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Leukemia and Female Genital Organs

RESEARCH ARTICLE

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Gynecologic Manifestations of Leukemia in Reproductive-Age Women: Ultrasound, Cytology, and Microbiota Findings

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Abstract

Objective: To evaluate the gynecologic and reproductive changes in women of reproductive age diagnosed with leukemia, with an emphasis on menstrual disturbances, vaginal microbiota alterations, and cytological abnormalities. **Methods:** A cross-sectional observational study was conducted involving 100 female patients aged 16 - 46 years with confirmed diagnoses of acute or chronic leukemia. Clinical and gynecological examinations were performed, including cytological assessment (Pap smear), vaginal microbiological analysis, and pelvic ultrasound. Statistical analysis was performed using descriptive methods and Student t-test. **Results:** Hyperpolymenorrhea was observed in 62% of participants, while 21% reported secondary amenorrhea. Vaginal microbiological analysis revealed Grade III–IV dysbiosis in 77.7% of patients, with dominant growth of Candida spp., Staphylococcus aureus, and E. coli. Cytological abnormalities were detected in 50% of cases, including ASCUS (40%) and LSIL (5%). In 28% of cases, leukemic blast cells were identified in cervical smears. Ultrasound findings included enlarged ovaries and uteri in 35% of patients, with evidence of solid infiltrative changes in the external genitalia and mammary glands in isolated cases. **Conclusion:** Leukemia in women of reproductive age is frequently associated with menstrual disorders, significant disturbances in vaginal microbiota, and cytological abnormalities, including evidence of leukemic infiltration. Early gynecological screening in such patients is essential to ensure the timely management of reproductive health complications.

Keywords: Acute leukemia- cervical cytology- gynecologic manifestations

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Introduction

The problem of treatment of acute and chronic leukemia is one of the urgent problems of modern oncohematology. Progressive growth of morbidity dictates the need for a detailed study of this pathology. Factors contributing to the development of leukemia include: chromosomal abnormalities, radiation, toxic effects of the environment, myelodysplasia [1]. The substrate of acute leukemia is immature, young cells - blasts. It is known that in acute leukemia due to infiltration of bone marrow by blast cells and suppression of normal hematopoietic sprouts, the corresponding clinical symptoms develop - anemic syndrome, hemorrhagic syndrome, tumor intoxication and the addition of a secondary infection. Involvement in the tumor process of the reproductive system of women in the pathological process in leukemia diseases is accompanied by various menstrual dysfunctions, most often in the form of meno- and metrorrhagia [2].

Among other manifestations of hemorrhagic syndrome in female genital organs is such a formidable complication as hemorrhage in the ovaries. Fatal intra-abdominal bleeding can occur during ovulation. Another manifestation of menstrual dysfunction in blood diseases is amenorrhea, which is more common in chronic forms of leukemia [3, 4]. In addition, due to immunodeficiency against the background of deep granulocytopenia, bacterial and fungal lesions of the external genital organs are often encountered [5, 6].

Objective

To assess menstrual function and to evaluate the impact of different forms of leukemia on the condition of the female reproductive organs in patients of reproductive age.

Materials and Methods

This cross-sectional study was conducted between

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January 2021 and December 2023 at the Department of Hematology and the Department of Obstetrics and Gynecology of the participating institution. The study included 100 women of reproductive age diagnosed with leukemia and 40 age-matched healthy controls. The diagnosis of leukemia was established by hematologists based on peripheral blood analysis, bone marrow aspiration, cytomorphological evaluation, and immunophenotyping. The distribution of leukemia types included acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL). The control group consisted of clinically healthy women undergoing routine gynecological examination at the same institution during the same period. Inclusion criteria for the main group were female sex, age 18–45 years, confirmed diagnosis of AML, ALL, CML, or CLL, and provision of written informed consent. Inclusion criteria for the control group were age 18–45 years, absence of hematological malignancy, absence of acute infectious disease at the time of examination, and informed consent. Exclusion criteria for both groups included pregnancy, previous hysterectomy or cervical surgery, known gynecologic malignancy, current sexually transmitted infection requiring systemic treatment, antibiotic therapy within four weeks prior to sampling, and hormonal therapy within three months prior to enrollment. All participants were recruited consecutively during the study period.

