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Recurrence of Sellar and Suprasellar Tumors in Children Treated with hGH —Relation to Immunohistochemical Study on GH Receptor—

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Abstract. Purpose: GH replacement therapy is required in the majority of children with GH deficiency after treatment of sellar and suprasellar tumors. Owing to the high cell proliferative ability of human GH (hGH), its influence on tumor recurrence has been debated. We retrospectively studied the immunohistochemical expression of the GH receptor in various tumor tissues, in order to investigate the relation between tumor recurrence and hGH replacement. Methods: GH replacement therapy was performed in 25 patients (8 boys and 17 girls) after the treatment. Tumor recurrence was noted in 4 patients (craniopharyngioma: 2 patients, pilocytic astrocytoma and germinoma: 1 each). Immunohistochemical study of GH receptor in tumor tissue was carried out in those recurrent and recurrence-free cases, by using MAb 263 as a primary antibody. Results: Two patients with recurrent craniopharyngioma were positive for MAb 263, but 1 recurrence-free patient was negative. Patients with pilocytic astrocytoma (recurrent and recurrence-free: 1 each) were all positive. Five patients with germinoma (1 with recurrence and 4 without recurrence) were all negative. Conclusion: In the patients with craniopharyngioma treated with GH, a positive immunohistochemical expression of GH receptor in tumor tissue may indicate a high probability of recurrence. In our cases, GH receptor was positive in astrocytomas and negative in germinomas, with or without recurrence. It is therefore speculated that each brain tumor may have its specificity in GH receptor expression.

Key words: Brain tumor, Children, GH receptor, Recurrence

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GH replacement therapy is required in the majority of children with GH deficiency after treatment of sellar and suprasellar tumors. Owing to the high cell proliferative ability of GH, its influence on tumor recurrence has been debated [2, 3]. It is now understood that GH does not increase the risk of brain tumor recurrence. But brain tumor recurrence was reportedly noted after GH replacement therapy [2]. We retrospectively studied the immunohistochemical expression of the GH receptor in various tumor tissues (craniopharyngioma, pilocytic astrocytoma, and germinoma), in order to investigate the relation between tumor recurrence and GH replacement.

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Materials and Methods

The present study included 25 patients, 8 boys and 17 girls, with a mean age of 12 years, who received GH replacement at the Department of Neurological Surgery, Chiba University Hospital between 1968 and 1996. Among the 25 patients tumor recurrence

or regrowth was noted in 4 patients (craniopharyngioma: 2 patients, pilocytic astrocytoma and germinoma: 1 each). Immunohistochemical study of GH receptor in tumor tissue was carried out in those recurrent and recurrence-free cases (craniopharyngioma 1 patient, pilocytic astrocytoma 1 patient, and germinoma 4 patients), by using MAb 263 as a primary antibody. MAb 263 is from a panel of mouse MAbs reactive with the GH-binding proteins of rabbit, rats, humans, and other species [4]. Tumor tissues were fixed with 10% buffered formalin, embedded in paraffin, and sectioned. The immunohistochemical study was carried out using sections deparaffinized in xylene and rehydrated through a graded series of ethanol to phosphate buffered saline. Endogenous peroxidase activity was blocked by placement in 3% hydrogen peroxidase in methanol for 15 min. One hundred microliters of the primary antibody (10 mg/ml; diluted 1 : 200 in PBS-0.5% BSA, pH 7.2) was applied to the sections for 30 min. Slides were then washed for 15 min in PBS-0.2% gelatin. These sections were then saturated with the second antibody (goat anatomized antibody; 15 μl/ml) for 10 min. The antigen-antibody complex was visualized by the avian-biotin-peroxidase complex method. Meyer's hematoxyline was used as a nuclear counter stain.

Results

Craniopharyngioma

Case 1: A 13-year-old girl received GH replacement therapy for poor growth after treatment for a brain tumor. Four months after GH therapy, tumor recurrence was noted. MAb 263 positive cells were seen at high concentration in this tumor tissue (Fig. 1a). Recurrence-free patient's tumor tissue was not stained for MAb 263 (Fig. 1b).

