

Bone Marrow Evaluation for Lymphoma

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Indications

- One of the most common indications for a bone marrow biopsy is to evaluate for malignant lymphoma.
- BM Bx. routinely performed after patients have been diagnosed with Lymphoma for Stage and extent of disease.
- Also performed during course of the disease to determine response to therapy or to evaluate for progression of disease.

Rosenberg, Boiron et al 1971; Bartl, Frisch et al 1984

Indications...

Ponzoni and Li 1994....

- Occasionally Bone marrow biopsy are performed to make an initial diagnosis of Lymphoma in suspicious clinical settings, e.g isolated splenomegaly or inaccessible lymphadenopathy, unexplained peripheral cytopenia, FUO
- Lymphomas are diagnosed on routine BM biopsies when lymphomas are not clinically suspected.

Incidence of BM involvement

- Presence of Lymphoma in BM is regarded as dissemination and represents Stage IV disease.
- Overall incidence of BM involvement by Lymphoma is 35-50%.
- Considerable variability of involvement within Lymphoma subtypes e.g FL and SLL involve BM in up to 60% to 85% of cases respectively

Unilateral vs. Bilateral

- Bruning, Bloomfield et al. 1975. & Coller, Chabner et al. 1977.

Studies revealed that the yield of lymphoma detection is significantly higher when Bilateral in contrast to unilateral posterior Iliac crest trephine biopsies are performed.

Biopsy Size Recommendation

Mckenna and Hernandez 1988

Study revealed that trephine biopsy Size also correlates with the frequency with which lymphoma is identified in the specimens, therefore each biopsy is recommended be at least 2cm long. In addition, multiple levels representative of each paraffin embedded tissue should be examined

Challenges

- Even though pathologist commonly evaluate BM biopsies for lymphoma, often it is very challenging for following reasons
 - Benign Lymphoid aggregates are commonly encountered in older patients (after 50y of age, with significance unknown) & in pt.'s with autoimmune disorders e.g RA, SLE, AIHA, ITP & they can be exceedingly difficult to distinguish from malignant lymphoma even with the help of ancillary techniques.

Deverell et al. 1997; Theile, Zirbes et al. 1999

Challenges....

In patients with a prior diagnosis of lymphoma, assessment is complicated by the fact that lymphoma in the marrow may differ from the original extramedullary lesion, in that the marrow frequently exhibits a more indolent or low grade morphology.

(Crisan and Mattson 1995; Discordant morphologic features in bone marrow involvement by malignant lymphomas: use of gene rearrangement patterns for diagnosis.)

Conlan, Bast et al. 1990

- 20-40% of cases show discordant morphology with a different morphologic appearance of lymphoma in the bone marrow compared to extramedullary site.
- Follicular Lymphomas and Large B-cell lymphomas are the most common lymphomas to exhibit discordant morphology with less aggressive component usually present in BM.
- Reasons of Discrepant morphology not well understood; may be difference in the microenvironment of BM
- Better remission and longer survival in DLBCL with discordant involvement than concordant disease.

Challenges....

When a lymphoid lesion is determined to be malignant, classification of lymphoma must be addressed. Usually straight forward in pts. with a previous diagnosis of lymphoma, but determining the lymphoma subtype is pts. without prior diagnosis may be difficult and challenging and requires extensive knowledge of various lymphoma subtypes and appropriate use of ancillary studies.

Reliability of lymphoma classification in bone marrow trephines.

- Buhr, and Langer, et al. 2002
 - Retrospectively compared lymphoma diagnoses, rendered exclusively on bone marrow trephines without knowledge of lymph node diagnosis in 124 patients, with the results of the reference centers that had reviewed lymph node (n = 90) or extra nodal biopsies (n = 34). The overall concordance rate was higher than 84% . We conclude from our results that bone marrow trephines are a reliable tool, not only for establishing bone marrow infiltration, but also for the subtyping of lymphomas.

