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Case Report

Pediatric recurrent intracranial hypertension secondary to All-Trans Retinoic Acid treatment in a patient with acute promyelocytic leukemia: value of retinal nerve fiber layer thickness in management

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ABSTRACT

Background. All-trans retinoic acid (ATRA) is an essential agent in the treatment of acute promyelocytic leukemia (APL). However, careful monitoring is required due to its potential side effects, particularly intracranial hypertension (IH).

Case Presentation. Here, we report a 15-year-old girl who presented with headache, blurred vision, vomiting, and was found to have left homonymous hemianopsia and an acute cerebral infarct. Etiological investigations revealed acute promyelocytic leukemia and treatment with ATRA was initiated. However, this treatment was complicated by repetitive episodes of IH, which improved with discontinuation of ATRA but recurred whenever reinitiation was attempted. Despite this side effect, the patient was able to complete the planned ATRA course under medical treatment of IH, guided by retinal nerve fiber layer (RNFL) thickness measured using optical coherence tomography (OCT).

Conclusions. Changes in papilledema were detected on OCT earlier than on clinical examination. This case illustrates the reversibility of IH secondary to ATRA therapy, the feasibility of completing ATRA treatment despite the side effect of IH, the importance of medical treatment for IH in combination with appropriate dose adjustments, and the accuracy and convenience of RNFL thickness as a biomarker for treatment efficiency. Managing IH in the context of a chronic systemic disorder requires a collaborative approach, close follow-up, and individualized management.

Key words: acute promyelocytic leukemia, ATRA, intracranial hypertension, papilledema, retinal nerve fiber layer thickness.

All-trans retinoic acid (ATRA), a metabolite of vitamin A, has been shown to significantly improve outcomes for patients with acute promyelocytic leukemia (APL), in which the prognosis was poor before the introduction of this agent.[1] APL's response rate to ATRA is high, but of limited duration; its combination with arsenic trioxide (ATO) and chemotherapy

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prolongs remission and results in a 10-year overall survival rate of over 85%.[1] ATRA's potential side effects include intracranial hypertension (IH), and pseudotumor cerebri syndrome, occurring in up to 13% of pediatric and 2-7% of adult patients.[2] This can lead to interruption of treatment. Studies have reported that treatment can be carried out by discontinuing ATRA and restarting it at lower doses.[3]

Early diagnosis and appropriate management of IH secondary to ATRA are critical for the success of treatment in APL. IH can present with headache, visual field defects, and cranial nerve palsies. A definitive diagnosis is made by measuring intracranial pressure via lumbar puncture (LP).[4] The IH diagnostic criteria, which provide a standardized framework for diagnosis, are provided in Supplementary Table I.[4] However, LP carries a certain risk in APL patients due to their tendency for bleeding; therefore, clinical follow-up of symptoms and opthalmological examination findings are important in practice, although the assessment of the fundus can be challenging in young children. Noninvasive imaging methods such as ocular ultrasound, fundus autofluorescence, and optical coherence tomography (OCT) are increasingly being used as complementary tools.[5]

Only a few reports have been published on the management of recurrent IH in pediatric patients under ATRA treatment. We describe the treatment details of a case with APL and recurrent IH and underline the use of retinal nerve fiber layer (RNFL) thickness as a biomarker.

Case Presentation

A 15-year-old girl presented with a one-month history of left frontal headache associated with blurred vision and relieved by vomiting. Her vision returned to baseline once the pain subsided. She reported recurrent herpes labialis infections for the previous three months, as well as loss of appetite, malaise, and a 7 kg weight loss in the month prior to presentation. The family history was positive for migraine in her aunt and grandmother. Physical and ophthalmological examination findings were unremarkable except for left homonymous hemianopsia. The patient's body mass index (BMI) was 25 kg/m^2 at the 73rd percentile. The complete blood count revealed pancytopenia (white blood cell: 1.2×10^3/μL, neutrophil count: 0.2 ×10^3/μL, hemoglobin: 8.8 g/dl, platelet count: 74 ×10^3/μL). Two atypical cells were detected on the peripheral blood smear. Brain magnetic resonance imaging (MRI) revealed an acute infarction in the territory of the right posterior cerebral artery (PCA) (Supplementary Fig. 1). MR angiography demonstrated that the right distal PCA (P2 segment) was significantly thinner and showed poorer branching compared with the left. Further laboratory investigations for autoimmune and infectious etiologies, including viral serology (herpes simplex virus, varicella zoster virus, human immunodeficiency virus, Epstein-Barr virus, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), antinuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA), antiphospholipid antibodies, and antineutrophil cytoplasmic antibodies (ANCA), were negative. Bone marrow aspiration revealed a 95% predominance of blast cells and flow cytometric analysis was compatible with APL-M3, confirmed by cytogenetic analysis showing t(15;17). Cerebrospinal fluid (CSF) protein (23 mg/dL), glucose (86 mg/dL), and opening pressure (23 cm H_2O) were within normal ranges. CSF cytology revealed no atypical cells. Treatment with ATRA (25 mg/m^2/day) and ATO (0.15 mg/kg/day) was started. The course of the treatment and clinical parameters of the patient's follow-up are shown in Fig. 1.

