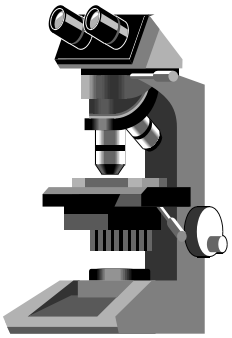
CALIFORNIA
TUMOR TISSUE REGISTRY

# "HEMATOLYMPHOID PATHOLOGY"

Minutes – Subscription B

September 2015



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**September B 2015**

## FILE DIAGNOSES

**CTTR Subscription B September 2015**

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Case 9: **SPLENIC MARGINAL ZONE B-CELL LYMPHOMA**

Case 10: **LYMPHOMA, (MALToma),** Thyroid

## CASE #1: Accession No. 31833

## DIAGNOSIS: STROMAL-RICH VARIANT OF HYALINE VASCULAR CASTLEMAN DISEASE, Retroperitoneal

Diagnoses submitted in decreasing order of frequency:

Castleman disease, hyaline vascular type
Castleman disease
Follicular dendritic cell tumor arising in a background of Castleman disease
Castleman (hyaline vascular variant) and follicular dendritic cell sarcoma
Follicular dendritic cell sarcoma associated with Castleman disease
Follicular dendritic cell sarcoma
Intermediate dendritic cell tumor
Inflammatory pseudotumor
Angioimmunoblastic T-cell lymphoma

### Discussion

**Stromal Rich Variant of Hyaline - Vascular Castleman Disease**

Histologic sections of this mass show many lymphoid follicles with regressive germinal centers. Many follicles show expanded mantle zones with some onion-skinning pattern. The lymphoid follicles are penetrated by small capillaries with hyalinized walls. In addition there is prominent interfollicular hypervascularity with proliferation of spindled and ovoid cells in a storiform pattern forming fascicles. These cells have plump eosinophilic cytoplasm and indistinct cell borders. Nuclei are elongated with vesicular or finely granular chromatin and occasional distinct nucleoli. The spindle cells show mild cytologic atypia with a low mitotic rate (0-1/HPF). Immunohistochemical stains helped characterize the immunophenotype of the interfollicular spindle cells. The residual follicles showed mixed T-cells and B-cells with no overt abnormality. A possible composite tumor with follicular dendritic cell component was considered. The final diagnosis is Stromal-Rich Variant of Hyaline-Vascular Castleman Disease.

Castleman Disease, aka angiofollicular hyperplasia, giant lymph node hyperplasia, is a rare lyphoproliferative disorder of unknown etiology. The disease may be localized or less often multicentric. Hyaline - vascular type is a localized type seen more commonly in young patients who present with an isolated mass, most often in the mediastinum. Patients are frequently asymptomatic. Histologic features include small lymphoid follicles with concentric layering of lymphocytes, hyaline deposits in germinal centers, transfixing collagen-ensheathed arterioles ("lollipop" sign) and interfollicular vascular hyperplasia.

The **Stroma-Rich variant of Castleman Disease of hyaline-vascular type** (CDHV) is a newly identified entity that shows overgrowth of a variety of stromal cells. This condition encompasses proliferation of small vessels and myoid cells. Its characteristics include an asymptomatic, solitary nodule that predominantly develops in the retroperitoneum, and may be of a hyperplastic nature. Patients are cured by simple excision.

**Plasma cell type** is associated with HHV8, seen in older patients and is symptomatic. Microscopic features include interfollicular sheets of plasma cells. No hyaline vascular changes are present.