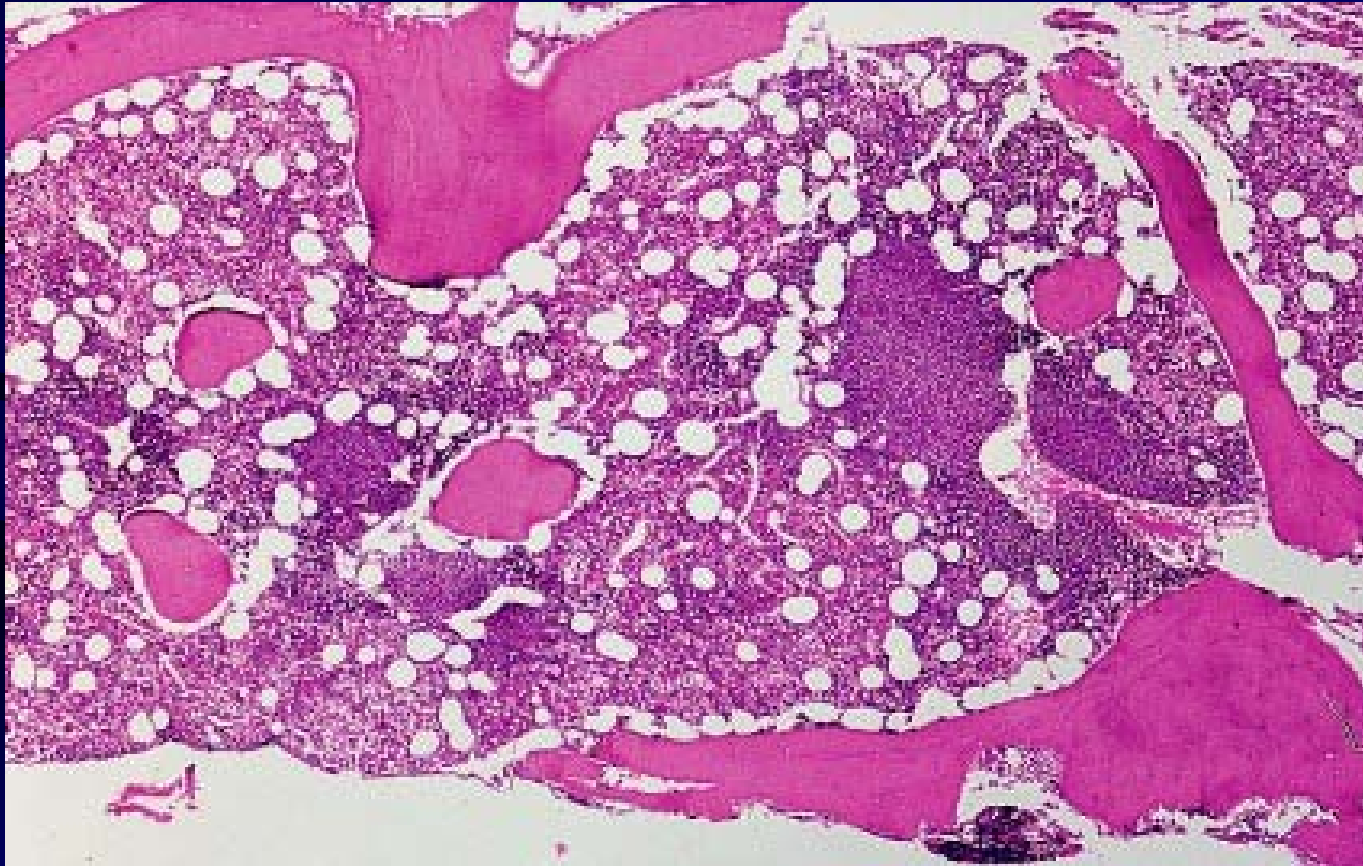
Distinction of Benign Lymphoid Infiltrates from Malignant Lymphoma