On day 2 of the second course of ATRA, the patient complained of an itchy, raised maculopapular eruption on the upper limbs that quickly spread to the trunk and lower limbs, and persisted despite the administration of antihistamines and systemic steroids. Skin

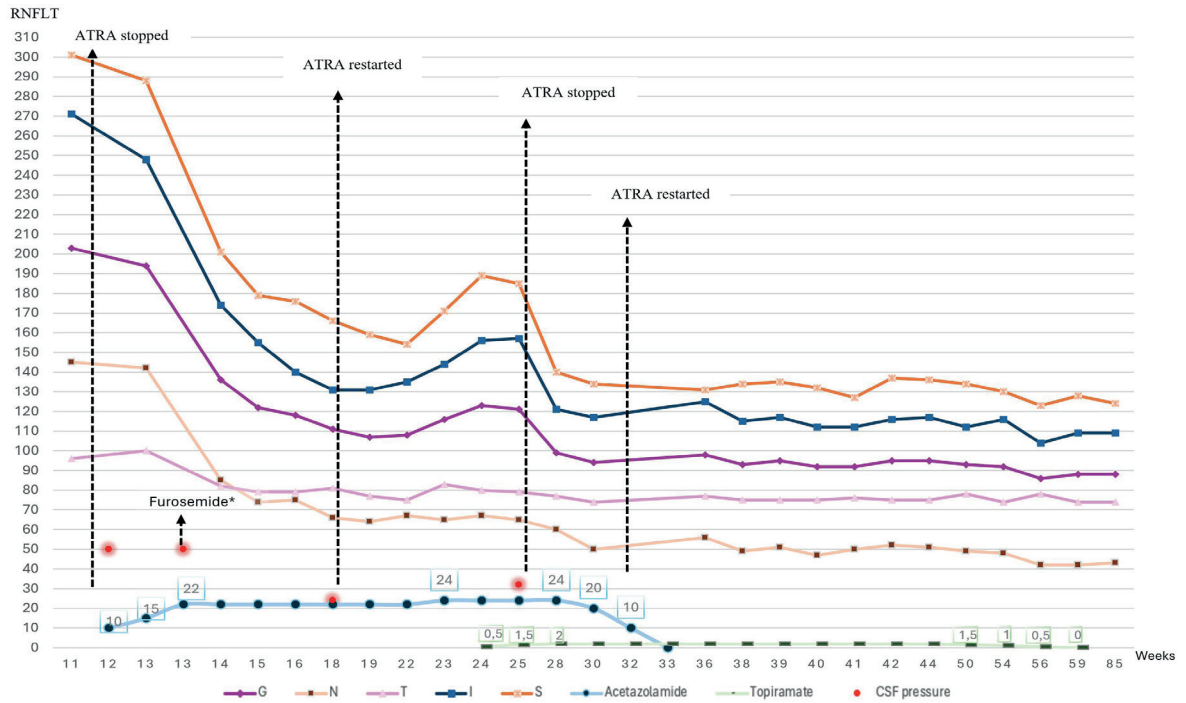


Fig. 1. Changes in average retinal nerve fiber layer thickness over time weeks and treatment.

ATRA, All-trans retinoic acid; CSF, cerebrospinal fluid; RNFLT, retinal nerve fiber layer thickness. Retinal regions for RNFLT G, Global; N, Nasal; T, Temporal; I, Inferior; S, Superior. Furosemide*: 1 mg/kg single dose. Acetazolamide and topiramate dosage units: mg/kg/day. CSF pressure unit: cmH_2O.

biopsy was compatible with drug eruption. ATRA and ATO were discontinued. The rash disappeared within 4-5 days. Desensitization was performed prior to restarting the two drugs, and treatment was restarted after 2 weeks.

