Malignant Astrocytoma of the Optic Nerve in a Child

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ABSTRACT: Malignant gliomas of optic nerve and chiasm are rare, rapidly fatal neoplasms of adulthood. This report documents the occurrence of a malignant astrocytoma of the optic nerve in an 11-year-old boy who 9 years previously had a cerebellar medulloblastoma treated with surgery and irradiation. This malignant optic nerve glioma followed the same aggressive clinical course as that seen in adults, with death 9 months after diagnosis despite surgery and chemotherapy. Radiation may have been an important factor in the development of this malignant tumor which is almost never seen in the pediatric age group.

RÉSUMÉ: Astrocytome malin du nerf optique chez un enfant. Les gliomes malins du nerf optique et du chiasma sont des néoplasies rares, rapidement fatales de l'âge adulte. Nous rapportons un cas d'astrocytome malin du nerf optique chez un garçon de 11 ans qui avait été traité 9 ans auparavant pour un médulloblastome cérébelleux par chirurgie et irradiation. Ce gliome malin du nerf optique a eu une évolution clinique aussi agressive que celle que l'on rencontre chez l'adulte, le décès étant survenu 6 mois après le diagnostic, malgré la chirurgie et la chimiothérapie. L'irradiation a possiblement été un facteur inportant dans le développement de cette tumeur maligne qui ne survient presque jamais dans la population d'âge pédiatrique.

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Primary gliomas of optic nerve and chiasm are uncommon tumors, constituting 1% and 6% of central nervous system and orbital neoplasms respectively.[1] Approximately 85% of these lesions occur before 15 years of age and are regarded as slowly progressive benign neoplasms with only rare instances of malignant transformation recorded.[2,3] In contrast, optic gliomas arising in adults can be highly malignant, pursuing an aggressive course regardless of therapeutic intervention.[4-7] Adults with these malignant tumors frequently have signs and symptoms suggestive of optic neuritis[4,6] but clinical presentation may also mimic retinal vein occlusion,[4-7] temporal arteritis[8,9] or compressive lesions of optic pathways.[5,10]

This report describes a rapidly lethal high grade astrocytoma of the optic nerve in an 11-year-old boy who presented with neovascular glaucoma. The neoplasm was diagnosed 9 years after he received surgery and radiation for a cerebellar medulloblastoma and may have been related to the latter form of treatment.

Case Report

An 11-year-old boy presented to his family physician in May 1989 with a 2 week history of discomfort and redness of the left eye. It was noted that the vision was markedly reduced and the pupil was dilated and non-reactive. The child was then referred to the Children's Hospital, Winnipeg for ophthalmological assessment.

The ocular history was unremarkable apart from the recent onset of discomfort in the eye. The child had no systemic complaints. Family was non-contributory. However, in January 1980, at age two, he had been treated for medulloblastoma of the right cerebellar hemisphere. At that time he had presented with vomiting, hydrocephalus and papilledema, and computed tomography (CT) scan showed a mass in the right cerebellar hemisphere (Figure 1). Surgery confirmed the presence of a cystic cerebellar tumor; all visible neoplasm was excised along with a portion of cerebellar cortex. In March 1980 he received, in 27 sessions over 40 days, 5400 rads of radiation to the posterior fossa. This was supplemented by 4400 rads to the whole brain including the posterior optic nerves in 22 treatments over 33 days and 3600 rads to the spine in 20 treatments over 30 days. In June 1980 a CT scan demonstrated no recurrence of tumor, and from that time until 1989 there were no further problems.

On examination, the left eye had light perception only. The conjunctiva was injected, and the cornea was edematous. Rubeosis iridis was evident. It was difficult to see the fundus; however, there were scattered intraretinal hemorrhages around the vascular arcades and the retina appeared edematous. The disc on the left was pale. Left intraocular pressure was 50 mm Hg. The right eye showed some peripheral cortical lens opacities, but was otherwise normal with 20/20 visual acuity. There was no proptosis of either eye.

A diagnosis of neovascular glaucoma was made. Initial management included oral acetazolamide, topical steroids and atropine to help clear the cornea for better fundoscopy and to relieve discomfort. A CT scan was subsequently obtained because of the uncertain etiology. This demonstrated thickening of the intra-orbital optic nerve compared with the right side, but no other orbital or intracranial abnormalities (Figure 2). CT myelogram was normal, as were cerebrospinal fluid studies.

