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Clinico-Epidemiological Aspects of Acute Myeloid Leukemia - An Observational Study.

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ABSTRACT

Background: Acute myeloid leukemia (AML) is characterized by an increase in the number of myeloid cells in the marrow and an arrest in their maturation, frequently resulting in hematopoietic insufficiency (granulocytopenia, thrombocytopenia, or anemia), with or without leukocytosis. The aim of the present research is a) to study the various modes of presentation and clinical course of different types of acute myeloid leukemia in adults, b) to evaluate how a comprehensive knowledge of the clinical presentation could be utilized for making out early diagnosis, which may be of help in treating acute myeloid leukemia and prognosticate the disease outcome and c) to look into possible etiological factors like toxins, chemicals, radiation and diet. **Methods:** Patients aged more than 12 years with acute myeloid leukemia admitted in a Tertiary care Medical Institute in North Kerala during a period of one and half years constituted the study population. These patients were followed up for a period of 6 months after the induction phase. The detailed interview protocol included the clinical features, past illnesses, exposure to radiations or toxic chemicals, residence near high-tension electric lines or coastal areas, dietary habits, addictions etc. A thorough physical examination was done according to the proforma. The data were analyzed with the help of appropriate statistical methods. **Results:** Acute myeloid leukemia in adults is more common in females. Acute myeloid leukemia seem to have a high prevalence as the age advances (25.3% cases above 60 years). Fever of unknown origin was the presenting complaint (34.9%) in a significant number of patients. Fever and tiredness were the commonest symptoms (79.5%), followed by bleeding manifestations. Patients were symptomatic for an average duration of 2 weeks before diagnosis. Commonest sign was pallor (89%) followed by lymphadenopathy, hepato-splenomegaly, and bleeding manifestation. Residence near high-tension lines and exposure to pesticides appears to be related to leukemeogenesis. Possibly several other, yet unidentified, environmental and genetic factors influence prognosis. **Conclusion:** The comprehensive knowledge of the clinical presentation could be utilized for making out early diagnosis, which may be of help in treating acute myeloid leukemia and prognosticate the disease outcome.

Keywords: Acute Myeloid Leukemia, Epidemiology, Signs, Symptoms.

INTRODUCTION

Acute myeloid leukemia (AML) is characterized by an increase in the number of myeloid cells in the marrow and an arrest in their maturation, frequently resulting in hematopoietic insufficiency (granulocytopenia, thrombocytopenia, or anemia), with or without leukocytosis. Until the 1970s, the diagnosis was based solely on the pathological and cytological examination of bone marrow and blood. The clinical evaluation, therapy, and prognosis of patients with AML have changed dramatically over the last 2 decades.[1,2]

The initial evaluation of a patient with acute leukemia should be directed at defining the factors that are important in assessing the long-term prognosis and planning therapy. Molecular, cytogenetic, and immunologic studies have contributed to the understanding of the pathogenesis and prognosis of the AML. A history of environmental or occupational exposures to known or suspected leukemogenic agents or antecedent illnesses that predispose affected persons to the development of AML must be considered in establishing the diagnosis, planning treatment, and evaluating the response to therapy.[3,4]

The incidence of acute myeloid leukemia (AML) is ~3.6 per 100,000 people per year, and the age-adjusted incidence is higher in men than in women (4.4 versus 3.0). AML is a disease of adulthood, with a mean age at diagnosis of 63 years, and the incidence increases with age.[5-7]

Genetic predisposition, drug and environmental exposures, and occupational factors have been implicated as possible leukemogenic agents in children and adults. Leukemeogenesis is believed to be a multistep process that requires the susceptibility of a hematopoietic progenitor cell to inductive agents at multiple stages.[2,8]

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AML is a clonal disorder, with all leukemic cells in a given patient descending from a common progenitor. Studies have demonstrated differing patterns of clonal involvement among patients so that in some (generally younger) patients, only the frankly myeloid leukemia blasts are clonal, whereas in other (often older) patients, normal appearing monocytes, platelets, and red cell precursors might also be of clonal origin. Studies of clonality have also given the surprising result that some patients treated to complete remission with recovery of entirely normal-looking hematopoiesis might still have clonal hematopoiesis, a result consistent with the hypothesis of a multistep pathogenesis for AML.[9-11]

