Pseudotumor Cerebri Caused by All-Trans-Retinoic Acid : A Case Report

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Abstract

Pseudotumor cerebri is a condition characterized by increased intracranial pressure with normal cerebrospinal fluid composition. It is usually associated with many medical conditions and drugs. It has been reported that all-trans-retinoic acid can induce pseudotumor cerebri. The authors report a 35-year-old patient diagnosed with acute promyelocytic leukemia who developed pseudotumor cerebri after receiving all-trans-retinoic acid. The patient was treated with 60 mg/day of all-trans-retinoic acid. Two weeks later, she had severe headache and blurred vision. The neurological examination revealed papilledema and decreased visual acuity. Other physical examinations were unremarkable. Brain CT was normal. Additionally, lumbar puncture was performed and the CSF finding was normal except for high CSF pressure. According to modified Dandy criteria, the diagnosis was pseudotumor cerebri. The patient's symptoms disappeared after all-trans-retinoic acid was discontinued. To our knowledge, this is the first case report in Thailand.

Key word : Pseudotumor Cerebri, All-trans-retinoic Acid, Acute Promyelocytic Leukemia

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Pseudotumor cerebri is a well-defined disorder characterized by increased intracranial pressure with papilledema, normal or small ventricles and normal cerebrospinal fluid (CSF) composition (1). Pseudotumor cerebri can be diagnosed by using modified Dandy criteria (Table 1)(2). Many case series have reported conditions and drugs associated with pseudotumor cerebri (Table 2)(3). The drugs include antibiotics (tetracycline, nalidixic acid, nitrofurantoin), indomethacin, oral contraceptive

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Table 1. Modified Dandy criteria for the diagnosis of pseudotumor cerebri.

Signs and symptoms of increased intracranial pressure.
Absence of localizing findings on neurologic examination.
Absence of deformity, displacement, and obstruction of the ventricular system and otherwise normal neurodiagnostic studies except for increased cerebrospinal fluid pressure.
Awake and alert patient.
No other cause of increased intracranial pressure present.

Table 2. Drug induced pseudotumor cerebri.

Antibiotics (tetracyclines, nalidixic acid, nitrofurantoin, sulfamethoxazole).
Steroids and oral contraceptives.
Psychiatric drugs (chlorpromazine, fluoridazine, lithium carbonate).
Miscellaneous (amiodarone, etretinate, perhexiline maleate, indomethacin, phenytoin).

pills, vitamin A and all-trans-retinoic acid (ATRA). ATRA has been used to treat acute promyelocytic leukemia (APL) since 1986 and a high complete remission rate ranging from 75-90 per cent has been achieved[4]. Adverse effects of ATRA include retinoic acid syndrome, renal failure and thrombosis. Pseudotumor cerebri is also one of the ATRA side effects and is more frequently found in children[5]. We report a 35 year-old APL patient who developed pseudotumor cerebri after treatment with ATRA.

CASE REPORT

A 35 year-old woman was diagnosed with APL. Her height was 160 centimeter and her weight was 48 kilograms. She was treated with 60 mg/day of ATRA. Two weeks later, she developed severe headache and blurred vision. The headache gradually increased in intensity for three days. The physical examination revealed papilledema and decreased visual acuity (20/50) in both eyes and normal visual field. Other physical examination were within normal limits. Complete blood count revealed: white blood cell count 18600 cells/mm^3, platelet count 118000 cells/mm^3. There were 79 per cent promyelocytes, 2 per cent neutrophils, 9 per cent lymphocytes and 10 per cent monocytes. Brain CT scan was normal. CSF pressure was 300 mm of water, protein was 31 mg/dl. The CSF and blood sugar ratio was 50 per cent. Additionally, there was no cell found in the CSF. Other investigations including blood chemistry, urine examination and chest-X-ray were unremarkable. The diagnosis of pseudotumor cerebri was made according to modified Dandy criteria. ATRA was then discontinued. One week after the patient stopped taking ATRA, her symptoms disappeared.

