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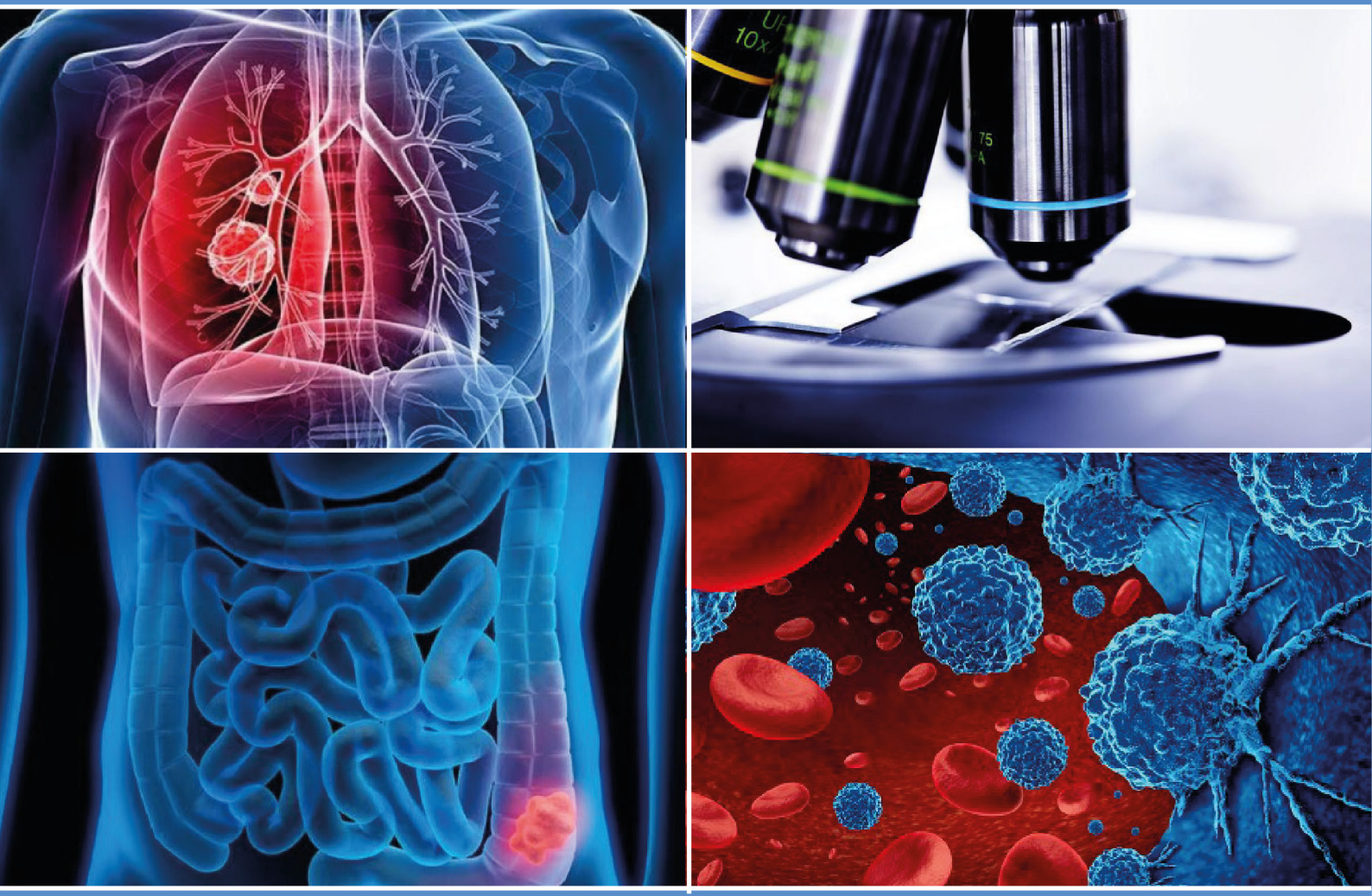

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Journal of Current Hematology & Oncology Research

Original Article

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Association of histopathologic parameters with angiogenesis and endoglin in laryngeal squamous cell carcinoma

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ABSTRACT

Aims: Laryngeal squamous cell carcinoma (LSCC) is one of the most prevalent head and neck cancers, characterized by declining survival rates. Understanding prognostic factors is essential for improving patient outcomes, particularly in the context of angiogenesis. This study was designed to comprehensively evaluate the expression of endoglin (CD105) as a marker of angiogenesis in LSCC and to determine its potential association with microvascular density (MVD) and other histopathological parameters.

Methods: Forty-two previously untreated patients who underwent laryngectomy and neck dissection were retrospectively included in the current analysis. Regions of highest vascularization ("hot spots") were delineated, and MVD was assessed using CD105 immunostaining.

Results: Findings from this study reinforce the hypothesis that MVD might not constitute a reliable prognostic biomarker in LSCC, highlighting the complex and multifactorial nature of tumor angiogenesis.

Conclusion: MVD has been reported as an independent prognostic indicator in various malignancies; however, evidence regarding CD105 expression in LSCC remains extremely limited. Previous studies have yielded conflicting results concerning the prognostic significance of MVD in head and neck SCCs, underscoring the complexity of tumor biology. This study adds to the existing discourse, attributing discrepancies to the absence of tumor-specific markers, intratumoral heterogeneity, and methodological variations.

Keywords: Larynx, squamous cell carcinoma, endoglin, CD 105, angiogenesis

INTRODUCTION

LSCC is the second most common malignancy of the head and neck, and its 5-year survival rate continues to decline globally.[1] Neoplastic angiogenesis, a hallmark of cancer, plays a critical role in tumor growth and progression.[2] MVD has been widely reported as an independent prognostic factor in various human malignancies. However, the prognostic significance of MVD in head and neck SCC remains controversial.

Endoglin (CD105) is a highly specific marker of angiogenesis and has been implicated in the prognosis of several solid tumors.[3] Compared to other commonly utilized endothelial markers, CD105 offers greater specificity for detecting active angiogenesis.[4] Nonetheless, only a limited number of studies have examined the association between CD105 expression and clinical outcomes in LSCC.

Given the paucity of data on CD105 expression in LSCC, this study aims to investigate its relationship with key clinicopathological parameters.

METHODS

This study was conducted in 2002 at Haseki Training and Research Hospital. This study was prepared in 2002 as a thesis titled "The relationship of histopathological parameters with angiogenesis and endoglin in laryngeal squamous cell carcinoma." All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Patients who underwent total or subtotal laryngectomy with neck dissection for previously untreated primary LSCC were included. Clinical data, including age, sex, histological and nuclear grade, primary tumor (T)

classification, and nodal (N) status, were retrospectively retrieved from institutional medical records.

Hematoxylin and eosin (H&E)-stained slides were reviewed for each case, and blocks without hemorrhage or necrosis were selected for further analysis. For immunohistochemistry, 4 µm-thick sections were prepared from the selected paraffin-embedded blocks and stained with CD105 antibodies to assess MVD.

Areas of highest vascularization ("hot spots") were identified under low-power magnification. Within these regions, three microscopic fields were examined at ×200 and ×400 magnification using an Olympus BX50 dual-head microscope. Evaluations were performed simultaneously by two experienced pathologists to minimize interobserver variability, and the highest microvessel counts were recorded.

Regions exhibiting inflammation, necrosis, or adjacent normal tissue were excluded from microvessel evaluation. A single CD105-positive endothelial cell or a cluster of endothelial cells clearly demarcated from tumor cells and surrounding stroma was considered a microvessel. Clusters of positively stained endothelial cells were counted as individual microvessels regardless of lumen formation[5] (**Figure 1, 2**).

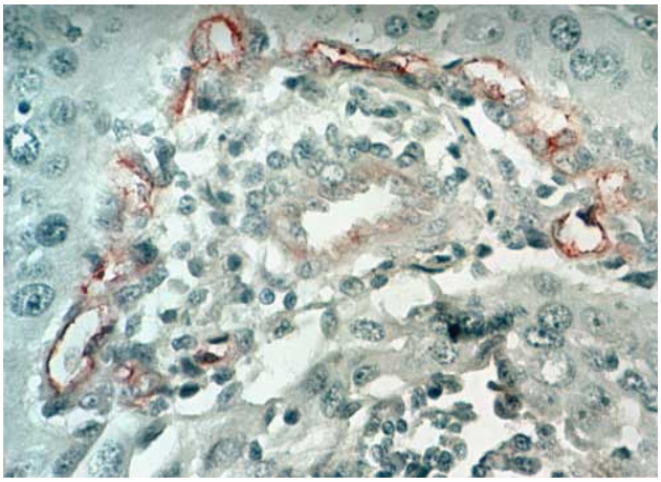

Figure 1. Proliferating microvessels between the tumor and stroma that stain positively with CD105 (CD105 x500)

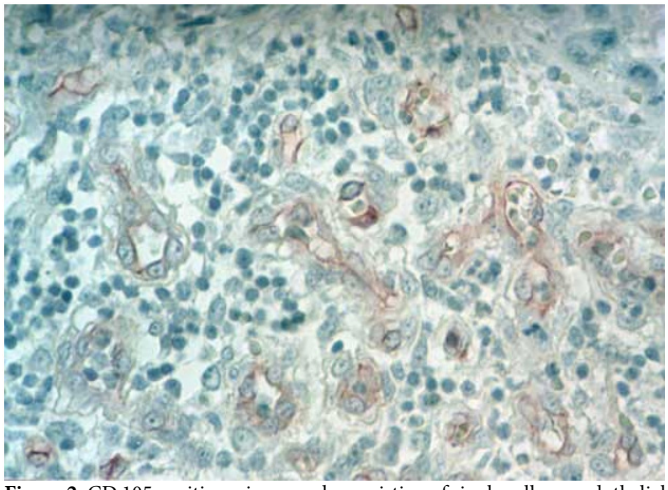

Figure 2. CD 105 positive microvessels consisting of single cells or endothelial cell clusters around the tumor. There is lymphoplasmacytic cell infiltration in between (CD105 x500)

Statistical Analysis

The data analyses were performed using SPSS software (version 22.0; IBM Corp.). Correlations between variables were assessed using Spearman's rank correlation coefficient. A p-value <0.05 was considered statistically significant.

RESULTS

Patient Demographics and Clinical Features

The study included 42 patients (41 males, 1 female) with a mean age of 58.6 years (range: 38–80). Fifteen patients (35.7%) were ≤60 years, and 27 (64.3%) were older than 60 years. Neck dissection was performed in 34 patients; 17 cases (50%) had lymph node metastasis.

Tumor Characteristics

- **Tumor grade:** Grade I in 11 patients (26.2%) (**Figure 3**), grade II in 21 (50%), grade III in 10 (23.8%) (**Figure 4**).

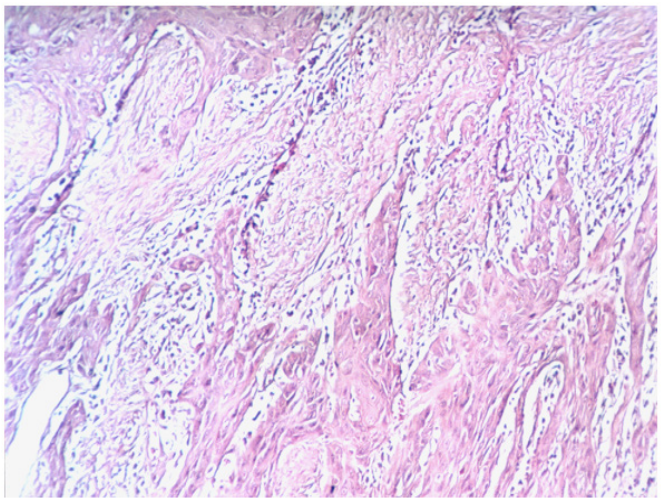

Figure 3. Grade I squamous cell carcinoma, mild lymphoplasmacytic cell infiltration (H&Ex 125)

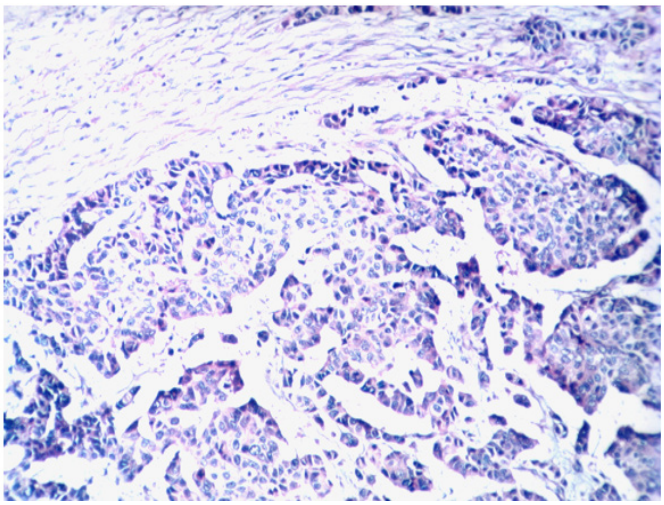

Figure 4. Grade III squamous cell carcinoma (H&E x125)

- **Tumor size:** ≤2.0 cm in 9 cases (21.4%), 2.1–4.0 cm in 23 (54.8%), ≥4.1 cm in 10 (23.8%).
- **Tumor localization:** Supraglottic (n=27, 64.3%), glottic (n=9, 21.4%), infraglottic/transglottic (n=6, 14.3%).

Histopathological Features

Lymphoplasmacytic infiltration was mild in 14 patients (33.3%) (**Figure 3**) and severe in 28 (66.7%). Desmoplastic stromal response was mild in 19 cases (45.2%) and intense in 23 (54.8%). Tumor invasion was expansile in 19 (45.2%) and infiltrative in 23 (54.8%). Increased desmoplasia correlated with infiltrative invasion (**Table 1**).

