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Frequency of Asparaginase-Associated Pancreatitis in Patients Presenting with Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma

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ABSTRACT

Background: L-asparaginase is a vital component of chemotherapy protocols for acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL), significantly improving remission and survival rates. However, its use is associated with serious adverse effects, including asparaginase-associated pancreatitis (AAP), which can interrupt treatment and increase morbidity. The reported incidence of AAP varies from 2.5% to 16% globally, but local data among young adults are limited. This study aimed to determine the frequency of AAP in young adults diagnosed with ALL and LBL at a tertiary care cancer hospital in Pakistan. **Methods:** A cross-sectional study was conducted at the Department of Medicine, Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, over six months following synopsis approval. One hundred patients aged 16–25 years with confirmed diagnoses of ALL or LBL were enrolled through non-probability consecutive sampling. **Results:** The mean age of participants was 20.6 ± 2.8 years, with 55% males and 45% females. Eighty-five percent were diagnosed with ALL and 15% with LBL. Asparaginase-associated pancreatitis was identified in seven patients (7%). No significant associations were observed between AAP and age, gender, WBC count, disease duration, or duration of asparaginase therapy ($p > 0.05$). Overall mortality was 5%, including one patient with pancreatitis. **Conclusion:** The frequency of asparaginase-associated pancreatitis in young adults with ALL and LBL was 7%, aligning with international data. Routine biochemical and radiological monitoring during chemotherapy is recommended for early detection and timely management to reduce treatment-related morbidity.

INTRODUCTION

Acute lymphoblastic leukemia is the most frequent malignancy in children, representing 25–30% of all childhood malignancies and the second most frequent malignancy in young adults(1). Although treatment outcome has improved owing to advances in chemotherapy, there is still a group of patients who experience severe adverse events. L-Asparaginase is an effective antineoplastic agent used in the chemotherapy of acute lymphoblastic leukemia(2, 3).

L-asparaginase is utilized as a part of the induction therapy for acute lymphoblastic leukemia, achieving remission in 83–95% of the younger patients. L-asparaginase is an essential drug in the treatment of acute lymphoblastic leukemia(4). However, it is also known to induce several acute complications, such as acute pancreatitis and hypersensitivity reactions(5). Other side effects include liver dysfunction, coagulation defects, and central nervous system depression(4).

Asparaginase-associated pancreatitis is one of the most common complications occurring in patients with asparaginase-treated acute lymphoblastic leukemia(6). Patients with asparaginase-associated pancreatitis typically present with nausea, vomiting, and sudden abdominal pain, which is most commonly located in the epigastric region. Patients may also present with pain radiating to the back or shoulders (7, 8).

Acute pancreatitis induced by L-asp has been noted in 2.5% to 16% of the treated patients. Much less work has been done in the adult population receiving the same chemotherapy as in the adult / young adolescent population. In a study, asparaginase-associated pancreatitis was found in up to 17% adults presenting with acute lymphoblastic leukemia and lymphoblastic lymphoma(9).

Determine the frequency of asparaginase-associated pancreatitis in young adults presenting with acute lymphoblastic leukemia and lymphoblastic lymphoma. Literature has shown that the frequency of asparaginase-associated pancreatitis varies in different studies. But limited work has been done before, and no study has been done in the local set-up before. Therefore, it is important to attain the magnitude for the local adult population and confirm the extent of the problem in the local adult

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population. So that in the future, we may implement more appropriate preventive and improved management protocols and reduce the chances of asparaginase-associated pancreatitis in such sensitive cases. This will help to improve our practice and knowledge, and in the future, we will implement the findings in the local setting.

MATERIAL AND METHODS

This cross-sectional study will be conducted at the Department of Medicine, Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, over a period of six months following approval of the research synopsis. A total of 100 patients will be enrolled, calculated using the WHO sample size calculator with a 95% confidence level, 5% margin of error, and an estimated 6.7% prevalence of asparaginase-associated pancreatitis among adults diagnosed with acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma. A non-probability consecutive sampling technique will be employed. Patients aged 16 to 25 years of either gender, diagnosed with ALL or lymphoblastic lymphoma according to the operational definition, will be included. Exclusion criteria will comprise patients with distant metastasis, chronic pancreatitis, pancreatic malignancy, pancreatitis secondary to trauma, biliary duct obstruction, or hyperlipidemia as confirmed from medical records.

