Diencephalic Tumor: a rare coincidence in retinoblastoma survivors?

Maria Antonietta De Ioris[1], Ida Russo[2], Paola Valente[3], Giovanna Stefania Colafati[2], Iside Alessi[4], Antonino Romanzo[5], Luca Buzzonetti[5], Angela Mastronuzzi[1], and Andrea Carai[3]

[1]Ospedale Pediatrico Bambino Gesù
[2]Ospedale Pediatrico Bambino Gesu
[3]Bambino Gesù Children's Hospital
[4]Bambino Gesu Pediatric Hospital
[5]Bambino Gesù IRCCS Children's Hospital

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Abstract

Retinoblastoma(RB) patients have a high risk to develop second malignant neoplasm (SMN). Diencephalic tumors(DT) are rare in paediatric age. A retrospective review was performed over 21 years period. Out of 169 RB patients, 3 presented a DT. Two patients presented a Rb1 germline mutation and none received radiotherapy. DT in previously treated RB patients seems a peculiar SMN. However, considering the site, the short time interval from RB and the absence of radiotherapy, an alternative pathogenic mechanism could be supposed. The same embryological origin of the retina and the diencephalon should be considered and biological studies are needed.

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De Ioris MA[1], Russo I[1], Valente P[2], Colafati GS[3], Iside A[1], Romanzo A[2], Buzzonetti L[2], Mastronuzzi A[1] and Carai A[4]

[1]Department of Hematology/Oncology, Gene and Cell Therapy Bambino Gesù Children's Hospital IRCCS, Rome, Italy

[2]Ophtalmology, Department of Surgery, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

[3]Imaging Department, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy.

[2]Neurosurgery, Department of Surgery, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

Correspondance:

Maria Antonietta De Ioris, MD, PhD

Department of Hematology/Oncology, Gene and Cell Therapy Bambino Gesù Children's Hospital IRCCS, Rome, Italy. Email:*mantonietta.deioris@opbg.net*Tel +39 0668594664

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Tabe 1, Supplemental files 2 Figure

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Keywords

Retinoblastoma, diencephalic tumor, second malignant neoplasm, radiation therapy

Abbreviations

Dienchephalic tumor	DT	Retinoblastoma tumor suppressor gene	*Rb1*
Retinoblastoma	RB	Central Nervous System	CNS
Second Malignant Neoplasm	SMN	Magnetic Resonance Imaging	MRI

ABSTRACT

Retinoblastoma(RB) patients have a high risk to develop second malignant neoplasm (SMN). Diencephalic tumors(DT) are rare in paediatric age. A retrospective review was performed over 21 years period. Out of 169 RB patients, 3 presented a DT. Two patients presented a Rb1 germline mutation and none received radiotherapy. DT in previously treated RB patients seems a peculiar SMN. However, considering the site, the short time interval from RB and the absence of radiotherapy, an alternative pathogenic mechanism could be supposed. The same embryological origin of the retina and the diencephalon should be considered and biological studies are needed.

INTRODUCTION

Retinoblastoma (RB) is the most common intraocular tumor representing about 3-4% of childhood malignancies. RB can occur as hereditary form characterized by germline mutation of the Retinoblastoma tumor suppressor gene (*Rb1*); a *Rb1* germline mutation is observed in familial RB, in bilateral form and in 10-15% of sporadic unilateral RB [1-4].

The 5 year-overall survival rate is 90-95% in developed countries, resulting in a large population of long-term survivors with an increased risk of second malignant neoplasms (SMNs), particularly for patients affected by hereditary RB and/or treated with radiotherapy [4,5, 11-18].

Diencephalon tumors (DT) account for less than 5% of pediatric CNS neoplasms and are usually glial lesions; specifically, more than a half are low-grade gliomas [19]. Surgical removal of these lesions is difficult and generally not advised. Radiation of histologically unconfirmed diencephalic tumors has been previously used but not actually recommended [20-22].

We previously reported on a case of DT that occurred in a patient treated for a RB [23]. We reviewed our RB series in order to identify DTs.

RESULTS

Between January 1999 and December 2019, 169 RB patients were diagnosed at Bambino Gesù Children's Hospital. The RB database was checked in order to identify patients with DT and clinical records and imaging findings were reviewed.

Three of 169 (1, 7%) patients presented a DT during the follow-up period. In all the tumor was detected at a magnetic resonance images (MRI) follow-up. Table 1 resumed clinical and genetic characteristics and treatment of the three RB patients with a DT.

Case 1

A 7-month-old previously healthy male was treated for a bilateral RB. After 57 months from RB diagnosis, a routine brain MRI showed a single small rounded lesion localized at the right anterior thalamus (Fig 1A). Due to the small diameter of the lesion and its deep location, next to the internal capsule, neither open surgery nor a stereotactic biopsy were suggested. After seven month at progression, the child received stereotactic radiotherapy (total dose 54 Gy) and he is alive at 163 months from the DT diagnosis (Fig 1C).

