymphoid cells associated with the small cleaved cells. These are an important marker to distinguish this process from mantle cell lymphoma, in which one does not see such large basophilic transformed cells. Lennert emphasized the ubiquitous mixture of large noncleaved with small cleaved cells in all neoplasms of germinal centers, designating these "centroblastic-centrocytic" lymphomas, with either diffuse or follicular growth pattern (33). This case presumably represents progression from low grade follicular small cleaved cell lymphoma to diffuse small cleaved cell lymphoma, and the proximity to retroperitoneum is a somewhat unfavorable clinical finding.

Because many cases originally described as "diffuse small cleaved cell" lymphoma correspond to mantle cell lymphoma, many pathologists now ask if there is indeed such a thing as diffuse small cleaved cell lymphoma. The answer is "yes", and the presence of large transformed cells is the way to recognize the entity. (\*Case 15--1976 Seminar). The number of such cases identified in our retrospective SWOG study was small, however they seem to behave as moderately indolent disease (17).

**Diagnosis:** Follicular small cleaved cell lymphoma, with areas of diffuse growth pattern.

### High-grade B-cell lymphomas

While the differential diagnosis for low-grade lymphomas usually centers around the distinction of chronic hyperplasia versus neoplasia, most high grade lymphomas are easily recognized as malignant. Instead, the difficulty comes in distinguishing the process as lymphoma rather than morphologic simulators, such as granulocytic/monocytic sarcoma, poorly differentiated carcinoma, or even sarcoma. Nowadays, immunostaining is a reliable and rapid method for recognizing such mimickers.

Only rarely do we encounter the question of high grade malignancy versus a benign hyperplasia, and when this is the case our clinical colleagues are usually rather impatient for an answer! Examples of this spectacular differential diagnostic problem include the post-transplant lymphoproliferative disorders (34) and acute viral reactions, even in immunocompetent patients, such as acute EBV infection (1).

Peripheral T-cell lymphomas, regardless of histology or immunophenotype, are usually aggressive clinically, and almost always systemic at presentation. However, they are very infrequent in the West. The vast majority of high grade lymphomas are of B-cell differentiation, and a significant minority present as early stage disease, sometimes arising in extranodal sites (35). In constructing a therapeutic strategy, clinicians are interested not only in the grade of lymphoma but also in its stage and in patient performance status (35).

Survival data for patients with high grade lymphoma have not changed much over the past 20 years. About 30-40% of patients can be effectively cured with intensive therapy, whereas the remainder succumb to disease within the first three years. Stage of disease is a powerful prognostic factor, with the big separation being between stage I and all other stages. Other factors explaining differences in survival have not been forthcoming. Although the Working Formulation distinguished "diffuse large cell" and "diffuse large cell, immunoblastic" types, placing the former within the intermediate grade grouping and the latter within the high grade grouping, subsequent long-term follow-up studies have failed to justify this distinction (37). Furthermore, the

International Lymphoma Study Group carried out an interobserver comparison which failed to show reproducibility in making this distinction. Therefore, in the REAL classification system there is only "large B-cell lymphoma" without a separate immunoblastic type.

## CASE 11

**Contributor:** Henry Slosser, M.D.  
Pasadena, CA

**Tissue From:** Inguinal lymph node

**ACCESSION #**27676

**Clinical Abstract:** This 79-year-old female presented with a left groin mass.

**Gross Pathology:** The 8 gram, 3 x 2 x 2 cm node had a soft consistency and a homogeneous tan cut surface.

**Discussion:** The presentation of this mass lesion in the left inguinal region reminds us that it may clinically simulate incarcerated hernia (13) (see also cases 3 and 10). At low magnification one sees diffuse expanses of clear cellularity interrupted focally by proliferative cellular fibrosis. There are zones of very subtle follicular growth pattern. At higher magnification, one can appreciate regional variation in proportionate cellularity: the predominating cells are large and vesicular with cleaved or oval nuclei, however there is also a moderate proportion of small cleaved cells as well. Overall, these features suggest progression of a low-grade follicular lymphoma, probably clinically inapparent for some time, now transforming into a more aggressive disease process. Access to the retroperitoneum recommends intensive therapeutic control of this process.

