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Navigating Two Hematological Malignancies: Diagnosis of CML in the setting of untreated CLL: A Case report

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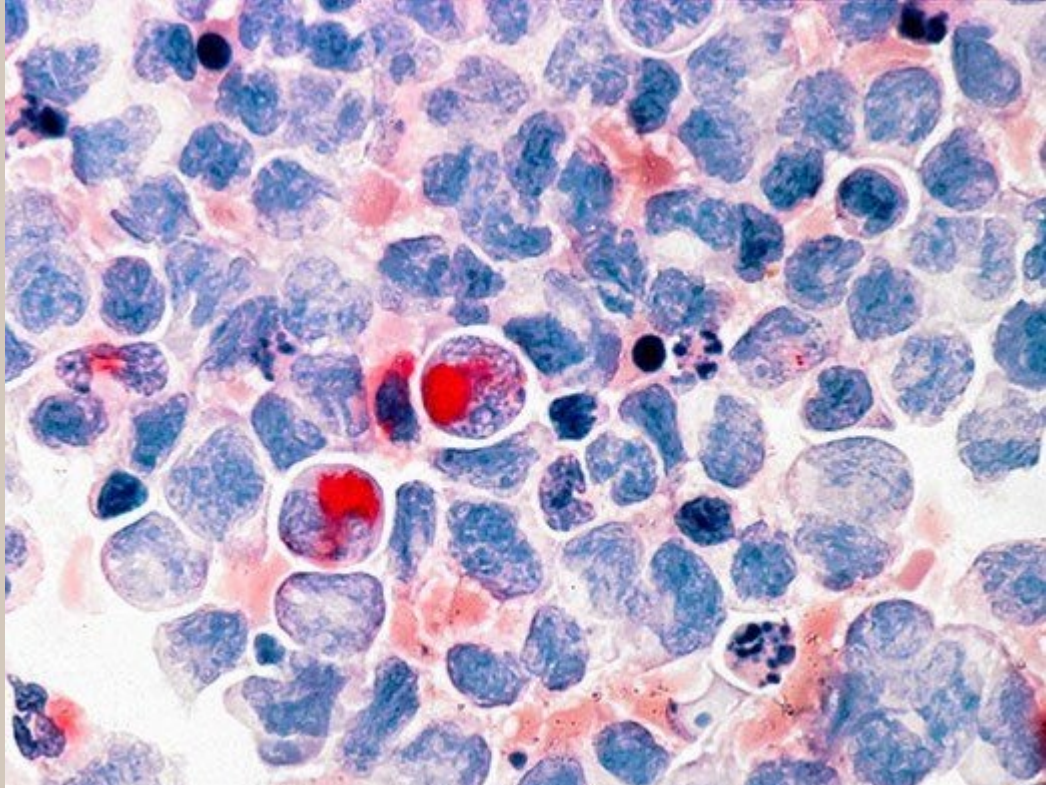
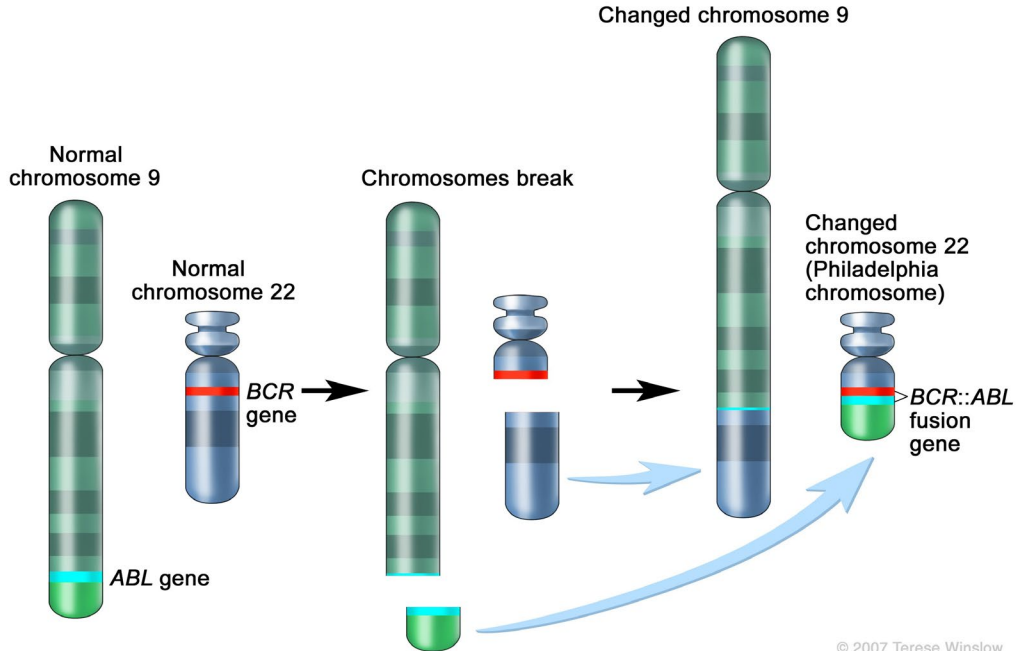




Patient History

- In February 2022, a 65-year-old female presented with fatigue, sweating, hearing loss, and a long-standing history of chronic diarrhea and dyspepsia. she also reported recurrent viral and bacterial infections

- In May 2022, the patient was hospitalized for a urinary tract infection (UTI) with systemic inflammatory response syndrome (SIRS) and urosepsis, and experienced two episodes of COVID-19 infection in February and September 2022

- In October 2022, he developed a painful scalp rash and noticed enlargement of the right cervical lymph nodes.

