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Multiple malignancies in a patient with bilateral retinoblastoma

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Abstract
A case is presented of a patient with bilateral retinoblastoma, treated at infancy with surgery, chemotherapy and radiotherapy, who subsequently developed at least four additional histologically distinct malignancies: a Ewing sarcoma of the left fibula, two extraskeletal osteosarcomas of the left lower extremity, a mucoepidermoid carcinoma of the right parotid gland and a squamous cell carcinoma of the left paranasal cavity.

In addition to retinoblastoma, patients with a germline *RB-1* mutation are at high risk of second primary malignancies. An additive carcinogenic effect of cytotoxic therapy in these patients has been assumed. Patients with hereditary retinoblastoma should be under life-long follow-up programmes including a regular head and neck examination for detection of new primaries, especially in the radiation field of the presenting retinoblastoma.

Key words: Retinoblastoma; Neoplasms, multiple primary

Introduction

Retinoblastoma (RB) is well known as a childhood intraocular malignancy with an incidence of 1 in 18 000 live births. It is more common among males with a sex ratio of 1.7:1 (Winther *et al.*, 1988). The disease is usually diagnosed before the age of four and may even be present at birth. Symptoms are leucocoria (white pupillary reflex), strabismus or a mass in the fundus noticed during ocular examination (Shields and Augsberger, 1981).

The disease may present in two ways, hereditary (34 per cent) or sporadic (66 per cent) (Winther *et al.*, 1988). RB is the most classical example of a malignancy caused by inactivation of a tumour suppressor gene, a model described by Knudson more than 20 years ago. Both copies of the gene must be inactivated for tumour development to occur (Knudson, 1971). The gene responsible for retinoblastoma is known as *RB-1* and is located on the long arm of chromosome 13 (13q14) (Friend *et al.*, 1986). In hereditary retinoblastoma, the child has inherited one RB-gene which harbours a mutation and the mutated gene is present in all somatic and germ cells. A retinoblastoma will develop when a somatic mutation inactivates the second allele in a retinal cell. Familial retinoblastoma is transmitted in an autosomal dominant pattern with 90 per cent penetrance (ie. 90 per cent of the carriers develop a retinoblastoma). In the sporadic form of the disease two mutational events are required in a retinal cell, the second mutation occurring in a descendant of a cell that has already acquired the first genetic injury. The product of the *RB-1* gene plays a key role in the regulation of the cell cycle at the START checkpoint in the late G1 phase, at which the cell commits itself to another round of DNA replication (Weinberg, 1995). Deregulation of the cell cycle by inactivation of *RB-1* is therefore an important event in oncogenesis.

Retinoblastoma has a high local cure rate after surgery and/or radiotherapy. However, long-term survivors of bilateral retinoblastoma are at high risk of developing secondary primaries (Draper *et al.*, 1986; Winther *et al.*, 1988; Strong, 1993; Fontanesi *et al.*, 1995).

Although second primary tumours in these patients were initially attributed to radiation therapy, it has become clear that patients with hereditary retinoblastoma are at risk also without prior radiotherapeutic treatment (Draper *et al.*, 1986; Winther *et al.*, 1988; Kay *et al.*, 1996). The following case illustrates the striking cancer proneness of a long-term survivor of bilateral retinoblastoma, who developed at least four subsequent malignancies among which there were mucoepidermoid carcinoma of the parotid gland and a squamous cell carcinoma of the paranasal cavity, which may have been radiotherapy-related.

Case report

The medical history of this 34-year-old woman started in 1962 when she was one-year-old, and presented with a retinoblastoma in her left eye for which she was treated by enucleation and combination of chemotherapy (data incomplete) and external beam radiotherapy. One year later a second retinoblastoma developed in her right eye, which was treated in the same way. Irradiation was delivered by cobalt^{60}-external beam treatment using a two-field technique to a total dose of 40 Gy. No data are available concerning fractionation size or the additional use of a radium application.

To our knowledge she was the first case of retinoblastoma in her family, although other cases of cancer were reported. Her mother suffered from a colon carcinoma and

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an ovarian carcinoma, a brother of her father was treated for 'bone cancer'. Unfortunately, no further details of these cases are available. The patient gave birth to two children, of whom one developed bilateral retinoblastoma at the age of one year.