Pilocytic astrocytoma

Case 2: A 12-year-old girl had a history of surgery for optic glioma when she was 1 year old. GH replacement therapy was started at the age 4 years and discontinued at the age of 7 years when the complication of precocious puberty occurred. Tumor regrowth was noted at the age of 10 years. MAb 263 positive cells were seen in tumor tissue (Fig. 2a). In a recurrence-free case of pliocytic astrocytoma, tumor tissue was stained for MAb 263 (Fig. 2b).

Germinoma

Case 3: A 15-year-old girl with a retarded growth had an intra- and suprasellar mass on brain CT scan. Stereobiopsy was performed and the histological diagnosis was germinoma. She received GH therapy after treatment for the tumor. The tumor recurrence was noted after 2 years and 6 months of GH therapy. Her tumor tissue was negative for MAb 263 (Fig. 3a). In recurrence-free cases of germinoma (4 cases),

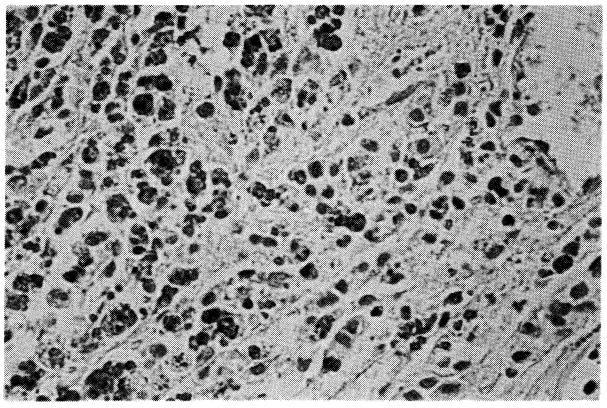


Fig. 1a. In the patient with recurrence of craniopharyngioma, MAb 263 positive cells were seen at a high concentration in this tissue (MAb 263, ×400).

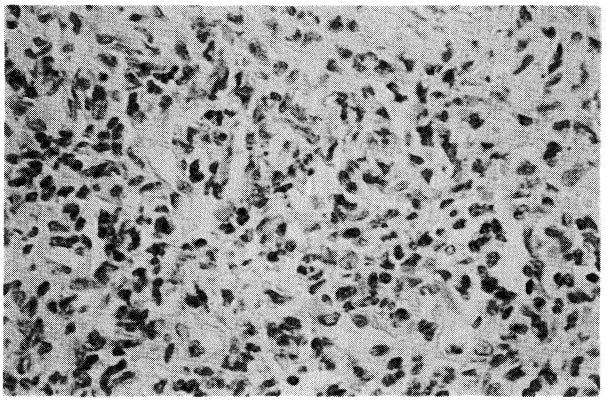


Fig. 1b. In the patient wihout recurrence of craniopharyngioma, tumor tissue was not stained for MAb 263 (MAb 263, ×400).

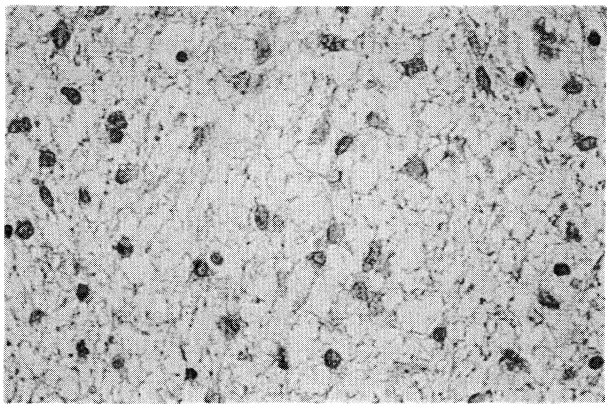


Fig. 2a. Slightly positive cells were seen in the patient with pilocytic astrocytoma with recurrence (MAb 263, ×400).

