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Seasonality in acute promyelocytic leukemia: Fact or myth?

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Abstract:

BACKGROUND: Acute promyelocytic leukemia (APL) is a biologically and clinically distinct subtype of acute myeloid leukemia (AML) Etiological and seasonal factors that play a role in APL still unclear.

OBJECTIVES: The aim of the study was to retrospectively evaluate the available data to assess the impact of seasonal variations on incidence of APL over a period of 6 years.

PATIENTS AND METHODS: A retrospective, observational study based on APL record of a Hematology Nasiriyah Center from January 2014 to January 2020 was processed. The collected data of diagnosed (APL) patients at this center for 6 years was analyzed, and APL presenting in each month of the year was also assessed for any evidence of seasonality.

RESULTS: Fifty-eight cases of APL were included in this study: there were 22 males (37.93%) and 36 females (62.07%). The mean age was 31.1 ± 14.4 years (minimum 15 and maximum 67). We found a pronounced peak of APL occurrence in March (within winter and early spring months) and decline in summer to zero point in August, which was repeated periodical all studied 6 years.

CONCLUSIONS: Seasonal pattern of APL was observed. Investigation of specific seasonal risk factors would be informative in explaining the etiology behind the observed variation.

Keywords:

Acute promyelocytic leukemia, Iraq, leukemia, spring, winter

Introduction

Acute leukemias show geographical variations in occurrence, age, and sex distribution as well as French–American–British classification subtypes, possibly due to ethnic and environmental factors.[1] Acute promyelocytic leukemia (APL) is a biologically and clinically distinct subtype of acute myeloid leukemia (AML), first characterized by the fusion of promyelocytic leukemia and retinoic acid receptor alpha genes[2] and second characterized in 80%–90% of cases by a severe hemorrhagic syndrome attributable to different pathogenetic mechanisms Third, the HLA-DR superficial antigen, positive in all acute nonlymphocytic leukemias, is always negative in APL.[3]

Evidence suggests that antigenic stimulation consequent to community-acquired infections may contribute to the risk of AML.[4] Viruses have long been known as etiologic factors for different kinds of malignancies, for example, Epstein–Barr virus (in causing Burkitt's lymphoma). Some seasonal pattern of viral infection onset might be expected.[5] Therefore, seasonal changes in the incidence of AML came to light spot over the last two decades searching solid evidence but still with mixed results.[6-8]

Several studies have suggested a seasonal variation in the presentation and diagnosis of leukemias and lymphomas.[9,10] This has given rise to a number of conflicting reports as to whether a peak in the incidence

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exists and if so when it occurs. Inconsistency between results may itself be informative, perhaps reflecting various levels of between-population heterogeneity and different patterns of seasonality induced by possible causative agents.[11] To our knowledge, seasonality has been scantly reported in Iraq, and there is a lack of information about leukemia seasonality, especially in south of the country.

Every year, in Nasiriyah center, we are facing a gush of APL patients at the beginning of winter to the end of fall. Hence, the aim of the study was to retrospectively evaluate the available data to assess the impact of seasonal variations on incidence of APL over a span of 6 years.

Patients and Methods

The study analyzed the clinical and laboratory data of patients with APL who attended to Nasiriyah Hematology Center. The standardized diagnosis for APL was done by flowcytometry on sample of either peripheral blood or bone marrow aspiration. All 58 patients diagnosed with APL from January 2014 to January 2020. We excluded cases without recorded month and year of diagnosis. The collected data from questionnaire were designed to include findings: history, age, gender, and the history of fever, bleeding from any site, as well as examination data: APL classification, white blood counts, platelets count, hemoglobin (Hb) concentration, and disseminated intravascular coagulation (DIC) presence. Examination findings including pallor, fever, bleeding (gum and central nervous system [CNS]), epistaxis, pneumonia, hepatomegaly, hematoma, and breathlessness were also considered.

The study was approved by review ethical committee in Nasiriyah Hematology center and due to retrospective nature of this report, a consent form was not required. It has been recognized from the patient records that all of the studied patients had given informed consents at the time of hospitalization and before the administration of chemotherapy and other relevant diagnostic/therapeutic standard of care.

Statistical analysis

The collected data were processed by GraphPrism version 8.0 (GraphPad Software 2365 Northside Dr. Suite 560 San Diego, CA 92108, USA) for analysis. Nominal data of variables including pallor, fever, bleeding, and hepatomegaly were recorded as frequency/percentages. The variables in the blood including Hb, white blood cell count (WBCs), and platelet count were recorded as mean ± standard deviation for each group. The groups were further analyzed separately for gender distribution. Two-way ANOVA test was applied to assess for significance and *P* value of APL cases diagnosed of the same month of consecutive 6 years. *P* value considered statistically significant when taken to be ≤ 0.05.

Results

This study consisted of 58 patients of AML attended to the Hematology Nasiriyah Center in Thiqar province, South Iraq, over a period of 6 years. The mean age of the study cohort was 31.1 years.

