

1 **BRIEF REPORT**

2 **Chronic myeloid leukemia following treatment for bilateral retinoblastoma**

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CML	Chronic myeloid leukemia
RB	Retinoblastoma

25 **ABSTRACT**

26 In contrast to their higher incidence of radiation-induced solid tumors, patients with bilateral
27 retinoblastoma (RB) have a low risk of developing therapy-related hematological malignancies. We
28 present the first case of a patient with bilateral RB to develop chronic myeloid leukemia (CML) 15
29 years after multimodality therapy, comprising systemic chemotherapy and external beam radiation
30 to the orbits. We discuss the possible etiology of therapy-related CML in long-term survivors with
31 bilateral RB, although the possibility of *de novo* CML cannot be completely excluded in the present
32 case.

33 **INTRODUCTION**

34 The overall survival rate of patients with intraocular retinoblastoma (RB) exceeds 95%.¹ In addition
35 to conventional treatment modalities, such as enucleation and external beam radiation, systemic
36 chemotherapy, focal laser therapy, cryotherapy, brachytherapy, and the recently established
37 selective ophthalmic arterial and intravitreal injection have been performed for ocular salvage and
38 vision preservation.²⁻⁴ Since the majority of patients with RB now survive into adulthood, late
39 adverse effects have become a focus for clinical and research areas. Therapy-related malignancy is
40 one of the most severe late adverse effects.¹ Patients with bilateral RB, who invariably have
41 germline *RB* gene mutation, are at significant risk of therapy-related malignancy.⁵ In contrast to
42 their higher incidence of radiation-induced solid tumors, patients with bilateral RB have a low risk
43 of developing therapy-related hematological malignancies,⁵⁻⁸ and the etiologies of therapy-related
44 hematological malignancies in these patients remain largely unknown.

45 In the present study, we report a rare case who developed chronic myeloid leukemia
46 (CML) 15 years after the treatment for bilateral RB.

47

48 **RESULTS**

49 A 4-month-old male infant with bilateral RB was successfully treated by enucleation of the right eye,
50 41.8 Gy of external beam radiation to the orbits, 6 months of chemotherapy with vincristine and
51 cyclophosphamide, and cryotherapy and photocoagulation for the left eye. He had no family history
52 of malignancy. He experienced local relapse with vitreous seeding four times thereafter, during

53 which he received multiple rounds of systemic chemotherapy, comprising etoposide,
54 cyclophosphamide, and pirarubicin, in combination with intra-arterial and intravitreal injections of
55 melphalan, cryotherapy, and brachytherapy for the left eye. He finally underwent enucleation of
56 the left eye at the age of 10 years, which resulted in long-term remission. The cumulative doses of
57 chemotherapy drugs were as follows: etoposide, 1000 mg/m²; cyclophosphamide, 19.6 g/m²;
58 pirarubicin, 310 mg/m²; cisplatin, 90 mg/m²; carboplatin, 750 mg/m²; and vincristine, 51 mg/m².

59 At 25 years old, laboratory studies during annual follow-up revealed a white blood count
60 count of $32.3 \times 10^9/L$ (myelocytes, 11%; metamyelocytes, 2%; neutrophils, 69%; basophils, 5%;
61 monocytes, 4%; lymphocytes, 9%), hemoglobin of 14.0 g/dL, and a platelet count of $218 \times 10^9/L$,
62 although he did not have any clinical symptoms. Biochemical examination revealed marked
63 elevation of lactate dehydrogenase (711 U/L) and uric acid (7.3 mg/dL). Bone marrow aspiration
64 revealed distinct hypercellularity and a markedly increased myeloid:erythroid ratio (8.43) without
65 increased blasts. Karyotype analysis demonstrated a chromosome translocation, 46, XY,
66 t(9;22)(q34;q11.2), in all 20 bone marrow cells analyzed. Detection of the major *BCR-ABL* fusion
67 gene transcripts (2.9×10^6 copies/ μ gRNA) on quantitative polymerase chain reaction led to a
68 diagnosis of CML in chronic phase. Treatment with dasatinib (100 mg/day) normalized the white
69 blood count within 1 month. Bone marrow aspiration after 3 months revealed normocellular marrow,
70 and the quantitative polymerase chain reaction revealed a 4.2 log reduction of the major *BCR-ABL*
71 fusion gene transcripts (1.7×10^2 copies/ μ gRNA). Fluorescence *in situ* hybridization analysis for
72 the *BCR-ABL* fusion gene and cytogenetic karyotyping results were normal, achieving complete

73 cytogenetic response and an optimal response, according to the European LeukemiaNet
74 recommendations.⁹

75

76 **DISCUSSION**

77 Patients with bilateral RB have a high risk of developing secondary malignancies, with a
78 cumulative incidence of approximately 30% at 40–50 years from diagnosis.^{6,8} About half of
79 secondary malignancies are bone and soft tissue sarcomas, while only 0.5–0.6% are hematological
80 malignancies (Table 1).^{6–8} Although various types of leukemia and lymphoma have been observed
81 as secondary hematological malignances in patients treated for RB, there are no reports of
82 secondary CML. Moreover, etoposide or alkylator-containing chemotherapy, does not increase the
83 risk of secondary CML in the general population.¹⁰ Overall, there is no clear reason to assume an
84 association between chemotherapy and development of CML in the present case.

85 Howard et al. identified 164 patients with secondary CML in 376,835 long-term survivors
86 with breast cancer, representing an excess absolute risk of 2.06 per 100,000 person-years.¹¹
87 Dose-dependent increased risk of radiation-related CML has also been demonstrated in patients
88 with cervical cancer and ankylosing spondylitis, and in Japanese atomic bomb survivors.¹² The
89 frequency of secondary CML has decreased over time, possibly due to the recent progress in
90 radiation therapy techniques that allow minimal exposure of the bone marrow to radiation.¹¹
91 Secondary CML is an extremely rare event in patients with RB, considering that approximately
92 80% of patients received radiation therapy,^{6,8} which might be explained by the limited field of

93 radiation to the periorbital bone marrow. Thus, CML in the present case is likely associated with
94 radiation therapy, although the possibility of *de novo* CML cannot be completely excluded.

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96 **CONFLICT OF INTEREST**

97 The authors declare no conflict of interest associated with this manuscript.

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