**Diagnosis:** Diffuse large cell lymphoma (large cleaved cell variant), representing progression from follicular mixed type lymphoma.

## CASE 12

**Contributor:** Paul Ortega, M.D.  
Burlingame, CA

**Tissue From:** Axillary lymph node

**ACCESSION #**24429

**Clinical Abstract:** This 57-year-old Asian female presented with edema of the left leg and a right axillary mass of several months' duration. CT scan demonstrated a large retroperitoneal mass.

**Gross Pathology:** A 5.0 x 3.0 x 7.0 cm lymph node was uniformly replaced by soft, pink, homogeneous tissue.

**Discussion:** Nodal architecture is totally replaced by a diffuse cellular process with interspersed histiocytes imparting a "starry sky" pattern. High power microscopy reveals vesicular nuclei with several prominent nucleoli and a tag of basophilic cytoplasm. The mitotic rate is high. Associated histiocytes contain engulfed nuclear debris.

This is the highest grade type of malignant lymphoma, that earlier termed "small noncleaved cell" type in the Working Formulation. The cells are too pleomorphic for a Burkitt tumor, and so in the REAL classification this is termed "Burkitt-like" type.

Because high grade neoplasms converge in their microscopic appearance, it is important to rule out simulators such as granulocytic/monocytic sarcoma and even undifferentiated carcinoma. The distinction of this type of high grade lymphoma from lymphoblastic type lymphoma is critical, since each requires a different type of therapy, but can be treated effectively with the appropriate regimen (37). Although their microscopic appearances can be similar, in general Burkitt-like tumors have more coarse nuclear features, and the abundant basophilic cytoplasm speaks strongly against the possibility of lymphoblastic malignancy. Air-dried imprint or smear preparations are extremely useful when stained with Giemsa or similar method in bringing out the cytoplasmic features for this distinction. Furthermore, such air dried preparations are useful for the demonstration of Tdt, a disease-specific marker of lymphoblastic malignancy (38).

We know now from molecular studies that most of these high grade tumors have activation of the C-myc oncogene on chromosome 8, often by virtue of translocation to one of the immunoglobulin-encoding sites (on chromosome 2, 14, or 22) (39). Over the past decade we have seen an increased incidence in this type of high grade lymphoma in relation to HIV-infected individuals (40).

**Diagnosis:** Small noncleaved cell lymphoma, pleomorphic variant (Burkitt-like lymphoma).

### CASE 13

**Contributor:** William Sueoka, M.D.  
Thousand Oaks, CA

**Tissue From:** Cecum

**ACCESSION #**26420

**Clinical Abstract:** This 81-year-old Caucasian male presented with several months of chronic fatigue. His hemoglobin was 11.1 with no history of any bleeding source. A barium enema revealed a large tumor mass in the cecum.

**Gross Pathology:** A right colectomy specimen included a 6.0 x 4.0 x 4.0 cm exophytic ulcerating mass in the cecum which extended through the muscularis but apparently not the serosal layer.

**Discussion:** Beneath intact large bowel mucosa one sees a perfectly diffuse expanse of pale cells. At higher magnification one appreciates delicate vesicular nuclei and moderately abundant cytoplasm with juxtannuclear pale zones--plasmacytic features. There are abundant intranuclear inclusions, so-called Dutcher bodies. Mitotic figures are moderately abundant.

This case raises the issue as to what criteria serve to distinguish anaplastic plasmacytoma (extramedullary) from

immunoblastic lymphoma (with plasmacytic differentiation). Although, as one might predict in theory, there is in rare cases a small partial perfect overlap in regard to morphologic, immunologic, and clinical features between these two categories, in general one can usefully distinguish on the basis of distribution of disease and, in some cases, the nature of produced immunoglobulin. Plasmacytic neoplasia primary in lymph nodes is very rare (41). However, primary plasmacytomas of mucosal surfaces are more common, particularly in the gastrointestinal tract. These often produce IgA. Interestingly, among cases of plasma cell myeloma which undergo high grade transformation, there is a disproportionately high percentage which are lambda light chain and/or alpha heavy chain producing. For practical purposes, when a process produces IgM or IgG and arises in lymph node it is probably better considered immunoblastic lymphoma (42).