The identification of recurrent chromosomal abnormalities which can include translocations, point mutations, and gene duplications in AML cases followed by the cloning of many of the involved genes has provided important insights into the pathogenesis of AML. With further investigation, however, it is becoming clear that many of these abnormalities tend to affect a limited number of transcriptional or signal transduction pathways. Of those abnormalities that have been studied extensively, most are pro-oncogenic and are not simply innocent bystanders in the leukemic process.[12-15]

The presenting signs and symptoms of AML are nonspecific and are related to the decreased production of normal hematopoietic cells and invasion of other organs by the leukemic cells.[7]

Although anorexia is common, weight loss is unusual, generally reflecting the acute onset of the disease. Diffuse bone tenderness involving the long bones, ribs, and sternum is the initial clinical manifestation in 25% of patients. The bone pain, which can be severe, is caused by the expansion of the intramedullary space or direct involvement of the periosteum by the leukemic cells.[16]

The findings on physical examination relate to the interference with normal hematopoiesis by the leukemic cell. Anemia results in pallor and the onset of cardiovascular symptoms. Thrombocytopenia produces homeostatic defects, which result in petechiae and ecchymosis. Oozing from the gums, epistaxis, and excessive bleeding after dental procedures or minor trauma are common initial manifestations.[17,18]

Splenomegaly occurs in up to 50% of patients with AML, but rarely extending more than 5 cm below the left costal margin. A very large spleen suggests that the leukemia has evolved from an underlying myeloproliferative disorder. Lymphadenopathy is rare in AML.[19]

Skin involvement, or leukemia cutis, occurs in about 10% of patients and usually manifests as violaceous, raised, nontender plaques or nodules. Skin involvement is more common with the monocytic subtypes, including the acute monocytic and myelomonocytic leukemias. [38] Sweet's syndrome, acute neutrophilic dermatosis, is a cutaneous paraneoplastic syndrome that is associated with AML and other hematologic disorders.[9]

The traditional goal of the treatment of acute myeloid leukemia (AML) is to produce and maintain a complete remission (CR). Criteria for CR are a platelet count higher than 100,000/µL, a neutrophil count higher than 1000/µL, and a bone marrow specimen that has less than 5% blasts. In the 1960s, Freireich and colleagues demonstrated that patients who achieved a CR lived longer than patients who did not. The difference in survival time was entirely attributable to the duration of time spent in CR. In general, after 3 years have elapsed from the beginning of a CR, the probability of recurrence sharply declines, becoming less than 10%. Patients who have been in continuous CR for 3 years can, for operational purposes, be considered potentially cured.[20-24]

The aim of the present research is a) to study the various modes of presentation and clinical course of different types of acute myeloid leukemia in adults, b) to evaluate how a comprehensive knowledge of the clinical presentation could be utilized for making out early diagnosis, which may be of help in treating acute myeloid leukemia and prognosticate the disease outcome and c) to look into possible etiological factors like toxins, chemicals, radiation and diet.

MATERIALS AND METHODS

Patients aged more than 12 years with acute myeloid leukemia admitted in a Tertiary care Medical Institute in North Kerala during a period of one and half years constituted the study population. These patients were followed up for a period of 6 months after the induction phase

The detailed interview protocol included the clinical features, past illnesses, exposure to radiations or toxic chemicals, residence near high-tension electric lines or coastal areas, dietary habits, addictions etc. A thorough physical examination was done according to the proforma. All patients underwent investigations like CBC, urine routine, peripheral smear and bone marrow examination, chest X-ray, biochemistry investigations and other investigations where indicated.

After confirming the diagnosis of AML, treatment options were planned with the patients. Chemotherapy was given according standard induction regimen, which consists of daunorubicin, 45mg i.v. for three days, and cytarabine, 100mg i.v. by continuous infusion for seven days. Those who were not ready were given palliative chemotherapy of subcutaneous cytarabine.

The patients were followed up with clinical evaluation and laboratory investigations during the induction therapy. The various complications arising during this period were carefully evaluated. At the

end of induction, patients were evaluated clinically and with investigations including bone marrow examination to look for remission. The data were analyzed with the help of appropriate statistical methods.

