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To cite this article: Marcus C. de Jong, Annette C. Moll, Sophia Göricke, Paul van der Valk, W. A. Kors, Jonas A. Castelijns & Pim de Graaf (2016) From a Suspicious Cystic Pineal Gland to Pineoblastoma in a Patient with Familial Unilateral Retinoblastoma, *Ophthalmic Genetics*, 37:1, 116-118, DOI: [10.3109/13816810.2014.929717](https://doi.org/10.3109/13816810.2014.929717)

To link to this article: <https://doi.org/10.3109/13816810.2014.929717>



Published online: 18 Jun 2014.



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LETTER TO THE JOURNAL

From a Suspicious Cystic Pineal Gland to Pineoblastoma in a Patient with Familial Unilateral Retinoblastoma

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Patients with hereditary retinoblastoma (Rb) have an increased risk of developing pineoblastoma.¹ Unfortunately, most patients with concurrent pineoblastoma do not survive; Kivelä² has shown that only patients who were diagnosed by screening and had a tumor smaller than 15 mm had a chance of survival. However, not all pineal lesions found with screening at the time of retinoblastoma diagnosis are pineoblastomas. Pineal cysts are a relatively common finding in the general population. In children up to 5 years of age the prevalence of pineal cysts diagnosed with magnetic resonance imaging (MRI) is 2.0%.³ Potentially, about 50% of pineoblastomas can be found at baseline screening and another 25% during the first year after Rb diagnosis.² Therefore, baseline screening of the brain in newly diagnosed retinoblastoma is currently advised in imaging guidelines.⁴ In a recent study Rodjan and colleagues⁵ showed that the majority of pineoblastomas in Rb patients had a cystic appearance. Consequently baseline brain imaging with extended follow-up of pineal cysts might help early detection of pineoblastoma. We present a rare case of unilateral familial retinoblastoma and a suspicious cystic pineal gland on brain MR imaging that progressed into a pineoblastoma.

CASE REPORT

Our patient, a 13-day-old girl, was diagnosed with familial retinoblastoma of the right eye. She

underwent bilateral external beam radiotherapy (EBRT) over 5 weeks from the age of 1 month, fractionated at five times a week 2 Gy up to an aimed dose of 50 Gy per eye. The pineal gland was not in the radiation field, but unfortunately we could not obtain detailed dosimetric information. At the age of 19 months a new tumor in the right eye was treated with cryotherapy. An MRI examination – performed at that time for tumor staging of the eye tumor – also included T1-weighted sagittal images of the brain showing a prominent pineal gland measuring 9 × 6 mm with a multi-cystic anterior part and a solid posterior part (Figure 1A). The images revealed no other abnormalities. Due to the prominent size and the multi-cystic component of the pineal gland a follow-up MR examination was indicated. Because the patient was transferred to another hospital, a follow-up MRI examination was performed 9 months later. The follow-up scan showed an increase in size of the pineal gland to 12 × 8 mm, slightly compressing the tectal plate of the mesencephalon without hydrocephalus. Besides a multi-cystic part and a solid part – as was visible 9 months before – this time a fine nodular aspect of the cystic wall was identified on sagittal T2-weighted images (Figure 1B). The solid part of the pineal gland showed prominent contrast enhancement; there were no signs of other brain abnormalities (Figure 1C), particularly no intracranial or spinal leptomeningeal enhancement. Because of the increase in size of the pineal gland, progression of the solid component, the fine nodular aspect of the wall,

