

# **Case Presentation: A 79 Year-Old-Man with Fever, Cervical Lymphadenopathy and Leukemia**

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## **Case History:**

A 79-year-old man presented with fever, weight loss and cervical lymphadenopathy. His medical history was significant only for essential hypertension. CT scan revealed bulky abdominal lymphadenopathy and hepatosplenomegaly. The laboratory results showed anemia, thrombocytopenia and leukocytosis with circulating blasts suspicious for acute myeloid leukemia (Figure 1).

A bone marrow aspirate revealed a heterogeneous population of medium-sized atypical lymphoid cells with blastic appearance. The cells displayed variation in nuclear size and contour, 1-2 prominent large nucleoli and fine chromatin (Figure 2a & 2b). Few admixed small mature lymphocytes were also noted. The trephine biopsy specimen showed diffuse infiltration by atypical lymphoid cells, starry sky macrophages, brisk mitosis and frequent apoptosis. Focal areas of fibrosis were also noted (Figure 3a & 3b).

Flow cytometry analysis and immunostaining revealed a mature B-cell Immunophenotype: CD19+, CD20+, CD22, CD79+, CD10+, BCL2+, Lambda+, sIg-, CD34-, CD117-, Tdt-, CD3-, CD5-, CD13-, CD33-, myeloperoxidase (MPO)- (Figure 4 & 5 a-e).

Cytogenetics was consistent with a complex abnormal karyotype with rearrangements of chromosomes 2, 6, 8, 14 and 18, including t(8;14) and t(14;18) (Figure 6).

In situ hybridization (FISH) showed rearrangements involving both MYC and BCL2 genes (Figure 7a & 7b) confirming a 'double hit lymphoma'. Ki 67 labeling index was >90%.

No CNS involvement was present.

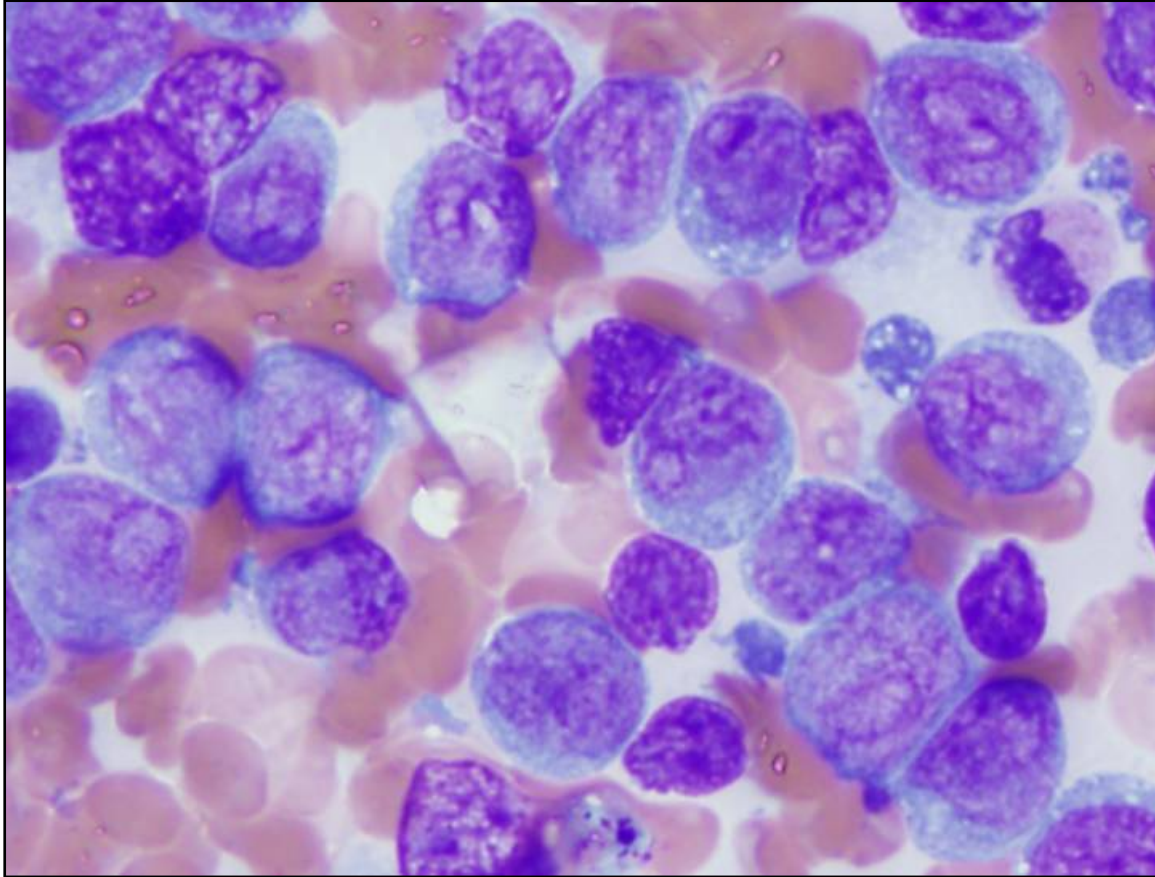


Figure 1: Peripheral blood (Giemsa stain, original magnification x 100). Heterogeneous population of medium-sized blasts with prominent large nucleoli.

