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Department of Neurosurgery and Division of Special Neuropathology, Neurological Institute of the University of Vienna and Departments of Neurosurgery and Pathology, Wagner-Jauregg-Hospital, Linz, Austria

Extracranial Metastases of Anaplastic Cerebral Gliomas

By

H. Schuster, K. Jellinger, A. Gund, and **H. Regele**

With 5 Figures

Summary

Seven cases are reported of anaplastic cerebral gliomas with metastases outside the neuraxis, seen among about 1500 gliomas. There were two children with anaplastic ependymomas, one adult with oligodendroglioma, and four young to middle-aged adults with astrocytomas grade III and IV. All patients had one or more craniotomies, and four had radiotherapy prior to the appearance of distant tumour deposits. The survival times ranged from 7 to 31 months in cases with gliomas grade II, and from 8 to 18 months with high grade astrocytomas. All seven tumours showed invasion of the meninges, ventricular walls, or both, and in four cases they transgressed the dura and surrounding bone or soft tissues. In six autopsy cases there was widespread dissemination of gliomas through the CSF pathways. Distant metastases involved regional or distant lymph nodes in six patients, the lungs in two, and the vertebrae, pleura, liver, or mediastinum in one patient each. The possible pathways for distant spread of intracranial gliomas and the factors which are considered responsible are briefly discussed.

Extracranial metastasis of anaplastic cerebral gliomas is rare, while spreading of some of these tumours through the cerebrospinal pathways is not infrequent (*cf.* Eade and Urich 1971, Rubinstein 1972). Acceptable cases of metastasizing gliomas have to meet the criteria outlined by Weiss (1955). These criteria are: 1. a single, histologically characteristic central nervous system tumour; 2. a clinical history indicating a primary tumour of the nervous system; 3. a complete postmortem examination carried out in sufficient detail to eliminate possible sites of origin for the tumour outside the neuraxis; and 4. a similar histological appearance of the central nervous system tumour and the metastases.

In a series of over 8,000 tumours of neuroectodermal origin, including medulloblastomas, from the files of the Armed Forces Institute of Pathology, Washington, only 35 developed distant metastases. Of these, 23 were glioblastomas, and three were other types of gliomas (Smith *et al.* 1969). In the recent review by Kretschmer (1974), 171 reported intracranial tumours with proven distant metastases were found. Of this total, gliomas accounted for 63 cases (43 glioblastomas, 16 ependymomas, and 4 oligodendrogliomas). Additional reports of comparable cases found in the literature included five glioblastomas (El-Gindi *et al.* 1973, Komatsu *et al.* 1972, Dolman 1974, Mrazek and Janda 1975), three undifferentiated gliomas (Eade and Urich 1971, Brander and Turner 1975), three oligodendrogliomas (Pe 1962, Cappelaere *et al.* 1972), and one malignant ependymoma (Høgaard *et al.* 1970). The organs affected by distant spread of gliomas are in decreasing order of frequency: the lungs (about 50%), skeleton (43%), mediastinal and cervical lymph nodes (25% each), liver (17%), skin, pleura and kidney (9%, 5%, 8% and 7%, respectively). Extracranial spread of gliomas most frequently develops following surgical intervention or through artificial shunts, but rare cases of glioblastomas have been described in which invasion of the dural veins or sinuses led to spontaneous extracranial metastases in the absence of a previous craniotomy (Anzil 1970; Bogdanovich 1958; Gropp 1955; Rubinstein 1967, Brander and Turner 1975). Recently Dolman (1974) reported a lymph node metastasis as a first manifestation of glioblastoma.

We are presenting a further series of seven cases of anaplastic gliomas with metastases outside the neuraxis, seen among about 1,500 intracranial gliomas listed during the past ten years in the files of the Neurological Institute of the University of Vienna. Only two of these cases have been previously reported (Jellinger *et al.* 1969; Koos and Miller 1971).

Case Reports

Case 1: St. L., a 58 year old woman, suffered from a left parietofrontal oligodendroglioma. At craniotomy one year after the onset of clinical symptoms the tumour was found to invade the overlying meninges. The surgical biopsy did not, therefore, show all the typical diagnostic features of an oligodendroglioma (Minauf and Jellinger 1968). The patient felt well for 2.5 years after surgery. No radiation therapy was administered. Two weeks before death aphasia and right sided hemiplegia again occurred suddenly, and the patient died in deep coma. Necropsy revealed a large oligodendroglioma (grade II) in the left frontoparietal region, with extensive invasion of the meninges (Fig. 1 A), and seeding along the cerebrospinal pathways. There were small osteoplastic tumour deposits in the bodies of the third and fifth lumbar vertebrae. Their

bone marrow spaces were affected by groups of tumour cells which histologically resembled the cerebral neoplasm (Figs. 1 B and C). Histologically, there was no evidence of tumour in other visceral organs.

