

Ewing Sarcoma and Sinonasal Neuroectodermal Tumors as Second Malignant Tumors After Retinoblastoma and Other Neoplasms

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Background. Excesses of various childhood cancers have been reported after retinoblastoma, including a trickle of Ewing sarcoma (ES) and perhaps histologically similar olfactory neuroblastoma, both of which are neural tumors. To update and advance this information, case reports were sought by an extensive review of the literature. **Procedure.** The search was made through the use of PubMed, and the Web of Science (Citation Index Expanded), keying on primary references. Three sinonasal cancers diagnosed as ES were immunohistochemically stained for MIC-2 protein (positive in ES). **Results.** Retinoblastoma occurred before ES in ten cases (seven bilateral). In four others, retinoblastoma (three bilateral) developed before sinonasal neural tumors (poorly differentiated). ES also occurred after 14 cancers other than retinoblastoma (five lymphomas, four leuke-

mias, and one each of five miscellaneous cancers). The predominance of retinoblastoma prior to ES differs markedly from the low-frequency of retinoblastoma among childhood cancers in the general population. On the contrary, cancers other than retinoblastoma were proportionate to those in the general population. Previously, retinoblastoma followed by excesses of osteosarcoma and soft tissue sarcomas has been attributed to the action of the inherited *RB-1* gene. The sinonasal tumors stained negative for MIC-2 protein. **Conclusions.** Heritable retinoblastoma may predispose to ES and perhaps to a subset of poorly differentiated neuroectodermal tumors in the sinonasal region that may be related to olfactory neuroblastoma. *Med. Pediatr. Oncol.* 36:290–294, 2001. © 2001 Wiley-Liss, Inc.

Key words: Ewing sarcoma; retinoblastoma; olfactory neuroblastoma; sinonasal neuroectodermal tumors; second malignant neoplasms; *RB-1* gene

INTRODUCTION

Because we noted several case reports of Ewing Sarcoma (ES) as second malignant neoplasms (SMN), we made an extensive search of the literature for ES occurring after any form of cancer. An excess of ES after retinoblastoma has been reported by Helton et al. [1], and a possible excess after other primary cancers has been reported by Aparicio et al. [2]. Four sinonasal neural cancers after retinoblastoma were reported as ES or primitive neuroectodermal tumors (PNET) [3–6].

ES of bone has been recognized as a member of a broader category designated as the Ewing sarcoma family of tumors. Included in this category are PNET, ES of soft tissue and bone, and a small cell tumor of the thoracopulmonary region known as an “Askin” tumor [7]. Epidemiologic clues to the origins of ES have been hard to find. It is rare among nonwhites, and it shares almost no similarities of occurrence with osteosarcoma [8], the other major bone cancer found in the young. The reason for this lack of similarity is apparently due to their different origins: mesenchymal for osteosarcoma, and neural for ES.

MATERIALS AND METHODS

The literature was searched with the use of PubMed, keying on ES as an SMN or as a multiple primary neo-

plasm. We then used the Web of Science (Citation Index expanded), keying for retinoblastoma on Eng et al. [9], and for ES-like sinonasal neural cancers by keying on Klein et al. [3] and Frierson et al. [4]. Several cases were reported more than once, and care was taken not to count them again. We also searched for ES as an SMN after retinoblastoma in the population-based Surveillance, Epidemiology and End-Results (SEER) Program of the National Cancer Institute, which covered about 10% of the US population, 1973–1995. Because sinonasal tumors with ES-like morphology can be either true ES or (usually) olfactory neuroblastoma, and because immunostaining for the protein expressed by the MIC-2 gene helps distinguish between the two, we obtained unstained

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TABLE I. Cases of Retinoblastoma Preceding ES of Bone*

Case	References	Rb laterality	Gender	Age at diagnosis		ES site	Country
				Rb	ES		
1	Kitchin [11] ^a	B	F	5 m	7 y	Femur	USA
2	Kitchin [11] ^a	B	F	5 m	14 y	Femur	USA
3	Kay [12]	B	F	18 m	4 y	Femur	USA
4	Helton [1] ^b	B	F	9 m	13 y	Calcaneus	USA
5	Mohney [14]	B	M	9 m	15 y	Metatarsal	USA
6	Ceha [15] ^c	B	F	12 m	18 y	Fibula	Holland
7	Shifter [19] ^d	B	F	1 m	10 y	Ulna	Denmark
8	Helton [1]	U	M	24 m	21 y	Ilium	USA
9	Helton [1]	U	F	12 m	11 y	Tibia	USA
10	Okeda [21]	U	F	6 m	12 y	Scapula	Japan

*Abbreviations: Rb, retinoblastoma; ES, Ewing sarcoma; B, bilateral; U, unilateral; M, male; F, female; m, months; y, years.

^aAlso reported by Wong [6] and Abramson [10].

^bAlso reported by Fontanesi [13].

^cAlso reported by Derkinderen [16], Moll [17] and Tucker [18].

^dAlso reported by Winther [20].

slides from Dr. Jagirdar [5] and Dr. Frierson [4], and a paraffin block from Dr. Klein [3]. We performed immunohistochemical staining for MIC-2 protein in these three ES-like sinonasal tumors.