In this case, although there was a demonstrated serum monoclonal spike for IgA-kappa; kappa light chain restriction was easily demonstrated in paraffin sections of the tumor, which was only faintly positive for CD45 (LCA). Bone marrow biopsy revealed no evidence of underlying plasma cell myeloma. Nevertheless, the patient's course was short, with skin nodules demonstrating involvement by plasma cell neoplasia only six months after colectomy. In general, anaplastic myeloma pursues an even more aggressive course than immunoblastic lymphoma (42).

**Diagnosis:** Anaplastic plasmacytoma, arising in cecum.

#### **CASE 14**

**Contributor:** Harold H. Brazil, M.D.  
Fairfield, CA

**Tissue From:** Porta hepatis lymph nodes                      **ACCESSION #24683**

**Clinical Abstract:** This 69-year-old female presented with a history of fever, weight loss and microcytic anemia. Lymph node and liver biopsies were performed. At the time of surgery, the surgeon was unable to identify a primary tumor mass within the abdomen. The spleen was said to have multiple, minute (1-2 mm) capsular nodules suggestive of old granulomas, but was not enlarged.

**Gross Pathology:** The 3.0 x 2.0 x 2.5 cm portion of lymph node had tan-yellow, rubbery parenchyma with a vaguely nodular appearance and focal streaks of hemorrhage seen along with stellate areas of yellow-tan necrosis.

**Discussion:** At low power one recognizes residual intact lymph nodal compartments interrupted by large expanses of a cohesive pale neoplastic cellularity. At higher power these expanses are composed of extremely pleomorphic large cells with abundant cytoplasm and multilobated nuclei. The mitotic rate is moderately high. There is focal sinus involvement by these neoplastic cells.

The pathologist would be remiss not to consider metastatic malignancies such as poorly differentiated carcinoma or malignant melanoma, as well as lymphomas and histiocytic tumors in the differential diagnosis. This case occurred 13 years ago, and at the time metastatic malignancy was high on the differential diagnostic list. However, mucin stains and melanin stains were negative and reportedly so was an immunostain for cytokeratin. In preparing this case for this Slide Seminar, an immunostain for CD30 was performed, showing strong uniform reactivity of the tumor cells for this antigen. Surprisingly, the tumor cells were also strongly positive for B-cell antigen CD20. A majority of anaplastic large cell lymphomas show some slight evidence of T-cell differentiation, not B-cell differentiation. This suggests the possibility that this may have arisen as a secondary event, namely high grade transformation from a clinically inapparent low-grade B-cell lymphoma, although I could find no evidence for this in this nodal sampling.

In the early 1980's Stein and his colleagues in Kiel developed their first monoclonal antibody of apparent interest, directed against a culture of Hodgkin's tumor cells. They named this antibody their "Ki-1" antibody, and found that in general this reacted with the tumor cells of Hodgkin's disease but not with those of non-Hodgkin's lymphomas. However, a peculiar grouping of cases showed strong reactivity for this antibody. Many of these cases had originally been diagnosed as metastatic malignancy of unknown origin or as histiocytic tumors. Eventually this grouping assumed the name "anaplastic large cell lymphoma" (43,44). Conceptually, this type of lymphoma represents a "bridge" between Hodgkin's disease and the non-Hodgkin's lymphomas (45).

We now know that CD30 is a marker of lymphoid cell activation. Its presence is not at all specific for this morphologically defined category of lymphomas. When morphology is used as a basis for defining anaplastic large cell lymphoma, a significant minority of cases show favorable survival experience, with or sometimes even without therapy. Initial cases reported as "regressing atypical histiocytosis" corresponded to this type of lymphoma (46). In fact, the majority of cases which we diagnosed as "malignant histiocytosis" 10 or 15 years ago would today instead be recognized as anaplastic large cell lymphoma (\*Case 12-1976 Seminar).

