Original Research

Incidence and Outcomes of Primary Cutaneous Anaplastic Large Cell Lymphoma: a SEER Population Based Study

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Primary cutaneous anaplastic large cell lymphoma (PC-ALCL) is the second most common type of cutaneous lymphoma of T cell origin. Despite its higher prevalence among dermal lymphoma, its overall incidence is rare; hence, its demographic characteristics and outcome is not well explored. Here, we have examined the epidemiologic features and outcomes in PC-ALCL in the population of the United States. First, we identified patients with PC-ALCL from the Surveillance Epidemiology and End Results database from 1975 - 2017. Cases with only histological and immunohistochemical or molecular evidence of diagnosis were included in the study. Age, sex, and race-standardized incidence rates (IR) were calculated. Survival was assessed using Kaplan-Meier curves and Cox proportional hazards models. Of all 569 cases documented as PC-ALCL, 93 patients fulfilled the inclusion criteria. We found the incidence of PC-ALCL to be highly correlated with increased age. There is a predominance of PC-ALCL in white male population. The survival analysis did not signify age of diagnosis, sex, or race as factors affecting the outcome for the patients. Although the site of primary tumor trends towards affecting survival, it does not meet statistical significance. PC-ALCL is a rare malignancy predominantly affecting older white male in the United States. The increased age is highly correlated with disease development, however, neither the demographic characteristics nor the site of the primary tumor affects the outcome for the patients.

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INTRODUCTION

Primary cutaneous anaplastic large cell lymphoma (PC-ALCL) is a neoplastic entity that presents with pleomorphic and anaplastic cells in the skin. More than 75% of PC-ALCL have the immunohistochemical signature of CD30+ cells.[1,2] Unlike its systemic counterpart, PC-ALCL only involves the skin and is uniformly negative for anaplastic lymphoma kinase (ALK) immunohistochemistry and rearrangement.[3,4] CD30+ cutaneous lymphoproliferative disorders can be considered among a spectrum containing mycosis fungiodes (MF) with large cell transformation, lymphomatoid papulosis (LyP), the pagetoid reticulosis variant of MF5 and PC-ALCL.[2,6,7] Hence, differentiating PC-ALCL from the others can be challenging. Hence, differentiating PC-ALCL from the others can be challenging; due to their overlapping histopathology, genetics, and immunological features, in the absence of compelling clinical correlation, a 'borderline' lesional diagnosis is sometimes made. Due to their overlapping histopathology, genetics, and immunohistochemical features, a 'borderline' lesion diagnosis is sometimes made.[2,6,11]

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Although PC-ALCL is considered clinically indolent with an excellent overall survival rate, very few studies have examined the epidemiology and survival of this disease in-depth.[8,9,11] In their long-term follow-up study, Bekkenk and colleagues investigated 90 patients with PC-ALCL, with 11 of them having local nodal involvement at the diagnosis. They found disease-related 5-year-survival in PC-ALCL patients to be 96% without nodal involvement and 91% with local node involvement.[9] In their single-center study involving 25 PC-ALCL patients, Liu and colleagues found the disease-specific survival to be 85%.[8] We queried the National Cancer Institute's SEER database to identify cases of PC-ALCL with immunohistologic or molecular confirmation and analyzed their epidemiological features and the disease-specific survival.

METHODS

Patient Selection

The National Cancer Institute's SEER database represents about 35% of U.S. population, and mines data from 18 population-based registered cancer institutes. We queried the National Cancer Institute's SEER database for cases of PC-ALCL from 1975 - 201710 and selected cases where the

diagnosis was coded as PC-ALCL according to the standard set by the International Classification of Disease for Oncology as histologic type 9718/3. Given the complexity of CD30+ lymphoid neoplasms of skin, any diagnosis without immunohistochemical or molecular confirmation was excluded. We also excluded patients whose age, race, survival time, and pathological diagnosis were unknown and whose pathological results were from autopsy or death certificates.

Variable Classification

Data on the age at diagnosis, primary site, sex, race, and treatment were obtained. Age of diagnosis was further stratified in the bins of 5 - 24 years, 25 - 44 years, 45 - 64 years, 65 - 84 years, and 85 years and above.