Case 2 (M. L.): In this 13 year old girl, a solid, mandarine sized ependymoma grade II was removed from the left parietal lobe on March 22, 1965. Post-operatively, no radiation therapy was given. Seven months later, the patient's

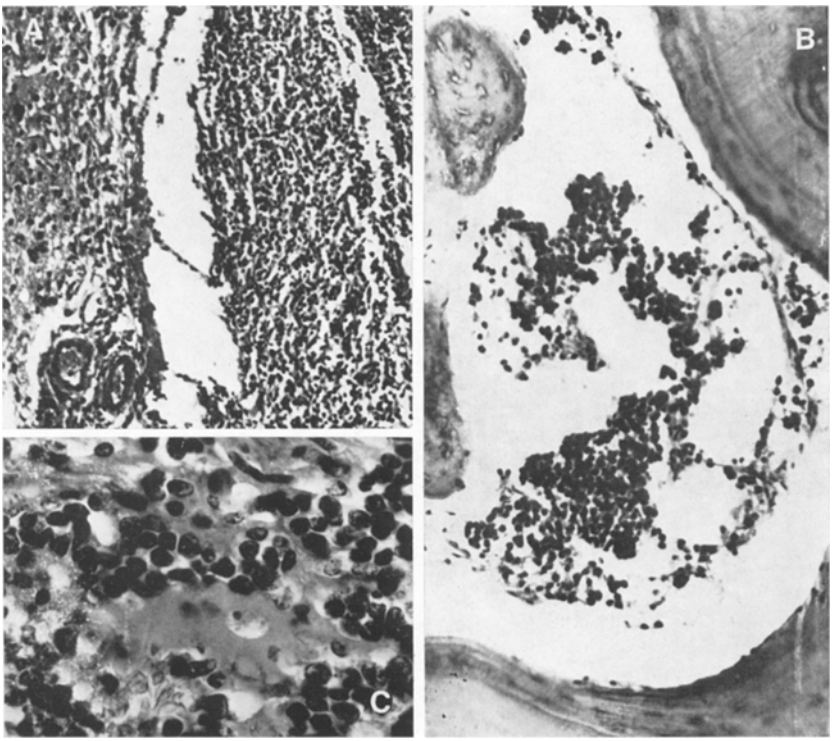

Fig. 1. Case 1; oligodendroglioma. A) Tumour in right frontal region invading the meninges. H. & E. ×100. B, C) Groups of tumour cells within narrow spaces of 3rd lumbar vertebral body. H. & E. ×100, ×400

symptoms recurred, and a large left frontoparietal tumour was removed on October 27, 1965. Histologically the tumour was an anaplastic ependymoma (grade II to III). At the time of the second craniotomy a bean sized subcutaneous preauricular lymph node on the left was excised. On microscopic study it showed neoplastic infiltration with the typical pattern of an anaplastic ependymoma (see Koos and Miller 1971, Fig. 52). Unfortunately, the patient was lost to follow up.

Case 3: P. H., a 7 year old boy, had developed left hemiparesis at the age of four years. Thirty one months before death, a large right parietal tumour weighing 125 grs was removed. Histologically, it proved to be an ependymoma with slight signs of anaplasia (Fig. 2 B). Post-operative radiotherapy (betatron)

