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Acute Myeloid Leukemia with Unreported Translocation (x; 3) (q24; p13): A case report

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Introduction

Acute myeloid leukemia (AML) is typified by the neoplastic clonal expansion of precursor cells and the cessation of differentiation in the bone marrow. (1). According to the American Cancer Society's projections for 2018, there were an estimated 19,520 new cases of AML and 10,670 deaths resulting from this disease in the United States. Additionally, it is estimated that approximately 0.5% of the US population will develop AML. (2). The age-adjusted mortality rates and incidence are reported as 2.8 and 4.3 per 100,000 individuals, respectively. Additionally, the 5-year survival rate is noted to be 27.4%. (3).

The dysregulation of epigenetics plays a key role in developing various diseases, including cancer. The deconvolution of 200 AML genomes, led by The Cancer Genome Atlas, has demonstrated that a considerable number of these AMLs exhibit mutations in epigenetic regulators. (4). Here, we now report an unusual case of AML with an unreported translocation associated with AML.

Case presentation

A 28-year-old non-smoker man initially presented with severe fatigue for a few weeks. He had been diagnosed with mild anemia, but no therapy was given. He also reported weakness and nighttime headaches. For any malignancies, his family history was unremarkable. During the examination, the patient's vital signs were found to be within the expected range of values. There was no observation of lymphadenopathy or splenomegaly. Lung and heart examinations were unremarkable. The initial complete blood count revealed a total leukocyte count of 4530/mm3. (48% blasts, 53.6% Neutrophils, 24.4% Lymphocytes), hemoglobin of 8.6 gm/dl, and a platelet count of 60,000/mm3 (Table 1). He was admitted to the Hemato-oncology ward due to his Bi-cytopenia.

His peripheral blood smear showed 5000/mm3 white blood cell counts with 50% Polymorph nuclear leukocytes (PMNs), 20% immature cells, 22% lymphocytes, and 8% monocytes with a platelet count of 60000/mm3 (Table 3). Red blood cells were hypochromic microcytic with Teardrops and anisocytosis. A diagnostic test for AML is a bone marrow biopsy. (Fig.2) It should also be noted that evaluating essential gene mutations such as FLT3 and NPM1c in our center was impossible. Additional diagnostic procedures, including a peripheral blood smear, bone marrow aspiration, and biopsy, were conducted in order to exclude the possibility of acute leukemia. His second PBS showed WBC: 10000/mm3 with PMN 46%, lymph18%, mono:8%, and blast:28%. Samples of bone marrow were taken for immunophenotypic, morphologic, and

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genetic analysis. His bone marrow aspiration and biopsy were reported as diluted without particles, but about 80% of cells were seen in filtered blasts.

In the cells analyzed, cytogenetic examination revealed an aberrant male chromosomal complement, with the only aberration being a translocation between the short arm of chromosome 3 and the long arm of chromosome X (Fig.1). This translocation is a brand-new anomaly in hematological malignancies that hasn't been documented in any of the references (such the Mitelman database). At first, we suspected a congenital anomaly, but after routinely culturing mitogen-stimulated peripheral blood cells, we found that the abnormality was disease-related and absent in normal cells. In his flow cytometry, CD13, CD33, CD45, CD117, and HLA-DR were 50%, 61%, 83%, 33%, and 46% reported, respectively (Table 2). The flow cytometric analysis and morphology revealed that the case was diagnosed with AML.

Induction chemotherapy was started for the patient with 7+3(cytarabine 100mg/m2/day continuous IV infusions for seven days and danorubicinb12mg/m2/day for three days). On his first and last induction days, CBC was reported in Table 1. After the end of the chemotherapy induction, the patient was discharged from the hospital in a wealth condition. The patient is also under the supervision of our center doctors for further treatment and follow-ups.

Discussion

According to our knowledge, this is the first patient of AML with translocation (x; 3) (q24; p13) to be described. Genetic analysis is essential in classifying AML (5-7). Cytogenetic abnormalities are common in 50% of patients with AML. Chromosome abnormalities are used to classify patients with AML, regardless of blast count. The cytogenetic analysis also reveals prognostic and therapeutic consequences abnormalities, can help evaluate the response to therapy, and will likely play a significant part in abnormality-tailored treatments in the future. Likewise, mutational analysis is particularly vital in diagnosing and treating AML (5).