The classical category was the most common phase of disease (39, 67.24%), while M3V category represented 19 (32.76%) of the entire cohort. There were involved 22 males and 36 females, in contrast to previous studies[12,13] that concluded male preponderance for AML; we found a clear overbalance toward female, 1.6:1 female-to-male ratio. The age of the patients ranged from 15 to 67 years; the mean age of males was 28.59 ± 14.05 years, while of females was 32.64 ± 14.32 years, and of the entire cohort was 31.1 ± 14.36 years. The distribution pattern of the patients segregated on the basis of age/gender and mean of blood indices is detailed in Table 1.

The results in Table 1 showed difference that not significant between males and females APL affected patients when compare by Hb concentration, WBC, platelet count, and presence of DIC, ($P > 0.05$).

Monthly distribution of APL reported cases by Nasiriyah Center over a span of 6 years is shown in Table 2. There are two peaks: the largest in spring (March - 15 cases = 26%), after increasing during winter (January - 11 cases = 18.97% and February 10 cases = 17.24%), a small peak in summer (July - 5 cases = 8.62%), and a plateau region of 4 cases

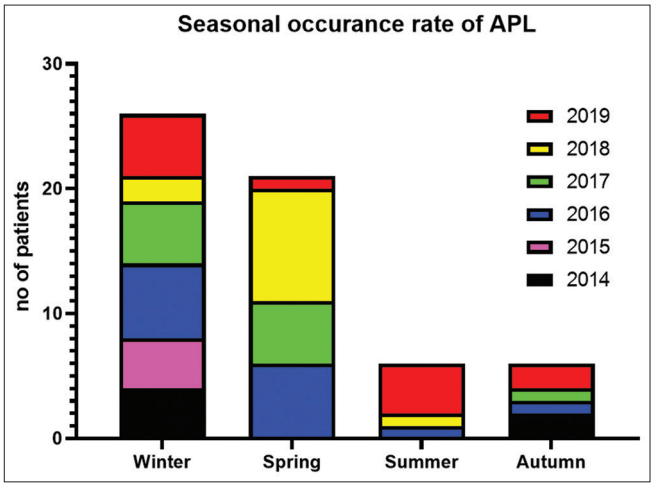

Figure 1: Distribution of acute promyelocytic leukemia incidence cases that recorded in Hematology Nasseriah Center 6 years (2014–2020) seasonally. Note a clear peak of winter, seasonal tendency (January, February) and spring (especially in March) and decline disease occurrence in summer and autumn. The two-way ANOVA statistical analysis of total months variation indicates a significant *P* value (0.0415)

Table 1: The mean age, hemoglobin, white blood cell counts, and platelet count of 58 cases of acute promyelocytic leukemia

Patient cohort	Age (years)	Hemoglobin (g/dl)	WBC (×10^9/L)	Platelet (×10^9/L)	DIC (yes)
Male	28.59±14.05	7.96±2.11	11.83±23.97	32.58±24.27	12/22 (54%)
Female	32.64±14.32	7.90±1.44	13.43±26.76	35.02±26.07	17/36 (47%)
Total	31.10±14.35	7.92±1.73	12.82±25.74	34.10±25.43	29/58 (50%)

DIC=Disseminated intravascular coagulation, WBC=White blood cell count, Hb=Hemoglobin

Table 2: Distribution of 58 cases of acute promyelocytic leukemia according to the season of presentation

Season	2014	2015	2016	2017	2018	2019	Total	Seasonally percentage	Cumulative percentage
Winter	4	3	6	5	2	5	25	43.10	43.10
Spring	0	0	6	5	9	1	21	36.21	36.21
Summer	0	0	1	0	1	4	6	10.34	10.34
Autumn	2	0	1	1	0	2	6	10.34	10.34
Total							58	100.00	100.00

(6.9%) in each of November and December. It is interesting,there is no APL case was diagnosed in August and during all 6 years that studies (data not shown). The period of decline followed by little bit arising in autumn months (September and October) is shown in Table 2 and Figure 1.

The pallor was the most common complaint of the APL patients (11 patients - 19.3%) followed by epistaxis (10 patients - 17.54%). Fever (7 cases (12.28%), pale/ bleeding (5 cases -8.7%). The complaint varied until; just bleeding, breathlessness, dental abscesses/bleeding, fever/hematoma, fever/ LAP/hepatomegaly, fever/ paler/bleeding, gum bleeding, hematuria, LAP/HSM, and pneumonia that were relatively infrequent (1 case for each), as shown in Table 3. Heterogeneity across seasons was statistically significant (P = 0.0417).

