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Risk for recurrence of intracranial germinoma

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Two recurrent cases of intracranial suprasellar germinoma, which relapsed 55 and 16 months, respectively, after the end of primary therapy, strongly effective against pure germinoma, are presented. β*-HCG was elevated in the cerebrospinal fluid and in the serum in both patients at the time of recurrence but not before. This and resulting treatment failures suggest that there were also other, more resistant elements within the primary tumor, which have not been identified in biopsy specimens. The problem of adequate diagnosis and its impact upon patients' survival is discussed.*

Key words: brain neoplasms; germinoma; recurrence

Introduction

Primary intracranial germ cell tumors are rare, comprising less than 1 % of all intracranial neoplasms in Western countries and 4 % to 10 % in Japan and Taiwan. 60 % to 70 % of these tumors are diagnosed during the first two decades of life.[1] Among them, intracranial germinomas (IG) represent up to 65 %. They arise from primordial germ cell and, as their counterparts testicular seminoma and ovarian dysgerminoma, represent the malignant correlate of a normal stage of embryonic development.[2]

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The occurrence of IG in other than the pineal and suprasellar regions is very rare.[1]

Because of their rarity, experience with IG is limited and the optimal approach to diagnosis and treatment is controversial.

IG are highly malignant, highly radiosensitive and respond to chemotherapy. Radiotherapy has been considered the treatment of choice. Radiation doses between 40 Gy to 55 Gy delivered to the primary intracranial site and, when tumor cells are found in the cerebrospinal fluid (CSF), 30 Gy to 35 Gy to the craniospinal axis with local boosts of 10 Gy to 15 Gy to known metastases are commonly used.[3] Long-term survival rates of 70 % to 100 % are reported.[4–9] However, in the cases of germ cell tumors other than germinoma, as well as those of mixed histology, more aggressive therapeutic approaches, utilizing also surgery and/or multidrug chemotherapy, are necessary.[1–4,6,7] Thus, surgi-

cal biopsy is mandatory for proper choice of treatment.[2,5,6,8–10] Information obtained from immunohistochemical stainings of tissue samples as well as from serum and CSF tumor biomarkers assay is an important contribution to the accuracy of initial histological diagnosis.[2,11–14]

Since the majority of patients are children and young adults, the aim of treatment is not merely to cure, but also to minimize the risk of late sequelae.[15] This is the main reason for attempts to decrease the total dose of radiation or to restrict the treatment volume. On the other hand, the tendency of IG to spread through the CSF with the reported risk of spinal seeding ranging from 0% up to 40%, makes such efforts questionable.[16] Therefore, to achieve complete tumor control by lower doses and/or reduced volumes of radiation it may be necessary to combine radiotherapy with chemotherapy. There are few reports on the role of chemotherapy in the treatment of initial, recurrent and metastatic IG.[10,17–22]

We have already reported our experience with IG in 7 patients, all without evidence of disease at the time of follow up.[10] Two late recurrences from that series are presented here. Both of them were located in the suprasellar region and relapsed 55 and 16 months, respectively, after the end of primary therapy, strongly effective against pure IG. The problem of adequate histological diagnosis and its impact upon patients' survival is discussed.

Case No. 1

A 9.5-year old girl with 12-month history of polydypsia, polyuria and 2 months of progressive visual deterioration, lethargy and introversion was admitted to the Pediatric Clinic of Clinical Centre in Ljubljana, Dept. of Child Neurology, in October 1986. She presented with growth failure (3 cm under the 3rd percentile, surplus of 7 kg), diabetes insipidus, hypocorticism, hypothyroidism, visual disturbance and psychic alteration. CT scan revealed a 0.5 × 0.5-cm tumor mass in the suprasellar region. A biopsy was performed on November 19, 1986 (Figure 1a). Histological examination

