Retinoblastoma (RB) is the most common intraocular malignancy found in children. It is caused by the inactivation of both copies of a tumor suppressor gene (Rb1), which participates in the control of cell cycling (1-3). Approximately one-third of these tumors are bilateral and associated with germinal mutations. All bilateral tumors and one-tenth of unilateral tumors are caused by a germline mutation inherited as an autosomal dominant trait (4, 5). This hereditary predisposition to retinoblastoma is caused by mutant alleles occurring at the q14 band of chromosome 13 (6). The association of bilateral RB with ectopic midline intracranial tumors, termed “trilateral” retinoblastoma (TRB), is a well-recognized but uncommon syndrome. The association of ocular RB with brain tumors was first reported in 1971 (7). This intracranial tumor arises most often in the pineal region but can also be a suprasellar or parasellar tumor, and is considered to be an isolated independent primary focus without evidence of retinal disease. This is the first reported case of TRB in Korea.

**CASE REPORT**

A 5-month-old female infant presented with poor eye contact and nystagmus for several days. Brain MRI revealed a well-circumscribed, lobulated mass, measuring 7.5 × 5.7 cm in the sella and suprasellar regions (Fig. 1). This mass showed heterogeneous signal intensity and variable contrast enhancement in both T1-weighted and T2-weighted images (Fig. 2). There was a permeative growth along the optic gyrus, but no ocular lesion was found in the preoperative brain MRI. The brain tumor was partially resected. Pathologic diagnosis of intracranial RB was made. Subsequently, with a suspicion of TRB, ophthalmoscopic examination was performed. It revealed an intraocular whitish subretinal mass, twice the diameter of a disc on the left eye. No histologic confirmation was obtained for the ocular lesion. The patient received chemotherapy with cytoxan, vancomycin, and adriamycin. Follow-up CT of the brain revealed shrinkage of the residual mass in response to chemotherapy and there was no evidence of metastasis or leptomeningeal spreading. She died of sepsis 6 months thereafter.

Pathologic examination of the removed brain tumor disclosed a dense proliferation of small, round, and blue cells with a high nucleus:cytoplasmic ratio, hyperchromatic nuclei and some mitoses. Many Flexner-Wintersteiner rosettes and Homer Wright rosettes were observed (Fig. 3). Calcifications and necroses were also frequently seen. The tumor showed dif-
fuse immunoreactivity for synaptophysin (Fig. 4). Immunostainings for S-100, GFAP, EMA, vimentin, CD99, and collagen IV were all negative. These findings were consistent with the diagnosis of intracranial RB.

**DISCUSSION**

TRB is a well-recognized syndrome that is characterized by unilateral or bilateral hereditary RB in association with a morphologically similar intracranial neoplasm localized in the
pineal gland or the sella or suprasella regions. This case demonstrated TRB with a sellar and suprasellar mass as well as unilateral retinoblastoma. TRB with unilateral RB has also been described as a forme fruste of TRB (8).

The intracranial tumor of TRB arises most often in the pineal gland but can occur in the suprasellar or parasellar regions as well. The association between suprasellar tumor and unilateral RBs is referred to as "sellar" TRB, whereas "pineal" TRB is referred to pineal tumor associated with unilateral RBs. Bejani et al. reported a case of suprasellar mass with intraocular RB, which showed nearly same presentation as the present case. The intracranial mass of sellar TRB tends to be the initial presenting tumor and is diagnosed at a younger age than the "pineal" variant since they more readily develop symptoms of increased intracranial pressure than pineal variants. It has a tendency to occur more frequently in females and is associated more often with unilateral ocular lesions, as is the case in our patient (9). Although the patients with suprasellar TRB are diagnosed earlier than those with pineal TRB, their prognosis remains poor and they usually die of metastatic disease or postoperative complications within 10 months from the diagnosis (10). Three cases of unilateral RB and sellar tumor without family history has been reported in English literature since 1977 (9, 11, 12).

Ocular disease in TRB presents much earlier than that in classic RB with a usual latent period between the diagnosis of ocular disease and the intracranial lesion (13, 14). As for our patient, ocular tumor was not discovered in the preoperative brain MRI, but was detected postoperatively by the fundoscopic examination. The ocular mass in this patient might be a concurrent lesion. According to several studies, the mean survival in patients with TRB varies from 1 to 28 months after diagnosis of the intracranial lesion and the disease is almost uniformly fatal with deaths most commonly due to cerebrospinal metastases (13, 15). In contrast, the 5 yr survival of unilateral ocular RB following adequate treatment is over 90% and slightly less in cases with bilateral lesions.

In TRB, the retinal tumor is usually small and there is often no optic nerve involvement, and both of these factors argue against cerebral metastasis (11, 16). The sellar mass of our patient can not be considered as a metastasis from the retinal lesion because there was no involvement of the optic nerve or uveal tract, or extracocular extension, as shown by ophthalmic examination as well as on MRI.

The ocular RB can extend to the brain by the optic nerve invasion or by spreading through the cerebrospinal fluid. Typically, cerebral metastasis represents multiple lesions with similar imaging characteristics, and the midline location is characteristic of the metastatic lesions: they are also often associated with skull vault, long bone, and pulmonary metastases. The present case showed no evidence of cerebrospinal fluid spreading or hematogenous metastasis.

In addition, metastatic RBs are morphologically different from primary intracranial RB. They are characterized by undifferentiated small round cells without Flexner-Wintersteiner rosettes resembling neuroblastoma, whereas the primary lesions are morphologically similar to ocular RB. The histologic findings of this case were similar to those seen in ocular RB.

It is less likely that this patient may have an ocular metastasis from intracranial retinoblastoma because orbital metastatic tumors in children are most often of embryonal or undifferentiated type, such as neuroblastoma, Wilms tumor, and Ewing sarcoma. And orbital metastasis of the intracranial tumors is extremely rare except medulloblastoma.

