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SHORT COMMUNICATION

Pseudotumour cerebri in acute promyelocytic leukemia on treatment with all-trans-retinoic acid (ATRA) - an experience from a teritiary care centre

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Abstract

Acute promyelocytic leukemia (APML) is considered to be sensitive to all-trans-retinoic acid (ATRA) which acts as a differentiating agent. ATRA is considered to be a well-tolerated agent and is known to achieve complete remission in acute promyelocytic leukemia. However, a few cases on long term all-trans-retinoic acid (ATRA) use can develop pseudotumor cerebri. Out of 32 patients with APML who were treated in our Centre over a 4-year-period, we encountered 6 patients who developed ATRA-related pseudotumor cerebri while on maintenance treatment. The patients ranged from 12 to 40 years of age. 3 patients complained of unbearable headache, 2 of diplopia and 1 of gross reduction in visual acuity. CT scans and MRI did not reveal any intracranial lesions. Cerebrospinal fluid (CSF) examination was normal with CSF manometry revealing a high CSF pressure (average of 345mmH_2O). Fundoscopy revealed papilledema in 5 patients and optic atrophy in 1 patient. The patients were successfully managed with decrease dose/discontinuation of ATRA, use of acetazolamide, corticosteroids and therapeutic CSF drainage.

Keywords: all-trans retinoic acid, anthracycline, differentiation, pseudotumour cerebri

INTRODUCTION

All-trans-retinoic acid (ATRA) is an important drug that is widely used in acute promyelocytic leukemia (APML) to induce differentiation. ATRA, a derivative of vitamin A, when combined with anthracycline-based chemotherapy yields a complete remission (CR) rate in excess of 90% in clinical trials involving patients with APML. However, ATRA has also been associated with several side effects, including skin problems (dryness, peeling, itching, and sun sensitivity), reversible elevation in liver enzymes, abnormal lipid levels, hypothyroidism, and headaches. Less commonly, ATRA has been associated with cerebral and myocardial infarction, corneal deposits secondary to hypercalcemia, scrotal ulcerations, Sweet's syndrome, Fournier's gangrene, APML differentiation syndrome, and pseudotumour cerebri. Pseudotumour cerebri, also known as idiopathic intracranial hypertension, is a disorder of raised intracranial pressure with no evidence of intracranial space occupying lesions (ICSOLs), infection or vascular abnormality. The aetiology of pseudotumor cerebri is uncertain. The syndrome classically manifests with headaches and visual changes. We describe our experience with cases encountered over a four-year period in our tertiary care centre.

MATERIALS AND METHODS

A study was conducted over a period of four years period from April 2010 to May 2014. All cases diagnosed as acute promyelocytic leukemia were included in the study. The diagnosis was established by a combination of history, clinical examination, complete blood counts, peripheral smear examination, bone marrow examination, immunophenotyping, PML-RARA by FISH/ RT-PCR and cytogenetics.

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RESULTS

Thirty-two cases of acute promyelocytic leukemia were reported during the period of study. 27 patients were adults and 5 cases were in the paediatric age group.

The clinical presentations of the majority of cases were related to bleeding from various sites. Two patients expired before the treatment was initiated. The international consortium on acute leukemias (ICAPL) chemotherapy protocol 2006 was initiated in all patients except for two cases of acute promyelocytic leukemia-variant, who were treated with arsenic trioxide. Clinically patients responded promptly to treatment.

Pseudotumour cerebri

During the course of treatment, three patients presented with unbearable headache (Table 1) for which symptomatic treatment was given but no relief was achieved. Initially, a functional aetiology was considered but subsequently when two of these patients developed diplopia and worsening of headache, these patients were subjected to CT head and MRI brain. However, both CT head and MRI were normal (Fig. 1). Subsequently fundoscopy showed papilloedema (Fig. 2) in these patients. Cerebrospinal fluid (CSF) examination was normal with CSF manometry revealing a high CSF pressure. Two more patients developed diplopia with fundoscopy showing papilloedema and one patient during maintenance phase presented with a gross reduction in visual acuity. The fundoscopy revealed optic atrophy.

The possibility of pseudotumor cerebri was considered. The patients were fully evaluated to exclude all other risk factors and causes (like obesity, endocrine abnormalities) including drug history.

Management and subsequent course

All-trans retinoic acid (ATRA) dose was reduced from 45 mg/m^2 to 25mg/m^2 in four patients and stopped in the other two cases with initiation of Acetazolamide 500mg, 8 hourly. Corticosteroids were added in two patients. Acetazolamide use was ineffective in one of our patient but subsequent lumbar puncture successfully relieved the signs and symptoms. All of our cases showed improvement within one week of ATRA withdrawal/dose reduction except the case of optic atrophy. Successful ATRA rechallenge was started at 25mg/m^2/d along with prophylactic acetazolamide 500mg/d.

All patients are on follow-up and achieved complete remission of APML. Tables 1 & 2 summarise the clinical characteristics, management and outcome of these APML patients with pseudotumour cerebri.