At the end of the third course of ATRA treatment, she presented with headache, vomiting, a new-onset visual field defect in the right eye, and expansion of the previous visual field defect on the left side. Bone marrow aspiration was normal. Ophthalmic examination revealed grade 3 papilledema (Fig. 2) and OCT confirmed thickening of the RNFL (Fig. 3). Brain MRI and MR venography showed no significant findings except for chronic infarction. On LP, the opening pressure was too high to measure, and the closing pressure was 30 cm H_2O. CSF protein (23.7 mg/dL) and glucose (65 mg/dL) levels were normal; no atypical cells were observed on cytology. The cumulative ATRA dose was determined as 3,360 mg, based on a daily dose of 25 mg/m² for a body surface area of 1.6 m². The patient developed symptoms of intracranial hypertension at the end of the third course of ATRA intake, which may suggest the impact of cumulative toxicity of the drug on the clinical picture. Acetazolamide (10 mg/kg/day) was started, and ATRA was stopped. The headache regressed in 2 days, while metabolic acidosis that developed on day 6 was treated with oral sodium bicarbonate. Because the right-sided visual field defect did not regress and fundus findings did not improve, a therapeutic LP was performed on the 7th day of treatment, where the CSF opening pressure was again not measurable and the closing pressure was 18 cm H_2O. The dose of acetazolamide was increased to 22 mg/kg/day, and a single dose of furosemide (1 mg/kg) was given. The right sided visual field defect regressed after one week. The papilledema regressed to grade 2, and the thickness of the RNFL decreased within one week. The dose of sodium bicarbonate was increased according to the metabolic acidosis (serum HCO_3^- values). After two weeks, the

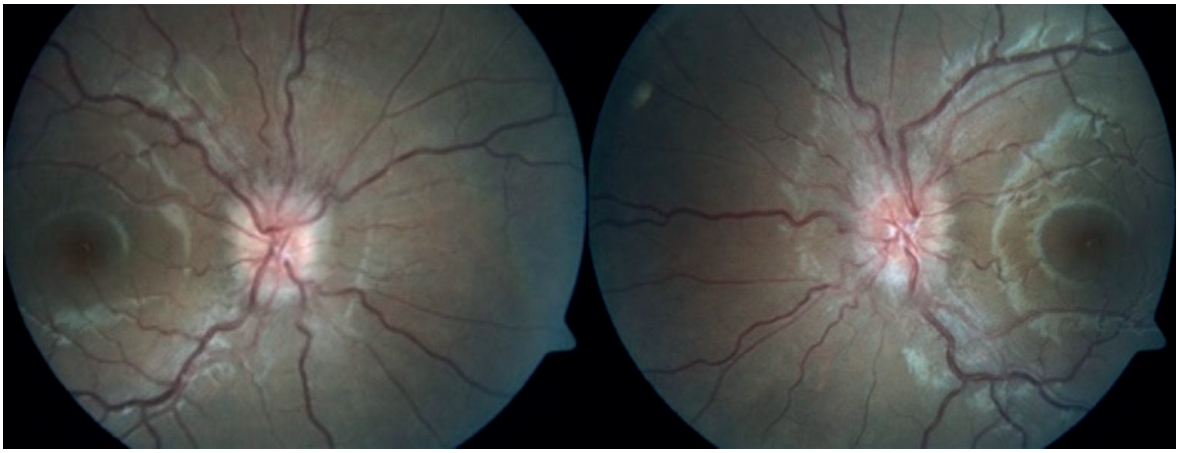


Fig. 2. Grade 3 bilateral papilledema. The optic disc margins are elevated in all quadrants. Circumferential halo is seen, some of the vessels are obscured while leaving the optic disc.