## CASE #2: Accession No. 31458

## DIAGNOSIS: EXTRAMEDULLARY PLASMACYTOMA, Lymph node neck

Diagnoses submitted in decreasing order of frequency:

Plasma cell myeloma
Plasmacytoma
Plasmacytoid lymphoma

Lymphoplasmacytic lymphoma
Plasmablastic large B-cell lymphoma, likely arising in HHV8 associated multicentric Castleman disease
Large B-cell lymphoma arising in multicentric Castleman disease
Marginal zone B cell lymphoma
Marginal zone lymphoma with plasma cell differentiation
Malignant lymphoma
Marginal zone B cell lymphoma
MALT lymphoma

**Discussion**
**Extramedullary Plasmacytoma**
The lymph node shows diffuse replacement of normal architecture by a plasma cell proliferation. A few residual follicles are present. Primary lymph node plasmacytomas (PLNPs) are rare malignant neoplasms and represent 2% of all extramedullary plasmacytomas. PLNPs can be diagnosed only after exclusion of metastatic multiple myeloma and metastatic upper respiratory tract plasmacytomas. 33 PLNPs have been described, primarily as single case reports, 7 of them arising in Castleman disease (CD), plasma cell type. The PLNPs not associated with CD show a male preponderance, with an average age of 56 years (range, 10-72 years). The tumors usually manifest as a localized neck mass. Lymph nodes may be large and frequently are associated with serum monoclonal proteins usually of IgG kappa type. Most patients present with localized disease at initial diagnosis and are cured after local excision or radiation therapy. Only a minority of PLNPs show plasmablastic morphology which can make distinction from immunoblastic lymphoma or other poorly differentiated hematopoietic and non-hematopoietic neoplasms difficult.

## CASE #3: Accession No. 29295

## DIAGNOSIS: INFECTIOUS MONONUCLEOSIS, Tonsils

Diagnoses submitted in decreasing order of frequency:

Infectious mononucleosis
EBV infection
Atypical lymphoid infection, rule out mononucleosis
Viral associated lymphadenopathy
Malignant neoplasm (Large cell lymphoma versus lymphoepitheliioma)
Malignant lymphoma
Hodgkin lymphoma
Kikuchi-Fujimoto disease
Acute tonsillitis, candida organisms

**Discussion**
**Infectious Mononucleosis**
Classic presentation of Epstein Barr Virus (EBV) in young adults is fever, sore throat, lymphadenopathy and malaise. Tonsillar enlargement is common. Massive enlargement may result in airway obstruction. The term kissing tonsils is used to describe extreme enlargement of both tonsils in patients with EBV infectious mononucleosis. Diagnosis is usually clinical and confirmed by blood tests. Tonsils and nodes show marked lymphoid hyperplasia and sinusoidal infiltration by immunoblasts that often have atypia and Reed-Sternberg cell features. There are polymorphous inflammatory cells. Early infections may show a prominent monocytoid B cell reaction. Necrosis is not prominent unless the patient is immunocompromised. In this patient a peripheral smear showed atypical lymphocytes; Monospot test and EBV tests were also positive.

## CASE #4: Accession No. 31078

## DIAGNOSIS: FOLLICULAR LYMPHOMA, GRADE 3A WITH PLASMACYTIC DIFFERENTIATION, Spleen

Diagnoses submitted in decreasing order of frequency:

Splenic marginal zone lymphoma
Lymphoproliferative disorder, favor marginal zone lymphoma
Primary splenic lymphoma
Follicular lymphoma
Lymphoma
Chronic myeloid leukemia
Primary myelofibrosis
Metastatic carcinoma
Malignant lymphoma
Hairy cell lymphoma
Hemangioma
Littoral cell hemangioma
Low grade B-cell lymphoma favor follicular lymphoma
Congestive splenomegaly hemolytic
Myeloid neoplasm

### Discussion

**Follicular Lymphoma**

The spleen shows expansion of the white pulp with large follicles and nodules in the interfollicular areas, mostly of CD20 positive B-cells. The neoplastic cells expressed bcl-2 in the interfollicular areas and bcl-6 within the follicles. The neoplastic follicles expressed IgD. There was marked restriction of plasma cells with lambda light chain immunoglobulin. The neoplastic cells were negative for, CD43, cyclin D1 and CD5.

**Follicular Hyperplasia**, the reactive follicular hyperplasia may be focal or diffuse. In adults etiologic factors include chronic or systemic infections and autoimmune diseases.

The diagnosis and classification of small B-cell lympho-proliferative disorders in splenectomy specimens is frequently challenging. The differential would include follicular hyperplasia and splenic marginal zone lymphoma. Morphologic features and ancillary testing is essential.