DISCUSSION

Acute promyelocytic leukemia comprises 5-8% of acute myeloid leukemia.[1] It occurs at any age but is usually seen in adults. Acute promyelocytic leukemia has a particular sensitivity with all-trans retinoic acid (ATRA) which acts as a differentiating agent at doses of 45 mg/m^2 orally until remission is achieved.[2,3] The outcome in acute promyelocytic leukemia treated optimally with ATRA and an anthracycline is more favorable than for any other acute myeloid leukemia cytogenetic subtype.[4,5]

TABLE 1: Characteristics of pseudotumour cerebri cases

Number of patients	6
Age range (years)	12-40
M:F ratio	1:1
ATRA dosage >20years <20years	45mg/m^2/day 25mg/m^2/day
Phase of chemotherapy	Maintenance
Symptoms (a) Diplopia (b) Headache followed by diplopia. (c) Diminution of vision	 2/4 3/4 1/4
Average CSF Pressure	345mmH_2O

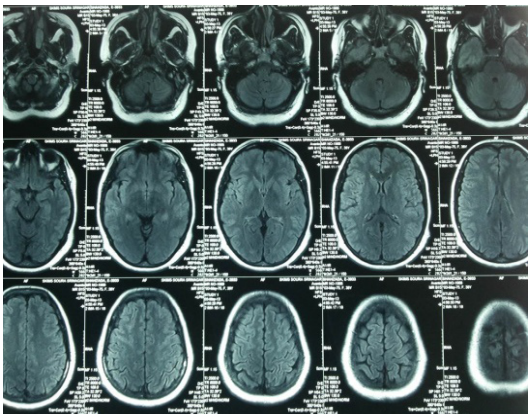

FIG. 1: Normal MRI of the brain

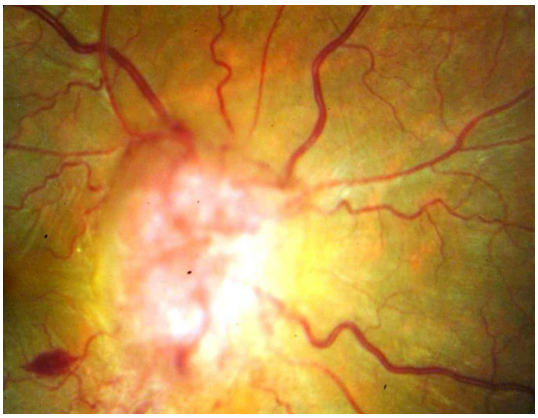

FIG. 2: Fundoscopy showing papilledema

ATRA, considered to be a well tolerated agent, can lead to few complications in the form of retinoic acid syndrome which includes fever, dyspnoea, chest pain, pulmonary infiltrates, pulmonary and pleural effusion and hypoxia. It has been documented that a few cases of acute promyelocytic leukemia on long term ATRA use can cause pseudotumour cerebri.

Pseudotumour cerebri is a clinical entity of uncertain etiology characterized by intracranial hypertension. The syndrome classically manifests with headaches and visual changes. According to the modified Dandy criteria, pseudotumour cerebri is diagnosed if (1) there are symptoms of raised intracranial pressure in the form of headache, nausea, vomiting, transient visual obscurations or papilloedema, (2) no localizing signs with the exception of abducens (sixth) nerve palsy, (3) the patient is awake and alert, (4) normal CT/MRI findings without evidence of thrombosis, (5) lumbar puncture opening pressure of more than 25 cm H_2O and normal biochemical and cytological composition of cerebrospinal fluid, and (6) no other cause for raised intracranial pressure can be found. The risk factors for development of pseudotumour cerebri include obesity, vitamin A (too much or too little), Cushing's disease, hypoparathyroidism, hypothyroidism, chronic kidney disease, anemia and drugs which includenon-steroidal anti-inflammatory drugs, oral contraceptive pills, nitrofurantoin, isotretinoin /All-Trans Retinoic Acid, minocycline, tamoxifen, nalidixic acid, lithium and steroids (stopping or starting them).

The exact mechanism of ATRA-induced pseudotumour cerebri is not clearly understood. It is postulated that ATRA at high doses increases cerebrospinal fluid production and impends CSF absorption at arachnoid villi as ATRA causes alteration of the lipid constituents of the arachnoid villi.[6] In one of the prior studies it was seen that the levels of CSF retinol were higher in patients with pseudotumour cerebri than in subjects without pseudotumour cerebri.[7] Table 3 shows a comparison of our study with previously reported cases of PTC after ATRA for APML in the literature.

CONCLUSION

Patients with acute promyelocytic leukemia on treatment with all-trans retinoic acid should be evaluated carefully during the course of treatment. Signs like headache, blurring of vision and altered visual acuity should be given

TABLE 2: Management and outcome of pseudotumour cerebri patients

Withdrawal of ATRA	2
Decrease in dosage	4
Acetazolamide (500mg, 8 hourly)	4
Corticosteroids*	2
Therapeutic lumbar puncture*	1
Average time to improvement	1 week
ATRA rechallenge	25mg/m^2/day

*Where Acetazolamide was ineffective.

TABLE 3: Comparison of our study with previously reported cases of PTC after ATRA for APML

	Number of patients	ATRA dosage	Phase of chemotherapy when symptoms first developed	Average time to improvement
Jeddi *et al* (2008)[8]	1	45mg/m^2/day	Induction	2 days
Schroeter *et al* (2000)[9]	1	25mg/m^2/d	Consolidation	1 week
Visani *et al* (1996)[10]	1	45mg/m^2/d	Induction	15 days
Yeh*et et al* (2006)[11]	1	45mg/m^2/d	Maintenance	4 weeks
Our study	6	45mg/m^2/d for>20 year 25mg/m^2/d for<20 year	Maintenance	1 week

consideration in view of pseudotumour cerebri, besides the malignancy itself. Additionally, this condition should be diagnosed as early as possible to prevent the sequelae of raised intracranial pressure such as optic atrophy.

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