- Morphology
- Immunohistochemistry
- Flowcytometry
- Molecular genetics

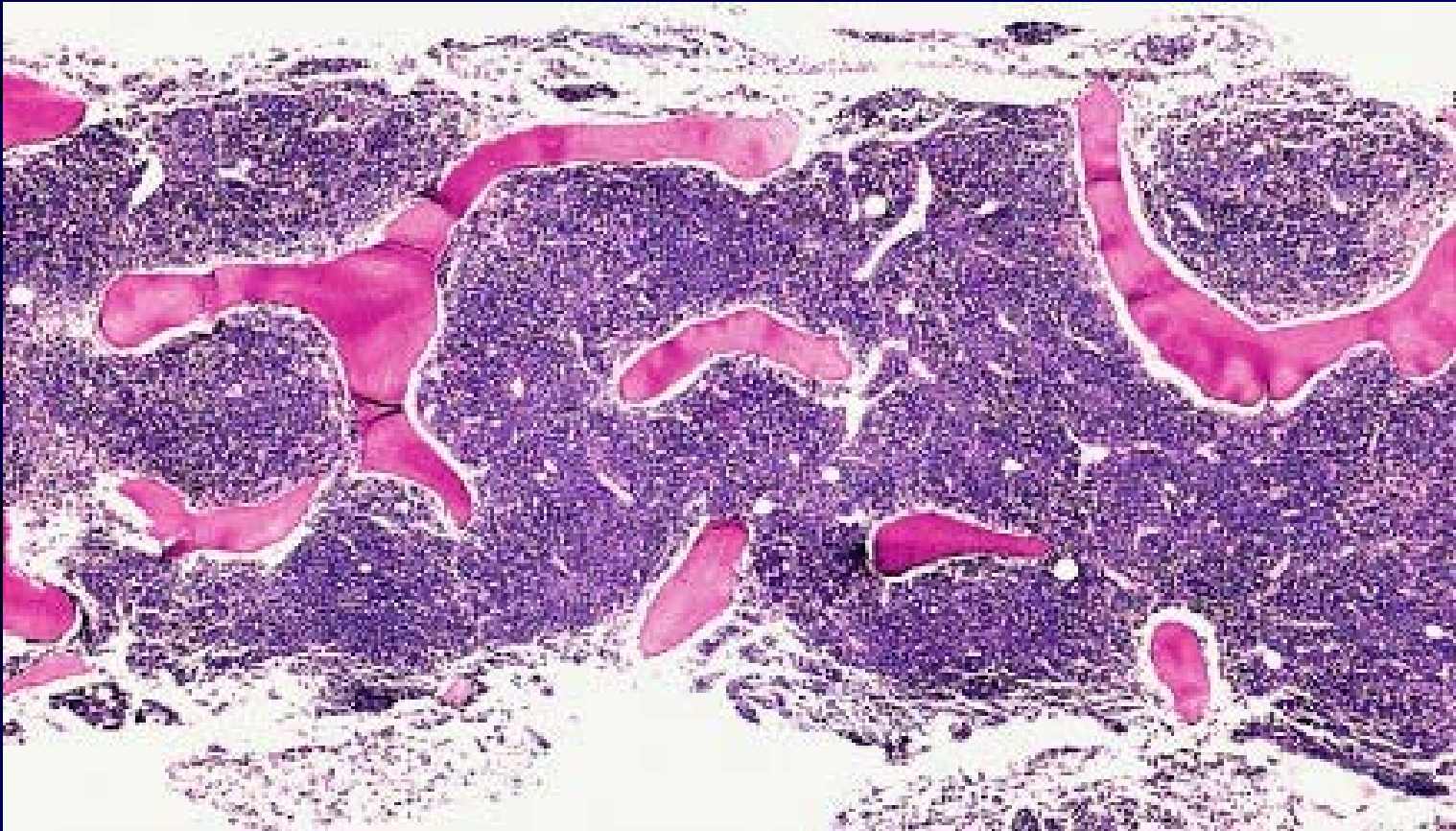
Pattern of Involvement

- One or combination of Five different Patterns
 - Focal Random
 - Focal Paratrabecular
 - Interstitial
 - Diffuse
 - Intrasinusoidal

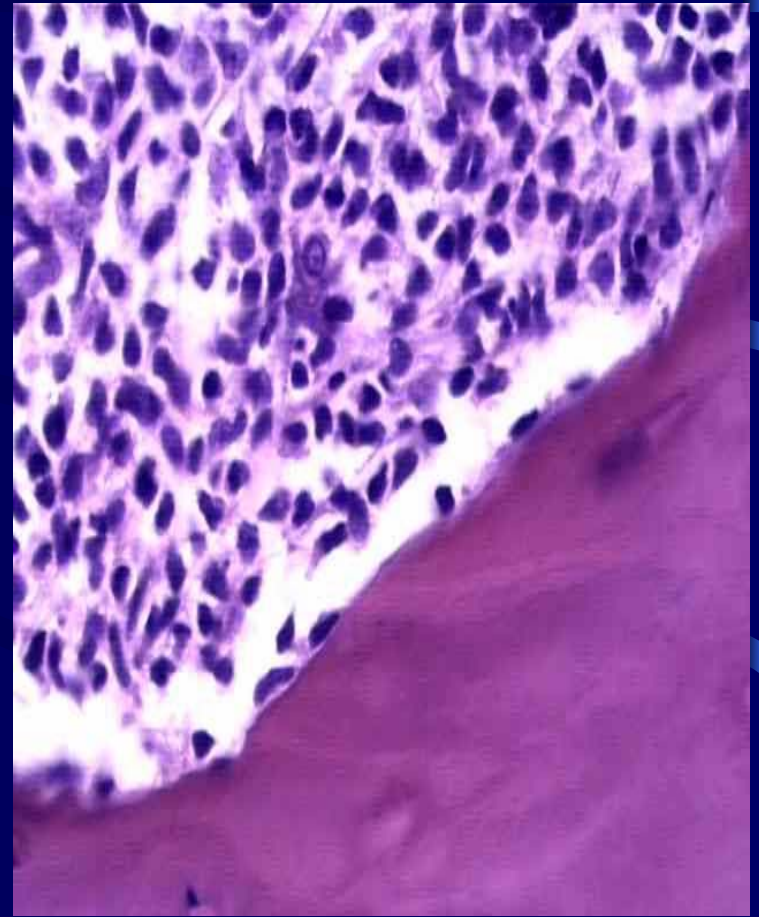
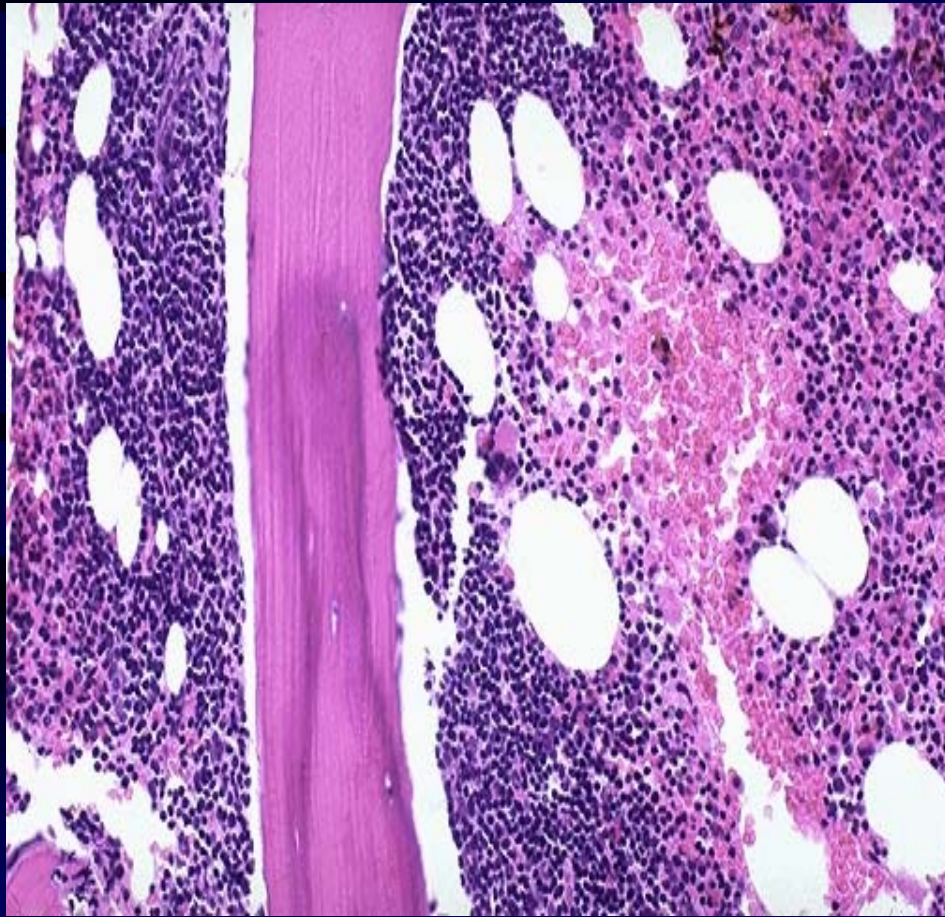
Focal Random