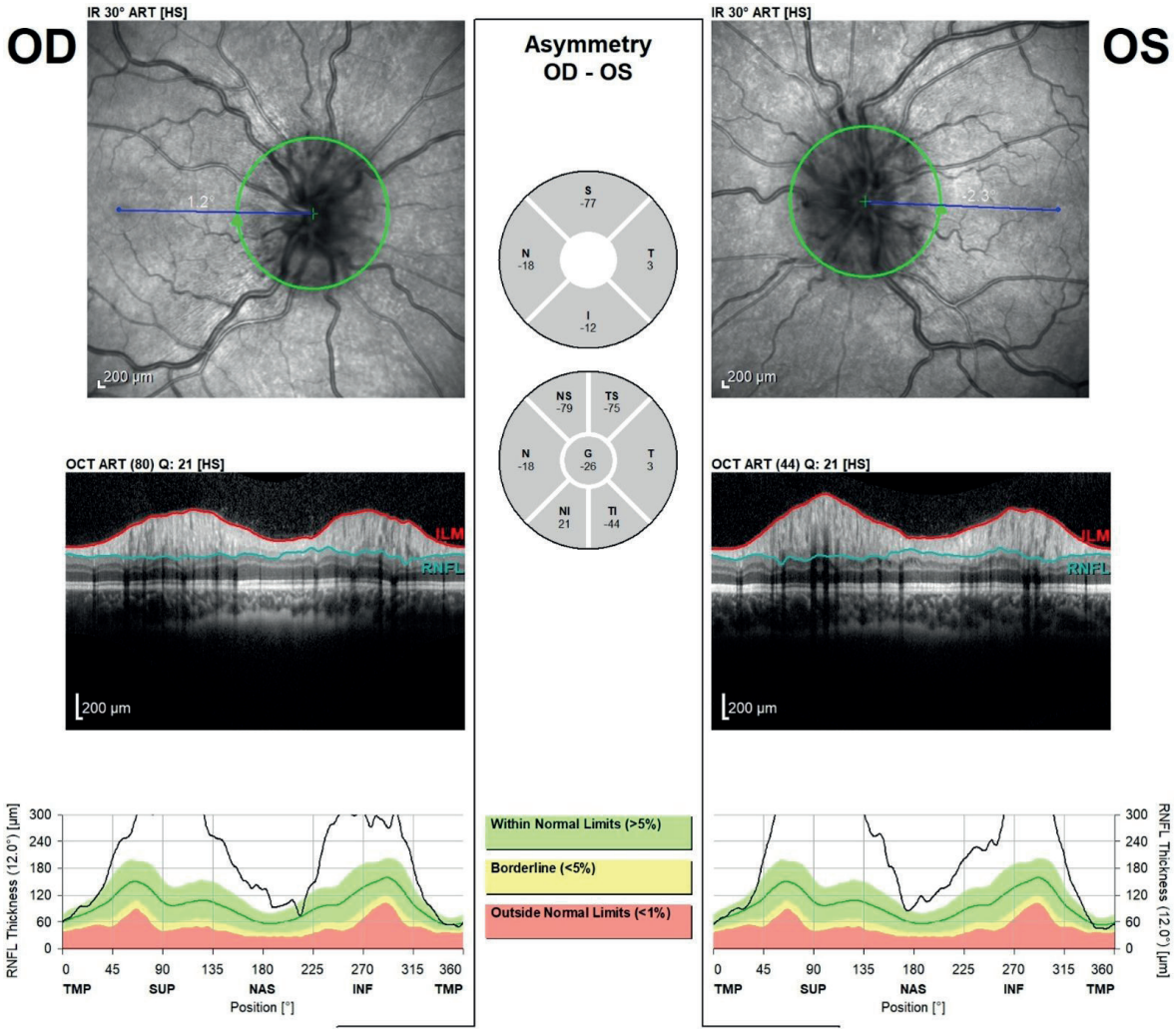


Fig. 3. Optical coherence tomography demonstrates marked thickening of the retinal nerve fiber layer (RNFL). The RNFL thickness shown in graphics is above normal limits. Green shows the normal RNFL limits. RNFL thickness below normal limits is represented with yellow (borderline) or red (outside normal limits).

papilledema regressed to grade 1-2. ATRA was restarted at half-dose and increased to the full dose after one week.

After day 12 of the current admission and before the fourth course of ATRA, bone marrow aspiration and LP were repeated to assess CNS remission and intracranial pressure. The CSF results were normal (pressure 24 cmH_2O), and ATRA was restarted at half dose, with a plan to increase to full dose after three days. One month later, the patient complained of worsening headaches and vomiting. Although no papilledema was observed, OCT findings revealed increased RNFL thickness and convolution of retinal blood vessels. Repeated brain MRI and venography were normal. Topiramate (0.5 mg/kg/day) was added to acetazolamide. A week later, grade 1-2 papilledema and increased RNFL thickness were observed. The topiramate dosage was increased. However, the ophthalmologic examination two weeks later revealed grade 2 papilledema. The opening and closing CSF pressures were 32 and 21 cm H_2O, respectively. Topiramate was increased to 1.5 mg/kg/day, ATRA was discontinued, and weekly detailed eye examinations were performed. The RNFL thickness was the first finding to show improvement (in week one), the papilledema regressed by week three, and pallor on the nasal side of the optic discs was observed by week four. ATRA treatment was restarted.