RESULTS

Table I shows data for ten cases with ES after retinoblastoma, which was bilateral in seven cases. All but two were females. The sites of four ES were unusual: the calcaneus, first metatarsal, ulna, and fibula. The age at diagnosis of retinoblastoma was 2 years or younger, and the median age of ES as an SMN was 13.5 years (range, 4–21 years). Three patients developed additional malignant tumors in the fields of radiotherapy, presumably radiation-induced: malignant fibrous histiocytoma at 18 years of age (Case 2); osteosarcoma at 4 years of age (Case 3); and three cancers (Case 6), including an extraskeletal osteosarcoma and mucoepidermoid parotid cancer at 29 years of age, and squamous cell carcinoma of the nose at 32 years of age.

The sinonasal neural cancers in four cases (Table II) resembled ES histologically, but they were negative by immunohistochemical staining for MIC-2 protein. Retinoblastoma had occurred at 2 years of age or younger, and was bilateral in three of the cases.

Fourteen ES occurred after primary cancers other than retinoblastoma (Table III): lymphomas in five cases (three were Hodgkin type), acute leukemia in four, (two myelogenous, two lymphocytic), neural cancers in two (brain stem glioma and adrenal neuroblastoma), and one each of Wilms tumor, malignant fibrous histiocytoma, and thyroid cancer. The median age at first neoplasm was 11.5 years (range, 3–25 years), and the median age of ES as an SMN was 17 years (range, 10–20 years, plus one at 30 years). Five of the 14 ES occurred at unusual sites: ribs/clavicle, ulna, fibula (two cases), and temporal bone.

Our search of the SEER Program disclosed no cases of ES reported as SMN after 476 cases of retinoblastoma, 1973–1995. The incidence of ES after retinoblastoma is unknown, so no test of statistical significance could be made regarding the four cases in our study. There were only two patients with the far more common osteosarcoma as an SMN.

DISCUSSION

The ten patients who had retinoblastoma before ES were younger than usual at diagnosis. In seven, the eye tumors were bilateral, which indicates germline transmission [31]. In the general population about 60% of all retinoblastomas are nonhereditary, 15% are unilateral hereditary, and 25% are bilateral hereditary [32]. Thus, among the ten cases, two or three were expected to have bilateral retinoblastoma as compared with seven observed.

Among males, the incidence of ES rises early in life and peaks at 15–19 years. The peak for females is much lower, earlier, and flatter [33]. The incidence then falls to near zero by 35 years, an age-ceiling for developing ES. After retinoblastoma the median age at diagnosis of ES in our series was 13.5 years, younger than usual (17 years), and only one case (case 11) was 30 years of age. Thus, an earlier age at diagnosis is found not only in hereditary retinoblastoma, but also in ES when it follows this cancer. In four of the ten cases ES was at an atypical site.

Cases 4, 8, and 9 (Table I), reported by Helton et al. [1], included two of the three children with unilateral retinoblastoma. The authors could find no further information about one child; the other had no family history of retinoblastoma and no evidence of a multifocal neoplasm in the affected eye, which, if found, would support germline transmission. The report on the third unilateral

TABLE II. Cases of Retinoblastoma Preceding Sinonasal Cancer Resembling ES but Classified as Olfactory Neuroblastoma (Esthesioneuroblastoma)

Case ^a	References	Rb laterality ^b	Gender	Age at diagnosis		MIC-2 protein
				Rb	S-N cancer	
1	Frierson [4]	B	F	7 m	38 y	Neg.
2	Frierson [4]	B	M	10 m	23 y	Neg.
3	Wong [6]	B	?	<12 m	34 y	ND
4	Klein [3] ^c	U	F	2 m	18 y	Neg.

^aOne case excluded: bilateral Rb at age 2 and nasal ES at age 12, not further described [22].

^bAbbreviations: see Table I footnote; S-N, sinonasal; Neg., negative; ND, not done.

^cAlso reported by Saw [5].

TABLE III. Cancers Other than Retinoblastoma that Preceded ES of Bone

Case	References	First cancer	Gender	Age (yrs) at diagnosis		ES site	Country
				FMN ^a	ES		
1	Anselmo [23]	Hodgkin disease	F	13	20	Chest	Italy
2	Davis [24]	Hodgkin disease	M	13	15	Chest	USA
3	Tucker [18]	Hodgkin disease	F	13	20	Ribs/clavicle	USA
4	Zoubek [25]	Large-cell lymphoma	F	12	20	Pelvis	Austria
5	Malkin [26]	NHL	NA	NA	NA	NA	USA
6	Aparicio [2]	ALL	M	3	15	Ulna	Spain
7	Tilly [27]	ALL	F	8	19	Sacrum	France
8	Aparicio [2]	AML	M	11	18	Fibula	Spain
9	Tucker [18]	AML	M	12	16	Pelvis	USA
10	Fisher [28]	Wilms tumor	F	5	10	Thorax	USA
11	Aparicio [2]	MFH	M	25	30	Pelvis	Spain
12	Tsunematsu [29]	Thyroid carcinoma	F	9	14	NA	Japan
13	Jiminez [30]	Neuroblastoma	NA	NA	NA	Fibula	Spain
14	Schwartz [22]	Brainstem glioma	NA	5	10	Temporal bone	Argentina