RESULTS

A total of 83 adult patients with newly diagnosed acute myeloid leukemia were studied. The patients included in the study were those who were admitted in the wards under Department of Medicine with diagnosis of AML and patients referred from peripheral hospitals with a diagnosis of AML.

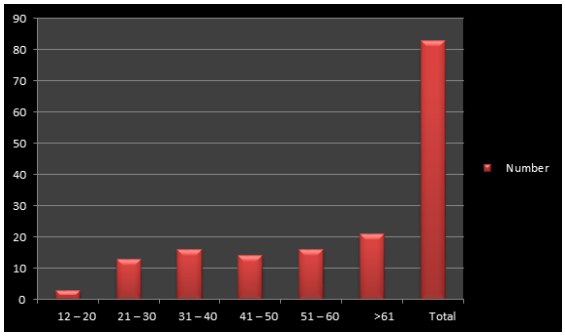

Figure 1: Age distributions.

The mean age of the study population was 48 years. It ranged from 13 years to 78 years. The distribution of patients according to age is shown in [Figure 1]. There were 39 males and 44 females in the study group [Figure 2].

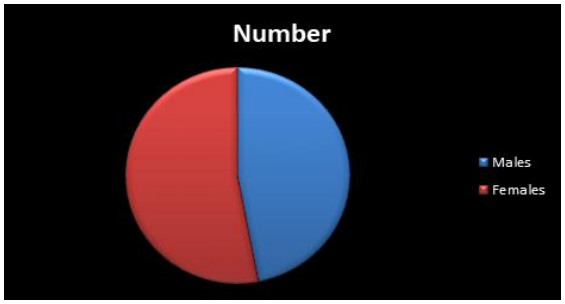

Figure 2: Sex distribution.

The patients included in the study came from Kozhikode and from 5 nearby districts reflecting the drainage population of the hospital. More than 50% of the patient came from Kozhikode district. One patient with diagnosed AML was referred from Ernamkulam district [Table 1].

Table 1: Residence.

District	Numbers	%
Kozhikode	47	56.6
Malappuram	17	20.5
Wayanad	6	7.2
Palakkad	5	6
Kasargode	4	4.8
Kannur	3	3.6
Ernamkulam	1	1.2
Total	83	100

Thirty-nine persons (47%) were either illiterate or had only primary education. Forty-four patients (53%) had high school level education. There were 3 graduates of who had professional training [Table 2].

Table 2: Education.

Formal Education	Number	%
Nil	18	21.7
1 to 7	21	25.3
8 to 10	25	30.1
11 to 12	16	19.3
Graduate	3	3.6

Thirty-three patients (39.8%) were involved in heavy labour. Eleven patients (13.3%) were farmers who were exposed to pesticides used in the fields. Nobody had occupational exposures to petrochemicals, high-tension electric voltages or radiation [Table 3].

Table 3: Occupation.

Occupation	Number	%
Student	6	7.2
Manual laborer	33	39.8
Housewife	24	28.9
Farmer	11	13.3
Others	9	10.8
Total	83	100

Majority of the patients were manual labourer and farmers (53%). Fifty-six patients (67.5%) belonged to low socioeconomic strata. Four patients belonged to high socioeconomic strata [Figure 3].

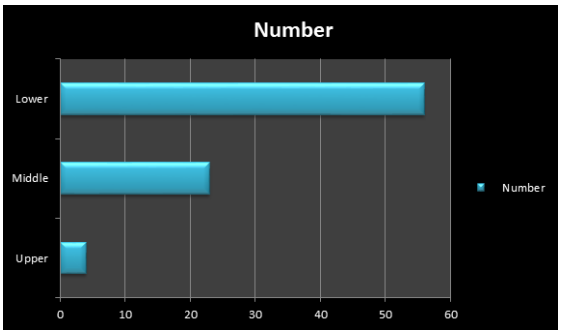

Figure 3: Socioeconomic class.