DISCUSSION

Pseudotumor cerebri is characterized clinically by modified Dandy criteria. This condition is intracranial hypertension due to an alteration in hydrodynamic of CSF[6]. There were reports that many medical conditions and drugs such as tetracycline and vitamin A were associated with pseudotumor cerebri. We reported a patient whose clinical manifestation and CSF finding met the modified Dandy criteria for diagnosis of pseudotumor cerebri. The patient's symptoms disappeared with no treatment within 1 week after ATRA withdrawal. ATRA has been reported to induce pseudotumor cerebri[4, 5,7-13]. The other side effects are retinoic acid syndrome, renal failure and thrombosis. ATRA-induced pseudotumor cerebri occurred frequently in children and usually associated with hyperleucocytosis condition[4]. However, the patient we reported had normal white blood cell count while pseudotumor cerebri was occurring. Additionally, ATRA- induced thrombosis is associated with hyperleucocytosis because of increased blood viscosity. Therefore venous sinus thrombosis was excluded.

Mahmoud et al[5]reported pseudotumor cerebri after ATRA administration in APL patients. Five of the nine patients had pseudotumor cerebri and two of them also had hyperleucocytosis. In this report, the patients with hyperleucocytosis developed pseudotumor cerebri earlier than the patients without hyperleucocytosis, the patients with and without hyperleucocytosis developed pseudotumor cerebri within 5 days and 15 days, respectively. The pathogenesis of ATRA induced pseudotumor cerebri is unclearly known. Jones et al[14], Voorhees and Orfanos[15] suggested that ATRA may effect triglyceride and cholesterol metabolism. In addition, it could alter the lipid constituents of the arachnoid villi, disrupting normal transport system and impeding absorption of CSF at the arachnoid villi.

After pseudotumor cerebri has been diagnosed, the causative drugs should be stopped imme-

diately. The aim of treatment is to preserve visual acuity. If the symptoms do not improve, lumbar puncture may be helpful. Diuretic and carbonic anhydrase inhibitor may be useful because they could decrease CSF pressure. If visual acuity deteriorates, there might be a role for surgery. The surgical treatment includes lumbar-peritoneal shunts and optic nerve sheath fenestration(6).

SUMMARY

It has been reported that all-trans-retinoic acid can induce pseudotumor cerebri. This is often used to treat acute promyelocytic leukemia. Physicians should be aware of this side effect. The drug should be discontinued immediately if pseudotumor cerebri occurs in order to prevent severe complications.

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ซูโดทูเมอร์ ซีรีไบร จากกรดออล–ทรานส์–เรติโนอิค : รายงานผู้ป่วยหนึ่งราย

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Pseudotumor cerebri เป็นภาวะที่มีความดันในสมองสูงขึ้นโดยที่ส่วนประกอบของน้ำไขสันหลังปกติ มีโรคและยาหลายชนิดที่สามารถทำให้เกิดภาวะผิดปกตินี้ได้ ยา all–trans–retinoic acid เป็นยาตัวหนึ่งซึ่งเคยมีรายงานว่าทำให้เกิด pseudotumor cerebri ผู้วิจัยรายงานผู้ป่วยหญิงอายุ 35 ปีที่ได้รับการวินิจฉัยว่าเป็นมะเร็งเม็ดเลือดขาวชนิด promyelocyte และได้รับการรักษาด้วย all–trans–retinoic acid หลังได้รับยา 2 สัปดาห์ ผู้ป่วยมีอาการปวดศีรษะและตามัว การตรวจทางระบบประสาทพบว่าประสาทตาบวมและการมองเห็นลดลง ผลการตรวจเอกซเรย์คอมพิวเตอร์สมองปกติ การตรวจน้ำไข–สันหลังอยู่ในเกณฑ์ปกติยกเว้นมีความดันสูง ผู้ป่วยได้รับการวินิจฉัยว่าเป็น pseudotumor cerebri จาก all–trans–retinoic acid ผู้ป่วยมีอาการดีขึ้นหลังจากหยุดยา รายงานนี้เป็นผู้ป่วยรายแรกของประเทศไทย

คำสำคัญ : Pseudotumor Cerebri, All–trans–retinoic Acid, Acute Promyelocytic Leukemia

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