Extraneural Metastases of a Cerebral Astrocytoma

INTRODUCTION
Extraneural spread of a cerebral glioma has been described infrequently. The present case provides an example of this unique mode of metastasis.

CASE HISTORY
A 4 year old boy was admitted to the Hospital for Sick Children in July 1975 with a history starting in September 1974. At that time, he began having minor seizures in which he stared, and he regressed in speech and motor ability. It is interesting that his mother, who had been concerned about him, was told by a psychic that her son had a brain tumor.

At the time of admission, he was neurologically intact with no signs of raised intracranial pressure. A brain scan showed increased uptake in the left temporal region, a CT scan showed a contrast enhancing mass in the left middle fossa, and a left carotid angiogram showed a large avascular mass in the left temporal lobe (Figure 1).

On July 24, 1975 through a left temporal craniotomy, 95% of a parenchymal temporal lobe tumor was grossly removed. The portion of the tumor which was adherent medially, in the region of the internal carotid artery, was left. The tumor was described as the size of an orange. Histological examination showed a sparsely cellular tumor in which the nuclei were round to oval in appearance and cytoplasm was abundant and formed prominent cytoplasmic processes. These processes strained positively with the glial fibrillary acidic protein (GFAP) stain and with the phosphotungsic acid hemotoxylin (PTAH) stain (Figure 2). The nuclei showed a mild variation in degree of chromaticity and size. The histology of this tumor was that of a fibrillary astrocytoma, low grade. Because some tumor had been left behind together with the mild pleomorphism in the tumor, he was subjected to a course of postoperative radiotherapy at the Princess Margaret Hospital. Seizures continued to be an intermittent problem for which he received anticonvulsant medication. A brain scan in March, 1976 and a CT scan in November 1976 showed no evidence of residual tumor (Figure 3). A psychometric assessment in May 1978 revealed a full scale I.Q. of 79.

In May 1979, he presented with a tender scalp lump 1 cm. in diameter in the region of the original craniotomy incision. A CT scan in June 1979 showed a large area of calcification adjacent to the frontal horn which was thought to be related to previous radiation. Following the CT scan, he was re-assessed on June 22, 1979 at which time the lump had enlarged and he was admitted for resection of this lesion.

This was carried out on June 25, 1979. The lump was neoplastic, was non-adherent to bone and was entirely within scalp. The tumor removed was extremely cellular with nuclei packed closely together and scant cytoplasm discernible. The nuclei were round and fairly regular, but the number of mitotic figures was extremely high. With both the PTAH and GFAP (Figure 4) stains, astrocytes could definitely be identified.

A typical cell on electron microscopy consisted of a nucleus with a slightly irregular and cleaved nuclear membrane. The cytoplasm was distended and filled by astroglial fibrils, some of them arranged in a haphazard fashion and others in whorl-like formation (Figure 5). The diagnosis of this tumor was a malignant astro-
In order to ensure that there was no residual tumor, a radical excision of scalp in the region of the lump was carried out and then scalp was rotated in from the right side of his head to repair the residual defect.

In March 1980, he presented with a lump in the right parietal region of scalp, in the area from which the rotation flap had been taken to repair the defect in the left temporal region. The lump was exquisitely tender and enlarging. This lump was excised on March 13, 1980. This mass consisted of a grossly well-demarcated tumor; however, microscopically, fragments of tumor completely surrounded by connective tissue were found around the periphery of the main mass of tumor. Histologically, the tumor was identical to the previous scalp excision. Because of the proximity of tumor to adjacent surgical excision lines, a wider dissection of scar tissue was later undertaken and this was negative for tumor.

In June, 1980, a third scalp lesion was excised. This lesion was different from the previous two scalp lesions in that there was now extensive necrosis and tumor cells could be identified in several small, venous channels. He was re-admitted on July 7, 1980 because of the development of an enlarged lump in the right side of his neck which was thought to be lymph node infiltrated with tumor. On July 8, 1980 a radical neck dissection was carried out and 8 of 20 lymph nodes were found to contain metastatic astrocytoma. During the course of the neck dissection, it was necessary to ligate and excise the internal jugular vein.

On the third post-operative day after his radical neck dissection, he developed headache. A CT scan at that time showed no evidence of any problem (Figure 6). He was subsequently discharged but re-admitted on July 29, 1980 because of diplopia, severe headaches, vomiting, and early papilledema. A repeat of the CT scan showed no change. A lumbar puncture showed a pressure of 500 mm. of water.

A diagnosis of pseudotumor cerebri, on the basis of venous obstruction, was made and he was treated with steroids. He rapidly improved and was discharged from hospital on August 7, 1980 in an asymptomatic state which has continued to the present.

There are several interesting aspects to this case. The first is that the histology of the tumor changed when it began to grow outside of the brain. The histology of the tissue that was received at biopsy from the left temporal lobe was a low-grade fibrillary astrocytoma without evidence of mitotic activity. However, the three nodules of tumor in the scalp and the tumor in the...
lymph nodes was clearly a malignant astroglial tumor of high cellularity with large numbers of mitotic figures. The reason for this change in degree of malignancy is not apparent. One could argue that the original sections of the tumor sampled were not representative of the entire tumor. However, a high-grade astrocytoma would be unlikely to be associated with a four-to-five-year survival. The other factor which may be instrumental in changing the biological activity of the tumor is the location in which the tumor is growing.