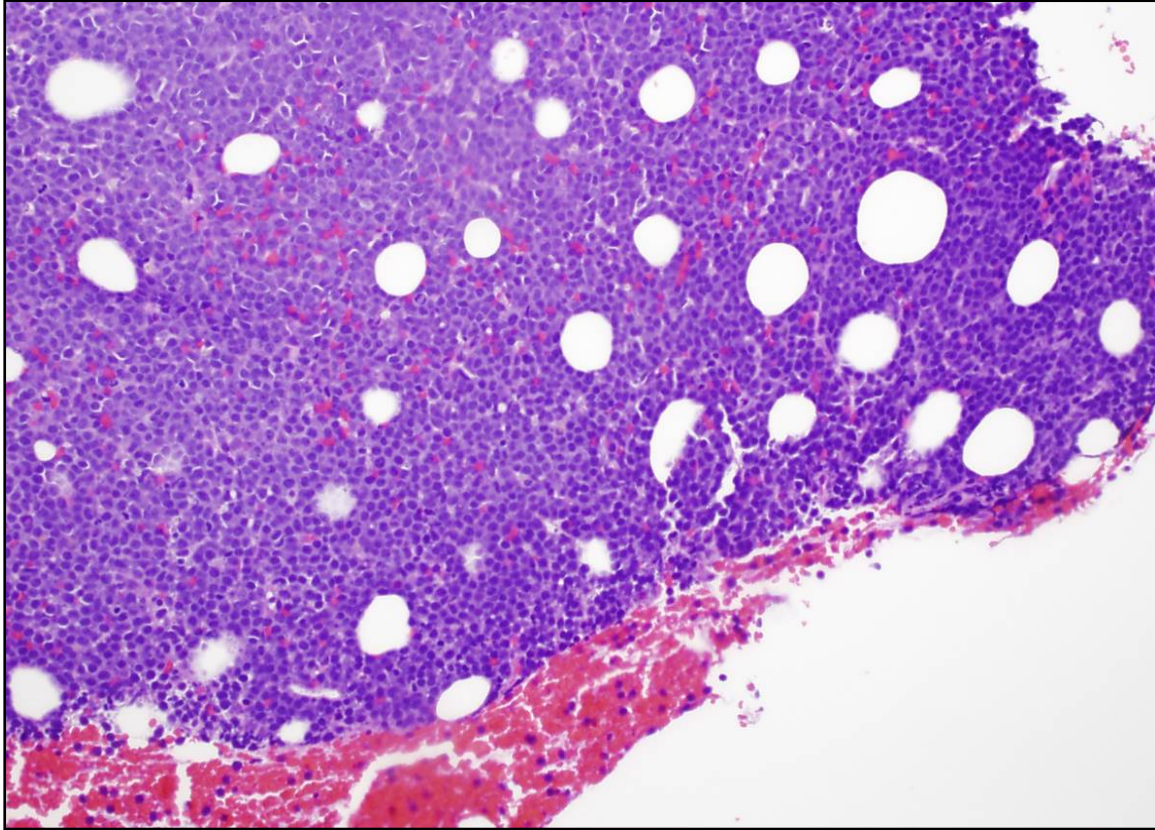


Figure 2a: Bone marrow clot (H&E, original magnification x 10). Diffuse replacement of the bone marrow and starry sky appearance.

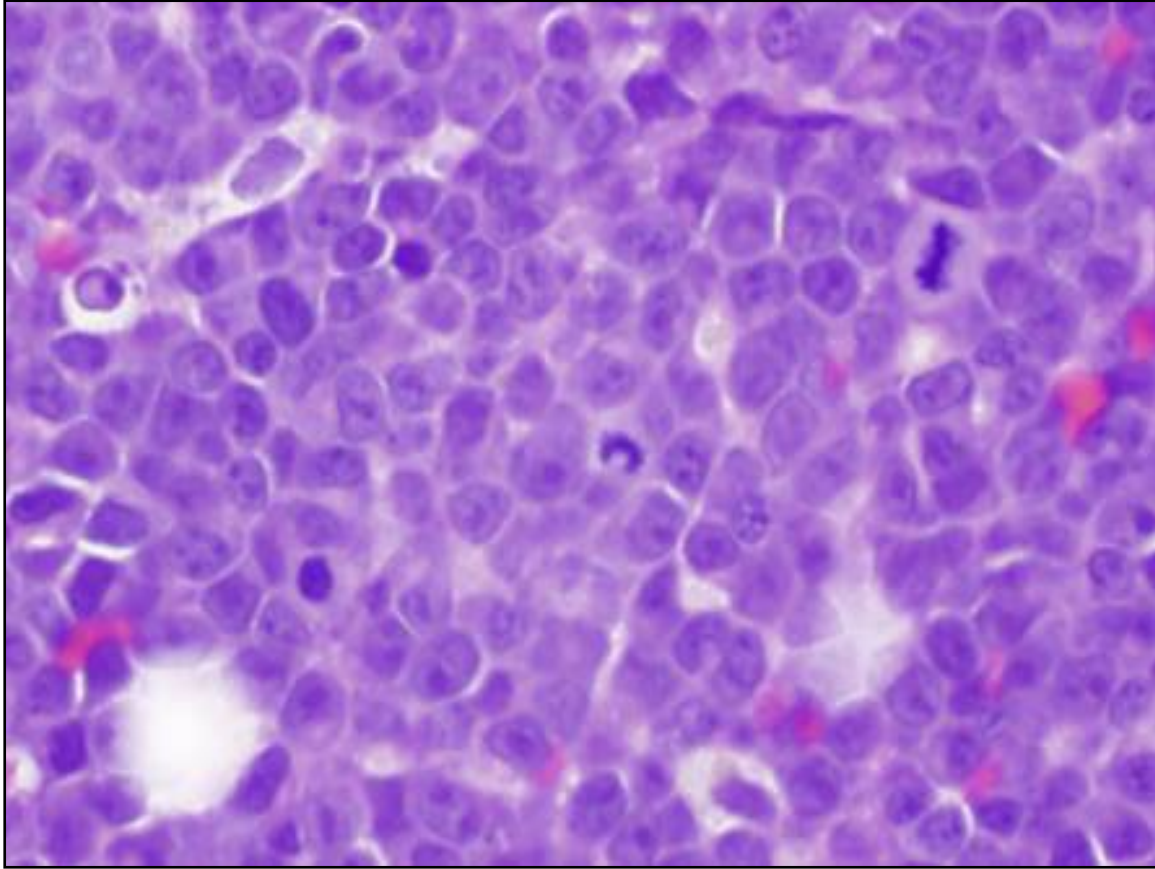


Figure 2b: Bone marrow clot (H&E, original magnification x 40). Atypical lymphoid cells with blastic appearance, prominent apoptosis and abundant mitosis figures.

