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Clinical Study

Radiation-induced spinal cord glioma subsequent to treatment of Hodgkin's disease: case report and review

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Summary

Radiation-induced neoplasms of the central nervous system generally present as meningioma or sarcoma. Spinal cord glioma after radiation therapy is rare and half of the cases documented occurred after treatment of Hodgkin's disease.A 39-year-old male presented with a 1-month history of gradually worsening neck ache and paraparesis. The patient had been treated for stage IB Hodgkin's disease 9 years previously with combined therapy: MOPP–ABV and a 40-Gray mediastinal radiotherapy from T1 to T10. Magnetic resonance imaging disclosed an intramedullary lesion from C6 to T2 and histopathological examination from biopsy demonstrated a malignant glioma. Despite chemotherapy and additional radiotherapy, the patient's neurological status worsened and he died 11 months after initial presentation.We suggest a strategy aimed solely at obtaining a tissue diagnosis to differentiate myelitis from tumor, and, in the event of tumor, confirming the strong likelihood of a high histopathological grade. The very limited survival associated with these tumors regardless of therapy advocates palliative therapies without attempting complete resection.

Introduction

Induction of neoplasia after therapeutic irradiation is well established and the widely accepted criteria include [1,2]: (i) the tumor developed in an irradiation field, (ii) there was a symptom-free interval of several years between initial irradiation and diagnosis of the tumor, (iii) tumor diagnosis was confirmed histologically, (iv) the new lesion had a different histology from the lesion originally irradiated. The majority of central nervous system (CNS) tumors as reported in the literature which are labeled as radiation-induced (RI) has been documented in the form of meningioma and sarcoma [2–5]. To date, RI gliomas are rare and usually intracranial [2,6]. Evidence of RI gliomas in the spinal cord is only circumstantial as very few cases have been documented [6–10]. Including the present case, half of these tumors occurred after irradiation for Hodgkin's disease (HD). The other cases developed after multiple fluoroscopies [8], after irradiation for thyroid carcinoma [6] and after medullomyoblastoma [10].

As the development of second cancer represents the most serious consequence of the curative therapy for HD, we report a new case of RI tumor occurring in the spinal cord after treatment of HD in order to demonstrate distinctive features and make some recommendations for managing such cases.

Case report

First presentation

In March 1993, this 30-year-old man presented with a 3-month history of progressive breathing discomfort. The chest radiograph and computerized tomography (CT) scan revealed a large anterior mediastinal mass (≥10 cm). A biopsy specimen was obtained via a left thoracotomy, and examination showed nodular-sclerosing HD. Abdominal CT, lymphangiogram and bone marrow examination were negative as well as palpation of lymph node areas. The patient was classified as stage IB HD. He was treated with combination chemotherapy: six cycles each of mustine, vincristine, procarbazine, and prednisone; and adriamycin, bleomycin, vinblastine (MOPP–ABV). Further CT scans demonstrated significant residual mass in the mediastinum, and radiotherapy was then recommended. Mediastinal radiotherapy from T1 to T10 was administered in October 1993 with a 25 MeV photon machine, delivering 40 Gy over 4 weeks at a daily dose of 2 Gy five times weekly. Close follow-up revealed neither residual mass nor evidence of recurrence.

Second presentation

Nine years later, in November 2002, the patient described a 1-month history of gradually worsening neck ache, lower extremity weakness and numbness, and bladder disturbances. On examination, there was mild paraparesis and patchy non-specific bilateral sensory abnormalities. Magnetic resonance (MR) images of the spine demonstrated a diffusely enlarged cervicothoracic spinal cord with evidence of homogeneous centromedullary contrast enhancement after intravenous injection of gadolinium from C6 to T2 (Figure 1). Lymph node areas, abdominal and thoracic CT scan, and bone marrow were negative and the patient was found to be in