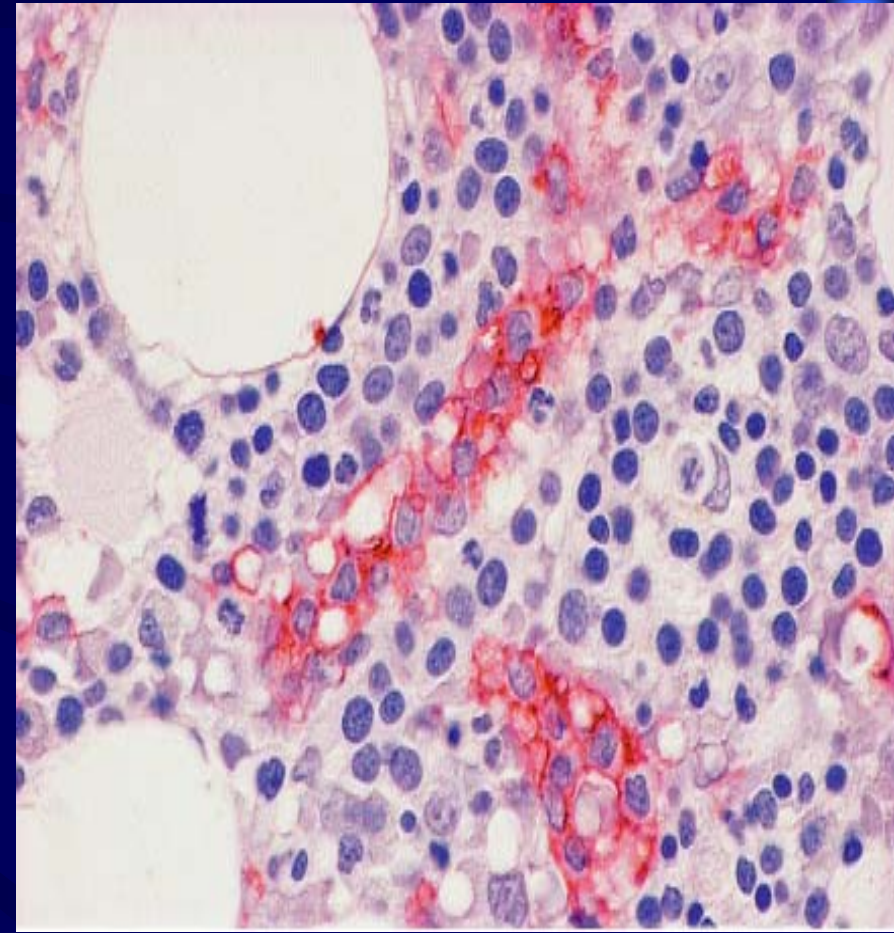
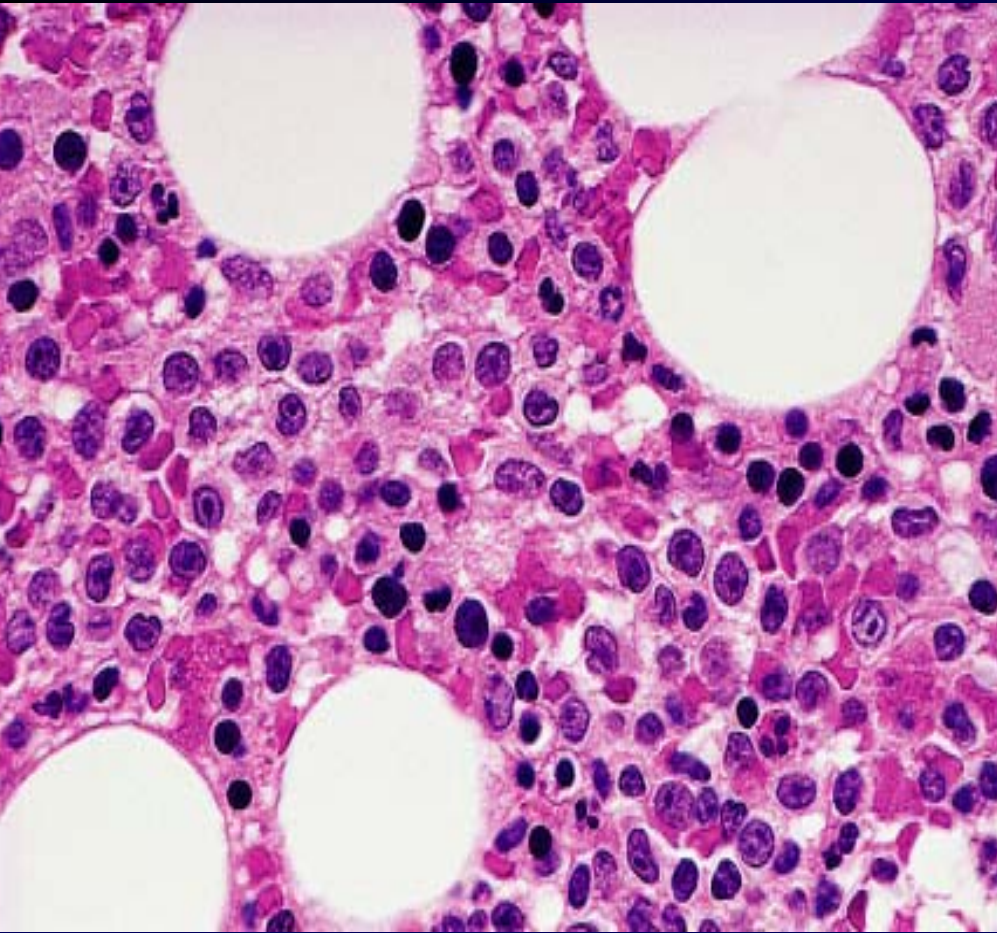
Diffuse



