Intracranial yolk sac tumor in a patient with Down syndrome

Case report

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The authors report a rare case of intracranial yolk sac tumor in a 13-year-old boy with Down syndrome who presented with left hemiparesis. Admission MR imaging revealed a tumor in the right basal ganglia. Serum \( \alpha \)-fetoprotein was markedly elevated. Yolk sac tumor was diagnosed radiologically and serologically. The standard therapy for intracranial yolk sac tumor is platinum-based chemotherapy with concomitant radiotherapy. However, the authors used reduced-dose chemotherapy and asynchronized radiotherapy because of the well-known low tolerance of patients with Down syndrome to chemotherapy. This treatment was successful with no complications. Blood cancers are frequently associated with Down syndrome, whereas solid tumors occur less frequently in these patients, and the risk of chemoradiotherapy is unclear. The results indicate that dose-reduction therapy can be effective for treatment of a brain tumor in a patient with Down syndrome. (DOI: 10.3171/2011.3.PEDS10500)

Abbreviations used in this paper: AFP = \( \alpha \)-fetoprotein; AML = acute myeloid leukemia; GCT = germ cell tumor; ICE = ifosfamide, cisplatin, etoposide.

Case Report

History and Examination. This 13-year-old boy with Down syndrome was admitted to our hospital complaining of left hemiparesis that had worsened gradually over 1 month. His consciousness was clear and he had no symptoms of increased intracranial pressure. The patient presented with moderate left hemiparesis without any other neurological deficit.

Neuroimaging. Admission MR imaging revealed a 50 × 45 × 30–mm tumor in the right basal ganglia. The tumor included cystic components that gave a heterogeneous signal on Gd-enhanced T1-weighted images (Fig. 1A–D). Spinal MR images obtained after addition of contrast material showed no mass (Fig. 1F). The serum AFP level was markedly elevated, to 42,500 ng/ml. The serum human chorionic gonadotropin and carcinoembryonic antigen were within their normal ranges. Based on these findings, we diagnosed yolk sac tumor radiologically and serologically without biopsy sampling. Whole-spine MR imaging did not indicate any dissemination.
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Treatment. The standard treatment for intracranial yolk sac tumor is platinum-based chemotherapy (commonly known as ICE, which consisted of the following: ifosfamide 900 mg/m²; cisplatin 25 mg/m²; etoposide 60 mg/m²) with concomitant radiation therapy (Fig. 2A). However, we attempted a dose reduction of ICE to 60% in the first course, based on the low tolerance of patients with Down syndrome to chemotherapy. To minimize potential complications, we also postponed radiation therapy until confirmation of the safety of chemotherapy was attained (Fig. 2B).

The 60% dose-reduced ICE therapy was effective, and MR images after the first course revealed tumor shrinkage (Fig. 3B). Although bone marrow suppression was seen during chemotherapy, it was controlled using granulocyte colony-stimulating factor and platelet transfusion. Because the initial ICE therapy did not induce severe bone marrow suppression, ICE therapy with a normal dosage was administered in subsequent courses. After 3 courses of ICE, radiation therapy (30 Gy for the whole brain, with an additional 20 Gy for the ventricle and 24 Gy for the whole spine) was administered asynchronously with chemotherapy. After radiation therapy, an additional 5 courses of ICE therapy were administered. Bone marrow suppression induced by these series of therapies was somewhat severe, but recovered with the use of granulocyte colony-stimulating factor and platelet transfusion. Mild pneumonia also occurred during the chemoradio-

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**Fig. 1.** Axial MR imaging study showing a mass in the right basal ganglia (A). The mass was heterogeneously enhanced after addition of Gd contrast material (B). Coronal (C) and sagittal (D) contrast-enhanced MR images. Axial T2-weighted MR image showing a polycystic mass with a high-intensity signal (E). Spinal MR image (F) obtained after addition of contrast material showing no mass.
therapy, but was resolved using antibiotics. There were no other complications related to the therapy.

Posttreatment Course. The sensitivity of the tumor to the therapy was quite high, and the size of the lesion was markedly reduced (Fig. 3B and C). After all 8 courses of chemotherapy were completed, the level of serum AFP had normalized; it had decreased to 2.4 ng/ml. Final MR imaging after the completion of therapy revealed a questionable residual lesion, but FDG-PET studies showed no uptake by the lesion, leading to an evaluation of complete remission. Tumor recurrence on follow-up MR imaging and elevation of serum AFP has not been seen in the 1 year and 9 months that have elapsed since chemotherapy.