Received 11 April 2014; accepted 26 May 2014; published online 18 June 2014

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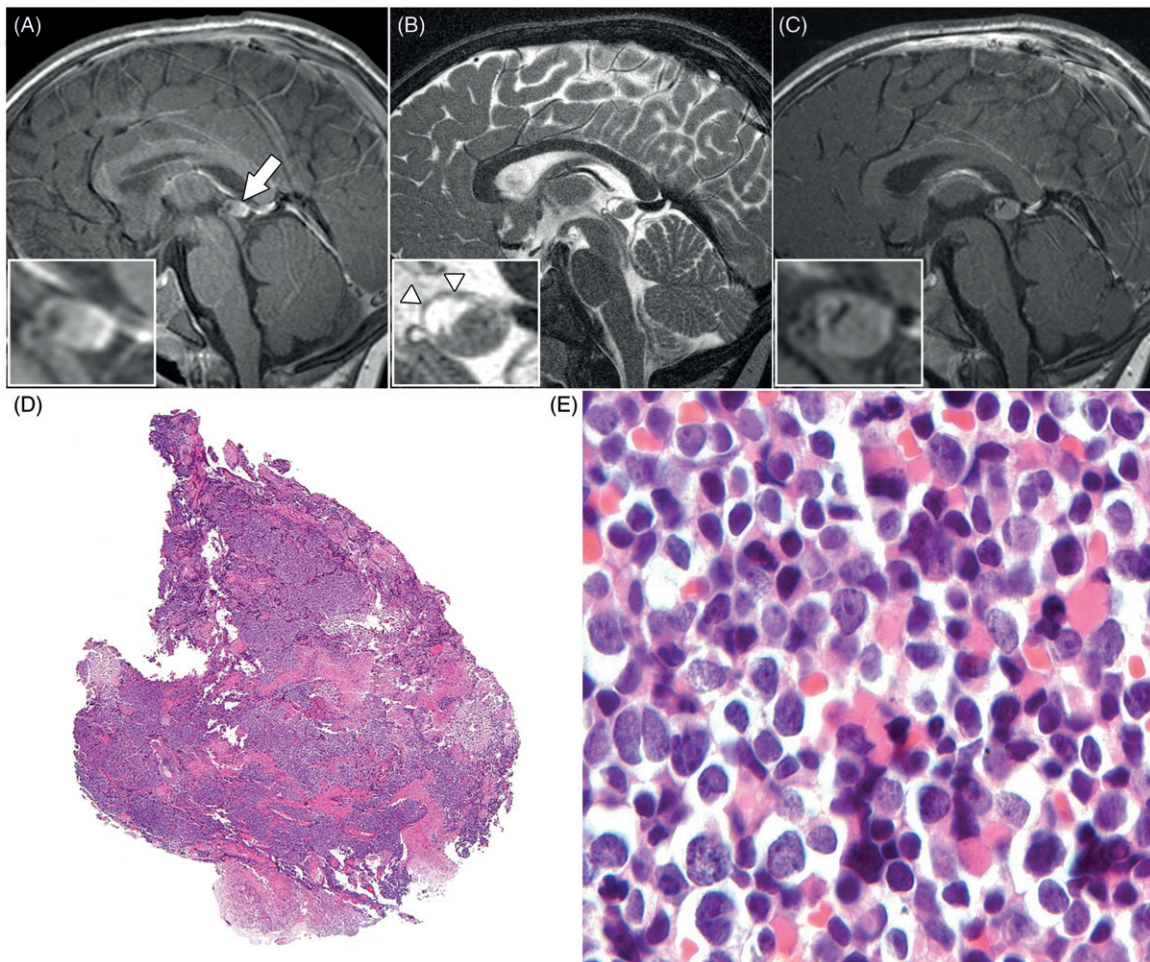


FIGURE 1. Sagittal T1-weighted magnetic resonance image (A) of the brain, showing a prominent pineal gland (arrow) with a multi-cystic anterior part and a solid posterior part. Sagittal T2-weighted magnetic resonance image (B), showing a fine nodular aspect of the cystic wall (arrowheads). The T1-weighted magnetic resonance image (C) shows prominent contrast enhancement of the solid part of the pineal gland combined with an increase in diameter compared with image (A). The histopathologic view (D) of the pineal tumor tissue stained with hematoxylin and eosin shows no necrosis or microvascular proliferation (original magnification $\times 2.5$). At a higher magnification (E) moderately polymorphous cells with little cytoplasm and relatively large nuclei were visible; cells in a mitotic stage could easily be seen (original magnification $\times 40$).

and pronounced contrast enhancement, the lesion was suspicious for pineoblastoma. Analysis of the cerebrospinal fluid revealed no abnormalities.