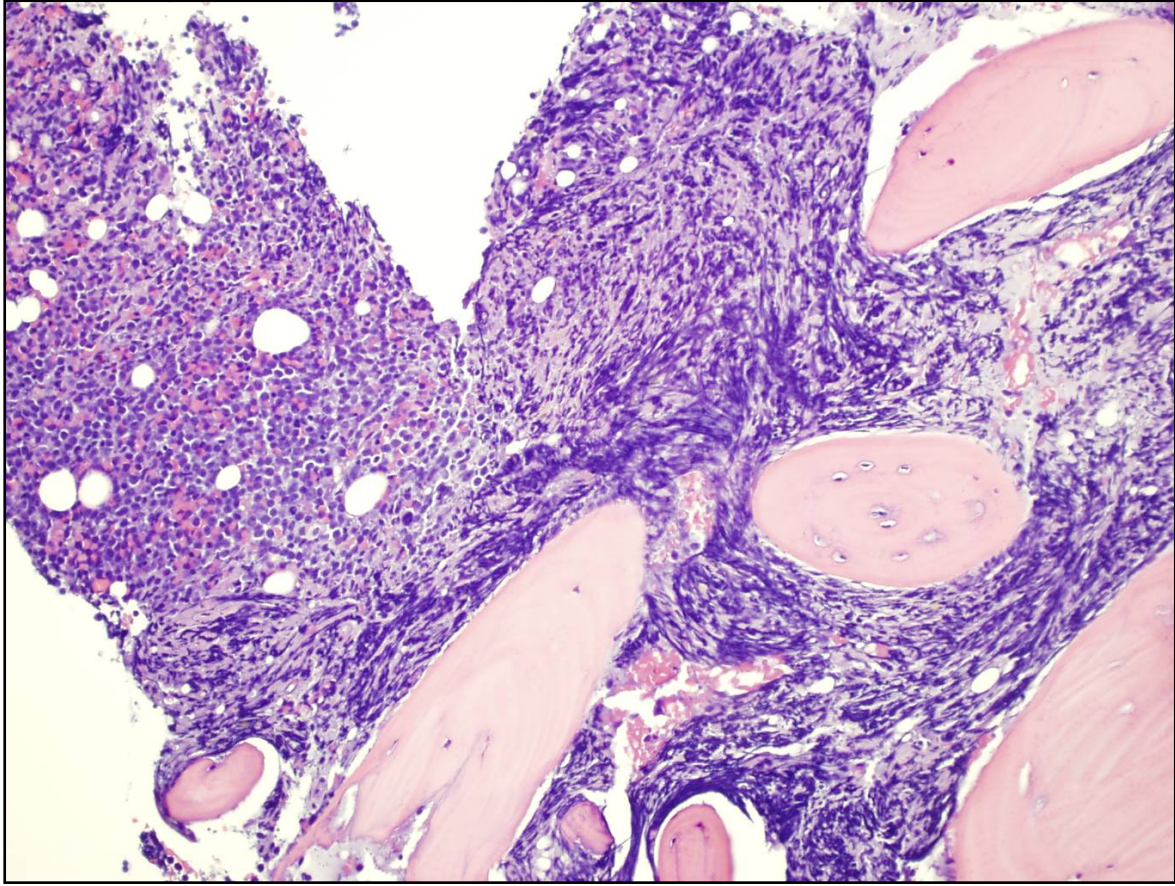


Figure 3a: Bone marrow trephine biopsy (H&E, original magnification x 10). Diffuse infiltration of the bone marrow and focal stromal reaction of fibrosis.

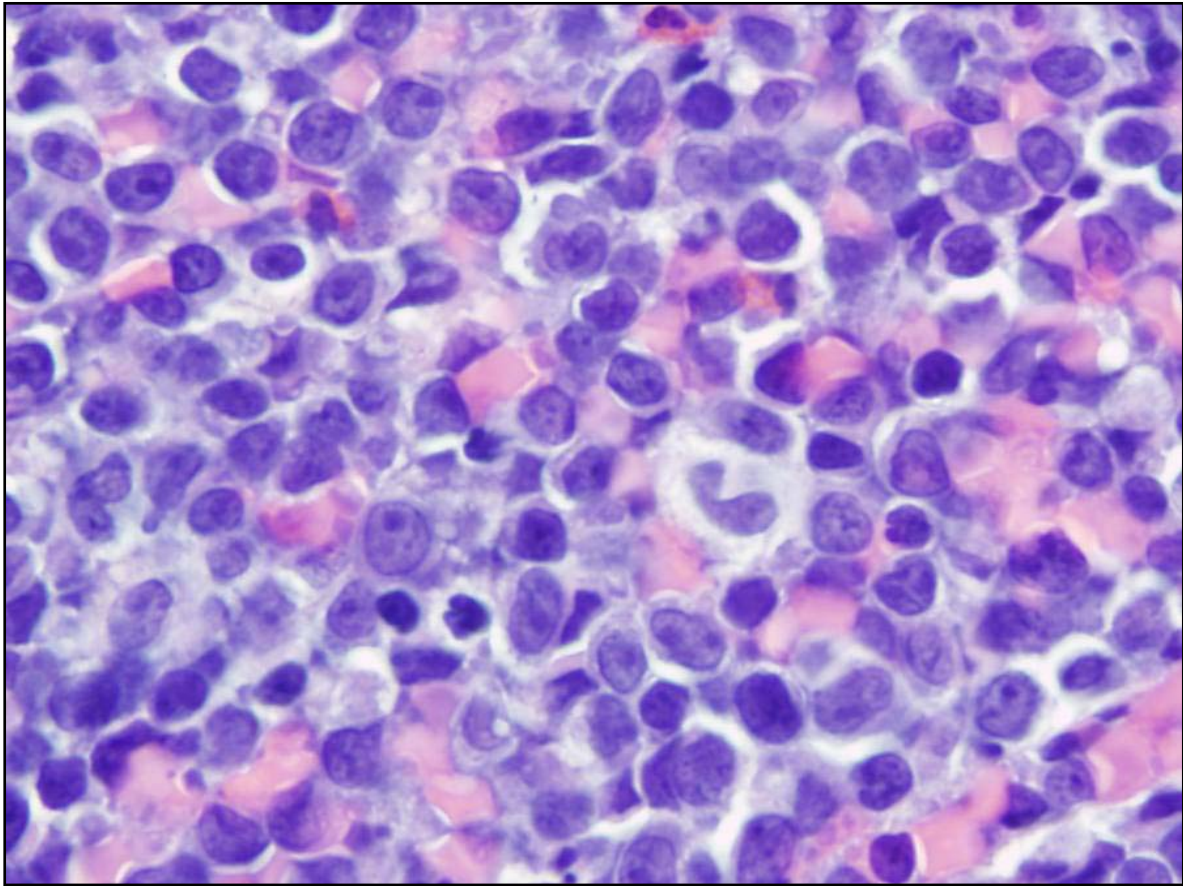


Figure 3b: Bone marrow trephine biopsy (H&E, original magnification x 40). Predominantly medium sized atypical cells with vesicular nuclei showing variation of size and nuclear contour.

