Case 3

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Fellow, advanced hematopathology (Molecular)

Fox Chase Cancer Center

Case 3

- An 84-year-old male with history of CLL , on BTK inhibitor and history of high-grade urothelial carcinoma
- New diagnosis of lung adenocarcinoma
- Presented for lung segmentectomy with mediastinal lymph node dissection

Digital Pathology (Whole Slide)

Mediastinal Lymph node(s) dissection Level 10L

View Slides

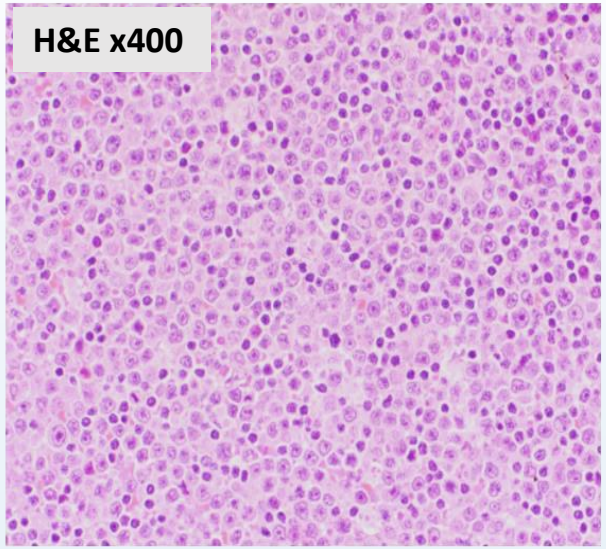
Summary of IHC (Case 3)

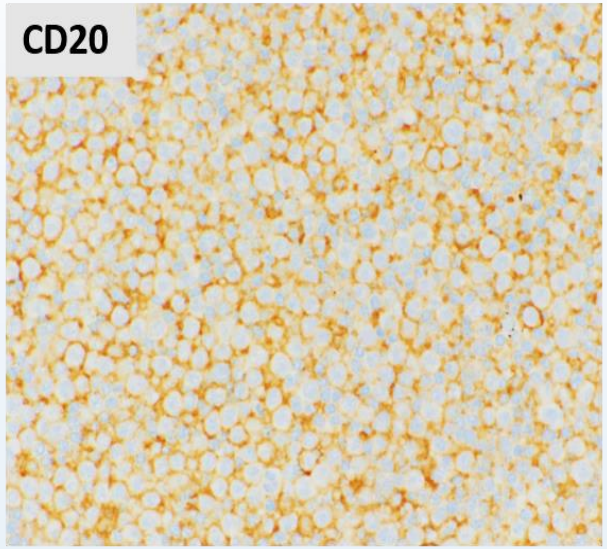
- Lymphoma cells are

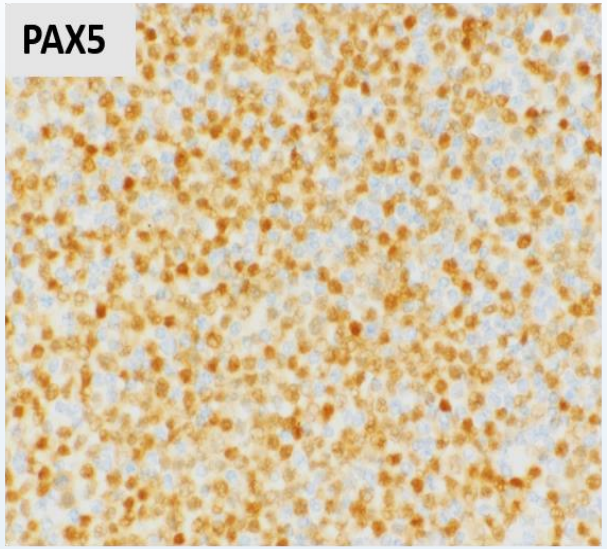
positive for
CD20, PAX5, CD5 (subset), BCL2

