THERAPY

Treatment strategy of pineal tumors in consideration of their pathomorphology

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Abstract

Background: **Tumors of the pineal gland are rare pathology. This paper reports on therapeutical considerations of histologically heterogeneous pineal tumors in a group of 15 patients and is presenting a special case of neuroaxial seeding.**
Methods: **Surgery and/or additional therapeutic procedures were performed in 13 of our 15 patients ("youngster" and "adults") in respect of pathomorphology. Details are reported concerning a 52-year-old man suffering from pineocytoma (WHO grade II), who underwent different kinds of therapy within 10 years follow-up.**
Results: **In the six "youngster" the histological assessment revealed two teratomas, one mixed pineocytoma/pineoblastoma, one astrocytoma and one epidermoid cyst. All neoplasms were treated surgically with good results. Additional radio-/chemotherapy was used in a case of teratoma and pineocytoma/pineoblastoma. From five successfully surgically treated "adults" (germinoma, pineoblastoma, pineocytoma, two cystic formations) in two of them (germinoma, pineoblastoma) additional radiotherapy was needed, another two patients (cystic formations) were healed after stereotactic puncture. The patient with pineocytoma showed recurrent neuroaxial seeding within 10 years in spite of repeated radiotherapy, though his neurological status remained stable (Karnofsky performance score of 100).**
Conclusion: **Precise histopathological assessment of pineal tumors is essential to guide optimal modern therapy modalities in order to assure a local tumor control.** ***(Fig. 3, Ref. 18.)***
Key words: pineal tumor, pinealocytoma, neuroaxial metastasis, therapy.

Tumors within pineal gland are rare pathology of the central nervous system (0.4 to 1 % of intracranial tumors) and can be classified into the following major groups: germ cell tumors, glial tumors, non neoplastic masses, and pineal parenchymal tumors (1 – 3). The latter are divided into the pineocytomas, tumors with intermediate differentiation, mixed tumors, and malignant, less differentiated pineoblastomas; they account for between 15 and 30 % of all pineal tumors (4).

Treatment modalities for pineal neoplasms have changed in recent years. In the past, surgical treatment of pineal tumors were subject to a high mortality rate of up to 90 %. For this reason, preference was given to more conservative management such as shunting and radiation therapy (5). The stereotactic biopsy technique has improved the differentiation and treatment of pineal tumors, while the development of microsurgical techniques and the recently adopted neuronavigation technique have changed the treatment strategy. Studies with different therapy modalities have shown more refined tumor handling. However, there is still no uniform concept for successful treatment of pineal tumors. There is the only valid consensus that the knowledge of the histopathology of neoplasm should be essential for planning rational treatment.

This paper reports on therapeutical consideration in our group of patients with tumors within the pineal gland and a case of

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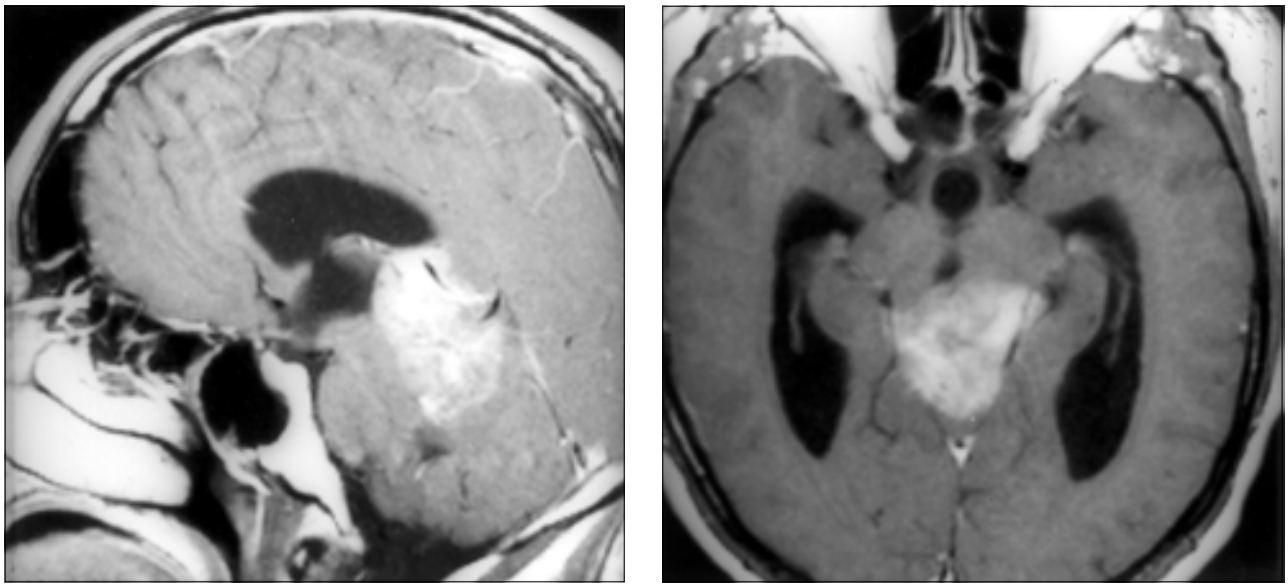