Gynecological examination, cervical cytology, vaginal sampling and pelvic ultrasound in leukemia patients were performed either at the time of initial diagnosis before initiation of chemotherapy or during the early phase of treatment prior to the development of severe cytopenia. The timing of assessment relative to diagnosis and chemotherapy initiation was recorded for each patient to minimize treatment-related bias. In the control group, examinations were performed during routine outpatient visits.

All participants underwent standardized gynecological examination in the lithotomy position under sterile conditions. From each subject, the following biological samples were collected: (1) a cervical sample for cytological examination (Pap smear), (2) a vaginal swab from the posterior fornix for microbiological analysis, (3) a cervical canal swab for bacteriological culture, and (4) vaginal secretion for immediate pH measurement. Sample collection was performed prior to ultrasound examination and before initiation of any local or systemic antimicrobial therapy. In leukemia patients, sampling was conducted either before the initiation of chemotherapy or during the early treatment phase prior to the development of severe cytopenia in order to minimize treatment-related influence on mucosal findings.

Immediately after collection, cytological smears were prepared on clean glass slides and fixed in 96% ethanol to prevent air-drying artifacts. Slides were labeled with coded identifiers to ensure blinded evaluation. Vaginal and cervical swabs intended for microbiological culture were placed into sterile transport medium and delivered to the laboratory within one hour of collection. Samples for Gram staining were air-dried and processed immediately. Vaginal pH was measured at the time of examination using calibrated indicator strips applied to the lateral vaginal wall.

Cervical cytological samples were obtained from the transformation zone using an Ayre spatula for the ectocervix and an endocervical cytobrush for the endocervical canal. The collected cellular material was evenly spread onto glass slides and immediately fixed with 96% ethanol. All smears were stained using the conventional Papanicolaou method according to standard laboratory protocols. Cytological evaluation was performed independently by two certified cytopathologists with experience in gynecologic cytology who were blinded to the clinical and hematological diagnosis of the participants. In cases of diagnostic discrepancy, consensus review was performed. Interpretation of cytological findings was conducted according to the The Bethesda System (2014 revision), an internationally standardized reporting system for cervical cytology that ensures uniform diagnostic terminology and clinical management guidance.

Specimen adequacy was first evaluated and categorized as satisfactory or unsatisfactory for evaluation based on cellularity, presence of transformation zone components, and absence of obscuring factors such as blood or inflammation. Only satisfactory smears were included in the final cytological analysis.

Cytological findings were reported under the following standardized categories: Negative for Intraepithelial Lesion or Malignancy (NILM), which includes normal cytology and reactive inflammatory changes; Atypical Squamous Cells of Undetermined Significance (ASC-US), defined as squamous epithelial abnormalities insufficient for definitive classification as intraepithelial lesion; Low-Grade Squamous Intraepithelial Lesion (LSIL), encompassing HPV-associated mild dysplasia and cervical intraepithelial neoplasia grade 1 (CIN 1); High-Grade Squamous Intraepithelial Lesion (HSIL), including moderate to severe dysplasia corresponding to CIN 2 and CIN 3; Atypical Glandular Cells (AGC); and other malignant or suspicious findings when present.

In addition to epithelial abnormalities, particular attention was paid to the identification of atypical hematopoietic elements. The presence of leukemic blast cells in cervical smears was documented separately and described morphologically, including nuclear-cytoplasmic ratio, chromatin pattern, nucleoli prominence, and cytoplasmic features. However, classification of epithelial lesions strictly followed Bethesda 2014 criteria to ensure international comparability of results.

All cytological assessments were conducted independently by two certified cytopathologists. In cases of discrepancy, slides were re-evaluated jointly to reach consensus diagnosis. Cytological examination was performed in both leukemia patients and control subjects under identical laboratory conditions to ensure comparability of findings.

