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RESEARCH ARTICLE

Neuro-Ocular manifestations as the primary presenting symptoms of acute promyelocytic leukemia and their outcome:- An experience from a teritiary care centre.

Yasir Bashir[1], Nusrat Bashir[2], Fahim Manzoor[2], Shuaeb Bhat[2], Sajad Geelani[3], Javid Rasool[4], Aleem Jan[5], Omar Rashid[6], Asif Ahmed[7], Basharat Mubeen[8], Suhail Sidiq[9]

1. Senior Resident, Department of Critical Care Medicine, Sher-I-Kashmir Institute Of Medical Sciences, Soura, Srinagar, Jammu & Kashmir, India.
2. Senior Resident, Department of Hematology, Sher-I-Kashmir Institute Of Medical Sciences, Soura, Srinagar, Jammu & Kashmir, India.
3. Associate Professor , Department of Hematology, Sher-I-Kashmir Institute Of Medical Sciences, Soura, Srinagar, Jammu & Kashmir, India.
4. Professor , Department of Hematology, Sher-I-Kashmir Institute Of Medical Sciences, Soura, Srinagar, Jammu & Kashmir, India.
5. Additional Professor , Department of Hematology, Sher-I-Kashmir Institute Of Medical Sciences, Soura, Srinagar, Jammu & Kashmir, India.
6. Consultant, Department of Ophthalmology, Government Medical College, Srinagar, Jammu & Kashmir, India.
7. Senior Resident, Department of Pediatrics, Sher-I-Kashmir Institute Of Medical Sciences, Soura, Srinagar, Jammu & Kashmir, India.
8. Senior Resident, Department of Pathology, Sher-I-Kashmir Institute Of Medical Sciences, Soura, Srinagar, Jammu & Kashmir, India.
9. Assistant Professor , Department of Critical Care Medicine, Sher-I-Kashmir Institute Of Medical Sciences, Soura, Srinagar, Jammu & Kashmir, India.

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Corresponding Author

Shuaeb Bhat
Senior Resident, Department of Hematology,
Sher-I-Kashmir Institute of Medical Sciences,Srinagar,Jammu &Kashmir, India.

Abstract

Aim: 1. To highlight the importance of early recognition of neuroocular manifestations in acute promyelocytic leukemia in order to intervene urgently and to prevent additional morbidity and mortality related to the disease.
2. To compare the outcome in patients presenting with neuro-ocular complications versus those patients who had no neuro-ocular complications.
Materials and Methods: This study is a retrospective study where in we evaluated 86 cases of acute promyelocytic leukemia diagnosed and treated over a period of 10 years.The evaluation comprised of finding usual symptoms and especially to segregate those cases who had neuroocular manifestations as their primary presenting symptom. **Results** In our study we found that out of 86 cases of acute promyelocytic leukemia, 16 cases had neuro-ocular manifestations as their primary presenting symptom. Median age in our patients was 33 years with male: female ratio of 0.7:1. 16 cases out of total 86 cases presented with neuro-ocular manifestations. All patients were started on ATRA as per IC-APL 2006 protocol except two patients out who were not eligible for ATRA were put on arsenic trioxide. In addition aggressive supportive care was provided. When we compared patients with neuro-ocular with patients without neuro-ocular manifestations, It was found that overall survival was lower in those who presented with neuro-ocular manifestations as compared to those without neuro-ocular manifestations. The morbiditiy was also more in those with neuroocular manifestations .

Conclusion: In all patients presenting with neuroocular bleeds ,acute promyelocytic leukemias should be considered as one of the possibilities. In addition theses patients should be managed more aggressively in terms supportive care.