Table 1. Histopathological features and invasion patterns

Feature	Mild	Intense
Lymphoplasmacytic infiltration	14 (33.3%)	28 (66.7%)
Desmoplastic stromal response	19 (45.2%)	23 (54.8%)
Tumor invasion pattern	19 (45.2%)	23 (54.8%)

Microvessel Density (MVD)

MVD was assessed at ×200 (MVD200) and ×400 (MVD400) magnifications using CD105 immunostaining. Statistical analysis revealed:

- No significant correlation between tumor grade and MVD200 or MVD400 (p=0.350, p=0.234) (**Figure 5, 6**).

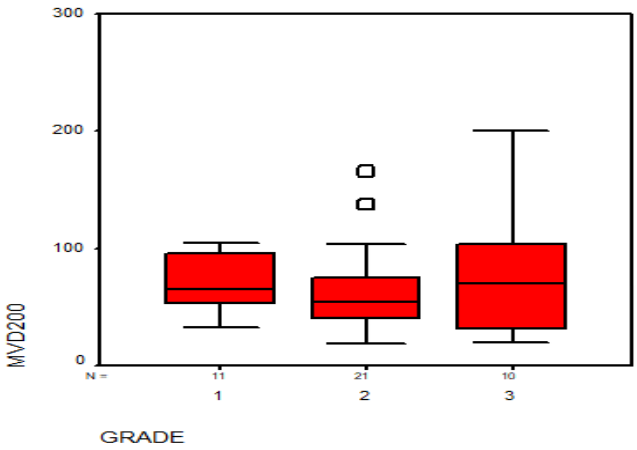

Figure 5. Distribution of MVD200 by grade

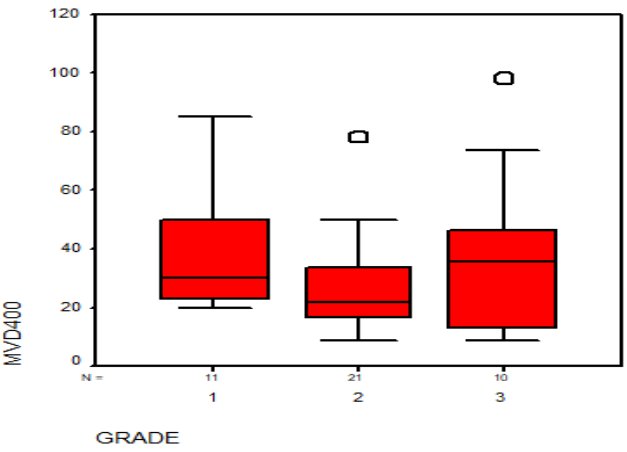

Figure 6. Distribution of MVD400 by grade

- No significant association between tumor size and MVD200 or MVD400 (p=0.498, p=0.338).
- Lymphoplasmacytic infiltration showed no correlation with MVD200 or MVD400 (p=0.367, p=0.479).
- Desmoplastic reaction: no correlation (p=0.263, p=0.259).
- Lymph node status: no correlation (p=0.970, p=0.109).
- Tumor localization: no association (p=0.374, p=0.471).
- Tumor invasion pattern: no correlation (p=0.221, p=0.490) (**Table 2**).

Table 2. Correlation of clinicopathological parameters with MVD at ×200 and ×400

Clinicopathological parameter	MVD200 (p-value)	MVD400 (p-value)
Tumor grade	0.350	0.234
Tumor size	0.498	0.338
Lymphoplasmacytic infiltration	0.367	0.479
Desmoplastic stromal response	0.263	0.259
Lymph node status	0.970	0.109
Tumor localization	0.374	0.471
Tumor invasion pattern	0.221	0.490

All p-values were calculated using Spearman's rank correlation coefficient. A p-value <0.05 was considered statistically significant

DISCUSSION

Despite significant advancements in diagnostic and therapeutic approaches, the survival rate of patients with LSCC has shown little improvement over recent decades. Traditional prognostic indicators such as TNM stage and histologic grade alone are insufficient for accurately predicting clinical outcomes, necessitating the identification of additional biomarkers to better stratify patients based on their risk of recurrence.[6] This study investigated the association between CD105 expression, MVD and key clinicopathological parameters in LSCC. Angiogenesis plays a critical role in tumor growth, invasion, and metastatic dissemination. CD105 is a well-recognized marker of neovascular endothelial cells and is markedly overexpressed in newly formed blood vessels within and around tumor tissue.

The prognostic significance of MVD remains controversial, with conflicting reports in the literature. In head and neck SCCs, a strong correlation has been demonstrated between MVD measured at ×200 and ×400 magnifications (p<0.001). However, in our study, no statistically significant relationship was found between MVD and tumor grade at either magnification (p=0.350 and p=0.234, respectively).

Our findings contrast with those of Kupisz et al.[7] and Beatrice et al.,[8] who reported a positive association between histologic grade and angiogenesis. Conversely, our results align with the observations of Burian et al.[9] and Hjalmar et al.,[10] who similarly noted no significant correlation between grade and angiogenesis. One plausible explanation for this discrepancy is the predominance of grade II tumors in our cohort, which may reflect the subjectivity of histologic grading. Furthermore, the relatively small sample size could have limited the statistical power to detect subtle associations.

Consistent with previous studies by Szafarowski et al.,[5] Zvrko et al.,[4] and Hjalmar et al.,[10] we also found no correlation between MVD/CD105 expression and patient demographics (age, sex) or other histopathologic characteristics. Comparable

findings have been reported in studies of breast carcinoma, renal cell carcinoma, and esophageal squamous cell carcinoma, suggesting that angiogenesis may not uniformly correlate with histologic grade across different tumor types.[11,12]

Similarly, no significant association was observed between tumor diameter and MVD (p=0.498 and p=0.338). This is consistent with the findings of Dray et al.[13] in head and neck cancer, as well as reports from studies involving breast, esophageal, and renal carcinomas.[11,12]

The relationship between peritumoral inflammatory infiltration and angiogenesis remains controversial. While our results showed no correlation (p=0.367 and p=0.479), Hjalmar et al.[10] suggested that increased lymphoplasmacytic infiltration might enhance angiogenesis via the release of pro-angiogenic mediators. Such differences may be attributable to variability in tumor location, sample size, and inflammatory response patterns.

Similarly, no significant correlations were found between desmoplastic stromal response and MVD (p=0.263 and p=0.259), or between tumor localization and MVD (p=0.374 and p=0.471). These observations are in line with findings by Hagedorn et al.[10] and Murray et al.,[14] indicating that angiogenesis in LSCC may occur independently of anatomic subsite or stromal reaction.

With respect to lymph node status, no significant association with MVD was noted (p=0.970 and p=0.109). However, prior studies, including those by Murray et al.[14] and Marioni et al.,[15] have demonstrated a positive correlation between angiogenesis and nodal metastasis, and Shpitzer et al.[16] reported that neovascularization served as an independent predictor of nodal involvement in early-stage tongue carcinoma. These discrepancies highlight the complexity of tumor biology and the need for larger, more homogeneous study cohorts.

Finally, no significant correlation was observed between invasion pattern (expansile vs. infiltrative) and MVD (p=0.221 and p=0.490). Although infiltrative tumors tended to exhibit higher MVD values, this trend did not reach statistical significance, likely due to limited case numbers. Similarly, age was not associated with angiogenesis, corroborating prior reports in LSCC and oral cavity SCC.[8,13,17]

CONCLUSION

This study found no significant correlation between CD105-assessed MVD and various histopathologic features in LSCC. These results indicate that CD105 expression may not serve as a reliable indicator of tumor angiogenesis in LSCC. Further prospective studies with larger sample sizes and standardized protocols are required to validate these findings.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was prepared in 2002 as a thesis titled "The relationship of histopathological parameters with angiogenesis and endoglin in laryngeal squamous cell carcinoma."

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

DOI: 10.51271/JCHOR-0068

Adults philadelphia-positive B–acute lymphoblastic leukemia in a moderate Health Access and Quality Index country

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ABSTRACT

Aims: To describe clinical and demographic characteristics, as well as to evaluate response and survival outcomes in Philadelphia positive (Ph+) acute lymphoblastic leukemia (ALL) Ecuadorian adults.

Methods: A retrospective, multicenter cohort study in patients aged >15 years diagnosed with Ph+ B-cell ALL was carried out. Diagnosis of B-ALL was established based on 2016 WHO classification and Ph+ mutation was confirmed in all cases.

Results: Sixty one (12.4%) were identified with Ph+ chromosome. Fifty-six were included in the analysis, 33 (58.9%) were male, and median age was 40.5 years [interquartile range (IQR): 25-51; range: 16-85]. 46 (82.1%) subjects were treated with imatinib. CR was achieved in 30 (53.6%) patients. Minimal residual disease (MRD) was reported in 13/41 (31.7%). Only 5/29 eligible patients underwent hematopoietic stem cell transplantation (HSCT). 9 (16.1) died in induction phase, all deaths were attributed to bacterial infections. Relapse was recorded in 7 (12.5%). Median overall survival (OS) for total cohort was 11 months (95% CI 8.1-13.9), with a 5-year OS of 26.8%. Imatinib 800 mg (p=0.020) and achieving CR (p=0.002) were associated with better OS.

Conclusion: Response and survival outcomes in Ecuadorian population are poorer compared to high income countries caused by high rate of induction death, low availability of MRD monitoring, lack of standardization of treatment protocols, restricted access to HSCT, and delayed initiation to TKIs therapy.

Keywords: Philadelphia positive, acute lymphoblastic leukemia, overall survival, poor outcomes, Ecuador, middle-low income countries

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is characterized by malignant transformation and proliferation of lymphoid progenitor cells in the bone marrow, peripheral blood, and extramedullary sites.[1] ALL exhibits a bimodal age distribution, with the first peak occurring around 5 years of age and the second peak approximately at 50 years of age. Although primarily considered a pediatric leukemia—accounting for 80% of cases—ALL also occurs in adults, representing 20% of cases.[2] The Philadelphia chromosome (Ph), resulting from the t(9;22) translocation is observed in approximately 20-30% of adults with ALL and is associated with a poorer prognosis compared to Ph-negative ALL.[3] The incidence of Ph-positive (Ph+) ALL increases with age, and patients often present with a particularly aggressive form of leukemia that is resistant to standard therapies, resulting in high relapse rates.[4]

The advent of tyrosine kinase inhibitors (TKIs) has significantly improved treatment response and survival outcomes in ALL, particularly in adults. Imatinib, the first TKIs approved for Ph+ ALL, when combined with intensive chemotherapy, has significantly increased complete response (CR) rates in newly diagnosed Ph+ adults ALL from below 50% in the pre-TKIs era to over 90% in post-TKIs era.[5,6] Furthermore, 5-year overall survival (OS) and disease-free survival (DFS) rates have improved from 43% to 50% and 32%

to 52%, respectively.[7-9] Second-generation TKIs, combined with either intensive or low-intensity chemotherapy, have demonstrated even higher CR rates compared to imatinib-based regimens.[10-12] Ponatinib, a third-generation TKIs, is an emerging treatment option for non-response patients.[13,14]

In Latin America, the prevalence of Ph+ ALL appears to be slightly lower than those reported in Anglo-Saxon populations. While rates of 20-30% have been observed in U.S. and European cohorts reaching up to 50% in individuals ≥50 years,[3] studies in Latin America report a prevalence ranging from 12% to 30% in multicenter and single-center analyses.[15] This discrepancy may be partially explained by the presence of Philadelphia-like ALL (Ph-like ALL), which it is not routinely assessed in many Latin American specialized centers.[16] Notably, the prevalence of Ph-like ALL appears higher in Latin America compared to other regions.[17]

Despite remarkable advances achieved in the post- TKIs era, survival and response outcomes in Latin American populations remain suboptimal compared to high-income countries.[18] Limited studies have focused specifically on the outcomes of Ph+ ALL in adults from developing countries. Most available information is derived from studies evaluating general ALL cohorts, which have reported less favorable results with TKIs treatment, particularly with imatinib.[18-20] In Ecuador, the prevalence of Ph+ ALL in adults is unknown, as well as response and OS outcomes. In this study, we conducted a multicenter analysis to evaluate the demographic and clinical characteristics, as well as treatment response, and survival outcomes in adults Ph+ ALL in Ecuador.

METHODS

Ethics

The study protocol was reviewed and approved by the Human Investigation Committee of the Technical University of Manabi (Date: 27.04.2023, Decision No: CEISH-UTM-EXT_23-01-5_BESV) and the institutional review boards of all participating centers. The study was classified as minimal risk due to its retrospective design, and requirement for informed consent was waived by the Human Investigation Committee. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This is a retrospective, multicenter cohort study aimed to describes epidemiological characteristics and analysis response and survival outcomes in patients aged >15 years diagnosed with Ph+ B-cell ALL from January 2015 to December 2023 across five reference centers in Ecuador.

Diagnosis of B-lymphoblastic leukemia was established based on the 2016 World Health Organization (WHO) classification,[21] with the presence of the Philadelphia chromosome confirmed in all cases via fluorescence in situ hybridization (FISH) or reverse transcription polymerase chain reaction (RT-PCR) for BCR-ABL. Imatinib, a first-generation tyrosine kinase inhibitor (TKI), is the only agent approved for first-line therapy of Ph+ ALL in the public healthcare system in Ecuador. In private healthcare settings, dasatinib is available; however, only one patient was switched from imatinib to dasatinib due to loss of response.

The lineage of ALL was determined using immunohistochemistry and/or flow cytometry (FC). The data registry included karyotype analysis by conventional cytogenetic techniques, and central nervous system (CNS) infiltration assessed at diagnosis through FC of cerebrospinal fluid (CSF) by the presence of more than 5 leukocytes/µL or greater, or the presence of lymphoblasts in CSF was considered positive.

