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Primitive Neuroectodermal Tumor (PNET) Treated with Interferon-β after Surgical Removal and Irradiation: Case Report

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Abstract. *This case report describes an 11-year-old boy with primitive neuroectodermal tumor (PNET), which remains the pediatric brain tumor with the worst prognosis despite combination treatment with surgery, irradiation and anti-cancer drugs. The boy was successfully treated with intratumoral administration of interferon-β (IFN-β) following surgical resection and irradiation. Two million units of IFN-β were locally administered into the post-operative cavity through the Ommaya's reservoir every two weeks after discharge. He was managed as an outpatient without serious side-effects to IFN. The patient has shown no tumor recurrence, mental retardation, or neuroendocrine impairment for over three years and has lived a normal school life with a full Karnofsky Performance Status score. The local administration of IFN-β may be warranted for maintenance therapy in children with PNET.*

Primitive neuroectodermal tumor (PNET) has been classed as a malignant brain tumor of childhood since it was proposed in 1973 as a novel entity among intracerebral undifferentiated growths (1-3). In the new WHO classification (2000), PNET belongs to an embryonal brain tumor category including medulloblastoma and the other neuroectodermal tumors (4), and is considered as highly malignant from the histological and clinical perspectives (1-5). Median survival in this tumor remains in the range of one to two and a half years despite a combination of surgical resection, radiotherapy and chemotherapy (5, 6). This poor prognosis is similar to that of glioblastoma. However, survival in medulloblastoma is longer although this malignancy resembles PNET in its occurrence in the embryonal period and pathological characteristics (4-6). While medulloblastoma occurring in the cerebellum can be completely resected, PNET is as difficult as glioblastoma to completely remove surgically, because of dissemination and the obscure boundary between the tumor substance and the normal cerebrum (3, 4, 6, 7). Thus, in addition to surgical removal, PNET has essentially been treated with maximum doses of irradiation to the whole brain and systemic administration of anti-cancer drugs, which frequently result in immunosuppression, neuroendocrine impairment and mental retardation due to their toxicity (6-9).

Interferon has frequently been used in Japan as maintenance therapy for malignant glioma after combination treatment and has been reported as relatively effective against recurrence when compared with cases undergoing no maintenance therapy (10-12). As described in the case report, we successfully performed local administration of interferon-β (IFN-β), into the post-operative cavity through the Ommaya's reservoir, in place of chemotherapy after surgical resection and irradiation for a pediatric patient with PNET. The patient has lived a normal life for over three years without recurrence.

Case Report

The patient was an 11-year-old boy, who complained of headache and vomiting, which progressively deteriorated. Right hemianopsia and bilateral papilledema were observed on physical examination. MRI revealed a giant cyst, about 7 cm in radius, with an enhanced mass visualized with contrast medium in the left hemisphere (Figure 1). The cystic mass severely compressed the left lateral ventricle, causing midline shift to the right. Cerebral angiography showed faint staining of the tumor shadow in the capillary and venous phases with no arterio-venous shunts apparent (data not shown). Craniotomy was performed for biopsy and aspiration of cyst fluid at Kochi Medical School Hospital, Japan, in July 2000. Haematoxylin-eosin staining of the surgical specimen indicated undifferentiated cells with relatively thick and