**Diagnosis:** Anaplastic large cell lymphoma, of (unusual) B-cell phenotype.

#### **CASE 15**

**Contributor:** Charles Osborn, M.D.  
Glendale, CA

**Tissue From:** Cervical lymph nodes

**ACCESSION #24451**

**Clinical Abstract:** This 37-year-old male presented with bilateral cervical adenopathy which had not responded to repeated courses of antibiotics. He was otherwise asymptomatic.

**Gross Pathology:** A left radical neck dissection included multiple firm, gray nodes ranging in size from 0.7 to 2.3 cm in maximum dimension. Most appeared to be replaced by homogeneous tan tumor.

**Discussion:** Low magnification reveals a peculiar pattern of lymph nodal replacement by a tumor composed of large cells with abundant cytoplasm and with clefts or spaces within expanses of tumor. High magnification confirms the anaplastic appearance of tumor cells, many of giant size with multiple nuclei or nuclear lobes. The differential diagnosis includes metastatic carcinoma, sarcoma, and anaplastic large cell lymphoma.

For those with experience in soft tissue pathology the features of alveolar rhabdomyosarcoma are easily appreciated. However, many pathologists are not aware of the capacity for such tumors to clinically present with widespread lymphadenopathy simulating lymphoid malignancy. In the head-and-neck region such sarcomas sometimes arise in the area of the parotid gland with regional nodal involvement. In exceptional cases, the tumor cells are so poorly differentiated as to microscopically simulate large cell lymphoma.

In this case the nature of the tumor was easily confirmed with staining for desmin.

This case was included to keep the seminar participants "on their toes", since high grade malignancies of entirely different histogenesis can show remarkable microscopic resemblance.

**Diagnosis:** Alveolar rhabdomyosarcoma, cervical lymph nodes.

## HODGKIN'S DISEASE

At least for practical purposes it is important to retain the distinction between Hodgkin's disease and other lymphomas. Hodgkin's disease is a grouping of malignant lymphomas with distinct clinical and pathologic features (47). Specifically, the process arises in lymph nodes and spreads along predictable routes of lymphatic circulation. It is highly sensitive to radiation therapy when localized, and to chemotherapy when more widespread. Microscopically, it is characterized by a hiatus between tumor giant cells and benign reactive host cellularity (48). As we study Hodgkin's disease with greater and greater scientific resolution, the distinction in some cases between Hodgkin's and non-Hodgkin's lymphoma becomes blurred (49). The hypotheses of Dr. Lukes, proposed 18 years ago (50), that the Hodgkin's tumor cells are aberrant lymphoid immunoblasts have subsequently been substantiated by a diversity of high resolution special studies. These include the close interrelationship between Hodgkin's and non-Hodgkin's lymphomas (22,23,49,51), and high sensitivity molecular probes showing lymphoid gene rearrangement patterns in the neoplastic cells of Hodgkin's disease (51-53). Detailed studies of intense immunoblastic proliferations in acute EBV infection have shown similarity between reactive immunoblasts and Hodgkin's tumor cells (54)

Nevertheless, for practical purposes, in most cases one can confidently distinguish between Hodgkin's disease and non-Hodgkin's lymphoma. When all else fails, I tend to rely on clinical findings more than those of sophisticated special studies.

## CASE 16

**Contributor:** Samuel K. Abul-Haj, M.D.  
Ventura, CA

**Tissue From:** Cervical lymph node

**ACCESSION #**21969

**Clinical Abstract:** This 54-year-old Caucasian female presented with bilateral axillary and inguinal lymphadenopathy, and was otherwise asymptomatic. Several months later she presented with generalized lymphadenopathy, accompanied by anemia and hepatosplenomegaly.