Fig. 1. MRI 4 weeks after onset of symptoms showed an inhomogenous tumor of the pineal gland.

unusual recurrent seeding of pineocytoma over the cranial and spinal axis during a 10-year period.

Patients and methods

From March 1991 to December 2001 we treated 15 patients suffering from space occupying lesions within the pineal gland.

Six of these patients were less than 18 years of age, so called „youngster". In five of them the tumor was resected, and in all but one ventriculo-peritoneal shunt was inserted to treat accompanied hydrocephalus. Histopathological assessment of the five tumor specimens revealed a teratoma in two patients, in the remaining three "youngster" one mixed pineocytoma/pineoblastoma, one astrocytoma (WHO grade II) and one epidermoid cyst were found out.

Nine patients belonged into the group above 18 years of age, so called "adults". In two of them no surgical treatment was performed, as in one patient a small cystic tumor formation within pineal region was recognized incidentally during computed tomography (CT) and the second patient with asymptomatic cystic pineal tumor did not consent to surgery. The other seven "adults" underwent surgery, whos`e tumors being completely resected in five patients. Histopathological assessment of those tumors revealed one germinoma, one pineoblastoma and one pineocytoma. In remaining two "adults" the only cystic formation without tumor cells was found.

Results

In the group of six "youngster" one patient with teratoma showed no neurological deficit after total tumor resection. In almost two years of follow-up, CT and magnetic resonance imaging (MRI) revealed no tumor evidence and the clinical course was uneventful. Another patient with teratoma showed symptoms of hypophyseal insufficiency 4 years after tumor resection. CT and MRI documented a new tumor mass at the base of the third ventricle. Chemotherapy, craniospinal radiotherapy (30 Gy) and external boost irradiation to the tumor bed (54 Gy) were administered (SIOP/CNS-GCT-96 protocol) (6). Follow-up showed neither new neurological deficit nor signs of tumor. However, complete hormone substitution had to be continued. The same therapy regime was prescribed for the third patient with mixed pineocytoma/pineoblastoma. His follow-up presented no new neurological deficit and no evidence of tumor has been registered to date. Similarly there were neither new neurological deficits nor evidence of tumor appearance in remaining two „youngster" with astrocytoma and epidermoid cyst.

In the group of 5 surgically treated "adults", the patient with germinoma underwent postoperative additional external cranial (40 Gy) and spinal (30 Gy) irradiation; two years after this therapy he showed no new neurological deficit. The patient with pineoblastoma presented postoperative evidence of hydrocephalus therefore a ventriculo-peritoneal shunt was inserted, followed by external beam radiotherapy with 56 Gy to the cranium and 36 Gy to the spine. To date, there has been neither evidence of tumor nor new neurological deficits. The history and the extent of treatment by the patient with pineocytoma is described in the following special case report. The cystic tumors in the remaining two "adults" were successfully treated using stereotactic puncture.

A special case – neuroaxial seeding with ten years follow-up

History: A 52-year-old man has experienced diplopia while looking down at the ground as well as progressive diminishing vision for about 4 weeks before admission. Furthermore he reported slight movement disturbance and a lack of fine motor control in both hands.

