Pseudotumour cerebri – A Rare Complication of ATRA Based Treatment of Acute Promyelocytic Leukaemia

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Abstract:
Acute promyelocytic leukaemia is a highly curable subtype of acute myeloid leukaemia and about 90% of these patients have good chance of survival with current all transretinoic acid based arsenic tri oxide or chemotherapy. However, a rare complication, pseudotumour cerebri may arise following All Trans Retinoic Acid (ATRA) therapy, which may provide obstacle to continue this promising therapy. We present the case report of a young female patient with acute promyelocytic leukaemia treated with Arsenic trioxide (ATO) and ATRA that subsequently develop abrupt onset of lateral rectus palsy.

Keywords: Acute promyelocytic leukemia; Pseudotumour cerebri; All trans retinoic acid

Introduction:
In Acute Promyelocytic Leukemia (APL), previously called Acute Myeloblastic Leukaemia-M3, balanced translocation t (15;17) (q24.1; q21.1) is frequently seen. This rearrangement is seen up to 13 percent of recently diagnosed AML and is more specific for APL [1]. APL is the most malignant form of AML with a median survival of less than one month, if the patient is untreated [2]. A crucial component of therapy is ATRA, which promotes differentiation of malignant promyelocytes to mature neutrophils. But, ATRA has also been associated with different adverse effects, including skin lesion, reversible elevation in hepatic enzymes, abnormal lipid profile, hypothyroidism and headaches. Less frequently cerebral and myocardial infarction, corneal deposits secondary to hypercalcemia, scrotal ulcerations, sweet’s syndrome, Fournier’s gangrene, acute promyelocytic leukaemia differentiation syndrome, and pseudotumour cerebri is seen as an adverse effect of ATRA [3]. Pseudotumour cerebri is characterized by headache, vision loss, cranial nerve palsies & papilloedema without any change in cerebrospinal fluid composition, and no other cause of intracranial hypertension found on neuro imaging or other investigations [4]. For this reason, we describe the case report of an eighteen yrs. lady diagnosed as a case of Acute promyelocytic leukemia treated with All trans retinoic acid and arsenic trioxide, who developed left lateral rectus palsy and bilateral visual loss due to pseudotumour cerebri.

Case Report:
We describe the case of a previously healthy but obese 18yr old female (Fig: 1) who presented with fever, nose bleeding and abdominal pain of two weeks duration. On examination there were no remarkable findings except for pallor and bony tenderness, by this time she received three units of blood transfusion. The investigation were as follows: Hb was 7.2 g/dl, total count of 7.5 x 109/L, platelet count of 44 x109/L, atypical cells 88%. APTT patient 34 sec, control 30.0 sec, PT patient 15 sec, control13.0 sec. D-dimer 3 microgram/ ml, FDP 200 microgram/ml Renal and liver function tests were normal. Considering the possibility of hematological malignancy
a bone marrow examination was done which revealed hyperactive marrow with shift to left, majority of cells of which are abnormal promyelocytes having abundant granular cytoplasm, eccentric nuclei, single prominent nucleoli and loose chromatin suggestive of acute promyelocytic leukaemia (Fig:4,Fig : 5). Considering the devastating nature of this as well as promising outcome with early treatment patient was started on treatment with ATRA. Later Real time PCR qualitative analysis showed Promyelocytic leukemia/ retinoic acid receptor alpha (PML- RARA) 68 % which strengthened the diagnosis. She got induction therapy with arsenic trioxide 10mg IV and all transretinoic acid (45mg/ m2 in 2 divided doses). On day eleven after starting treatment, patient developed headache and double vision. Subsequently, developed progressive visual impairment associated with vomiting but no history of seizure. Neurological examination showed left lateral rectus palsy. Fundus examination showed bilateral papilloedema (Fig :2). No other focal neurological deficits were evident. She was evaluated with CT head and MRI Brain and both were normal. MR Venogram was also done which ruled out cerebral venous sinus thrombosis. Suspecting a possibility of pseudotumourcerebri, we proceeded with CSF study which showed an opening pressure of 300 mm of water. The biochemical and cytological analysis of the CSF found to be normal. She was started on treatment with tablet acetazolamide 250 mg 4 times daily following which she improved dramatically. Dose modification of all Trans retinoic acid was done since...
the patient already reached day 44 of ATRA. Re aspiration of bone marrow carried on to see remission which showed complete morphological remission. So ATRA stopped for few days with a aim to reduce intracranial pressure more rapidly (Fig: 3). Usually cessation of ATRA leads to resolution of raised Intracranial pressure (ICP) within one to two months, including resolution of headache and disc edema[5].

Fig.-5: Bone marrow picture on diagnosis

Discussion:
Pseudotumourcerebri is an uncommon disorder with a yearly incidence of about 1/100,000 population [6,7]. These groups of patient present with headache, nausea, vomiting, pulsatile tinnitus and also diplopia. It can cause swelling of the optic disc, which may lead to progressive optic atrophy and blindness, if remain untreated [8].

Women of childbearing age is commonly affected with Pseudotumourcerebri. Probably obesity a risk factor for pseudotumourcerebri, on the basis of case-control studies. Lots of drugs are associated with pseudotumourcerebri like growth hormone, hypervitaminosis A and tetracyclines [9-11]. Clinical presentation of Pseudotumourcerebri are Headache (92 percent), Transient visual obscurations (72 percent), Pulsatile tinnitus (60 percent), Retrobulbar pain (44 percent), Diplopia (38 percent) and Sustained visual loss (26 percent). Recently modified Dandy criteria is used to diagnosis pseudotumourcerebri. This condition is treated with acetazolamide, loop diuretics, topiramate and serial lumbar punctures. In refractory cases surgery is required [12]. The pathogenesis of ATRA-induced Pseudotumourcerebri is less known. At higher doses of ATRA, the production of CSF is enhanced and alters the lipid constituents of arachnoid villi, disrupting the normal transport system as well as impending the absorption of CSF at arachnoid villi. Warner et al. reported that CSF retinol levels were much high in patients with idiopathic intracranial hypertension (IIH) than in the people without IIH [13].

The onset of symptoms was about 14 days (range 7 days to 10 months) after starting therapy. It was seen both during induction (78% cases), during consolidation (13%) and maintenance (33% cases). When patients with promyelocytic leukemia on treatment with ATRA develop headache and blurring of vision the possibility of sinus venous thrombosis versus idiopathic intracranial hypertension is considered [14]. Similarly, our patient developed features of idiopathic intracranial hypertension during induction phase of chemotherapy, her MR The venogram was normal, pseudotumourcerebri was considered as a diagnosis of exclusion and later CSF study confirmed the same. In patients with pseudotumourcerebri, whether ATRA should be withheld or not is clear. In our patient we treated with acetazolamide and continued the ATRA throughout the induction therapy. ATRA was stopped for a few days when bone marrow achieved full morphological remission at day forty four of induction therapy.

Conclusion:
Patient with acute promyelocytic leukemia on treatment with All trans retinoic acid (ATRA) should be carefully evaluated for the development of pseudotumourcerebri specially if complaints of decreased visual acuity, headache and diplopia with negative imaging findings. They should be evaluated with lumbar puncture, imaging and venography to establish pseudotumourcerebri. Early detection of pseudotumourcerebri will help to prevent future complication like optic atrophy. In addition, withholding treatment with All trans retinoic acid is not essential in most cases unless vision is seriously threatened.

References