^aAbbreviations: See Table I footnote; FMN, first malignant neoplasm; NA, not available; NHL, Non-Hodgkin lymphoma; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; MFH, malignant fibrous histiocytoma.

retinoblastoma, in a Japanese child (Case 10), provided no information in this regard. In their review of the literature Helton et al. [1] listed two cases twice; they were first reported by Kitchin [11], and again by Abramson et al. [10]. In Table I we excluded these duplicates. Could the SMN in this series of cases be due to chance? If so, one would expect the percentage distribution of initial cancers to resemble that of the general US white population under 15 years of age: leukemia, 31.4%; tumors of the central nervous system, 17.4%; lymphoma, 13.1%; and retinoblastoma, 2.6% of the total [34]. In our series there was a great preponderance of retinoblastoma, 14 of 28 SMN [ten ES of bone (Table I), and four sinonasal tumors (Table II)], whereas less than one was expected (2.6% × 28). The frequency of ES after retinoblastoma in the general population is too low to be detected in the SEER Program.

The median age at diagnosis of ES after cancers other than retinoblastoma was 17 years, and the anatomic site was unusual in 5 of 14 cases. The age at diagnosis and the preponderance of childhood leukemia or lymphoma (8 of 12 cases with ages known) resemble the experience of the general population, as noted above. These findings are likely due to chance.

Moll et al. [35] have reviewed the literature on the most frequent SMN among survivors of retinoblastoma, 1966–1995 (series with 50 or more cases). They found 243 SMN; 37% had osteosarcomas and 6.9% had soft tissue sarcomas mostly in the field of radiotherapy. Friend et al. [36] demonstrated homozygous deletions in the *RB-1* locus in mesenchymal tumors (osteosarcoma and soft tissue sarcomas) among patients with no personal or family history of retinoblastoma. We found two reports on the status of *RB-1* in sporadic ES. Ozaki et al. [37] tested two ES cases. One had a heterozygous deletion (ES of the clavicle) and the other had no deletion. Another study by Miller et al. [38] showed one of four ES had *RB-1* alteration.

It has long been known that retinoblastoma patients who have not had radiotherapy have an inherent excess of osteosarcoma near the knee [39]. In patients who were irradiated, the frequencies of osteosarcoma and soft tissue cancers near the eyes is increased in relation to dose [40], an interaction of heredity and the environment. In the genesis of the sinonasal neural neoplasms or of ES, there is no support for the role of radiation. Neither were found in a follow-up of 204 children in Germany who, just after WWII, were empirically treated for bone tuber-

culosis by injection of high doses of radium-224 [41]. Thirty-four children developed bone sarcomas, mostly osteosarcoma or fibrous histiocytic sarcoma, but no ES. Also, follow-up studies of groups exposed to radiotherapy have not shown an excess of these tumors [42].

Four small-cell sinonasal cancers were found in our search of the literature for ES as an SMN, all of which were reported to have histologic and immunohistochemical features of PNET similar to those observed in the ES family of tumors [4–6,9]. However, the ES family of tumors are characterized by the presence of specific translocations resulting in the formation of the ES-specific fusion transcripts, and expression of the MIC-2 surface protein [7]. We found no expression of MIC-2 protein in three small-cell sinonasal neoplasms that occurred after retinoblastoma. Furthermore, one of them was previously reported to be negative for the t(11;22) translocation [5]. The majority of nonhematological small-cell neoplasms of the sinonasal region are classified as olfactory neuroblastomas. Because some sinonasal small-cell neoplasms were found to exhibit the ES-specific t(11;22) translocation [43], or the *EWS/FLI-1* fusion product [44], it was suggested that olfactory neuroblastomas are related to ES. However, this was not confirmed in subsequent larger studies of sinonasal small-cell neoplasms, which showed that olfactory neuroblastomas lack *EWS/FLI-1* transcripts and MIC-2 protein [45–49]. The absence of MIC-2 protein and t(11;22) translocation in the sinonasal neoplasms that were encountered after retinoblastoma would suggest that they are not ES, but rather olfactory neuroblastomas. However, they appeared quite poorly differentiated histologically and behaved in an aggressive fashion clinically, in contrast to traditional olfactory neuroblastomas. It would be of interest to know if retinoblastoma has occurred in families of patients with olfactory neuroblastoma, as in families having one member with retinoblastoma and another with osteosarcoma [50].

CONCLUSION

In our series, the retinoblastomas were deemed to be hereditary and, therefore, the *RB-1* mutations (the first of two hits) affected all cells of the body. The role of the *RB-1* gene in the initiation of various SMN has been established [6,9,31]. ES appears to belong on this list, but to rule out atypical ES, archival specimens or new cases of postretinoblastoma ES should be studied for the MIC-2 protein and t(11;22) translocation, or *EWS/FLI-1* gene fusion. Also, deletions of *RB-1* should be sought in sporadic ES.

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