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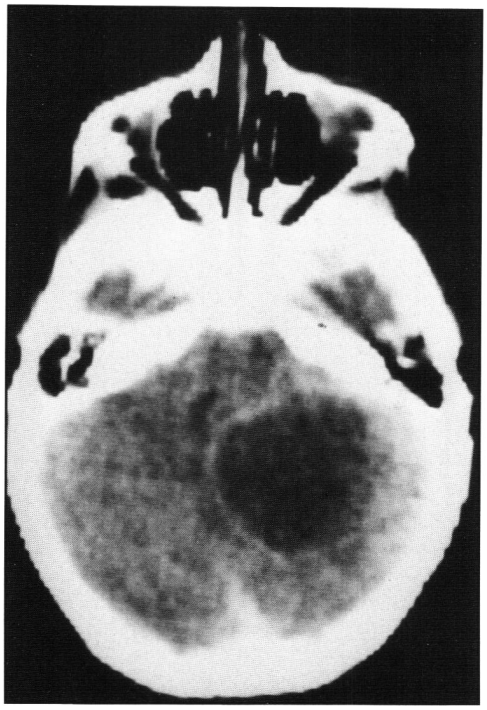

Figure 1 — Computed tomographic examination of brain with infusion (1980). A 4.5 cm peripherally enhancing lucent lesion is seen in the right cerebellar hemisphere displacing the fourth ventricle anteriorly and to the left.

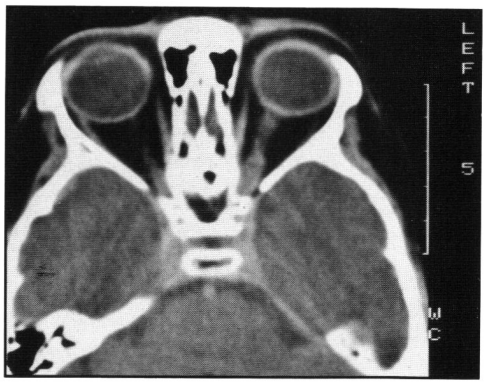

Figure 2 — Axial computerized tomography of orbits with contrast (June 1989) showing enlargement of the left optic nerve. Right optic nerve is not remarkable. Remainder of optic pathways, posterior fossa and cerebral hemispheres showed no significant changes.

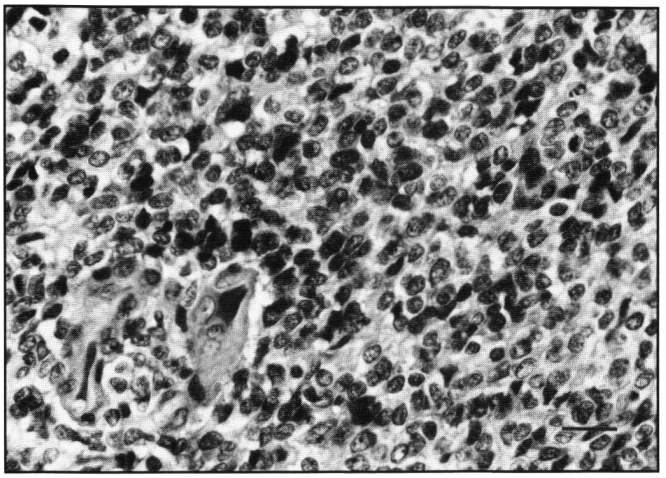

Figure 3 — Cerebellar medulloblastoma, hematoxylin and eosin, bar (bottom right hand corner) = 20 microns. Tumor is composed of numerous small cells with round to oval nuclei and scanty cytoplasm.

General physical examination disclosed no significant abnormalities; specifically, no stigmata of neurofibromatosis were evident.

The CT appearance of the optic nerve suggested either recurrence of the medulloblastoma, causing direct pressure on the optic nerve and subsequent ischemia, or a second pathology, unrelated to medulloblastoma (which appeared to have been adequately treated previously).

In view of the uncertain optic nerve pathology, as well as the poor prognosis for survival of the eye, enucleation was recommended, with an attempt to be made to obtain as much of the optic nerve as possible. In June 1989 the eye was removed together with most of the intraorbital optic nerve.