## CASE NO #5: Accession No. 31663

## DIAGNOSIS: FOLLICULAR LYMPHOMA, (WHO GRADE 2, NODULAR LYMPHOMA), Left inguinal

Diagnoses submitted in decreasing order of frequency:

Follicular lymphoma
Follicle center cell lymphoma, nodular and diffuse
Grade 1, 1-2, 2/3 follicular lymphoma
Malignant lymphoma, small cell
Diffuse large B cell lymphoma
B-cell follicular lymphoma
Large cell lymphoma

## Discussion

**Follicular Lymphoma (WHO Grade 2, Nodular Lymphoma)**, the lymph node shows effacement of nodal architecture by a nodular proliferation of back-to-back follicles of similar size and shape. The neoplastic follicles contain approximately 10 centroblasts per HPF. No areas of diffuse or large cell proliferation are present. The cells of the neoplastic follicles stain for CD 20, CD 10, BCL-2, and BCL-6. CD 21 highlighted the faint dendritic meshwork within the follicles. Cyclin D1 is negative.

Follicular Lymphomas (FL) are the most common form of non-Hodgkin Lymphoma in the US, and are indolent tumors. Middle aged and older adults are usually affected. These tumors are graded 1-3 (low to high grade). The cells of origin are the follicular center B cells. 90% cases show a t(14;18)(q32;q21) with bcl 2 overexpression and inhibition of follicular center cell apoptosis. FL is graded according to the number of centroblasts per high-power field (hpf), as follows: Grade 1 – 0-5 centroblasts/HPF, Grade 2 – 6-15 centroblasts /HPF, Grade 3 - >15 centroblasts/HPF.

Differential diagnosis includes reactive follicular hyperplasia. Reactive follicles are frequently irregular, surrounded by discrete mantles, show polarization and numerous tingible body macrophages.

## CASE #6: Accession No. 31712

## DIAGNOSIS: HISTIOCYTIC SARCOMA, Left groin

Diagnoses submitted in decreasing order of frequency:

Rosai Dorfman disease
Histiocytic sarcoma
Langerhans cell histiocytosis
Hodgkin lymphoma
Anaplastic large cell lymphoma
Storage disease
Infectious ?
IgG4 related disease
Eldheim-Chester disease
Dendritic cell sarcoma
Mixed cellularity Hodgkin lymphoma with extensive proliferation of histiocytes
Malignant mesenchymal sarcoma

## Discussion

**Histiocytic sarcoma**

Sections show a large mass consisting of a diffuse histiocytic proliferation of large histiocytic cells intermixed with neutrophils, plasma cells, eosinophils and lymphocytes. Multi-lobated nuclei and mitoses are present. The histiocytes are positive for CD 68and Cd 163, while T and B lymphocytes are positive for CD 3 and CD 20 respectively. Proliferation index varied from 5% to focally as high as 25% on Ki 67 immunostain.

Histiocytic sarcoma (HS) is a very rare and aggressive non - Langerhans histiocyte disorder of unknown etiology, with only a few hundred cases having been reported. It has been described in adults, but all ages may be affected. Patients usually present with B symptoms (weight loss, fever and sweats). Previously other hematopoietic malignancies, particularly T cell neoplasias have been diagnosed as HS. Presentation is usually extranodal. CD 163 a recently characterized hemoglobin scavenger receptor, is a specific histiocytic marker and is important in establishing the diagnosis of HS. Non-Langerhans histiocytoses are thought to be derived from the monocyte-macrophage lineage, and are CD 68 and lysozyme positive.

HS can occur as an isolated disease or in the context of other hematologic neoplasms, such as follicular lymphoma, myelodysplasia, or acute lymphoblastic leukemia. When HS occurs in the context of another hematologic malignancy, the two entities are often clonally related. The tumors are generally composed of sheets of large epithelioid cells with abundant eosinophilic cytoplasm, oval to irregular nuclei, vesicular chromatin, and large nucleoli. Necrosis, binucleated

cells and tumor giant cells may be seen. Nearly all tumors show a striking inflammatory infiltrate, most often of neutrophils or lymphocytes. Erythrophagocytosis may be present. Storage diseases, reactive histiocytosis, metastatic carcinoma, metastatic melanoma, and large cell non-Hodgkin lymphomas should be excluded by immunohistochemistry.