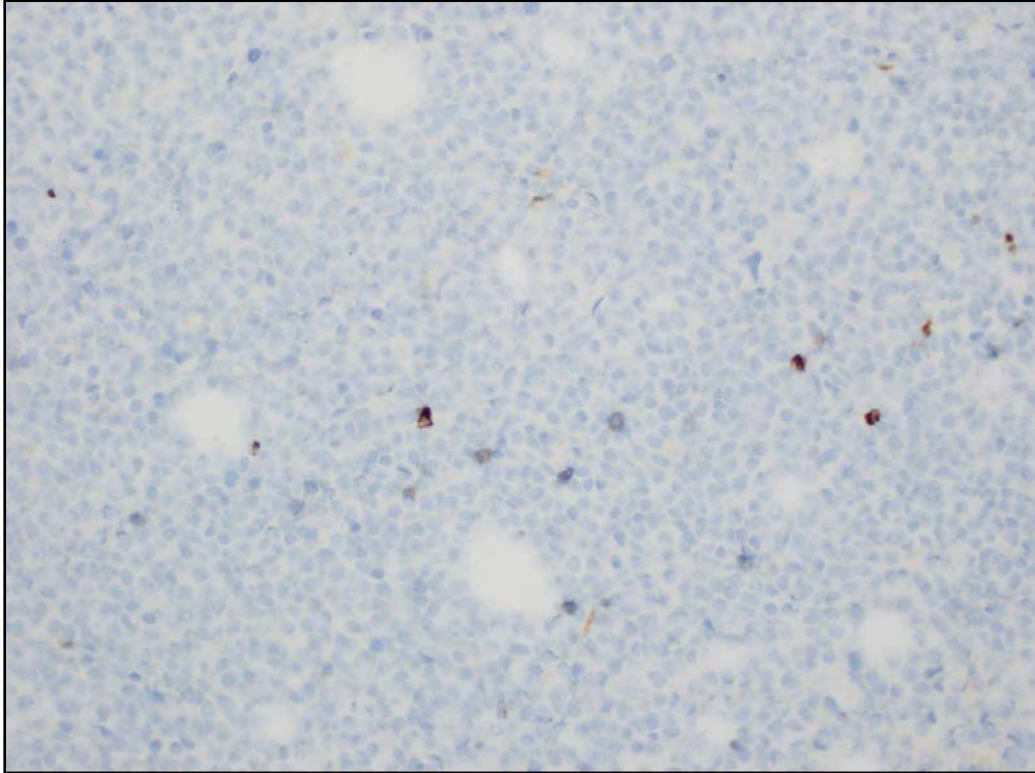


Figure 4a: Bone marrow trephine biopsy (Myeloperoxidase (MPO) stain, original magnification x 20). Negative neoplastic cells.

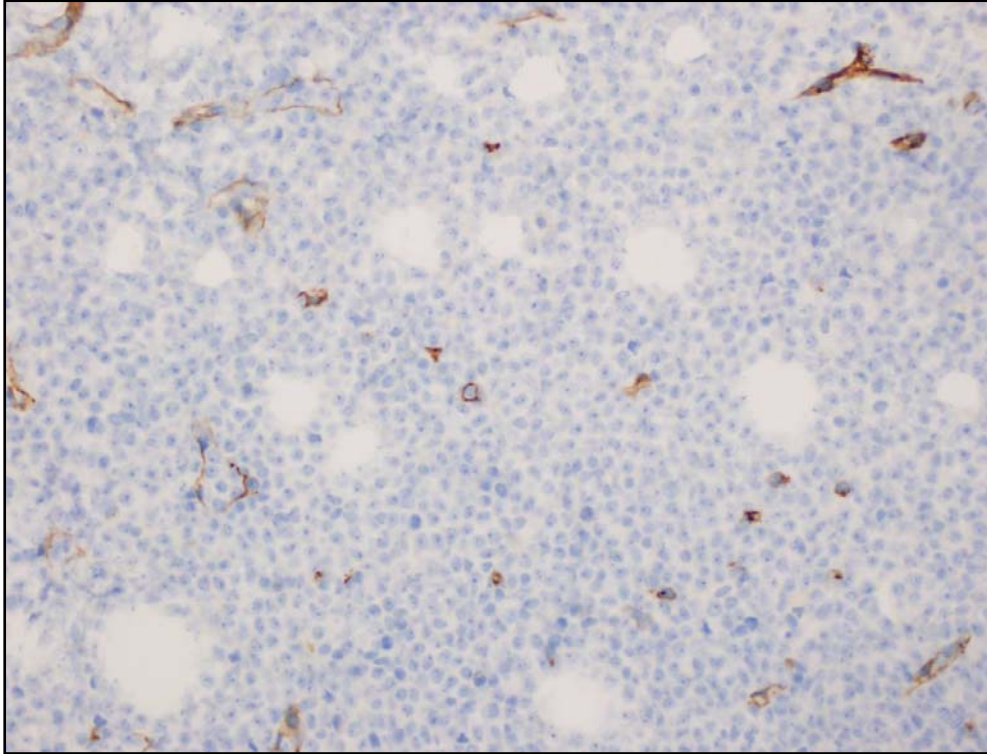


Figure 4b: Bone marrow trephine biopsy (CD34 Immunostain, original magnification x 20). Negative neoplastic cells. Positive vasculature.

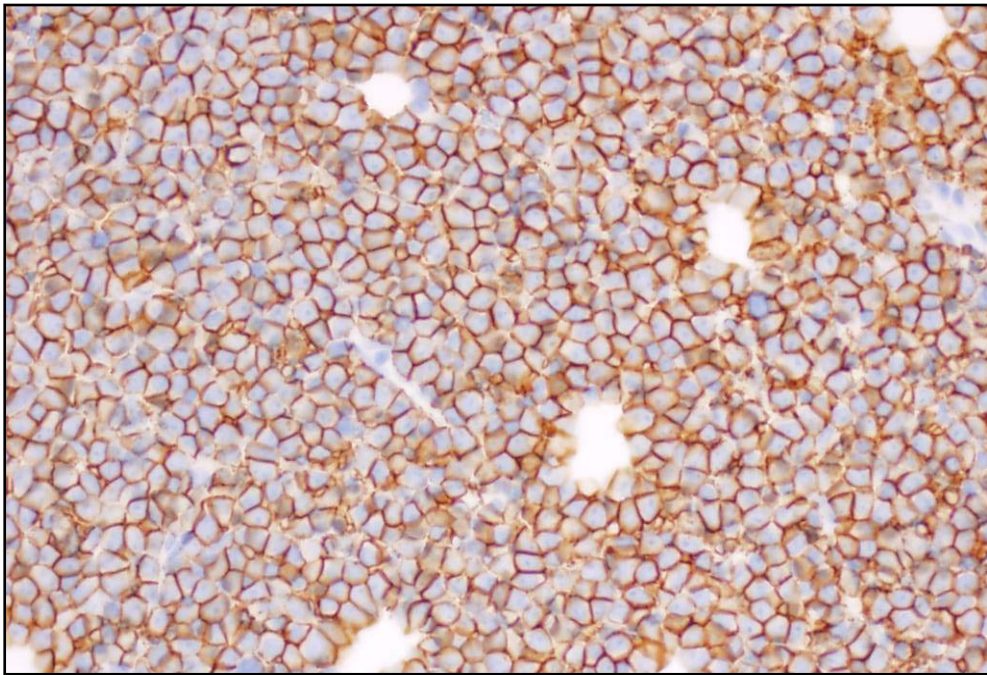


Figure 4c: Bone marrow trephine biopsy (CD20 Immunostain, original magnification x 40). Strong diffuse positivity in neoplastic cells.