Vaginal microbiological analysis was performed in both leukemia patients and control subjects. Vaginal specimens were collected from the posterior fornix using sterile cotton swabs during speculum examination, prior to any other vaginal manipulation. An additional swab

was obtained from the cervical canal for bacteriological culture. All samples were collected under aseptic conditions. Immediately after collection, one swab was used for direct microscopic examination, and a thin smear was prepared on a clean glass slide. The smears were air-dried and stained using the Gram staining method with standard laboratory reagents (crystal violet, Gram's iodine solution, 96% ethanol for decolorization, and safranin counterstain). Microscopic evaluation was performed under oil immersion (×1,000 magnification) to assess bacterial morphotypes, leukocyte count, epithelial cells, presence of clue cells, and fungal elements. Vaginal microbiota status was determined using the Nugent scoring system, based on quantitative assessment of Gram-positive Lactobacillus morphotypes, Gram-variable Gardnerella/Bacteroides morphotypes, and curved Gram-negative rods. Nugent scores were interpreted as 0–3 (normal microbiota), 4–6 (intermediate flora), and 7–10 (bacterial vaginosis).

For culture-based microbial analysis, the second swab was placed into sterile transport medium and delivered to the microbiology laboratory within one hour of collection. Specimens were inoculated onto 5% sheep blood agar, MacConkey agar (for Gram-negative enteric bacteria), and Sabouraud dextrose agar (for fungal detection). Culture plates were incubated aerobically at 37°C for 18–24 hours. Fungal cultures on Sabouraud agar were incubated for up to 48 hours. Bacterial growth was quantified semi-quantitatively and expressed in colony-forming units (CFU/mL).

Identification of isolated microorganisms was performed based on colony morphology, Gram staining characteristics, catalase and coagulase testing (for Staphylococcus species), oxidase testing (for Gram-negative organisms), and standard biochemical reactions according to established microbiological identification protocols. Candida species were identified by characteristic colony morphology on Sabouraud agar and confirmed by microscopic evaluation of budding yeast cells and pseudohyphae formation.

Vaginal pH was measured immediately after specimen collection using calibrated indicator strips with a measurement range of 3.8–6.0, applied directly to the lateral vaginal wall. A pH value >4.5 was considered elevated.

All microbiological procedures were performed under identical laboratory conditions for both study groups to ensure comparability of results.

Pelvic ultrasound examination was performed in both leukemia patients and control subjects. All examinations were conducted by a board-certified gynecologist with more than five years of experience in gynecologic ultrasonography, who was blinded to cytological and microbiological findings to reduce observer bias. Ultrasound assessments were carried out using an ALOKA SSD-630 ultrasound system (Aloka Co., Ltd., Japan) equipped with a 5 MHz transvaginal probe and a 3.5 MHz convex transabdominal probe. The transvaginal approach was used in sexually active women, while the transabdominal approach was applied when clinically indicated.

A standardized structured ultrasound reporting form was used for documentation. The following parameters were systematically evaluated: uterine size and position, myometrial echotexture, endometrial thickness and homogeneity, ovarian dimensions and morphology, follicular structure, presence of cystic or solid adnexal masses, and free pelvic fluid. Particular attention was given to findings suggestive of leukemic infiltration, including diffuse uterine enlargement, heterogeneous myometrial structure, ovarian enlargement with reduced follicular pattern, and solid infiltrative lesions of the adnexa or external genital region.

All ultrasound reports were reviewed and analyzed retrospectively using the recorded measurements and descriptive findings documented at the time of examination. Control group participants underwent the same ultrasound protocol under identical technical conditions to ensure comparability between groups. Hematological parameters, including complete blood count, bone marrow cytology, and coagulation profile, were obtained from medical records and analyzed in correlation with gynecological findings. Statistical analysis was performed using descriptive and inferential methods. Continuous variables were expressed as mean ± standard deviation, and categorical variables as absolute numbers and percentages. Group comparisons were performed using Student's t-test for continuous variables and chi-square test for categorical variables where appropriate. A p-value <0.05 was considered statistically significant.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board of the participating institution, and written informed consent was obtained from all participants prior to inclusion in the study.

