Introduction

Pseudotumor cerebri (PTC) or Idiopathic intracranial hypertension (IIH) is a disorder of elevated intracranial pressure (ICP) without any evidence of infection, vascular abnormality, space occupying lesion, hydrocephalus or alteration of consciousness.[1] All-trans-retinoic acid (ATRA) has been widely used in the treatment of acute promyelocytic leukemia (APL).[2]

Cases of pseudotumor cerebri associated with all-trans-retinoic acid treatment in acute promyelocytic leukemia (APL) have been frequently described in pediatric patients.[3] But it is rare in adults.

Case Report

A 25-year-old female patient presented to our clinic with fever and bleeding gums of three weeks duration. The clinical examination was normal except for a body temperature of 38.5°C. Systemic examination revealed no abnormality.

Hematological investigations showed hemoglobin of 10.7 g/dl, platelet count 200000/mm³; white blood cell count of 2900/mm³, differential count 30% blast cells, 6% neutrophils, 64% lymphocytes. Coagulation profile was normal. D-dimer was 10000 ng/ml. Serum biochemistry showed lactate dehydrogenase 566 U/L, peripheral smear showed normocytic normochromic anemia, reduced total count with predominant lymphocytes with atypical cells and adequate platelet count. Bone marrow examination showed 84% blasts which were peroxidase positive with moderate cytoplasm indented to bilobed nuclei with immature chromatin. Flow cytometry was suggestive of acute myeloid leukemia – M3 with CD13, CD33, CD64, CD117, CD45 positivity and negative HLA DR. Real time PCR (Polymerase Chain Reaction) qualitative analysis revealed the presence of typical fusion transcript PML-RARA (bcr1type) in the cells. Chromosomal analysis carried out using bone marrow showed 50% with 46XX; t (15;17) and 50% with 46XX. Detection of translocation t (15;17) by FISH using bone marrow showed PML-RARA fusion signal in 90% of interphase cells.

The patient was started on treatment with ATRA45 mg/m² p.o. (80 mg/day) plus daunorubicin 100 mg/day for four days. After three weeks of induction chemotherapy, the patient started complaining of headache and diplopia. Neurological examination was non contributory. Fundus examination showed bilateral papilledema. Magnetic resonance imaging of the brain was normal. Cerebro spinal fluid (CSF) analysis was normal except for an elevated CSF pressure. Thus a diagnosis of PTC was
made. ATRA was stopped and the patient was started on anti cerebral edema measures and steroids. Headache and diplopia subsided in two weeks. ATRA was restarted after one week. The patient achieved complete remission (CR) after induction chemotherapy without any neurological sequela.

### Discussion

All-trans retinoic acid (ATRA) is used as differentiation therapy for acute promyelocytic leukemia (APL). Even though, ATRA is a well tolerated drug, some patients may develop complications like dry skin, retinoid acid syndrome, hypertriglyceridemia, sweet's syndrome, hyperleukocytosis, and rarely myositis. The pathogenesis of ATRA-induced PTC is less understood. The mechanism of neurotoxicity is thought to be similar to the pathogenesis of hypervitaminosis A. At higher doses of ATRA, retinoids enhances the production of CSF and alters the lipid constituents of arachnoid villi, disrupting the normal transport system and impeding the absorption of CSF at arachnoid villi. Warner et al. reported that CSF retinol levels were higher in patients with idiopathic intracranial hypertension (IIH) than in the subjects without IIH. A progressive age-related reduction of RAR expression in the central nervous system has also been postulated as a reason for less chance of PTC in the adult APL compare to the children.

Even though hallmark of PTC or IIH is papilledema, it can also occur in the absence of papilledema. MR imaging of the optic nerves and pituitary gland may be of value in the diagnosis of pseudotumor cerebri in the absence of papilledema. The absorption of CSF at arachnoid villi. Warner et al. reported that CSF retinol levels were higher in patients with idiopathic intracranial hypertension (IIH) than in the subjects without IIH. A progressive age-related reduction of RAR expression in the central nervous system has also been postulated as a reason for less chance of PTC in the adult APL compare to the children.

### Table 1: Details of previously reported cases of PTC after ATRA for APML in the literature

| Authors          | Patients no. | Age (years) | Sex | Dose of ATRA given | Day of onset of PTC | Outcome of PTC | Overall outcome | Death |
|------------------|--------------|-------------|-----|-------------------|---------------------|----------------|-----------------|-------|
| Colucciello et al.[15] | 1            | 30          | M   | 45 mg/m²/d        | 2 weeks             | Resolved       | CR              | Nil   |
| HY Chen et al.[16]  | 1            | 17          | F   | 45 mg/m²/d        | 6 weeks             | Resolved       | CR              | Nil   |
| Tanaka T et al.[17] | 1            | 21          | F   | 45 mg/m²/d        | 11 days             | Resolved       | CR              | Nil   |
| Tiamkao et al.[18] | 1            | 35          | M   | 60 mg/d           | 2 Weeks             | Resolved       | CR              | Nil   |
| Visani G et al.[19] | 1            | 16          | M   | 80 mg/d           | 31 days             | Resolved       | CR              | Nil   |
| Vanier et al.[20]  | 1            | 4           | M   | 45 mg/m²/d        | 21 days             | Resolved       | CR              | Nil   |
| Naithani R et al.[21] | 1           | 9           | M   | 40 mg/d           | 12 days             | Resolved       | CR              | Nil   |
| F Sano et al.[22] | 1            | 18          | M   | 45 mg/m²/d        | 23 days             | Resolved       | CR              | Nil   |
| Naderi S et al.[23] | 1            | 20          | F   | 80 mg/d           | 10 days             | Resolved       | CR              | Nil   |

CR: Complete remission, PTC: Pseudo tumor cerebri, ATRA: All trans retinoic acid, APML: Acute promyelocytic leukemia

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Anoop, et al.: ATRA induced pseudotumor cerebri

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