Risk stratification was performed according medical research council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial criteria.[22] Patients were categorized as follows: (1) high risk—defined by the presence of one or more of the following: age ≥35 years, leukocyte count ≥30.000/mm^3, or CNS infiltration at baseline; and (2) standard risk—defined by the absence of all high-risk factors.

Age Groups Definition

Subjects were classified based on the AYA classification. Groups were defined as 15-39 years (AYA) and ≥40 years old.[23]

Treatment and Response to Treatment

Treatment protocols were recorded, 5 different protocols were prescribed during study time: BFM, HyperCVAD/MTX-ARAC, PETHEMA, CALGB 8811 and GATLA (Argentine Group for the Treatment of Acute Leukemia). One palliative management were recorded in our cohort. In addition, hematopoietic stem cell transplantation (HSCT) was registered.

Several imatinib formulations, including both generic and branded versions were documented in the study. The registered brands included CLINID® (Bago Laboratory), generic imatinib from Glucosamine Laboratory, and generic imatinib from Gutierrez Laboratories. To evaluate treatment response within the imatinib cohort, data were collected about dosage, interruptions in imatinib therapy, reasons for treatment discontinuation, delays in treatment initiation, and the overall duration of imatinib administration.

Response and survival outcomes were assessed using the following criteria: (1) post-induction CR, (2) post-induction minimal residual disease (MRD), (3) induction mortality rate (IMR), (4) relapse, (5) relapse-free survival (RFS), (6) 5-year OS, (7) median OS, and (8) event-free survival (EFS). (9) disease-free survival (DFS).

CR was evaluated based on the Cheson criteria, defined as the absence of extramedullary disease, no detectable peripheral blasts, bone marrow blasts <5%, neutrophil count ≥1.5×10^9/L, and platelet count ≥100×10^9/L; any deviation from these criteria was classified as non-response (NR).[24] MRD was assessed by FC and defined as <0.01%, corresponding to fewer than 1 leukemic cell per 10.000 mononuclear cells in a bone marrow sample.[25]

IMR was defined as the proportion of patients undergoing induction chemotherapy who died during the induction

phase due to treatment-related complications or toxicities, excluding deaths caused by disease progression or unrelated factors. Relapse was defined in CR patients as ≥5% blasts in the bone marrow, the presence of blasts in the peripheral blood, or evidence of extramedullary disease, according to the consensus of the European Working Group for Adult ALL (EWALL).[26]

RFS was defined as the time from achieving CR to relapse, death, or last follow-up, whichever occurred first. OS was evaluated as the time from diagnosis to death or last follow-up, with 5-year OS and median OS specifically reported. EFS was defined as the time from diagnosis to treatment failure, relapse, death, or last follow-up, whichever occurred first. DFS was defined as the time from diagnosis to recurrence of disease, development of a second primary cancer, death from any cause, or last follow-up, whichever occurred first.

Statistical Analysis

Study variables were summarized as means or medians, depending on their distribution, while categorical variables were presented as frequencies or percentages. Pairwise comparisons between subject groups were conducted using the Chi-square test, Fisher's exact test, or Mann-Whitney U test, depending on the data distribution and sample size.

Optimal cutoff values for age, delay in treatment initiation, and duration of imatinib therapy were determined using receiver operating characteristic (ROC) curve analysis and the corrected Akaike Information Criterion (cAIC) to evaluate response and survival outcomes.[27,28]

Survival analysis was performed using the Kaplan–Meier method to estimate 5-year OS and median OS, with comparisons between groups assessed using the log-rank test. Factors associated with treatment outcomes, including CR and IMR were evaluated using logistic regression. Associations between prognostic factors were analyzed through logistic regression for response outcomes. Relapse was assessed using the cumulative incidence function with death as a competing event, and the Fine-Gray model was employed to identify risk factors significantly associated with relapse risk.

MRD was included solely in the descriptive results due to the limited number of patients evaluated. For the analysis of treatment outcomes, only the BFM and HyperCVAD protocols were included in the assessment of treatment response and survival outcomes. Other protocols containing asparaginase (pediatric protocols) were aggregated with BFM as pediatric protocols for the purpose of survival analysis. A comparison of treatment outcomes between Imatinib doses of 400 mg and 800 mg was included in the analysis; 600 mg dose was not analyzed due to a lack of representative sample. Subgroup analyses within groups were not conducted because of inadequate sample sizes.

Statistical analyses were performed using SPSS Statistics for Windows, version 25.0 (IBM, 2015), and R software, version 4.4.2 (R Foundation for Statistical Computing, www.r-project.org). A p-value <0.05 was considered statistically significant.

RESULTS

A total of 653 adult patients were diagnosed with B-ALL during the study period, of whom 61 (12.4%) were identified with Ph+ chromosome. Five Ph+ subjects were excluded due to missing data on imatinib use, 56 Phi+ adult ALL subjects were included in the analysis. Of the 56 subjects, 33 (58.9%) were male, and median age was 40.5 years [interquartile range (IQR): 25–51; range: 16–85], and 25 (44.6%) belonged to the adolescent and young adult (AYA) group. Fifty-five individuals received chemotherapy, most frequent treatment protocols were HyperCVAD and BFM with 25 (44.5%) and 22 (40%), respectively. 47 (83.9%) patients were classified in high risk group. Normal karyotype was observed in 25 (44.6%) of those evaluated. CNS infiltration was assessed in 50 (89.3%) individuals, with blast cells confirmed in 9 (18%).

A detailed summary of the cohort's clinical and demographic characteristics is presented in **Table 1**.

Imatinib Therapy

46 (82.1%) subjects were treated with Imatinib plus conventional chemotherapy, 25 (54.3%), 6 (13%), and 15 (32.6%) were on dosage of 400 mg, 600 mg and 800 mg, respectively. 16 suspended Imatinib treatment during follow-up period, these were the recorded causes of suspension: septic shock (n=5), loss of response (n=5), lack of adherence (n=3), neutropenia (n=1), renal failure (n=1), non-availability and/or financial constraints (n=1). The median weeks of treatment with Imatinib was 29 [(IQR 7.5-42.5), range 0-105], and the median days of delay to initiate imatinib was 19 [(IQR 9-36), range 0 -363]. Only 9 subject initiated Imatinib therapy within 7 days after diagnose. The median weeks of treatment before loss of response was 13 weeks.

The median follow-up for the cohort was 31.0 months (95% CI: 21.0–60.0), with a minimum of 6 months and a maximum of 90 months.

Response to Treatment

CR was achieved in 30 (53.6%) patients. MRD negativity was achieved in 13 of 41 (31.7%) patients. Male gender in imatinib group was associated to better CR [OR 4 (95% CI 1.6-12.3) p=0.004].

Mortality

Nine (16.1%) died during the induction phase, all deaths were caused by bacterial infections (septic shock). Among protocols, induction deaths were 7 (31.8%), 1 (4%) for BFM, HyperCVAD, respectively.

Relapse

Relapse was recorded in 7 (12.5%). Median and 5-year RFS was 22 months (95% CI 10-no reached) and 37%, respectively. Cumulative incidence for relapse (CIR), considering death as a competing event, was 22.1% (95% CI 3.5–40.8), while the non-relapse mortality (NRM) throughout the follow-up was 40.8 % (95% CI 16.2–65.5), **Figure 1**.

Hematopoietic Stem Cell Transplantation (HSCT)

Only 5 of 29 eligible patients underwent HSCT, transplanted patients reached a median OS 29 months and a 5-years OS of 30%. Relapse was recorded in 1 (20%) of transplanted subject.

Table 1. Baseline characteristics of Phi+ B-ALL patients at diagnosis.*

Factors	Use of imatinib (n=56)			
	No imatinib (n=10)	Imatinib therapy (n=46)		
	n (%)	400 mg (n=25)	600 mg (n=6)	800 mg (n=15)
Median age [IQR (range)]	41 [27-64.75 (16-85)]	41.50 [24.25-51 (18-76)]		
AYA classification				
<40-year old	5 (50)	11 (44)	2 (33.3)	7 (46.6)
>=40-year old	5 (50)	14 (56)	4 (66.6)	8 (53.3)
Sex				
Male	8 (80)	12 (48)	3 (50)	10 (66.6)
Female	2 (20)	13 (52)	3 (50)	5 (33.3)
Leukocytes count				
<30.000mm^3	6 (60)	9 (36)	2 (33.3)	10 (66.6)
30.000mm^3-100.000mm^3	4 (40)	14 (56)	0	2 (13.3)
>=100.000mm^3	0	2 (8)	4 (66.6)	3 (20)
Risk group				
Standard	3 (30)	1 (4)	1 (16.6)	3 (20)
High	6 (60)	24 (96)	5 (83.3)	12 (80)
Karyotype				
Normal	5 (50)	18 (72)	1 (16.6)	1 (6.6)
Others CGT abnormalities	0	5 (20)	2 (33.3)	5 (33.3)
Too few metaphases	2 (20)	0	0	2 (13.3)
Hyperdiploid	1 (10)	0	2 (33.3)	1 (6.6)
Low hypodiploid	0	1 (4)	1 (16.6)	0
Complex	1 (10)	0	0	1 (6.6)
CNS infiltration				
No	7 (80)	19 (76)	3 (50)	12 (80)
Yes	1 (10)	3 (12)	2 (33.3)	3 (20)
Treatment protocols				
BFM	6 (60)	16 (64)	0	0
HyperCVAD	4 (40)	2 (8)	4 (66.6)	15 (100)
PETHEMA	0	3 (12)	2 (33.3)	0
CALGB 881	0	2 (8)	0	0
GATLA	0	1 (4)	0	0
HSCT				
No	1 (10)	11 (44)	2 (33.3)	10 (66.6)
Yes	1 (10)	1 (4)	2 (33.3)	1 (6.6)

IQR: Interquartile range, AYA: Adolescent and young adult, CNS: Central nervous system, GATLA: Grupo Argentino de Tratamiento de la Leucemia Aguda, HSCT: Hematopoietic stem cell transplantation.
*Percentages of every factor are within non imatinib group and imatinib's subgroup.

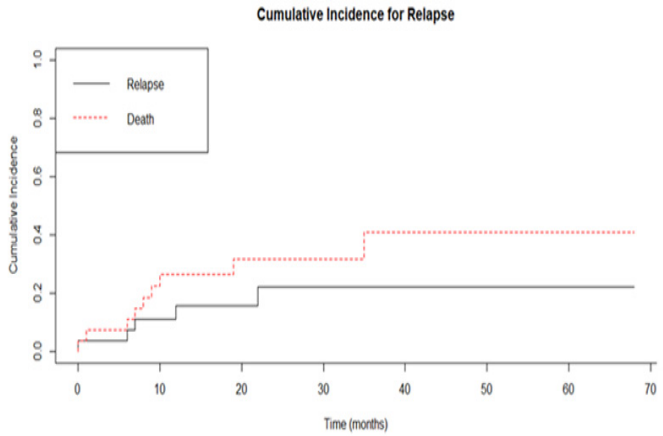

Figure 1. Cumulative incidence function. Cumulative incidence curves for relapse and non-relapse mortality (NRM)

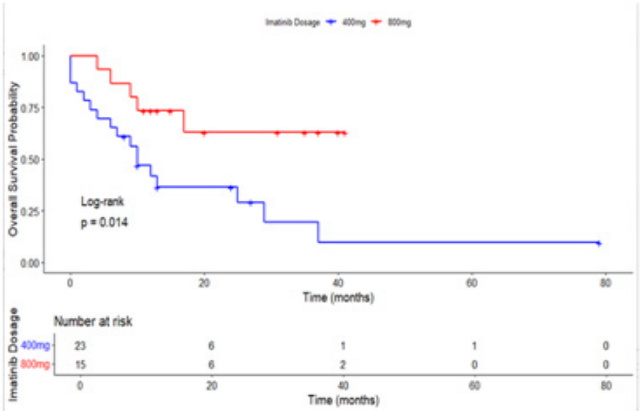

Figure 2. Kaplan–Meier curve. Overall survival (OS) in 800 mg vs 400 mg imatinib dosage

Survival Analysis

Median OS for total cohort was 11 months (95% CI 8.1-13.9), with a 5-year OS of 26.8%. OS univariate analysis showed statistically significant differences for: Imatinib dosage, 400mg dosage 5-years OS was 9.7% vs 62.9% on 800 mg (Figure 2). Median and 5-year DFS for total cohort was 19 months (95% CI 10-no reached) and 36.9%, respectively. Median and 5-year EFS for total cohort was 25 months (95% CI 10-no reached) and 34.5%, respectively. See Table 2 for factors influencing DFS and EFS.

In a univariate analysis significant differences in OS were observed for the following factors: imatinib 800 mg vs imatinib 400 mg; p=0.020 and for subject who achieved CR, p=0.002. Details of the univariate survival analysis are expressed in Table 3.