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INTRODUCTION

Acute promyelocytic leukemia (APL) is a unique subtype of the acute leukemias. It has distinct cytogenetics, clinical features, and biologic characteristics. Acute promyelocytic leukemia (APL) is caused by an arrest of leukocyte differentiation at the promyelocytic stage. The discovery and elucidation of the molecular pathogenesis for APL has led to the first and only targeted therapy for leukemia. Acute promyelocytic leukemia (APL) belongs to the group of myeloid neoplasms. The FAB classification refers to it as AML M3, whereas the present WHO classification lists it under "Acute myeloid leukemia with recurrent genetic abnormalities."[1]. Clinically, the manifestations of hemorrhage are often the most dramatic findings in the physical examination reflecting the underlying biologic properties of the transformed promyelocyte. Bleeding in patients with APL can be severe, with widespread bruising, petechiae, mucus membrane bleeding, CNS bleeding, pulmonary hemorrhages, gastrointestinal hemorrhage, and excessive blood loss from sites of trauma. In addition to being the most common cause of induction mortality, catastrophic bleeding can also occur before the diagnosis of APL has been made and treatment initiated. The body of biological information on APL establishes this leukemia as a unique entity that has to be promptly recognized to counteract the coagulopathy, especially in light of its striking response to treatment with all-trans retinoic acid (ATRA).

Materials and Methods:

This study is a retrospective study, where in we evaluated 86 cases of acute promyelocytic leukemia diagnosed and treated over a period of ten years. The evaluation comprised of finding out usual symptoms and especially to segregate those cases who had neuroocular manifestations as their primary presenting symptom. Diagnosis was established by combination of history, clinical examination, complete blood counts, peripheral smear examination, bone marrow examination, immunophenotyping, PML-RARA by FISH/RT-PCR and cytogenetics. In addition fundoscopy, computerized tomography (CT scan), magnetic resonance imaging (MRI), cerebrospinal fluid examination (CSF) and fundus flourescien angiography (FFA) were done as per need following clinical examination

Results:

Out of 86 patients diagnosed as acute promyelocytic leukemia, 16 cases presented with neuro-ocular manifestations. Male: Female ratio was 0.7:1 with median age of 33 years. These 16 cases had neuro-ocular manifestations in the form of Intracranial bleeds (3cases) (Figure. 1) , Subarachanoid haemorrhage(1case) (Figure. 2) ,1 cases presented as Meningitis, 2 cases of fundal hemorrhage and 3 cases of Vitreous haemorrhage (Figure.3).Central retinal vein occlusion (1case) (Figure 4) suspected on fundoscopy and confirmed on Fundus Flourescien Angiography. Anterior ischemic optic neuropathy (1case) (Figure .5) . 2 cases of Papilledema (Figure.6) and two cases of Conjuctival haemorrhage seen on fundoscopic examination. Average fibrinogen level was 0.8g/l , Prothrombin time and activated partial thromboplastin time were elevated for majority of the cases . Average presenting platelet count was 14000/cumm(Table .1) .Out of sixteen cases ,14 cases were treated as per IC-APL 2006 Protocol(Table.2) employing All trans retinoic acid(ATRA) 45mg/m2/day from day 1 until complete remission, Daunorubicin 60mg/m2/d(d2,4,6,8) . We added dexamethasone 2.5mg/m2/12h for 2 weeks in 4 patients who had WBC count >5000/cumm as per protocol. This was followed by three cycles of consolidation following which morphological and molecular remission was documented and then patients were put on maintainance for 2 years using 6-Mercaptopurine daily, Methotrexate weekly and ATRA for 2 weeks every 3 months. Two of our patients who couldnot effort ATRA were put on arsenic trioxide.Patients on ATRA were monitored for ATRA syndrome.Majority of our cases differentiated in 4-5weeks.Aggressive supportive care was given including platelet concentrates, fresh frozen plasma to maintain platelet count>50,000/cumm and fibrinogen levels>1.5mg/dl. In addition symptomatic treatment for neuro-ocular manifestations including fibrinolytic agents, lowering of intracranial pressure and decongestants was given. Out of sixteen cases, four patients with intracranial hemorrhage died within 48 hours of admission, two patients died during consolidation due to sepsis. Ten cases are on our follow up, out of which one patient developed bilateral optic atrophy while on ATRA ; possibly due to benign intracranial hypertension which was not appreciated early.

Figures:

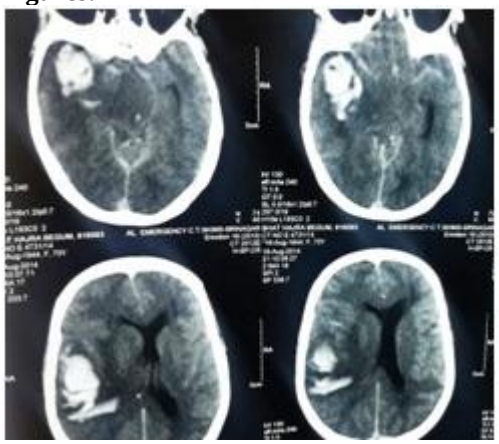

Fig.1: CT scan of the patient showing large parencymal bleed.