Statistical Methods

We used descriptive statistics to summarize demographic and clinical variables. Chi-squared test or Fisher's exact test was used to compare the clinicopathological characteristics between different cohorts. Spearman's correlation was used to quantify the relationship of ordinal age bins with the number of observed cases. The SEER database calculated the disease-specific survival time based on the date of diagnosis to death and reported it in months. Patients were followed until their death or until the cutoff date of December 31, 2017. December 31, 2017 was also used as the censoring date for patients who were last known to be alive. One patient had a survival of less than one month and was excluded from the survival analysis. Four (4) out of ninety-three (93) patients died of something other than PC-ALCL and were excluded from the survival analysis. Kaplan–Meier survival curves and log-rank tests were conducted to compare the disease-specific survival (DSS) between cohorts. Univariate and multivariate Cox proportional hazard models were utilized to find other variables that may affect prognosis. Statistical significance was considered at a two-sided p-value < 0.05. All statistical analyses were performed using SPSS Statistics 20 (IBM, New York, NY, USA).

RESULTS

Population Characteristics

Under the set criteria, a total of 93 individuals were identified with a diagnosis of PC-ALCL. Increased age significantly correlated with the number of total cases (Spearman's correlation, $\rho = 115$, $p = 0.00001$), suggesting an associated increased risk. Figure 1A shows the distribution of the age of diagnosis. The majority of patients were white (**Figure 1B**) and male (Figure 1C). Males were significantly overrepresented in the disease population at 62% (95% CI [52%-72%], $\chi2 = 5.69$, $df = 1$, $p = 0.02$). The racial distribution of patients with PC-ALCL did not significantly differ from the US's racial distribution ($\chi2 = 6$, $df = 4$, $p = 0.2$). The skin of the lower limb and hip was the predominant site of primary diagnosis. However, the incidence in other areas of the body was comparable (**Figure 1D**).