FL



MZL



Features Useful in Distinguishing Benign Vs Lymphoma

- Deverell, Best et al. 1997
- Thiele, Zirbes et al. 1999
- Kent, Variakojis et al. 2002
- Tucker, bardales et al. 1999
- Suarez, Wlodarska et al. 2000

Features Useful in Distinguishing Benign Vs Lymphoma

Benign

- Few in number
- Random Distribution
- Usually round, Well circumscribed
- Polymorphous cellular composition

Malignant

- Variable Number
- Freq. Paratrabecular
- Often irregularly shaped with infiltration into adjacent marrow
- Usually homogenous cellular composition (except some Peripheral T-cell lymphomas) atypical cytologic features may be present

Benign

- No interstitial or intrasinusoidal infiltration.
- Vascularity is often prominent.
- Germinal centers are occasionally present.

Malignant

- Interstitial or intrasinusoidal infiltration may accompany lymphoid infiltrates
- Vascularity is usually not prominent (except in peripheral T cell lymphomas)
- Germinal centers are not present(except in Spl. MZ lymphomas)

Benign

- Immunostain show mixture of B and T cells (exception occurs)

Malignant

- IMS show predominance of B-cells, aberrant phenotypes or monoclonal plasma cells suggests B-cell lymphoma. An aberrant T-cell phenotype suggests T-cell lymphoma.

Benign

- No monoclonal B-cell population or T-cell abnormalities by flow cytometry.
- No monoclonal B or T-cell receptor gene rearrangement by molecular analysis.

Malignant

- Immunoglobulin light chain restriction or T-cell abnormalities by flow cytometry.
- Monoclonal B or t-cell gene rearrangement by molecular analysis.