Three distinct regions on the short arm of chromosome 3 have been associated with tumorigenesis. One of the previously mentioned regions is situated at the chromosomal locus 3p13˜p14.2. (12). Historically, this region has been identified as a common human chromosomal problematic locus. (13)

It is hypothesized that the human chromosomal region 3p12-p23 contains at least three tumor suppressor genes associated with lung cancer, renal cell carcinoma(RCC), and other neoplasias. (14)(15)

A study was conducted in 2007 to examine the cytogenetic alterations in 38 instances of renal tumors in correlation with the histopathological observations. The present study reveals that the structural rearrangements observed in the 3p region were exclusive to clear cell renal cell carcinoma (RCC). Notably, the translocation event between chromosomes 3p13 and 5q22 was the most frequently observed structural rearrangement in this context. (12) The early stages of tumorigenesis are characterized by deletions occurring at the short arm of chromosome 3. (12)

Another study has demonstrated that the elimination of 3p13 characterizes a unique and forceful molecular subgroup of ERG-positive prostate cancers, conceivably instigated by the deactivation of numerous tumor suppressors. (16)

The gene FOXP1 displays broad expression across various adult tissues, however, neoplastic cells frequently manifest a significant alteration in the localization or level of FOXP1 expression. The genomic locus of the human FOXP1 gene is situated on chromosome 3p13.

Forkhead box P1 is a transcription factor that regulates tissue and cell-type-specific gene transcription during development and adulthood. It has potential tumor suppressor properties and is located within a tumor suppressor region. (17)

The involvement of FOXP1 has been observed in various physiological contexts, such as the development of B-cells, differentiation of monocytes, and regeneration of lung the epithelia. The gene in question exhibits

dual functionality in cancer, serving as both an oncogene in B-cell lymphoma, ovarian cancer, and hepatocellular carcinoma, and a tumor suppressor in T-cell lymphoma, NSCLC (Non-Small Cell Lung Cancer), and colorectal cancer. (18-25)

Additionally, there exists supporting evidence indicating that the expression of FOXP1 in cells affected by breast cancer helps reduce the production of cytokines that attract T-cells, thereby preventing the infiltration of stated cells. (18, 26)

FOXP1's function in T-cells may lead to T-cell lymphoma. (18, 26)

In 2023 Zhenya Tang et al. identified 17 AML patients with a pericentric inv(3) leading to MECOM rearrangement, one of them had breakpoints at 3p13 on 3p and 3q26.2 on 3q.(27)

45% of patients (N=5 of 11) in the study of Jelena D. Milosevic et al. carried deletions mapping to the transcription factors FOXP1.(29)

Previous studies have demonstrated that specific translocations in acute myeloid leukemia (AML) can predict response to therapy and overall survival. For example, patients with AML and the t(15;17) translocation, which results in the PML-RARA fusion gene, have a better response to all-trans retinoic acid (ATRA) therapy and a higher overall survival rate compared to those without this translocation (8, 9). Similarly, patients with AML and the t(8;21) translocation, have a more favorable prognosis than patients without this translocation (10, 11).

Katja Seipel et al. at 2020 concluded that in AML patients receiving aggressive induction chemotherapy and autologous stem cell transplant, FOXP1 predicts survival. Patients with high FoxP1 gene expression had shorter progression-free and overall survival.(28)

Levavasseur et al. have shown that Cytogenetically normal AML patients with high FOXP1 expression had worse survival. FOXP1 knockdown increased superoxide anion levels, oxidizing cells and increased cellular oxidative stress. (30)

This translocation may cause chemotherapy refractoriness in AML. Unidentified companion gene mutations may also cause refractory illness. Collecting and reporting uncommon chromosomal abnormalities may help explain AML's pathophysiology and prognosis. Early identification of the disease during the clinical course may lead to better patient outcomes and management in the future. This may facilitate the selection of patients for more aggressive chemotherapy regimens and allogeneic stem cell transplants.

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Table 1

CBC	Initial presentation	First day of induction	Last day of induction
WBC	4530	1530	330
NEUT	2420	310	140
LYMP	1100	710	180
MONO	370	410	10
EOS	20	0	0
BASO	20	10	0
LUC	590	90	0
HGB	8.6	8	7
HCT	27.5	27.0	22.6
PLT	60000	81000	46000
RBC	3480000	3350000	2850000

Table 2

Marker	**Percentage**	**Marker**	**Percentage**
CD19	0	CD10	0
CD22	0	CD11b	0
CD2	0	CD45	83
CD3	0	CD41	0
CD 7	0	CD34	0
CD13	50	CD38	66
CD15	0	CD64	5
CD14	5	CD117	33
CD33	61	HLA-DR	46
		GlycoA	0