DISCUSSION

TKI drugs has drastically shifted the management of Ph+ ALL subjects. Doubtlessly, incorporation of TKIs evolved the landscape of leukemia. Improvement in response and survival parameters were first observed in chronic myeloid leukemia,[29] and these benefits were subsequently trialed

Table 2. DFS and EFS univariate analysis of patients in Phi+ according to group

Factor	Median DFS	5-year OS	OS p value	Median EFS	5-year EFS	EFS p value
AYA group						
<40-years old	NA	63.5%	p=0.581	NA	62.3%	p=0.361
>=40-year old	20 (95% CI:5.5-39.5)	31.6%		13 (95% CI:5.5-44.4)	28.1%	
Imatinib						
Yes	23 (95% CI:2.9-43.1)	39.1%	p=0.058	25 (95% CI:0.3-49.6)	36.9%	p=0.207
No	6 (95% CI: NA)	0%		9 (95%CI: NA)	0%	
Sex						
Male	20 (95% CI:5.2-34.7)	39.9%	p= 0.932	25 (95% CI:6.5-43.3)	39.7%	p=0.703
Female	35 (95% CI: NA)	0%		10 (95% CI:0-25.5)	0%	
Risk group						
High	23 (95% CI:1.9-44)	35.5%	p=0.934	25 (95% CI:2.4-47.6)	33.3%	p=0.847
Standard	10 (95% CI: NA)	50%		11 (95% CI: NA)	50%	
Complete response						
No	NA	NA%	p=NA	0 (95% CI: NA)	0%	p<0.001
Yes	23 (95% CI:0.-46.2)	37.7%		25 (95% CI:0.6-49.3)	38.1%	
CNS infiltration at diagnosis						
No	23 (95% CI:9.8-14.1)	30.8%	p=0.432	25 (95% CI:0.6-49.3)	29%	p=0.383
Yes	NA	60%		NA	60%	
# of leukocytes/mm3 at debut						
<30.000	23 (95% CI: NA)	50%	p=0.805	25 (95% CI:0-50.8)	44.1%	p=0.932
30.000-<100.000	35 (95% CI:9.7-60.2)	25.7%		25 (95% CI:1.3-48.6)	25%	
>=100.000	12 (95% CI: 2.4-21.6)	33.3%		13 (95% CI:3.39-22.6)	33.3%	
Pediatric protocols						
No	NA	57.9%	p=0.101	NA	57.9%	p=0.038
Yes	10 (95% CI:94.5-15.5)	15%		10 (95% CI:6.7-13.2)	14%	

AYA: Adolescent and young adult, OR: Overall survival, DFS: Disease free survival, EFS: Event-free survival, MRD: Minimal residual disease, CNS: Central nervous system, NA: No reached values caused by disproportionate sample representation within groups

Table 3. Univariate analysis of Phi+ adults ALL patients treated with imatinib

Factor	n (%)	Median OS in months	5 year OS	p value
AYA group				
15-39 years	20 (43.5)	17 (95% CI:9-NA)	48.6%	p=0.225
≥40 years	26 (56.5)	10 (95% CI:7.6-12.4)	20.6%	
Sex				
Female	21 (45.7)	10 (95% CI:5.7-14.2)	12.8%	p= 0.055
Male	25 (54.3)	25 (95% CI:5.8-44.2)	39.2%	
Imatinib dosage				
400 mg	25 (62.5)	10 (95% CI:7.8-14.2)	9.7%	p=0.020
800 mg	15 (37.5)	NA	62.9%	
Risk group				
High	41 (89.1%)	12 (95% CI:6.6-17.4)	25.4%	p=0.336
Standard	5 (10.9%)	NA	60%	
Pediatric protocols				
Yes	24 (53.3%)	11 (95% CI:8.9-13)	15.7%	p=0.078
No	21 (46.7%)	25 (95% CI:7.6-42.4)	44.9%	
CR				
No	12 (30.8)	6 (95% CI:3-NA)	39%	p=0.002
Yes	27 (69.2)	29 (95% CI:11-NA)	15%	
CNS infiltration at diagnosis				
No	34 (80.9)	14 (95% CI:0-30.1)	29.6%	p=0.761
Yes	8 (19.1)	17 (95% CI:2.7-31.3)	33.3%	
# of leukocytes/mm^3 at debut				
<30.000	21 (45.6)	12 (95% CI:0-40.7)	41.6%	p=0.068
30.000-100.000	16 (34.7)	25 (95% CI:2.5-47.4)	28.9%	
>100.000	9 (19.7)	8 (95% CI:2.2-13.8)	11.1%	

AYA: Adolescent and young adult, CR: Complete response, CNS: Central nervous system, NA: No reached

in others leukemia diseases.[4] Although the advent of these new therapies brought a dramatic enhancement in adults-ALL,[8] however, the underscored subgroup of individuals with this particular mutation (BCR-ABL) exhibit substantial geographical variations in terms of in response and survival outcomes when results are assessed in populations outside US and Western European countries, especially outside prospective clinical trials.[19,30] This geographical variation notoriously applies to Latin American, a region in which the scarce epidemiological studies reported poorer response and survival outcomes.

Although, the entire Ph+ adults ALL landscape changed with the entrance on scene of TKIs, this genetic mutation once considered a poor prognostic marker, undergone a radical switch since the arrival of imatinib. Unfortunately, these benefits are not observed when assessing cohorts from low- and middle-income countries. Our results are consistent with this concerning situation, reflecting poorer outcomes, but also different epidemiological and cytogenetic characteristics. Demographical aspects of our cohort revealed a younger onset at diagnosis (median 40.5 years) compared to >50 years in most of international cohorts.[3,31,32] Although, studies from

lower-middle-income economies also reported a younger onset at diagnose.[18,33] A male predominance was seen in our cohort but, gender variations are observed across studies, any defined gender prevalence has not been established.[18,33,34]

Importantly, prevalence of Philadelphia chromosome in our cohort was 12.4%, a result lower than those reported in most studies, between 20-30%.[3,18,22,34] Differences in prevalence for t(9;22)/BCR-ABL1translocation is not rare, and variations across different regions has been reported. Values above 30% are more commons in Anglo-Saxons heritage regions.[31,35] Otherwise, some studies from Hispanic ascending countries have reported a Ph+ prevalence inferior than 20%.[15,36] Prevalence of this relevant mutation differs by age, race and ethnicity.[37] Some key aspects of this variability may be marked by the presence of mutations more prevalent in Latin America, highlighting the case of Philadelphia-like chromosome mutation, which has been observed to be more prevalent in black and Hispanic populations.[17,38] In the long term, assessment of the presence of this mutation and others through new and more advanced techniques such as next sequence generation (NSG) could eventually impact the management of ALL in Hispanic populations.

Response outcomes in our cohort were 53.6% and 31.7% for CR and MRD negativity, respectively. These results are well below (90% in CR and 70% in MRD) than those reported in imatinib clinical trials from high-income countries.[5,39-41] Survival outcomes were also inferior, 5-years OS and DFS were 26.8% and 36.9%, respectively. A real-world multicenter cohort from Brazil reported similar results, 4-year OS and RFS were 25.5% (95% CI 18.4-35.4) and 24.2% (95% CI 17.3-34), respectively. Nevertheless, significant differences are observed when comparing to high-income cohorts, with values of OS and DFS between 30-50%.[3] These results evidence worse outcomes in Latin American populations compared with those from the United States and Western Europe, highlighting the influence of socioeconomic factors on survival outcomes.

A significant difference in induction deaths and OS was observed in patients treated with Hyper-CVAD, this effect was attribute to high doses of imatinib used in Hyper-CVAD compared to other regimens. Use of high dosage of imatinib combined with reduced-intensity chemotherapy versus standard Imatinib/HyperCVAD has been associated to fewer induction deaths and higher rate of CR favored to former group.[42] These data warranted that treatment protocols including high dose of imatinib (800 mg daily) may be considered a feasible treatment option in Ph+ ALL patients from middle-lower income countries like Ecuador, in which high induction death rates and lower OS are observed. Additionally, Imatinib high doses plus steroids has been associated to higher complete remission rate and prolonged survival in elderly population without additional chemotherapy,[43] a notable treatment approach for a age population highly sensitive to chemotherapy-related toxicity.

Importantly, the incorporation of TKIs into treatment regimens has allowed for a significant reduction in the intensity of chemotherapy, thereby lowering treatment-related toxicity and decreasing induction mortality. This strategy is particularly effective in older patients, who are especially vulnerable to the adverse effects of intensive chemotherapy.[44-46] As a result, treatment paradigms in high-income countries are increasingly shifting toward reduced-intensity or even chemotherapy-free approaches, facilitated by the use of newer agents such as blinatumomab and more potent second- and third-generation TKIs, including ponatinib. These advances help to explain the substantial survival differences observed between our population and those reported in the U.S. and Europe.

Limitations

This study is not exempt to limitations, starting by inherent obstacles owns to retrospective research works, which prevent data collection related to treatment protocols being standardized recorded. Furthermore, heterogeneity of chemotherapy protocols added to the diverse formulations of imatinib used in this cohort, some of these brands without studies of equivalence or observation trials that attest to their effectiveness, limit to accurately interpret these results and elucidate the total effect attributable to imatinib. Another important aspect is lack of HSCT availability; a reduced number of patients did benefit from HSCT in this study, negatively impacting survival outcomes.

In spite of that MRD assessment was not available to evaluate all subject of this cohort, MRD has become the most precisely monitoring stratification tool in ALL, and also allow to promptly evaluate early response, helping to timely consideration of novel agents and need to switch TKIs during the follow-up period, as well as assisting to detect hematologic relapses earlier. Routinely MRD assessment is essential to achieve improvements in the management of ALL.

However, beyond these limitations, a significant improvement in response and survival outcomes in our cohort has been observed in Imatinib group, highlighting the fact that even in precarious conditions, as presented in this cohort, use of TKIs in adults Phi+ ALL represent the standard care of treatment to improve outcomes in Phi+ ALL in middle-lower income countries like Ecuador. This research is added to those few studies coming from developing countries, helping to elucidate the reality and factors associated to poor outcomes in these geographically, economically, and ethnically diverse populations.

CONCLUSION

Although, advent of TKIs totally changed landscape management of Phi+ adult ALL patients, yielding to better response and survival outcomes. However, populations from middle-lower incomes countries like Ecuador still face poor outcomes, most in part due to high rate of induction death, low availability of MRD monitoring, lack of standardization of treatment protocols, restricted access to HSCT, and delayed initiation to TKIs therapy. Breaking these barriers through public health policies as well as expand access to new groundbreaking therapies represent a major goal to achieve and improve outcomes in Ecuador, likewise other middle-lower incomes countries dealing with same adversities.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study protocol was reviewed and approved by the Human Investigation Committee of the Technical University of Manabi (Date: 27.04.2023, Decision No: CEISH-UTM-EXT_23-01-5_BESV).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Evaluation of public awareness and attitudes on Crimean-Congo hemorrhagic fever: a survey study in a rural area of western Anatolia of Turkiye

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ABSTRACT

Aims: Crimean-Congo hemorrhagic fever (CCHF) is a zoonotic viral disease caused by a virus belonging to the genus Nairovirus, with *Hyalomma* spp. being the primary vector. The purpose of this study is to examine the knowledge, attitudes, and behaviors of rural communities regarding CCHF, its symptoms, transmission modes, and related topics. Furthermore, this study aims to contribute to the development of public health education programs.

Methods: This cross-sectional survey was conducted through face-to-face interviews between June 25, 2024, and July 25, 2024, in the countryside of Balıkesir, Turkiye.

Results: A significant majority of participants (87.6%) were aware that CCHF is present in Turkiye, but only 47.6% were aware of its presence in their local region. This discrepancy suggests that while general awareness of CCHF is high, its perceived importance at a local level is lower.

Conclusion: The survey highlights both the strengths and weaknesses in public awareness and attitudes towards CCHF in a rural area of the Marmara Region. While there is general recognition of the seriousness of the disease, gaps in specific knowledge and preventive behaviors point to the need for targeted public health interventions. These gaps can be addressed through specialized education campaigns aimed at at-risk populations, improving societal attitudes and responses to tick bites, and ultimately benefiting the prevention, transmission, and diagnostic processes of CCHF in these vulnerable populations.

Keywords: Hemorrhagic fever, public awareness, virus, rural area

INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is a zoonotic viral disease caused by a virus belonging to the genus *Nairovirus*, with *Hyalomma* spp. being the primary vector. Clinical symptoms begin with fever, headache, myalgia, and fatigue, which can progress to bleeding, multi-organ failure, and death.[1] Thrombocytopenia is a common laboratory finding in CCHF infection.[2] Patients typically present with leukopenia and elevated levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and creatine phosphokinase (CPK).[3] Coagulation tests, including prothrombin time (PT) and activated partial thromboplastin time (aPTT), are often prolonged. Additionally, fibrinogen levels may decrease while fibrin degradation products are frequently elevated.[4]

The primary modes of transmission are through tick bites or contact with infected materials. Due to the wide geographic distribution of its vector, CCHF is one of the more common and potentially fatal tick-borne diseases.[2] It is prevalent in many regions worldwide.[3-6] The highest risk group comprises farmers living in outbreak areas, with most affected individuals engaged in agriculture and/or livestock farming.[5,6] A study conducted in Kosovo by Fajs et al.[7] demonstrated a seroprevalence rate of 4.0%.

Several factors may influence the transmission and mortality of the disease. Beyond viral virulence and treatment-related factors, aspects such as the method of tick removal and early diagnosis also impact the course of the disease. These factors are directly related to the knowledge, attitudes, and awareness of at-risk communities.[4-7] A high level of public knowledge can contribute to better recognition of the disease, and quicker access to treatment for CCHF.[6,8,9] Moreover, timely diagnosis plays a vital role in guiding therapy and minimizing the risk of nosocomial infections.[10]

Studies on knowledge, attitudes, and behaviors are particularly critical in public health for assessing existing

knowledge, forming behavioral strategies, and subsequently developing new public health programs.[11,12]

The purpose of this study is to examine the knowledge, attitudes, and behaviors of rural communities regarding CCHF, its symptoms, transmission modes, and related topics. Furthermore, this study aims to contribute to the development of public health education programs.

METHODS

Ethics committee approval for this study was received from the Balıkesir University Health Sciences Ethical Review Board (Date: 11.06.2024, Decision No: 2024/89). Before the start of data collection, each participant in the study provided written informed consent, and only those who willingly participated were included. After obtaining their informed consent, the participants completed the questionnaires. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This cross-sectional survey was conducted through face-to-face interviews between June 25, 2024, and July 25, 2024, in the villages of Eğerci, located in the Savaştepe district, and Çamuca, in the Balya district of Balıkesir, Turkiye. These locations were selected due to the previous observation of CCHF cases. Random sampling was employed to select participants.