- Recurrent infections accompanied by night sweats, progressive fatigue, and lymphadenopathy prompted the primary care physician to refer the patient to the hematology/oncology department for further evaluation.

Findings upon initial admission

CBC at admission

- WBC - 12.5 x 10^9/l
- LYM - 5.4 x 10^9/l
- RBC - 5.4 x 10^{12}/l
- Hb - 14.5 g/l
- PLT - 112 x 10^9/l
- ESR - 7 mm/h

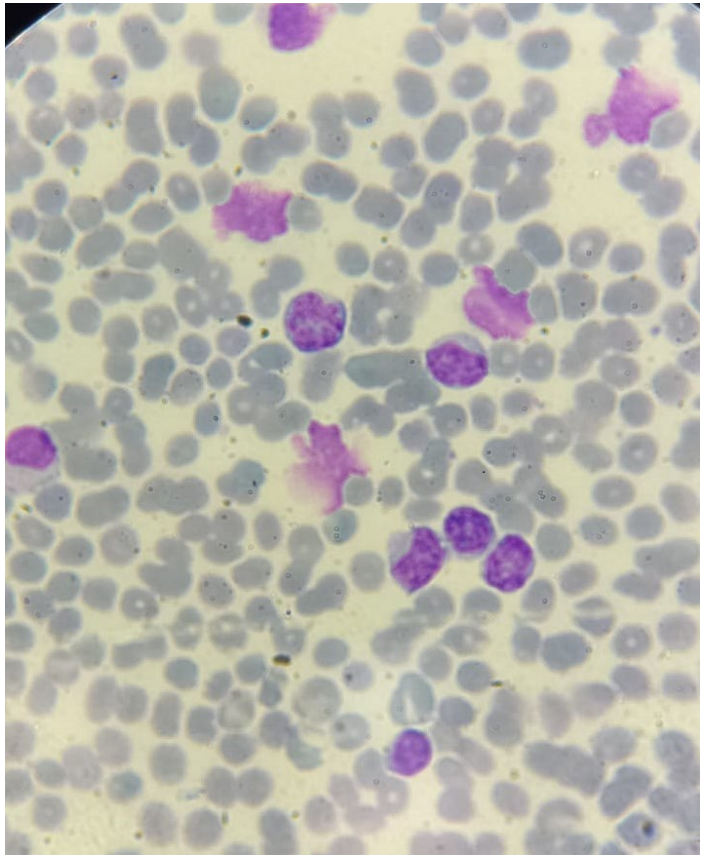
Clinical chemistry

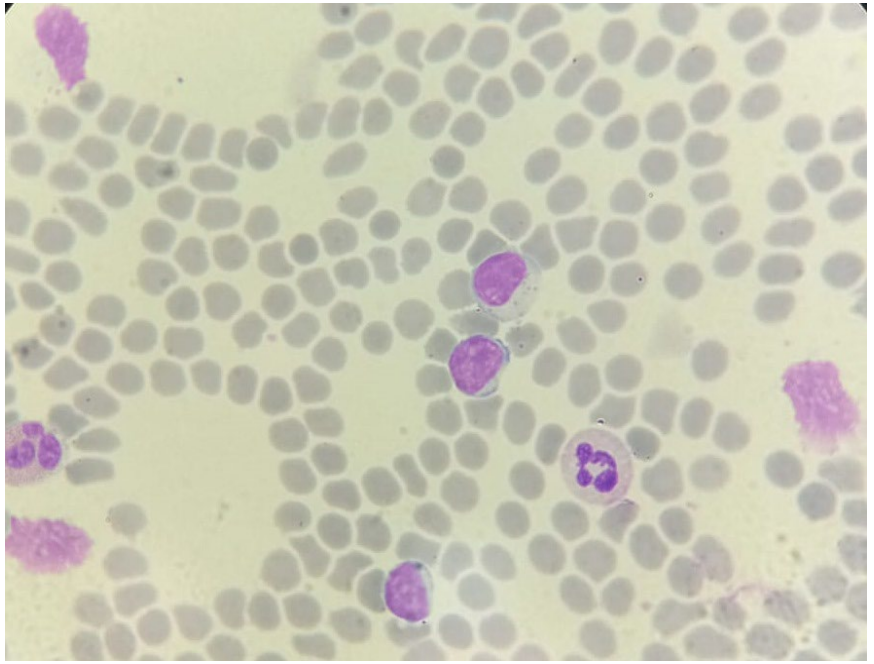
- Ferritin – 32.3 ng/ml
- B12 - 1306 pmol/l
- Folic acid – 5.6 ng/ml
- CRP - Normal
- LDH - 241 U/l
- Creatine, ALT, AST – Normal values