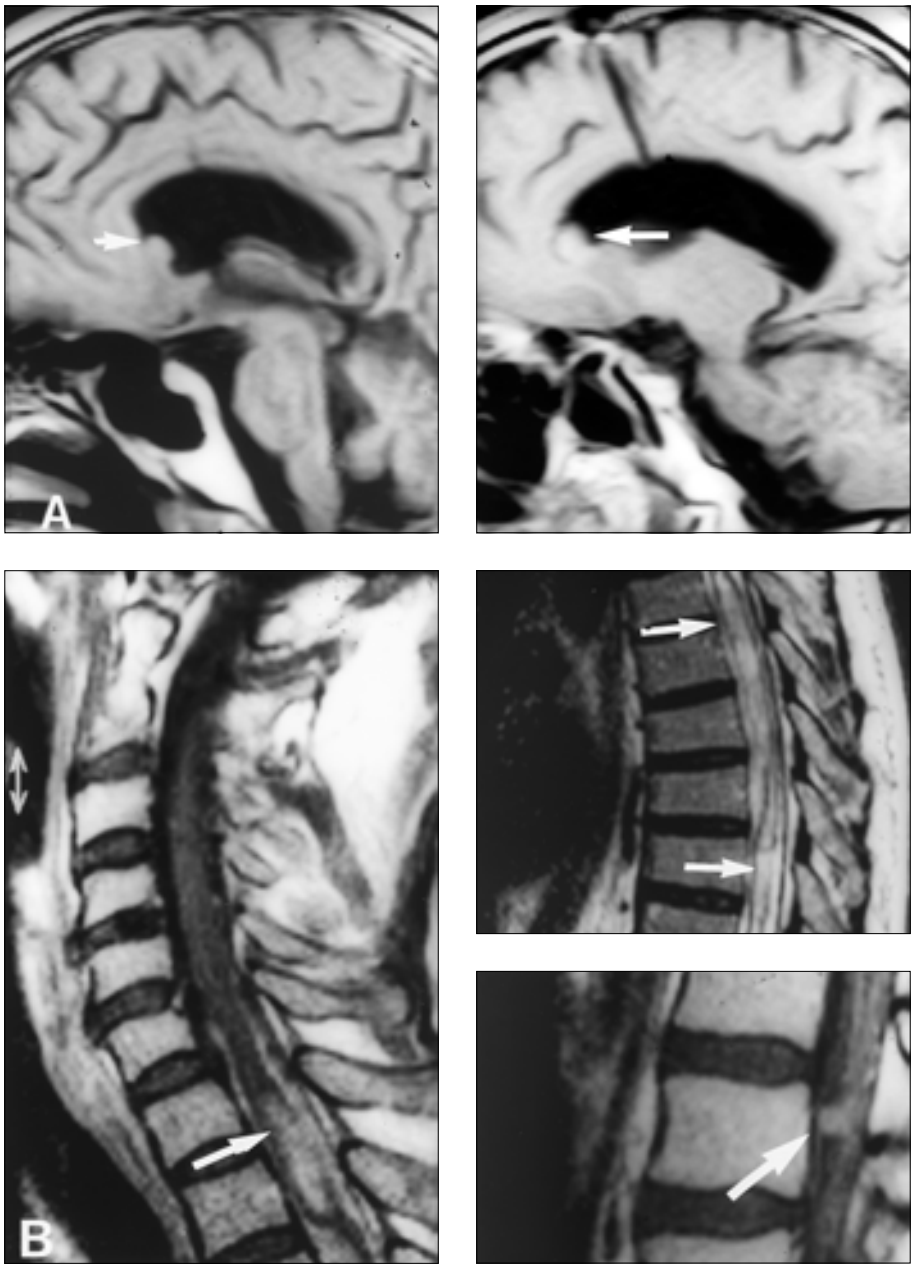

Fig. 2. MRI six and a half years after finishing treatment showed two hyperdensity areas near the frontal horn of the right lateral ventricle (A, arrows) and multiple lesions of cervical, thoracic and lumbal spine (B, arrows).

Examination: The clinical picture suggested mild abducens palsy on the right side and tremor of both hands; neither headache nor any other neurological deficit was recorded. Ophthalmic examination confirmed abducens palsy on the right side with diplopia and nystagmus. CT revealed an inhomogeneous tumor in the pineal region with calcification and surrounding brain edema. Both lateral ventricles and a third one were enlarged; the fourth ventricle was compressed and pushed downwards by the tumor. MRI documented an infiltrating tumor within the cerebellar peduncle and the quadrigeminal plate up to the pineal region, and its good enhancement after gadolinium (Fig. 1). Digital subtraction angiography (DSA) showed no pathological vascularization within and all around the tumor.

Surgery: A left occipital stereotactic biopsy was performed. Unfortunately the histopathological differentiation of this specimen was not conclusive between pineocytoma and medulloblastoma. At the next session, suboccipital craniotomy was performed and the tumor, which expanded into the both cerebellar peduncles, was resected.