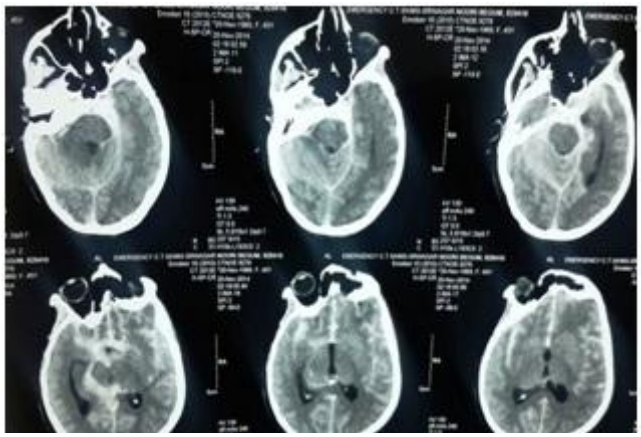

Fig.2:CT imaging showing subarachnoid hemorrhage.

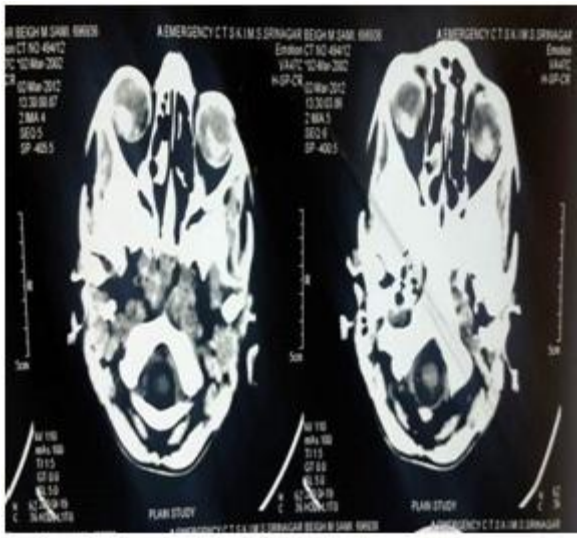

Fig.3: Vitreous hemorrhage seen in CT head.

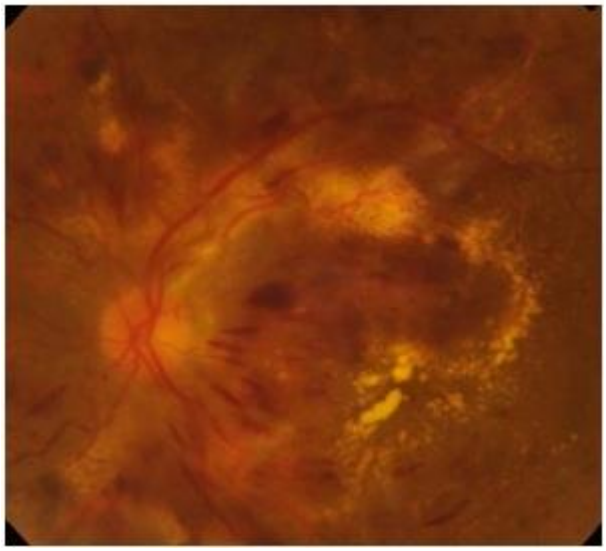

Fig.4: Central retinal vein occlusion showing extensive hemorrhage giving typical blood and thunder appearence.

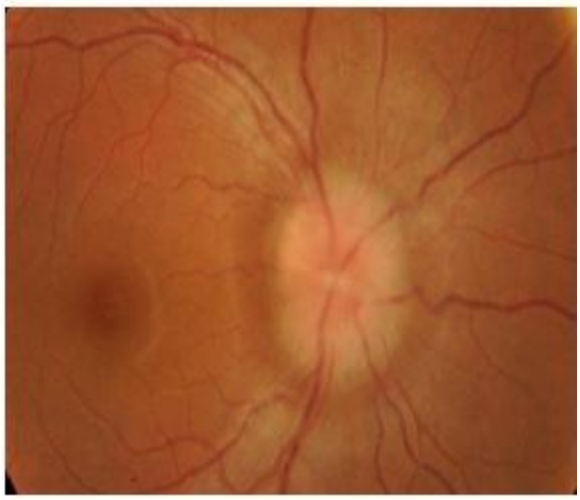

Fig.5; Fundoscopy showing disc edema in a case of anterior ischemic optic neuropathy.

