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BRIEF REPORT

Geographical Variation of Acute Promyelocytic Leukemia: A Single Center Study from Saudi Arabia

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Abstract

There is no obvious underlying cause for de novo acute promyelocytic leukemia (APL). Recently two case studies showed that the virus torque teno mini (TTMV) has a role in the pathogenesis of APL/APL-like disease. Few studies reported seasonal or geographical clustering of the disease. As no local published research addressed the effect of these two factors on the incidence of the disease, we aimed to study the relationship between geographical and seasonal factors and the incidence of APL in the local practice. This is a retrospective medical record-based study; that looked at the characteristics of the newly diagnosed APL patients in our center over a span of 5 years. Out of 26 patients, 12 (46%) belonged to two communities that live and work in the Kingdom of Saudi Arabia (KSA) and constitute 10% of the whole country's population. While only 4 patients (15%) were Saudi, they constitute the majority (64%) of the kingdom's population. The remaining 10 (39%) patients belonged to 7 other different communities (1-2 patients each). Geographic variation in the incidence of APL can explain these differences. There was no significant statistical difference in the incidence of new APL cases by month, consecutive months, or season. More research, to study the possible role of environmental and infective factor(s) in the pathogenesis of the disease, is justified.

Keywords

Acute promyelocytic leukemia, Geographical, Seasonal, Saudi Arabia

Introduction

Acute promyelocytic leukemia (APL) constitutes 10% of acute myeloid leukemia (AML) cases. APL has particular clinical features, diagnostic criteria, and treatment regimens. Disease-related coagulopathy is a well-recognized cause of early morbidity and mortality. PML/RARA rearrangement-associated chromosomal translocation (15;17) is the usual diagnostic abnormality. The introduction of all-trans-retinoic acid (ATRA) and, later on, arsenic trioxide (ATO) medications have made a dramatic improvement in the disease outcome [1]. Chemotherapy, radiotherapy, and chemical exposure are among the known causes of secondary AML and APL [2-6]. However, there is no obvious cause for de novo APL [7]. Few studies had reported seasonal or geographical clustering of the disease, suggesting a possible underlying causative environmental factor [4,7,8]. Recently two case studies demonstrated a causative relation between torque teno mini virus (TTMV) and APL [9,10].

No local publication had addressed the geographical or seasonal variability in APL. About one-third of people, who live and work in the Kingdom of Saudi Arabia, belong to communities from different countries [11]. The aim of this study is to look at the characteristics of the newly diagnosed APL patients in our center taking into consideration both the environmental and geographical factors.

Patients and Methods

This is a medical record-based retrospective study, including all newly diagnosed APL patients in King Saud Medical City, a tertiary care center in Riyadh city (capital of SA) over 5 years. Patients' inclusion criteria are age 14 years and above with de novo APL. Both male and female patients were included. The only exclusion criterion was a history of receiving chemotherapy or radiotherapy for cancer or other diseases. The study was approved by the Institution Review Board. The

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Table 1: Patients characteristic (n 26).

Characteristic	Result	Remark
Male: Female	23:3	
Age year	16-71	
WBC 10^9/L	0.7-178	
HB g/L	40-114	
Platelets 10^9/L	4-63	
Number of patients with prolonged INR	20	
Number of patients with prolonged PTT	10	
Number of patients with Low fibrinogen	9	Base line result available for only 14 patients

Table 2: Patients geographical origin.

Geographical origin	Number of patients (%)
Bangladesh	7 (27)
Yemeni	5 (19)
Saudi	4 (15)
Sudanese	2 (7.6)
Egyptian	2 (7.6)
Somali	2 (7.6)
Jordanian	1 (3.8)
Pakistani	1 (3.8)
Eritrean	1 (3.8)
Indian	1 (3.8)
Total	26 (100)

Table 3: Patients diagnosed each month.

Month	Number of patients
January	4
February	1
March	2
April	3
May	1
June	3
July	2
August	2
September	1
October	2
November	4
December	1
Total	26

chi-square test of homogeneity was used to test the hypothesis of no difference in the number of APL cases by month (the null hypothesis). T-test was used to compare means between the numbers of patients diagnosed from October to April with those diagnosed from May to September. Statistical significance was set at $p < 0.05$ (two-tailed), 95% CI of difference.