## CASE #7: Accession No. 31652

## DIAGNOSIS: NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA, Lymph Node

Diagnoses submitted in decreasing order of frequency:

Hodgkin lymphoma, nodular lymphocyte predominance
Lymphocyte-rich classical Hodgkin lymphoma
Hodgkin lymphoma, nodular sclerosing
B-cell lymphoma (Hodgkin type possible)
B-cell lymphoma
T-cell rich B-cell lymphoma

### Discussion

**Nodular Lymphocyte Predominant Hodkgin Lymphoma**

This patient with a remote history on "non-Hodgkin Lymphoma" presented with anemia and axillary lymphadenopathy. The biopsy shows effaced nodal architecture by a nodular infiltrate consisting predominantly of small lymphocytes and histiocytes, and intermingled large cells with large multi-lobated "popcorn" nuclei. Rare Reed-Sternberg appearing cells are also present. The large cells are positive for CD 20, PAX-5, CD 45 and negative for CD 15 and CD 30. Cells immunostaining as T cells showed rosetting around the large atypical cells. These findings favor a Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL).

NLPHL is a rare subtype of Hodgkin Lymphoma (HL) with unique clinicopathologic features (5% of HL cases). The estimated incidence of NLPHL is ~ 1.5 per 1,000,00 people per year.

The hallmark histologic feature is the presence of malignant LP cells, unusual $CD20^{+}CD15^{-}CD30^{-}$ variants of Reed-Sternberg cells, embedded within a nodular pattern of infiltrating lymphocytes. Because of their microscopic appearance and increased number of nucleoli, a more descriptive term, "popcorn cells," has been used. At least 1 nodule containing a mixture of LP cells and small B cells is required for a diagnosis of NLPHL. Unlike malignant Reed-Sternberg cells in classical HL (cHL), LP cells lack expression of CD15, CD30, and Epstein-Barr virus. A typical B-cell phenotype is seen. Compared with classical HL, NLPHL shows a slightly older median age at presentation (30–40 years), greater male predominance and usually peripheral nodal involvement. The differential diagnosis includes progressive transformation of germinal centers, lymphocyte-rich classical HL, and T-cell/histiocyte-rich large B-cell lymphoma, the latter of which may share a common biologic relationship. The vast majority of patients present with limited stage disease, the standard treatment for which is radiotherapy. Because consistent CD20 expression represents a hallmark of NLPHL, studies are evaluating the role of the anti-CD20 antibody rituximab. Response rates to primary therapy exceed 90%, although relapses are common and may occur years after the initial diagnosis. Secondary malignancies, particularly non-Hodgkin lymphoma, may also occur at a frequency similar to that of relapsed NLPHL.

## CASE #8: Accession No. 31562

## DIAGNOSIS: CLASSICAL HODGKIN LYMPHOMA, Nodular sclerosis type

Diagnoses submitted in decreasing order of frequency:

Classical Hodgkin lymphoma

Classical Hodgkin Lymphoma, Nodular sclerosis Type
Lymphoctye-depleted classical Hodgkin lymphoma
Nodular sclerosis syncytial variant
Classical Hodgkin lymphoma arising on a background of sclerosing Hashimoto thyroiditis
Hodgkin lymphoma, lymphocyte-depleted
Anaplastic lymphoma
Large cell lymphoma

## Discussion

**Classical Hodgkin Lymphoma (cHL), Nodular Sclerosis Type**, sections show a cellular neoplasm with focal necrosis, replacing thyroid tissue. The neoplasm is composed of sheets of lymphoid cells with large nodules divided by collagenous fibrous septae. Scattered dark mummified cells and many large uninucleate and multinucleated cells with prominent eosinophilic nucleoli are present. Background shows many small lymphocytes and scattered plasma cells. Immunostains showed the large cells to be CD 15, CD 30, EBV LMP-1 and MUM1 positive and negative for CD 20, Pan CK, CD 45 and CD 3. The surrounding thyroid tissue shows Hurthle cell change.

