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ALL-TRANS-RETINOIC ACID AND PSEUDOTUMOR CEREBRI IN A YOUNG ADULT WITH ACUTE PROMYELOCYTIC LEUKEMIA: A POSSIBLE DISEASE ASSOCIATION

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ABSTRACT

Pseudotumor cerebri or *idiopathic intracranial hypertension* is a neurological syndrome characterized by signs and symptoms of intracranial hypertension without clinical or radiological evidence of infective or space occupying lesions. Iatrogenic factors are frequent; in particular, cases of pseudotumor cerebri associated with all-*trans*-retinoic acid treatment in acute promyelocytic leukemia (APL) have been frequently described in pediatric patients. We report on a case observed in an older patient (young adult age) and give diagnostic and therapeutic guidelines.

Key words: pseudotumor cerebri, all-trans-retinoic acid, acute promyelocytic leukemia, therapy, retinoids

All-*trans*-retinoic acid (ATRA) is able to induce complete remission of acute promyelocytic leukemia (APL) in more than 80% of cases both in adults and in children.[1-3] ATRA is considered a safe agent. Nevertheless, adverse reactions have been observed to affect various organs and districts (skin, liver, lung, blood, metabolism, heart and vascular system, central nervous system).[1-3] Some of these have been described only in subjects affected by APL, whereas others, such as pseudotumor cerebri (PTC), are possible in other conditions. In this context, we describe a case of PTC occurring in a young adult patient and review the literature.

Case Report

R.S., a 16-year-old male presented in January 1994 with bleeding, macrohematuria and fever (38.5°C). Blood tests showed: hemoglobin 8.6 g/dL; platelets 23×10^9/L; WBC 1.09×10^9/L, differential count: 60% blast cells (promyelocytes with Auer rods), 6% neutrophils, 34% lymphocytes; LDH 430 U/L; PT 60%; FDP 1,280 µg/mL. Bone marrow biopsy, karyotype examination and molecular biology were compatible with a diagnosis of APL.[4] The patient was treated with ATRA 45 mg/m^2 p.o. (80 mg/day, total dose) plus daunorubicin 100 mg/day for three days and 60 mg/m^2 on day 4.

Thirty-one days after beginning treatment the patient started complaining of headache, diplopia and tinnitus. WBC count was 5.8×10^9/L and platelets were 197×10^9/L; bone marrow biopsy and karyotype confirmed achievement of complete remission. Neurological examination was negative. Ophthalmological examination documented a visual acuity of 9/10 in both eyes. Pupillary reactions were normal and slitlamp examination results were normal. Fundus oculi examination showed that both optic disks were blurred and elevated; in addition, we observed venous engorgement, tortuous vessels and scattered, flame-shaped peripapillary hemorrhages. Golman perimetry revealed bilateral enlargement of the blind spot and a concentric contraction of the peripheral field. Visual evoked potentials (*pattern reversal*) were normal.[5] A cerebral computed tomography (CT) examination per-

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formed the same day and 15 days later failed to detect the presence of space occupying lesions or ventricular space enlargement. Diagnosis of PTC was therefore made. ATRA was stopped on the day of onset of intracranial hypertension symptoms and the patient was treated with acetazolamide. Because of a scarce response to the pharmacological treatment, a lumbar puncture was performed after 15 days. It showed a strong elevation of cerebrospinal fluid (CSF) pressure (310 mm of water), and the fluid was clear and colorless in appearance. Cytochemical and microbiological evaluation was negative. A total amount of 28 cc of CSF were removed, leaving final CSF pressure of 150 mm of water. This procedure was followed by prompt clinical improvement. No recurrence of symptoms was noted and no other ATRA-related side effects were observed. The patient has been in continuous complete remission for 17 months; he completed the chemotherapy protocol, including autologous bone marrow transplantation, without any neurologic problem.

Discussion

PTC is a diagnosis of exclusion and a confirmed diagnosis requires the following widely accepted criteria:[6]

1. signs and symptoms of intracranial hypertension;
2. awake and alert patient;
3. lack of focal neurological signs except for those referable to intracranial hypertension and those lacking in locational value, such as VI cranial nerve (abducens) palsy;
4. normally-sized and shaped cerebral ventricles and absence of space occupying lesions on neuroimaging studies (the finding of small ventricles and of *empty sella* is, however, consistent with the diagnosis);
5. documented elevation of cerebrospinal fluid pressure (200 mm of water in non obese and 250 mm H_2O in obese patients[6]);
6. normal composition of cerebrospinal fluid;
7. no other identifiable causes of intracranial hypertension.

A correct diagnostic approach consists of physical examination and computerized tomography (CT); nuclear magnetic resonance (NMR) is not considered a mainstay for the diagnosis of PTC since the shape of ventricular enlargement is adequately described by CT. Lumbar puncture could be helpful to confirm diagnosis. The case described here is a typical example of PTC arising in a young adult (16 years old) following treatment with ATRA, without the simultaneous use of other drugs with a potential risk of inducing PTC; furthermore, clinical and instrumental documentation satisfied all accepted criteria for a diagnosis of PTC, as listed above.

The pathogenesis of ATRA-induced PTC still remains to be established. It could be seen as a manifestation of vitamin A overdose; high doses of ATRA induce an over stimulation of RAR-α (retinoic acid receptor), which proves to be helpful in gaining control over the leukemic myeloid clone (in which the receptor is expressed in an aberrant form) but which is frankly *pathological* in other tissues, including the central nervous system. In fact, the existence of retinoid receptors and related cytoplasmic binding proteins has been demonstrated in the nervous system.[7,8] The retinoids seem to have a fundamental morphological action in the nervous system.[9] In particular, ATRA is involved in fundamental aspects of the development of the central nervous system.[9] A change in the metabolic pathways related to retinoids after embryonic development, or an action exerted by retinoids not at the level of the nerve cells – neurons and glial cells – but on the structures of the blood-brain barrier or on the structures related to the production and drainage of cerebrospinal fluid (choroid plexuses and arachnoid villi, respectively) could be postulated.

An association between ATRA and PTC was previously described in ten pediatric patients treated for APL with ATRA at doses ranging from 45 to 80 mg/m^2/day.[10-12] PTC was also reported in children treated with ATRA for neoplasms other than APL, whereas clinical trials performed on young adults or adults treated with higher dosages (up to 150 mg/m^2/day) for pathologies other than APL did not show any evidence of toxicity on the central nervous system. At present, the appropriate management

of patients who experience this syndrome is still unclear. Major analgesic drugs, such as codeine or morphine sulphate, or temporary ATRA discontinuation in non responding cases may help in reducing the severe headache, nausea and vomiting; acetazolamide or furosemide is recommended to reduce CSF pressure, as is lumbar puncture with removal of CSF in order to maintain a final CSF pressure of no more than 150 mm of water.

An age-related change in RAR response to retinoid stimulation in the central nervous system, or a progressive age-related reduction of RAR expression in the central nervous system could be postulated. However, the case described highlights the possibility of a diagnosis of PTC in APL patients no longer in the pediatric age, suggesting that PTC should be considered at all ages in the diagnostic procedure for APL patients submitted to ATRA treatment.

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