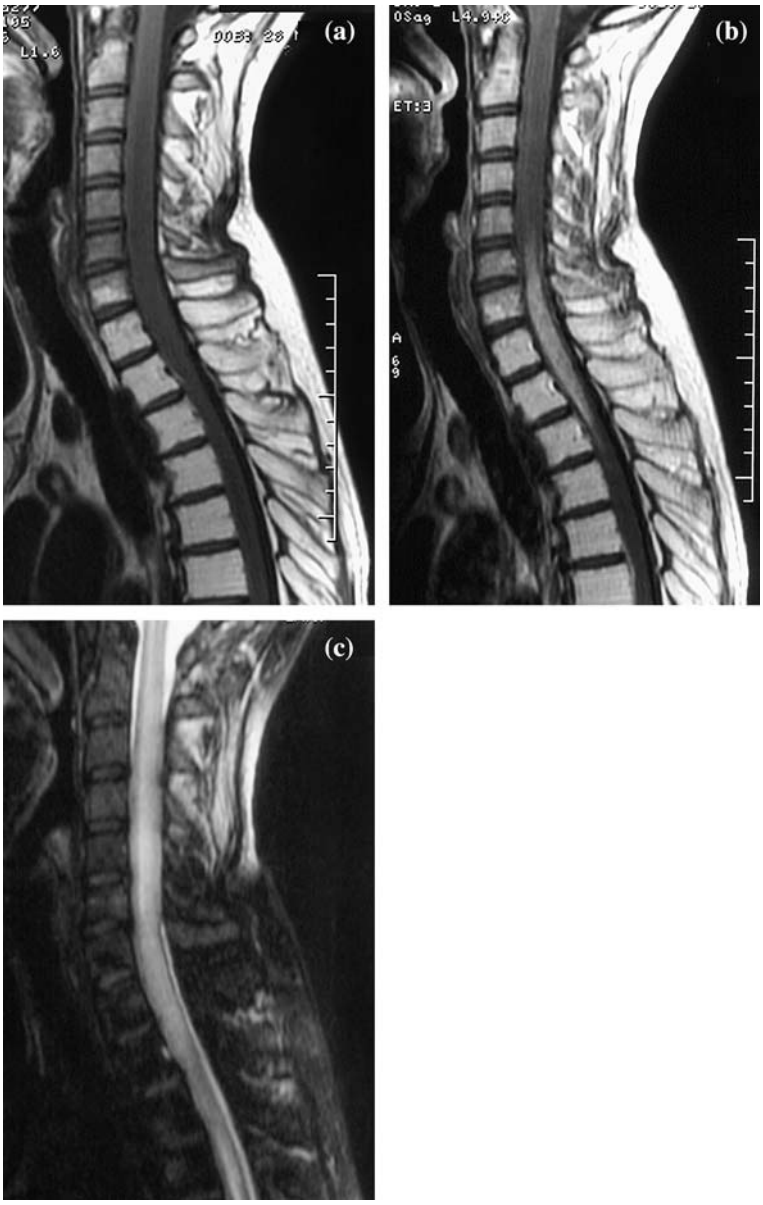

Figure 1. (a) Sagittal T1-weighted MR image showing diffuse enlargement of the cervical and upper thoracic spinal cord. The signal of the vertebral bodies is more hyperintense below the C7 level due to the previous irradiation. (b) Contrast-enhanced sagittal T1-weighted MR image showing a hyperintense signal within the spinal cord from C6 to T3. (c) Sagittal T2-weighted MR image showing an intramedullary hyperintense signal of the whole cord with enlargement of the cervical and upper thoracic portions.

complete remission from HD. Cerebrospinal fluid by lumbar puncture did not reveal any abnormal cells. Subsequently, the patient underwent surgery of the lesion at the T1 level via a C7-T2 laminectomy. On operation, the cord was found to be tense and diffusely enlarged. A midline myelotomy revealed a red-gray lesion that could not be separated from the normal tissue. The tumor was considered to be unresectable and only a biopsy was performed. The final histological diagnosis was a malignant glioma (Figure 2). Postoperatively, his paraparesis worsened with a T5 sensory level and he was then confined to a wheelchair. The patient was treated with six cycles of etoposide, cisplatin and fotemustine. In May 2003, he started to complain of increasing pain in the lower limbs, chest, shoulders, and paresthesias in both hands. Spinal MRI and clinical evaluation remained unchanged. In August, the patient was readmitted because of dysphagia, breathing difficulties, permanent neck ache and severe worsening of neurological status. Neurological examination revealed sensory-motor deficit in both hands and complete paraplegia. Spinal MRI revealed upward and downward enlargement of the lesion (Figure 3). Spinal radiotherapy was given delivering 54 Gy in 30 fractions to the tumoral site. Ascending tetraplegia progressively occurred and the patient died in October 2003 from respiratory insufficiency.