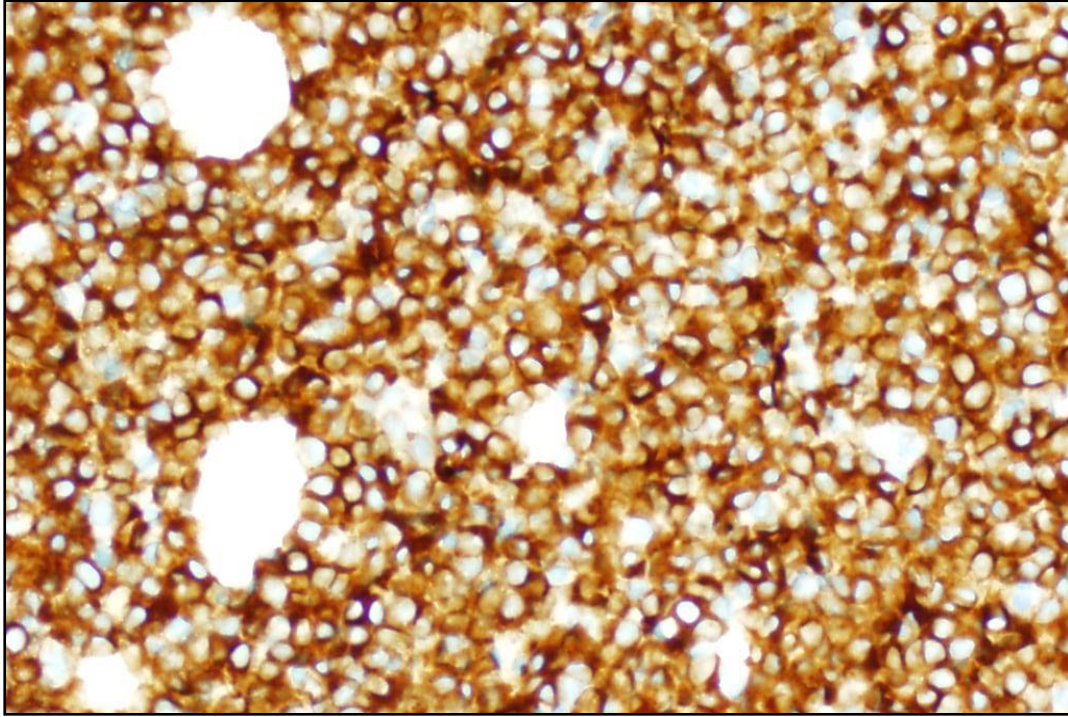


Figure 4d: Bone marrow trephine biopsy (CD79a Immunostain, original magnification x 40). Strong diffuse positivity in neoplastic cells.

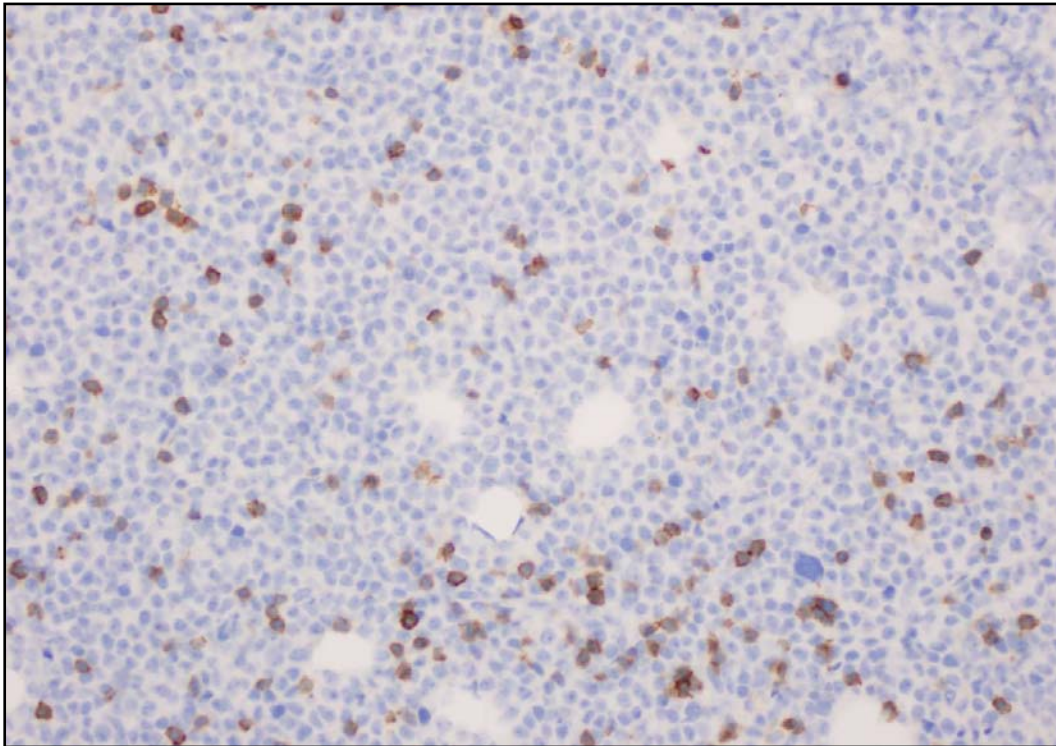


Figure 4e: Bone marrow trephine biopsy (CD3 Immunostain, original magnification x 20). Focal positive T-cells.

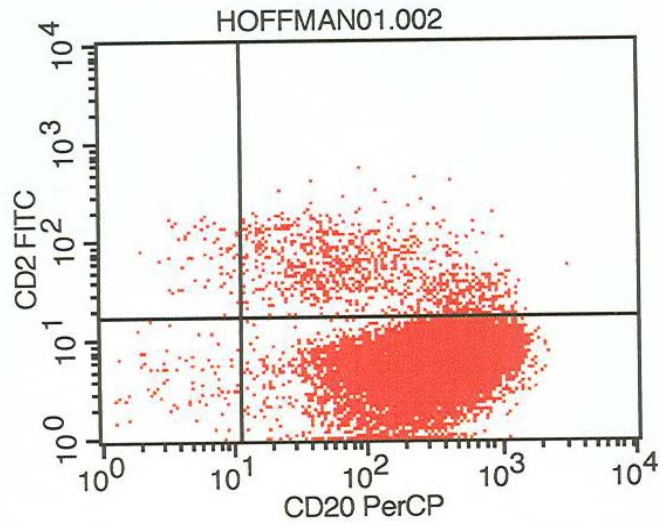


Figure 5a: Flow cytometry: CD20 positive abnormal B-cell population.

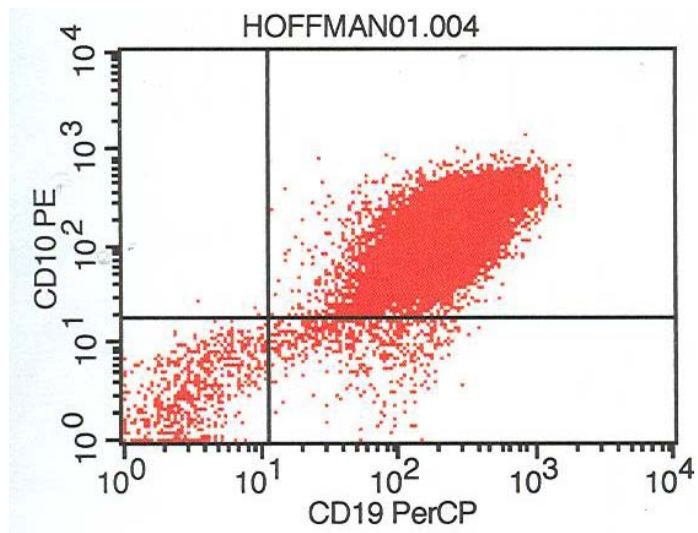


Figure 5b: Flow cytometry: Co expression of CD20 and CD10.