Hodgkin Lymphoma comprises approximately 11% of all lymphomas in western countries and has a bimodal age distribution, with a first peak in young adults and a second peak around 59 years of age. HL is currently classified as two distinct disease entities: nodular lymphocyte-predominant HL (NLPHL) and classical Hodgkin lymphoma (cHL). The characteristic Hodgkin and Reed-Sternberg (HRS) cells in cHL and the lymphocytic and histiocytic (L and H) cells in NLPHL, account for only 1% to 5% of the entire tumor mass and grow in a unique tumor microenvironment composed of many different cell types, including T cells, B cells, macrophages, neutrophils, eosinophils, plasma cells, mast cells, and fibroblasts.

cHL is further divided into four histologic subtypes: nodular-sclerosis classical Hodgkin lymphoma (NSCHL), lymphocyte-rich classical Hodgkin lymphoma (LRCHL), mixed-cellularity classical Hodgkin lymphoma (MCCHL), and lymphocyte-depletion classical Hodgkin lymphoma (LDCHL) Although this classification is mainly based on histopathology, recent studies have demonstrated that these entities are biologically different, with different clinical behaviour.

NSCHL is the most frequent subtype of CHL in USA, where it corresponds to 75–80% of all HL cases; however, the incidence of these subtypes varies greatly among other geographical areas. It is characterized by: sclerosis (broad collagen bands), lacunar cells, and nodular pattern. Some neoplastic cells appear to be “mummified” because of apoptotic changes.

Differential diagnosis includes: Anaplastic Large Cell Lymphoma (T cell markers are positive), Primary Mediastinal (thymic) Large B cell lymphoma, Carcinoma

## CASE # 9: Accession No. 29649

## DIAGNOSIS: SPLENIC MARGINAL ZONE B-CELL LYMPHOMA,

Diagnoses submitted in decreasing order of frequency:

Splenic Marginal zone lymphoma
Splenic diffuse red pulp small B cell lymphoma
Primary splenic lymphoma
Lymphoma
High grade B cell lymphoma
Lymphoplasmacytic lymphoma
Chronic lymphocytic leukemia
Diffuse large B cell lymphoma
Hairy cell lymphoma, leukemia

## Discussion

**Splenic Marginal Zone B Cell Lymphoma**

Sections show splenic tissue with a markedly congested red pulp, and a nodular and diffuse white pulp infiltrate with an absence of normal follicles. The lymphoid infiltrate is massive and involves primarily white pulp and extends into the red pulp in many areas. The neoplastic lymphoid cells are intermediate in size an exhibit variable degrees of plasmacytoid differentiation. Some of the lymphoid cells are larger, with vesicular chromatin and a prominent nucleolus. The presence of immunoblast-like cells suggests the possibility of a more aggressive course. Special studies confirm the diagnosis of a B cell lymphoma with lambda light chain restriction. The negative CD 10, CD 5, CD 23 and Cyclin D1 in the neoplastic B-lymphoid cells rule out follicular lymphoma and mantle cell lymphoma.

Splenic marginal zone lymphoma (SMZL) is a specific low-grade small B-cell lymphoma. Characteristic features are splenomegaly, moderate lymphocytosis with villous morphology, intrasinusoidal pattern of involvement of various organs, especially bone marrow, and a relative indolent course. Tumor progression with increase of blastic forms and aggressive behavior are observed in a minority of patients. Autoimmune phenomena, such as primary biliary cirrhosis, rheumatoid arthritis, immune thrombocytopenia, appearance of lupus anticoagulant, and autoimmune hemolytic anemia, represent the most frequent associated conditions.

Histologically, the splenic architecture can be retained in initial phases. Hyperplastic white pulp shows expansion of marginal zones with frequent merging and coalescence. Residual reactive follicles with germinal centers can be occasionally noted. Germinal centers can be frequently involuted. Neoplastic cells extend from the marginal zone to the red pulp with variable involvement. The sinuses are filled up with neoplastic cells morphologically identical to the cells seen in the marginal zones. Cytologically, the neoplastic cells are medium sized with a round or slightly irregular nucleus, clumped chromatin, frequent small nucleolus, and a moderate amount of cytoplasm with distinct borders sometimes of villous appearance.