After two months, optic disc pallor was more marked, but RNFL thickness was normal. Acetazolamide was tapered off over five weeks. Topiramate was given for one more month after the last ATRA treatment and discontinued within two months during follow-up.

The patient's planned 7-month, seven-course chemotherapy was completed without other complications over a total of 11 months. There was no relapse of IH and APL during a 2 year-follow-up.

Informed consent was obtained for publication.

Discussion

Acute promyelocytic leukemia is a unique subtype of acute myeloid leukemia (AML) in which the ATRA/ATO combination has transformed a frequently fatal disease into one with a high cure rate. IH is a known complication of ATRA and was reported to be 18% in a single-center study from our country.[1,6] There are few reported cases of recurrent IH after reinitiation of ATRA in the literature.[2] Montesinos et al.[2] found an incidence of IH of 3.1% in all age groups and recurrence of IH despite discontinuation of ATRA in 28% of cases. APL accounts for 5-10% of pediatric AML cases.[1] IH risk has been found to be high in pediatric patients, especially during the first 2-3 weeks of APL induction therapy regimens.[7] According to the literature, cessation of ATRA is sufficient to resolve IH in approximately 30% of patients.[2] In others, drugs such as acetazolamide or topiramate or therapeutic LP may relieve the signs and symptoms, as in our patient.[1] The treatment should be tailored according to the patient's presentation, but reliable parameters are needed for follow-up. Papilledema can last up to 3 months, and treatments like acetazolamide may require adjustments for up to 6 months in IH.[8-10] As in our patient, recurrent LP or add-on treatment may be necessary. With improvement in symptoms, ATRA treatment can be resumed. Previously reported pediatric IH cases and their characteristics, as well as the distribution of IH in APL case series are shown in Table I.

A recent study[11] reported that vitamin A derivatives were responsible for 16.2% of cases of drug-induced IH, which is mostly caused by acne medications. These findings indicate that caution should be exercised with regard to IH when using vitamin A and its derivatives for any purpose.

This case illustrates the challenge faced in managing IH in a malignant disease requiring ATRA treatment. Our patient had multiple problems due to her disease: the presentation

of APL with ischemic infarction is very rare.[12] In our patient, the cerebrovascular complication of APL resulted in visual field defects observed at the time of diagnosis. Their presence complicated the distinction of visual impairment caused by IH. Although APL is a disease prone to thrombosis, the IH due to ATRA is not the result of venous thrombosis. ATRA increases the production of CSF and alters the lipid structure of the arachnoid villi, resulting in impaired CSF reabsorption.[1] On the other hand, IH secondary to intracranial leukemic infiltration has also been reported under ATRA treatment.[13] Therefore, differential diagnosis is important for treatment and follow-up.

Monitoring of IH is particularly important in cases with recurrent IH. Ophthalmological examination, a practical and non-invasive method, is essential.[5] Imaging findings are not sensitive to IH: as in our patient, MRI may be normal and does not reflect changes in IH immediately.[14] Measurement of CSF pressure is accurate but requires an invasive procedure. Therefore, sensitive and reliable biomarkers are needed for the detection of IH. In our patient, relying only on symptoms and papilledema only would not have given the chance of adequate and timely treatment, and complications of IH could have developed. According to our experience, measuring RNFL thickness by OCT provides early and objective information.[5] In the future OCT may also be used to measure three-dimensional optic nerve head parameters to distinguish IH from other optic neuropathies.[14]

In our country, OCT is available in training hospitals and university hospitals.

Conclusion

Children with APL treated with ATRA need close follow-up for IH. OCT is helpful in diagnosis, follow-up, and treatment decisions. IH can be resolved, and vision can be preserved by adjusting ATRA doses and administering appropriate drug treatment for IH within an individualized approach.

Supplementary materials

Supplementary materials for this article are available online at https://doi.org/10.24953/turkjpediatr.2026.6693.