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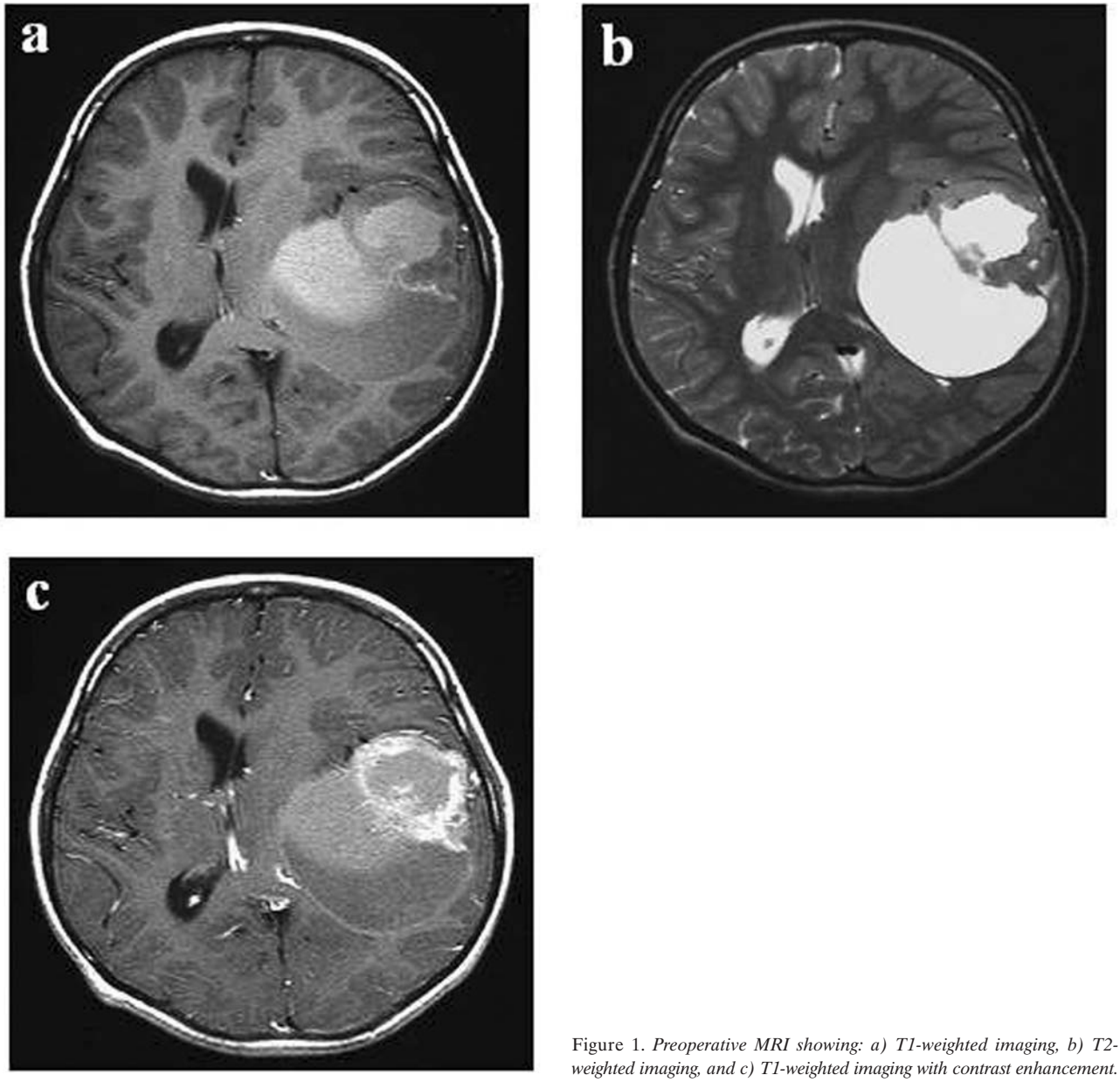

Figure 1. *Preoperative MRI showing: a) T1-weighted imaging, b) T2-weighted imaging, and c) T1-weighted imaging with contrast enhancement.*

multiple nuclei (Figure 2a), leading to a pathological diagnosis of PNET. Furthermore, immunochemistry revealed positive staining for the glial marker GFAP and for the neuronal marker NSE, and also nestin expression of an embryonal marker (Figure 2b, 2c, 2d) (13). However, synaptophysin, another neuronal marker of higher specificity, was negative (Figure 2e). The MIB-1 index was over 30% (Figure 2f), suggesting a high proliferative potential.

Two weeks after the pathological diagnosis of PNET by biopsy with aspiration of cyst fluid, most of the tumor was surgically removed; however the area next to the speech center was not excised. Irradiation was subsequently performed with doses of 50 Gy to the enhanced mass and 20 Gy to the rest of the brain (Figure 3a). Aspiration through an Ommaya's reservoir inserted in the post-operative cavity was repeated twice because of a further increase in cyst fluid during irradiation. Two weeks after radiotherapy, one million units of IFN-β (Feron; Daiichi Pharmaceutical Company, Tokyo, Japan) were locally administered twice into the surgical cavity through the Ommaya's reservoir. No severe side-effects such as psychological depression or liver dysfunction were observed and only a transient fever was detected. After discharge, two