## CASE #10: Accession No. 29039

## DIAGNOSIS: LYMPHOMA, (MALToma), Thyroid

Diagnoses submitted in decreasing order of frequency:

Marginal zone lymphoma (MALT lymphoma)
Marginal zone lymphoma
Marginal zone lymphoma with plasmacytoid differentiation
Lymphoplasmacytic lymphoma
Malignant B-cell lymphoma
Plasmacytoma
Plasmacytoid lymphoma
Hodgkin Lymphoma

**Discussion**

**MALT Lymphoma with Plasma Cell Differentiation**

Primary thyroid lymphomas constitute up to 5% of all thyroid malignancies and can be divided into non-Hodgkin lymphomas (NHLs) of B- and T-cell types, as well as Hodgkin lymphomas. Mucosa-associated lymphoid tissue (MALT) lymphomas are a relatively recently recognized subset of B-cell NHLs, and are listed as extranodal marginal zone lymphomas. Extranodal marginal zone B-cell lymphomas mucosa-associated lymphoid tissue (MALT type) frequently occur in the mucosa of the gastrointestinal tract. However, they may also occur in other sites including the thyroid. Primary involvement of the thyroid is rare, usually arising in the setting of chronic lymphocytic thyroiditis (Hashimoto disease) in older patients. Clinically, patients present with an enlarging neck mass causing respiratory difficulty. Thyroid MALT lymphomas are characterized by an indolent course and tend to remain localized.

The neoplastic cells are characterized by an infiltrate of "centrocyte-like" cells (small- to medium-sized lymphocytes with abundant cytoplasm and irregularly shaped nuclei), but scattered transformed blasts (large cells) also are present. A characteristic feature is the presence of lymphoepithelial lesions. Tumors express pan-B antigens (CD19, CD20, CD22,

CD79a), and show monotypic immunoglobulin expression with light-chain restriction. CD5 expression may be associated with a more aggressive clinical course.

## References/Suggested Reading:


1. Angiomyoid proliferative lesion: an unusual stroma-rich variant of Castleman's disease of hyaline-vascular type. *Viscows Arch* 2002; Oct 44(4):400-5.
2. Primary lymph node plasmacytomas (plasmacytic lymphomas). *Am J of Clin Pathol*; 2001: Jan, 115(1):119-26.
3. Infectious mononucleosis. The spectrum of morphologic changes simulating lymphoma in lymph nodes and tonsils. *Am J Surg Pathol* 1987; Feb 11(2):122-32.
4. Follicular lymphoma of the spleen. Multiparameter analysis of 16 cases. *Am J Clin Pathol* 2009; May, 131(5):656-62. Howard, M, Dufresne S, et al.
5 Extranodal histiocytic sarcoma: clinicopathologic analysis of 14 cases of a rare epithelioid malignancy. *Am J. Pathol* 2004; 28: 1133-44. Hornick JL, Jaffe E, et al.
6 Hodgkin lymphoma: an update on its biology with new insights into classification. *Clin lymphoma myeloma* 2009; Jun 9(3):206-16. doi: 10.3816/CLM.2009.n.042. Mani H and Jaffe ES.
7 Hodgkin's lymphoma: the pathologist's viewpoint. J Clin Pathol 2002; Mar;55(3):162-176. Pileri, S.A., Ascani S, et al.
8 Splenic marginal zone lymphoma. *Blood* 2003, Apr 1; 101(7/2464-72). Epub 2002; review. Franco, V, Florena A, et al.
9 Maltoma of thyroid: A rare thyroid tumour. *Case Rep Olotaryngol* 2013; 740241 doi:10.1155/2013/740241. Epub 2013; Feb 11. Latheef, N, Shenoy V, et al.
10 Malignant lymphoma of the thyroid gland: a clinicopathologic study of 108 cases. *Am J Surg Pathol* 2000; May; 24(5):6223-39. Derringer GA, Thompson LD, et al.