Most of the patients included in the study had symptoms for more than 2 weeks (90.3%). Twenty-nine patients were referred as fevers of unknown origin. Various types of bleeding manifestation were present in fourteen patients. Four patients had un-resolving pneumonia at the time of presentation. Four patients had altered sensorium of which three of them had intracerebral hemorrhage. One patient was referred from the department of Obstetrics and Gynecology as a case of septic abortion. One patient who was admitted in the department of orthopaedics as a case of septic arthritis was referred to department of medicine as he had abnormal findings in routine blood investigations. Two patients had diminished vision due to papillodema and fundal hemorrhages. One patient was referred as a case of

connective tissue disorder. One patient had deep vein thrombosis. Eight patients were referred due to persistent tiredness. Eight patients were evaluated for other complaints, which on follow up were diagnosed as AML. Two of these patients were initially managed as infectious mononucleosis. Two patients were treated as cases of un-resolving pneumonia [Table 4].

Table 4: Presenting complaint.

Symptoms	Numbers
Fever of unknown origin	29
Bleeding manifestation	14
Respiratory infection	7
Septicemia	3
Tiredness	8
Altered sensorium	4
Diminished vision	2
Others	16
Total	83

Sixty-six patients (79.5%) had reported fever. Fatigue was present in 77% patients. Malaise and anorexia was present in 48%. Forty-two percent of the patients had weight loss. Abdominal fullness and pain were present in 15.7 and 14.5% respectively. Bone and joint symptoms were present in 14.5% cases. Bleeding from gums was seen in 19 patients but other bleeding manifestations like ecchymosis, epistaxis, hemoptysis, malena, abnormal vaginal bleeding & bleeding per rectum were also common. Other symptoms like palpitation, cough with expectoration, chest pain, pedal edema, neck swelling and weakness were present in some of the patients [Table 5].

Table 5: Symptom analysis.

Symptoms	Number	%
Fever	66	79.5
Fatigue	64	77.1
Malaise	40	48.2
Anorexia	40	48.2
Weight loss	35	42.2
Abdominal fullness	17	20.5
Abdominal pain	13	15.7
Bone and joint pain	12	14.5
Skin bleeds	9	7.2
Other bleeds	39	47

Emphasis was given in identifying any factors, which predispose to leukemia. Nine patients had their residence near high-tension electric lines. Five patients were residing in a coastal area. Four patients gave history of frequent exposure to pesticides by inhalation from the farm close to the house, once every month for last 3-7 years. None of the patients had previous exposure to X-rays or anticancer therapy. Eight patients had systemic hypertension and were on regular antihypertensive drugs. Diabetes mellitus was present in 9 patients, 6 were on oral hypoglycemic agents, one was on insulin and the remaining were on diet and lifestyle modifications. One male was on Carbamazepine for seizure disorder. History of antituberculous treatment was present in four patients. Six patients had COPD and two had Bronchial asthma. All were on symptomatic treatment measures. Four patients were on Ayurvedic treatment for various ailments and three patients gave history of Homeopathic treatment. Two patients with history of myocardial infarction had undergone CABG [Table 6].

Table 6: Environmental and genetic factors

	Number
Residence near high tension electric lines	9
Residence near coastal area	5
Prolonged medications	27
Chemical or dye exposure	4
Prior anticancer treatment	0
Exposure to X-rays	0
Down' syndrome	0

Analysis of family history revealed consanguinity in three patients. There was one case of leukemia in family of the patients studied [Figure 4].

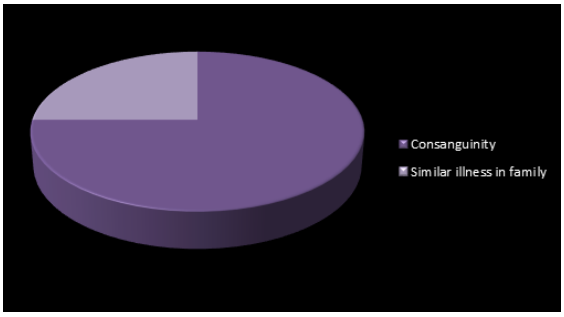

Figure 4: Family history.

A detailed diet history was taken from every patient. Four patients were strict vegetarians, of which two of them had been on vegetarian diet for the last 5 years. Apparently adequate intake of fruits and vegetables were present in the diet of only 54.2% of patients. None had any food faddism [Table 7].