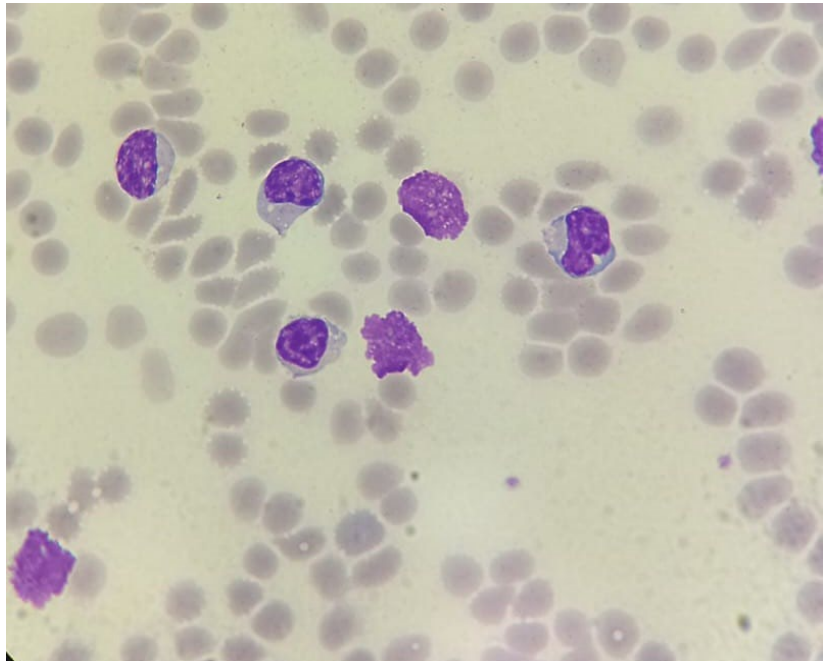
Ultrasound

- Slightly enlarged, hypoechogenic anterior and posterior cervical lymph nodes
- Multiple small lymph nodes detected bilaterally in the supraclavicular and subclavicular regions.
- No evidence of hepatosplenomegaly

Bone marrow smears







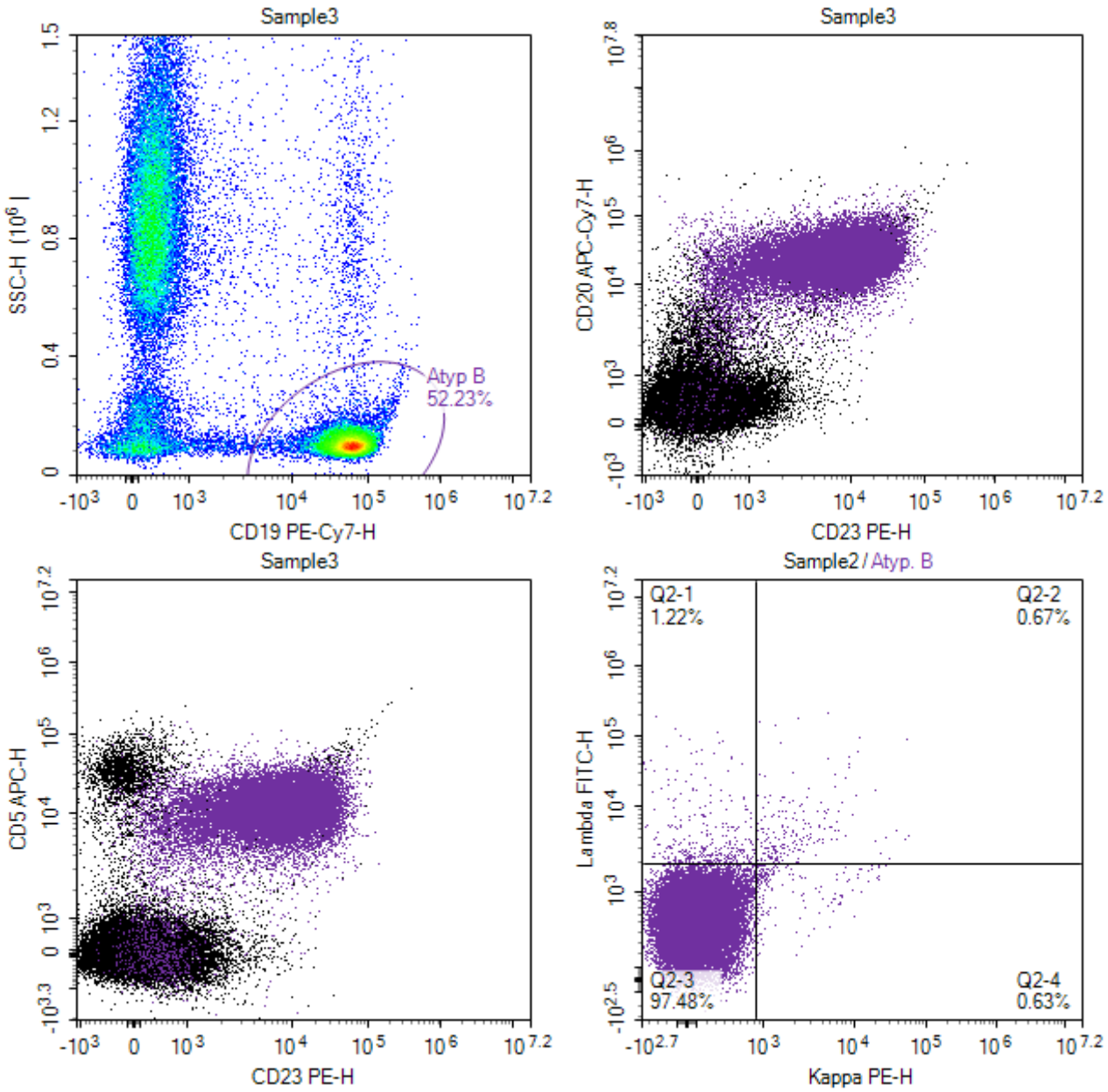
Both peripheral blood and bone marrow smears revealed 50-56% small to medium-sized atypical lymphocytes with abundant cytoplasm, accompanied by the presence of smudge cells.