Literature review

Two cases of RI gliomas of the spinal cord have been previously reported after treatment for HD [7,9]. Characteristics of these patients and our case are

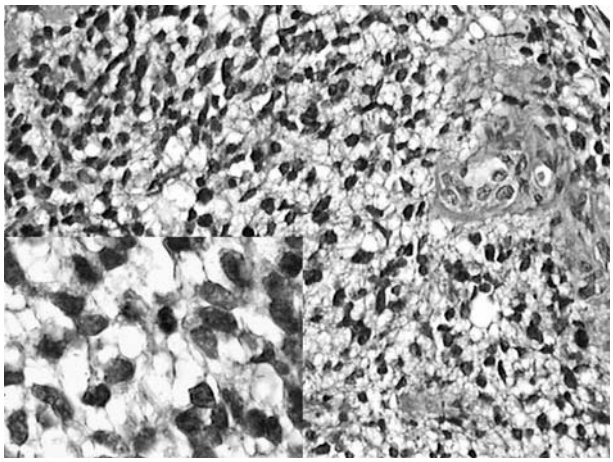

Figure 2. Microscopic view. Neoplastic cells are round to oval with scanty vacuolated cytoplasm and densely packed around proliferative vessels (HES; ×400). Inset: marked anisocaryosis and mitoses are observed (HES; ×1000).

summarized in Table 1. These cases concerned only males ranging in age from 19 to 30 years at the time of radiation therapy. The mean latency until diagnosis of spinal cord tumor was 7.5 years (range from 6 to 9) and the mean age of the patients at presentation was 31 years (range 26–39).

Discussion

The literature on second malignancy after HD has grown considerably since the first reports in the 1970s [11,12]. After treatment of HD, the risk of second solid tumors has been observed after a period of 10 years in contrast with the risk of second acute leukemia or non-Hodgkin's lymphoma observed within the first 10 years [13,14], and might account for a deficit of 10% after 20 years [15]. This risk has been seen to be greater in patients who received both intensive radiation therapy and combination chemotherapy [12,13,15]. A significant correlation was also found between the radiation field size and the risk of second malignancy [14,15]: subtotal or total nodal irradiation increased the risk of solid tumor twofold compared with local irradiation such as the mantle field. Furthermore, this risk cannot be eliminated by using a sophisticated photon energy source [16]. Extended-field radiotherapy is now being abandoned by most study groups in favor of involved field irradiation with lower doses (20–30 Gy) [17]. Considering the radiation dose-related risk, comparison of our illustrative case with the five previous cases of RI gliomas of the spinal cord reveals a noteworthy feature: spinal cord tumor occurrence was associated with moderate doses of radiation or the penumbra area of the radiation field. This feature has already been observed in RI intracranial gliomas [6,18] and is consistent with Upton's [19] remarks that maximum carcinogenic effect is rather associated with moderate doses than with high doses of radiation. Radiation carcinogenesis is usually represented by a curve where cancer incidence is lowest with low radiation doses due to cellular repair, is highest with intermediate doses, and reaches a plateau and declines due to excessive cellular damage with high doses [7,19].

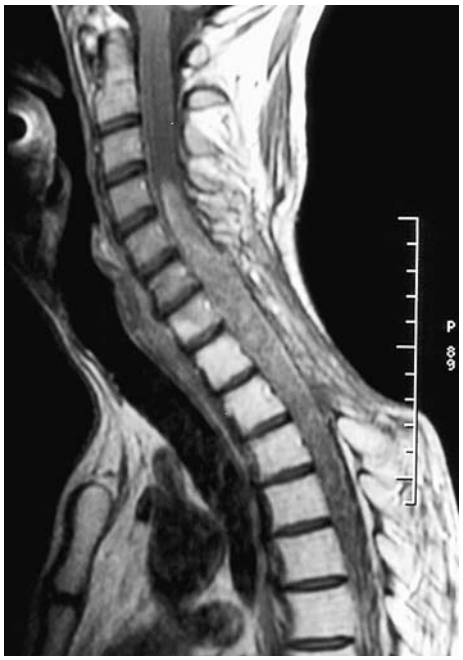

Figure 3. Contrast-enhanced sagittal T1-weighted MR image showing an extensive hyperintense signal occupying the entire vertebral canal below the C4 level.