Eligible patients admitted to the medical wards will be recruited after obtaining informed consent. Demographic and clinical data, including age, gender, white blood cell count, disease duration, duration of asparaginase use, underlying diagnosis, and lymphoma stage, will be documented. All patients will undergo clinical assessment for abdominal pain, and venous blood samples will be collected for determination of serum amylase and lipase levels in the institutional laboratory. Additionally, contrast-enhanced computed tomography (CT) of the abdomen will be performed to evaluate for pancreatitis. Radiological findings such as focal or diffuse pancreatic enlargement, heterogeneous enhancement, irregular or shaggy glandular margins, peripancreatic fat stranding, fascial plane thickening, and intraperitoneal or retroperitoneal fluid collections will be interpreted as indicative of pancreatitis, in accordance with the operational definition. All patients diagnosed with pancreatitis will receive standard management as per institutional protocol. Data from all participants will be systematically recorded in a structured proforma for subsequent analysis.

Data Analysis: Data was entered and analyzed by using SPSS 25. Normality of quantitative variables (age, WBC count, duration of lymphoma, and duration of asparaginase use) was assessed using the Shapiro–Wilk test. A p-value > 0.05 was considered indicative of normal distribution. For quantitative variables like age, WBC count, duration of lymphoma, and duration of using asparaginase, the mean and standard deviation will be calculated. For qualitative variables like gender, underlying disease, stage of lymphoma, and asparaginase-associated pancreatitis will be presented as frequency and percentage. Data will be stratified for age, gender, WBC count, duration of lymphoma, and duration of using asparaginase, time of onset of pancreatitis post chemotherapy, ICU admission, mortality, underlying disease, and stage of lymphoma. Chi-square test will be applied to compare asparaginase-associated pancreatitis in stratified groups. P-value≤0.05 will be considered significant.

RESULTS

Among the 100 patients enrolled, the mean age was 20.6 ± 2.8 years, with a slight male predominance (55% male, 45% female). The majority of cases were diagnosed with acute lymphoblastic leukemia (85%), while 15% had lymphoblastic lymphoma. Most participants were classified as stage III (60%), and 40% were stage IV. The mean WBC count was 41,230 ± 22,810/µL, indicating significant leukocytosis consistent with active disease. The mean duration of lymphoma was 2.1 ± 5.4 months, while the mean duration of asparaginase therapy was 87.3 ± 52.1 days, reflecting variable treatment exposure among patients.

Table 1

Demographic Characteristics of Study Participants (n = 100)

Variable		Frequency	Percentage
Age (Mean ± S.D)		20.6	2.8
Gender	Male	55	55.0
	Female	45	45.0
Underlying Disease	Acute Lymphoblastic Leukemia (ALL)	85	85.0
	Lymphoblastic Lymphoma (LBL)	15	15.0
Stage of Disease	III	60	60.0
	IV	40	40.0
WBC Count (/µL)		41,230	22,810
Duration of Lymphoma (months)		2.1	5.4
Duration of Asparaginase use (days)		87.3 ±	52.1

Table 2 demonstrates that asparaginase-associated pancreatitis (AAP) occurred in 7 out of 100 patients (7%), while 93% did not develop this complication. The overall mortality rate in the cohort was 5%, with 95% of patients surviving during the study period. This finding indicates that although the frequency of AAP was relatively low, it represents a clinically significant adverse effect due to its potential to increase morbidity and mortality among patients undergoing asparaginase-based chemotherapy. The results are comparable with international data reporting AAP incidence between 2.5% and 16%.

Table 2

Frequency of Asparaginase-Associated Pancreatitis and Mortality (n = 100)

Variable		Frequency (n)	Percentage (%)
Asparaginase-Associated Pancreatitis	Positive	7	7.0
	Negative	93	93.0
Mortality	Positive	5	5.0
	Negative	95	95.0

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Table 3

Stratification of Asparaginase-Associated Pancreatitis with Effect Modifiers (Chi-Square Test, P ≤ 0.05 Significant)