Results

Menstrual abnormalities

The main group included 100 women with leukemia aged 16–46 years (mean 32.0 ± 0.44 years). Heavy and prolonged menstruation (hyperpolymenorrhea) was reported by 62 patients (62.0%). Bleeding was described as bright red with clots and lasted from 9–10 up to ≥22 days. In 60 cases (60.0%), uterine bleeding occurred concomitantly with epistaxis, gingival bleeding, or cutaneous hemorrhages. Twenty-one patients (21.0%) presented with secondary amenorrhea (absence of menstruation for ≥3 months). Among these, 18 (85.7%) reported onset after initiation of chemotherapy, whereas 3 (14.3%) reported amenorrhea prior to leukemia diagnosis and treatment.

Vaginal microbiota and pH

Vaginal microbiological analysis was performed in 90 patients with leukemia. Pruritus, burning, and abundant vaginal discharge were reported by 52% of examined patients. On gynecological examination, mucosal edema, hyperemia, and abundant cheesy or purulent discharge were documented in symptomatic individuals.

Bacterioscopic evaluation demonstrated grade II

vaginal purity in 16 patients (17.7%), whereas 70 patients (77.7%) exhibited grade III–IV purity (Table 1). The frequency of grade III–IV findings was 7.7-fold lower in the control group. Vaginal pH correlated with purity grade: in patients with grade I–II purity, mean pH was 5.5 ± 0.11, whereas in the control group with grade I–II purity, pH remained approximately 4.0. Grade III–IV purity was not observed in controls.

Bacteriological culture identified pathogenic and opportunistic microorganisms, including Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus hemolyticus, Streptococcus viridans, Enterococcus faecalis, and Escherichia coli, with colony counts ranging from 10^5 to 10^8 CFU/mL. Candida species (Candida albicans) were detected in 18 patients (18.0%).

Cervical cytology and blast cells

Cytological examination was performed in 80 patients with leukemia and 20 controls (Tables 2). A normal cytological pattern was identified in 4 patients (5.0%) in the leukemia group and in 16 controls (80.0%). Reactive inflammatory changes were observed in 40 patients (50.0%) and in 4 controls (20.0%).

Atypical squamous cells of undetermined significance (ASC-US) were identified in 32 patients (40.0%) with leukemia. Low-grade squamous intraepithelial lesion (LSIL) was detected in 4 patients (5.0%). ASC-US and LSIL were not observed in controls (Table 2).

Blast cells were detected in cervical smears of 28 patients (28.0%) with leukemia. Morphological characteristics corresponded to the hematological subtype: myeloblasts with high nuclear-to-cytoplasmic ratio and prominent nucleoli in myeloblastic variants; smaller lymphoblasts with scant cytoplasm in lymphoblastic variants; and polymorphic promyelocytes with abundant granularity in acute promyelocytic leukemia.

Ultrasound Findings Suggestive of Leukemic Infiltration

Pelvic ultrasound was performed in 98 patients presenting with hyperpolymenorrhea. During active uterine bleeding, endometrial thickness ranged from 1–2 mm to 5 mm. However, two patients (one with AML and one with ALL) demonstrated marked endometrial thickening (12–13 mm) on days 9–12 of bleeding. Diagnostic curettage was performed at platelet counts of 136×10^9/L and 124×10^9/L, respectively, and histological examination confirmed glandular hyperplasia.

Ovarian enlargement with structural alteration was identified in several cases. The ovaries measured up to 50 × 42 mm and were characterized by cortical compaction and reduced follicular differentiation. In one patient, the ovary was markedly enlarged, palpable through the anterior abdominal wall, and associated with localized pain. Ovarian infiltration was documented in three patients (two with ALL and one with AML).

Diffuse uterine enlargement corresponding to a 6–7-week gestational size was observed in two patients (ALL and CML) without a prior gynecologic history of uterine enlargement.