Flow cytometry Findings

- Flow cytometry identified 56% of atypical B cells consistent with CLL/SLL as positive for CD19, CD22, CD23, CD200, CD5, and negative for CD38 and ZAP70 demonstrating aberrant κ and λ light chain restriction.
- Absolute atypical B lymphocyte count in venous blood exceeded 5 x 10^9/l quantitative threshold.

A diagnosis of CLL was made

- Rai Stage 0, Modified Risk Status - Low



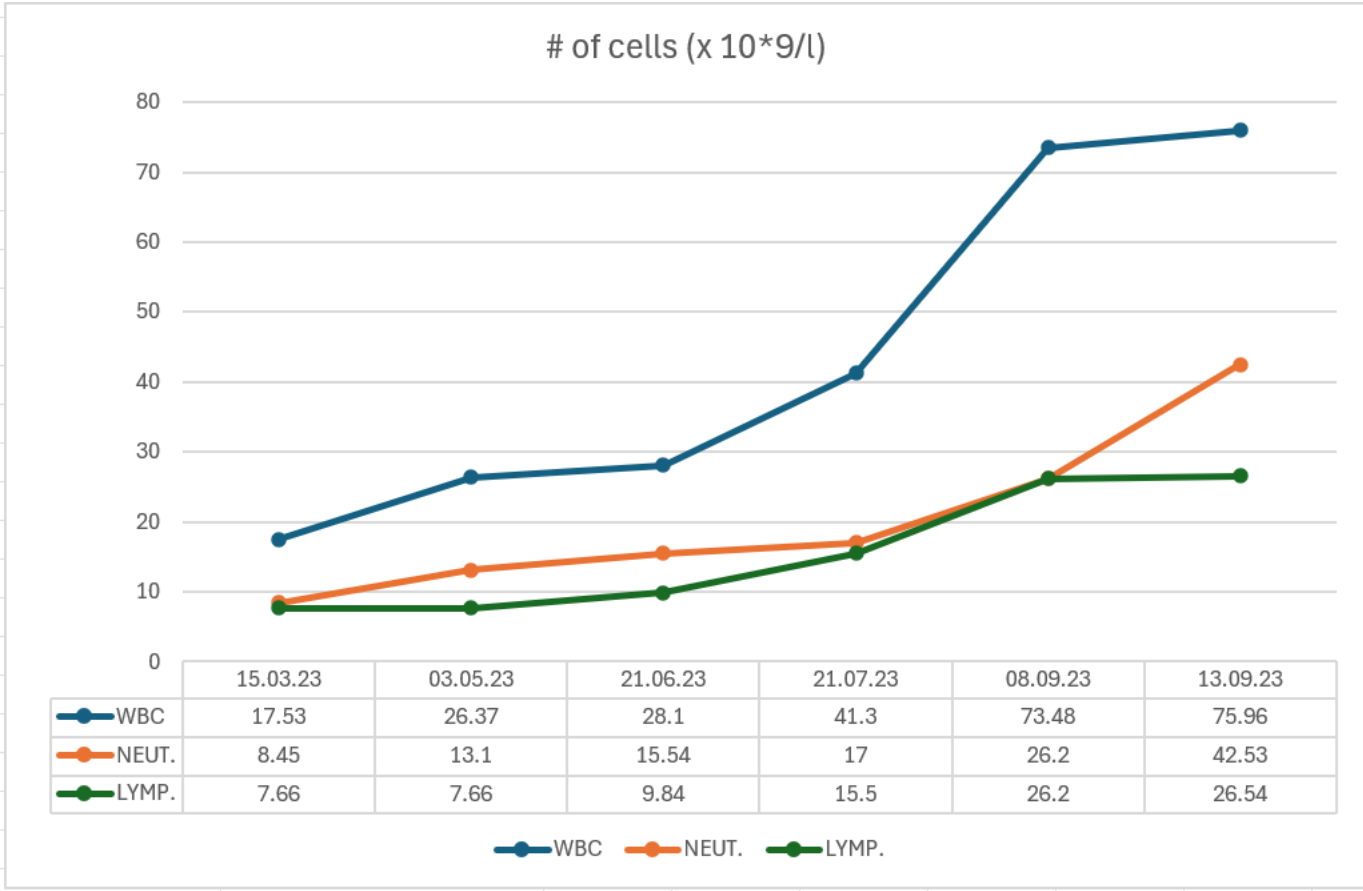
Management

- The patient was not treated for CLL and was instead placed on a “watch and wait”.
- She was treated for Eustachian tube infection with nasal and ear antibiotic sprays.
- Scalp folliculitis was treated with topical 1% salicylic acid and triamcinolone spray.