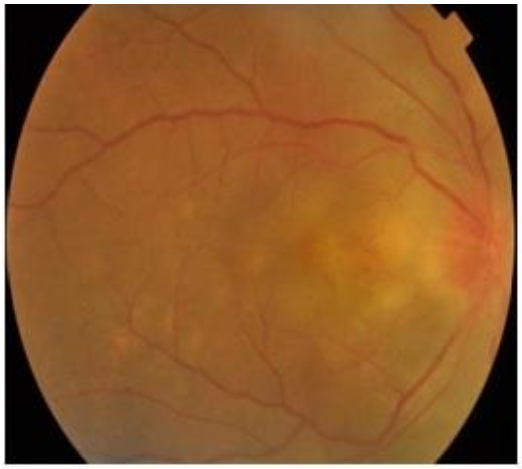

Fig.6: Fundoscopy showing papilledema.

TABLES

Table :1

Clinical and biological characteristics at diagnosis

Median Age(Years)	33 years
Male/Female ratio	0.7:1
Hematological parameters • Median hemoglobin(g/dl). • Median WBC count(/cumm) • Median platelet count (/cumm) • Bone marrow examination **Coagulation profile** • Prothrombin time(median) • Activatedpartialthromboplastin(median) • Fibrinogen levels(median)	 6.0g/dl 6590/cumm. 14000/cumm. APML-Hypergranular(12/16), APML-Hypogranular(4/ 16). 23 seconds 40seconds 0.8 g/l
Neuroocular manifestations and diagnostic modalities used. 1. Intracranial Hemorrhage 2. Subarachanoid hemorrhage 3. Fundal haemorrhage 4. Viterous haemorrhage 5. Anterior Ischemic Optic Neuropathy 6. CRVO 7. Papilledema 8. Conjunctival Hemorrhage 9. Meningitis	 3(16) CT Scan head. 1(16) CT Scan head. 2(16) Fundoscopy. 3(16)(CT scan orbit) 1(16)MRI 1(16)Fundoscopy ,FFA. 2(16)Fundoscopy 2(16)Fundoscopy 1(16)CSF examination.
Cytogenetics Secondary cytogenetic abnormalities	t(15;17)-14cases,t(11;17)-2 cases.
Molecular genetics	PML-RARA(14),ZBTB16-RARA(2)

Table:2

Treatment and outcome in patients with neuro-ocular manifestations

Protocol	Induction regimen	n	CR	Molecular remission	Post remission	Death(s) in Consolidation	OS(2 year)
IC-APL 2006	ATRA+ Daunorubicin +Dexamethasone*	14			3 Cycles of consolidation followed by maintainance for 2 years with ATRA every 3 months ,6MP daily,MTX weekly.(12Patients).	2	
	ASO- In cases who were non-eligible for ATRA.	2			ASO 10 days a month for 6 months		
	+ **Aggressive supportive care-** fresh frozen plasma, fibrinogen / cryoprecipitate and platelet transfusions to maintain the fibrinogen concentration and platelet count. + **Fibrinolytic agents**		12(75%%)	12(75%%)			62.5%
ED(With in 48hrs)		4	0	0			

IC-APL-International consortium on acute promyelocytic leukemia,*If WBC >5000/cumm, CR-complete remission, ED-early deaths, ATRA-all trans retinoic acid, ASO-arsenic trioxide.