BM Evaluation for Lymphoma: Pearls and Pitfalls

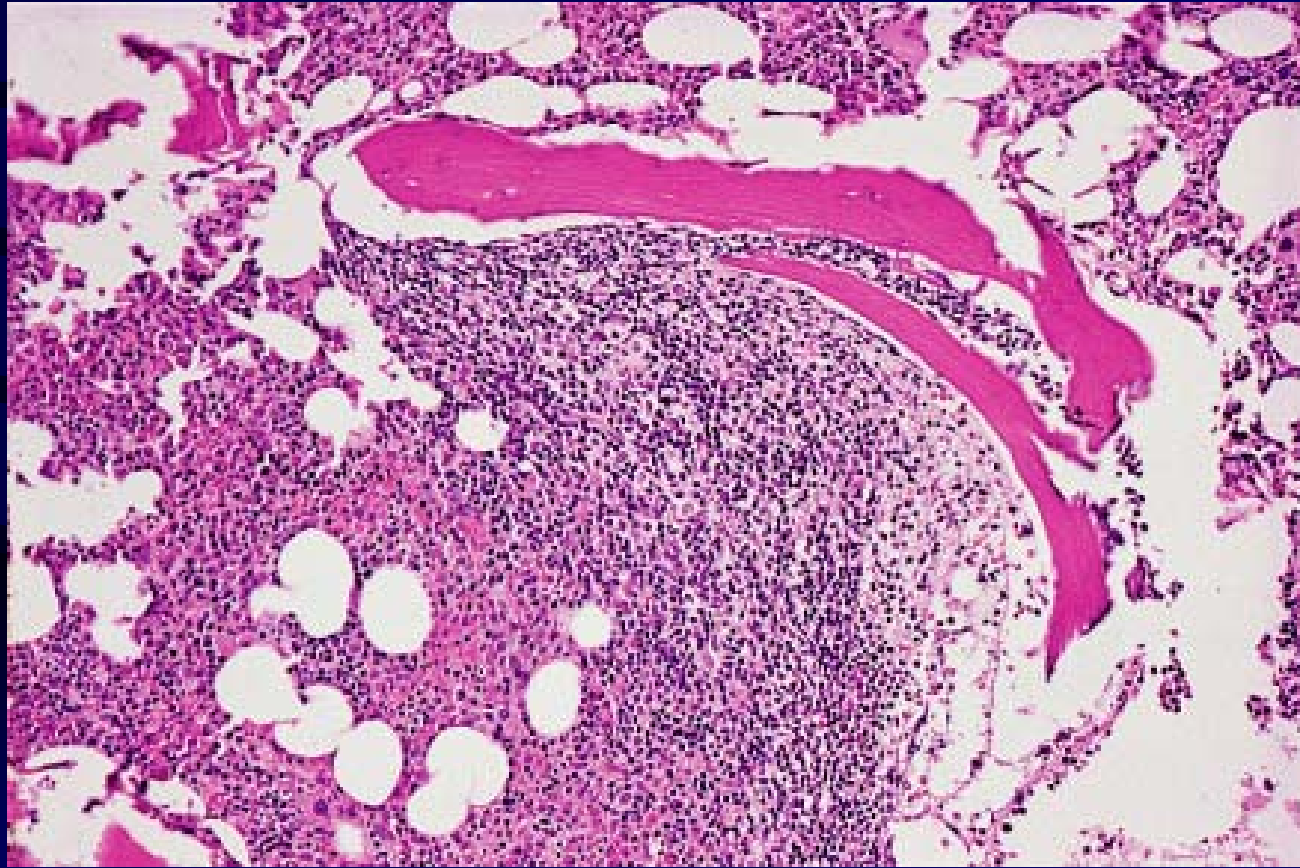
Pearls

- Benign Lymphoid aggregates can occur with lymphoma.
- Distinct paratrabecular lymphoid aggregates essentially excludes the diagnosis of CLL/SLL.

Pitfalls

- Small focal random lymphoid aggregates may represent lymphoma
- Exclusively Paratrabecular lymphoid infiltrates are most common in follicular lymphoma but can be present in other lymphomas including MCL.

