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SUCCESSFUL MANAGEMENT OF APL DIFFERENTIATION SYNDROME MANIFESTING WITH LIFE THREATENING HYPOTENSION

Clinical Hematology

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ABSTRACT

Acute promyelocytic leukemia (APL) accounts for 5 to 20 percent of cases of AML. APL represents a medical emergency with a high rate of early mortality, often due to hemorrhage from a characteristic coagulopathy.The differentiation syndrome can occur during APL induction therapy with manifestations like fever, hypotension, dyspnea, weight gain, and musculoskeletal pain. Sometimes patient can present with atypical manifestation for which high index of suspicion and institution of preemptive steroids will be key factors in patients survival. Our case is 47 yrs old male of intermediate risk APL who had severe hypotension during APL induction treatment due to differentiation syndrome . Hypotension required inotropic support but successfully managed with steroids and temporary cessation of differentiating agents.

KEYWORDS

BACKGROUND

Acute promyelocytic leukemia (APL) accounts for 5 to 20 percent of cases of AML.[1] APL represents a medical emergency with a high rate of early mortality, often due to hemorrhage from a characteristic coagulopathy. It is critical to start treatment with a differentiation agent without delay as soon as the diagnosis is suspected.The differentiation syndrome occurs in approximately 25 percent of patients with APL during induction therapy.[2] The typical symptoms and signs of the differentiation syndrome (DS) include fever, hypotension, dyspnea, weight gain, and musculoskeletal pain .High degree of clinical suspicion & early institution of preemptive steroid therapy remains key in the management of DS.

CASE SUMMARY

47 yrs old male, non co morbid , presented with history of fever with chills and fatigue since 7 days. On examination he was febrile and pale with no organomegaly. Patients complete blood count showed pancytopenia with occasional faggot cells (Hemoglobin -9.2 g/dl,WBC count- 1.2 x 10 ^{9}/L Lymphocytes 25%Monocytes 3% Promyelocytes 72%, Platelet count 32 x 10 ^{9}/L) for which patient undergone bone marrow aspiration and biopsy suggestive of APL. (Figure 1)

FISH showed PML-RARA translocation confirming the diagnosis. Patient was categorized as a intermediate risk APL. Patient's baseline ECG, 2D ECHO, coagulation profile,renal function tests (RFT)& electrolytes were normal. Patient was started on Inj. ATO 0.15 mg/kg/day and cap. ATRA 45 mg/m^2/day as per institutional protocol. On day 5 of treatment patient started complaining of severe giddiness with profuse sweating. There was no history of associated chest pain, palpitations, fever, loose motions,blood loss, pallor or fasting state. On examination, pulse rate was 110 /minute with blood pressure of 60/30 mm of Hg. On respiratory system examination there were no adventitious sounds, heart sounds were normal. Still, possibility of acute coronary syndrome was considered. Patients ECG was not suggestive of Acute coronary syndrome. (Figure 2)

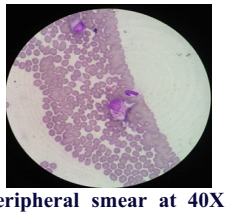

Figure no 1: Peripheral smear at 40X showing 'faggot cell' (Abnormal promyelocyte containing multiple auer rods)

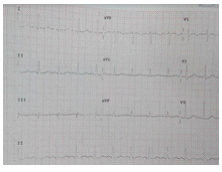

Figure no 2: ECG of patient during hypotensive episode

Patients TROP-T test (quantative as well as qualitative) was negative. Immediately saline bolus administered but no satisfactory improvement in BP noted hence patient immediately started on inotropic support with dopamine and subsequently noradrenaline added in view persistent hypotension. Patient 2 D ECHO was not suggestive of any significant abnormality.Possibility pf pulmonary thromboembolism was also ruled out by normal CT pulmonary angiography.

Complete hemogram on the same day showed increase in WBC count of 20.2 x10^9/L (Promyelocytes 90 Lymphocytes 10)

Table 1 : Details of patients signs ,symptoms along with laboratory parameters.

Day of treatment	Symptoms	BP (mm of Hg)	WBC count(x10^9/L)	Sr. creatinine	ATO and ATRA
1	Fever and fatigue	122/86	1.2 x10^9/L	0.8 mg/dl	Given
2	No fever		1.4 x10^9/L	0.8 mg/dl	Given
3	-		2.3 x10^9/L	0.9 mg/dl	Given
4	-		4.8 x10^9/L	0.8 mg/dl	Given
5	Giddiness, sweating	60/30 started dopamine and noradrenaline	20.2 x10^9/L	0.9 mg/dl	Both drugs withheld
6	Giddiness	90/60 on dopamine and noradrenaline	22.7 x10^9/L	2.2 mg/dl	Both drugs withheld
7	Giddiness	94/70 on dopamine and noradrenaline	1.2 x10^9/L	2.1 mg/dl	Both drugs withheld
8	Giddiness	100/70 on dopamine	1.2 x10^9/L	1.9 mg/dl	Both drugs withheld
9	-	100/70 on dopamine low dose	1.2 x10^9/L	1.7 mg/dl	Both drugs withheld
10	-	106/76 on dopamine low dose	4.3 x10^9/L	1.2 mg/dl	Both drugs withheld
11	-	110/70 dopamine stopped	3.9 x10^9/L	1.0 mg/dl	ATO restarted
12	-	110/74	3.2 x10^9/L	0.8 mg/dl	ATO continued
13	-	116/78	3.0 x10^9/L	0.8 mg/dl	ATRA restarted and both the drugs continued further in induction

