Osteoporosis and Spondylolisthesis after Comprehensive Treatment for Brain Tumor: A Case Report

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Abstract. A 10-year-old boy who presented with hypopituitarism was diagnosed with suprasellar germinoma based on the findings of brain magnetic resonance imaging (MRI). Dissemination of the tumor to the spinal cord was also evident. The patient was first treated with irradiation to both the brain and spinal cord, followed by chemotherapy with cisplatin (CDDP) and etoposide (VP-16). Peripheral blood stem cell transplantation (PBSCT) with extensive chemotherapy was performed when he was 14 years old. During and after the treatment for the brain tumor, he was placed on hormone replacement with corticosteroid hormone, l-thyroxine, and 1-deamino-8-D-arginine-vasopressin (DDAVP). Growth hormone was also replaced after 2 years from PBSCT. The patient was noted to have gait disturbance, osteoporosis and spondylolisthesis of the lumbar vertebrae (L) at 18 years old. His mean bone mineral density (BMD) of the 2nd to 4th lumbar vertebrae was 0.59 g/m². There was no evidence of recurrence of the tumor. It is possible that a high dose of local irradiation, long-term corticosteroid hormone replacement, and a hypogonadal state are related to the onset and progression of the skeletal abnormalities.

Key words: brain tumor, spondylolisthesis, osteoporosis, irradiation, corticosteroid hormone

Introduction

Brain tumor is the most frequent among solid malignancies in childhood (1). Therapies for brain tumor, including surgical removal, chemotherapy and irradiation have improved the survival rate in children (1) and the recent induction of bolus chemotherapies combined with hematopoietic stem cell transplantation has also proved beneficial to patients (2). Surgical intervention, irradiation, and endocrinological changes after therapy for brain tumor affect the quality of life (QOL) of the patients; a large number of patients are hormone-deficient at diagnosis, and need hormone replacement including corticosteroid hormone, thyroid hormone, and gonadotropins during and after brain tumor therapy. In particular, it is not easy to administer an appropriate dose of corticosteroid hormone when
endogenous secretion is not completely damaged, and an overdose of corticosteroid hormone is believed to adversely affect bone metabolism. Moreover, a high dose of irradiation to the brain and spine also affects the metabolism of vertebral bones as well as the balance of hormone secretion. Aisenberg et al. (3) reported that bone mineral density (BMD) at the femoral neck and distal radius was significantly reduced in 40 young adults with childhood cancer who had been treated with chemotherapy and/or radiotherapy. We present here a patient who developed spondylolisthesis and osteoporosis after the comprehensive treatments for brain tumor.

**Case Report**

A 10-year-old boy, who had polydipsia and polyuria, was diagnosed with central diabetes insipidus in April 1990. His urine osmolality was 148 mOsm, and it did not increase even after water deprivation for 4 hours. Urine osmolality reached 512 mOsm after an injection of vasopressin. Brain tumor, which was clinically diagnosed as suprasellar germinoma, was found by brain MRI after decreased levels of serum GH and free T4 became obvious. Dissemination of the tumor was found in the conus medullaris by spine MRI. Endocrinological examinations revealed TSH 1.52 µU/ml (normal 0.2–4.0 µU/ml), free T4 0.49 ng/dl (normal 1.0–2.0 ng/dl), LH 1.0 mIU/ml (normal for matched age 0.07–1.83 mIU/ml), FSH 1.0 mIU/ml (normal for matched age 0.48–4.66 mIU/ml), testosterone 0.1 ng/ml (normal for matched age 0.08–0.2 ng/ml), ACTH 17.3 pg/ml (normal 9–60 pg/ml) and cortisol 7.1 µg/dl (normal 5–15 µg/dl). The response to growth hormone (GH) secretion after an injection of GH releasing hormone (GRH) was poor. The serum IGF-I level was 0.14 U/ml (normal 1.0–3.0 U/ml). In order to reduce the tumor mass, radiation therapy [32.4 Gray (Gy) to the whole brain and spinal cord fractionated to 18 times, 50.4 Gy to the local spinal cord] was started in July 1993. Chemotherapy with paraplatin (CBDCA), nimustine hydrochloride (ACNU) and VP-16, combined with PBSCT was performed in February 1994. Because hypopituitarism was not improved after the irradiation and chemotherapy, and diminished secretion of ACTH and cortisol was apparent, hormone replacement therapy (hydricortisone 15 mg/day, 1-thyroxine 75 µg/day and DDAVP) was started. After PBSCT, no recurrence of germinoma was obvious in either blood examination or computed cranial tomography. Growth hormone was also replaced under frequent and careful observation.