Table 3

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PERIPHERAL BLOOD	Before bone marrow biopsy	Simultaneous? with bone marrow biopsy
WBC	5000	10000
Immature cell	20%	28%
PMN	50%	46%
LYMPHOCYTE	22%	18%
Monocyte	8%	8%
Platelets count	60000	60000

Fig 1

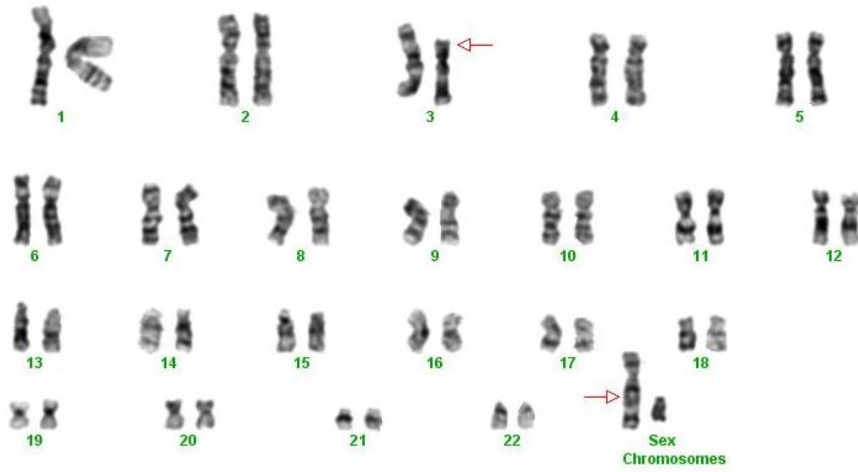

Fig 2

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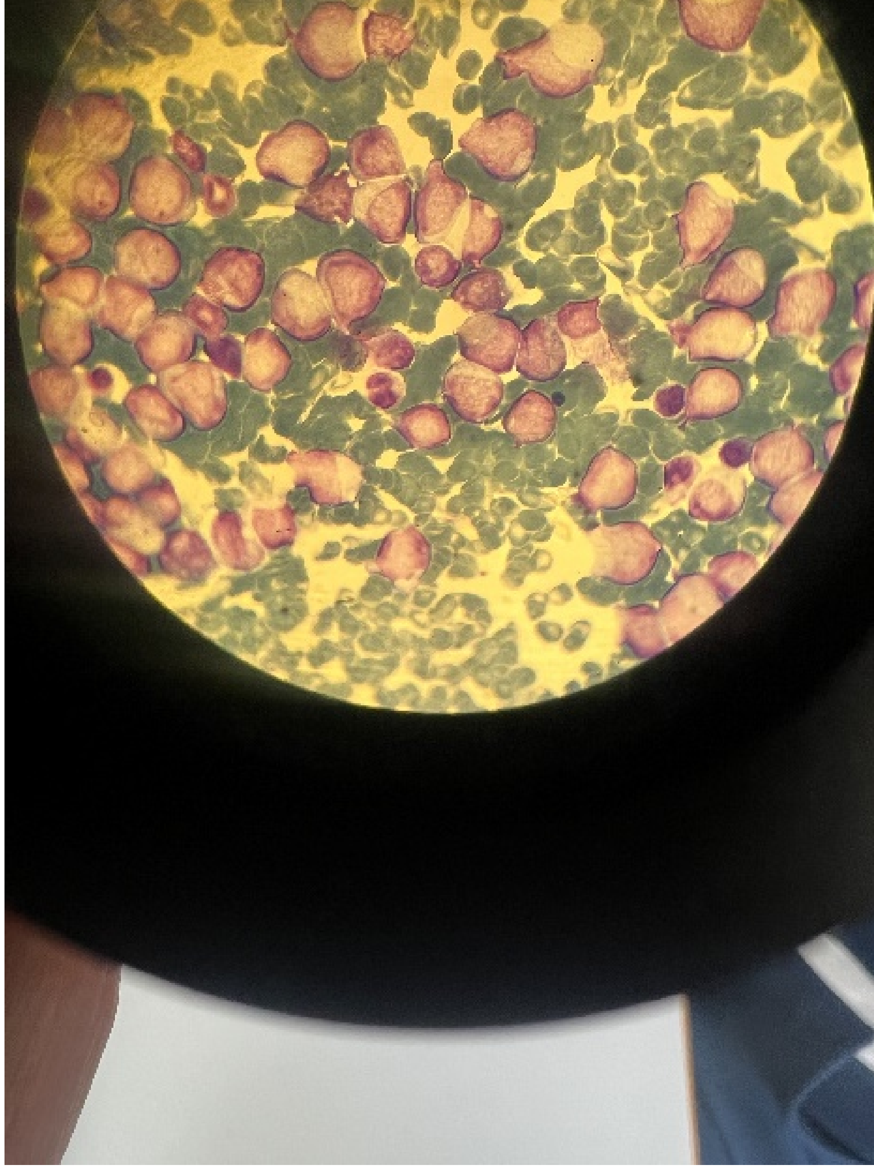