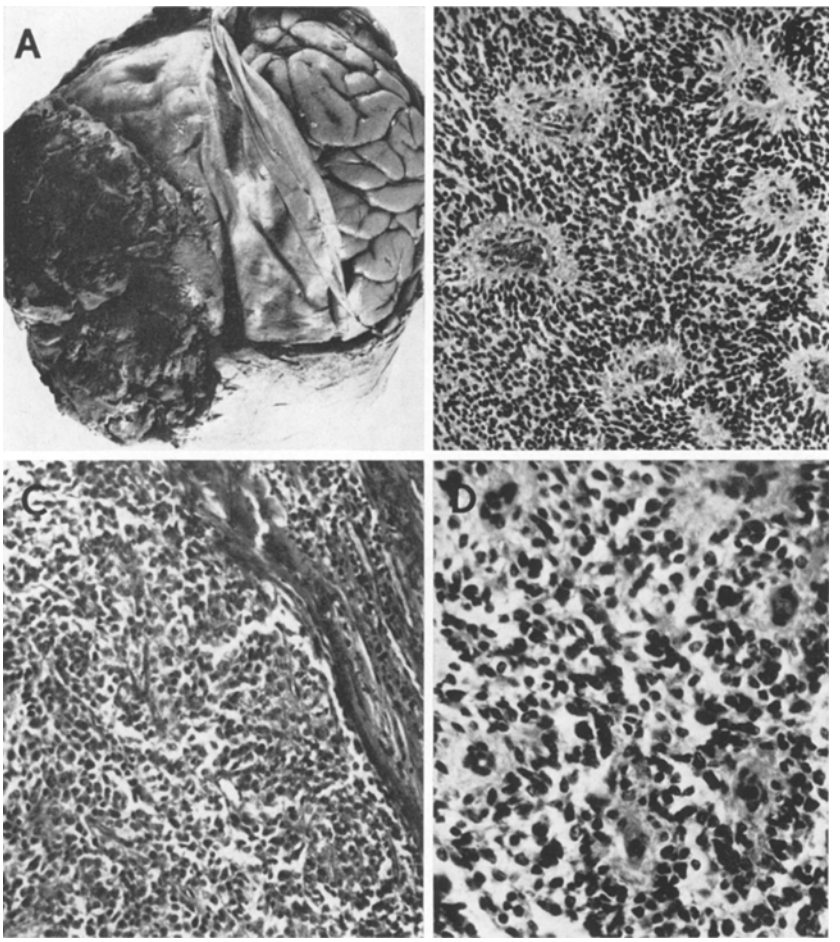

Fig. 2. Case 3; ependymoma. A) Large tumour of left hemisphere grossly invading the dura. B) Biopsy specimen of cerebral ependymoma. H. & E. ×100. C) Autopsy specimen of cervical lymph node with metastatic tissue. H. & E. ×100. D) High power of lymph node metastasis showing perivascular rosettes of ependymoma. H. & E. ×300

was administered. Eighteen months later, an orange sized tumour was removed from the same site. On microscopic study, it showed increased anaplasia. Because of CSF blockage a ventriculoperitoneal shunt was inserted some weeks later. A further course of radiotherapy (cobalt) was given. Three months before death the tumour was found to permeate the area of the previous craniotomy with gross invasion of the skin. At the same time enlarged lymph nodes were detected in the right cervical region. Due to the child's poor condition no biopsy was performed. Death occurred from acute increase of intracranial pressure due to obstruction of the shunt catheter. Autopsy disclosed a large necrotic tumour

occupying large areas of the right cerebral hemisphere with broad invasion of the overlying dura and skin (Fig. 2 A). There was spreading of the anaplastic ependymoma through the CSF pathways into the left frontal region and right lobe of the cerebellum. In the right cervical region plum sized lymph nodes were present; their structure was almost completely replaced by neoplastic tissue which histologically proved to be identical to that of the primary brain tumour (Figs. 2 C and D). No further evidence of tumour was found elsewhere in the body.

Case 4: F. M., a 42 year old woman underwent craniotomy for a left temporal glioma which was removed seven months prior to death. Histological study revealed an anaplastic protoplasmatic astrocytoma. No radiation therapy was given. Five months later the right temporoparietal region was reexplored. The dura was adherent to the recurrent tumour which was removed with the invaded parts of the dura. Histologically, a pleomorphic astrocytoma with signs of glioblastoma was identified. At autopsy, two months later, a large left temporoparietal glioblastoma grossly invading the dura of the posterior fossa and permeating the left occipital sinus was found. There was dissemination of the tumour into the left frontal lobe. In addition, greyish-white neoplastic tissue was found in the left deep cervical lymph nodes, in the mediastinum, and bilaterally in the pleura with broad invasion of the superficial areas of the left lung. Histologically the tumour tissue proved to be identical to that of the primary brain tumour. No other extracranial neoplasm was found.

Case 5: K. F., a 46 year old male developed a left hemiparesis nine months prior to death. One month later, an egg sized tumour was completely removed from the right parietal region. Histological study of the biopsy specimen revealed a monstrocellular astrocytoma. No radiotherapy was given. Three months later, the patient's symptoms recurred, and a second craniotomy was performed. A large tumour in the right parietotemporal region was only partially excised. Histologically the tumour tissue proved to be identical to that previously removed. Postoperative radiation therapy (telecobalt) was administered. Two months later, the tumour tissue was found to invade the dura and the galea at the site of craniotomy. Some involved areas were excised, and histological study confirmed the neoplastic permeation of the subcutaneous tissues (Fig. 3 A). A further course of radiotherapy (cobalt) was given to the skull. Three months later, the patient died with clinical and radiological signs of metastases in the liver and the lungs. Autopsy revealed a monstrocellular astrocytoma in the right temporal lobe grossly invading the dura and overlying skin. In the liver and both lungs were found many circumscribed greyish nodules which histologically showed the same type of neoplasm as the brain tumour (Figs. 3 B and C).

Case 6: St. H., a male aged 20 years, developed acute hemiparesis 17 months prior to death. At craniotomy, a haemorrhagic tumour was excised from the left parasagittal parietal region. Histology showed an undifferentiated glioma which, in places, resembled a medulloblastoma. Four months later, an apple sized tumour was removed. It was shown histologically to be an anaplastic fusicellular glioma with occasional giant cells and pseudopalisading round necrotic areas (Fig. 4 B). Postoperative radiotherapy (telecobalt) was given. Eight months after the second craniotomy, a walnut sized lymph node in the left cervical region was removed. Histological study of the biopsy specimen showed almost complete replacement of the original lymph node structures by necrotic gliomatous tissue similar to that previously removed from the brain (Figs. 4 C and D).