**Gross Pathology:** A moderately large (3 cm) cervical lymph node was received.

**Discussion:** This case represents an extreme challenge in distinguishing between Hodgkin's disease and non-Hodgkin's lymphoma. At low magnification appearances suggest a non-Hodgkin's lymphoma, possibly a peripheral T-cell neoplasm with features of angioimmunoblastic lymphadenopathy. Suggestive findings include a diffuse replacement of the node by an extremely heterogeneous, complex process with some vascular proliferation and with striking selective sparing of the marginal sinuses. Indeed, some expert reviewers originally favored interpreting the process as this variant of T-cell lymphoma. The clinical presentation, with widespread lymphadenopathy, was also more in keeping with non-Hodgkin's lymphoma than with Hodgkin's disease. However, careful high magnification examination reveals scattered diagnostic Reed-Sternberg cells. These tend to be present within areas of slightly pleomorphic small lymphoid cells exhibiting abundant clear cytoplasm. As has been published, Reed-Sternberg cells can arise within B-marginal zones (monocytoid B-cell areas), and on the basis of morphology alone this possibility is suggested here (55).

This case is much better understood today by means of monoclonal antibody immunostains applied to paraffin sections, than was possible when the biopsy was carried out 13 years ago. There is strong selective reactivity among the large bizarre Reed-Sternberg cells and mononuclear variants for CD30 (Ber-H2), and the surrounding lymphocytes are demonstrated to be T-cells not B-cells, strongly reactive for CD45RO (UCL-1) and not for CD20 (L26).

The distinction between peripheral T-cell lymphoma and Hodgkin's disease can be extremely difficult (56), and this may be for good reason: sometimes neoplastic T-cells come to closely resemble Hodgkin's tumor cells with very incomplete immunophenotypes, not only in relation to their cytomorphology.

This patient's rapid downhill course with death in less than two years suggests that the morphologic resemblance to T-cell lymphoma may reflect intrinsic biologic similarities.

**Diagnosis:** Hodgkin's disease, mixed cellularity type, simulating non-Hodgkin's immunoblastic lymphoma.

## CASE 17

**Contributor:** Patrick W. Riley, M.D.  
Reno, NV

**Tissue From:** Parotid gland, attached  
lymph nodes

**ACCESSION #25815**

**Clinical Abstract:** This 72-year-old male had a 3-month history of a lump in the right neck. The patient was otherwise healthy and denied weight loss. CT scan revealed several lobular densities down to the level of the hyoid bone. Physical examination revealed a firm indurated mass extending from the submandibular space posteriorly and superiorly to the angle of the mandible. No other adenopathy was noted.

**Gross Pathology:** A 26 gram parotid gland with attached lymph nodes had overall dimensions of 6.5 x 3.5 x 2.5 cm. The parotid gland measured 4.5 x 3.0 x 2.0 cm, and the largest lymph node measured up to 2.5 cm in greatest diameter.

**Discussion:** Lymph nodes are massively enlarged by a heterogeneous expansion of the interfollicular substance with some focal sparing of follicular structures. The mottled appearance is imparted by abundant epithelioid histiocytes. There are several neoplastic processes which can be difficult to distinguish, based on the dense interspersation of these variants of histiocytes. These include peripheral T-cell lymphoma (so-called lymphoepithelioid or "Lennert's" lymphoma (57), lymphoplasmacytic lymphoma (29), and mixed cellularity Hodgkin's disease (58). In this case, careful scrutiny at intermediate and high magnification reveals scattered atypical mononuclear cells and occasional diagnostic Reed-Sternberg cells. For some reason, in this variant of mixed cellularity Hodgkin's disease the neoplastic cells typically show less abundant cytoplasm and more basophilic nuclear features than is typical for Hodgkin's disease, rendering its distinction from non-Hodgkin's lymphomas, particularly lymphoepithelioid cell peripheral T-cell lymphoma, particularly difficult.

Again, immunostains are of great utility in recognizing this variant of Hodgkin's disease: the scattered neoplastic cells react strongly for CD30 and, in most cases, for CD15.

Interestingly, this variant form of mixed cellularity disease more often occurs in the elderly than other forms of Hodgkin's disease, and possibly in relation to this is clinically unfavorable (58).

Recent studies indicate that the tumor cells in this variant are almost always positive for (clonal) EBV genome (59).