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Ethical approval

Since this is a case study, ethical committee approval has not been obtained. Informed consent has been obtained from the family.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: PY, DY, GH; data collection: PY, GFY, SA; analysis and interpretation of results: PY, GFY, ŞÜC, GH; draft manuscript preparation: PY, DY, GH. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

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Conflict of interest

The authors declare that there is no conflict of interest.

Table I. All-Trans retinoic acid induced intracranial hypertension in pediatric acute promyelocytic leukemia: case characteristics and series distribution.

References	IH	LP	Age (y)	ATRA dose mg/m^2	Days¶	ATRA treatment during IH	Treatment for IH	Outcome
Smith et al.[15]	Definite	+	6	80	7-10	i+r	NA	CR
Mahmoud et al.[16]	NA	NA	NA	45	3	c	NA	CR
	NA	NA	NA	45	3	c	NA	Died
	NA	NA	NA	45	3	d	NA	CR
	NA	NA	NA	45	13	d	NA	CR
	NA	NA	NA	45	17	d	NA	CR
Varadi et al.[17]	Definite	+	17	45	NA	d	Acetazolamide	CR (BMT)
Visani et al.[18]	Definite	+	16	45	31	d	Acetazolamide	CR
Decaudin et al.[19]	Definite	+	16	45	20	c	Serial LP	CR
Sano et al.[20]	Definite	+	18	45	23	d	Glycerin	CR
Chen et al.[21]	NA	NA	17	NA	42	NA	NA	NA
Tallman et al.[22]	NA	NA	4	45	13	NA	Dexamethasone	Died
Schroeter et al.[23]	Probable (Intracranial pressure unknown	+	8	25	65	d	Steroid, mannitol Acetazolamide	CR
Guirgis et al.[24]	Definite	+	16	50 mg‡	57	c	Acetazolamide	CR
	Probable	-	17	90mg‡	21	c	Acetazolamide	CR
Vanier et al.[25]	Probable (a leak in the manometer)	+	4	45	27	i+r	Fluconazole discontinued	NA
Naithani et al.[26]	NA	NA	9	45	12	i+r	Acetazolamide Mannitol	CR
Labrador et al.[27]	Definite	+	15	25	35	i	Acetazolamide	CR

¶ The day of ATRA treatment, on which IH developed, #total number of patients with IH, ‡mg per day, *during induction, * *during consolidation
ATRA, all-trans retinoic acid; BMT, bone marrow transplant; c, continuation; CR, complete remission; d, discontinuation; IH, intracranial hypertension; i, interruption; LP, lumbar puncture (and high CSF pressure was documented); r, dose reduction; y, years

Table I. Continued.

References	IH	LP	Age (y)	ATRA dose mg/m²	Days¶	ATRA treatment during IH	Treatment for IH	Outcome
Rasul et al.[28]	Definite	+	16	NA	21	d	Serial LP Dexamethasone Lumbar shunt	NA
Abla et al.[29]	Definite	+	13	25	4	i+r	Acetazolamide	CR
Coombs et al.[30]	Probable	-	8	45	4	r	Dexamethasone	CR
	Probable	+	11	45	13	c	NA	CR
	Probable (No papilledema)	+	15	45	47	i+r	NA	CR
Schwartz et al.[31]	Definite	+	10	25	NA	i or d	Dexamethasone	CR
Shirai et al.[32]	Definite	+	11	45	46	c	Acetazolamide, prednisolone	CR
Molinaro et al.[33]	NA	NA	12	NA	NA	i	Acetazolamide, dexamethasone	CR
Our case	Definite	+	15	25	90	i	Dexamethasone, acetazolamide, furosemide (single dose), topiramate, serial LP	CR

IH distribution in APL case series

	IH	Patients# (PTC incidence)	Age (y)	ATRA dose mg/m²	IH treatment
Warrell et al.[34]	Definite Probable	2 (18.1%)	9-75	45	Dexamethasone, serial LP, analgesics
Frankel et al.[35]	NA	2 or 3 (NA)	9-75	45	Dexamethasone, LP
Tallman et al.[36]	NA	at least 4 (2.3%)	1-81	45	Unknown
Bapna et al.[37]	NA	2 (13.3%)	3.5-15	45-90	Dexamethasone
Mandelli et al.[38]	NA	5 (2%)	2.2-73.9	45	Unknown

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ATRA, all-trans retinoic acid; BMT, bone marrow transplant; c, continuation; CR, complete remission; d, discontinuation; IH, intracranial hypertension; i, interruption; LP, lumbar puncture (and high CSF pressure was documented); r, dose reduction; y, years

Table I. Continued.