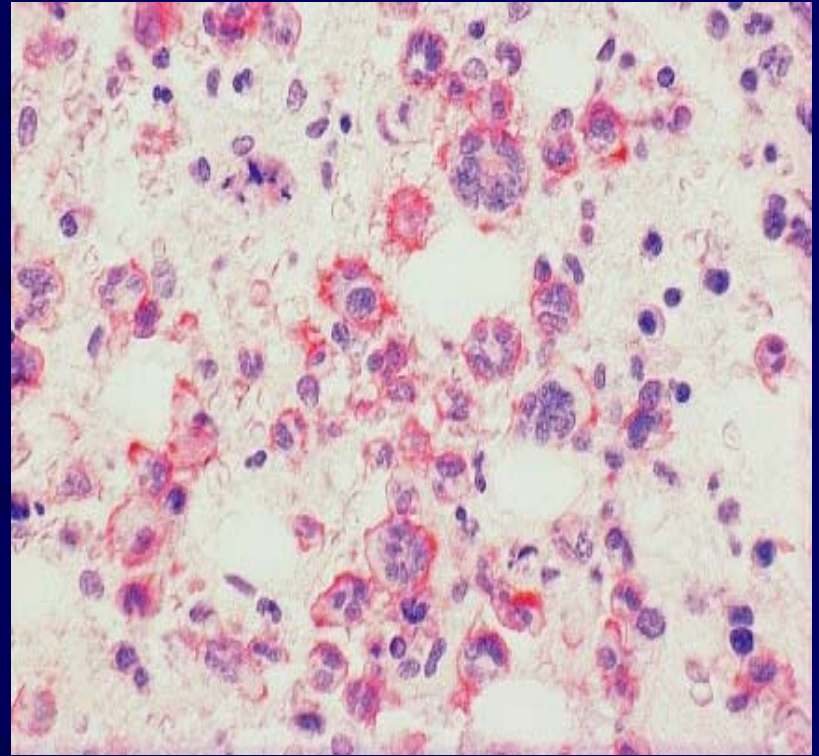
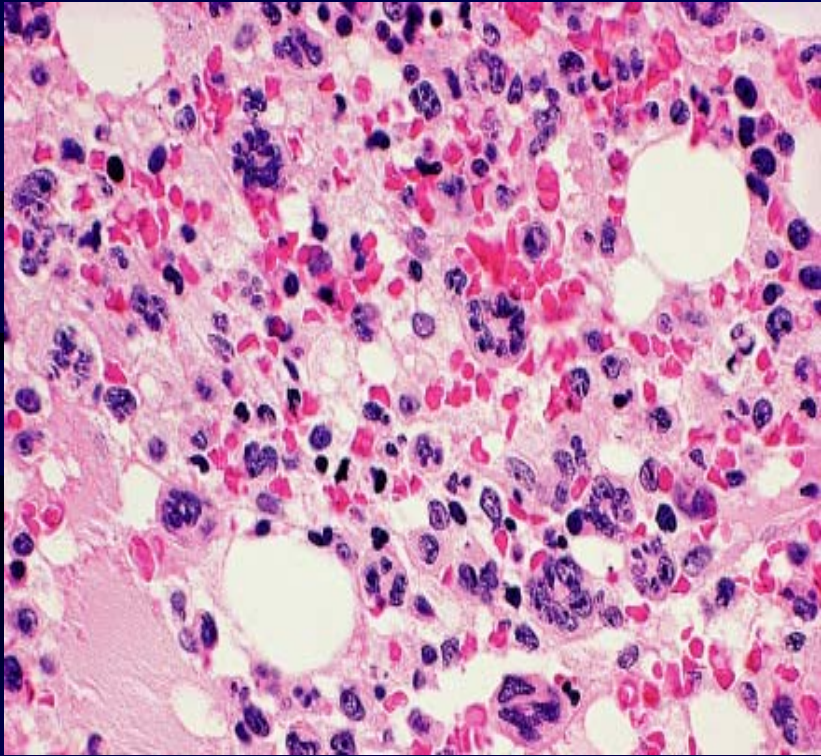
SLVL



Pearls and Pitfalls.....

- Intravascular localization of lymphoid infiltrates indicates a malignant proliferation.
- Benign lymphoid aggregates are usually morphologically heterogeneous.
- Anaplastic large cells lymphoma and NK/T-cell lymphoma can infiltrate the bone marrow as scattered single cells; immunostain may be required for their detection.
- Lymphoma, Particularly T-cell types, can be heterogeneous.