Pathology

Cerebellar Tumor

The cerebellar tumor removed in 1980 consisted grossly of soft, gelatinous grey-tan tissue fragments mixed with cerebellar cortex, aggregating 5.0 × 4.5 × 1.0 cm. Light microscopy showed sheets of small cells with scanty, ill-defined cytoplasm and hyperchromatic, relatively uniform round to oval nuclei (Figure 3). Mitoses were numerous and diffuse infiltration of cerebellar cortex was evident. No cellular differentiation or specific architectural arrangements could be discerned in routine histologic sections. On electron microscopy, tumor cells were poorly differentiated with few cytoplasmic organelles and no cell junctions; rare cells showed astrocytic differentiation and contained intracytoplasmic filament bundles confirmed retrospectively as glial fibrillary acidic protein (GFAP) by immunoperoxidase technique. Final diagnosis was cerebellar medulloblastoma.

Optic Nerve Tumor

The enucleated left globe measured 24 × 23 × 25 mm. Excised optic nerve consisted of a portion of nerve measuring 4 mm in length × 4 mm on cross section attached to the eye and two separately submitted pieces of optic nerve with a total length of 22 mm and diameter of 6 mm. Dura was intact and unremarkable grossly but the nerve substance had a pale fleshy appearance with focal hemorrhages. On sectioning the globe, the optic nerve head was pale but not enlarged. Adjacent small retinal hemorrhages were seen but there were no other significant intraocular findings. Histologic sections revealed infiltration and replacement of normal optic nerve by neoplastic astrocytes. Malignant cells, including many giant forms, had hyperchromatic irregular pleomorphic nuclei (Figure 4). Mitoses were frequent but necrosis was minimal. Immunoperoxidase studies showed the neoplasm was positive for GFAP, S100 and vimentin, while electron microscopy demonstrated tumor cells with irregular nuclei, numerous intracytoplasmic intermediate filament aggregates and interdigitating cell processes (Figure 5); these findings confirmed the astrocytic lineage of the tumor. Tumor involved both attached and

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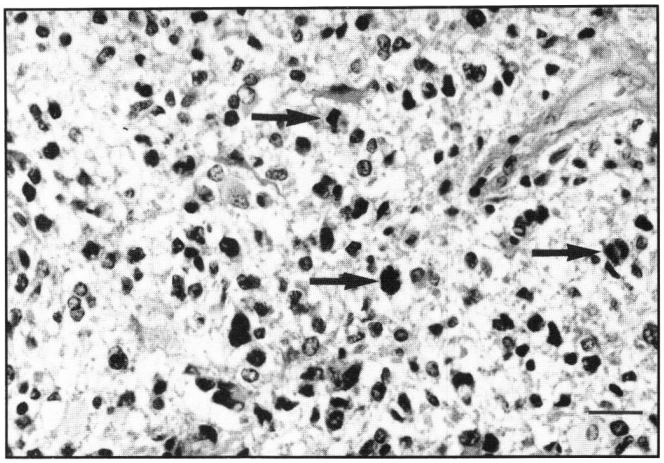

Figure 4 — Grade 3 astrocytoma, hematoxylin and eosin, bar (bottom right hand corner) = 20 microns. Note the pleomorphic tumor cells in a fibrillary background. Arrows indicate mitoses.

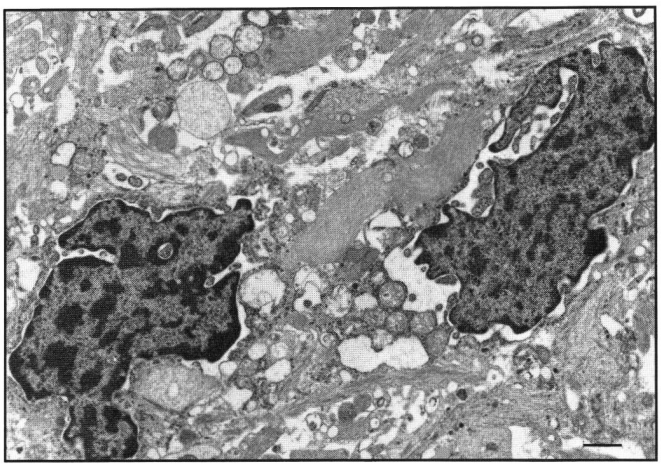

Figure 5 — Electron micrograph of malignant astrocytoma, bar (bottom right hand corner) = one micron. Tumor cells contain, within interdigitating cell processes, numerous bundles of intermediate filaments, shown immunohistochemically to be glial fibrillary acidic protein.