What are the general factors favoring extraneural metastases? One factor has been the artificial occurrence of distant dissemination following surgical shunting procedures (Hoffman et al., 1976). Another factor, which appears to be the most important one, is operative intervention with access of tumor to extrameningeal tissue through the surgical defect (Lwinnicz & Rubenstein, 1979). It appears that the tumor, when it gains such access, is then able to infiltrate the lymphatics or venous channels and thus be disseminated widely. Finally, there are reports of extraneural metastases in patients that have had no surgery. (Anzil, 1970; Brander & Turner, 1975; Dolman, 1974) Presumably, in these cases, there was spontaneous tumor invasion of dural sinuses with subsequent extraneural dissemination.

Do some tumors have a greater propensity to metastasize outside of the nervous system than other tumors? In a review of the literature undertaken by Lwinnicz and Rubenstein, (1979), the two tumors which appeared to have a greater tendency to metastasize outside of the nervous system were medulloblastoma and ependymoma.

Are extraneural metastases related to a longer post-operative survival time? This does not seem to be necessarily true. Certainly, with the glioblastoma multiforme group, the survival time ranged from six-to-twelve months with metastases, similar to the survival time associated without metastases. However, prolonged survival does play a role in a relatively high proportion of metastasizing ependymomas, particularly of the myxopapillary, histological variety. In this group, the clinical history may range from ten-to-thirty years.

How do gliomas get out of the nervous system? The documented
sites of exit (Liwnicz & Rubenstein, 1979) are over the cranial convexity, the floor of the middle fossa, posterior fossa, spinal canal, shunt, and unknown sites. The article by Liwnicz and Rubenstein listed the respective incidences of tumor exit sites remote from the operative site. They found that direct extrameningeal tumor extension over the cranial convexity was as common as sites remote from the operative flap as through the operative flap.

When the tumor gets out of the central nervous system, where does it go? There are certain trends with different types of tumors. For example, astrocytomas tend to go to lymph nodes, medulloblastomas to bone, glioblastomas to lung and lymph nodes, and ependymomas to lung.

What is the mechanism of metastatic tumor formation? The mechanism of extraneural metastases appears similar to that of metastasizing neoplasms of non-neural origin and includes several steps. Single cells become detached from the primary growth and then migrate to blood vessel boundaries (Vasiliev & Gelfand, 1976). The tumor cells penetrate through the vascular walls at the primary site and then become disseminated through the circulation and arrest within a specific target organ. Why some tumors choose a particular target organ is not clear (Nicolson, 1977). Exit of tumor cells through the vascular wall of the target organ into the stroma results in the formation of micrometastases (Chew et al, 1976). The transformation of micrometastases to overt metastases depends on several factors. One factor is thought to be penetration of blood vessels originating from host tissues. It is clear that gliomas evoke vascular neo- genesis and contain high levels of tumor angiogenesis factor which is known to be mitogenic for capillary endothelium (Folkman & Tyler, 1977). The role of the cell-mediated response to tumors would be operative during blood-borne dissemination and could hinder the establishment of micrometastases or transformation of micrometastases to overt metastases.

In addition to the question of metastatic spread there are several other features of interest in this case. The prospect for cure of a cerebral hemisphere astrocytoma by radiation is real. Fifty-two children were irradiated post-operatively at the Princess Margaret Hospital, Toronto, from 1958-1977. The 10 year survival rate is 34% (Figure 7). Only one patient has relapsed after the initial 4 years of follow-up. The 5 year survival rate was greater following a grossly complete resection, 62%, (N = 11), compared with a partial resection, 29% (N = 29); was greater for Grade I - II, 50% (N = 16), compared with Grade III - IV, 27% (N = 31). The presence of macroscopic cysts was a favorable factor. The sub-group with the lowest survival rate was patients with Grade III - IV non-cystic astrocytomas: One of 5 completely resected patients survived 5 years compared with 1 of 13 patients not completely resected. There is evidence that the local control rate is dose-dependent. In recent years, children older than 2 years have been locally irradiated using a dose of 5250 rads in 28 fractions in 5 to 6 weeks. While higher control rates might be possible with higher doses, the cost effectiveness at higher doses in general is judged to be excessive.

It follows that the prospect for continuing control of the primary tumor in this patient is very good. This
was the only patient among the 52 patients reviewed who developed regional systemic relapse. His subsequent management by serial resections has controlled his systemic disease to date. Further cervical relapse may be an indication for additional radiation treatment, for a high local control rate can be anticipated following excision of all macroscopic tumor.

A further feature of this case was the development of pseudotumor cerebri. Pseudotumor cerebri has been ascribed to many different etiologies (Greer, 1962). Venous obstruction is a well known cause of pseudomotor cerebri and in this case iatrogenic obstruction of the venous return from the brain was sufficient to invoke this particular syndrome.

CONCLUSION

Modern neurosurgical treatment and radiotherapy allows for a much higher rate of cure of cerebral astrocytomas. Possibly with the prolonged longevity of these patients, we may begin seeing more cases of extraneural spread of these tumors. It is surprising that in our case, the glioma cells lay dormant within the scalp for so many years before finally forming an aggressive tumor lump. This must, in some way be related to patient immunity to this neoplasm.

REFERENCES