ALCL



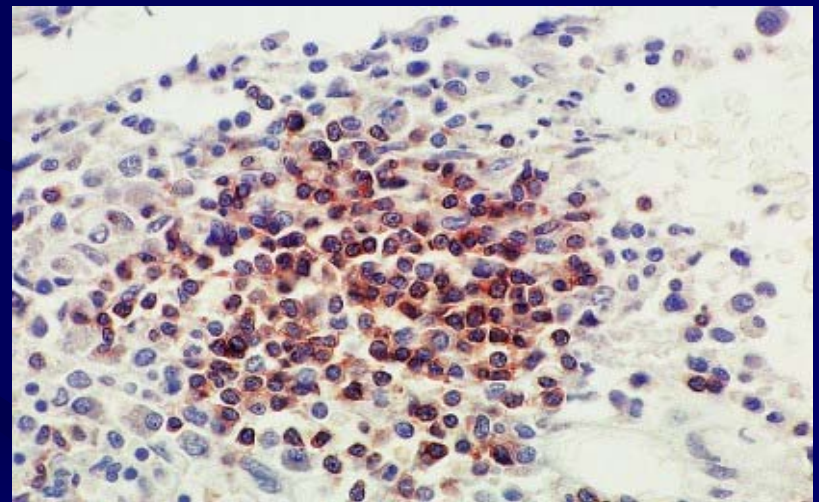
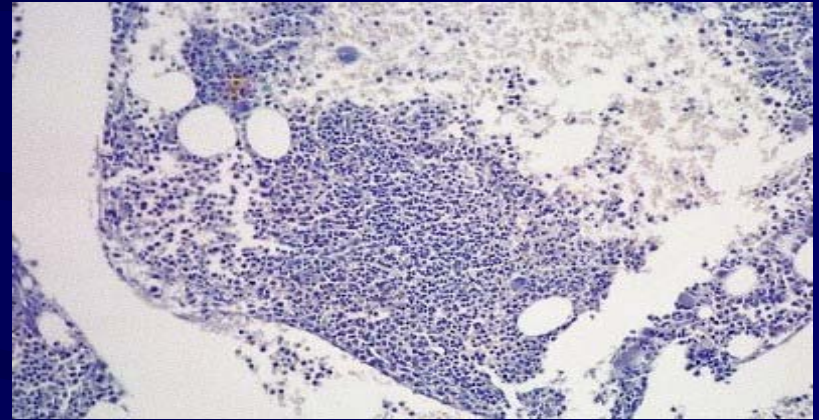
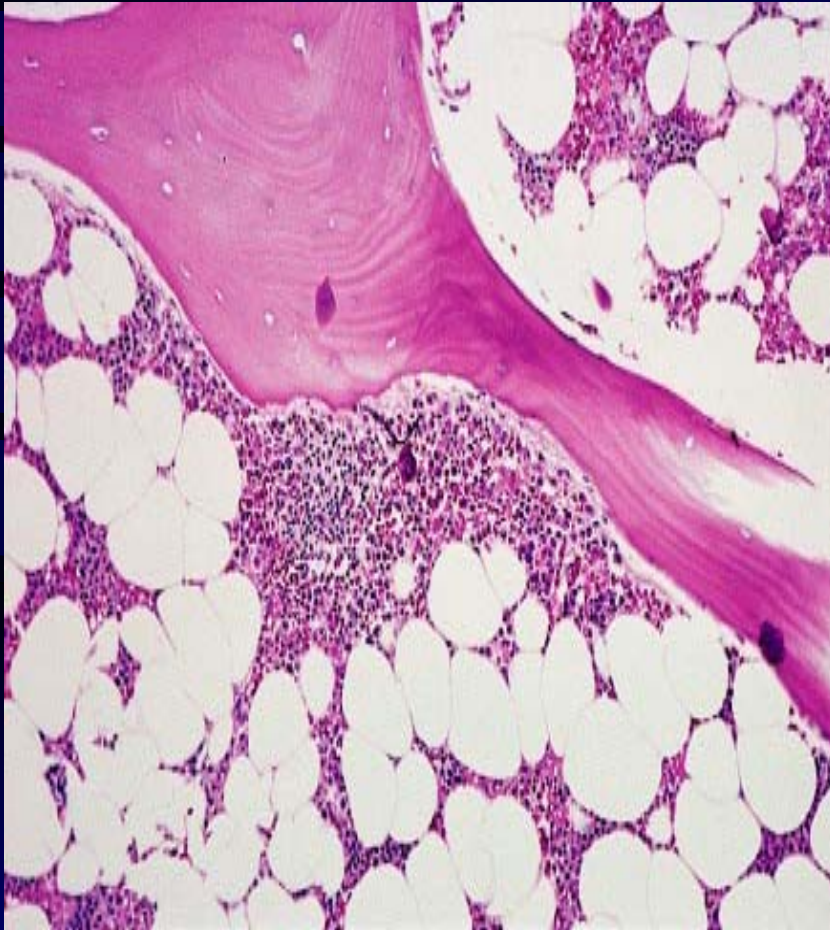
Pearls and Pitfalls.....

- Germinal centers usually indicate benign lymphoid infiltrates and are most commonly seen in pt.s with autoimmune disease.
- Lymphoid infiltrates associated with lipogranuloma are benign.
- SMZL involving the BM is associated with germinal centers in about 30% of cases.
- Non-infectious granulomas can accompany many lymphomas including indolent B-cell lymphomas, T cell lymphomas & Hodgkin lymphoma.

Pearls and Pitfalls.....

- Paratrabecular lymphoid infiltrates almost always indicate lymphoma.
- IMS essential for evaluation of BM involvement by lymphomas that have prominent intrasinusoidal component e.g Intravascular large B-cell lymphoma, SMZL, & hepatosplenic –cell lymphoma.
- Paratrabecular, multiple, or large lymphoid infiltrates that mimic lymphoma but are T-cell rich and benign(lack B-cells) can persist after Rituximab therapy for B-cell lymphomas.
- Small cell carcinoma, when discohesive, can be confused with lymphoma especially in bone marrow aspirate smears.

Post Rituximab Treatment



Pearls and Pitfalls.....

- Low level monoclonal B-cell populations may be identified by flow cytometry in “healthy” individuals with no evidence for lymphoma.
- Systemic Polyclonal Immunoblastic Proliferations (SPIP).

Systemic Polyclonal Immunoblastic Proliferations (SPIP)

- Rare and unusual reactive lymphoplasmacytic proliferations encountered in the setting of Acute immune disorder.
- Disorder involves PB, BM, LN, and frequently other organs such as spleen and Liver.
- Leukocytosis with absolute lymphocytosis including reactive lymphocytes, immunoblasts, and plasma cells.
- Anemia & Thrombocytopenia almost always present, with anemia is frequently immune mediated with a positive antiglobulin test.

SPIP...

- Polyclonal Hypergammaglobulinemia
- BM aspirate & Bx. show numerous lymphocytes, immunoblasts and plasma cells with inconspicuous to large lymphoid aggregates.
- Flow shows polyclonal B-cells.
- Cytogenetic abnormalities found in subset of patient .
- Clinical behavior variable.
- Majority respond to steroid but other require chemotherapy.

Thank you