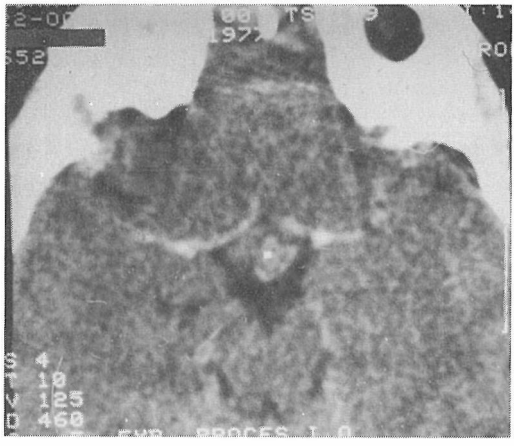

Figure 1a. CT scan of Case No. 1; before treatment.

revealed pure germinoma. Immunohistochemical staining for human chorionic gonadotropin (HCG) and alpha-fetoprotein (AFP) was not performed. No malignant cells were found in the CSF; assayed levels of HCG beta subunit (β-HCG) and AFP were in normal ranges, in the serum as well as in the CSF. Three courses of chemotherapy with cyclophosphamide, 80 mg/kg body weight on 2 consecutive days was administered, with intervals of 3 weeks. CT scan showed complete disappearance of tumor after the second course (Figure 1b).

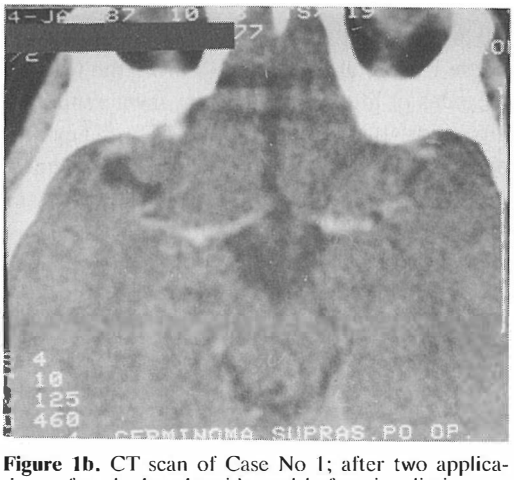

Figure 1b. CT scan of Case No 1; after two applications of cyclophosphamide and before irradiation.

Subsequently, she was treated on a linear accelerator with 8 MV X-rays and a dose of 30 Gy was delivered in 15 fractions over 22 elapsed days, to the tumor bed only, trough two opposing fields 8×8 cm of size. This therapy was completed in March 16, 1987. The girl had no neurological disturbances, except mild anisocoria of the right eye. Diabetes insipidus and anterior pituitary dysfunction were compensated for with hormonal substitutional therapy.

After a disease-free interval of 39 months, β-HCG in the serum was found to be elevated to 9.2 IU/L (normal, ≤ 5 IU/L), but CT scan revealed no intracranial recurrence (Figure 1c, d). Tumor marker levels in the CSF were not

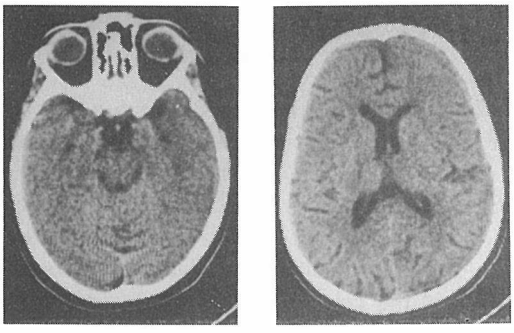

Figure 1c, d. CT scans of Case No. 1; 39 months after therapy, when β-HCG in the serum was found to be elevated.

assayed. October 1991, 55 months after the completion of therapy, CT scan showed relapse in the suprasellar region and ependimal dissemination in both lateral ventricles (Figure 1e, f).