Patient did not have fever, significant weight gain (more than 5 kgs), dyspnoea and other features of APL differentiation syndrome. Patient had renal failure but was it due to persistent hypotension or due to differentiation not clear. In view of increase in WBC counts, APL on treatment with differentiating agents and timing of events, possibility of APL differentiation syndrome was considered. Patients started on Inj dexamethasone 10 mg twice a day and treatment with ATO and ATRA was discontinued. Hydroxyurea started for cytoreduction and dose modified as per daily WBC counts. Patient continued on inj dexamethasone for 6 day then tapered and stopped over next 5 days. Patient required inotropic support for 5 days after which patients BP remained in normal range. On Day 10 of treatment patients WBC count was 4.3 x 10^9/L with creatinine of 1.2 mg/dl. ATO restarted on same day. ATRA was added after 48 hours. Patients further induction and consolidation chemotherapy was uneventful. Now patient has completed 4 yrs post treatment completion and his RQ PCR for PML-RARA done at 3 yrs post completion is negative and now off monitoring.

DISCUSSION

Acute promyelocytic leukemia distinct variant of AML. APL is currently classified as acute promyelocytic leukemia with t(15;17)(q24.1;q21.2);*PML-RARA* in the World Health Organization classification system.[3]Using these two parameters Sanz divided APL in three prognostic categories.[4]

- Low risk – WBC ≤10,000/microL and platelets >40,000/microL
- Intermediate – WBC ≤10,000/microL and platelets ≤40,000/microL
- High risk – WBC >10,000/micro.

Low risk and intermediate risk are treated similarly with ATO and ATRA based induction and consolidation therapies while high risk receives anthracyclines and cytarabine in addition to ATO and ATRA. Two years maintenance therapy based 6 MP, methotrexate and ATRA given in high risk patients.[4]

The differentiation syndrome is a potentially fatal complication of induction chemotherapy in patients with APL. Presence of the following signs and symptoms are considered in diagnosis of differentiation syndrome : dyspnea, unexplained fever, weight gain greater than 5 kg, unexplained hypotension, acute renal failure, and, particularly, a chest x ray demonstrating pulmonary infiltrates or pleuropericardial effusion. Patients with 4 or more of the above signs or symptoms were classified as having severe differentiation syndrome, while those with 2 or 3 signs or symptoms were considered to have moderate differentiation syndrome. No single sign or symptom was considered sufficient to make a diagnosis of the syndrome.[5]When it occurred within 7 days of the start of therapy,differentiation syndrome is considered as "early " and it will be called "late" if it occurred more than 7 days after the start of therapy.[5] In our case there was presence of severe hypotension along significant increase in WBC count , there was presence of acute renal failure which was noted on next day ,etiology of which also can not be ascertained.

Because of the life-threatening nature of the full-blown syndrome, a use of corticosteroids at the very earliest symptom or sign suggestive of DS has been suggested .(figure 2) Dexamethasone, at a dose of 10 mg twice daily by intravenous injection, is commonly used. Severe differentiation syndrome may necessitate temporary stopping of differentiating agents which can be reinstituted as symptoms improve.[6] As in our case hypotension was life threatening, we have temporarily stopped differentiating agents and immediately started dexamethasone. As patient responded to treatment and it do not recurred on restarting of drugs indicate it was not a direct effect of drugs.

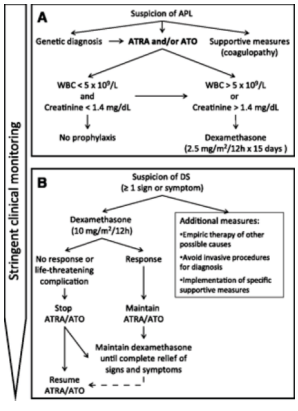

Figure 2 Current algorithm for the management of DS in the PETHEMA trials. (A) Prophylaxis. (B) Treatment.[6]

CONCLUSION

During induction treatment of APL, manifestations like severe hypotension can appear without or minimal other features of differentiation syndrome. Possibility of differentiation syndrome should always be entertained if other causes like sepsis, acute coronary syndrome, arrhythmias, pulmonary thromboembolism are ruled out. Low threshold for diagnosis of differentiation syndrome with early institution of steroid treatment can prevent further morbidity and mortality in such life threatening situations. Successful reintroduction of APL treatment agents after resolution of life threatening differentiation syndrome.

COMPETING INTERESTS

The authors declare that there is no conflict of interests regarding publication of this paper.

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