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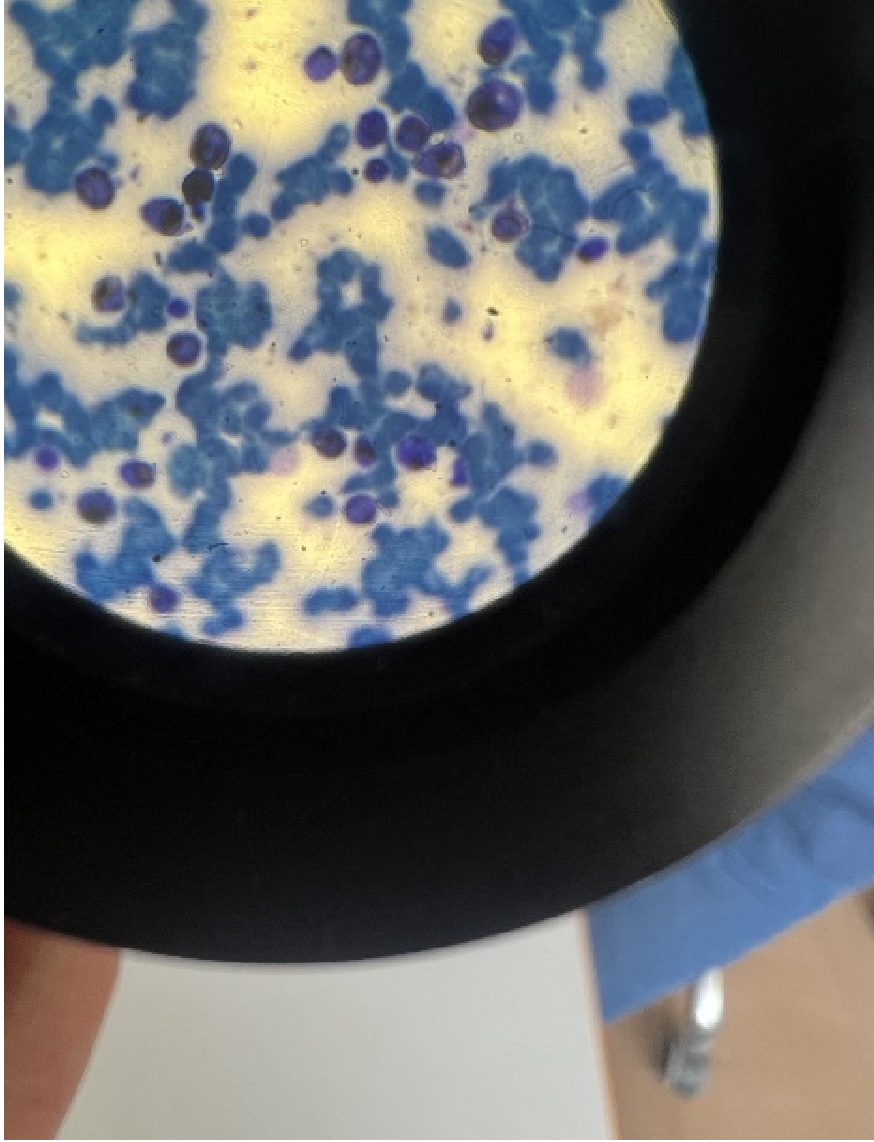