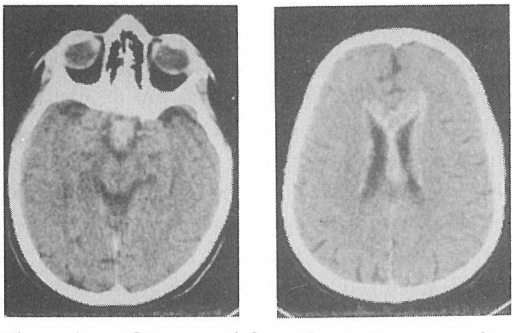

Figure 1e, f. CT scans of Case No. 1; 55 months after therapy, when relapse was confirmed both biochemically and radiologically.

The assayed serum level of β-HCG was elevated even higher, up to 39 IU/L and in the CSF up to 320 IU/L (normal, ≤ 1.5 IU/L). AFP levels in serum as well as in the CSF were in normal ranges, but the CSF cytology was suspicious for tumor cells. At that time the examination revealed mild visual and equilibrium disturbances, atrophy of optic nerves and serious growth failure (13 cm under the 3rd percentile, surplus of 17 kg). One course of intravenous combination chemotherapy with cisplatinum (20 mg/m^2) and etoposide (60 mg/m^2), for 5 successive days and intrathecal methotrexate (10 mg/day), consecutively 4 times with 4-day intervals were administered, extreme myelotoxicity developed and the girl died on November 4, 1991, because of the consequences of pancytopenia. Histopathological examination after autopsy revealed no residual tumor or metastasis in the central nervous system.

Case No. 2

This 10.5-year old girl was admitted to the Pediatric Clinic of Clinical Centre in Ljubljana, Dept. of Child Neurology, in October 1987 with 7-months history of polydypsia, polyuria and excessive increase of body weight. On examination she was 126 cm high (3 cm under the 3rd percentile) and her weight was 32 kg (surplus of 7 kg). There were no neurologic disturbances. Endocrine evaluation confirmed diabetes insipidus, hypothyroidism and hypocorticism. CT scan revealed a sharply delineated lesion in the suprasellar region, 2 cm in its greatest dimension, displacing the neighbouring structures. On October 16, 1987 a partial resection of the tumor was performed. Histopathological examination revealed pure germinoma. Diagnosis was supported by negative immunostaining for AFP and HCG. Examination of the CSF showed no malignant cells and the levels of tumor markers were found to be within normal limits in the serum and in the CSF. Three courses of chemotherapy with cyclophosphamide, 80 mg/kg body weight on 2 consecutive days, repeated every 3 weeks, were admi-

nistered thereafter. No residual tumor was seen on CT after the end of the second course. Radiation therapy was started to the tumor bed on a linear accelerator with 8 MV X-rays. A dose of 30 Gy was delivered in 15 fractions over 22 elapsed days through two opposing fields 8 × 8 cm of size. The girl had no neurological disturbances after completion of therapy. With adequate hormonal substitutional therapy she was able to return to normal life-style.

On June 1989, 16 months after therapy, CT scan showed a tumor relapse in the suprasellar region. Assayed levels of tumor biomarkers in the serum were in the normal ranges but β-HCG value in the CSF was elevated up to 5.4 IU/L with no malignant cells. As the girl was completely free of clinical symptoms, her parents declined therapy. They only gave their consent in October 1989, when a considerably larger tumor and infiltration of ventricular walls were seen on CT scan. The level of β-HCG in the CSF was even higher, up to 13.1 IU/ L. Again, the CSF was free of malignant cells and serum levels of tumor markers were in normal ranges. Two courses of combination chemotherapy with cisplatinum (20 mg/m^2) and etoposide (60 mg/m^2) were administered, for 5 successive days, with 3-week interval. Because of clinically significant myelotoxicity, chemotherapy was discontinued and radiotherapy introduced. Whole brain irradiation trough two opposing fields and a radiation dose of 32.4 Gy delivered in 18 fractions over 25 elapsed days was performed on a cobalt-60 machine. Complete response was observed on CT scan and the CSF level of β-HCG fell to normal.