separately submitted portions of the optic nerve including the resection line and the optic nerve head which, along with adjacent retina, was disorganized and gliotic. Malignant cells infiltrated the pia and focally, the arachnoid, but no collections of tumor cells were visible in the subarachnoid space. There was no histologic evidence of preexisting benign optic nerve glioma and no areas resembling the previous medulloblastoma were seen. Diagnosis was grade 3 astrocytoma of optic nerve. Additional intraocular findings included rubeosis iridis, ectropion uveae and peripheral anterior synechiae consistent with neovascular glaucoma; hemorrhage involving peripapillary sensory retina; old vitreous hemorrhage; and abnormalities of posterior lens cortex, presumably related to previous radiation.

Subsequent Management

It was felt by the attending oncologists that further radiotherapy should not be carried out in view of the previous irradiation for medulloblastoma. Magnetic resonance imaging (MRI) done just prior to chemotherapy showed no visible abnormalities apart from changes in the orbit consistent with previous eye enucleation. A course of "8 in 1" chemotherapy[11] was started in July, with two sessions of drug administration at two week intervals. The child developed nephrotoxicity from cis-platinum, which was switched to carboplatinum. Two more courses were given over the next 3 months.

In November, a few weeks after a course of chemotherapy, the lens opacities previously seen in the right eye were noted to have increased and the vision had deteriorated to 20/50. The visual field, though somewhat unreliable, appeared full, indicating no obvious chiasmal pathology.

CT scan in December 1989 showed a mass in the left optic canal and chiasm with extension into the hypothalamus (Figure 6). Chemotherapy was therefore discontinued and palliative radiotherapy was given to the orbit.

In February 1990 the patient became hyperphagic and somnolent. CT scan showed an increase in the suprasellar mass, and "drop" metastases in the 3rd, 4th and lateral ventricles (Figure 7). The patient died just over a week later. No autopsy was performed.

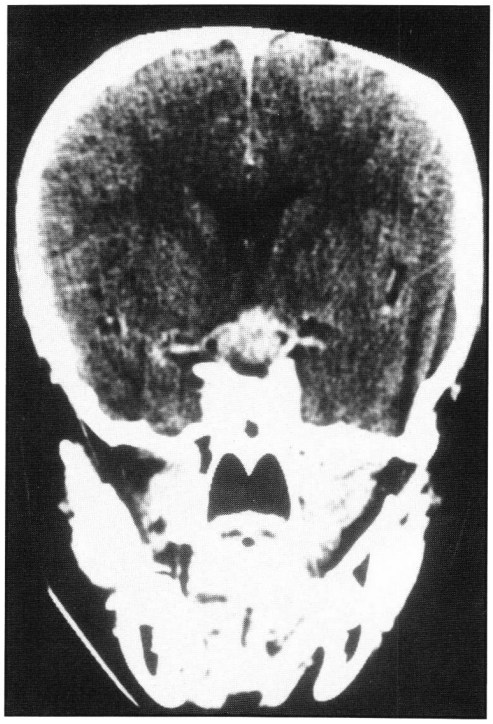

Figure 6 — Axial computed tomography coronal views of suprasellar region (December 1989). An enhancing lobulated suprasellar mass is seen, compatible with posterior extension of malignant astrocytoma to involve hypothalamus and optic chiasm.

Discussion

The discovery of malignancy in an individual with a previous, apparently successfully treated, malignant neoplasm necessitates consideration of both metastatic disease and a new

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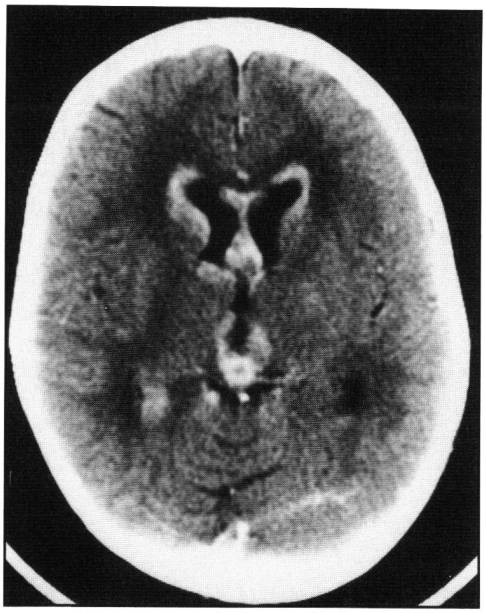