Results

Between September 2017 and September 2022 a total of 26 new patients with APL were included. The male to female is 23:3. Of note M:F of expatriates who live and work in SA is 68%:32% [11]. The patients' age ranged between 16-71 (mean 31) years. Results of blood count and coagulation parameters were noted. All the patients had the typical t(15;17) with PML/RARA rearrangement, except one patient with t(11;17) (Table 1).

Twelve (46%) patients came from two communities (Bangladesh n 7, Yemen n 5), they together constitute about 10% of the whole Saudi Arabia (SA) population. While only 4 (15%) patients were Saudi which constitutes 64% of the SA population [11-13]. The remaining 10 (39%) patients came from 7 other different communities (1-2 patients each); from different areas of Asia and Africa (Table 2).

Considering the timing, the number of patients diagnosed per individual month was 1-4 (mean 2.1), the peak was in January and November. 13 (50%) patients were diagnosed during spring and summer while the other half were reported during autumn and winter time. Irrespective of the season, 17 patients were diagnosed between October and April (mean 2.4) while the other 9 were reported between May and September (mean 1.8). There was no significant statistical difference in incidence of new APL cases by month ($p = 0.85$), consecutive months ($p= 0.35$), or season (Table 3).

Discussion

Our study showed geographical variability in the incidence of APL. However, no statistically significant seasonal difference was demonstrated in our local practice.

There is no obvious underlying cause for de novo APL. Previous studies reported geographical clustering, that was attributed to chemical exposure [5-7]. Other research also showed APL seasonal variation in the incidence of APL. [4,7,8]. More recently two studies confirmed fusion between torque teno mini virus (TTMV) fusion and the RARA gene in 3 patients with APL/APL-like disease [9,10].

In Saudi Arabia, about one-third of the population who lives and works in the Kingdom, are from different communities of different countries/regions [11]. This

gave the privilege to look at the disease incidence among patients from different geographical origins. 12 (46%) of cases were from two communities (Bangladesh and Yemen), which constitute 10% of the whole SA population. While only 4 (15%) patients were Saudi, who constitutes 64% of the whole country's population. There is no published data about the incidence of APL from either of the two countries; however chemical exposure and dietary factors had been reported from Bangladesh as a possible underlying cause of cancer [14,15]. A study on commonest cancer in Yemen, showed leukemia was the highest in males and it came next to breast cancer in females (no mention of the type of leukemia whether acute, chronic, myeloid, or lymphoid) [16]. Previous studies showed both national and international geographical variation in the incidence of APL. L Zhang, et al. reported a significant difference in APL proportion between Switzerland (2%) and Nicaragua (50%) of the total AML cases in children [4]. In another study by Andrew Y Li, et al., they showed clustering of cases from certain areas of the USA [7]. Consistent with previous studies our work showed a difference in the disease incidence between patients of different communities.

Regarding the seasonal variation, our study did not show a significant statistical difference in the newly diagnosed patients with APL. However seasonal differences were reported in a number of previous researches. Melda Comert, et al. in a study from Turkey showed more patients with APL were diagnosed during winter and autumn than during summer [8]. In Brazilian study, Karine SN Barroso, et al. found an association between APL and rainfall season in one area, while such association was lacking in other areas of the country [17]. In a 6-year of single-center study from Iraq, Amer S Mohammed, et al. also reported more incidence of APL in winter and early spring [18]. In the current study, in spite of the apparent variation, there was no statistically significant difference by month, season, or other consecutive months. However, the small number of patients has to be taken into consideration. Limitations of the current work are being a single-center study and the relatively small number of patients included.

In conclusion: There is no obvious cause for the de novo APL. Recently a causative relation between the disease and the TTMV virus had been independently reported in two case studies. Previous studies reported geograpgical and seasonal differences in APL. Our study showed geographical variation in the incidence of APL. However no statistically significant seasonal difference was demonstrated. More research, to study the possible role of environmental and infective factor(s) in the pathogenesis of the disease, is justified.

Declaration

The author has no conflict of interest to declare.

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