Statistical Analysis

Categorical data were presented as frequencies (n) and percentages (%), while continuous (measured) data were summarized using mean, standard deviation, and minimum-maximum values. The data were visualized using various formats, including pie charts.

All collected data were entered into the SPSS software package (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) and subsequently analyzed using the same program.

RESULTS

The survey included a total of 338 participants, with 61.3% (n=207) being male and 38.7% (n=131) female. The average age of the participants was 51.0 years, with a standard deviation of 15.9 years. Among the male participants, the mean age was 50.3 years (±15.4), while for the female participants, the mean age was 52.3 years (±16.4). The occupations represented among the participants were as follows: retirees (19.2%, n=65), housewives (18.6%, n=63), and individuals engaged in agriculture and animal husbandry (16.9%, n=57), workers (8.9%, n=30), tradesmen (6.9%, n=23), and students (4.8%, n=16). Individuals in other occupations accounted for the remaining 24.7% (n=84).

In terms of educational background, 30.8% (n=104) were primary school graduates, 9.2% (n=31) were secondary school graduates, 25.4% (n=86) had completed high school, 30.8% (n=104) were university graduates, and 3.8% (n=13) had never attended school.

Regarding exposure to CCHF, 9 of the participants reported a personal or family history of CCHF, while 327 had no such history. Additionally, 296 were aware that CCHF occurs in Turkiye, and 161 of the participants indicated that it is present in their local region. When asked about the availability of a vaccine for CCHF, 257 of the participants responded 'no,' while 78 of the participants answered 'yes.' In terms of causative agents, 162 of the participants correctly identified viruses as the cause of CCHF, whereas others incorrectly identified. Regarding transmission, 89.6% of the patients correctly stated that CCHF is transmitted by ticks, while 7.7% of the patients mentioned mosquitoes, and 2.7% of the patients incorrectly cited contaminated water.

When asked how they would respond to finding a tick on their body, 80.1 % (n=271) indicated they would go to a hospital for tick removal, while 10.7% (n=36) would remove it with tweezers, and 9.2% (n=31) would remove it by hand. In terms of protective behaviors, 77.8 % (n=263) agreed that using protective equipment, such as gloves and boots, during animal contact can help prevent CCHF transmission, while 12.13% (n=41) were undecided, and 8.9 % (n=30) disagreed. Four individuals did not respond to the question regarding the protective behaviors.

In addition, in one of the survey questions, participants were asked what the symptoms of CCHF disease would be. Tho choices were bleeding, high fever, muscle-joint pain, and fatigue. 47.3% (n=159) of the participants answered that bleeding, high fever, muscle-joint pain, and fatigue would be symptoms of CCHF. Another 19.0% (n=64) answered that high fever, muscle-joint pain, and fatigue would be the symptoms. High fever alone was answered as the sole symptom by 17.0% (n=57) of the participants. A combination of bleeding, high fever, and muscle-joint pain was answered by 4.2% (n=14), while 3.0% (n=10) of the participants answered combination of bleeding and high fever. Additionally, 2.7% (n=9) of the participants answered that combination of high fever and fatigue would be the sypmtoms, and another 2.7% (n=9) answered that bleeding would be the only symptom. High fever and muscle-joint pain sypmtom combination were answered by 0.9% (n=3), and 0.9% (n=3) answered bleeding, high fever, and fatigue sypmtom combination. However, 0.9% (n=3) answered that fatigue would be the only symptom, and another 0.9% (n=3) answered that muscle-joint pain would be the only symptom. On the other hand, 0.6% (n=2) answered that muscle-joint pain and fatigue symptoms would be together. Two individuals did not respond to the question regarding the symptoms of CCHF disease.

Out of the study group, 93.5% (n=315) of the responders stated that CCHF is a fatal disease, while 6.5% (n=22) believed that it is not. 1 people did not respond to this question (**Figure**).

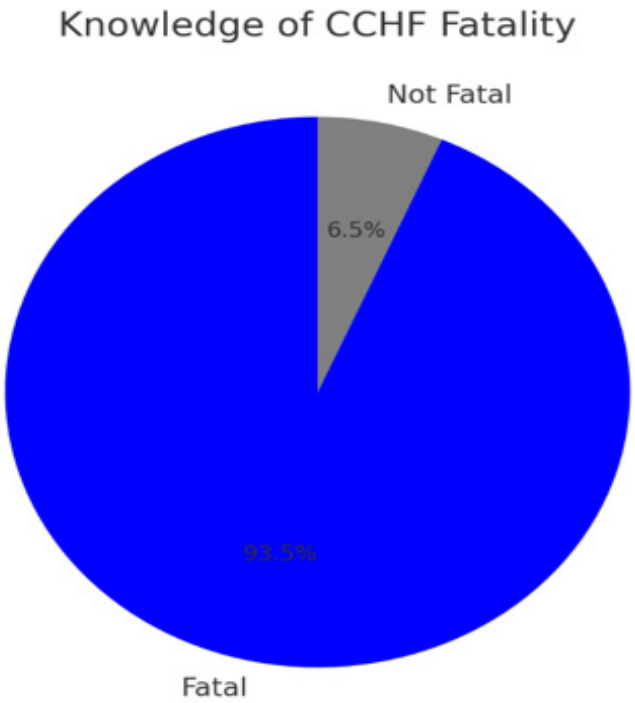

Figure. Knowledge of the fatality of Crimean-Congo hemorrhagic fever

DISCUSSION

The aim of this study was to evaluate the knowledge, attitudes, and behaviors of a rural community in Southern Marmara (Turkiye) regarding CCHF symptoms and modes of transmission. A significant majority of participants (88.9%) were aware that CCHF is present and as a fatal disease (80%), but only 47.9% were aware of its presence in their local region. This discrepancy suggests that while general awareness of CCHF is high, its perceived importance at a local level may be lower. As individuals who do not perceive CCHF as a local threat may be less inclined to adopt preventive measures, potentially increasing their risk of infection transmission. Nejati et al.[13] conducted a study in Iran, where participants displayed a good attitude toward CCHF prevention by recognizing the importance of using safety equipment both during animal slaughter and while handling livestock. Besides, Abazari et al.[14] suggested that the health belief model can predict preventive behaviors for CCHF. Furthermore, a study conducted in Pakistan examined the public's knowledge, attitudes, and practices concerning CCHF were not high, with approximately 70.3% of participants reporting that they took precautions against tick bites.[11] Similarly, 77.8% of participants in our study agreed to use protective equipment during animal slaughter or contact to prevent CCHF transmission. However, this highlights the need for further education, especially in rural areas where the risk of tick exposure is higher due to agriculture and livestock farming activities.

Public health campaigns should emphasize the importance of preventive behaviors, such as wearing protective clothing and checking for ticks after outdoor activities. Such campaigns could be implemented through community meetings, local health centers, and agricultural cooperatives to effectively reach at-risk populations. Educating these communities about risk factors and control measures could help reduce CCHF transmission and improve disease prevention.

People living in endemic areas should regularly inspect their clothing and skin for ticks during rural area wandering. Additionally, practical measures, such as wearing gloves or other protective clothing to prevent direct skin contact with infected tissue or blood, should be adopted.[10,15] Our study also found that the majority of participants expressed a strong willingness to attend informational meetings about CCHF. This reflects a societal desire and willingness to participate in educational initiatives to raise awareness and adopt preventive measures against this disease.

Public health campaigns should emphasize the critical importance of preventive behaviors, such as wearing protective clothing and checking the body for ticks after outdoor activities. These campaigns can be implemented through community meetings, local health centers, and agricultural cooperatives to effectively reach the most at-risk populations. Educating the risky population about risk factors and preventive methods could further help reduce the spread of this disease.[2,8,11-17] Almorish et al.[17] evaluated the knowledge and attitudes of slaughterhouse workers in Yemen towards CCHF and they reported that the majority of respondents had poor knowledge.

The findings of this study may help to assist the Ministry of Health and associations in developing strategies and interventions to raise public awareness and prevent future outbreaks.

Limitations

The limitations of our study include the relatively small sample size, which may not fully represent the broader population of the Marmara Region. Additionally, the cross-sectional nature of the survey provides only a snapshot of awareness and attitudes, without capturing changes over time.

CONCLUSION

The survey highlights both the strengths and weaknesses in public awareness and attitudes towards CCHF in a rural area of the Marmara Region. While there is general recognition of the seriousness of the disease, gaps in specific knowledge and preventive behaviors point to the need for targeted public health interventions. These gaps can be addressed through specialized education campaigns aimed at at-risk populations, improving societal attitudes and responses to tick bites, and ultimately benefiting the prevention, transmission, and diagnostic processes of CCHF in these vulnerable populations.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethics committee approval for this study was received from the Balıkesir University Health Sciences Ethical Review Board (Date: 11.06.2024, Decision No: 2024/89).

Informed Consent

All participants provided written informed consent.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

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Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Review

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Cancer stem cells

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ABSTRACT

Cancer stem cells (CSCs) are at the center of processes such as tumor heterogeneity, drug resistance, metastasis, and post-treatment recurrence in tumor biology. Due to their self-renewal and differentiation capabilities, these cells play a significant role in the course of disease by exhibiting resistance to conventional therapies. In malignancies with a high risk of recurrence and metastasis, such as ovarian cancer (OC), the development of new therapeutic strategies targeting CSCs has become critically necessary. This review presents the biological characteristics of CSCs and current treatment approaches in light of the literature, offering a comprehensive perspective on the subject.

Keywords: Cancer stem cells, tumor biology, tumor metabolism

INTRODUCTION

Cancer stem cells (CSCs) represent a heterogeneous cell population positioned at the top of the hierarchical structure in tumor development, with demonstrated capacity to generate an entire tumor tissue from a single cell. Through their abilities for self-renewal and differentiation, they are distinguished from progenitor or precursor cells. CSCs have been identified in solid neoplasms such as breast, brain, bone, prostate, ovary, skin, liver, bladder, lung, colon, pancreas, and head and neck tumors, as well as in hematological malignancies.[1]

These cells retain biological characteristics specific to pluripotent stem cells and are characterized by mechanisms such as the expression of CD133, CD44, and aldehyde dehydrogenase (ALDH), along with the reactivation of developmental signaling pathways like Wnt/β-catenin, Notch, and Hedgehog. Moreover, with their enhanced adaptive capabilities under stress conditions, they exhibit resistance to conventional therapies such as chemotherapy and radiotherapy, and are associated with tumor recurrence.[2] Therefore, therapeutic approaches that directly target CSCs are considered promising strategies for enhancing the effectiveness of oncological treatments.[3]

CANCER STEM CELLS METABOLISM

CSCs are metabolically specialized to produce energy using various substrates in order to survive under diverse microenvironmental conditions. As with normal stem cells, glucose is of vital importance for CSCs, and the presence of glucose in the microenvironment has been shown to significantly increase the number of stem cell-like cancer cells. CSCs exhibit significantly higher glucose uptake, lactate production, glycolytic enzyme expression, and intracellular ATP levels compared to other cells.[4] Among stem cell markers, CD44 is known to play a critical role in glycolytic metabolism.[5] The active maintenance of glycolysis is essential for the survival of CSCs and the sustained progression of the tumor.[6] Although glycolysis stands out as the primary energy production pathway in CSCs, recent studies have demonstrated that mitochondrial oxidative metabolism is also actively utilized by these cells.[7] Some studies have shown that CSCs possess higher ATP levels despite lower glucose consumption and lactate production compared to differentiated cancer cells.[8] Moreover, CSCs have been reported to utilize not only glucose but also various amino acids, such as glutamine and lysine, as energy sources. In addition, fatty acid oxidation may serve as an alternative metabolic pathway for energy production in these cells.[9]

CANCER STEM CELLS SIGNALING PATHWAYS

The persistence of CSCs and their ability to evade therapeutic interventions depend on the active maintenance of various intracellular signaling pathways. Recent studies have revealed that therapeutic strategies targeting these signaling pathways yield successful results in both cell culture and animal models. While signaling pathways such as Sonic Hedgehog (Shh), Wnt, fibroblast growth factor (FGF), Notch, and bone morphogenetic protein (BMP) play crucial roles in normal cell development and morphogenesis, they also hold critical

functions in tumor formation and progression. Targeting these pathways offers a potential approach for the elimination of CSCs and for overcoming therapy resistance mechanisms.[10]

The Notch Pathway

The Notch signaling pathway is a mechanism that operates through cell-cell interaction and plays a critical role in various fundamental biological processes such as embryonic development, tissue homeostasis, and cell differentiation. Notch receptors are key components of an extensive signaling network that regulates cellular fate determination, proliferation, apoptosis, and stem cell renewal in complex organisms. This pathway functions through four distinct membrane-bound Notch receptors (Notch1, Notch2, Notch3, Notch4) and their ligands (Jagged1, Jagged2, Delta-like 1, Delta-like 3, Delta-like 4).