Figure 7 — Axial computed tomography examination of brain (February 1990) shows significant progression of intracranial lesions. Abnormal contrast enhancement of subependymal areas of 3rd, 4th and lateral ventricles is noted, consistent with drop metastases from the astrocytoma.

primary. With regard to our patient's optic tumor, two possibilities exist: either it is a primary high grade astrocytoma of the optic nerve or it represents a metastatic glial element of the medulloblastoma. While rigorous scientific proof to discount the latter contention cannot be provided, we believe that the former hypothesis is the most logical supposition for the following reasons. The two tumors are histologically dissimilar and each shows classical diagnostic features with light and electron microscopy and immunocytochemistry. Occasional medulloblastoma cells demonstrated astrocytic differentiation but this is a well recognized phenomenon which does not alter the initial diagnosis.[12] In view of this finding, however, it could be argued that the optic nerve neoplasm is medulloblastoma in which all cells show glial differentiation. This would surely be an exceptional circumstance, necessitating both late recurrence and metastasis. With regard to the latter, the most frequent mechanism of central nervous system metastasis for medulloblastoma is dissemination via the subarachnoid space. In the one reported instance of isolated metastasis from medulloblastoma to optic nerve,[13] the optic nerve sheaths were also involved, suggesting subarachnoid or meningeal spread. Multiple sections of optic nerve in our case revealed no subarachnoid tumor cell collections and CSF cytology was negative for malignancy. Recurrences of medulloblastoma usually follow Collin's rule: the period of risk for recurrence equals the patient's age plus 9 months (in our case 2 years + 9 months = 33 months). It has been estimated that approximately 2% of cases develop relapses after expiration of the risk period[14] with the majority of these occurring within 2 years post risk period. Although exceptions have been documented,[14,15] there are only rare reported instances where the ratio of actual recurrence period/period of risk was greater than that of our case.[14]

Long term follow-up studies of typical gliomas of optic pathways in children indicate that they are true neoplasms which generally behave in a benign fashion although prognosis depends on location; histologically benign chiasmal tumors have a much poorer outlook than those confined to optic nerve regardless of treatment (44% versus 85% survival, mean 17 years), largely due to extension into adjacent vital brain structures.[16,17] In contrast, optic nerve/chiasm gliomas in adults not infrequently are high grade malignant uniformly fatal neoplasms, unresponsive to surgery, radiation or chemotherapy.[4-10] Not only did our patient's optic nerve glioma resemble the malignant adult type histologically, it also pursued a fulminant course with death occurring 9 months after diagnosis, despite subtotal excision and chemotherapy. Most adult cases have presented with decreased visual acuity and on examination have shown either papilledema with peripapillary hemorrhages or normal optic discs .[4-10] Neovascular glaucoma, an initial finding in our case, was unusual even in adults, and if it occurred, developed late rather than at presentation.[7,18] In the pediatric age group neovascular glaucoma is an uncommon clinical problem and necessitates exclusion of intraocular malignancy such as retinoblastoma. Occasional benign optic nerve gliomas in children have been associated with neovascular glaucoma possibly due to venous stasis.[19] Interference with central retinal vasculature may also have been a factor in our patient as the central retinal vein was distorted and narrowed adjacent to and within the lamina cribrosa.