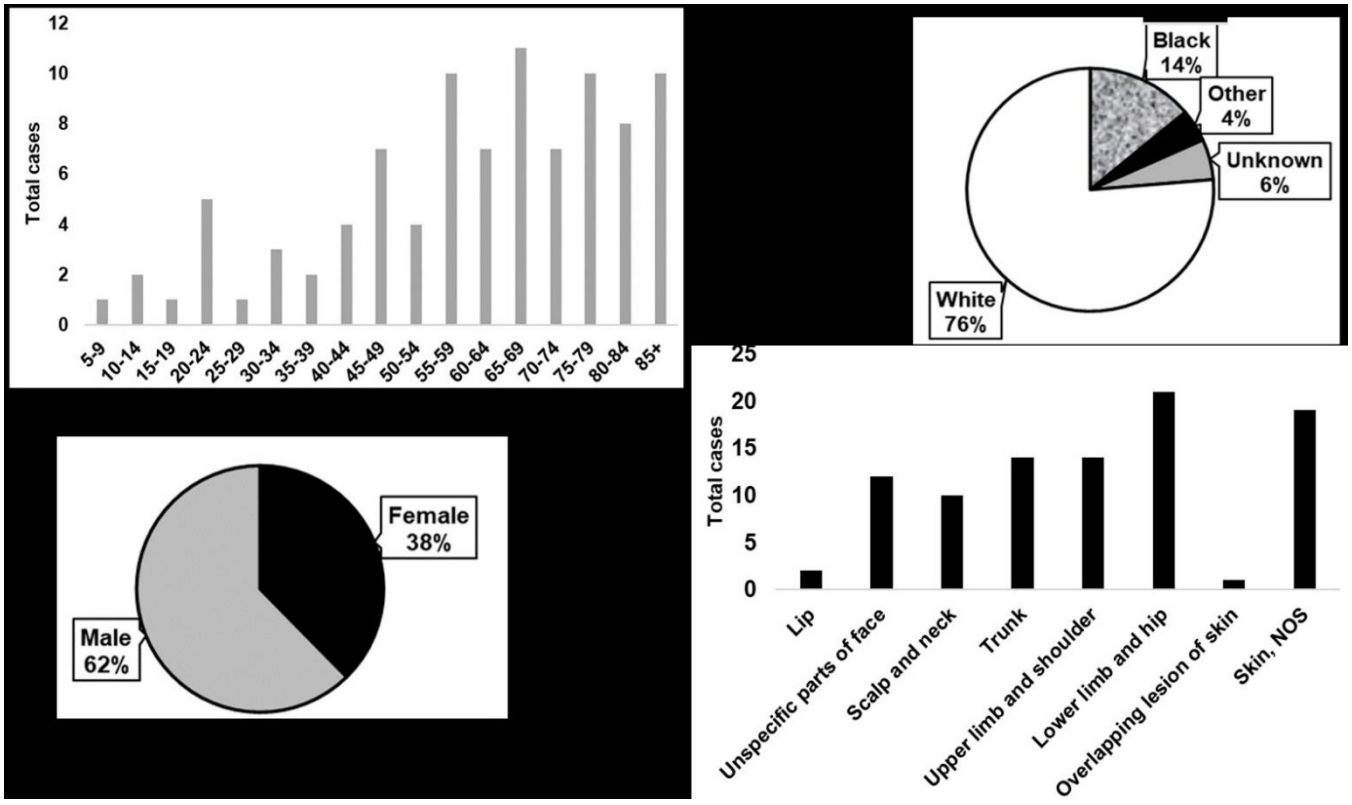

Figure 1. Demographic characteristics of PC-ALCL patients in SEER database. (**A**) Bar graph showing age of diagnosis, Pie charts showing (**B**) race and (**C**) sex of the patient population. (**D**) Bar graph showing the primary site of the tumor.

