

doi: 10.5455/2319-2003.ijbcp20141027

Case Report**A case report of all-trans retinoic acid-induced pseudotumor cerebri in an adult patient of acute promyelocytic leukemia****Akhil Kapoor^{1*}, Narender Kumar², Raj Kumar Nirban¹, Ashok Kalwar¹, Harvindra Singh Kumar¹**

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ABSTRACT

All-trans retinoic acid (ATRA), a derivative of vitamin A, is the first line drug for acute promyelocytic leukemia (APL). At the same time, ATRA is also associated with various side effects, including some life threatening conditions. We describe a case of ATRA-induced pseudotumor cerebri in an adult patient of APL.

Keywords: All-trans retinoic acid, Pseudotumor cerebri, Adult, Acute promyelocytic leukemia

INTRODUCTION

All-trans retinoic acid (ATRA), a derivative of vitamin A, is the first line drug for acute promyelocytic leukemia (APL). When combined with anthracycline, a complete remission (CR) rate of >90% is obtained in the patients with APL.^{1,2} At the same time, ATRA is also associated with various side effects, including some life threatening conditions. The common side effects include skin problems (dryness, itching, peeling, and photo sensitivity), transient elevation in liver enzymes, hyperlipidemia, headache, and hypothyroidism.³ Other adverse effects include hypercalcemia, myocardial infarction, corneal deposits, Fournier's gangrene, scrotal ulcerations, Sweet's syndrome, APL differentiation syndrome, and pseudotumor cerebri (PTC). PTC or idiopathic intracranial hypertension is

characterized by elevated intracranial pressure in the absence of infection, vascular abnormality, hydrocephalus, space occupying lesion or alteration in the level of consciousness.⁴ There have been few reports of PTC with ATRA treatment in the pediatric patients;^{5,6} however, it is much rarer in the adults.⁷

CASE REPORT

A 32-year-old male patient presented to our hospital with fever and gum hyperplasia from 2 months. On examination, the patient had severe pallor and bleeding from the gums. Hematological investigations revealed hemoglobin of 5.7 g/dl, white blood cell count - 22,400/mm³, platelet count - 40,000/mm³; the differential count 40% blast cells,

8% neutrophils, 56% lymphocytes. The coagulation profile was normal. The peripheral blood film showed normocytic normochromic anemia, hyperleukocytosis with predominant lymphocytes with atypical cells and sparse platelets. The circulating blasts had coarse reddish-purple granules and Auer rods in the cytoplasm with convoluted nuclei and prominent nucleoli consistent with promyelocytes. Bone marrow examination revealed 78% blasts which stained myeloperoxidase positive. Flow cytometry analysis was performed to confirm the diagnosis, and it was suggestive of acute myeloid leukemia - FAB M3 type with CD13, CD33, CD45, CD64, CD79a positive and negative for HLA-DR. The hybrid fusion transcript for PML-RARa (bcr1 type) was detected in the leukocytes of peripheral blood by the real time polymerase chain reaction qualitative analysis. The chromosomal analysis was performed using bone marrow sample, and it showed 50% with 46XY; t(15;17) and 50% with 46XY. Fluorescence in situ hybridization showed PML-RARa fusion signal in 94% of interphase cells. The patient was started on ATRA 45 mg/m² (70 mg/day orally) along with daunorubicin 100 mg/day for 3 days. After 2 weeks of induction chemotherapy, the patient developed symptoms of headache and diplopia. There was bilateral papilloedema on fundus examination. Magnetic resonance (MR) imaging of the brain failed to reveal any abnormality. On performing lumbar puncture, cerebrospinal fluid (CSF) opening pressure of 300 mm of water was found without any cytological or biochemical abnormality. Hence, a probable diagnosis of ATRA induced PTC was made, and ATRA was stopped. The patient was started on acetazolamide 1000 mg twice daily and steroids, and there was complete resolution of the symptoms in 5 days. ATRA was reinstated after 2 weeks. CR without any neurological complications was achieved after completion of induction chemotherapy.

DISCUSSION

ATRA is a retinoid that is used as a differentiation therapy for APL. Retinoids control normal cell growth, cell differentiation, and cell death during embryonic development and in certain tissues later in life.⁸ PTC is an uncommon disorder with an incidence of about 1 case/1 lac population per annum; however, it primarily affects obese women of childbearing age.⁹ Drug-induced PTC is implicated to be associated tetracyclines, growth hormone, oral contraceptives, thyroid analogs, vitamin A derivatives, lithium, and withdrawal of steroid. There is little knowledge about the exact pathogenesis of ATRA-induced PTC. It is thought to increase the production of CSF and modify the lipid component of arachnoid villi causing reduced absorption of CSF.¹⁰ There is a progressive age-related decline in the RAR expression in the central nervous system explaining the reduced risk of PTC in the adult APL as compared to the pediatric patients.¹¹

A modified Dandy criterion is used for the diagnosis of PTC.⁴ The manifestations of PTC include headache, nausea,

vomiting, pulsatile tinnitus, diplopia, and papilledema, with a normal CSF composition and brain imaging. Progressive optic atrophy and even blindness may occur if it is left untreated. There have been reports that have confirmed that PTC may occur in the absence of papilloedema.¹² Visani et al. reported that PTC is a complication of ATRA therapy occurring predominantly in pediatric patients typically within 2 weeks of initiation of the treatment.¹¹ MR imaging of the optic nerves and pituitary gland may suggest the diagnosis of raised intracranial tension (ICT) such as flattening of the posterior sclera, swelling of the perioptic subarachnoid space, vertical tortuosity, and elongation of the optic nerve, squashed pituitary gland or empty sella.² However, these changes are visible only after few days of starting of clinical signs of raised ICT.

Tiamkao and Sirijirachai reported a case of PTC in a 35-year-old male after 2 weeks of starting ATRA 60 mg/day.¹³ Tanaka et al. reported a case of female with APML developing PTC on 11th day of starting ATRA.¹⁴ Vanier et al. described a similar case in a 4-year-old child.⁵ Similarly, Naithani et al. presented a report of PTC in a year old boy developing PTC on 12th day of instituting ATRA.⁶ Our case highlights the prospect of PTC while on therapy with ATRA even in the adult APML.

CONCLUSIONS

A strong clinical suspicion is indispensable to stop ATRA at the onset of neurotoxicity to prevent long-term complications. Furthermore, the decision to reinstitute ATRA should be taken at the right time to increase the chances of attaining CR.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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doi: 10.5455/2319-2003.ijbcp20141027

Cite this article as: Kapoor A, Kumar N, Nirban RK, Kalwar A, Kumar HS. A case report of all-trans retinoic acid induced pseudotumor cerebri in an adult patient of acute promyelocytic leukemia. *Int J Basic Clin Pharmacol* 2014;3:918-20.