Findings revealed progressive leucocytosis, neutrophilia and lymphocytosis

Other findings

- Slightly enlarged, hypoechogenic anterior and posterior cervical lymph nodes
- Cytology smears continuedly proved persistence of atypical B lymphocytes and smudge cells
- Multiple small lymph nodes detected bilaterally in the supraclavicular region.
- No evidence of hepatosplenomegaly
- Three hypoechogenic thyroid nodules with vascularization were identified in the isthmus, left, and middle lobes
- Following the FNA biopsy, a diagnosis of autoimmune thyroiditis was made (Bethesda category 2).



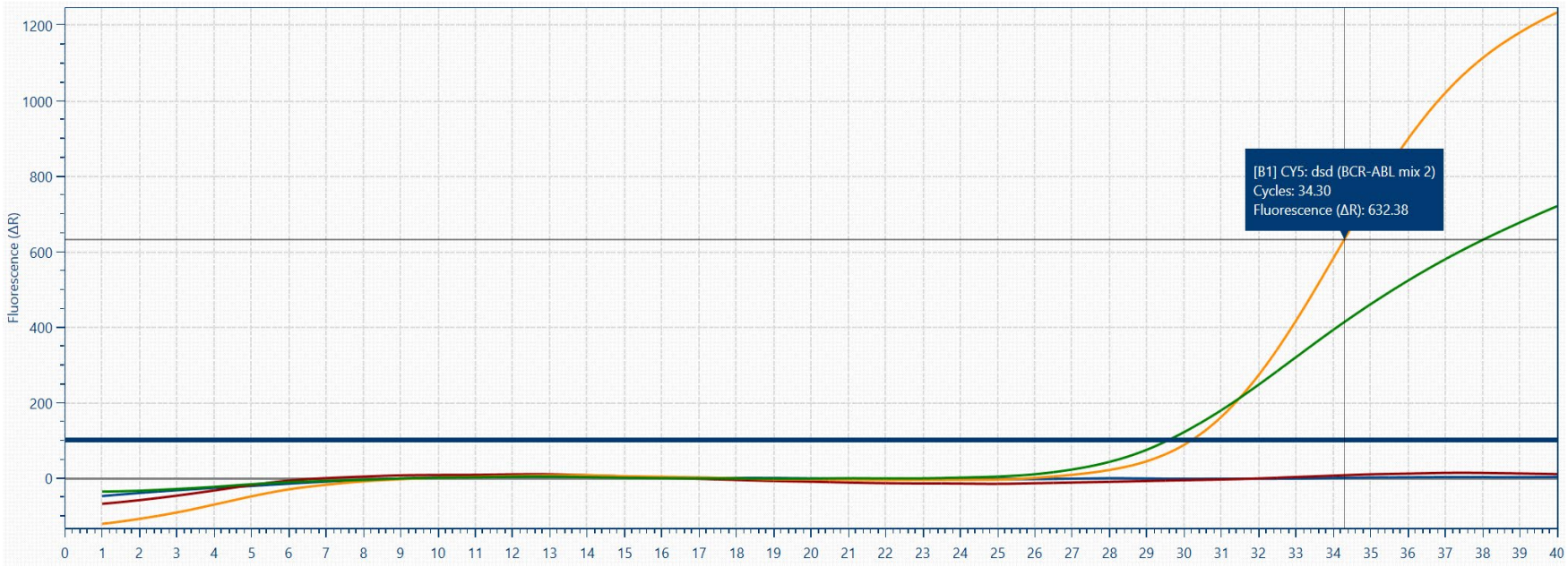
	15.03.23	03.05.23	21.06.23	21.07.23	08.09.23	13.09.23
WBC	17.53	26.37	28.1	41.3	73.48	75.96
NEUT.	8.45	13.1	15.54	17	26.2	42.53
LYMP.	7.66	7.66	9.84	15.5	26.2	26.54

Given the progressive, unexplained leukocytosis accompanied by neutrophilia and basophilia, trephine morphology and IHC was performed

- The findings were consistent with CLL/SLL, characterized by strong positive staining for CD20, CD23, and CD5 in lymphoid aggregates, while showing negative staining for CD3, CD38, and CD34.
- **In addition to atypical lymphocyte aggregates, the study revealed prominent myeloid hyperplasia with an excess of myelocytes and segmented granulocytes.**
- Co-occurrence of CML with CLL was suspected
- Genetic testing was performed to evaluate the t(9;22) translocation, a hallmark of CML, to confirm the suspected diagnosis.