Variable		AAP Positive	AAP Negative	p-value
Age Group (years)	16–20	3	45	0.74
	21–25	4	48	
Gender	Male	4	51	0.91
	Female	3	42	
WBC Count (/μL)	< 50,000	5	67	0.63
	≥ 50,000	2	26	
Duration of Lymphoma (months)	0–12	6	87	0.68
	> 12	1	6	
Duration of Asparaginase (days)	≤ 90	4	58	0.84
	> 90	3	35	
Underlying Disease	ALL	6	79	0.89
	LBL	1	14	
Stage of Disease	III	4	56	0.79
	IV	3	37	
Mortality	Positive	1	4	0.46
	Negative	6	89	

Stratified analysis revealed no statistically significant association between AAP and demographic or clinical parameters, including age, gender, WBC count, disease duration, or duration of asparaginase therapy (all p > 0.05). AAP occurred slightly more frequently in the 21–25-year age group and among males, though the differences were not significant. Similarly, disease stage and underlying diagnosis (ALL vs. LBL) did not influence pancreatitis risk. These results suggest that AAP may occur unpredictably and is not strongly linked to conventional clinical or biochemical risk modifiers within this age group.

DISCUSSION

In the present cross-sectional study conducted at Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, the frequency of asparaginase-associated pancreatitis (AAP) among young adults with acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) was found to be 7%. The study population included patients aged 16–25 years, with a mean age of 20.6 ± 2.8 years, and a slight male predominance (55%). Most patients were diagnosed with ALL (85%), while 15% had LBL. The majority were in stage III of disease (60%) with a mean WBC count of 41,230/μL. The mean duration of asparaginase use was 87.3 ± 52.1 days. Among the 100 participants, seven developed pancreatitis, and five (5%) died during the study period.

The 7% frequency of AAP observed aligns with previously reported global estimates, which range from 2.5% to 16% depending on population, dosing regimen, and diagnostic sensitivity (7, 9). Studies conducted in pediatric and young adult populations have reported similar frequencies, suggesting that AAP remains a significant treatment-limiting toxicity despite improvements in supportive care(2). In contrast, some pediatric cohorts, especially those treated with intensified regimens, have reported higher incidences exceeding 10–15%. Such variability can be attributed to genetic susceptibility, differences in drug formulation (native E. coli vs. pegylated asparaginase), and variations in treatment protocols (10, 11).

Importantly, no statistically significant associations were found between AAP and gender, age, WBC count, lymphoma duration, or asparaginase exposure time(3). This finding is consistent with prior evidence indicating that AAP is idiosyncratic rather than dose-dependent (12). Although prolonged exposure increases risk by cumulative sensitization, early-onset pancreatitis has been observed even after initial doses, implying a multifactorial mechanism involving direct pancreatic acinar injury, immune-mediated hypersensitivity, and metabolic derangements(13).

Biochemically, the diagnosis in our study was confirmed through serum amylase and lipase elevations, coupled with CT findings demonstrating pancreatic enlargement, fat stranding, and peripancreatic fluid radiological patterns consistent with those described in international studies(13, 14). These findings reinforce the role of combined biochemical and imaging assessment for accurate and timely detection of AAP.

The pathophysiological basis of asparaginase-induced pancreatitis involves depletion of circulating asparagine, an amino acid essential for lymphoblast proliferation but also for normal exocrine pancreatic function. Depletion impairs protein synthesis within pancreatic acinar cells, leading to cellular stress, inflammation, and autodigestion (14). Additionally, hypersensitivity reactions mediated by immunoglobulin E and cytokine cascades may amplify tissue injury. Genetic studies have also identified variants in the ULK2, PRSS1, and CFTR genes as predisposing factors, suggesting a heritable component to toxicity(7).

In this cohort, mortality associated with AAP was 1% (one out of seven cases), which is lower than rates reported in some international series where severe necrotizing pancreatitis led to fatality rates of up to 5–10%. The lower mortality here could reflect early detection and adherence to institutional management protocols involving prompt withdrawal of asparaginase, aggressive fluid resuscitation, and supportive care. Nonetheless, given the potential for recurrence upon drug re-challenge, most guidelines recommend permanent discontinuation of asparaginase following grade III–IV pancreatitis (1).

One of the few efforts from Pakistan to quantify AAP frequency among young adults. The 7% prevalence aligns with international data, emphasizing that asparaginase toxicity is a universal concern transcending regional differences. Limitations include the single-center design, moderate sample size, and lack of detailed biochemical monitoring or genetic analysis, which could refine risk stratification. However, the study contributes valuable baseline data for the South Asian context and underscores the necessity for vigilance in recognizing and managing this potentially life-threatening complication.

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