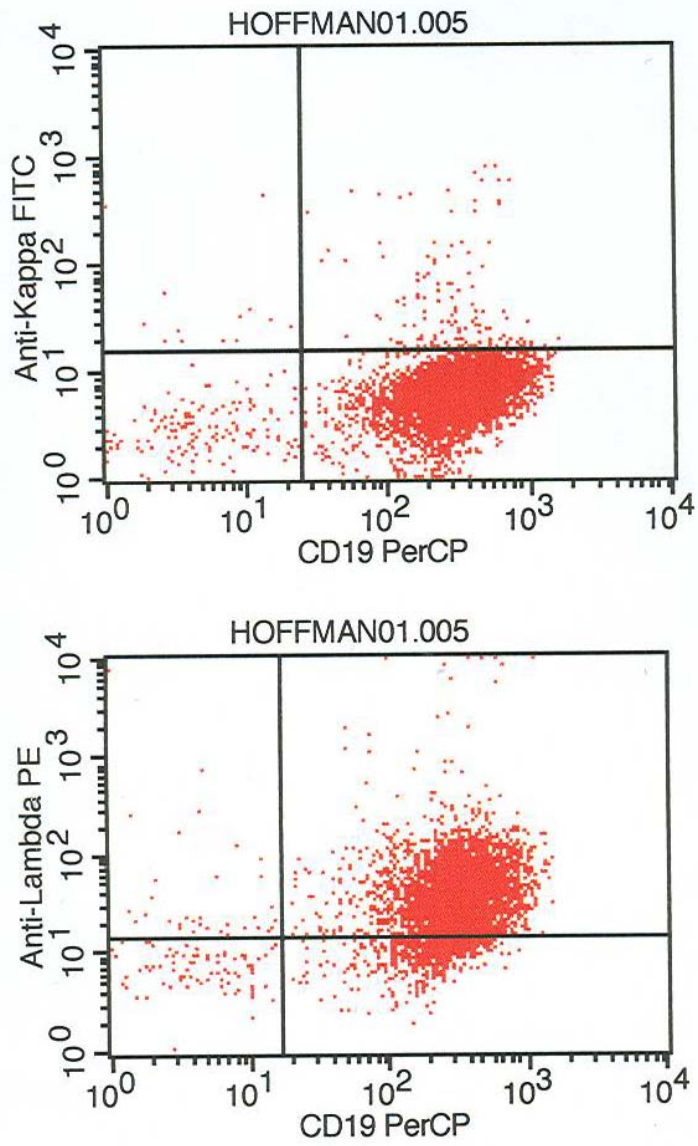


Figure 5c: Flow cytometry: Lambda clonal CD19 positive neoplastic B-cells.

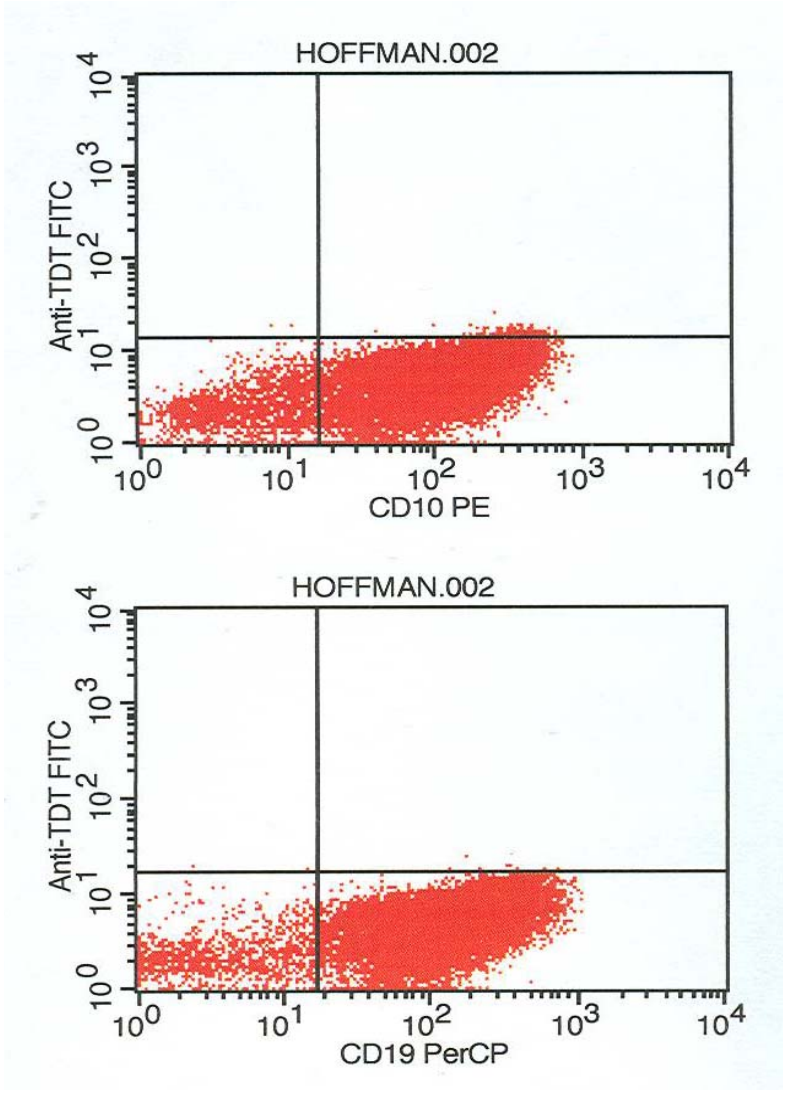


Figure 5d: Flow cytometry: Tdt negative neoplastic B-cells.