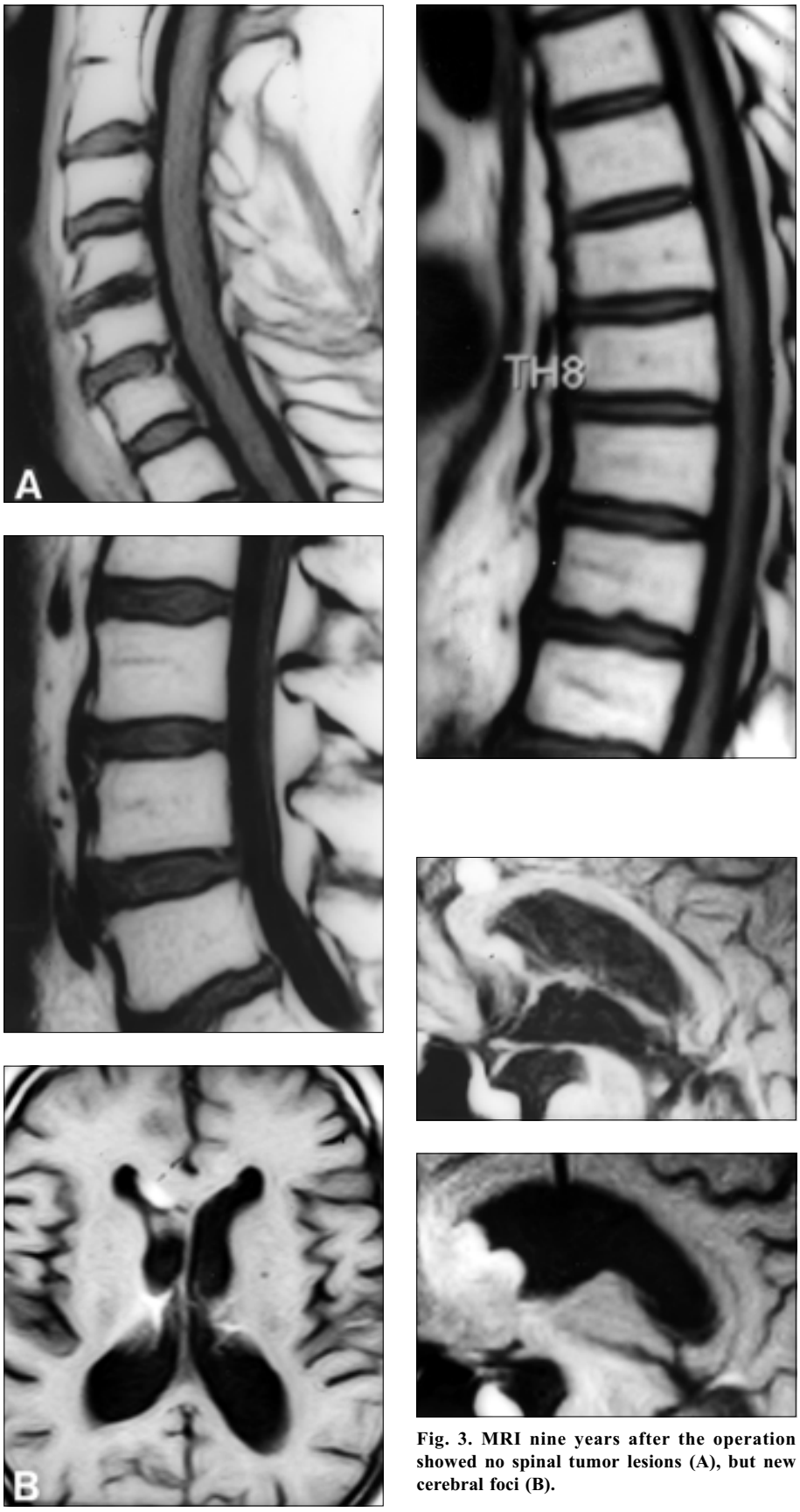

Fig. 3. MRI nine years after the operation showed no spinal tumor lesions (A), but new cerebral foci (B).

Pathological findings: Histopathological assessment of the tumor tissue confirmed a pineocytoma (WHO grade II).

Additional treatment: In the following days a ventriculo-peritoneal shunt was inserted in view of the evidence of hydrocephalus. The treatment was accomplished with cranial external irradiation (45 Gy center dose).