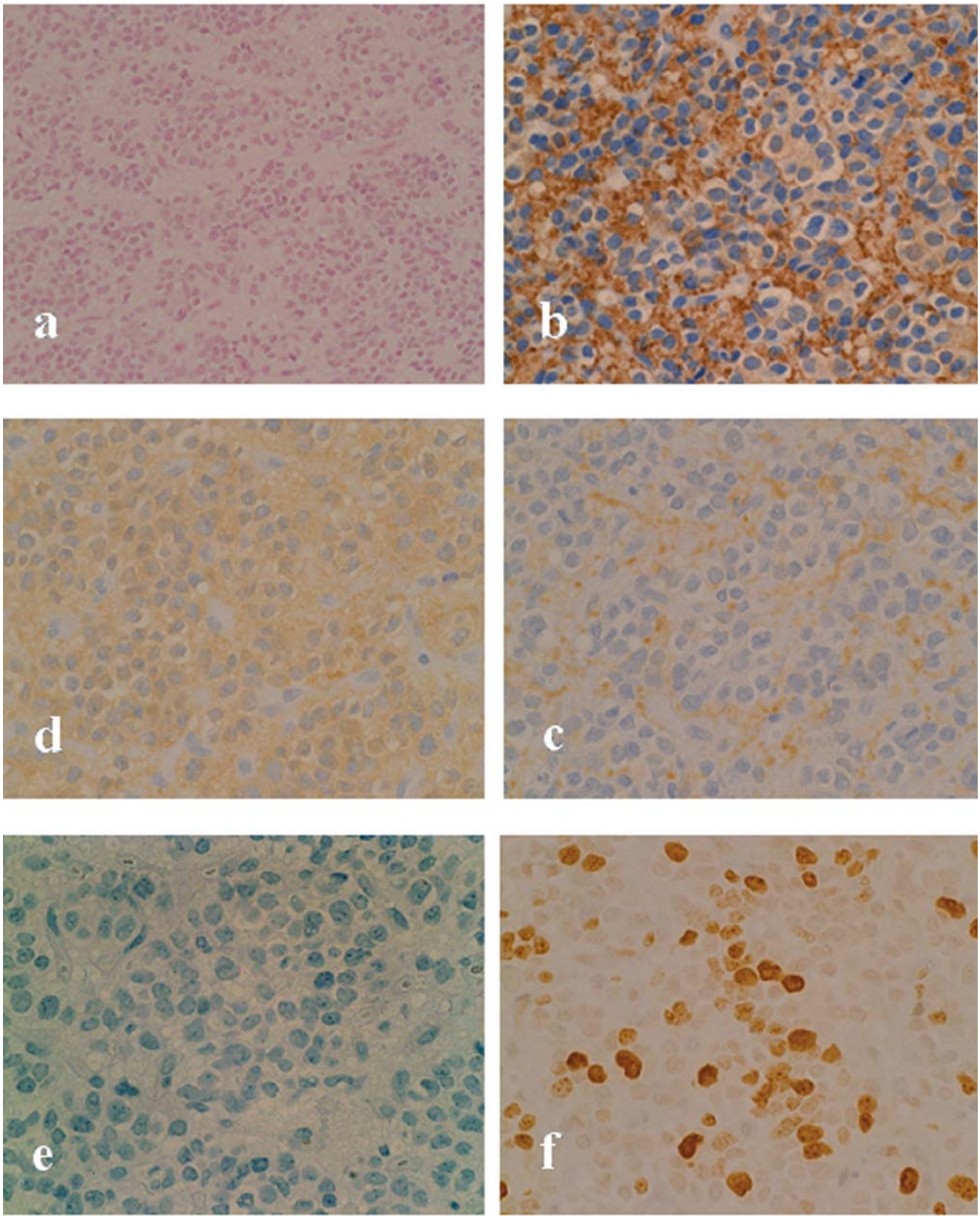

Figure 2. *Histology and immunohistochemical staining of surgical specimen: a) haematoxylin-eosin staining, b) nestin, c) GFAP, d) NSE, e) synaptophysin, f) MIB-1. Magnification: a, x20; in b-e, x40.*