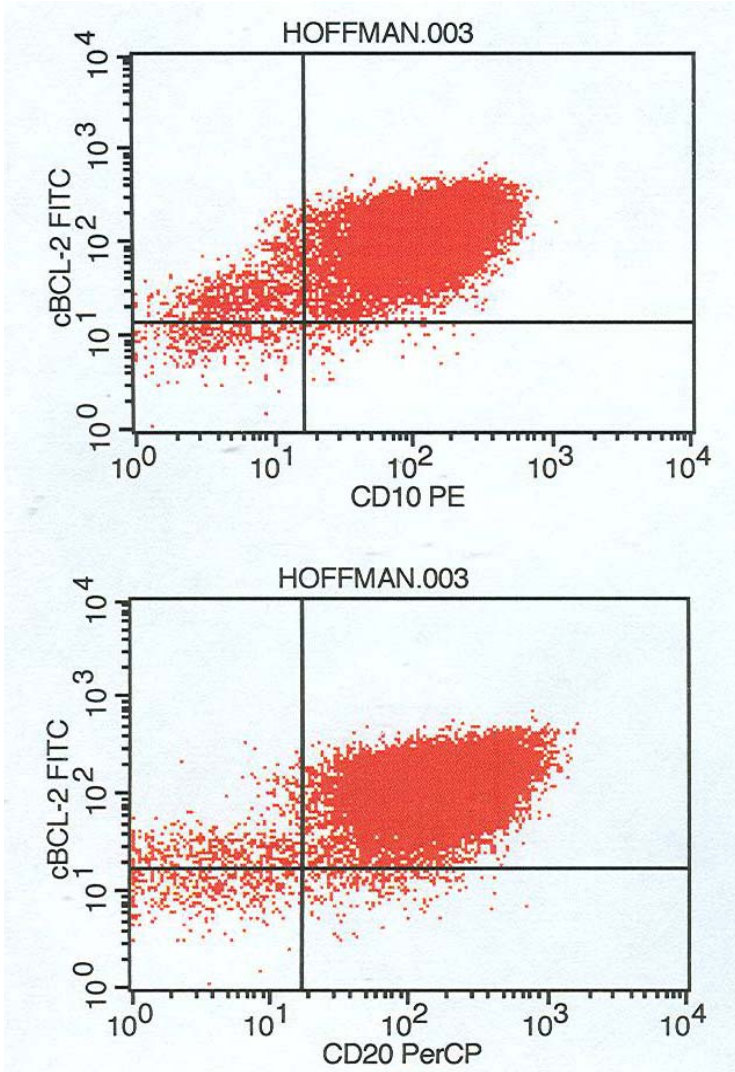


Figure 5e: Flow cytometry: Bcl-2 positive neoplastic B-cells

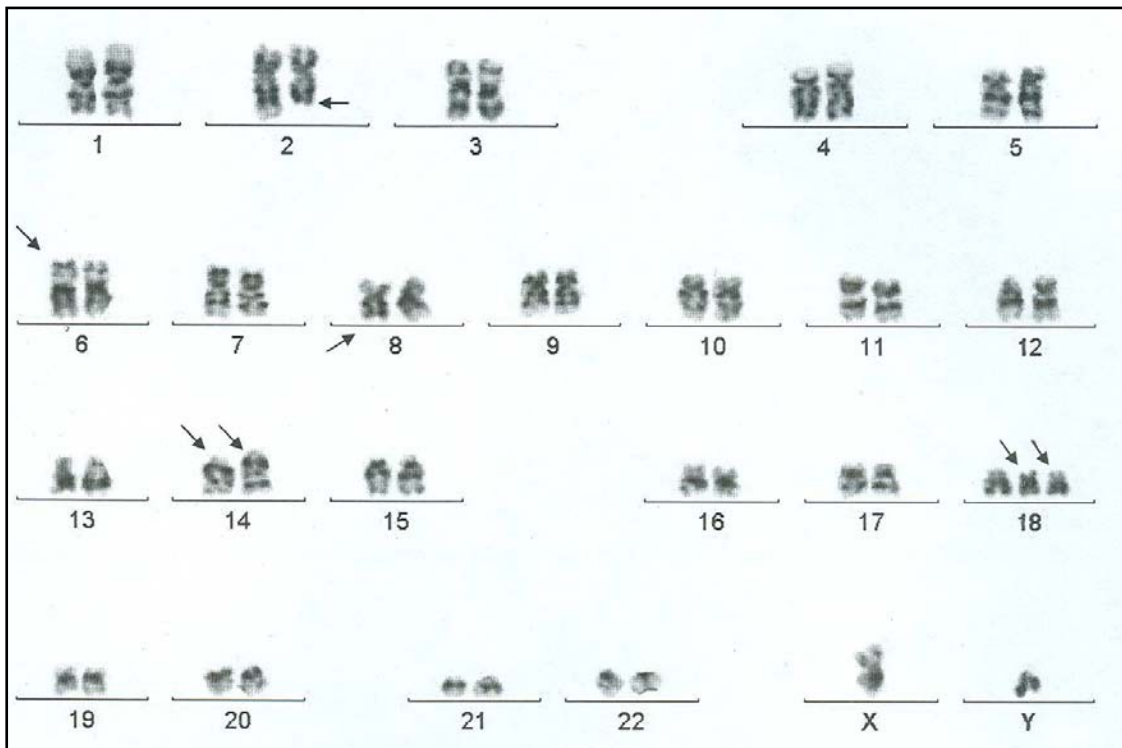


Figure 6: Cytogenetic: Chromosome analysis reveals a complex abnormal karyotype with rearrangements of chromosomes 2, 6, 8, 14 and 18, including t(8; 14) and t(14; 18).