Review of the English language literature discloses 4 previously reported pediatric cases of high grade astrocytoma/anaplastic glioma involving optic nerve and chiasm. Udvarhelyi et al.[20] mentioned 2 individuals, one a 5-year-boy with macrocephaly and diminished visual acuity of 3 years duration, the other a 6-year-old boy who presented with unilateral rotatory nystagmus and decreased vision. Both children had midline/suprasellar tumors with optic nerve/chiasm involvement. Wong et al.[21] listed among their series of optic gliomas a high grade astrocytoma in a 6-year-old boy who died post operatively; the tumor involved not only optic nerve and chiasm but also hypothalamus and third ventricle. Brooks et al.[22] reported a 13-year-old girl with hypothalamic symptoms and a suprasellar tumor with hypertrophied chiasm but biopsy was unsuccessful, yielding no neoplastic or neural tissue. An additional instance of anaplastic astrocytoma involving optic chiasm and neighbouring tissues in a neonate was published in a journal from Japan.[23] All of these cases support Miller's contention that "optic glioma" is a non-specific term which has no implication regarding site of tumor origin;[24] these tumors may have originated in the chiasm but their advanced state at the time of diagnosis cannot exclude origin in 3rd ventricle or hypothalamus with forward extension into optic structures. The fourth case is also incompletely documented as no histologic verification was obtained. Representative biopsy is essential for accurate diagnosis as other neoplasms or inflammatory conditions may clinically mimic optic gliomas.[24] Our patient had CT demonstrated left intraorbital optic nerve enlargement, histologically proven to be a high grade astrocytoma. Although some tumor was evident at the optic nerve resection margin, both pre- and initial post-operative CT and MRI scans showed no enlargement of chiasm, right optic nerve or tumor within hypothalamus and ventricular tissues. Further, the patient presented with neovascular

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glaucoma and no hypothalamic symptoms, also suggesting origin within anterior optic pathways. As the disease progressed, a suprasellar mass and hypothalamic symptoms did become apparent, consistent with posterior extension of the tumor.

The occurrence of an unusual neoplasm such as a malignant optic nerve glioma in an individual from an age group where these tumors are practically unknown stimulates a search for predisposing factors. Benign optic nerve gliomas are frequently associated with neurofibromatosis and 3 of 4 patients with malignant degeneration had this condition.[2,3,25] In our patient, there was no evidence of either a pre-existing benign glioma or neurofibromatosis. Recently, a number of reports documenting an association between irradiation and gliomas have been published, including a post-radiotherapy optic chiasm malignant glioma in an adult.[26] The initial conditions for which the radiation had been given are diverse and include benign and malignant intracranial tumors such as pituitary adenomas,[26,27] craniopharyngiomas[28] and medulloblastomas,[29-32] hematologic malignancies, particularly leukemias in children,[33] and even scalp lesions such as hemangiomas[34] and tinea capitis.[35] Criteria which must be fulfilled in order to implicate radiation in the pathogenesis of these gliomas are well established:[36] a considerable length of time must have elapsed between radiation and glioma development; the glioma must occur in the irradiated area; the glioma must differ histologically from the initial tumor (if there had been one); and the incidence of gliomas post irradiation must be higher than in controls. Although a causal role for radiation cannot be proved, our patient meets these conditions. Nine years elapsed between the diagnosis of medulloblastoma and optic nerve glioma. The eyes including the region of the optic nerves had received radiation, supported by the presence of bilateral cataractous change and by review of radiation simulation films. The development of astrocytomas and glioblastoma multiforme after radiation for medulloblastoma has been recorded.[15,29-32] In two of these cases ,[29,30] the malignant glioma developed at the site of previous medulloblastoma but in the other patients,[15,31,32] the gliomas (one high grade and two low grade) were supratentorial. Supporting evidence can also be gained from animal experiments which have shown glioblastomas arising in 3 of 10 monkeys 3 to 5 years after receiving 600-800 rads while spontaneous tumor development in controls was in the order of 1%.[37]

Children who have had one malignant tumor are at increased risk for second malignancies. The cumulative probability for these individuals developing new cancer has been reported to be in the order of 12%.[38] Presumably this due to a combination of factors including genetic susceptibility, so called "tumor diathesis",[32] and the effects of radiation and chemotherapy. Data from experimental and human studies suggests radiation plays a complex role in tumor initiation, promotion and progression. The exact mechanism of radiation oncogenesis remains uncertain; both direct and indirect (free radical mediated) damage to critical cellular proteins and DNA with possible oncogene activation and/or anti oncogene inactivation merit consideration.[39] Radiation quality, dose, dose rate, tissues radiated and host factors such as immunocompetence and preexisting chromosomal abnormalities are also relevant. Well known tumor associations in the pediatric age group which raise the question of synergism between radiation, chemotherapy and genetic factors are the subsequent development of osteogenic sarcomas in heritable retinoblastoma patients and the frequent occurrence of hematologic malignancies and/or solid tumors in children with previous lymphoma or leukemia. Our case further emphasizes the importance of long term follow-up of children with cancer, even if they are apparently cured of their disease, as well as the necessity for histologic evaluation of any suspected neoplasm.

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