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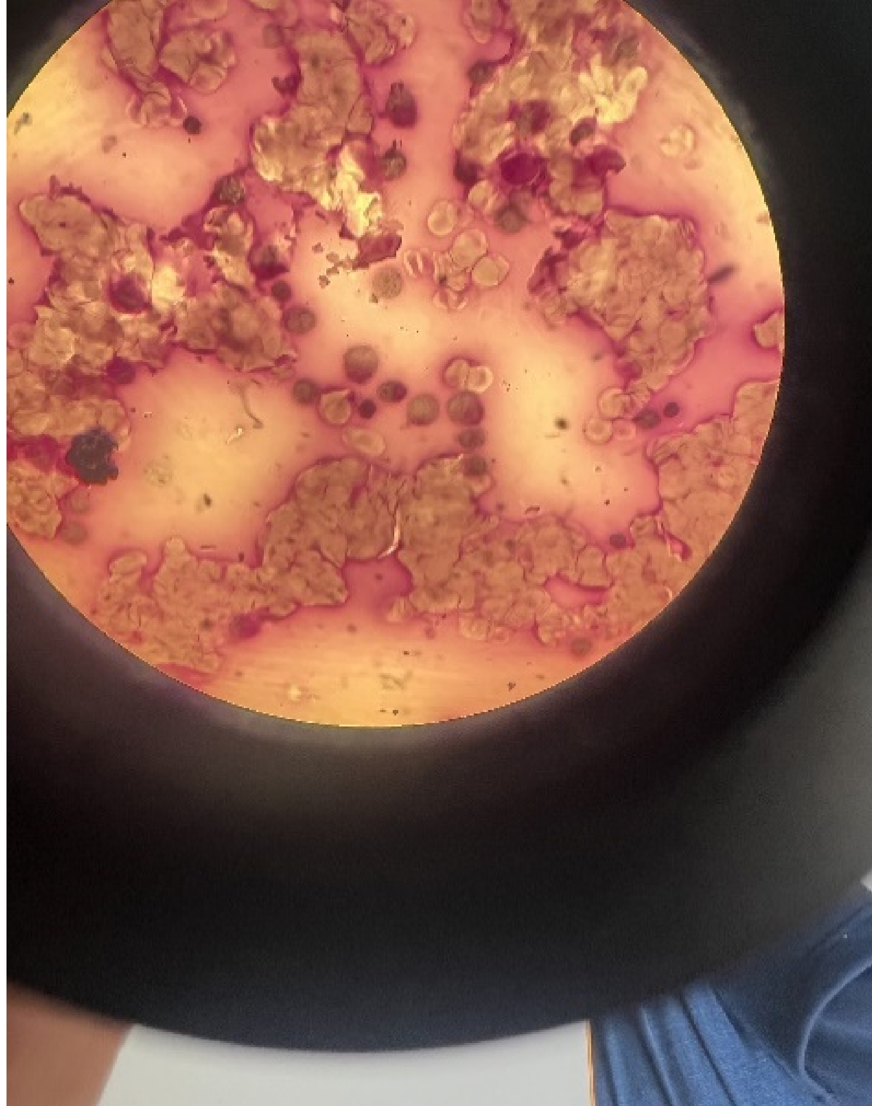

1. Wright's Giemsa stain
2. Sudan staining (heavily positive)
3. Periodic acid-Schiff (PAS) Stain

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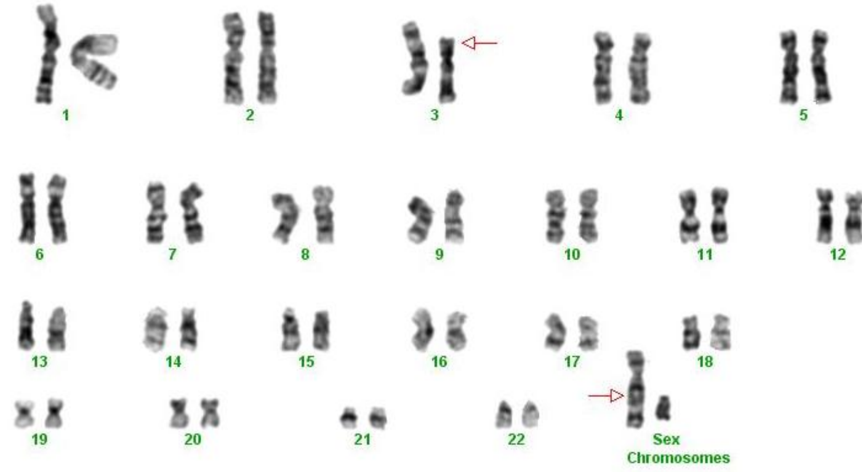