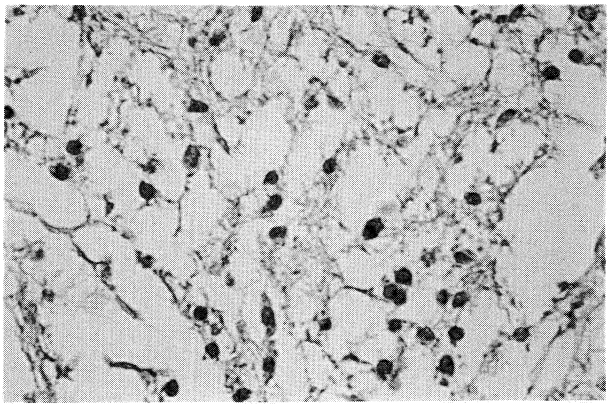
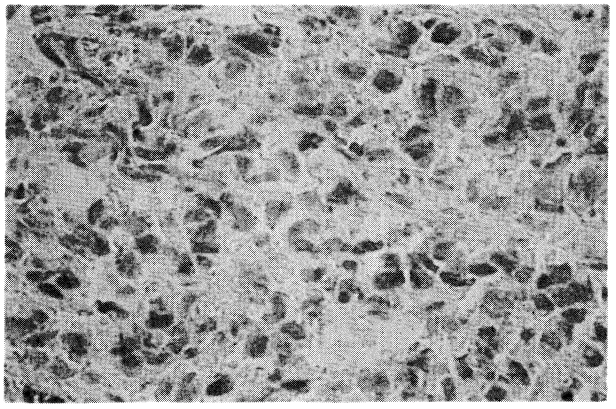
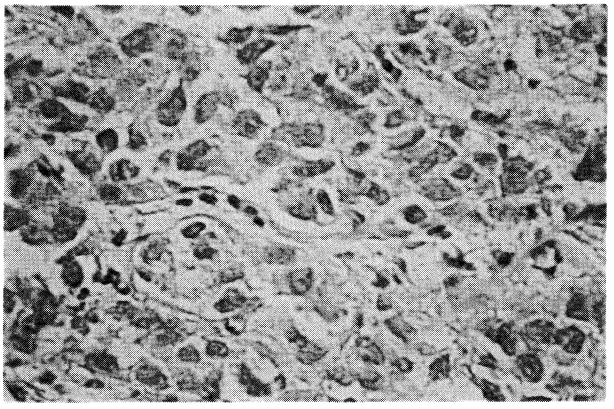


Fig. 2b. In the patient without recurrence of pilocytic astrocytoma, tumor tissue was slightly positive for MAb 263 (MAb 263, ×400).



a



b

Fig. 3a and 3b. Tumor tissues in the patients with germinoma were negative for MAb 263 regardless of recurrence (3a: with recurrence, 3b: without recurrence) (MAb 263, ×400).

tumor tissues were all negative for MAb 263 (Fig. 3b).

Discussion

The effect of human growth hormone (hGH) on the growth of brain tumors in childhood is not clearly established. Because hGH has the ability to increase cell proliferation, it is recommended that GH therapy should be a delayed usually for 1 to 2 years until the lesions are inactive and antitumor therapy is completed [2]. Recently there have been reported about the influence of GH replacement therapy on tumor recurrence in a large number of cases [3, 5, 6]. Despite the theoretical arguments, it is pointed out that there is no evidence of an increased risk of tumor recurrence after GH therapy [3, 5]. On the other hand, there was the case of enlargement of a pilocytic astrocytoma in a boy after a trial with hGH treatment [2]. We should therefore continue to be cautious about the administration of hGH to children with growth impairment who have had only partial removal of brain tumors. To the best of our knowledge, our study is the first on GH receptor expression in an immunohistochemical study on brain tumor tissue. Since only a small number of cases were included in this study, further studies are necessary to identify the factors that determine recurrence in GH therapy. In summary, patients

with craniopharyngioma treated with GH, a positive immunohistochemical expression of GH receptor in tumor tissue may have a high probability of recurrence. GH receptor was positive in astrocytomas and negative in germinomas, with or without recurrence. It is therefore speculated that each brain tumor may have its specificity for GH receptor expression.

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