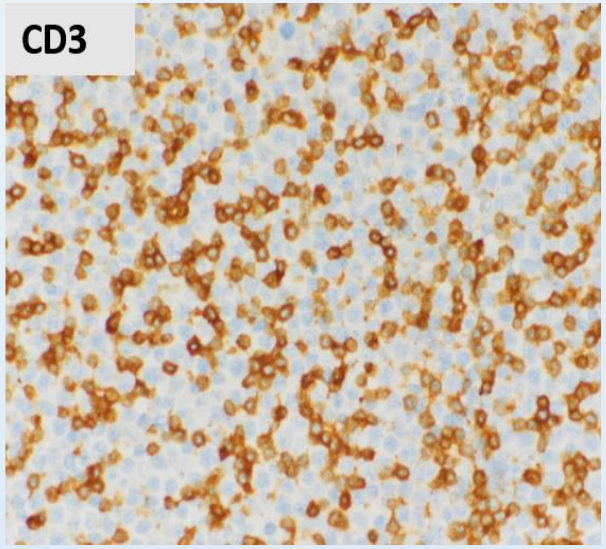
Ki-67 proliferative index is 50%.

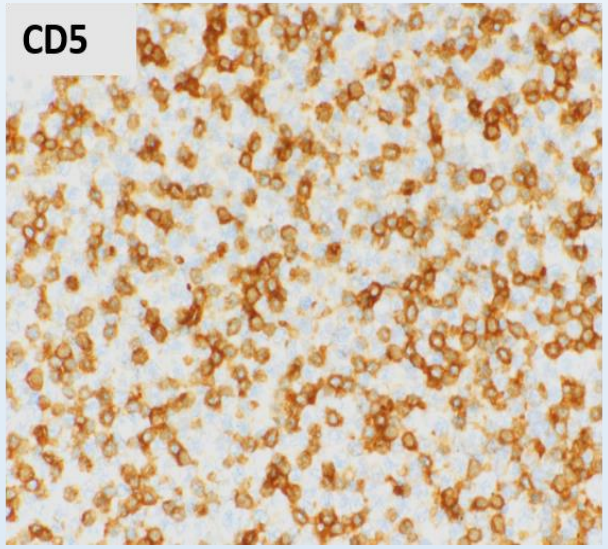
negative for
CD10, BCL6, MUM1, cyclin D1, MYC, CD30, and CD3.

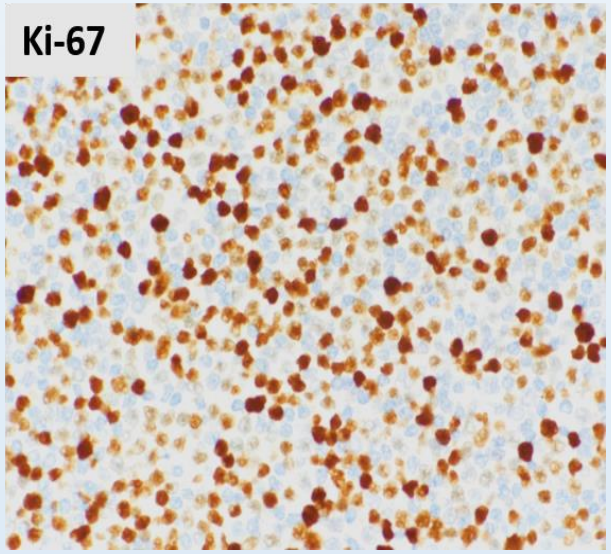












Details of peripheral blood and Flow cytometry

Peripheral blood (Oct 2020):

