Acta Med. Nagasaki 33 : 134−141

An Autopsy Case of Oligodendroglioma with Extracranial Metastases — A Statistical Review of Reported Cases —

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Received for publication, June 13, 1988

ABSTRACT : An autopsy case of oligodendroglioma with extracranial metastases through blood vessels and cerebro-spinal fluid in a 44-year-old female is reported. Post-mortem examination revealed that the tumor involved the left frontal region, optic chiasma, cauda equina, spinal cord, subarachinoid space and bone (sternum, spine, ribs). Microscopic appearances showed the features of rapid anaplastic transformation. Glial fibrillary acidic protein (GFAP)-positive neoplastic oligodendrocytes were found in some areas of the honey-comb structure with prominant vascular stromata in recurrent and metastatic lesions. The histogenesis of this tumor may be interpreted as the constant or temporary production of GFAP by neoplastic oligodendrocytes as a sign of reversion to the fetal oligodendroglia without necessarily implying astrocytic hitogenesis. The present case is the second case of oligodendroglioma with extracranial metastases reported in Japan.

INTRODUCTION

Extracranial metastases of primary brain tumors had until 1983 been reported for approximately two hundred cases in Japan[1]. However, extracranial metastases of oligodendroglioma is very rare. In Japan, NAKAMURA *et al.* reported only one case of diffuse bone marrow metastasis by anaplastic oligodendroglioma in 1985[2]. In connection with this rare event, it has been pointed out that, in general, common factors in cases of remote metastases from cerebral tumor were; (1) multiple operations, (2) radiation, and (3) prolonged survival[3]. Nevertheless, the mechanism involved in the appearance of distant metastases of a primary tumor of CNS has not been completely clear. We believe that a fundamental understanding of the oncogenesis of glial cells is essential in order to study the mechanism of extracranial metastases. This paper demonstrates convincingly by its histological and immunohistochemical documentation the extracranial metastases of an oligodendroglioma and reviews the relatively small number of previously documented similar cases.

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CASE REPORT

This 44-year-old woman had suffered from convulsion attacks since 1972. She had been given phenobarbital and diazepam, but symptoms of headache, nausea and vomiting occurred in May 1982. A calcified mass lesion of the right frontal area was revealed by CT scan (Fig. 1) and she was admitted to Nagasaki University Hospital for the first time in 1982 for removal of the tumor. In June, 1982, bifrontal osteoplastic craniotomy and partial removal of the tumor was performed. The surgical pathologic diagnosis was that of mixed oligodendroglioma and astrocytoma (Fig. 2). Subsequently, irradiation of 4200 rad was given to the frontal region and ACNU was administered. In August, 1982, gait disturbance occurred. Because a low density area was detected in the left frontal lobe by CT scan, she was admitted a second time to the same hospital. Radiation necrosis had been suspected and she had improved while on treatment with steroids. In December, 1984, she was admitted a third time because of speech and eye movement disturbance. Pancytopenia and fresh hemorrhagic area in the left frontal lobe was revealed by blood examination and CT scan. Moreover, it was especially noteworthy that the serum level for LDH was high. The value was 2423 IU/L in December, 1984. Aspiration biopsy of sternal bone marrow was carried out. The pathological report was malignant bone tumor with unknown origin. She had been put on steroids and her general condition had appeared fair, but in February, 1985, her condition rapidly deteriorated with occurrence of left hemipalsy and consciousness disturbance. On 13 March, she went into a shock condition and on the following day she died. Thirteen years had passed since her symptoms had begun. An autopsy was performed.

SURGICAL FINDINGS

Bifrontal osteoplastic craniotomy was performed. At first, the right side was observed. When the dura was opened, a tumor extending from the right superior frontal gyrus to the middle frontal gyrus was discovered. The tumor present at the surface measured approximately 2.5×1.5 cm in diameter. The boundaries of the tumor and the surrounding edematous brain tissue were ill-defined. When the left side was observed, another yellowish-brown tumor that was in contact with the interhemispheric fissure was found at a 3.0 cm depth from the surface of the cortex. The lesions were partially removed by means of suction. In the microscopical features of the lesions (Fig. 2), the tumor was cellular and composed of two sorts of cells. One element had compact collections of uniform cells with regular central nuclei and clear cytoplasmic halos. Alcian blue stain showed positiveness in the interstitium. In another element, there were large cells with abundant eosinophilic or vague cytoplasm. The latter cells were similar to those of fibrillary astrocytoma. The position of nuclei were eccentric or centric. Mitotic figures and pleomorphism were rarely seen in any area. GFAP stain was negative in the cytoplasm of typical oligodendroglioma cells with clear perinuclear halos, while it was diffusely positive in the cytoplasm of large cells with eosinophilic abundant cytoplasms and eccentric or centric neuclei. There were separate GFAP-negative cell and GFAP-positive cell populations. In addition, foci of calcification were seen throughout the tumor. Therefore, the tumor was diagnosed as mixed oligodendroglioma and astrocytoma.

AUTOPSY FINDINGS

Gross findings : The patient was 154 cm in height and 48 kg in weight. She appeared well-developed and well-nourished. The brain weighed 1150 gm, and there was a large cystic area with yellow fluid remaining in the right frontal lobe. Its internal wall was yellowish-brown in color. A hemorrhagic area was also present in the parenchyma of the brain adjacent to the cystic lesion and in contact with the lateral ventricle (Fig. 3). There also were multiple, ill-defined, grayish-brown small nodules with hemorrhages in the left frontal region, optic chiasma, cauda equina, spinal cord, and bone marrow of the spine (Fig. 4), sternum and ribs. The duodenum was acutely perforated and

fibrinous exudates covered the peritonium. In addition, bile stasis of the liver, severe pulmonary congestion and edema, and hemorrhagic diathesis were encountered.