Table 7: Diet history.

	Number	%
Strict vegetarians	4	4.8
Adequate fruits & vegetables	45	54.2
Food faddism	0	0

Forty patients (48.2%) had some sort of addiction. Smoking habits were present in 32 patients (38.5%). One of the females was a smoker. Alcohol intake was present in 13 patients (15.6%). Pan chewing was seen in 18 patients (21.7%). Substance abuse was not observed in any of the patients [Table 8].

Table 8: Addictions.

Addictions	Number
Smoking	32
Alcohol use	13
Pan chewing	18

DISCUSSION

Eighty three adults with Acute Myeloid Leukemia were included in the present study. Seventy-eight

patients were worked up and the diagnosis was established from this institution. Incidentally, most of the patients were referred to this institution because of their persistent symptoms or due to abnormal results of their routine blood investigations. Eight patients who were evaluated for other conditions, which on follow up were confirmed as AML. Five patients had their disease diagnosed from peripheral hospitals and referred to this hospital.

The Medical Institute, where this study was conducted is a major tertiary level government hospital, which caters to the population of Kozhikode, Malappuram, Palakkad, Kannur, Wyanad and Kasargode districts of Kerala. In the present study majority of patients were residents of Calicut district (57%) followed by Malappuram (21%).

Acute Myeloid Leukemia (AML) is the most common malignant disease-affecting adults. It accounts for approximately 80% of acute leukemia in adults. A study by Ghosh S et al [21], adult AML accounted for 76% of all acute leukemias.

The incidence of AML progressively increases with age and in adults over the age of 65 years, the incidence is approximately 30 times the incidence of AML in children.

In adults, the age distribution of AML is reported to be uniform with a median age of 30 to 60 years with median age of presentation at the age of 50 in many western studies. But Indian studies show a higher incidence in adolescents and young adults. Study by L. Kumar et al [23] showed median age at presentation as 30 years. Study by Kasthuri et al,[24] showed that 46% of adult AML were within the age group of 21-30 years. In a previous study conducted in our institution by Salim et al,[22] 43% of patients were in the 14-20 age group. The present study reports that AML in adults has a fairly uniform distribution above 20 years of age, with increased incidence above 60 years (25.3%).

In this study group, 47% of patients were males and the male to female ratio observed is 1:1.3. Previous literature shows a male preponderance. Study by L. Kumar et al [23] showed a male preponderance of 2:1. Study by Ghosh S et al,[21] had a male preponderance of 2.5:1. In a previous study conducted in our institution by Salim et al,[22] the value was 1:1.

Among the patients included in the present study, 40% were manual laborers, most of them had no formal education. 67.5% of patients belonged to lower socio economic class and four patients were from the upper class. This probably reflects the composition of the population who attends this hospital.

All patients in the present study were symptomatic. More than eighty percentages of the patients were symptomatic for more than 2 weeks. Most of these patients were referred due to their persistent symptoms or due to abnormal investigation results on routine blood investigations. The mean duration between onset of symptoms and the diagnosis of AML was 4 weeks. In the study the Salim et al,[22] this duration was longer (6 weeks). Improvement in the diagnostic methods and prompt referral to a tertiary care center could have contributed to this.

Fever was the most common symptom (79.5%). Study by L. Kumar et al,[23] had observed fever in 82% cases. Salim et al,[22] had documented fever in all patients. Usually it was low-grade irregular fever and sometimes high grade and intermittent. Fever in leukemia may be due to release of several pyrogenic cytokines during the rapid turnover of leukocytes or tissue destruction or due to the increase in metabolic rate. Infections contribute to fever significantly since these patients had defective immunity. This observation is consistent with that from all Indian and Western studies. Tiredness and easy fatiguability were also uniformly present. Anorexia and weight loss was observed in 48% and 42% patients respectively. These constitutional symptoms result from the profound alteration of the body metabolism and the rapidly progressive anemia.