RT-PCR Findings

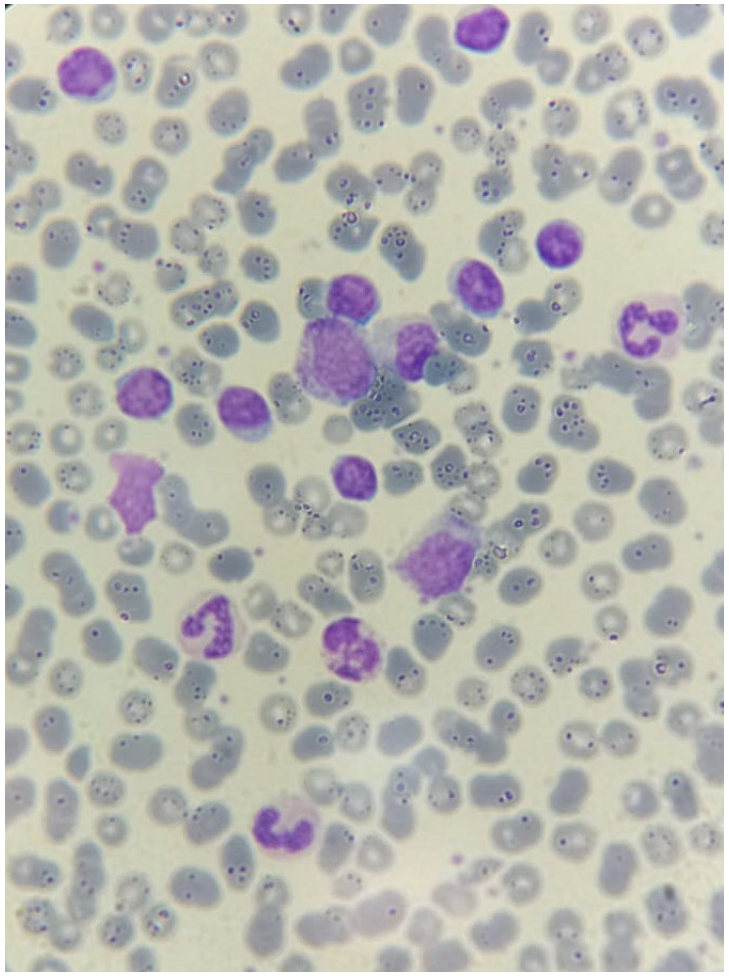
RT-PCR testing identified the **Mbcr (P210)** isoform of the **BCR::ABL1** fusion gene associated with the **t(9;22)(q34;q11)** translocation.