RI spinal cord gliomas occurred in young adults and this age distribution was also observed in RI intracranial gliomas [2]. However, considering the fact that most of these tumors are malignant, it does not differ from the age distribution of malignant spinal cord gliomas observed in the overall population [20]. The histopathological diagnosis of malignant astrocytoma in our patient concurs with the trend toward an increased incidence of malignancy in RI gliomas. The only non-high grade RI spinal cord tumor was a fibrillary astrocytoma following multiple fluoroscopies [8]. All the other spinal cord tumors induced by irradiation were of high histopathological grade which contrasts with the usual low grade described for spinal cord astrocytomas [21]. This observation has also been made in RI intracranial gliomas [2,6] that have also been identified as the most malignant RI tumor category [5]. The mechanism of oncogenesis of RI gliomas after treatment for HD is likely to be multifactorial [12]: (i) impairment of cellular immunity in advanced HD, (ii) immunosuppressive effects of radiation and chemotherapy, (iii) direct cellular effects of these treatments. The oncogenetic role of irradiation in inducing a second neoplasm in the CNS has been suggested via chronic inflammation which, coupled with immunodeficiency, may result in "misregeneration" of the cells in the CNS [7,22]. In general, this risk appears to be lower if intermittent therapy is used instead of continuous prolonged treatment as the lymphoreticular system has a chance to recover between the pulses of treatment [23].

Apart from RI spinal cord gliomas, other spinal complications of irradiation for HD have been reported

Table 1. Data of patients with RI glioma of the spinal cord after irradiation for Hodgkin's disease

Case	Author, year	Age at radiation (years)	Radiation dose (Gray)	Latency period (years)	Tumor type	Tumor location	Follow-up period
1	Clifton et al. [7], 1980	21	50	6	Glioblastoma multiforme	Cervicothoracic	10 weeks[a]
2	Bazan et al. [9], 1990	19	40	7	Astrocytoma grade II–III	Cervical	6 months
3	Present case	30	40	9	Anaplastic glioma	Cervicothoracic	11 months[a]

[a]Date of death.

such as vertebral sarcoma, meningioma and myelopathy [16,24,25]. Clinical presentation and MR observation of an intramedullary spinal cord lesion within the field of prior radiation therapy may be non-specific since radiation myelitis, necrosis or RI tumor may occur [9,26]. Radiation myelitis is more common than RI neoplasms but it was usually observed within 9–15 months following irradiation [27]. However, myelitis has been reported as late as 6 years after irradiation [27] so that the latent periods of radiation myelitis and RI tumor may overlap and be insufficient for distinguishing one from the other. For that reason, and although radiation myelitis was more frequent, we support the idea of a systematic histopathological diagnosis in such lesions. Furthermore, on the basis that a RI spinal cord tumor will certainly be malignant and given the limited survival time of patients with malignant spinal cord glioma (6 months) despite chemo- and radiotherapy [20] and the inability of surgery to improve neurological deficits in such patients, a different approach based solely on a tissue diagnosis would be more suitable in this rare condition. If the histopathological analysis demonstrates a low-grade tumor, then the patient may undergo an attempt at complete resection.

In conclusion, RI spinal cord glioma after treatment for HD is an exceptional situation but should be included in the list of well-established second solid tumors associated with irradiation in this disease. In the situation of an intramedullary spinal cord lesion within the field of prior irradiation, we suggest a strategy aimed solely at obtaining a tissue diagnosis to differentiate myelitis from tumor, and, in the case of a tumor, to confirm the strong likelihood of a high histopathological grade. The very limited survival of such patients regardless of therapy advocates palliative therapies without attempting complete resection.

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