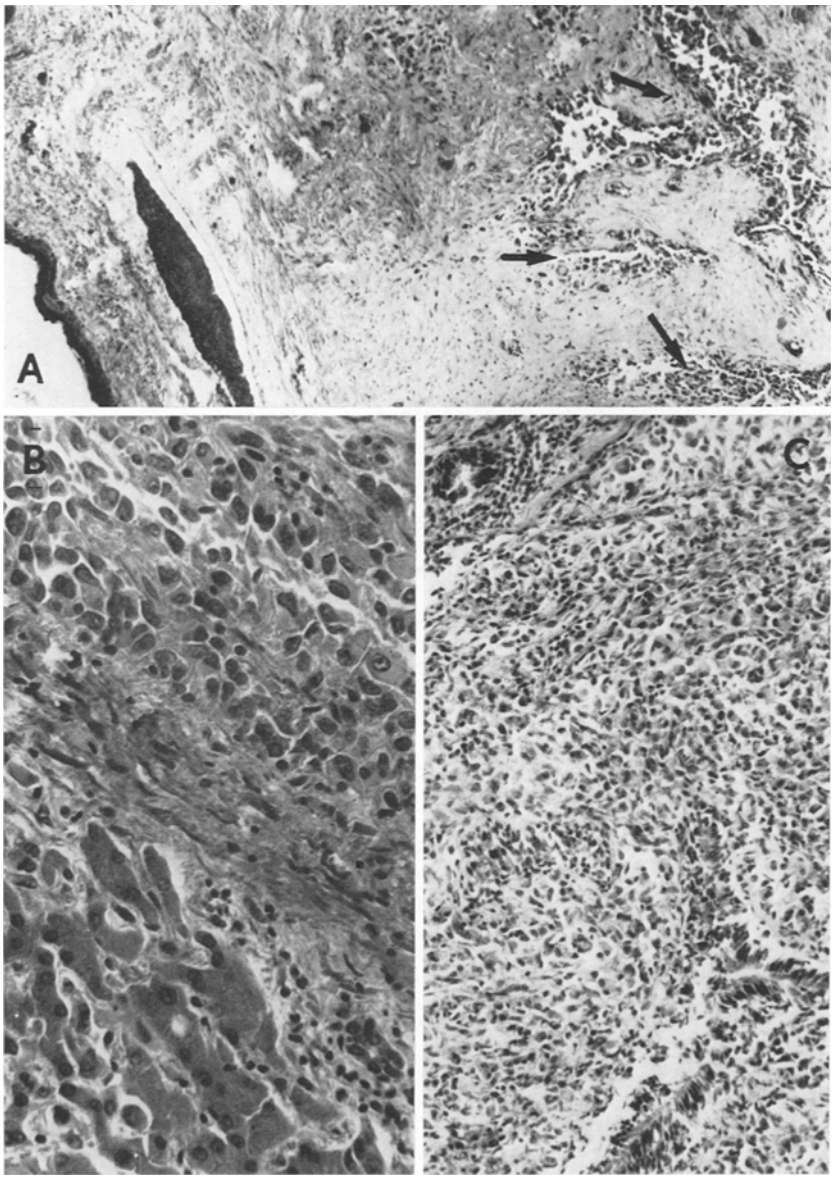

Fig. 3. Case 5; anaplastic astrocytoma. A) Gross invasion of subcutaneous areas of galea by astrocytomatous tissue (arrows). H. & E. ×35. B) Metastatic nodule of anaplastic astrocytoma in the liver. H. & E. ×300, C) Anaplastic astrocytomatous tissue in the lung. H. & E. ×100