Tumor-like infiltration of the external genitalia was detected in five patients. Four patients (4.0%) exhibited solid infiltrative lesions of the labia majora, and one patient demonstrated vaginal mucosal infiltration. The lesions were round, poorly demarcated, immobile, slightly painful, and ranged from 2.5 to 8 cm in diameter. Cytological examination confirmed the presence of blast cells in all cases.

Additionally, one 15-year-old patient with ALL presented with bilateral mammary gland enlargement and tenderness. Ultrasound examination revealed diffuse glandular compaction consistent with leukemic infiltration (Table 3).

Table 1. Vaginal pH According to Vaginal Purity Grade in Leukemia Patients and Healthy Controls

Group	n	Vaginal Purity Grade	Vaginal pH (Mean ± SD)	p-value*
Leukemia patients	60	Grade I–II	5.5 ± 0.11	<0.001
		Grade III–IV	6.7 ± 0.04	—
Healthy controls	20	Grade I–II	4.0 ± 0.03	—
		Grade III–IV	0 (0%)	—

*P-value compares leukemia patients with Grade I–II purity to healthy controls with Grade I–II purity. No healthy controls exhibited Grade III–IV vaginal purity.

Table 2. Cervical Cytology Findings in Leukemia Patients and Healthy Controls

Cytological Classification (Bethesda 2014)	Leukemia Patients (n=80)	Healthy Controls (n=20)	p-value
Class I: Normal (NILM)	4 (5.0%)	16 (80.0%)	<0.001
Class II: Reactive inflammatory changes	40 (50.0%)	4 (20.0%)	<0.01
ASC-US	32 (40.0%)	0 (0%)	<0.001
LSIL	4 (5.0%)	0 (0%)	<0.05

Abbreviations: NILM, negative for intraepithelial lesion or malignancy; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion.

Table 3. Genital Organ Infiltration According to Leukemia Type

Site of Infiltration	AML (n=36)	ALL (n=34)	APL (n=8)	CML (n=12)	CLL (n=10)	Total (N=100)
External genitalia / vagina	3 (8.3%)	2 (5.9%)	1 (12.5%)	1 (8.3%)	1 (10.0%)	8 (8.0%)
Uterine body	2 (5.6%)	1 (2.9%)	1 (12.5%)	2 (16.7%)	1 (10.0%)	7 (7.0%)
Ovaries	1 (2.8%)	2 (5.9%)	0	0	0	3 (3.0%)
Endometrium	0	1 (2.9%)	1 (12.5%)	1 (8.3%)	0	3 (3.0%)
Mammary glands	0	1 (2.9%)	0	0	0	1 (1.0%)

Note: Some patients presented with infiltration at more than one site. Percentages are calculated within each leukemia subtype. Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; APL, acute promyelocytic leukemia; CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia.

Discussion

This study demonstrates that leukemia in women of reproductive age is frequently associated with menstrual dysfunction, disturbances of vaginal microbiota, inflammatory and atypical cytological findings, and evidence of genital organ infiltration on imaging and cytology. These findings directly address the study objective of evaluating the impact of different forms of leukemia on menstrual function and the condition of the female reproductive organs.

Menstrual abnormalities represented one of the most prominent clinical manifestations. Excessive and prolonged uterine bleeding in patients with leukemia is consistent with the well-established effects of thrombocytopenia and coagulation disorders in hematologic malignancies [3, 4]. Similar observations have been reported in women with acute leukemia, particularly during early disease stages or induction therapy [2]. Hemorrhagic syndrome contributes to endometrial instability and prolonged bleeding.

Secondary amenorrhea, particularly following chemotherapy, aligns with evidence regarding the gonadotoxic effects of cytotoxic agents [7, 8]. Alkylating agents and anthracycline-based regimens are known to impair ovarian reserve through follicular depletion and stromal fibrosis [7]. The ultrasound findings of ovarian compaction and reduced follicular structure in affected patients may reflect early ovarian dysfunction. Thus, both disease-related hematologic disturbances and treatment-related ovarian toxicity likely contribute to the observed menstrual disorders.