Table 3: Main signs of presentation

Presentation	no of patients	%
pale	11	19.30
epistaxis	10	17.54
fever	7	12.28
pale/bleeding	5	8.77
fever/bleeding	4	7.02
pale/fever	4	7.02
CNS bleeding	2	3.51
fever/hepatomegaly	2	3.51
HSM/Bleeding	2	3.51
bleeding	1	1.75
breathlessness	1	1.75
dental abscess/bleeding	1	1.75
fever/hematoma	1	1.75
fever/LAP/Hepatomegaly	1	1.75
fever/palor/bleeding	1	1.75
gum bleedding	1	1.75
Hematuria	1	1.75
LAP/HSM	1	1.75
pneumonia	1	1.75
total	57	100.00

Discussion

The seasonality of different malignant diseases incidence such as ALL, AML, CLL, lymphoma, and CNS tumors,were well decumented several years ago.[9,10,14] However, till this moment, there is controversial as a strange, conflicting phenomenon. The researchers were divided between a supporter of its existence by statistical evidence and opponents, who explained its seasonal frequency for technical reasons.

in this study, we noted the diagnosis of APL was increase in months of January and February to reach the peak on incidence in March and that was represented 62% of annual occurance of the disease that repeatedly happened during 6 consecutive years. This is in line with the previous studies that indicated the seasonal tropism of the disease, even in the same months which we indicated.[15] However, other researchers found the same phenomenon but in months other than what we have inferred in this research. For example, Drapkin *et al*. and Ehsan *et al*. found that the months September and October were the plateau of disease occurrence.[8,15] In these cases, perhaps, the reason of seasonal tropism (winter and early spring months) is the spectrum of infectious disease associated with it, including viral infections such as diarrhea and flu. It has been suggested that the peak of leukemia incidence might occur when pathogens are feasible in a susceptible population and other risk factors act in concert. Subsequently, acute infection or reactivated chronic infection could be responsible for induction of leukemia, appearance of symptoms, and incidence of diagnosis.[16] This study is identical to that of the studies by Eatough *et al*. and Douglas *et al*., not only the months of the peak incidence of the disease, but also the month of the disappearance and recession of the disease (in August).[4,5] In the current study, we encountered a problem of small sample size, which

makes statistical analysis not accurately representative of society, while other researchers with sufficient sample size were able to compare even the seasonal variation of disease incidence and linked it to age and gender. For example, Gregory *et al*. found seasonal variation especially among males (P = 0.009) and it was present in aged 65 years and older (P = 0.018), whereas no such effect was found among females and younger age groups.[7] Gregory *et al*. used a sample size of 20,000 USA patient's data extracted from the registry of 1992–2008 period. in contrast to gender assiciation mentioned above , the mean age of study cohort was 31.1 years, and this finding in consistent with was seen in.[17] Even the unusual summer APL cases emergence [4 cases during summer of 2019 in comparison with previous 4 years, Table 2] may be due to clustering phenomenon, but not aberrance of seasonality reputation.

The macro-environment (pollution, infections) or organic microenvironment (dysregulation of the immune system) can be the triggering factor of the process of leukemogenesis.[18] Seasonal variations in correlation with mitogenic responses and in the quantity of circulating lymphocytes, neutrophils, CD4 and CD8 cells, and interleukin 6 have been reported.[19-21] Further, specific seasonal variations including a peak in lymphocyte aryl hydrocarbon hydroxylase activity in summer months[22] and increased number of circulating B-cells in winter months[20] were proposed as explanations for thecause of variation. Besides this, we should not ignore the fact that during these months, people are more likely to be seen by doctors for seasonal conditions such as influenza. Such complaints may lead to tests or procedures, leading to the diagnosis of AML[23] such as APL. Other investigators have suggested that observed seasonal variation in cancer might be the result of lower diagnosis rates during vacation months, such as summer.[24]

Since there is no known etiology of APL which has its own clinical laboratory characteristics, so there is still a need for a clear explanation for the climate influence in the incidence of APL. Due to inclear causes of disease seasonality, it is easy for us to assume many cause, no matter how it is strange or far-fetched, such as rainfall winter season that can affect the distribution (dilution) of pollutants or by factors that proposed by Cox *et al*.[25] such as seasonal differences in dietary consumption, population mobility, ,antenatal exposure to infectious or seasonal environmental factors.[25] Such conditions in singly or cumulatively way may negatively influence leukemogenesis.

However, the realistic assumption of seasonality of APL disease to be accurate should be based on taking the history of the disease, such as exact beginning of the symptoms and monitoring the presence of comorbid conditions,that patient may have ignored, analyze leukemia patients for the detection of specific antiviral antibodies, in order to find any correlation between viral infections and malignancies. Without resolving such limitations, the seasonality phenomenon of this disease is remaining not more than an observation, resulting from a diagnosis bias or other uncontrolled factors.

Conclusions

In agreement with previous studies in other countries, the current study provided further evidence which indicated a seasonal variation in the incidence of APL by using data derived from disease record of Nasiriyah governorate in ThiQar province/Iraq, over six years of observation based in single-center experience. Other comorbid situations should be considered to identify the true reasons underling seasonal occurrence of several liquid malignancies such as APL.

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Conflicts of interest
There are no conflicts of interest.

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