September 1990 a second recurrence of disease was observed, following a 1-month history of visual disturbance. CT scan showed tumor in the suprasellar region and subependimal dissemination in ventricles, supra- as well as infratentorial. Malignant cells were found in the CSF and its β-HCG level was elevated up to 16 IU/L, but the serum tumor markers' values were within normal range. Two courses of chemotherapy with cisplatinum (20 mg/m^2) and etoposide (60 mg/m^2) were administered. CT scan showed only moderate cerebral atrophy. No tumor cells were found in the CSF and the β-HCG level was within normal range. Examination revealed serious growth failure (10 cm under the 3rd percentile, surplus of 24 kg). She was extremely adipose and had a cushingoidal appearance, congestive cardiomyopathy, visual, auditory and equilibrium disturbances, hemiparesis and panhypopituitarism.

At the third relapse, on March 1991, there were only ependimal infiltration on the CT scan, with no suprasellar tumor. Only symptomatic and hormonal substitutional therapy was administered. The girl died June 12, 1991, 40 months after completion of primary therapy. Autopsy was not performed.

Discussion

Intracranial germ cell tumors constitute a group of histologically distinct tumor types and their responsiveness to various treatment modalities differ considerably.[1–4, 6, 7, 19] The initial histological diagnosis is of critical importance for appropriate treatment planning and it is known to exert the greatest impact upon survival of patients with these tumors. Therefore, surgical biopsy is mandatory.[2, 5, 6, 8–10] This has been made possible only in recent years as new microsurgical and stereotactic techniques have been introduced and surgical biopsy has become less hazardous.[6] On the other hand, there is no evidence that excision adds to therapeutic efficacy.[9, 23] The opinion that surgical biopsy results in an increased frequency of spinal seeding and subsequent treatment failure has not been confirmed.[5, 7, 10, 23]

As the IG are highly radiosensitive, long-term survival rates of 70 % to 100 % are attained by radiation therapy only.[4–9] Taking into account the results they obtained, some authors stated that diagnosis of IG can be made only on the basis of clinical criteria including typical age, tumor site, CT findings and rapid response to initial localized radiation trial to a dose of 20 Gy.[1, 4, 7] In their opinion there is no advantage gained from an initial tissue diagnosis. However, this may not be the case in mixed

tumors that also contain nongerminomatous germ cell tissue components. Here the beneficial effect of a radiotherapy trial may be misleading. It is not likely that such conservative treatment could produce the same effect on other, more radioresistant tissue elements in these tumors. Consequently, in spite of the substantial reduction of tumor mass soon after the beginning of radiation, the end result may be a treatment failure. Thus, in the case of tumors of mixed histology as well as intracranial germ cell tumors other than germinoma, an initial tissue diagnosis is helpful in directing treatment to more aggressive therapeutic regimens, including surgical resection and/or multidrug chemotherapy.[2,5,6,8,10]

Serum and CSF tumor markers such as AFP and β-HCG are important noninvasive diagnostic indicators of tumor nature, in spite of their nonspecificity originating from the present histological classification of germ cell tumors.[2,14] They are also an important measure of therapeutic efficacy since their concentrations reflect the number and activity of the cells responsible for their production.[2,11–14] Elevated levels of AFP are seen in lesions which contain elements of endodermal sinus tumor, elevated levels of β-HCG are seen in those with choriocarcinoma or syncytiotrophoblastic giant cells only and both are seen in embryonal carcinoma. Pure IG produces neither markers.[11,13] In general, the CSF levels are higher than the serum levels or may be elevated in the former whilst being normal in the latter.[11] These statements are consistent with an intracranial origin of these tumors and with our own observations. As reported by Allen *et al.*, in their series there was an excellent correlation between the histological diagnosis obtained from surgical specimens and anticipated presence of tumor markers in either serum or CSF.[11]

In an attempt to improve the accuracy of tissue diagnosis, immunohistochemical stainings for AFP and HCG was introduced.[13,14] Its value is confirmed by high correlation between tissue immunoreactivity and initial histological diagnosis as well as AFP and/or β-HCG elevation in body fluids. However, the reverse is not true. Ho and Liu stated that 8/33 tumors in their series (24%, 5 germinomas and 3 endodermal sinus tumors) with established elevation of serum AFP or β-HCG showed no correlation when studied immunohistochemically.[14] Improper sampling of biopsy specimens that do not include all tissue components of mixed tumor may be the main reason.