Case 2

A 29-month-old previously healthy female received treatment for unilateral RB. After 15 months from RB diagnosis, a routine brain MRI showed a lesion localized at the left internal pallidus. A chemotherapeutic treatment was proposed only after tumor progression and Li Fraumeni syndrome was excluded [23]. The histology showed a pilocytic astrocytoma. The child is alive at 98 months from the diencephalic tumor progression.

Case 3

A 20-month-old previously healthy male was treated for a bilateral RB. After 53 months from diagnosis, a brain MRI showed a small rounded lesion on the internal pallidus, next to the knee of the internal capsule (Fig 2A). No indication was given for stereotactic biopsy, due to high risk of neurological impairment in an asymptomatic patient. The lesion is stable without any treatment at 88 months from the DT diagnosis (Fig 2B).

DISCUSSION

RB is the most common eye tumor with a favorable outcome. Indeed, a large cohort of RB survivors is recorded presenting an increased risk of developing SMNs. The cumulative incidence of SMNs in RB survivors is about 10% at 25 years and up to 36-48% at 40-50 years from diagnosis for familial/hereditary cases, while it is about 5% at 40-50 years post-diagnosis for sporadic forms [12, 15-16]. The most common observed SMNs are soft tissue sarcoma, osteosarcoma and carcinoma while melanoma, leukemia and Central Nervous System (CNS) tumors are less frequently reported. The association with radiotherapy is widely reported with a 3.1-fold increased risk of SMNs [12-18, 25-26]. The CNS malignancies are relatively rare, accounting for about 10% of all SMNs mostly representing by radiation induced meningioma's [12, 13, 16, 25, 26]. At 30 years post diagnosis, Shinohara et al [5] reported a cumulative incidence of SMNs lower for patients with unilateral than for those with bilateral forms, 1,7% versus 28,5% respectively ($p< 0{,}0001$). No CNS tumor was reported. Sixty-four per cent of patients had received radiation therapy.

These reports clearly pointed out that a CNS tumor in RB survivors is rare and almost associated with a previous radiotherapy in the SMNs field or/and with germline *Rb1* mutation.

We reported three cases of second CNS tumor in RB patients previously treated for intraocular disease. Notably, none of the patients received radiotherapy. The lack of this well-known risk factor for CNS second tumor lead us to consider a genetic predisposition as a possible pathogenic mechanism for the SMN occurrence. An *Rb1* mutation was detected in the two bilateral RB cases but surprisingly, none of the reported *Rb1* mutations entered in the group of 11 recurrent CGA/TGA nonsense *Rb1* mutations associated with a higher risk of SMNs [18]. For the sporadic RB patient, we supposed a predisposing genetic field but the family history was mute for tumors and a Li Fraumeni syndrome was excluded.

All three reported patients developed tumors localized in the diencephalic region, a peculiar site for the intracranial lesion. A recent meta-analysis by de Jong *et al* [27] provided data about bilateral RB focusing on intracranial midline tumor occurred in these patients. Concerning diencephalic lesions, the authors reported a median size of 42 mm larger than the size observed in our cases. Moreover, in de Jong series, the tumors are typically diagnosed simultaneously with intraocular retinoblastoma and an improved overall survival -57% at 5 years- was observed after the wider use of both conventional and high dose chemotherapy with stem-cell rescue.

In our series, the time interval between RB and the DT occurrence is relatively short -less than 5 years- in all cases; the occurrence of SMNs before 5 years from RB diagnosis is quite rare while a brain RB relapse was excluded by the proven astrocytic histology in one case and by the MRI findings suggesting a glial origin.

There are no other reports of DT in RB survivors. Recently, Dalvi et al reported on low-grade glioma in 0,4 % of RB survivors suggesting a possible increased risk in RB patients.

We reported on three cases of DT occurred in previously treated RB patients. According to our experience, a wait and see strategy should be proposed and biopsy should be performed whatever is possible. Consi-

dering the peculiar site, the short time interval between tumors and absence of radiotherapy treatment, an alternative pathogenic mechanism could be supposed. Further analysis of large RB cohort with biological studies are needed to address a possible common pathogenic mechanism considering the shared embryologic origin of the retina and the diencephalon.

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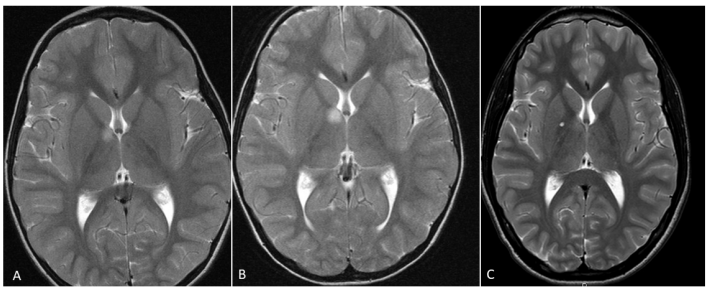
`TABLE 1.pdf` available at https://authorea.com/users/372098/articles/490260-diencephalic-tumor-a-rare-coincidence-in-retinoblastoma-survivors



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