Postoperative course: The neurological symptoms disappeared gradually and there was no radiographic evidence of tumor remnant. More than six years after surgery, the patient reported progressive ataxia and spasticity of the legs to a varying degree. CT and MRI of the cranium and spine showed two small areas of hyperdensity near the frontal horn of the right lateral ventricle (Fig. 2A) and multiple lesions over the entire spinal cord (Fig. 2B). The examination of cerebrospinal fluid (CSF) revealed mononuclear cells, lymphocytes and monocytes in uniform ratio, some with round-oval, irregularly formed nuclei. Furthermore there were cell clots with larger nucleoli and a basophilic cytoplasm as evidence of paraneoplastic meningeosis. Supplementary radiation therapy (35.6 Gy) was administered over the entire neuroaxis. Thereafter, the patient's clinical course was uneventful with a Karnofsky performance score (KPS) of 100. The follow-up 9 years after the operation showed slight ataxia and spasticity of the legs. CSF examination revealed no pathological findings apart from a few tumor cells, and MRI documented no spinal tumor invasion (Fig. 3A) but new cerebral lesion at the right frontal horn of the lateral ventricle (Fig. 3B). The patient underwent next additional external cranial radiation therapy (50 Gy). The last folow-up within 10 years presented stable clinical status without distinguished conspicuousness in neuroimaging.

Discussion

Tumors of the pineal gland are rare (0.4 to 1 % of intracranial tumors) without predominance relating to the sex or age. With regard to their great pathomorphological variation they can be divided into the four major groups: germ cell tumors, glial tumors, non-neoplastic masses, and pineal parenchymal tumors. Pineal parenchymal tumors can be further subdivided into the pineocytomas, tumors with intermediate differentiation, mixed tumors, and malignant, less differentiated pineoblastomas (7).

The rationale and therapy planning of the pineal tumors have undergone radical changes in recent decades, with no acceptance of the rather conservative treatment strategies, which were the method of choice in the past. The introduction of sophisticated imaging techniques as well as histopathological procedures allows more precise differentiation of neoplasms with regard to optimizing treatment modalities. Greater knowledge of the intracranial anatomy, progress in microsurgical technique and, more recently, the adoption of neuronavigation have contributed to more radical surgical treatment on the one hand, while development and progress in radiotherapy and chemotherapy have made the treatment of such tumors safer and more effective on the other.

Nevertheless, the management of pineal tumors is not uniform till this day.

There is no doubt that the first step in management of pineal tumors must be precise histopathological assessment of these tumors. For some benign tumors within pineal region like meningeomas or non-tumorous processes, e.g. vascular lesions and infections, radical surgery alone seems to be the best treatment (8). For pineal tumors the application of modern diagnostic procedures and surgical tools is essential, in order to confirm their definitive histological entity for appropriate management, which can eliminate the risk of tumor progress or its expansion. Bruce and Stein reported that 15 % of their patients with lesions of the pineal region had mixed tumors (9); this points to the fact that stereotactic biopsy alone can provide incorrect or incomplete results.

Pineal parenchymal cell tumors (pineocytoma, tumor with intermediate differentiation, pineoblastoma and mixed pineocytoma/pineoblastoma) should be subjected to combined therapy consisting of surgical treatment and adjuvant chemotherapy and/or radiotherapy (10). This concept should be given preference in view of the poor results reported by D'Andrea et al. in children undergoing surgical and supplementary radiation therapy (11). Radiotherapy seems to be successful in the most frequent pineal tumors and germinomas (3, 12), although the combination with chemotherapy is apparently more effective, especially in treatment of malignant tumors (13). There are various application schemes, all of them platinum-based, though the results of these therapeutic modalities differ widely from no effect to complete remission (14).

There is no agreement on whether or not pineocytomas have a seeding potential. Some authors believe that pineocytomas cannot spread metastases and that if they do so, then they are not exclusively pineocytomas (15, 16). However, other authors have reported that pineocytomas and pineoblastomas can spread metastases through the CSF, the latter much more frequently than the former (17, 18). This claim is also supported by the medical history of our former described special case. Seeding of pineocytoma has been recorded mostly in children. This group of patients seems to be a high-risk group for the spreading of metastases.

The recent discussion has centered on whether radiation therapy of the entire neuroaxis is necessary in all patients with pineal parenchymal tumors, except for patients with pineocytomas. In our opinion any patient with pineocytoma, and above all the children as a group of high-risk patients, should be considered for postoperative radiation of the entire neuroaxis. With regard to the literature and in view of our experiences concerning the rare seeding of pineocytoma, it is essential to follow up any patient with a pineocytoma very carefully, using available techniques including CSF and neuroimaging evaluation.

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