One month after the MRI examination the lesion was surgically removed. In the period until the resection the patient did not show any clinical symptoms. One day after the resection, magnetic resonance images showed a completely resected pineal gland. Histopathologically, the tumor showed no necrosis or microvascular proliferation (Figure 1D). The resected tumor consisted of moderately polymorphous cells with little cytoplasm and relatively large nuclei (Figure 1E). No rosettes (which are typical for pineocytoma) were visible. Cells in a mitotic stage could easily be found (Figure 1E). Tumor cells were negative for glial fibrillary acidic protein (GFAP), Cytokeratin AE1/AE3, and chromogranin, but strongly positive for synaptophysin. MIB-1 (cell

proliferation marker) labeling was estimated at 30–40%. The tumor was diagnosed as a pineoblastoma WHO grade IV.⁶

After surgery the patient subsequently received chemotherapy according to the ARET0321 protocol stage 4b,⁷ consisting of four courses of vincristine, cisplatin, cyclophosphamide and etoposide followed by high doses of carboplatin, thiotepa and etoposide concluded with autologous stem cell reinfusion. The most recently performed MRI examination (35 months after resection) showed no tumor recurrence. Up until the last visit to the outpatient clinic (35 months since resection, 44 months since the first brain scan, and 63 months since Rb diagnosis) the patient was clinically doing well.

In our patient, the first MRI examination was not performed at the time of Rb diagnosis, but rather at a new retinoblastoma tumor 19 months later. This raises

the question whether this pineal cyst was already present at Rb diagnosis or not, and if so would it have been visible on magnetic resonance images? In a registry-based study, Moll and co-authors⁸ have shown that out of seven pineoblastoma patients six were treated with EBRT for retinoblastoma before the age of 1 year suggesting that radiotherapy before this age might increase the risk of developing pineoblastoma. Maybe scattered X-rays from the EBRT in the first months triggered malignant deregulation of the pineal gland, but we are unsure if this could have happened in our patient.

It is a challenge to correctly distinguish a benign pineal cyst from a developing pineoblastoma. A normal pineal gland is no larger than 10 mm with a signal intensity on T1- and T2-weighted images comparable to that of grey matter.^{9,10} On MR images cystic pineal lesions present as isointense lesions relative to cerebrospinal fluid with contrast enhancement of the wall on T1-weighted images and hyperintense lesions on T2-weighted images. Pineoblastomas can either present as a completely solid lesion, as a completely cystic lesion, or as a combination of both.⁵ Whereas benign pineal cysts usually present as a cystic pineal gland with a discrete rim contrast enhancement and a thin smooth wall, a pineal cyst is considered suspicious when the wall is irregularly thickened and more than 2 mm thick.^{11,12} Intracystic septations can be seen in both benign and malignant lesions, but a fine nodular aspect of the wall is considered to be a suspicious finding.^{9,10} If a pineal cyst remains stable on follow-up MR images, this is considered to be a benign cyst and no further follow-up is recommended.

In conclusion, follow-up is not long enough to declare this patient cured from pineoblastoma, but she is still in complete remission 32 months after the end of therapy, and if anything it underlines the importance of early detection followed by adequate treatment. If there is any suspicion concerning the pineal gland on magnetic resonance images of the brain in retinoblastoma patients we recommend performing follow-up MRI examination. The optimal follow-up schedule is still unknown. In a multi-center study we are investigating the value of performing follow-up MRI examination of pineal cysts 3 months after baseline brain screening (and if any doubt remains with a third MRI examination after another 3 months).

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

FUNDING

M.C.J. is financially supported in part by grants from the ODAS Foundation, Delft, The Netherlands.

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