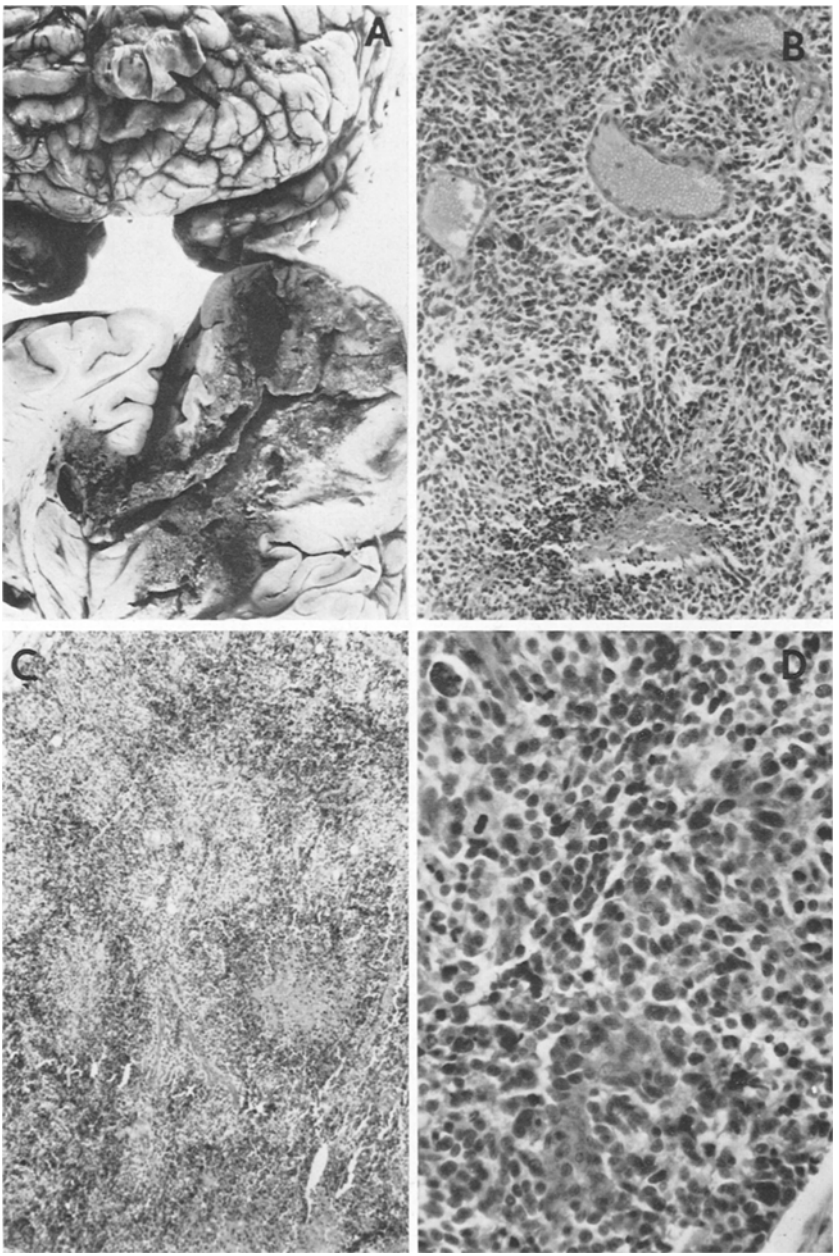

Fig. 4. Case 6; glioblastoma multiforme. A) Large necrotic tumour involving ventricular walls with metastatic deposit in left frontal pole. B) Biopsy specimen of brain tumour removed at second craniotomy, showing anaplastic glioma with occasional giant cells and pseudopallisading round necroses. H. & E. ×100. C) Biopsy specimen of cervical lymph node. Its structure almost completely replaced by necrotic gliomatous tissue. H. & E. ×90. D) High power of lymph node metastasis shows anaplastic gliomatous tissue. H. & E. ×90

Radiotherapy was given to the cervical region. Afterwards, the patient received combined chemotherapy (Israel *et al.* 1967), but his condition deteriorated, and he died five months after excision of the lymph node metastasis. At autopsy, a large necrotic glioblastoma in the left cerebral hemisphere was found. It invaded the corpus callosum, basal ganglia and the ventricular walls. There was neoplastic spread to the left frontal pole (Fig. 4 A), the cerebellum, and the leptomeninges of the posterior fossa. Histologically, the region of the excised cervical lymph nodes showed postradiation scars, but there was no evidence of extraneural gliomatous deposits.

Case 7: Sch. O., a 55 year old male, underwent craniotomy 18 months prior to death. A large left frontal tumour was completely removed by lobe resection. Histology showed an anaplastic astrocytoma (grade III). Postoperative radiation therapy (betatron, 6,000 rads) was given. The patient felt well for one year. Fourteen months after craniotomy, swelling of the cervical lymph nodes and left exophthalmos were observed. X-rays showed neoplastic invasion and destruction of the base of the skull (left anterior and middle fossa), of the left orbit, and of the ethmoids. Excision biopsy of a right cervical lymph node showed its invasion by gliomatous tissue. Radiation therapy (betatron, rapid electrons) given to the neck resulted in rapid disappearance of the lymph node swellings. Additional chemotherapy was administered, but the patient's condition deteriorated, and he died two months later. Autopsy showed a large fusicellular glioblastoma in both frontal lobes grossly invading the basal dura (Fig. 5 A), the base of the skull, and the paranasal sinuses (Fig. 5 B). There was neoplastic spread to the posterior fossa meninges, and bilateral deposits in the cervical lymph nodes histologically showing the same type of tumour (Fig. 5 C) were found.