Bone and joint pain were present in 14.5% of patients in the present series. Most of the patients had pain over the sternum, ribs and over the large joints. Massive proliferation of blasts in the medullary canal and under the periosteum are the presumed causes. In the series by Salim et al[22] the incidence of this symptom was 30%. In this series, one patient was admitted in the orthopaedics department with painful swelling of the knee joint. He was initially managed as septic arthritis. But later other investigations proved it to be AML.

Neurological manifestations were present in 4 patients at the time of presentation. Three of these patients had intra-cerebral bleed, which was confirmed by CT Scan of head.

There is ample evidence in literature that ionizing radiation, especially X-radiation, is leukemogenic. This was first observed in the survivors of the atom bomb blast in Japan. Incidence peaked after 6-7 years of the exposure. Patients with lymphoma treated with radiotherapy have increased incidence of acute leukemias and myelodysplastic disorders. Concern is also expressed over the frequent use of diagnostic X-rays. In the present study, history of exposure to any form of radiation was searched for. Five patients had their residence in coastal areas, which might have exposed him to terrestrial radiation. No patients had significant exposure to diagnostic X-rays or therapeutic irradiation.

Acute leukemia has got high incidence in genetic disorders like Down's syndrome, Bloom syndrome, Fanconi's anemia, Ataxia telangiectasia, IgA deficiency and X-linked agammaglobulinemia. None of these were present in the study population.

A few investigators have reported the association between leukemias and high-tension electric wires near patient's residence. Such wires can expose

occupants of the residence to very low levels of alternating magnetic fields that may produce physiological effects leading to leukemeogenesis. The present study identified nine patients with their residences near high-tension electric wires. The definite causal relationship cannot be established by this study.

Leukemia is more common in people who have been exposed for substantial periods to benzene vapour, industrial dyes and a variety of synthetic chemicals, pesticides, food additives, emissions from vehicles and runoffs in drinking water. Prior exposure to cytotoxic drugs especially alkylating agents also predispose to leukemia by increasing the chromosome breakage. The present study observed significant exposure to pesticides in four patients. One of these patients was a farmer who was exposed to the chemical for more than 20 years.

One interesting observation in the present study is that four patients were taking strict vegetarian diet. Two of these patients became strict vegetarian only for the last 5 years. Their diets were rich in pulses, nutrients and calories. 54% had adequate fruits and vegetables in their diet. So, probably diet has no role in the leukemeogenesis in AML. Even then, there were 46%who were taking diet deficient in fruits and vegetables. In a similar study by Salim et al[22] on ALL only 37% had adequate nutrition. There may be several yet unidentified protective factors in the diet, especially in fruits and vegetables, which may prevent the chromosomal and molecular alterations leading onto leukemeogenesis. Further studies are required regarding this aspect. Probably other environmental factors might have contributed the development of AML in these patients.

Among the physical signs, pallor was the most common (89%). Studies by L. Kumar et al [23] and Ghosh S et al,[21] showed similar values. In the previous study conducted in our institution by Salim et al [22] the value 83.3%. Anemia was seen in 96.3% of patients in the present study. 90.6% of them had hemoglobin between below 10 gm/dl. In the series by Salim et al and L. Kumar et al,[22,23] anemia was present in 93.2% and 96% respectively. Replacement of marrow by tumour is the primary cause of anemia. The malignancy may also lead to a shortened RBC survival, a hypoproliferative response to erythropoietin and an impaired release of iron. Cytokines including tumour necrosis factor (TNF) and some interleukins may contribute to these. Blood loss through the mucosa of gastrointestinal tract may be another reason for anemia. Other cause includes hemolysis and hypersplenism.

CONCLUSION

1. Acute myeloid leukemia in adults is more common in females.
2. Acute myeloid leukemia seem to have a high prevalence as the age advances (25.3% cases above 60 years)
3. Fever of unknown origin was the presenting complaint (34.9%) in a significant number of patients.
4. Fever and tiredness were the commonest symptoms (79.5%), followed by bleeding manifestations. Patients were symptomatic for an average duration of 2 weeks before diagnosis.
5. Commonest sign was pallor (89%) followed by lymphadenopathy, hepatosplenomegaly, and bleeding manifestation.
6. Residence near high-tension lines and exposure to pesticides appears to be related to leukemeogenesis. Possibly several other, yet unidentified, environmental and genetic factors influence prognosis.

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