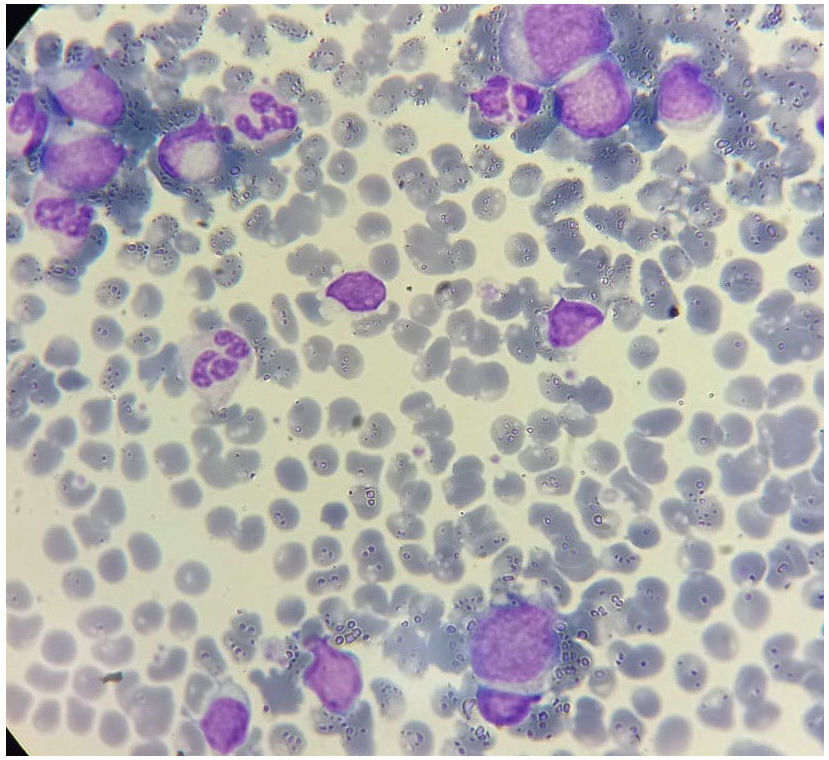


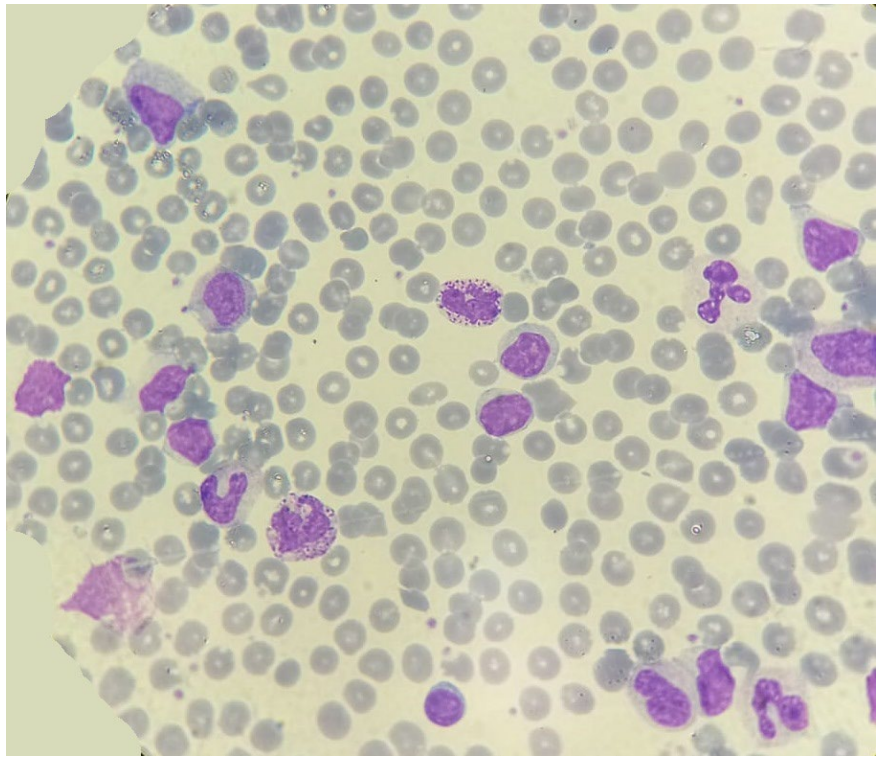
CBC at CML diagnosis timepoint:
RBC – 4.2 x 10^{12}/l, HGB – 120.0 g/l, PLT – 627 x 10^{9}/l, WBC – 120 x 10^{9}/l,

Myeloblast – 4%, Promyelocyte – 6%, Myelocyte – 10%, Metamyelocyte – 11%, Bands – 4%%, Seg – 31%, Basophil- 9%, Eosinophil – 1%, Lymphocyte- 30%, Monocyte- 2%, ESR – 26.

Peripheral blood smear







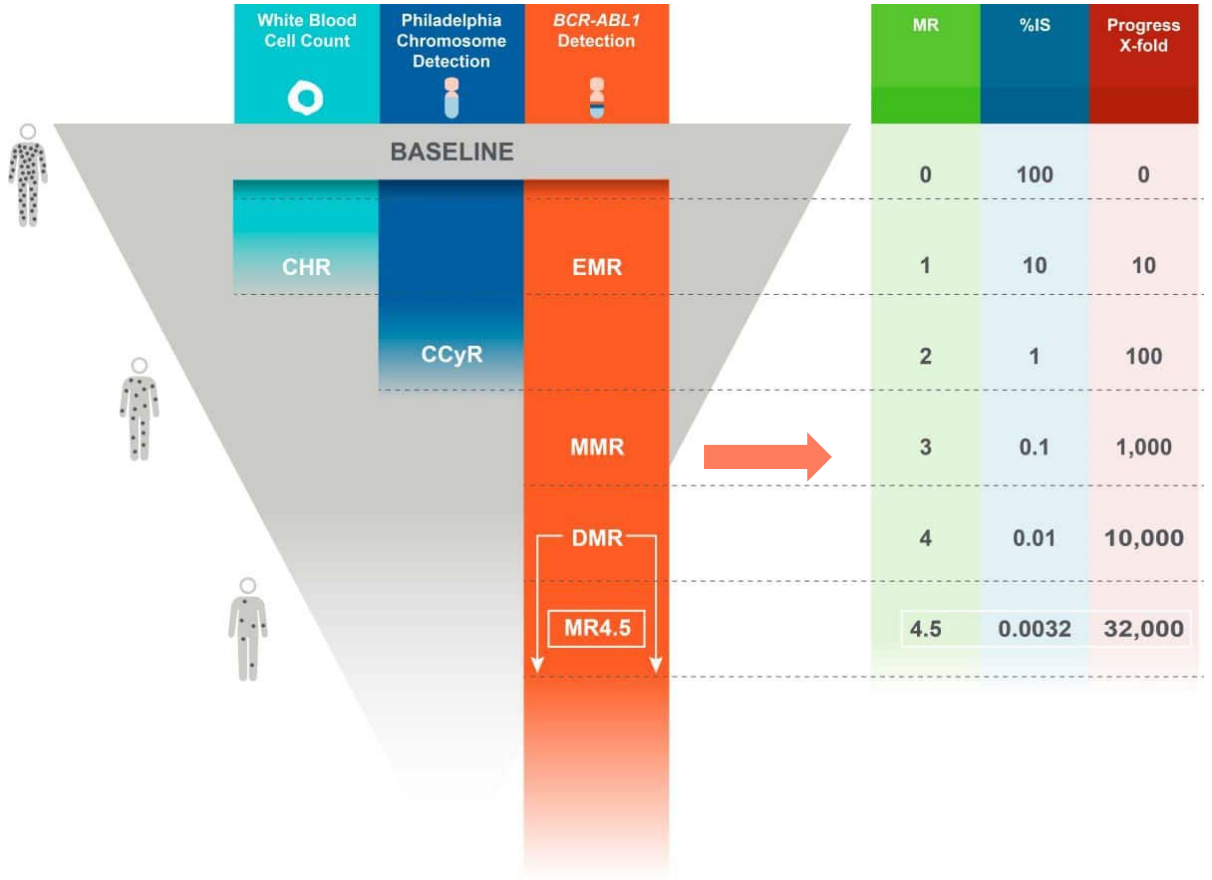
Peripheral blood smear at CML diagnosis confirmed the persistence of atypical lymphocytes, smudge cells and granulocytes at different stages of differentiation