Discussion

This series of seven cases of extracranial metastases of anaplastic gliomas includes four males and three females ranging in age from 7 to 58 years at the age of death. There were two children with anaplastic ependymomas of the cerebral hemispheres, one adult with oligodendroglioma, and four young to middle-aged adults with anaplastic astrocytomas and or glioblastomas (Table 1). All patients had one ore more craniotomies prior to the appearance of distant tumour deposits. Radiation therapy was administered to the primary tumour area in four, and additional chemotherapy was given in two. Four patients did not receive irradiation or chemotherapy. The survival periods from the time of the initial surgical procedure until death varied from 7 to 31 months in cases with gliomas of grade II, and from 8 to 18 months in anaplastic gliomas grade III and IV. All the gliomas showed invasion of the meninges, and in four cases the neoplasm transgressed the dura and invaded the surrounding skull, skin, or paranasal sinuses. In six autopsy cases there was widespread dissemination of gliomatous tissue through the CSF pathways. Distant metastases involved regional or distant lymph nodes in six cases, the lung in two cases, and the vertebrae, liver, pleura and mediastinum in one patient each.

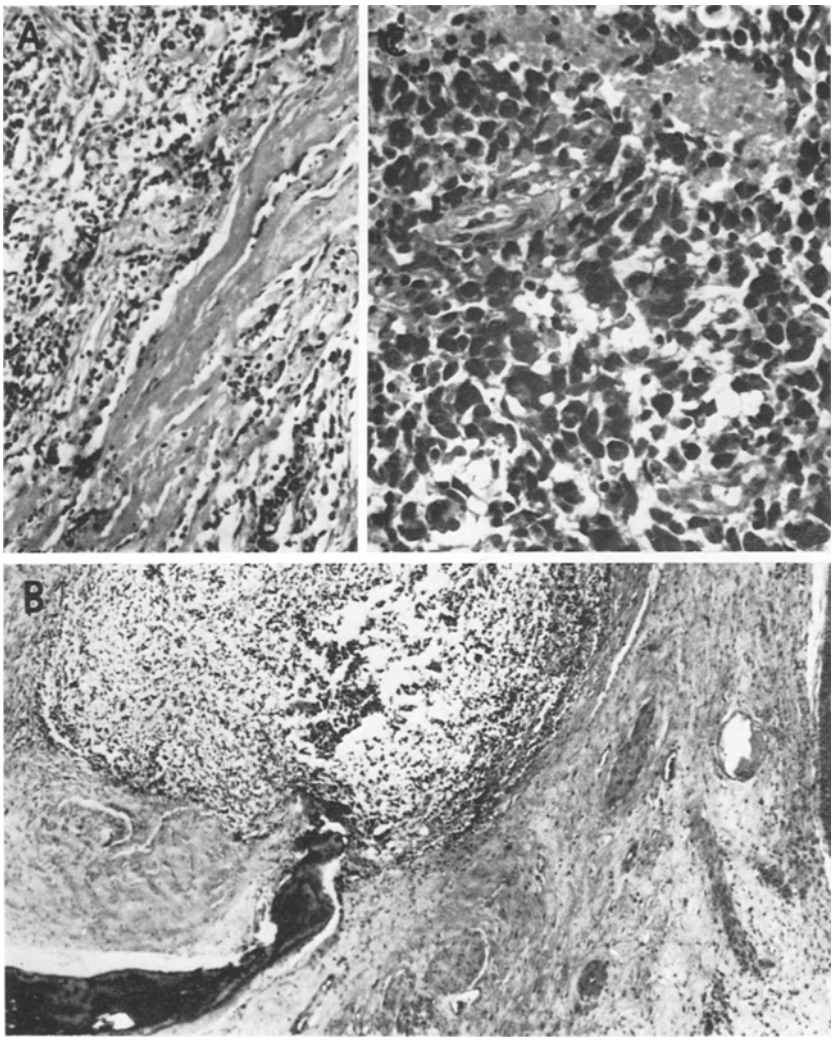

Fig. 5. Case 7; astrocytic glioblastoma. A) Gliomatous permeation of frontobasal dura. H. & E. ×90. B) Gliomatous tissue invading paranasal sinus. H. & E. ×55. C) Metastatic glioma in cervical lymph node. H. & E. ×300

It appears that the formation of metastases, both intracranial and extracranial, principally depends on the natural tendency of the tumour cells to detach and implant themselves elsewhere, and also on the opportunity to do so. It is believed that the prerequisites for the spreading of gliomas beyond cranial confines are cranial surgery,

frequent invasion of the meninges or ventricular surfaces, radiation therapy, and prolonged survival (*cf.* Kretschmer 1974). These factors, however, are not valid in cases of spontaneous extracranial spread of gliomas in the absence of previous craniotomy, where direct neoplastic invasion of the cerebral veins or dural sinuses have been demonstrated (Rubinstein 1967, Anzil 1970).