In particular, the Notch3 receptor has been reported to be overexpressed in high-grade serous OC. The overexpression of Notch3 leads to upregulation of pathways necessary for the development of CSCs in serous OC cell lines (**Figure 1**).[11] Administration of Notch pathway inhibitors combined with cisplatin resulted in significant reductions in both cancer stem cell population and tumor cell number.[12] The Notch signaling pathway is also associated with cervical cancer. Numerous studies have demonstrated increased Notch expression in cervical carcinoma cells. However, there is also evidence suggesting that in advanced-stage HPV-infected tumors, the expression level of Notch1 is decreased, and Notch signaling may suppress HPV-mediated transformation. These data indicate that the role of the Notch pathway in cervical carcinogenesis is complex and context-dependent.[13]

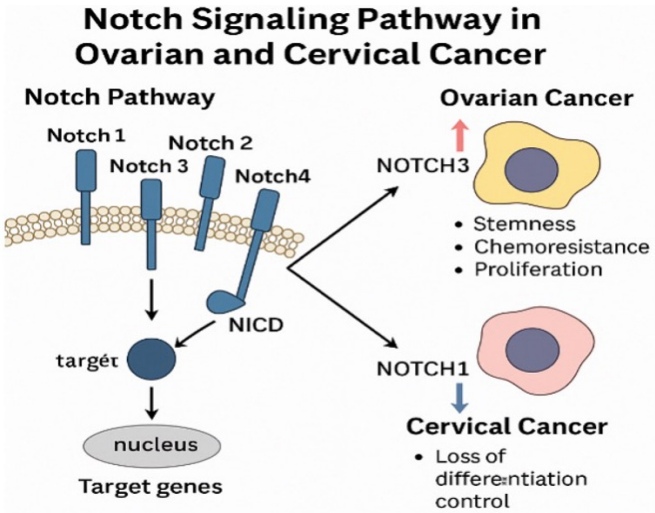

Figure 1. Differential activation of the Notch signaling pathway contributes to tumor progression in ovarian cancer and may play a suppressive role in HPV-related cervical cancer

The Wnt Pathway

The Wnt signaling pathway is one of the fundamental cellular signaling mechanisms involved in various developmental processes, including embryonic development, cell proliferation, and differentiation.[14] This pathway plays a critical role in the formation and maintenance of CSCs. Particularly, disruptions in Wnt signaling are thought to mediate the transformation of somatic stem cells into a CSC phenotype by conferring regenerative capacity.[15] Irregularities in the Wnt pathway have been associated with the emergence and persistence of leukemic stem cells as well as the development of various solid and hematologic malignancies.[16] Moreover, CSCs are believed to develop resistance to conventional chemotherapy agents through this pathway, which may adversely affect therapeutic outcomes (**Figure 2**).

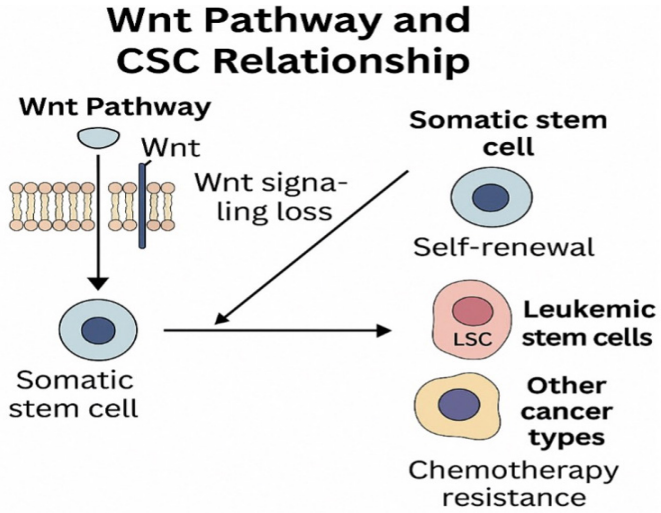

Figure 2. Wnt pathway alteration supports CSC self-renewal, survival, and resistance to therapy

Sonic Hedgehog (Shh)

The Hedgehog (Hh) signaling pathway plays a vital role in regulating cellular proliferation, differentiation, and tissue organization during vertebrate embryonic development. Recent studies have revealed striking similarities between embryogenesis and tumor formation.[17] In particular, there are significant overlaps between the two processes in terms of the acquisition of invasive cell properties, epigenetic regulations, gene expression profiles, the presence of oncofetal proteins and metabolic properties (e.g. high proliferative capacity, suppression of immune response). These similarities indicate that the Hedgehog signaling pathway is a determining element not only in developmental processes but also in malignant transformation and tumor progression.

TGF-β

Transforming growth factor-β (TGF-β) is a multifunctional cytokine involved in numerous biological processes, including early embryonic development, organogenesis, immune responses, tissue repair, and homeostasis. The effects of TGF-β on fibrosis and cancer are highly complex and context-dependent, varying with stage of the disease and cellular environment. While it acts as a tumor suppressor in early stages, it may promote tumor progression in advanced stages.[18] Its pathological overexpression contributes to the development of fibrotic diseases and various cancer types by inducing epithelial-mesenchymal transition (EMT), extracellular matrix (ECM) accumulation, and the formation of cancer-associated fibroblasts (CAFs). Therapeutic approaches targeting the TGF-β signaling pathway are considered promising strategies, particularly for reshaping the tumor microenvironment (TME) and preventing metastasis. However, due to its potential for systemic cytotoxicity, the clinical application of TGF-β-focused therapeutics remains limited.

IL-6/JAK/STAT3

The IL-6/JAK/STAT3 signaling pathway is hyperactivated in many types of cancer and is often associated with poor prognosis. JAK/STAT3 signaling, activated via IL-6 within the TME, increases the proliferation, survival, invasive capacity and metastatic potential of tumor cells, while also allowing immune escape by suppressing the antitumor immune response (**Figure 3**). Therefore, therapeutic strategies targeting the IL-6/JAK/STAT3 pathway are considered an effective therapeutic approach due to their potential of both directly inhibiting tumor cell growth and enhancing the antitumor capacity of the immune system.[19]

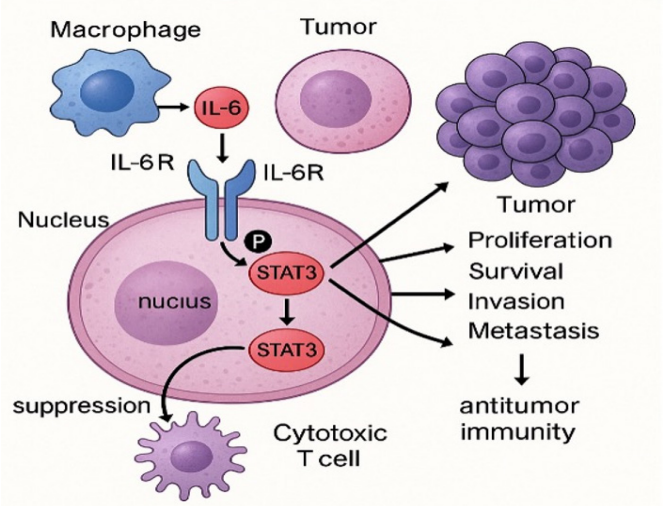

Figure 3. The IL-6/JAK/STAT3 pathway supports cancer progression and immune evasion through persistent signaling activation

NF-κB Pathway

In OC, BRCA1 mutation is constitutively associated with the activation of the p65 subunit of NF-κB;20, 21 in OC cases treated with DNA damage repair inhibitors, activation of the p50 subunit of NF-κB has been observed. This reciprocal dependence between NF-κB and BRCA1 is considered responsible for chemotherapy resistance in OC. Inhibition of the NF-κB signaling pathway induces apoptosis in cisplatin-resistant OC cell lines and reduces the number of $CD44^+$ ovarian cancer stem cells (OCSCs).[22]

CAFs, which are one of the main components of the TME, stimulate the overexpression of the ECM proteoglycan versican, which binds to the CD44 molecule on OCSCs and activates NF-κB and c-Jun N-terminal kinase (JNK) signaling.[23,24]

Furthermore, interleukin-17 (IL-17), which enhances the formation of $CD133^+$ cell spheroids and the self-renewal capacity of OCSCs, exerts these effects through the NF-κB and p38 mitogen-activated protein kinase (p38 MAPK) pathways.[25] OCSCs are capable of autocrine stimulation via cytokines that activate inflammatory signaling pathways, thereby contributing to tumor progression.[26,27]

$CD133^+$ OCSCs stimulated by IL-23 enhance their self-renewal capacity through the activation of the NF-κB and STAT3 pathways.[28] Activation induced by chemokine ligand-5 (CCL5) and its receptors promotes the migration of $CD133^+$ OCSCs and their differentiation into endothelial cells via NF-κB and matrix metalloproteinase-9 (MMP-9).[29]

Constitutive NF-κB activity has been attributed to $CD44^+MyD88^+$ OCSCs, and activation of the TLR/MyD88/NF-κB pathway has been associated with an increase in the number of OCSCs.[30]

CANCER STEM CELL HETEROGENEITY

Intratumoral heterogeneity is defined as the ability of cancer cells to exhibit genetic, epigenetic, and phenotypic differences even within the same tumor tissue. In a study conducted by Gerlinger and colleagues,[31] primary renal carcinomas and their metastatic lesions were examined, revealing that only 31–37% of somatic mutations were shared between intratumoral regions, with the remainder showing regional differences.

It was also determined that this heterogeneity occurs through the loss of function of multiple tumor suppressor genes and that gene expression profiles indicative of both good and poor prognosis exist in different regions. Recent analyses have shown that epigenetic variations such as allelic composition, ploidy, and promoter hypermethylation differences also contribute to intratumoral diversity.[32]

This diversity is a significant factor complicating the targeting and treatment of CSCs. The fact that CSC-specific markers do not show a consistent (uniform) expression pattern across different cancer types hinders the development of a universal marker set. For example, although markers such as CD133, CD44, CD166, CD24, and ALDH1 have been used in CSC isolation in many solid tumors, their expression varies significantly among tumor types.[33] While CD133 is identified as an effective CSC marker in glioblastoma, the $CD44^+/CD24^-$ phenotype is considered a more meaningful isolation criterion in breast cancer.[34,35] Differences in marker expression profiles among different subtypes of the same cancer or among similar subtypes in different patients significantly complicate the development of targeted therapeutic approaches specific to CSCs.

TREATMENTS TARGETING CANCER STEM CELLS

Due to their role as the source of therapy-resistant cells, CSCs are currently receiving increasing attention as therapeutic targets. Current evidence indicates that specific biomarkers, abnormally activated cellular signaling pathways, the immunosuppressive TME, and immune escape mechanisms play significant roles in the formation and maintenance of CSCs. Targeting these components may facilitate the elimination of CSCs by inducing their differentiation, thereby increasing the efficacy of cancer treatment. Various CSC biomarkers have been identified in different types of cancer. Among the most extensively studied are CD44, CD133, ALDH, and epithelial cell adhesion molecule (EpCAM). CD44 is a surface glycoprotein widely expressed in CSCs and generally associated with poor prognosis. In a phase I clinical trial targeting CD44, the monoclonal antibody RG7356 was shown to inhibit tumor growth by blocking CD44's binding to hyaluronan (HA).[36] In another study conducted in small cell lung cancer (SCLC) patients, HA-irinotecan complex therapy targeting CD44 was reported to yield favorable clinical outcomes. CD133 is another biomarker that plays

a particularly significant role in tumor dissemination. A clinical study conducted in patients with hepatocellular carcinoma (HCC) demonstrated that CART-133 cell therapy targeting CD133 exhibited significant antitumor efficacy. EpCAM is a prominent biomarker highly expressed in CSCs and evaluated as a therapeutic target. In a study conducted in bladder cancer patients, the therapeutic agent VB4-845 targeting EpCAM successfully inhibited tumor growth in patients resistant to or intolerant of Bacillus Calmette-Guerin (BCG) therapy.[37] ALDH enzymes are among the biomarkers that play a crucial role in determining the biological activity of CSCs and tumor progression. Studies conducted in patients with colorectal liver metastases (CRLM) have shown that curcumin significantly reduced CSC proliferation by specifically targeting both ALDH and CD133 biomarkers.[38] Moreover, the combination of curcumin with 5-fluorouracil and oxaliplatin enhanced chemotherapeutic efficacy, more effectively inhibiting cancer cell growth. In light of these findings, treatment strategies targeting CSC biomarkers show promise in slowing cancer progression and reducing the risk of therapy-related recurrence.[39]

Targeting CSC Signaling Pathways

Various signaling pathways, such as Wnt/β-catenin, Hedgehog, Notch, and epidermal growth factor receptor (EGFR), play critical roles in the immortalization, reprogramming, and development of chemoresistance in CSCs. Therapeutic targeting of these pathways is among the promising strategies for CSC elimination. For example, Porcupine inhibitors have the potential to eliminate both proliferative CSCs activated via canonical Wnt pathways and dormant CSCs stimulated by non-canonical Wnt pathways by inhibiting the release of Wnt ligands. In Notch pathways, targeting ligands or receptors can exert therapeutic effects by suppressing aberrant signaling. In this context, delta-like ligand 4 (Dll4), a key component of the Notch pathway, plays a pivotal role particularly in angiogenesis processes. Phase I clinical trials have demonstrated that therapeutic agents such as demcizumab and enoticumab, which target Dll4, exhibit antitumor activity both as monotherapies and in combination treatment forms. In addition, oncogenic signaling pathways such as NF-κB, STAT3, and PI3K/Akt also play roles in the regulation of CSC self-renewal, survival, and differentiation capacities. These pathways contribute to the maintenance of the stem cell-like phenotype by controlling the expression of numerous target genes, including cytokines, growth factors, and genes associated with apoptosis.[40]