The decision to treat our patients with cyclophosphamide and low doses of radiation to limited fields resulted from the histological diagnosis of pure germinoma, a negative body fluids tumor biomarkers assay, known chemosensitivity of IG for cyclophosphamide and on the basis of our own good experiences with combined treatment of sporadic cases in the past as well as literature reports.[19] In our two patients local recurrence of disease was established 55 and 16 months, respectively, after the end of primary therapy strongly effective against pure IG. In all probability, there were also other, more malignant tissue elements within the primary tumor, which have not been initially identified. Since only a part of the tumor was histologically examined, and the components are known to be unevenly distributed, there is a question of how representative were the samples.[12,14] Resulting treatment failures suggest that the therapy was aggressive enough only to eradicate the major, germinomatous part of the tumors, whereas others, more resistant components remained vital and proliferate afterward. While the β-HCG elevation beyond the normal ranges, detected at the time of tumors' relapse, resulted from the proliferation and secretion of the β-HCG producing cells, still vital after therapy, the absence of simultaneous AFP elevation indicate that only the presence of syncytiotrophoblastic giant cells alone or together with cytotrophoblastic cells forming choriocarcinoma's elements of the mixed tumors were responsible for the treatment failure. In both cases, i.e. germinoma with syncytiotrophoblastic giant cells or with choriocarcinoma tissue components, more aggressive therapeutic approaches are necessary.[1–4,6,7]

There is also a possibility that new primary and not recurrent tumor has occurred in the

suprasellar region. This may especially be the case in our first patient, since after a disease-free interval of 55 months the chance for relapse is considerably diminished. Wara *et al.* reported that the average interval from end of treatment to the development of recurrence in their series has been 1.8 years.[4] On the other hand, Edwards *et al.* established local tumor recurrence 4 years after initial treatment[6] and recurrences later than 5 years after the original diagnosis have also been noted.[24]

In view of the known propensity of IG to spread throughout CSF spaces[16] and the age of patients which restrains the therapeutic aggressiveness because of the risk for late sequelae,[15] the opinions about their optimal management differ. On the basis of clinical experience, local irradiation of tumor bed with doses of 40 Gy to 55 Gy is recommended. When spinal seeding is proven, 30 Gy to 35 Gy of craniospinal irradiation is given with local boosts of 10 Gy to 15 Gy to identified metastases and the primary tumor.[3] In attempts to reduce radiation dose, introduction of adjuvant chemotherapy in treatment regimens may be valuable, particularly in young children who have limited radiation tolerance.[15] Cyclophosphamide as well as cisplatinum and etoposide containing chemotherapeutic shedules in the treatment of the initial and recurrent IG seem to be sufficient when given together with lower doses of radiation, ranging between 30 Gy to 40 Gy, while the poor outlook for nongerminomatous germ cell tumors requires that they should receive chemotherapy followed by standard radiation dose of 50 Gy or even more. [10, 18, 19, 22]

To conclude, in an attempt to treat rationally, the treatment for IG as well as for others, nongerminoma germ cell tumors has to be adjusted for the histologically specific tumor type. Small biopsy specimens are not satisfactory because they usually do not contain all tissue elements of the mixed tumors. Adequate tissue sampling is of crucial importance. In such context the value of immunohistochemical staining is also uncertain. Detection of serum and CSF tumor biomarkers provides very valuable information about tumor nature. Unfortunately, they cannot be the sole means for diagnosis because they are not specific and absence of their distinct elevation in body fluids is sometimes misguiding as it is a rapid tumor response to therapy. The diagnosis and treatment decision must be made on firm grounds, such as adequate tissue sample and clinical findings: age, tumor site and CT scan. Even so, it is delicate. Otherwise, it is questionable.

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