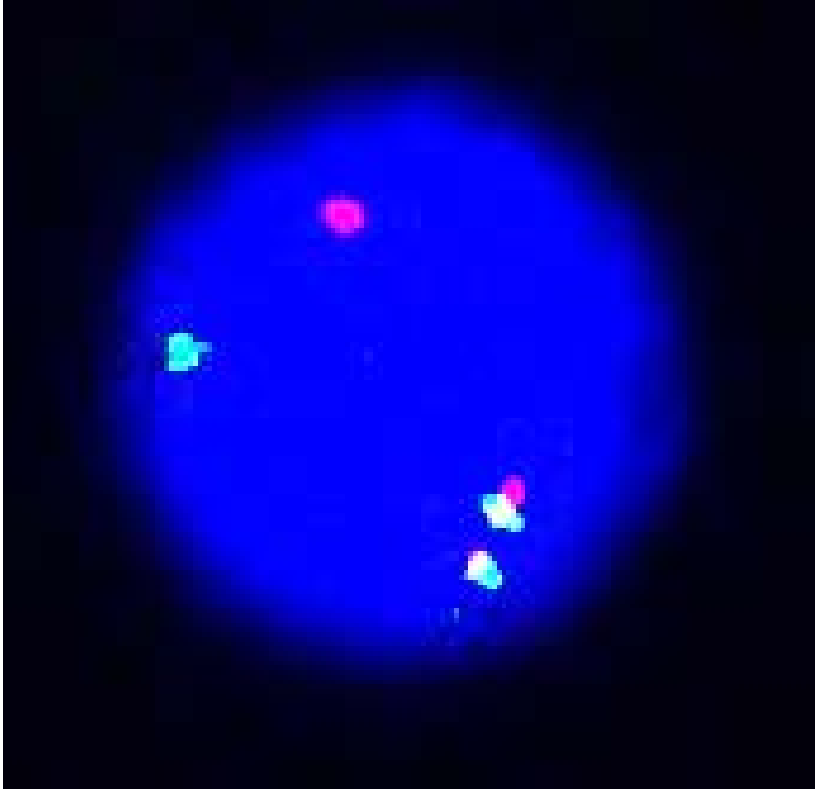


Figure 7a: FISH Analysis: t(14;18)(q32;q21)/IGH/BCL2

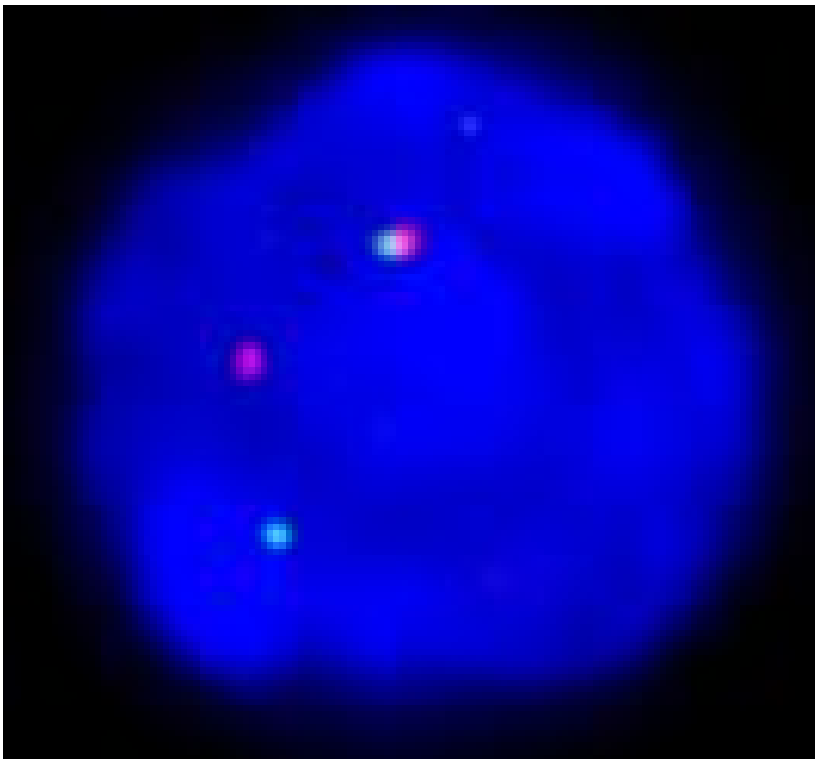
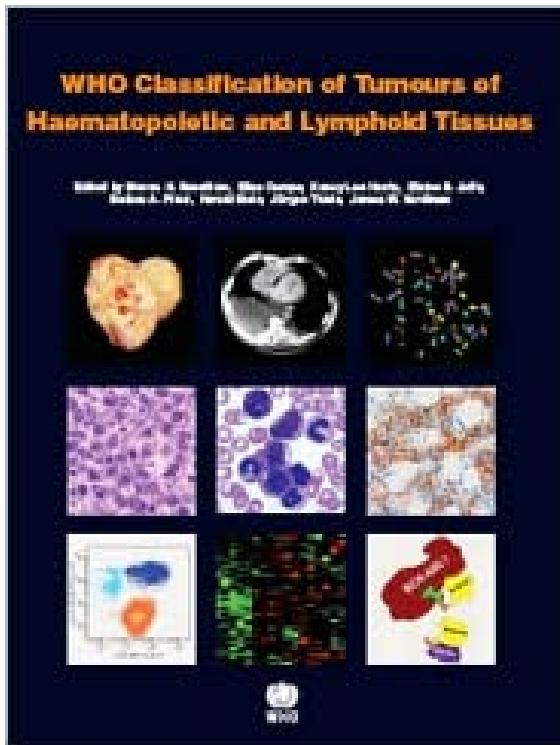


Figure 7b: FISH Analysis: t(8;14) (q24.1;q32)/MYC/IGH

What is your diagnosis?

## Pathologic Diagnosis:



*Before 2008: Follicular lymphoma with Blastoid transformation.*

*2008: B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma (DLCL) and Burkitt's lymphoma (BL)*

## Definition:

- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL are aggressive lymphomas that have morphological and genetic features of both DLBCL and BL.
- Some of these cases were previously classified as Burkitt-like lymphoma. Some transformed follicular lymphomas may fall into this category.
- This is a heterogeneous category that is not considered a distinct disease entity.

## Epidemiology:

DLBCL/BL are relatively infrequent and mainly diagnosed in adults.

Male : female ratio 1:1.

Age range: 44-68 years, median: 59. (Young et. al. Am J Clin Pathol 2008; 129:157-166)

## Sites of involvement:

More than half of the patients present with widespread, often extranodal disease. Unlike BL, there is no preferential localization in the ileocecal region or jaws. The bone marrow and peripheral blood may be involved as well.

## Clinical features:

Patients present with lymphadenopathy or mass lesions in extranodal sites. Some patients have leukemic presentation.

**Morphologic, Immunophenotypic and Genetic Features**

	<b>BL</b>	<b>BL/DLBCL</b>	<b>DLBCL</b>
<b>Morphology</b>			
Only small/medium-size cells	Yes	Common	No
Only large cells	No	No	Common
Mixture	No	Sometimes	Rare
<b>Proliferation (Ki-67/MIB)</b>			
>90%, homogeneous	Yes	Common	Rare
<90%, heterogeneous	No	Sometimes	Common
<b>BCL2 expression</b>			
Negative/weak	Yes	Sometimes	Sometimes
Strong	No	Sometimes	Sometimes
<b>Genetic features</b>			
MYC rearrangement	Yes (>95%)	Common (35-50%)	Rare
BCL2 rearrangement (no MYC)	No	Rare	Sometimes
BCL6 rearrangement (no MYC)	No	Rare	Sometimes
Double hit	No	Sometimes (15%)	Rare
MYC-Simple karyotype	Yes	Rare	Rare
MYC-Complex karyotype	Rare	Common	Rare

## **Recommendations**

- Cases that morphologically resemble BL may be placed in this category (BL/DLBCL) when BCL2 is moderately to strongly positive.
- Cases of otherwise typical DLBCL with a MYC translocation should not be placed in this category.
- Conversely, cases with a IG-MYC rearrangement as the only abnormality likely represent BL even if they are morphologically atypical.

## **Pathogenesis**

- BL/DLBCL may arise from clonal evolution of its preceding follicular lymphoma (FL) germinal center B cells.
- FLs undergoing transformation typically retain the t(14;18) translocation, subsequent secondary genetic abnormalities (double hit) are believed to be important for the evolution of the disease.
- Several cytogenetic events including gains in 2q, 6p, 7p, 12q and 17q and losses in 5p and 8q, c-myc gene rearrangement, TP53 gene mutation, bcl-6 gene mutations and somatic mutations of the translocated bcl-2 gene have been implicated in the pathogenesis of transformation.

## **Prognosis**

B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL are aggressive lymphomas, for which the most appropriate therapeutic approach is not established. The double hit lymphomas show frequent involvement of the BM, PB and CNS; most cases are resistant to current therapies, which seems to be independent of the complexity of the other cytogenetic abnormalities.

## References

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