The patient was symptom-free until the age of 20, when she noted a painful swelling of the left knee. A Ewing sarcoma was diagnosed in the left fibular head. Considering her visual impairment, a limb-sparing procedure was performed. A course of radiotherapy was given to a total dose of 50 Gy in five weeks in another hospital, no exact details of field alignment or dosimetry are available. A year of adjuvant chemotherapy followed consisting of four courses of actinomycin, adriamycin, vincristine and cyclophosphamide. Due to side-effects, the complete course of chemotherapy was not completed. Nine years later she presented again with pain in her left knee. Two separate tumours were diagnosed in the anterior tibialis muscle without connection to bony structures and outside the region of the previous Ewing sarcoma. She underwent a through-knee amputation and histological examination was compatible with extraskeletal osteosarcoma (Figure 1). No direct connection between the two histologically identical tumours could be found. Thus, it was impossible to differentiate between two independent primary tumours or a primary with a metastasis. In the same year another neoplasm presented in the right parotid gland, which was treated with parotidectomy. Histology showed a mucoepidermoid carcinoma (Figure 2). She was treated postoperatively with radiotherapy to the right parotid fossa to a total dose of 60 Gy in six weeks.

Again, three years later, she presented with a period of epistaxis, due to a tumour in the left nasal fossa with invasion of the ethmoid sinuses, and medial part of the left orbit and base of the skull. A biopsy showed a poorly differentiated squamous cell carcinoma with basaloid features (Figure 3). This tumour was not amendable by surgery. Since the tumour-site was in a previously irradiated area, she was treated with palliative chemotherapy consisting of cisplatin and 5-FU. After two courses she refused further treatment and died shortly thereafter.

Discussion

Although the local cure rate of retinoblastoma is excellent after enucleation and radiotherapy, survivors of the hereditary type of RB have a more than ten-fold relative risk for developing additional primary cancers (Winther *et al.*, 1988). In the group of non-hereditary retinoblastoma the relative risk is significantly lower. The genetic cases predominate during infancy. The median latency period from curative ocular treatment to the clinical manifestation of a second primary tumour is about 16 years, corresponding to the tumour-free interval of 19 years in our patient.

Irradiation and chemotherapy may put these patients at further risk, although second malignant neoplasms are also common in patients who have not received these treatments (Kay *et al.*, 1996). In a series of 882 retinoblastoma patients, Draper *et al.* 1986 described 30 patients with a second primary neoplasm. The most common type of secondary malignancies following retinoblastoma was osteocarcinoma, with eight cases in and 10 outside the radiation field. Other tumour types included soft tissue sarcoma, melanoma, acute lymphoblastic leukaemia, brain tumours and carcinomas. A similar spectrum of secondary neoplasms in retinoblastoma patients is also reported in other series, with tumours