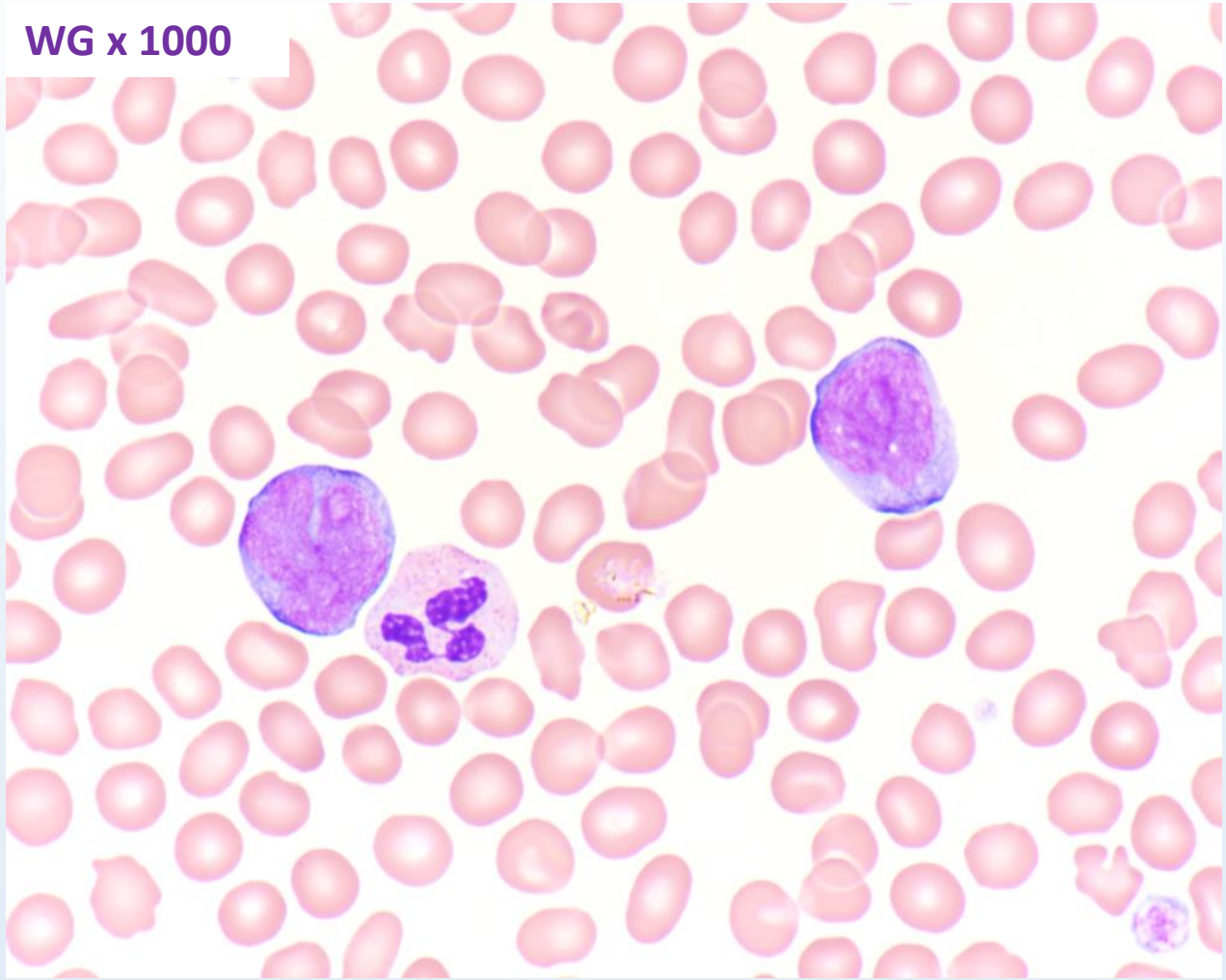
WBC: 23.7 K/mm3

Flow cytometry:

Gated Lymphs: 38%

Kappa-restricted B-cells (82%)