Targeting the Tumor Microenvironment and Immune Response

The TME represents the chronic inflammatory and immunosuppressive milieu necessary for the sustainability of CSCs. This inflammatory environment disrupts the normal functions of various stromal cells, leading to the secretion of biological agents that contribute to drug resistance and the establishment of immunosuppressive conditions. Therefore, a properly functioning host immune system is critically important in preventing inflammation-induced disruptions in TME homeostasis. In this context, various therapeutic strategies aimed at disrupting the TME are considered effective approaches for the elimination of CSCs. One of the key components of the TME, CAFs, plays a central role in the maintenance of CSCs and the development of drug resistance. Studies involving therapeutic agents developed against the surface markers of these cells have shown that tumor growth can be suppressed.[41] Transforming growth factor-beta (TGF-β) is one of the most studied cytokines derived from the TME. TGF-β supports tumor development by suppressing T lymphocyte-mediated immune responses through signaling pathways activated in stromal cells.[42] Clinical studies have reported therapeutic efficacy of agents such as M7824 and galunisertib that target TGF-β.[43] Interleukin-6 (IL-6) plays a central role in both inflammation and tumor development. Research has shown that high IL-6 levels contribute to cisplatin resistance in non-small cell lung cancer (NSCLC) patients. However, the monoclonal antibody siltuximab, which targets IL-6, has demonstrated limited clinical efficacy in advanced-stage solid tumors.[44] $CD8^+$ T lymphocytes play a fundamental role in regulating adaptive immune responses. These cells eliminate abnormal cells with high specificity by recognizing antigenic peptides presented via major histocompatibility complex class I (MHC-I). Upon stimulation with interferon-gamma (IFN-γ), the expression of molecules such as TAP (Transporter associated with Antigen Processing), ERAP (endoplasmic reticulum-associated aminopeptidases), and IFN-γ, which contribute to MHC-I antigen presentation, is increased. Although these components are not strictly essential for cellular proliferation, their deficiencies can lead to reduced MHC-I levels and impaired antigen presentation capacity.[45] Antigen presentation via MHC-I is a critical step for effective responses by $CD8^+$ T cells.[46] Nevertheless, CSCs have developed various mechanisms to escape immune surveillance. These mechanisms include suppression of dendritic cell (DC) function and downregulation of MHC-I expression.[47] It has been shown that CSCs can alter DC phenotypes, thereby limiting their accumulation in the microenvironment in ways that hinder T lymphocyte activation.[48] In the TME, activation of immune checkpoint molecules such as CTLA-4 (cytotoxic T-lymphocyte antigen 4) and the PD-1/PD-L1 (programmed death-1/programmed death-ligand 1) axis reorganizes immune homeostasis and allows tumor cells to evade immune responses. Immune checkpoint inhibitors (ICIs) targeting these pathways have demonstrated promising antitumor effects in various human cancers.[48] However, the efficacy of these agents often depends on IL-12 secretion derived from DCs.[49] Moreover, in tumors with low MHC-I expression, ICIs may exacerbate T cell dysfunction rather than correct it.[50] Accordingly, supporting antigen processing and presentation pathways, along with the development of combination therapies with ICIs, are among the promising strategies for effectively targeting CSCs.

Targeting Differentiation

Poorly differentiated tumors derived from CSCs typically exhibit more aggressive and malignant characteristics. Differentiation-based therapeutic approaches developed in this context aim to inhibit tumor progression by promoting the maturation of undifferentiated tumor cells into more mature and well-differentiated cell phenotypes. Differentiation-inducing agents such as retinoic acid (RA), cyclic adenosine monophosphate (cAMP), sodium butyrate, and various cytokines have been shown to be effective in certain cancer types. Among these agents, all-trans retinoic acid (ATRA) has demonstrated significant anticancer activity by inducing terminal differentiation

in patients with acute myeloid leukemia (AML) and acute promyelocytic leukemia (APL).[51] In recent years, next-generation differentiation-inducing agents targeting mutant isocitrate dehydrogenase (IDH) 1 and IDH2 enzymes have achieved clinical success in AML treatment and received regulatory approval in this field. IDH1 and IDH2 mutations epigenetically affect the cellular differentiation process by increasing histone and DNA methylation, leading to the suppression of differentiation. Additionally, epigenetic modulators such as DNA methyltransferase inhibitors (DNMTis) and histone deacetylase inhibitors (HDACis), which increase MHC-I expression, have also been shown to have a role in differentiation processes.[52] IDH1/2 mutations have been observed not only in hematologic malignancies but also in solid tumors. The differentiation-inducing effects of inhibitors developed against these mutations are currently being investigated in various clinical trials. Vaccines targeting IDH1 and agents such as ivosidenib and olutasidenib, have shown potential in reducing tumor burden and improving progression-free survival.[53] The dual inhibitor vorasidenib, which targets both IDH isoforms (IDH1 and IDH2), has demonstrated promising antitumor activity particularly in recurrent or progressive, contrast-enhancing-negative IDH-mutant low-grade gliomas.[54] Neomorphic mutations in the IDH1/2 genes impair the homologous recombination (HR) repair mechanism, which renders these tumors sensitive to poly (ADP-ribose) polymerase (PARP) inhibitors. Based on this rationale, the Olaparib combination study represents a phase II trial in which patients with solid tumors harboring IDH1/2 mutations were treated with olaparib as monotherapy. Both in this study and in similar research, PARP inhibitors have been reported to exhibit clinical efficacy either as monotherapy or in combination regimens.[55]

CONCLUSION

CSCs play a central role in the processes of treatment resistance, relapse, and metastasis in many solid and hematologic malignancies. The self-renewal and differentiation capabilities of CSCs render conventional treatment strategies largely ineffective, positioning CSC-targeted therapies as a priority in modern oncology practice. The data presented in this review highlight the breakthrough potential of treatment strategies targeting CSC biomarkers, signaling pathways, the TME, and immune evasion mechanisms. However, the high degree of heterogeneity and plasticity displayed by CSCs complicates the prediction of treatment responses, underscoring the importance of personalized and targeted therapeutic approaches. In the future, it is expected that clinically effective, multi-component, and combination-based treatment strategies that specifically target CSCs while minimizing systemic toxicity will occupy a broader place in clinical practice.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report

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Isolated myeloid sarcoma causing obstructive jaundice in duodenal ampulla: a very rare case

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ABSTRACT

Isolated myeloid sarcoma (MS) is a malignant neoplasm of myeloid origin that is located in extramedullary tissues. MS is rare; only 10-19% of MS cases originate from the gastrointestinal tract (GIT). These patients usually present with non–specific symptoms associated with the GIT, thus, the diagnosis is easily overlooked and patients are misdiagnosed. In this article, we present a case of isolated MS localized in the duodenal ampulla that presented with cholestatic jaundice. On magnetic resonance imaging (MRI) and MR cholangiography (MRCP), a 3.8×3.5 cm mass lesion was visualized in the duodenal ampulla. A diagnosis of MS was made based on an endoscopic retrograde cholangiopancreatography biopsy. It was recognized as an isolated MS after further examination. An idarubicin and cytarabine–based chemotherapy regimen was administered for induction and allogeneic HSCT was administered as post–remission consolidation therapy. The patient remains in remission under follow–up in the 6th month after allogeneic HSCT. Isolated MS is a rare hematologic neoplasia comprised of immature granulocytic cells. Although it can be detected in any part of the body, hepatobiliary, and particularly, pancreatic involvement is much less frequent. The optimal treatment of the disease is not elucidated due to the lack of relevant data and large prospective studies in the literature. The most recommended treatments are the systemic chemotherapies used in AML remission induction treatment. The authors think that HSCT must be considered after the induction of remission in MS, as it offers an advantage in terms of overall survival and leukemia–free survival.

Keywords: Myeloid sarcoma, duodenal ampulla, pancreas, hepatobiliary, granulocytic sarcoma

INTRODUCTION

Myeloid sarcoma (MS), also known as granulocytic sarcoma and chloroma, is a tumor characterized by the infiltration of extramedullary tissues by immature granulocytic series cells.[1] MS is encountered particularly frequently in concomitance with acute myeloid leukemia (AML), during the course of the disease, or its recurrence after allogeneic HSCT. Less commonly, it can occur during the course of accelerated or blastic phases of chronic myeloid leukemia, myelodysplastic syndrome, and other myeloproliferative diseases.[2,3]

Isolated MS, also known as non–leukemic MS; is defined as the form of MS with no findings of AML in bone marrow aspiration and biopsy. The incidence of MS has been estimated to range from approximately 2% to 18%, with a modest male predominance and a peak occurrence among adults aged 46 to 59 years.[4] Although MS can develop in any part of the body, including soft tissues, bones, central nervous system, mediastinum, lymph nodes, and skin; only 10-19% of the cases derive from the gastrointestinal tract (GIT).[3,5-7]

In MS, the clinical presentation may vary according to the clinical symptoms and findings associated with the primary disease, and tumor location and size. Patients with MS involving the GIT usually manifest non–specific symptoms such as abdominal pain, nausea, jaundice, intestinal obstruction, or gastrointestinal bleeding; hence, MS can be easily overlooked or misdiagnosed. Therapeutic strategies are diverse and may include systemic chemotherapy, novel targeted agents, immunotherapy, individualized application of allo-HCT, and local modalities such as RT, with surgery being employed only on rare occasions.[8] In this article we present a very rare case of isolated MS localized in the duodenal ampulla based on endoscopic biopsy with obstructive cholestasis according to clinical and laboratory tests.

CASE

A 19–year–old male patient presented to our hospital with abdominal pain, nausea, and bilious vomiting that

had persisted for one week and jaundice in the body that had persisted for one month. The patient also reported light–colored feces and a weight loss of 6 kg. On physical examination, the skin and sclerae were icteric; the epigastric region was mildly tender with no palpable masses, lymphadenopathy, or hepatosplenomegaly. Other systemic examinations were within normal limits. The patient did not have any known chronic diseases or a history of drug, alcohol, or tobacco use. Family history was not significant.

Laboratory test results were as follows: hemoglobin, 15.3 g/dl (normal range, 12-16 g/dl); white blood cell count, 4.78×10^9/L (normal range, $4\text{-}10\times10^9$/L); platelet count 167×10^9/L (normal range, $150–400\times10^9$/L); lactate dehydrogenase 680 IU/L (normal range, 120-246 IU/L); total bilirubin 20.7 mg/dl (normal range, 0-1.1 mg/dl); direct bilirubin 16.7 mg/dl (normal range, 0-.035 mg/dl); creatinine 0.69 mg/dl (normal range, 0.6-1.2 mg/dl); alanine aminotransferase, 452 U/L (normal range, <31 U/L); aspartate aminotransferase, 202 U/L (normal range, <34 U/L); alkaline phosphatase, 329 U/L (normal range, 30-120 IU/L); γ–glutamyl transpeptidase, 629 U/L (normal range, 0-55 IU/L).

Further tests were conducted for a preliminary diagnosis of choledocholithiasis or periampullary region pathologies. Dynamic magnetic resonance imaging (MRI) and magnetic resonance cholangiography (MRCP) visualized a 3.8×3.5 cm mass lesion consistent with a tumor that was localized lateral to the pancreatic head and in the duodenal ampulla and causing a sudden interruption in the choledochal duct and dilatation proximally (**Figure 1A, B**). Diagnostic endoscopic retrograde cholangiopancreatography (ERCP) was performed. A mass lesion with fragile mucosa that obstructed the lumen at the level of the duodenal papilla and extended distally was detected. A tissue biopsy was obtained from the lesion; however, transpapillary biliary cannulation could not be performed due to the change in the anatomical position secondary to the lesion. Bilirubin levels increased and persistent nausea and vomiting were observed during follow-up due to obstructed bile flow into the duodenum. Percutaneous transhepatic cholangial drainage (PTCD) was performed on the patient to ensure bile drainage and mitigate the symptoms of jaundice.

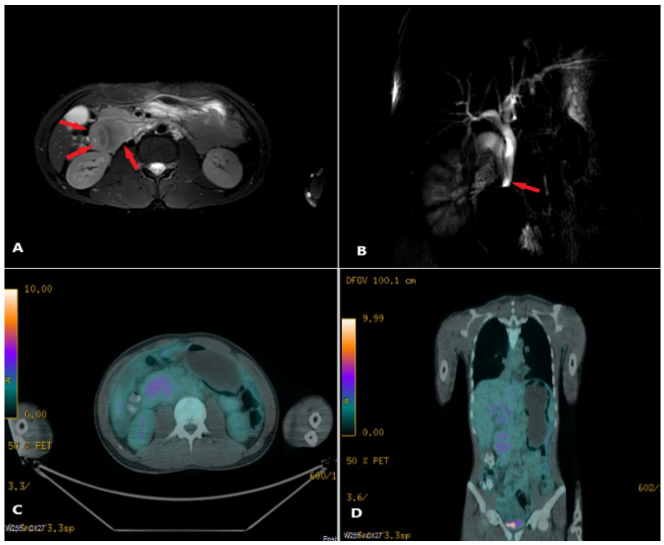

Figure 1. MRI and MRCP visualized a 3.8×3.5 cm mass lesion consistent with a tumor that was localized lateral to the pancreatic head and in the duodenal ampulla (**A**) and causing a sudden interruption in the choledochal duct and dilatation proximally (**B**).

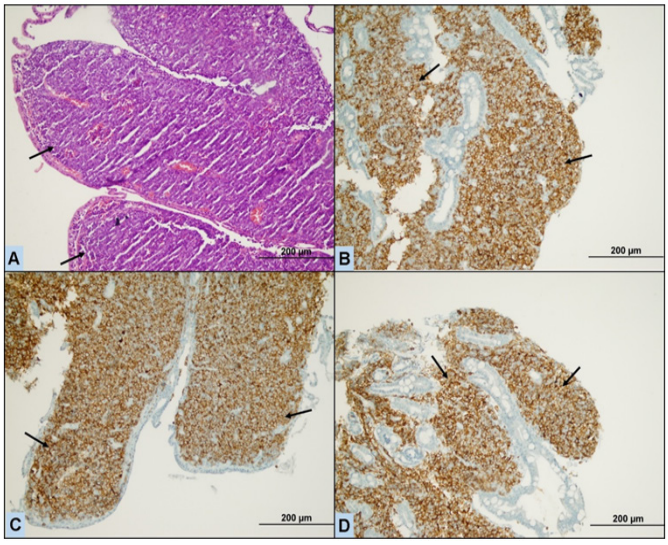

Figure 2. Hematoxylin–eosin (HE) stained image (**A**) showing a diffuse infiltration of medium and large atypical cells (arrows), with scant eosinophilic cytoplasm, vesicular nuclei and occasional nucleoli (HE X200). Immunohistochemistry showing diffusely staining of the tumor cells (arrows) for MPO (**A**), CD117 (**B**) and CD34 (**C**) (original magnifications X200).