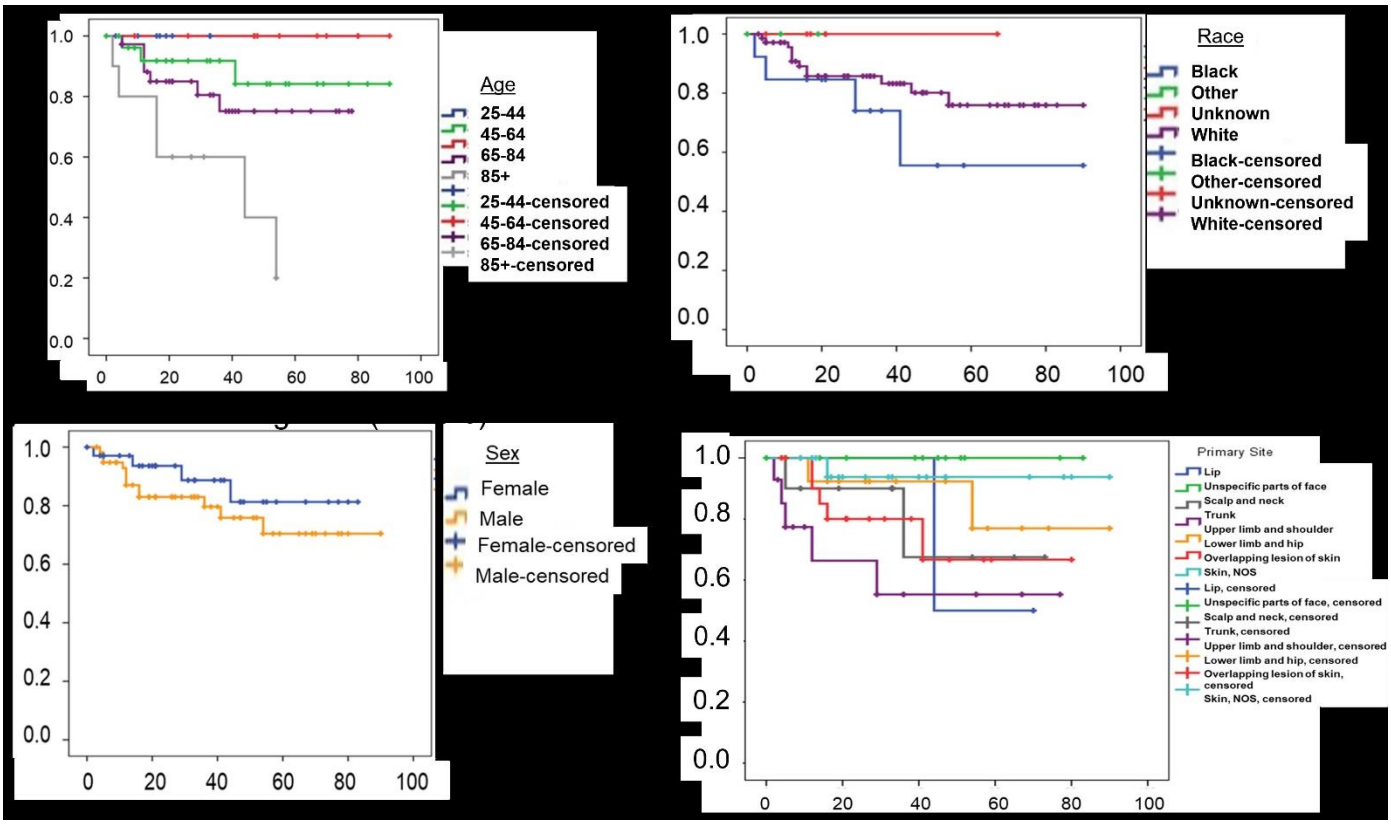

Figure 2. Survival analyses showing effect of age, sex, race, and the primary site of the tumor in patients' survival. (**A**) The age of diagnosis was simplified in the bins of 5 - 24 years, 25 - 44 years, 45 - 64 years, 65 - 84 years, and 85 years and above. Kaplan Meier survival curve is drawn to assess the effect of age of diagnosis on the outcome of the patients. Kaplan Meier survival curves are also employed to assess the effect of (**B**) race, (**C**) sex, and (**D**) primary site of diagnosis on patients' outcome.

Survival and Prognosis

Kaplan-Meier DSS analysis was performed to assess the possible influence of race, sex, age, or primary site location on the prognosis in patients with PC-ALCL. Qualitatively, age appeared to be one of the greatest factors influencing survival (**Figure 2A**), and while this trended strongly, it was not a statistically significant observation ($\chi2 = 19.8$, df = 16, p = 0.2). Although males were disproportionately represented among PC-ALCL patients, sex did not affect survival (**Figure 2C**, $\chi2 = 1.1$, df = 1, p = 0.3). Similarly, race had no significant effect on the length of survival (Fig. 2B, $\chi2 = 2.4$, df = 3, p = 0.5). The location of the primary tumor showed a trend affecting survival (**Figure 2D**); while this was quantitatively the most remarkable observation, it did not reach the threshold of statistical significance ($\chi2 = 11.3$, df = 6, p = 0.08).

CONCLUSIONS

This study evaluated the clinical and demographic variables of PC-ALCL patients in the United States. Since PC-ALCL is a rare malignancy, a database-driven analysis may provide meaningful insight into its characteristics. Our primary goal was to understand the disease distribution among the population and consider whether demographic characteristics may affect outcomes.

A small sample size limits the strength of the conclusions drawn with our study. By making the inclusion criteria more rigorous and only including patients for whom immunohistochemical and/or molecular diagnostic evidence is present, our sample size was reduced to ninety-three patients. Given the complexity of the CD30+ dermal lymphoma, we strongly felt that this rigorous criterion is essential. Another limitation of this study lies in its retrospective nature and the potential for missed cases within the database, owing to misclassification of data and inaccurate coding. However, any such error in classification should theoretically be random and thus might not introduce a specific bias to the dataset.

PC-ALCL appears to predominantly affect older adults and rarely affects children or individuals under the age of 20 (only four out of ninety-three patients). This observation supports previous reports.9 Its incidence is significantly higher amongst males. Even though the incidence of PC-ALCL is higher in the white population, it does not significantly differ from the

population's racial distribution. Increased age is highly correlated with disease development. However, neither demographic characteristics nor the primary tumor site affected the outcome for the patients. This review may shed light on the critical features of PC-ALCL in order to promote a better understanding of this rare malignancy.

CONFLICT OF INTEREST DISCLOSURES

The authors have no conflict of interest to disclose.

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