Four main theories have been advanced to explain distant spread of intracranial tumours (Zeitelhofer and Kraus 1952, El-Gindi *et al.* 1973). These are local implantation of tumour cells during surgical intervention and spread through the lymphatic channels, the blood vessels, or the artificial tubes used to divert the CSF. It has been demonstrated that gliomas implanted to other sites in the body will continue to grow (Zimmerman 1957, Smith *et al.* 1969). The occurrence of gliomatous metastases in lymph nodes draining the operative field on the same side as the craniotomy is in favor of lymphatic spread (El-Gindi *et al.* 1973). Haematogenous spread causing tumour deposits in the skeleton, lungs, liver and other visceral organs may be due to vascular invasion by glioma cells (Kung *et al.* 1969, Anzil 1970) and release of tumour cells into the systemic circulation during or after operative intervention (Morley 1959). Metastatic spread of gliomas after shunting procedures is well established (Wolf *et al.* 1954, Brust *et al.* 1968, Wakamatsu *et al.* 1971, Eade and Urich 1971).

Even so, the rarity of remote metastases of gliomas is still not clearly understood. The following factors have been regarded as essential (Willis 1973, Kretschmer 1974): 1. the still unresolved problem of intracranial lymphatics and their equivalents (*cf.* Földi 1972); 2. the specific structure of cerebral venous channels with early occlusion by tumour compression (Willis 1973); 3. the short average postoperative survival period of the patients which hardly permits widespread dissemination of malignant gliomas; 4. immunological reactions and host immunity to gliomas which may prevent continuing growth of implanted glioma cells (Ridley 1975).

Prior neurosurgical interventions and prolonged postoperative survival seem to be the most important factors associated with the development of extracranial metastases of brain tumours (Smith *et al.* 1969, Kretschmer 1974). The appearance of distant metastatic spread of gliomas, however, is not necessarily connected with widespread dissemination, previous craniotomy, or radiotherapy, or long survival period (Anzil 1970, Dolman 1974). In spite of recent progress in cancer immunology, including immunological reactions to gliomas (Ridley 1975) and immunological factors in metastases formation (Fisher and Fisher 1975), the role of these particular factors needs further elucidation.

Table 1. *Extracranial Metastases of Anaplastic Gliomas*

Case	No biopsy/ autopsy	Age [1] Sex	Type of tumour	Location	Operations	X-ray, Chemotherapy	Total course [2]	Metastases
1	N 46-65 + 249-67	58 F	oligodendroglioma II	L. frontoparietal	1	no	29 months	3rd and 5th lumbar vertebral bodies
2	N 93-65 N 336-65	13 F	ependymoma II	L. frontoparietal	1	no	7 months	L. preauricular lymph node (2nd craniotomy)
3	N 262-71 N 141-73 + 388-74	7 M	ependymoma II	R. parietal R. hemisphere → dura	2	X-ray	31 months	L. frontal; R. cerebellum; R. cervical lymph nodes
4	N 285-74 N 69-75 + 241-75	42 F	anaplastic astrocytoma (grade III)	L. temporooccipital → dura post. fossa	2	no	8 months	L. cervical lymph nodes; pleura; mediastinum-superficial lung
5	N 446-74 N 59-75 N 164-75 + 351-75	46 M	monstrocellular astrocytoma	R. temporoparietal → dura → bone → skin	3	X-ray	8 months	liver; lungs
6	N 102-71 N 257-72 N 116-72 + 380-72	20 M	heteromorphic glioma → glioblastoma multiforme	L. parietal → L. hemisphere → meninges → ventricles	2	X-ray + Polychemotherapy	17 months	L. frontal pole; brain stem; meninges; L. cervical lymph nodes
7	N 345-71 N 454-72 + 215-73	55 M	astrocytoma grade III → glioblastoma	Bilat. frontobasal → dura → bone → paranasal sinuses	1	X-ray + Chemotherapy	18 months	brain stem meninges; Bilat. cervical lymph nodes

[1] At death or histological confirmation of metastasis.
[2] After first craniotomy.

References

Anzil, A. P., Glioblastoma multiforme with extracranial metastases in the absence of previous craniotomy. Case report. J. Neurosurg. *33* (1970), 88—94.

Bogdanovich, N. K., K voprosu o metastaziruyushchikh opukholyakh golovnagu mozgu. Arkh. Path. (Moskau) *20* (1958), 83—86.

Brander, W. L., Turner, D. R., Extracranial metastases from a glioma in the absence of surgical intervention. J. Neurol. Psychiat. Neurosurg. *38* (1975), 1133—1135.

Brust, J. C. M., Moiel, R. H., Rosenberg, R. N., Glial tumor metastases through a ventriculo-pleural shunt. Arch. Neurol. (Chic.) *18* (1968), 649—653.