CD19, CD20(dim)+, CD23+, FMC7-, CD5+, CD79b+, CD38+, CD10-

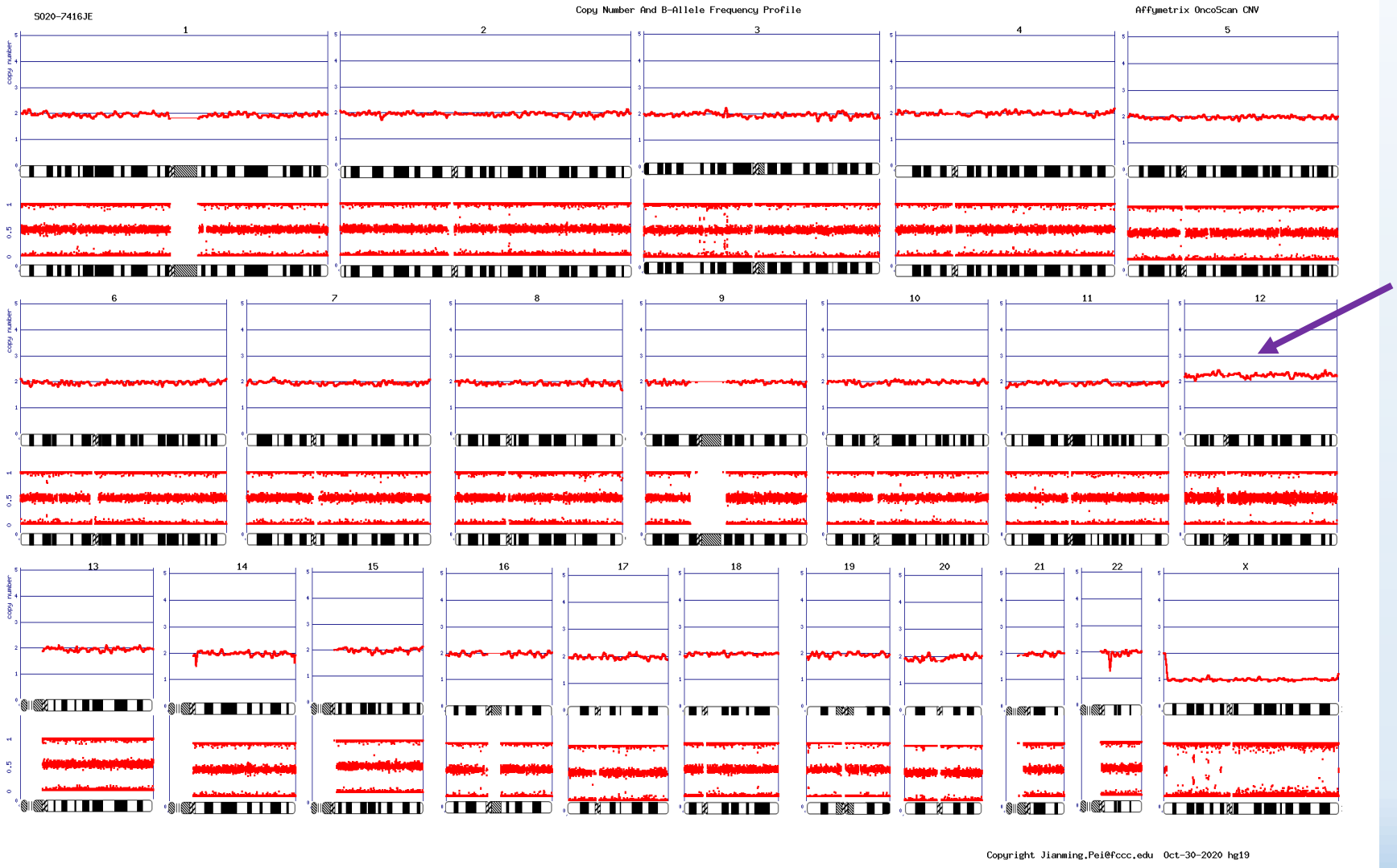


Numerous circulating atypical medium to large sized lymphoid cells with irregular nuclei and prominent nucleoli

Diagnosis ???

Diffuse large B-cell lymphoma, consistent with Richter transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)

Cytogenetics: Case 3



- Cytogenomic microarray analysis (CMA) detected **trisomy 12** in a mosaic state representing about **30% of cells**.