**Diagnosis:** Hodgkin's disease, mixed cellularity type, epithelioid cell-rich variant.

## CASE 18

**Contributor:** Shelley Tepper, M.D.  
San Francisco, CA

**Tissue From:** Axillary mass

**ACCESSION #25446**

**Clinical Abstract:** This 78-year-old male presented with a six-month history of an enlarging left axillary mass. Past medical history was significant for a chronic dermatologic disease diagnosed as mycosis fungoides eighteen years earlier

**Gross Pathology:** A 6.0 x 3.0 cm portion of fat contained a well-circumscribed mass of firm white tissue. Areas of apparent necrosis were noted.

**Discussion:** This case was initially interpreted by several expert reviewers as aggressive non-Hodgkin's lymphoma, "probably T-immunoblastic type". It serves to demonstrate the great morphologic diversity within nodular sclerosing Hodgkin's disease, and how some morphologic variants of this process can resemble high grade non-Hodgkin's lymphoma, or even metastatic malignancy!

At low magnification one sees expanses of large neoplastic cells growing as rather continuous "syncytial" cellular proliferations. At this magnification, one can appreciate a sclerosing response emanating from capsule and trabecula, at least focally. Only with careful scrutiny can one identify areas in which the large neoplastic cells are scattered individually. Here, one can recognize tumor cells as lacunar variants of nodular sclerosing Hodgkin's disease, as described and illustrated in the original Lukes-Butler-Hicks classification of 1966 (60).

Dr. Lukes was familiar with the protean morphologic manifestations of nodular sclerosing Hodgkin's disease, and alluded informally to a "sarcomatous variant". In more recent times, the Stanford group coined the term "syncytial variant" for this simulator of high grade non-Hodgkin's lymphomas and metastases (61). In fact, so completely can this variant simulate metastatic malignancy that subsequently a publication from Stanford has described two cases which were initially mistaken to be syncytial variant Hodgkin's disease, but instead turned out to be metastatic carcinoma (62)!

Again, immunostains are of great value nowadays in sorting out this difficult differential diagnosis. In this case, the tumor cells strongly express both CD30 and CD15. Of course, they are negative for epithelial markers (cytokeratin) and melanoma markers (S100 protein).

**Diagnosis:** Hodgkin's disease, nodular sclerosis type, aggressive histologic variant, simulating (non-Hodgkin's) large cell lymphoma.

## CASE 19

**Contributor:** Mel Anderson, M.D.  
Alhambra, CA

**Tissue From:** Left neck mass

**ACCESSION #**23291

**Clinical Abstract:** This 8-year-old female presented with a four month history of a mass in her left neck and recent onset of a sore throat. A soft, bulging parapharyngeal mass was found pushing the left tonsil forward. There was also a 3.0 cm node palpable in the upper posterior cervical chain, and anterior to this a 1.0 cm mobile node. Two courses of antibiotics failed to produce improvement. Labs: WBCs 9,300, segs 58%, bands 2%, lymphs 34%, monos 4%, eosinophils 2%, RBC 4.85, hemoglobin 13.4, hematocrit 39.2.

**Gross Pathology:** A large, soft, encapsulated lymph node was 3.5 x 2.5 x 1.5 cm. It had a uniform glistening tan, bulging cut surface without mottling or caseation. Two similar nodes were 2.0 x 1.4 x 1.3 cm and 0.8 x 0.6 x 0.4 cm.

**Discussion:** Slides of this cervical lymph node show features classic for lymphocyte predominant Hodgkin's disease of the nodular variant (nodular L & H type of the original Lukes-Butler-Hicks classification). There is focal preservation of intact nodal elements, but most of the lymph node is expanded by a mixture of abnormal, mottled nodules and peculiar large follicles which Lennert described as "progressively transformed germinal centers." These consist of expanded mantle zones surrounding large, irregularly outlined germinal centers. High magnification examination of the mottled nodules discloses scattered L & H variant Reed-Sternberg cells, as well as dispersed and clustered epithelioid histiocytes. Paraffin immunostains are useful in confirming the morphologic impressions. CD20 staining highlights the scattered L & H cells which stain strongly for this antigen. Because the cells are surrounded by a collarette of T-cells they stand out by virtue of their non-staining "halos" (63).