Most of the theories on the origin of TRB are based on Knudson’s proposal, suggesting that two genetic events (“hits”) take place, triggering the development of hereditary RB. The first mutation is inherited and the second mutation, which takes place in the retina, is acquired during life (17). Bader et al. believed that these two genetic “hits” are responsible for the occurrence of intracranial RB, and originally stated that the “second primary” tumors are found in the so-called “third eye”, the pineal gland (18). There are two theories that may explain the occurrence of a suprasellar variant: Susceptibility to RB gene mutation may be shared by additional cells such as germinal matrix cells in CNS, since the optic primordia develop from the diencephalon. The other hypothesis for suprasellar TRB is the occurrence of tumors from ectopic photoreceptor cells in the sellar area. This theory is supported by the reports on ectopic retinal epithidium in an intracranial portion of the optic nerve (11, 19).

Present case has a possibility of congenital intracranial tumor due to early presentation of 5 months.

The risk of occurrence of RB in siblings of patients with TRB varies between 1 and 7%, depending on the presence of a family history (13, 14, 20). Although we must consider lag time bias, which may be attributable to the time of screening or the intractability of this tumor, a screening for intracranial disease can be beneficial for children with bilateral and hereditary RB. The intracranial lesion in our patient might have been missed, had it not been for the detailed examination of the ocular fundus since she had no family history and the lesion was very small. Careful retinal screening of patients with ‘sellar’ or other non-pineal RB may uncover patients with TRB. Since TRB is often hereditary, the diagnosis has implications for genetic counseling, as siblings of the patient may also have the disease. The patients may initially present with a suprasellar tumor or concurrent intraocular RB with suprasellar tumor. The importance of meticulous search for retinal lesions in children with parasellar RB is stressed to assure the diagnosis of sporadic heritable forms of ‘sellar’ TRB and referral for genetic counseling.
REFERENCES

1. Mayol X, Grana X. pRB, p107 and p130 as transcriptional regulators: role in cell growth and differentiation. Prog Cell Cycle Res 1997; 3: 157-69.
2. Sellers WR, Kaelin WG Jr. Role of the retinoblastoma protein in the pathogenesis of human cancer. J Clin Oncol 1997; 15: 3301-12.
3. Herwig S, Strauss M. The retinoblastoma protein: a master regulator of cell cycle, differentiation and apoptosis. Eur J Biochem 1997; 246: 581-601.
4. Gallie BL, Dunn JM, Hamel PA, Muncaster M, Cohen BL, Phillips RA. How do retinoblastoma tumours form? Eye 1992; 6: 226-31.
5. Draper GI, Sanders BM, Brownbill PA, Hawkins MM. Patterns of risk of hereditary retinoblastoma and applications to genetic counseling. Br J Cancer 1992; 66: 211-9.
6. Sparkes RS, Murphree AL, Lingua RW, Sparkes MC, Field LL, Funderburk SJ, Benedict WF. Gene for hereditary retinoblastoma assigned to human chromosome 13 by linkage to esterase D. Science 1983; 219: 971-3.
7. Jensen RD, Miller RW. Retinoblastoma: epidemiologic characteristics. N Engl J Med 1971; 285: 307-11.
8. Whittle IR, McClellan K, Martin FJ, Johnston IH. Concurrent pineoblastoma and unilateral retinoblastoma: a forme fruste of trilateral retinoblastoma? Neurosurgery 1985; 17: 500-5.
9. Bejjani GK, Donahue DJ, Selby D, Cogen PH, Packer R. Association of a suprasellar mass and intraocular retinoblastoma: a variant of pineal trilateral retinoblastoma? Pediatr Neurosurg 1996; 25: 269-75.
10. Blash L, McCormick B, Abramson D, Ellsworth R. Trilateral retinoblastoma-incipience and outcome: a decade of experience. Int J Radiat Oncol Biol Phys 1994; 29: 729-33.
11. Jakobiec FA, Tso MO, Zimmerman LE, Danis P. Retinoblastoma and intracranial malignancy. Cancer 1977; 39: 2048-58.
12. Skalski M, Egelhoff JC, Kollias SS, Mazewski C, Ball WS. Trilateral retinoblastoma with suprasellar involvement. Neuroradiology 1997; 39: 41-3.
13. Pesin SR, Shields JA. Seven cases of trilateral retinoblastoma. Am J Ophthalmol 1989; 107: 121-6.
14. De Potter P, Shields CL, Shields JA. Clinical variations of trilateral retinoblastoma: a report of 13 cases. J Pediatr Ophthalmol Strabismus 1994; 31: 26-31.
15. Bader JL, Meadows AT, Zimmerman LE, Rorke LB, Voute PA, Champion LA, Miller RW. Bilateral retinoblastoma with ectopic intracranial retinoblastoma: trilateral retinoblastoma. Cancer Genet Cytogenet 1982; 5: 203-13.
16. Bader JL, Miller RW, Meadows AT, Zimmerman LE, Champion LA, Voute PA. Trilateral retinoblastoma. Lancet 1980; 2: 582-3.
17. Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA 1971; 68: 820-3.
18. Wurtman RJ, Moskowitz MA. The pineal organ (first of two parts). N Engl J Med 1977; 296: 1329-33.
19. Torczynski E, Jacobiec FA, Johnston MC, Font RL, Madewell JA. Synophthalmia and cyclopia: a histopathologic, radiographic, and organogenetic analysis. Doc Ophthalmol 1977; 44: 311-78.
20. Kingston JE, Plowman PN, Hungerford JL. Ectopic intracranial retinoblastoma in childhood. Br J Ophthalmol 1985; 69: 742-8.