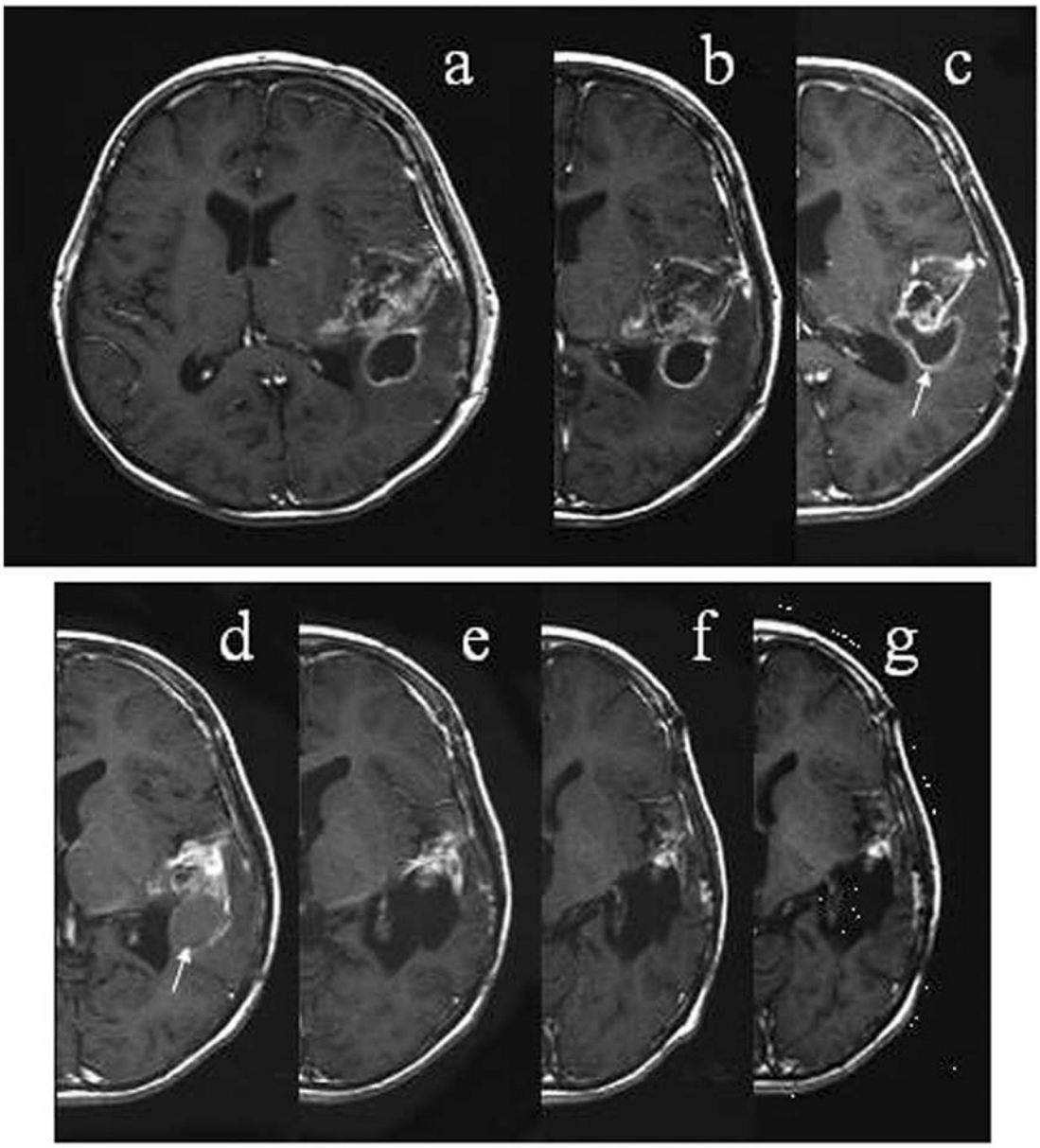

Figure 3. *Follow-up MR images: a) immediately, b) 2, c) 4, d) 6, e) 8, f) 12, g) 36 months after discharge with fulfilment of surgical resection and irradiation. Arrows indicate hemorrhage in the post-operative cavity.*

million units of IFN-β were similarly administered every two weeks into the post-operative cavity as maintenance therapy. Hemorrhagic fluid in the cavity was initially observed four months after discharge on MR imaging (Figure 3c) and continued for two months (Figure 3d). Multiple aspirations through the Ommaya's reservoir were performed and the hemorrhage completely resolved eight months after discharge (Figure 3e). Subsequently, MRI showed gradual reduction of the remnant tumor adherent to the left lateral ventricle wall (Figure 3f). No tumor re-growth has been detected so far on MRI, more than three years since the initial therapy (Figure 3g). The patient has shown no mental retardation and neuroendocrine impairment and has been noted to be cheerful and a fine high school student with a Karnofsky Performance Status (KPS) score of 100.