Table:3

Outcome in patients with neuro-ocular manifestations versus Patients without neuro-ocular manifestations

Total number of patients(n=86)	Patients presenting with neuro-ocular manifestations	Patients without neuro-ocular manifestations
Total number of patients	16	70
CR	12	63(90%)
MR	12	63
Early deaths	4	Nil
Late deaths	2	4
Morbidity	2	Nil
OS(2 Year)	62.5%	94.2%

Discussion:

Acute promyelocytic leukemia (APL) was first described as an entity in the late 1950s in Norway and France as a hyper acute fatal illness associated with a hemorrhagic syndrome. Analysis of leukemic cells isolated from peripheral blood and bone marrow showed that TF antigen and procoagulant activity were greatly increased in AML subtypes M3 and M4 [5,2] . APL is uncommon in children less than 10 years of age, but its incidence increases during the teen years to reach a plateau during early adulthood. It then remains constant until it decreases after 60 years of age [3]. Acute promyelocytic leukemia (AML-M3) is characterized by the t(15;17)(q22;q11-21) translocation described by Rowley et al[6]. This translocation reflects the molecular rearrangement of the PML gene, located at 15q22, with the RARA gene, located at 17q21[4], and is considered to be critical for the pathogenesis of the disease since it blocks differentiation during the promyelocytic stage of myeloid maturation 4. Clinically, APL has a high frequency of hemorrhage due to disseminated intravascular coagulation (DIC), which contributes to the high mortality rate of this disease [5, 6].Complications related to hemorrhages due to DIC are serious issues in APL patients; hemorrhages have been reported to occur in 90% of APL patients [7]. Moreover, many studies conclude that hemorrhage is the primary cause of death in APL cases [8, 9.] Identification of t(15;17) or its molecular equivalent, the rearrangement of genes PML/RARA, is associated with a good response to ATRA therapy, coagulopathy resolves promptly, usually within the first 48 hours and remission can be achieved in a high proportion of patients with an increased survival rate when associated with conventional chemotherapy [10.] Despite the reversal of the coagulopathy by prompt ATRA therapy, hemorrhagic complications remain the major cause of early deaths, accounting for more than 50% of patients with and without ATRA therapy[11,12]. Risk factors for bleeding include a high white count greater than 20,000/μL at presentation and severe thrombocytopenia. The pathogenesis of the bleeding is multifactorial, with a combined effect of disseminated intra-vascular coagulation (DIC), excessive fibrinolysis and thrombocytopenia.Almost all patients with APL manifest DIC at the time of diagnosis. Apart from the hemorrhagic and infiltrative complications observed in the skin and mucous membranes, the ocular fundus provides an unequaled direct view of the hematologic effects of blood dyscrasias in the living patient.Clinical and pathologic studies indicate that the ocular manifestations of blood dyscrasias are frequent. Treatment of acute promyelocytic leukemia (APL) for most patients is the simultaneous administration of all-trans retinoic acid (ATRA) and anthracycline-based chemotherapy for induction and consolidation, as well as ATRA-based maintenance. In addition, supportive care is also critical for the successful outcome in individual patients. [13]Once the suspicion of APL is established on the basis of morphologic criteria, the disease should be managed as a medical emergency, starting supportive measures and ATRA therapy even before the genetic diagnosis is available. Providing adequate supportive

therapy is critical for those of patients who develop fatal hemorrhages during the diagnostic evaluation, before beginning antileukemic therapy, or during the first days of induction. It seems reasonable, therefore; that rapid initiation of ATRA and supportive measures to reverse the ongoing coagulopathy may lower the risk of lifethreatening hemorrhages in these patients. Treatment of the coagulopathy should be based on liberal transfusion of fresh frozen plasma, fibrinogen, or both, as well as on aggressive platelet support to maintain thefibrinogen level above 1.5 g/L (150 mg/dL) and the platelet counts above 30 to 50 × 109/L , until disappearance of all clinical or laboratory signs of coagulopathy.The benefit of heparin, tranexamic acid, or other anticoagulant or antifibrinolytic therapy to attenuate the hemorrhagic risk remains questionable. Treatment of the underlying cause of the ocular fundus manifestations (i.e., anemia, thrombocytopenia, retinal or choroidal leukemic infiltrate, hyperviscosity syndrome, circulating neoplastic white blood cells, and/or bone marrow infiltration) will often result in improvement or complete resolution of the ocular fundus findings.[14]

Conclusion:

In all patients presenting with neuroocular bleeds ,acute promyelocytic leukemias should be considered as one of the possibilities. In addition these patients should be managed more aggressively in terms of supportive care.

Conflicts of interest-None

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