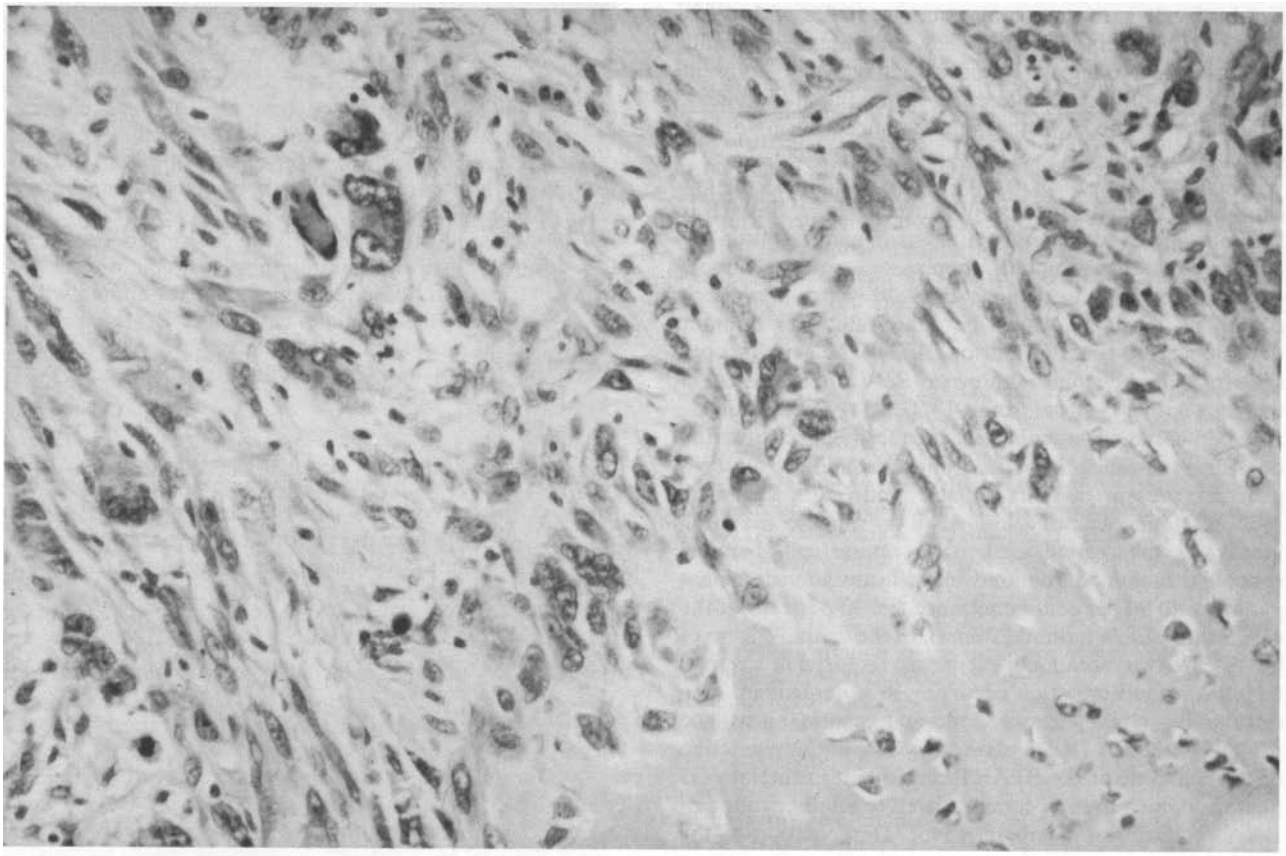

FIG. 1

Osteosarcoma of the left knee area. A polymorphic mesenchymal proliferation with bizarre giant