Cappelaere, P., Cla, A., Adenis, L., Demaille, A., Laine, E., Les métastases des tumeurs cérébrales primitives en dehors du névraxe. Bull. Cancer *59* (1972), 235—254.

Dolman, C. L., Lymph node metastasis as first manifestation of glioblastoma. J. Neurosurg. *41* (1974), 607—609.

Eade, O. E., Urich, H., Metastasizing gliomas in young subjects. J. Path. (Edinbg.) *103* (1971), 245—256.

El-Gindi, S., Salama, M., El-Henawy, M., Farag, S., Metastases of glioblastoma multiforme to cervical lymph nodes. J. Neurosurg. *38* (1973), 631—634.

Fisher, E. R., Fisher, B., Immunologic factors in experimental metastases formation. Int. J. Radiol. Oncol. *1* (1975), 87—92.

Földi, M., Physiologie und Pathophysiologie des Lymphgefäßsystems. In: Altmann, H.-W., *et al.* (eds.): Handbuch der allgemeinen Pathologie, Vol. III, Part 6, pp. 239—310. Berlin-Heidelberg-New York: Springer. 1972.

Gropp, A., Über ein metastasierendes „Gliom". Z. Krebsforsch. *60* (1955), 590—596.

Højgaard, K., Johansen, A., A case of ependymoma with remote metastasis. Acta path. microbiol. scand. Suppl. *212* (1970), 198—200.

Jellinger, K., Minauf, M., Salzer-Kuntschik, M., Oligodendroglioma with extraneural metastases. J. Neurol. Psychiat. Neurosurg. *32* (1969), 249—253.

Komatsu, K., Inaba, Y., Hiratsuka, H., Extensive extra-cranial metastases of glioblastoma multiforme. Brain Nerve (Tokyo) *14* (1972), 339—351.

Koos, W. T., Miller, M., Intracranial tumors of infants and children. Stuttgart: G. Thieme. 1971.

Kretschmer, H., Die extrakranielle Metastasierung intrakranieller Geschwülste. Zbl. Neurochir. *35* (1974), 81—112.

Kung, P. C., Lee, J. C., Bakay, L., Vascular invasion by glioma cells. An electron microscopic study. J. Neurosurg. *31* (1969), 339—345.

Minauf, M., Jellinger, K., Meningeales Wachstum von Oligodendrogliomen. Acta Neurochir. (Wien) *19* (1968), 269—280.

Morley, T. P., The recovery of tumour cells from venous blood draining cerebral gliomas. A preliminary report. Can. J. Surg. *2* (1959), 363—365.

Mracek, Z., Janda, J., Glioblastoma multiforme s extrakranialnimi metastazami. Cs. Neurol. Neurochir. *38* (1975), 19—24.

Pe, K. M., Oligodendroglioma with extracranial metastases. Zhong Waike Z. *11* (1962), 635—637.

Ridley, A., Immunological reactions to gliomas. In: D. Williams, ed., Modern trends in Neurology, Vol. 6, p. 249—266. London: Butterworths. 1975.

Rubinstein, L. J., Extracranial metastases from a malignant astrocytoma in the absence of previous craniotomy. J. Neurosurg. *26* (1967), 542—547.

— Tumors of the central nervous system. Atlas of Tumor Pathology, 3rd edit., Fasc. 6. Washington, D.C.: Armed Forces Institute of Pathology. 1972.

Smith, D. R., Hardman, J. M., Earle, K. M., Metastasizing neuroectodermal tumors of the central nervous system. J. Neurosurg. *31* (1969), 50—58.

Wakamatsu, T., Extracranial metastasis of intracranial tumor. Acta path. jap. *22* (1974), 155—169.

— Matsuo, T., Kawano, S., Teratomo, S., Watsumara, H., Glioblastoma with extracranial metastasis through ventriculopleural shunt. J. Neurosurg. *34* (1971), 697—701.

Weiss, L., A metastasizing ependymoma of the cauda equina. Cancer *8* (1955), 161—171.

Willis, R. A., The spread of tumors in the human body. 3rd ed. London: Butterworths. 1973.

Wolf, A., Cowen, D., Stewart, W. B., Glioblastoma with extracranial metastasis by way of a ventriculopleural anastomosis. Trans. Amer. Neurol. Ass. *79* (1954), 140—142.

Zeitelhofer, J., Kraus, H., Über die extrakranielle Metastasierung der Gliome. Zbl. Neurochir. *12* (1952), 347—358.

Zimmerman, H. M., An explanation of certain glioma problems. J. Mt. Sinai Hosp. *24* (1957), 1357—1362.

Authors' address: Prof. Dr. K. Jellinger, Head, Division of Special Neuropathology, Neurologisches Institut der Universität, Schwarzspanierstraße 17, A-1090 Wien, Austria.