NGS of 141 genes related to hematological malignancies did not reveal any actionable or otherwise pathogenic variants

Panel Gene Content:

ABL1, ADA, ANKRD26, ASXL1, ASXL2, ATM, ATRX, BCL6, BCOR, BCORL1, BCR, BIRC3, BLM, BRAF, BRCA1, BRCA2, C17orf97, CALR, CARD11, CBL, CBLB, CBLC, CDKN2A, CEBPA, CHEK2, CREBBP, CRLF2, CSF1R, CSF3R, CTCF, CUX1, DAXX, DDX41, DNM2, DNMT1, DNMT3A, EED, EGFR, ELANE, EP300, ETNK1, ETV6, EZH2, FAM154B, FAM47A, FAM5C, FAS, FBXW7, FLRT2, FLT3, GATA1, GATA2 GJB3, GNAS, HNRNPK, HRAS, IDH1, IDH2, IKZF1, IKZF3, IL7R, JAK1, JAK2, JAK3, KAT6A, KCNA4, KCNK13, KDM6A, KDR, KIT, KLHDC8B, KLHL6, KMT2A, KMT2C, KRAS, LRRC4, LUC7L2, MAP2K1, MLH1, MPL, MSH2, MSH6, MYC, MYD88, NBN, NF1, NOTCH1, NPAT, NPM1, NRAS, NSD1, NTRK3, OR13H1, OR8B12, P2RY2, PAX5, PCDHB1, PDGFRA, PHF6, PML, PMS2, PRAMEF2, PRF1, PRPF40B, PRPF8, PTEN, PTPN11, RAD21, RB1, RELN, RUNX1, SETBP1, SF1, SF3A1, SF3B1, SH2B3, SH2D1A, SMARCB1, SMC1A, SMC3, SRP72, SRSF2, STAG2, STAT3, STXBP2, SUZ12, TAL1, TERC, TERT, TET2, TNFRSF13B, TP53, TPMT, TUBA3C, U2AF1, U2AF2, WAS, WRN, WT1, XPO1, ZRSR2

Management and Follow



1 December 2023

The patient started treatment with imatinib at 400 mg/day

She has been undergoing regular monitoring of residual BCR::ABL1 transcripts to assess the treatment efficacy

27 May 2024

qPCR monitoring results indicate that the patient has achieved a Major Molecular Response **(MMR) tier: BCR::ABL1 percentage is at 0.034% (IS), MR - 3.47**

CBC results on 25.07.24:
RBC – 4,5 x 10^{12}/l, HGB – 145,0 g/l, **PLT – 380 x 10^9/l, WBC – 6.8 x 10^9/l,**

Myelocyte – 10%, Bands – 2%, Seg – 33%, Basophil-<1%, Eosinophil – 2%, **Lymphocyte- 50%,** Monocyte-6%, ESR – 7.

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Discussion points

- Co-occurrence of CML in the setting of untreated CLL is extremely rare event. The mechanism of developing myeloproliferative and lymphoproliferative disorders in the same patient is still obscure.
- It was hypothesized that the myeloid and lymphoid malignancies may have originated from the concurrent stem cell activation by shared risk factors or unknown hereditary cancer syndromes [1].
- It is believed that stochastically acquired genetic aberrations are more likely to contribute to these individual diseases
- Can we select an efficient scheme to treat both CLL and CML: - Studies evaluating the use of venetoclax in combination with BCR-ABL1 TKIs to treat CML showed a 75% overall response rate and 10.9 months' overall survival [2]
- Imatinib or dasatinib? [3,4]
- Vigilance is essential for hematologists to ensure the early discovery of rare co-occurrences of unrelated hematological malignancies

References

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2. Maiti A, Franquiz MJ, Ravandi F, et al. Venetoclax and BCR-ABL tyrosine kinase inhibitor combinations: outcome in patients with Philadelphia chromosome-positive advanced myeloid leukemias. Acta Haematol 2020;143:567-73.
3. Tecchio C, Nichele I, Todeschini G, et al. Dasatinibinduced response in a rare case of chronic lymphocytic leukaemia associated with chronic myeloid leukaemia. Br. J. Haematol 2009;146:222-3.
4. Boddu P, Gibbons J, Burger J, et al. Co-occurrence of chronic myeloid leukemia with chronic lymphocytic leukemia: a report of two cases. Leuk Lymphoma 2019;60:1568-71.

Thank you