- **FISH** negative for MYC amplification and rearrangements of BCL6, MYC, BCL2 genes.

Molecular studies: Case 3

NGS (275 gene panel)

Gene	Protein Change	cDNA Change	Allele Freq	Significance
BCOR	p.Glu1348fs (E1348fs)	c.4038_4039delAG	29.7%	**TIER 2**
Tumor Mutation Burden: 4.8 Muts/Mb				

Ibrutinib withheld a week prior the surgery

Diagnosis ???

Interesting Feature(s) of Submitted Case

- **Briefly interruption of** a single agent BTK inhibitor by a scheduled oncologic surgery.
- **An incidental finding** of lymph nodes with histologic evidence of **DLBCL and circulating large B-cells**.
- **No clinical signs or symptoms of transformation.**
- No cytogenetic and molecular **evidence of progression.**
- The patient did not resume any CLL-directed therapy post-operatively for approximately 2.5 years until he had progression of CLL which prompted resumption of BTK-targeting therapy (no evidence of hypermetabolic LNs on PET-CT imaging
- Alive as per last follow up

Final Diagnosis:

“Pseudo-Richter’s Transformation” of Chronic lymphocytic leukemia/small lymphocytic lymphoma **following cessation of BTK-inhibitor therapy**

- **a small case series (Slonim et al., 2020)**
- **5 patients (Four males/one female)**
- **Ibrutinib cessation for surgery or acute infection**

Retrospective review (Hampel et al., 2020)

143 patients

ibrutinib cessation temporarily for peri-procedural management or drug toxicity.

A case report (Min Shi et al., June 2024)

1 patient

Acalabrutinib cessation (3 days before and after right ear resection

› Br J Haematol. 2020 Oct;191(1):e22-e25. doi: 10.1111/bjh.16948. Epub 2020 Jul 17.

Pseudo-Richter transformation of chronic lymphocytic leukaemia/small lymphocytic lymphoma following ibrutinib interruption: a diagnostic pitfall

Liron Barnea Slonim [1], Shuo Ma [2 3], Amir Behdad [1 2], Qing Chen [1]

Affiliations + expand

PMID: 32677079 DOI: 10.1111/bjh.16948

› Oncologist. 2020 Nov;25(11):974-980. doi: 10.1634/theoncologist.2020-0388. Epub 2020 Sep 20.

Disease Flare During Temporary Interruption of Ibrutinib Therapy in Patients with Chronic Lymphocytic Leukemia

Paul J Hampel [1], Timothy G Call [1], Kari G Rabe [2], Wei Ding [1], Eli Muchtar [1], Saad S Kenderian [1], Yucai Wang [1], Jose F Leis [3], Thomas E Witzig [1], Amber B Koehler [1], Amie L Fonder [1], Susan M Schwager [1], Daniel L Van Dyke [4], Esteban Braggio [3], Susan L Slager [2], Neil E Kay [1], Sameer A Parikh [1]

Affiliations + expand

PMID: 32886416 PMCID: PMC7648348 DOI: 10.1634/theoncologist.2020-0388

Case Reports › Mayo Clin Proc. 2024 Jun;99(6):867-868. doi: 10.1016/j.mayocp.2024.01.015. Epub 2024 Apr 30.

Pseudo-Richter Transformation of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma After Temporary Acalabrutinib Interruption

Min Shi [1], Ji Yuan [2]

Affiliations – collapse

Affiliations

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2 Hematopathology Division, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN. Electronic address: yuan.ji@mayo.edu.

Histologic evidence of DLBCL

resumption of ibrutinib led to resolution.

Of four patients who underwent biopsy, **two** had evidence of histologic transformation (vs CLL alone in other two patients)

- Asymptomatic
- Aberrant CD5
- No evidence of disease on PET/CT

Take Home Message

- Larger studies will be needed to better characterize this underrecognized phenomenon.

- Pseudo-Richter transformation can be effectively managed by resuming BTK inhibitor therapy