Gait disturbance due to muscle weakness of the bilateral dorsal pedes was noted in March 1998. Neurological examinations revealed the diminution of the bilateral achilles tendon reflex (ATR), but not the patellar tendon reflex (PTR), paresthesia ranging from the hip to bilateral calves, and atrophy of muscles of the lower extremities. We speculated that damage to the 1st sacral nerve of the spinal cord (S1) was the main cause of these neurological abnormalities. X-ray examinations showed biconcave deformity of the 4th and 5th lumbar vertebrae (L4 and L5), which is a characteristic finding in osteoporosis, and spondylolisthesis of the 5th lumbar vertebrae (L5) (Fig. 1). Mean BMD of the L2-4 measured by dual energy X-ray absorptiometry (DEXA) was 0.59 g/cm², which is about 60% of the normal value for matched age. These findings suggest that the displaced vertebral body might compress and damage the sacral nerve of the spinal cord. The boy’s height was 156.9 cm (–2.4 SD) and his body weight was 50.1 kg (–1.25 SD). His bone age was equivalent to that of a boy 14 years and 9 months old. Serum alkaline phosphatase (ALP) levels were 401 U/l (124–367 U/l), calcium 10.0 mg/dl (8.7–11.0 mg/dl), and phosphorus 3.1 mg/dl (2.5–4.5 mg/dl) (Table 1). Serum cortisol, and urinary 17-hydroxycorticosteroid (17-OHCS) and free cortisol were normal, but serum LH, FSH and testosterone were lower than the control levels. Parathyroid
hormone and osteocalcin levels were 0.30 ng/ml (0.12–0.5 ng/ml) and 10.1 ng/ml (3.1–12.7 ng/ml), respectively. Urinary deoxypyridinoline was normal. The stage of development of the external genitalia and pubic hair was Tanner I (4). The volume of the bilateral testes was 3 ml. Tumor recurrence was not apparent in either MRI findings or blood examinations. The patient started to take alfacalcidol and oral calcium to increase the calcium deposit in bone.

**Discussion**

We have presented a patient who developed spondylolisthesis, after successful treatment of suprasellar germinoma with irradiation and chemotherapy combined with PBSCT. Moreover, the patient's vertebral bones were severely osteoporotic, which made deformity of the vertebrae vulnerable. The patient had neurological abnormalities such as the diminution of ATR, paresthesia and atrophy of muscles of the lower extremities, which were probably caused by the sacral nerve damage due to spondylolisthesis. These abnormalities are probably multifactorial; the irradiation damage, corticosteroid intake and hypogonadism may all have contributed.

We speculate that a high dose of irradiation to the spine in this patient was most likely to have damaged the bone structure and caused the deformity of vertebrae (L4, 5). There are some studies on the changes in bone pathophysiology in animal models after irradiation. There is evidence that radiation damage to mature bones is mediated primarily through changes in the fine vasculature (5). Okunieff et al. (6) showed that radiation exerts a chronic antiangiogenic effect accompanied by decreased bone perfusion. These mechanisms may contribute to the bone damage caused by irradiation. Irradiation is known to damage the involved peripheral nerves as well as the bone. Anesthetkinesia caused by disturbance of the peripheral nerve sometimes occurs after radiation therapy (7). It is therefore possible that S1 in this patient may have been impaired by a high dose of irradiation.

The administration of corticosteroid hormone also induces bone changes, especially osteoporosis. One of the problems in children with rheumatic diseases receiving corticosteroid therapy is a decrease in BMD, but the adverse effect of corticosteroid hormone, when adequately administered to compensate for the reduced secretion of intrinsic hormone, is unclear. The intrinsic secretion of corticosteroid hormone persisted in the patient, but it was very low compared to that in healthy subjects. The patient received corticosteroid hormone (10 mg/m² body surface area) as a replacement therapy for 8 years before the onset of osteoporosis. His serum cortisol and ACTH levels were 11.2 µg/dl (normal 4.0–18.3 µg/dl) and 14.8 pg/ml, respectively, and urinary free cortisol and 17-OHCS levels were 129 µg/day (normal 35–160 µg/day) and 5.6 mg/day (normal 2.9–11.6 mg/day), respectively during HRT, indicating that the dosage of corticosteroid hormone did not exceed physiological levels.
Patients with 21-hydroxylase deficiency or Addison's disease have corticosteroid hormone-deficiency and need corticosteroid substitution therapies. Several investigations (8, 9) reported that these patients had decreased BMD, and that the bone density was negatively correlated with current and cumulative corticosteroid dosages. These reports showed that the decreased BMD in these diseases is a result of the over-substitution of corticosteroids. Reid (10) recommended that all patients treated with corticosteroid hormone for more than 6 months should be considered for bone densitometry and should be offered appropriate medication if the values are towards the lower end of the young normal range or if there is already evidence of fractures occurring after minimal trauma.

Hypogonadism is also reported to induce a decrease in BMD in both men and women. Our patient had hypogonadotropic hypogonadism for about 7 years before the onset of osteoporosis. Hypogonadal osteoporosis is considered to be caused by hormonal imbalance with a marked decrease in anabolic hormones including estrogen, androgen and testosterone and an increase in catabolic hormones including corticosteroid hormone (11). The effectiveness of testosterone therapy in increasing BMD in hypogonadal men also indicates the importance of this hormone in bone mineralization (12).

Taken together, these findings indicate that careful attention should be paid to skeletal and neurological findings in patients who receive brain tumor therapies.

References