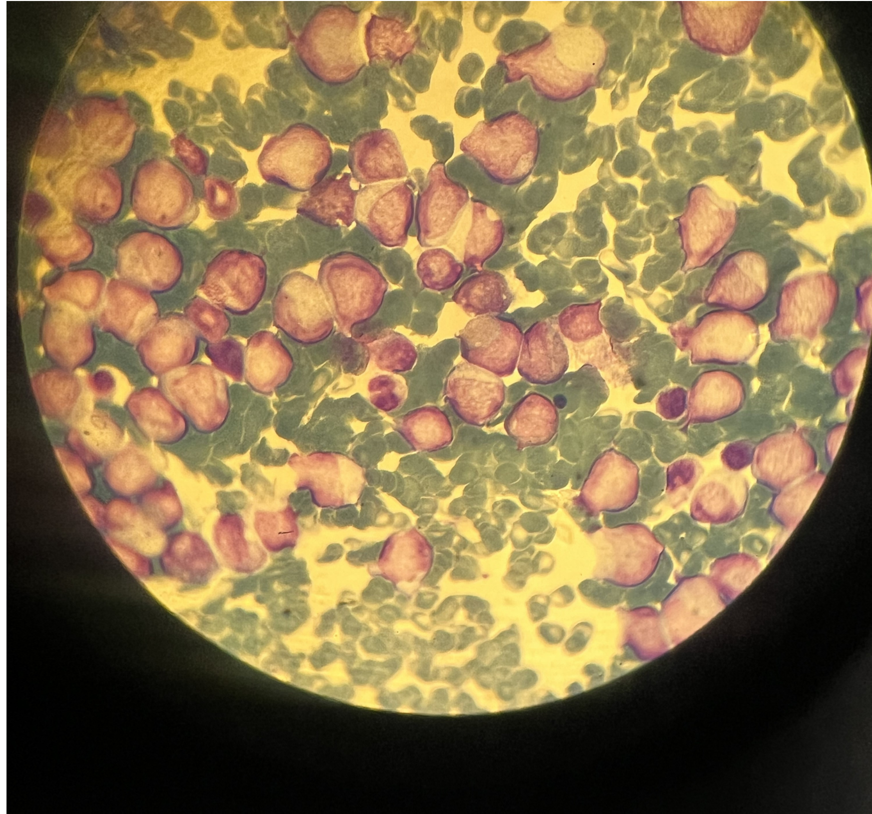

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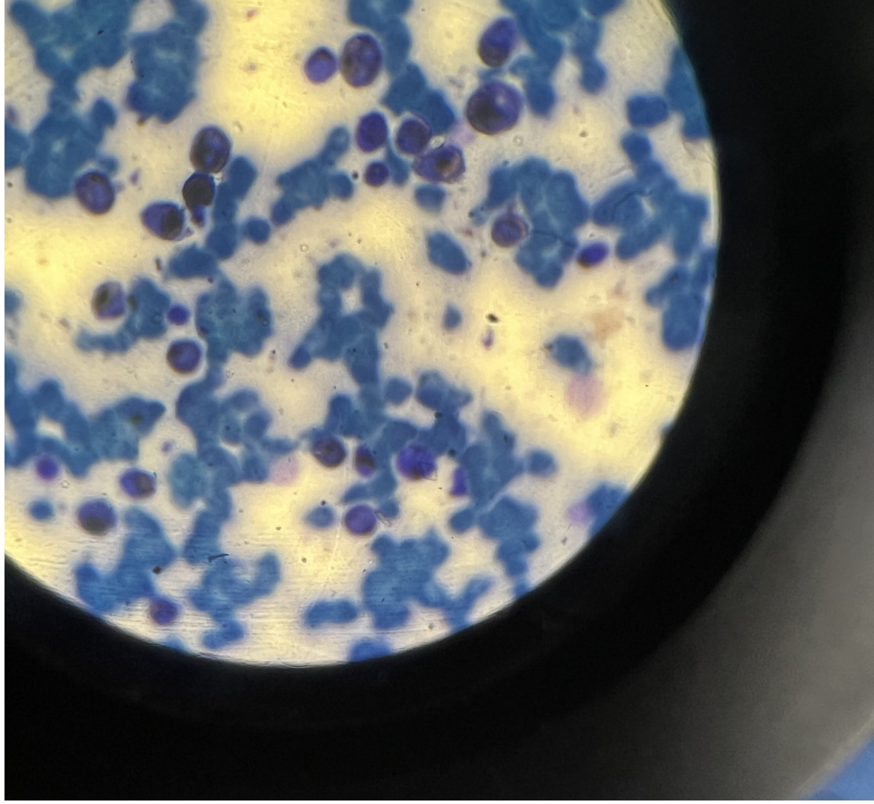

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