In the original 1966 classification, Lukes, Butler and Hicks emphasized the extremely favorable clinical behavior of this type of Hodgkin's disease (60). However, their observation was immediately deemphasized and obscured in the simplified four-part "Rye modification" in deference to the wishes of the clinicians, who wanted a simpler system (64). However, in 1979 a group of Europeans, Poppema, Kaiserling and Lennert rediscovered the nodular variant as "nodular paragranuloma" (65). On the basis of the association with progressively transformed germinal centers, as well as some very basic immunostaining, they proposed that this was a B-cell process unrelated to other forms of Hodgkin's disease. Furthermore, they observed that clinical manifestations and age distribution also serve to separate this process from other types of Hodgkin's disease (66).

These observations have been confirmed many times over in the ensuing years with ever increasingly sophisticated techniques. Today we sharply demarcate lymphocyte predominant Hodgkin's

disease as a special form of B-cell proliferation. In general, it is extremely favorable and usually early stage. However, occasionally it achieves advanced stage, and in this situation it is difficult to distinguish from low-grade non-Hodgkin's lymphoma in extranodal samples (67). It is interesting that this patient presented with a mass in Waldeyer's ring tissues. Two of the cases reported in Dr. Siebert's recent study consisted of (B-cell) lymphocyte predominant Hodgkin's disease presenting in the nasopharynx (67).

**Diagnosis:** Hodgkin's disease, lymphocyte predominance type (nodular variant, B-cell phenotype), involving nasopharynx, and cervical lymph node.

## CASE 20

**Contributor:** Richard Clatch, M.D.  
Oak Lawn, IL

**Tissue From:** Axillary lymph nodes

**ACCESSION #27706**

**Clinical Abstract:** This 36 year old man had asymptomatic gradual enlargement over 6 years of axillary lymph nodes.

**Gross Pathology:** A mass of axillary fat was received measuring 12 x 7 x 7 cm. This contained numerous discrete lymph nodes, ranging in size from 0.2 to 6 cm in dimension.

**Discussion:** Microscopic findings in case 20 are almost identical to those from Case 19, except that there are a few nodules which contain a high proportion of large lymphoid cells with features overlapping those of L & H variant Reed-Sternberg cells and conventional immunoblasts. This reminds us of the capacity for the extremely indolent lymphocyte predominant process to transform or progress into more aggressive lymphomatous disease. There are at least three variations on this theme.

In the first place, when one receives a lymph node which is massively enlarged by lymphocyte predominant Hodgkin's disease, thorough sampling will often disclose foci of nodular expansion by a more aggressive-appearing process, as is encountered here. Generally, there seems to be no implication regarding more aggressive biologic potential in such cases.

Second, in a significant minority of cases straightforward transformation to diffuse large cell lymphoma, usually of B-cell phenotype, is encountered (68).

Finally, in some cases there is a more aggressive histology which corresponds to an increased proportion of L & H variant cells growing in a diffuse growth pattern throughout the involved lymph node. This was described early on as "mixed cellularity Hodgkin's disease arising in nodular lymphocyte predominance type" (69). Others have more recently described this phenomenon as "transitional" progression of lymphocyte predominant Hodgkin's disease (70). Interestingly, there are conflicting data as to the clonal versus polyclonal nature of the large cells in both the

conventional histologic presentation of lymphocyte predominant Hodgkin's disease and in the "transitional" phase of this process (71,72). Everyone agrees at least that, in those cases which are morphologically straightforward large B-cell lymphomas arising out of lymphocyte predominant Hodgkin's disease, the process is clonal!

Needless to say, the distinction between "T-cell rich B-cell lymphoma" and aggressive histologic variant forms of lymphocyte predominant Hodgkin's disease is highly controversial (71-73).

**Diagnosis:** Hodgkin's disease, lymphocyte predominance type (nodular variant, B-cell phenotype), showing focal progression to large cell lymphoma.

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