cells and formation of osteoid (H & E; × 200).

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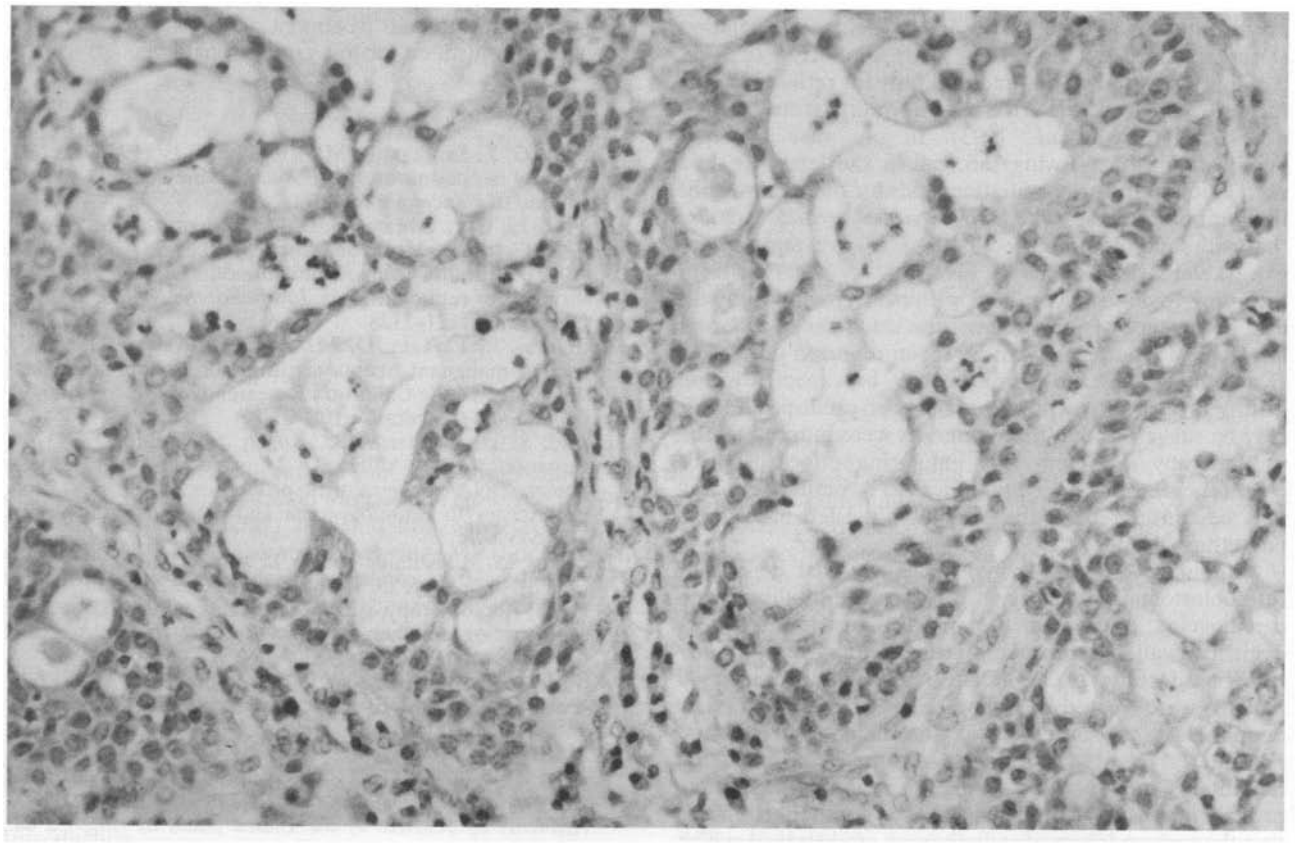