References	IH	LP	Age (y)	ATRA dose mg/m²	Days¶	ATRA treatment during IH	Treatment for IH	Outcome
IH distribution in APL case series								
	IH	Patients# (PTC incidence)	Age (y)	ATRA dose mg/m²			IH treatment	
Douer et al.[39]	Definite	4 (5.8%)	5-82	90 (liposomal)			Unknown	
Mann et al.[40]	NA	1 (5%)	1.8-16.3	15-45			Unknown	
Testi et al.[41]	NA	10 (8.1%)	1-18	25			ATRA discontinuation (1/10)	
Ortega et al.[42]	NA	4 (6%)	2-17	25			Interruption and re-starting ATRA at reduced dose (2/4), ATRA discontinuation (2/4)	
Montesinos et al.[2]	NA	30*+ 2** (in total 3.1%) (in pediatric 13%)	NA	25 (in pediatric age)			ATRA interruption (9/32 had recurrent PTC)	
Gregory et al.[43]	Definite	3 (11%)	1-18	45			Unknown	
Imaizumi et al.[44]	NA	5 (8.6%)	0.9-16	45			Unknown	
Jeddi et al.[45]	NA	1 (2.6%)	4-64	25 (≤20 years)			Unknown	
Avvisati et al.[46]	NA	16 (2%) (in 10/16 <18 years)	1.4-74.7	25			Analgesics, furosemide, dexamethasone, ATRA discontinuation	
Dorantes-Acosta et al.[47]	NA	1 (9.1%)	1.4-12.7	45			Dexamethasone	
Testi et al.[48]	NA	15 (5.8%)	1-21	25			Analgesics, diuretics, temporary ATRA discontinuation	
Aksu et al.[6]	Definite	3 (18%)	1.5-17	25			Serial LP, acetazolamide, dexamethasone, topiramate (in 1/3)	
Kutny et al.[49]	NA	At least 5 (6%)	<18	45			Interruption and re-starting ATRA, Dexamethasone	

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ATRA, all-trans retinoic acid; BMT, bone marrow transplant; c, continuation; CR, complete remission; d, discontinuation; IH, intracranial hypertension; i, interruption; LP, lumbar puncture (and high CSF pressure was documented); r, dose reduction; y, years

Table I. Continued.

References	IH	LP	Age (y)	ATRA dose mg/m^2	Days¶	ATRA treatment during IH	Treatment for IH	Outcome
IH distribution in APL case series								
	IH	Patients# (PTC incidence)	Age (y)	ATRA dose mg/m^2			IH treatment	
Strocchio et al.[50]	NA	2 (11.1%)	4.8-17.5	25			Interruption and re-starting ATRA	
Zhang et al.[51]	NA	3 (4.3%)	1-17	25			Unknown	
Spezza et al.[52]	NA	3 (14.3%)	1-16	25			Unknown	
Breviglieri et al.[53]	Probable	6 (19%)	1-17	45 (≥14 years) 25 (<14 years)			Acetazolamide	
Khan et al.[54]	NA Probable	3 (15%)	3-13	25			Dexamethasone, Mannitol, ATRA discontinuation Dexamethasone, ATRA discontinuation or interruption	
Kutny et al.[55]	NA	12* (7.8%) 7** (4.6%)	1.1-21.7	25			Unknown	
Testi et al.[56]	NA	5 (4.6%)	1.1-14.4	25			ATRA interruption	
Vaid et al.[57]	Probable	11 (17.2%)	5-60	25 (in pediatric age)			Acetazolamide, ATRA dose reduction (in 6/11)	
Roy et al.[58]	NA	3 (4.8%)	0.9-12.2	26±3.7			Unknown	
Javed et al.[59]	NA	6 (11.7%)	12-58	25			Unknown	
Singh et al.[60]	NA	12 (6.6%)	12-66	25-45			Unknown	
Maldonado et al.[61]	NA	4* (18.2%)	2-18	45			Continued ATRA	

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ATRA, all-trans retinoic acid; BMT, bone marrow transplant; c, continuation; CR, complete remission; d, discontinuation; IH, intracranial hypertension; i, interruption; LP, lumbar puncture (and high CSF pressure was documented); r, dose reduction; y, years

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