Histopathological sections of the duodenum biopsy specimens showed that medium to large cells with pronounced nucleoli and minimal to moderate eosinophilic cytoplasm infiltrate the lamina propria diffusely. Immunohistochemically, MPO, CD117, and CD34 were diffuse positive in tumor cells. In contrast, positive immunoreactivity was not observed with CD3, CD20, CD10, terminal deoxynucleotidyl transferase (TdT), and cytokeratin (not shown) (**Figure 2**).

According to these results, the patient was diagnosed with MS. The peripheral blood smear, bone marrow aspiration, and biopsy performed after the tissue diagnosis was made did not detect AML infiltration and immunophenotyping was normal. Analysis of the bone marrow–derived blood sample revealed no positive findings on flow cytometry, cytogenetic evaluation, or molecular genetic testing. A fluorodeoxyglucose positron emission tomography/computed tomography (FDG–PET/CT) was performed prior to the treatment. A focal lesion with moderate metabolic activity was detected in the pancreatic head and duodenal ampulla region (standardized uptake value maximum [SUV max], 4.2) (**Figure 1C, D**). A standard idarubicin and cytarabine regimen (12 mg/m2 idarubicin on days 1-3 and 100 mg/m2 cytarabine on days 1-7) was administered. After induction chemotherapy, tumor size decreased significantly. One course of high–dose cytarabine (3 g/m2 q12h on days 1, 3, 5) was administered as post–remission therapy. And then the patient received allogeneic HSCT from an HLA–matched, related donor as consolidation therapy. The patient currently remains in remission under follow–up in the 6th post–transplant month.

DISCUSSION

Isolated MS is a rare malignant neoplasm that is characterized by the infiltration of myeloid cells into tissues. Although isolated MS can originate from any organ or tissue, pancreatic involvement is rare, and only a few cases

have been reported.[3,8-10] Since the patients may present with findings of obstructive jaundice, the diagnosis is often mistaken for choledocholithiasis, and to a lesser extent, other periampullary region pathologies. Particularly in patients with no known history of hematologic malignancy, the diagnosis of MS can be delayed or erroneous.[11] Accordingly, our case presented with the chief complaint of cholestatic jaundice symptoms, and an MS localized in the duodenal ampulla was diagnosed based on further tests.

Various imaging methods are utilized in the diagnosis of MS. The FDG–PET/CT method was shown to be a good option, particularly in isolated MS or MS concomitant with AML, in the determination of the localization and size of the tumor, detection of multiple tumors, and evaluation of the response to the treatment.[12] In our case, FDG–PET/CT was used to examine diffuseness prior to the treatment and to evaluate the response after the treatment, and the outcome was deemed effective.

The optimal treatment for MS patients could not be identified due to the rarity of the disease, the variability of the onset and localization of the tumor, genetic diversity, and the lack of prospective randomized studies. Data concerning the treatment options for the disease are obtained from case reports and small case series that are mostly retrospective studies. Essentially, the prognosis is known to be poor and the great majority of patients lose their lives if not treated.[8,9,11,12]

Currently accepted treatment options include local therapies (surgery or radiotherapy or a combination), systemic chemotherapy, allogeneic HSCT, and targeted therapies. Systemic chemotherapy was shown to reduce the rate of progression to acute leukemia and increase overall survival in isolated MS. There are also no prospective studies on allogeneic HSCT in MS patients and the available data belong to retrospective, small patient groups. In these studies, allogeneic HSCT was shown to provide an advantage in terms of both overall survival and leukemia–free survival. Therefore, the authors recommended accepting allogeneic HSCT as an effective treatment option for consolidation or in the case of recurrence in appropriate patients.[13] In our case, we administered systemic chemotherapy for remission induction and allogeneic HSCT for consolidation. Our patient remains in complete remission under follow–up in the 6th month after allogeneic HSCT.

CONCLUSION

Isolated MS is a rare hematologic neoplasia comprised of immature granulocytic cells. Although it can be detected in any part of the body, hepatobiliary, and mainly, pancreatic involvement is much less frequent. The optimal treatment of the disease is not elucidated due to the lack of relevant data and large prospective studies in the literature. The most recommended treatments are the systemic chemotherapies used in AML remission induction treatment. The authors think that allogeneic HSCT must be considered after the induction of remission in MS, as it offers an advantage in terms of overall survival and leukemia–free survival.

ETHICAL DECLARATIONS

Informed Consent
The patient signed and free and informed consent form.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

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Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report

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A rare disease: primary bone lymphoma case report

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ABSTRACT

Primary bone lymphoma (PBL) is a rare subtype of non-Hodgkin lymphoma, comprising a small proportion of primary bone malignancies and extranodal lymphomas. It typically presents with nonspecific symptoms such as localized bone pain, leading to delayed diagnosis. In this case report, we present a 39-year-old male with no prior comorbidities who applied with right hip pain and was ultimately diagnosed with diffuse large B-cell lymphoma of the femur, germinal center phenotype. Radiological findings revealed a large intramedullary lesion with cortical destruction, and diagnosis was confirmed histopathologically. Despite initial treatment with R-CHOP chemotherapy, the disease showed partial resistance, necessitating second-line R-ICE therapy and localized radiotherapy. Post-treatment imaging demonstrated regression of destructive findings, and PET-CT showed minimal residual activity. The patient has remained symptom-free and under observation since 2020. This case emphasizes the importance of a multidisciplinary approach, combining imaging, histopathology, and multimodal therapy in the effective management of PBL, and contributed to the growing body of evidence guiding the prognosis and therapeutic strategy of this rare entity.

Keywords: Primary bone lymphoma, DLBCL, B Cells, germinal center, R-CHOP, FDG-PET

INTRODUCTION

Primary bone lymphoma (PBL) is defined by the World Health Organization (WHO) as one or more bone lesions without distant visceral or lymph node involvement, or as a single bone lesion with or without regional lymph node involvement. PBL is an uncommon subtype of lymphoma. One to three percent of non-Hodgkin lymphomas, five percent of extranodal non-Hodgkin lymphomas, and three percent of primary bone malignancies are PBLs.[1]

While PBL can affect anyone at any age, males are more likely than women to be diagnosed with it between the ages of 45 and 60.[2] Among the most typical clinical signs are palpable mass, soft tissue edema, pathological fracture, and localized bone pain. Nonspecific clinical signs frequently cause a delay in diagnosis; the disease is diagnosed using a mix of imaging investigations and clinical examination, with histological and immunohistochemical examination serving as confirmation. While PBL can arise in any region of the skeleton, the femur, humerus, tibia, spine, and pelvis are the most frequently affected. PBL imaging results are quite erratic and nonspecific.[3] The majority of PBL instances are particularly derived from germinal center centrocytes and fall within the B-cell-like subtype of germinal center cell origin. Based on the existence of miRNA with a particular prognosis, histogenesis, gene expression, and mutation profile, PBL is acknowledged as a unique clinical entity. The prognosis for PBL is good, particularly when combination chemoradiotherapy is used.[4]

In our case, we wanted to examine such cases through a patient diagnosed with PBL, to enable a better understanding of this rare disease and to contribute to the literature.

CASE

A 39-year-old male patient with no known disease applied to the physical therapy and rehabilitation outpatient clinic with a complaint of pain in the right hip. MRI scans were performed. On MRI scans a lesion was present extending along an approximately 20 cm craniocaudal segment, starting from the proximal diaphyseal section of the right femur to the distal diaphyseal section, located intramedullarily. The lesion appeared markedly hypointense on T1-weighted sequences and hyperintense on T2-weighted sequences, demonstrating intense contrast enhancement on post-intravenous contrast sequences. Along the lesion tract, proximally extending approximately 12 cm, there was a solid, well-defined, contrast-enhancing component surrounding the femur, more prominently anteriorly, measuring up to approximately 20 mm in thickness at its thickest point on

contrast-enhanced series. In the proximal diaphyseal section of the femur, limited areas of significant cortical destruction were observed anteriorly. A bone biopsy was taken from the lesion on the MRI. Histopathological examination confirmed the diagnosis of diffuse large B-cell lymphoma with high Ki-67 index, LCA, CD20, BCL-6 and vimentin positive, germinal center phenotype. BCL-2 was negative in bone marrow biopsy, while c-myc and bcl-2 were not tested in the lesion biopsy. No lymph node involvement was detected as a result of PET-CT taken at the time of diagnosis. Bone marrow involvement was not detected in the patient who underwent bone marrow biopsy. In addition, the patient was started on the R-CHOP regimen as chemotherapy. Since the desired treatment response was not obtained in the MRI taken after 6 cycles of R-CHOP chemotherapy regimen, the patient was given 3 cycles of R-ICE chemotherapy regimen as second-line therapy. Curative radiotherapy was applied to the pelvic area for 24 days along with chemotherapy. As a result of the MRI taken for the response to the 2nd line treatment, the destructive findings disappeared and the subsequent PET-CT showed that "an intramedullary lesion showing slightly increased FDG uptake was observed in the proximal right femur (SUVmax: 2.81)", so it was decided to follow the patient without treatment. (**Figure**). The patient continues his regular follow-up without treatment (**Table**). The patient has been symptom-free since 2020, and his findings have been under follow-up (**Table**).

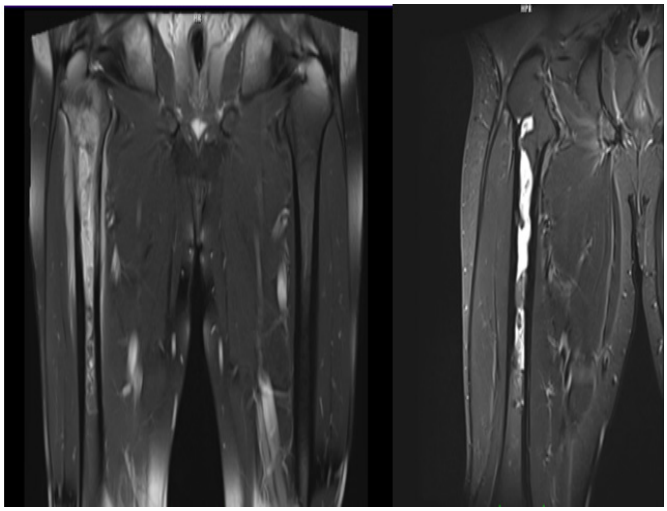

Figure. Femur MRI images of the patient before and after treatment

DISCUSSION

The precise and universally accepted definition of PBL remains a subject of ongoing debate within the medical community. While the disease has been increasingly recognized, there is still no consensus on a standard risk stratification model that accurately predicts the likelihood of its development. Existing scoring systems, although useful in broader oncological contexts, fail to address the specific features and biological behavior of PBL. As a result, clinicians often rely on a combination of clinical judgment and limited prognostic tools when managing these cases.

Among the prognostic models historically employed, the International Prognostic Index (IPI) has been one of the most widely used. However, its utility in the context of PBL has proven to be restricted. This is primarily due to the distinct clinical presentation and progression pattern of PBL compared to other forms of non-Hodgkin lymphomas. In light of this, alternative markers have been explored to better assess disease prognosis and guide therapeutic decisions.

The International Extranodal Lymphoma Study Group (IELSG) 14 study has provided valuable insights in this regard. Notably, the study highlighted the potential prognostic significance of elevated lactate dehydrogenase (LDH) levels in patients with PBL. An increase in LDH may reflect a higher tumor burden or more aggressive disease behavior, thus offering a practical biochemical marker for clinicians in evaluating disease progression. Additionally, several case series in the literature underscore the potential role of radiotherapy as a critical component in the treatment regimen for PBL, often in combination with chemotherapy.[5]

In our own clinical experience, we observed that both LDH levels and radiotherapy played pivotal roles in patient management. Monitoring LDH levels throughout the course of the disease provided important information about the patient's response to treatment and overall prognosis. Furthermore, the inclusion of radiotherapy in the treatment protocol contributed significantly to local disease control, emphasizing its therapeutic value. These observations support the growing body of evidence advocating for a more individualized approach to PBL management, incorporating both biochemical markers and multimodal therapy strategies.

Our findings can be compared with the report by Nishida et al.,[5] who described a case of primary isolated bone marrow diffuse large B-cell lymphoma achieving long-term complete remission with R-CHOP chemotherapy. While our case required second-line therapy and radiotherapy to achieve disease control, both reports highlight the potential for durable remission in PBL with multimodal treatment. This comparison emphasizes the variability in treatment response and the importance of individualized management strategies.

Table. Laboratory values of the patient during treatment and follow-up

	Date	ESR	Hemoglobin (gr/dl)	WBC (10^3/µL)	Platelet (10^3/µL)	LDH (U/l)
At the time of diagnosis	17.04.2019	19	15.3	6.3	260	685
After 1. line of chemotherapy	06.08.2019		12.9	7.1	247	320
After 2. line of chemotherapy	16.12.2019	32	12.6	5.7	45	355
Latest values	21.05.2025	17	15.2	7.07	238	212

ESR: Erythrocyte sedimentation rate, WBC: White blood cell, LDH: Lactate dehydrogenase

CONCLUSION

As a result, PBL represents a rare yet clinically significant subtype of non-Hodgkin lymphoma, characterized by its distinct presentation, biological behavior, and imaging challenges. Despite its low incidence, timely diagnosis and effective management are critical to improving patient outcomes. Our case study reinforces the importance of recognizing key biochemical markers, such as elevated LDH levels, in disease monitoring and highlights the therapeutic value of radiotherapy as part of a multimodal treatment approach. By documenting and analyzing individual cases like ours, we hope to contribute to the growing body of knowledge on PBL and support the development of more refined diagnostic and prognostic strategies for PBL. Further multicentric case series are essential to optimize diagnostic and therapeutic algorithms for this uncommon malignancy.

ETHICAL DECLARATIONS

Informed Consent
The patient signed and free and informed consent form.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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