FIG. 2
Mucoepidermoid carcinoma of the parotid gland with predominantly mucinous, intermediate and clear cells (H & E; × 100).

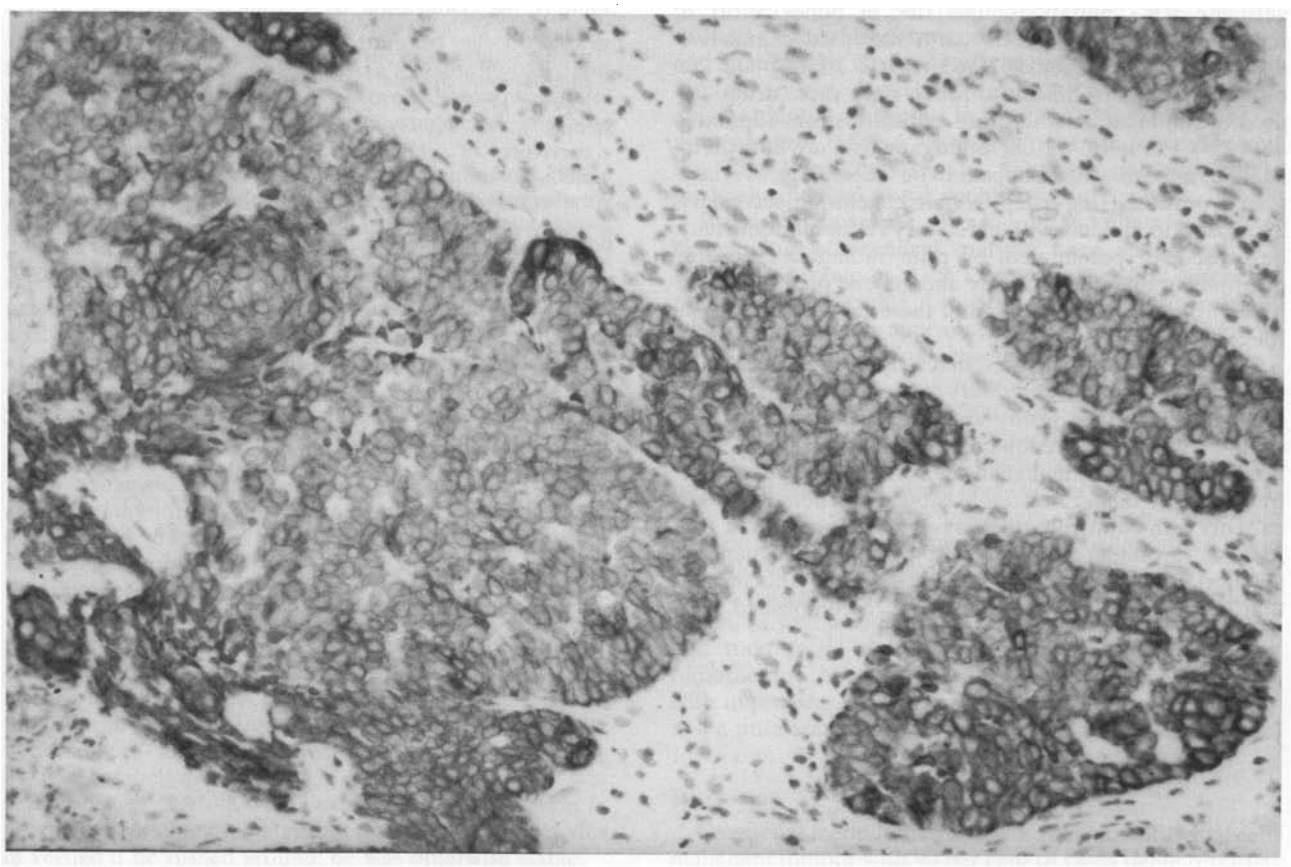

FIG. 3
Non-keratinizing squamous cell carcinoma with basaloid features (anti-keratin immunostaining with haematoxylin-counterstain, × 100).

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arising outside as well as inside the field of irradiation (Draper *et al.*, 1986; Eng *et al.*, 1993). In a series of 1,458 patients it was shown that radiotherapy for retinoblastoma further increased the risk of mortality from second neoplasms (Eng *et al.*, 1993). In our case the first manifestation of a Ewing sarcoma in the left knee had no relation to the prior radiation fields for the treatment of the retinoblastomas. The two separate second tumours that subsequently presented at the left knee-region were extraskeletal osteosarcomas; histologically different from the prior Ewing sarcoma and within the radiation fields. The occurrence of subsequent bone sarcomas of different histological type is rare, but has been reported previously (Kay *et al.*, 1996) and may especially be expected in the setting of a patient with genetic cancer predisposition. It may be suggested that these tumours were induced by the radiotherapy treatment. An enhancing effect of prior chemotherapy may have played a role. A similar aetiology may be considered for the tumour in the left nasal fossa and ethmoid sinuses.

Although it seems rational to assume that hereditary retinoblastoma patients have a high susceptibility to the carcinogenic effects of radiation, there is no direct evidence available to prove this assumption. In a population based study of 175 Danish patients, in which 48 patients were treated by radiotherapy, no second primary neoplasms were observed in the field of irradiation (Winther *et al.*, 1988). Comparisons between irradiated hereditary and sporadic forms of retinoblastoma may provide an answer to this question, on the understanding that the type and dose of radiotherapy are identical, which presumably can only be tested in a prospective fashion. Also chemotherapy may have a potentiating effect for the development of secondary neoplasms in patients with germline *RB-1* mutations. The risk of bone cancer is reported to increase linearly with increased cumulative dose of alkylating agents (Hawkins *et al.*, 1966). On the other hand, this is difficult to prove since these drugs are used in combination with other cytostatic drugs (Smith *et al.*, 1989). Furthermore, chemotherapy data are difficult to analyse, since they often appear to be incomplete, as is also seen in our case (Eng *et al.*, 1993). In conclusion, secondary neoplasms in patients with hereditary retinoblastoma may be caused, or potentiated, by prior radiation exposure, prior polyagent chemotherapy and genetic predisposition. Most probably, a combination of these factors may play a role.

This case report illustrates, that long-term survival after multiple neoplasms in hereditary retinoblastoma patients is achievable and may justify an aggressive approach with combined modality treatment. Our patient developed at least four secondary malignancies during the 33 years after treatment of bilateral retinoblastoma. As demonstrated, patients with curatively-treated retinoblastoma are at risk for the development of second primary malignancies, amongst others in the head and neck region. This implies that life-long follow-up should be accomplished. An aggressive combined treatment according to standard protocols is justified for this group of patients.

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