The predominance of grade III–IV vaginal dysbiosis and elevated vaginal pH reflects disruption of the normal lactobacillus-dominant microenvironment. Similar alterations in vaginal flora have been described in immunocompromised patients and those undergoing chemotherapy for hematologic malignancies [5, 9]. Neutropenia and impaired mucosal immunity facilitate colonization by opportunistic bacterial and fungal organisms. The high prevalence of Candida species and mixed aerobic flora in this cohort supports previously reported associations between systemic immunosuppression and genital infections [5].

Cytological evaluation revealed predominantly reactive inflammatory changes, with a smaller proportion of ASCUS and infrequent LSIL. This pattern suggests that most epithelial abnormalities were secondary to inflammation rather than true dysplastic transformation. Comparable findings have been described in immunocompromised populations, where inflammatory cytological patterns are more frequent than high-grade intraepithelial lesions.

Importantly, the detection of leukemic blast cells in cervical smears indicates direct involvement of genital mucosa in the leukemic process. Extramedullary infiltration is a recognized manifestation of leukemia, particularly in acute forms. Reports of leukemic infiltration involving the skin, mucosa, and other organs support the systemic nature of the disease. The presence of blasts in cervical cytology in this study extends these observations to the lower genital tract.

Ultrasound findings of ovarian and uterine enlargement, as well as tumor-like infiltrates of the external genitalia and isolated mammary involvement, further support extramedullary spread. Infiltrative changes were more frequently observed in acute leukemia subtypes, consistent with their more aggressive biological behavior. Similar clinical presentations have been described in case-based reports of genital organ infiltration in hematologic malignancies [6]. Such findings may mimic benign gynecologic pathology, underscoring the need for careful diagnostic evaluation.

Clinically, these results highlight the importance of integrating gynecological assessment into routine management of women with leukemia. Early identification of abnormal uterine bleeding, vaginal infections, and cytological abnormalities enables timely supportive therapy and appropriate monitoring for possible extramedullary involvement. From a scientific perspective, the findings contribute to a broader understanding of reproductive organ involvement in systemic hematologic disease.

Several limitations should be acknowledged. The single-center, cross-sectional design limits generalizability and precludes evaluation of longitudinal changes during chemotherapy. The sample size within individual leukemia subtypes was relatively small, restricting detailed subgroup comparisons. Hormonal profiling and long-term reproductive outcomes were not assessed, limiting conclusions regarding fertility preservation. In addition, microbiological analysis relied primarily on culture-based methods without molecular characterization of the vaginal microbiome.

In conclusion, leukemia in women of reproductive age is associated with a broad spectrum of gynecologic manifestations, including hemorrhagic menstrual disorders, vaginal dysbiosis, predominantly inflammatory cytological changes, and, in some cases, direct leukemic infiltration of genital tissues. Recognition of these manifestations supports the need for multidisciplinary collaboration between hematologists and gynecologists to optimize clinical management and reproductive health outcomes.

Author Contribution Statement

Conceptualization: N.M.M., K.P.I. Methodology: N.M.M., D.T.B., G.A.A. Investigation: D.T.B., D.T.A., G.A.A. Data curation: D.T.B., D.T.A. Formal analysis: N.M.M., K.P.I. Visualization: D.T.A. Writing – original draft preparation: N.M.M. Writing – review and editing: D.T.B., D.T.A. Supervision: N.M.M. All authors have read and approved the final version of the manuscript.

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This study was conducted as part of a doctoral research project approved by Tashkent State Medical University.

Ethical Approval

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board (IRB) of the Scientific Center of Hematology and the Women's Health Center, Tashkent, Uzbekistan. Written informed consent was obtained from all participants prior to inclusion in the study.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Registration Statement

This study was an observational cross-sectional study and was not registered in a clinical trial registry, as registration is not required for this type of study.

Conflict of Interest

The authors declare that they have no conflicts of interest related to this study.

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