Discussion

In general, the frequency of solid cancer in patients with Down syndrome is lower than that in individuals without this disorder. This was originally thought to be due to the shorter life span of children with Down syndrome, but is now understood to be caused by overexpression of the Dscr1 or Dyrk1a gene on chromosome 21, which suppress production of vascular endothelial growth factor and tumor angiogenesis. There are 22 case reports of brain tumor in patients with Down syndrome, including 13 cases of GCT. Intracranial GCT in patients with Down syndrome manifests with a higher occurrence of yolk sac tumor (5 of 14, including our case) and more frequently occurs in the basal ganglia (8 of 14), compared with GCT in individuals without Down syndrome (Table 1). Moreover, all the patients in reported cases of GCT occurring in individuals with Down syndrome are Asian. The mechanisms underlying these characteristics are unclear, but our case also conforms to these characteristics, which suggests that it is a typical case of intracranial GCT in a patient with Down syndrome.

Standard therapy for intracranial GCT is platinum-based chemotherapy combined with radiotherapy. In Japan, 3 courses of ICE with concomitant radiotherapy followed by 5 additional courses of maintenance ICE therapy are administered as standard therapy for intracranial yolk sac tumor, based on results of a clinical study.
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of 153 cases of intracranial GCT. The sensitivity to chemotherapy is generally high among patients with Down syndrome, but complications related to chemotherapy also tend to occur. Therefore, dose-reduction multidrug chemotherapy is the standard therapy for AML in Down syndrome. The pharmacological characteristics and risks of complication with cytarabine and methotrexate therapy for AML in patients with Down syndrome are well established. In contrast, the risk of complications with other chemotherapy drugs, including platinating agents, have not been investigated in individuals with Down syndrome.

Of the 13 previously reported cases of intracranial GCT, 9 were treated with platinum-based chemotherapy and/or radiotherapy. Two (22.2%) of these 9 patients died due to complications related to chemoradiotherapy (Table 1), and there were 4 deaths among the 13 cases (30.8%) due to complications related to surgery or chemotherapy. It is noteworthy that the mortality rate related to therapy in cases of intracranial GCT in patients with Down syndrome is very high compared with that for patients without Down syndrome. This is consistent with the low tolerance of patients with Down syndrome to chemotherapy.

In our case, we decreased the dosage of the first course of ICE and administered asynchronized radiotherapy with chemotherapy to prevent complications. Generally, the therapeutic effect is greater for synchronous chemotherapy with radiation, but this therapy needs to be administered more carefully than asynchronous chemotherapy because it has more frequent complications, such as bone marrow suppression. Therefore, we decided to use asynchronous chemotherapy to avoid complications, and we were able to obtain a sufficient therapeutic effect. This suggests that asynchronous chemotherapy and radiation are useful in a patient with Down syndrome, and this approach warrants further study.

This protocol resulted in no complications related to the therapy, and gave a good outcome. It is difficult to be certain that the reduced dosage was linked to the low complication rate. However, this case shows that careful planning of chemoradiotherapy is required for intracranial GCT in a patient with Down syndrome.

Conclusions

The standard therapy for residual tumor after chemoradiotherapy is not established. Ushio et al. reported excellent outcomes in patients with a GCT and a poor prognosis who underwent aggressive surgery for the residual lesion (salvage surgery) after initial chemotherapy (neoadjuvant therapy). Thus, aggressive salvage surgery based on this protocol may be most effective for a normal pineal tumor, but in our case salvage surgery involved a high risk because the tumor had developed at the basal ganglia, producing an unresectable lesion. Therefore, we chose to observe the clinical course after using FDG-PET studies to confirm that the residual lesion had no cell viability. Tumor recurrence has not been seen in the 1 year and 9 months that have elapsed since chemotherapy, and this suggests that our approach was appropriate for a basal ganglia tumor.

Disclosure

The authors report no conflict of interest concerning the mate-

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* BG = basal ganglia; BLM = bleomycin; CBCDA = carboplatin; CDDP = cisplatin; Chemo = chemotherapy; CPA = cyclophosphamide; CR = complete response; germ = germinoma; im tera = immature teratoma; NA = not applicable; NC = no change; NR = not reported; Patho = pathological; PD = progressive disease; pneum = pneumonia; PR = partial response; RT = radiation therapy; VCR = vincristine; vent = ventricle; VP-16 = etoposide; YST = yolk sac tumor.
Y. Maeda et al.

References


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