Discussion

PNET is a cerebral embryonal tumor composed of undifferentiated or poorly-differentiated neuroepithelial cells which display divergent differentiation along neuronal or glial lines (1-5). In this case, the tumor predominantly possessed glial characteristics in the positive expression of GFAP, while neuronal markers other than NSE were

negative. PNET generally exhibits as poor a prognosis as glioblastoma and glial differentiation may predict poor clinical outcome in PNET since the relative risk of relapse in GFAP-positive PNET is reported to be 6.7-fold greater than in the GFAP-negative PNET (14).

Medulloblastoma, often referred to as infratentorial or cerebellar PNET with regard to its pathological and embryonal properties (2,5), is the most common malignant brain tumor of childhood (3,5). In a very similar manner to the therapeutic protocol for medulloblastoma, children with PNET undergo adjuvant chemotherapy after irradiation but only show an overall 5-year survival rate of 34%, in contrast to 85% for children with medulloblastoma (15-17). Studies of adjuvant chemotherapy performed in medulloblastoma in the 1990s demonstrated a survival benefit for post-surgical radiation (5-7). Nevertheless, medulloblastoma remains a management challenge for oncologists because the optimal sequence and dosage for each treatment modality has not yet been defined (6, 7). Effective management strategies for medulloblastoma frequently result in profound neuroendocrine and neuropsychological sequelae (7).

On the other hand, in PNET, craniospinal radiotherapy can give a relatively high likelihood of long-term survival and even now remains the main curative modality. Chemotherapy, irrespective of whether this is administered pre- or post-irradiation or at both times, does not adequately increase the survival rate, which may result in the considerable discrepancies in clinical outcome between medulloblastoma and PNET (6, 8, 15).

IFN, particularly IFN-β, has been used to treat patients with malignant glioma since the 1980s (10-12, 18-21). Many experimental studies have shown that IFN-β may produce direct cytocidal or cytostatic effects, or may act as a biological response modifier *via* regulation of cellular immunity, for example, interfering with the TNF-α-related apoptosis induced by dendritic cells (22-24). A clinical trial of IFN-β for recurrent malignant glioma indicated anti-tumor activity, although the therapeutic index may be narrow (18, 19). Initial and maintenance combination treatment with IFN-β, MCNU (Ranimustine), and radiotherapy were relatively effective in patients with previously untreated malignant glioma (20). Furthermore, a case of recurrent glioma has been reported in which survival of 4 years was achieved with intratumoral administration of IFN-β (12).

Concerning PNET, two recurrent cases receiving outpatient maintenance therapy with IFN-β after irradiation have been reported by Tanaka *et al.*, in which effective suppression of tumor growth occurred without serious side-effects (21). One of two cases showed cystic hemorrhage during IFN treatment after irradiation. This case has survived for 8 years to date, without recurrence of tumor (personal communication).

In the present case, hemorrhage in the cyst into which the Ommaya's reservoir tube was inserted was also observed for two months after radiotherapy. It is still unknown whether the hemorrhage is due to an intrinsic tendency of PNET, a direct cytocidal effect of IFN-β, or radiation necrosis. Local administration of IFN-β continued for the hemorrhagic period and almost the entire remnant tumor gradually disappeared after the hemorrhagic event. Intratumoral hemorrhage would cause intermingling of tumor cells and immunocytes and may raise anti-tumor activity by cellular immunity *via* lymphocytes or dendritic cells and so on.

No matter how variable IFN may be in its function, it yields at least the advantage of minimum neurotoxicity, especially with local administration, when compared to chemotherapeutic drugs (11, 12). As we believe that IFN is one of the most suitable agents for incorporation in a protocol of maintenance therapy for children with PNET, we selected a treatment strategy of IFN maintenance therapy without using any chemotherapeutic drugs, after surgical resection and irradiation. In fact, the presented case has been free of recurrence, has not developed mental retardation or neuroendocrine impairment and has experienced a three-year remission as an outpatient without chemotherapy. The patient's ability to perform in daily life has been evaluated, showing a full KPS score.

Further case studies investigating immunotherapy with IFN-β in place of anti-cancer drugs for PNET are needed because PNET remains one of the malignant brain tumors of childhood exhibiting the worst prognosis under conventional treatment protocols. Thus, we propose that a large clinical trial of pediatric patients with PNET should be performed using the following protocol; as extensive a surgical resection as possible, high dose irradiation and maintenance therapy with local administration of IFN-β. We believe this case report will interest neurosurgeons frustrated by the lack of effective treatment options for children with PNET.

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