Microscopical findings : There was a conspicuous proliferation of tumor cells around the hemorrhagic lesion in the right frontal lobe. The tumor cells had ill-defined cytoplasm with pleomorphic nuclei. In the lesion of the optic chiasma, tumor cells showed typical sphenoidal neuclei and clear perinuclear cytoplasmic halos suggesting oligodendroglioma (Fig. 5). A high density of cells forming perivascular pseudorosettes was found in parts. Each cell was oval or round in shape and the nuclei showed slight pleomorphism and hyperchromatism but the nucleoli were vague. In the lesion of the lumbar bone marrow (Fig. 6), the tumor cell density was higher. The rim of the cytoplasm was vague and gliofibrillary, and the N/C ratio was high. The nuclei were round or oval in shape and showed anaplasia and hyperchromatism. There were no perinuclear halos and they tended to be anaplastic. The lesions of the spinal cord (Fig. 7), cauda equina, sternum, and ribs were nearly the same.

GFAP stain was partially positive in the tumor of the lumbar bone marrow (Fig. 8) ; that is to say, GFAP-positive and GFAP-negative tumor cells were intermingled and random in the histologic section. GFAP positiveness was seen in the perinuclear narrow cytoplasmic rim. These findings were different from those at the operation. We thought that the tumor had transformed into an anaplastic one and metastazied to the bones. Also, in the stain of s-100 α and s-100 β protein (indirect method), scattered positive cells in both sections were found. These features suggested extracranial metastases of the oligodendroglial tumor. The cause of death was fibrinous peritonitis with perforated duodenal ulcer. Table 1 shows the result of immunohistochemical examination using GFAP, S-100 α, S-100 β, MBP and Leu-7. Table 2 summarizes the final pathological diagnosis.

DISCUSSION

Generally, extracranial metastases of a brain tumor are rare, but in recent years are increasing. According to the report of BRAIN TUMOR REGISTRY IN JAPAN, the incidence of metastases in the spinal cord was 2.2% and that outside CNS was 0.6%[4]. SMITH *et al.* reported that in over 8000 tumors of neuroectodermal origin from the AFIP file, only 35 cases developed metastases outside the neuraxis(0.44 %) [5]. Of these, only one was oligodendroglioma with extracranial metastases. Including the present case, a total of 18 cases is listed in table 3.

The age of patients ranged from 7 weeks to 58 years, with an average of 31.7 years. Twelve of the 18 cases (67%) occurred in patients between 20 and 50 years of age : six of the 18 were men and 11 were women. In one instance (case 6) , the sex of the patient was not recorded. In 17 cases, the location of the primary tumor was supratentorial and in one case it was in the spinal cord. The distribution of the metastases was as follows : 12 (67%) in bone, six (33%) in lymph nodes, four (22%) in the lungs and pleura, two each in skeletal muscle and the liver, and one each in the peritonium, adrenal gland, and parotid gland. Bone metastases occurred in vertebrae (11 cases), iliac bone and ribs (three cases each), sternum (two cases) and femur (one case).

Fifteen of 18 patients underwent craniotomy and resection of their tumor. Radiation was performed on nine of 18 patients. Seven patients received radiotherapy in addition to surgical treatment. The survival time from onset to death among 17 of the patients ranged from eight months to 13 years, with an average of 4.5 years. The survival time in case 2 was unknown. In comparison with the average survival time (8.5 years) of oligodendroglioma without metastases reported by Roberts[6], shortening of survival time (4.3 years) occurred in cases of extracranial metastases.

Why did this rare, remote metastases in our case occur? Generally, it has been said that the two main factors to which extracranial metastases of glioma is most commonly attributed are surgical treatment or radiotherapy. The concrete hypothesis has been proposed that the negative pressure in the lumen of the cerebral veins and permeation of the meningeal venous

system induced by craniotomy could cause suction of tumoral cells[7)8)]. Also, the effect of irradiation is not negligible[9)]. Although we do not clearly know its effect on glioma, it remains a matter for conjecture what part the radiotherapy played in the differentiation and metastasis of glioma. The present case involved both treatments, but we cannot document the mechanism involved in the appearance of the distant metastases of the recurrent glioma.

In addition, metastatic lesions displayed an alveolar pattern or epithelial-like structure[10)] and showed morphologically rapid anaplastic transformation in comparison with the tumor at the operation : high density of cells, pseudorosette formation , and hyperchromatic and pleomorphic nuclei were noted. This may be one factor of metastases in our case. Schmitt in 1983 stated that rapid anaplastic transformation of glioma in adulthood occurred spontaneously because of genetic instability or repeated action of carcinogens, such as irradiation[11)].

There have been many studies on the histogenesis of the oligodendroglial tumor. The presence of astrocytes in oligodendroglioma is well known ; they may be regarded as reactive elements or as neoplastic components of mixed oligo-astrocytoma. Because immuno-reaction to GFAP is mainly regarded as a sign of astroglial histogenesis and differentiation, we mainly used this protein and reviewed the result.

In our case, GFAP stain of lumbar marrow showed some tumor cells with a narrow GFAP-positive cytoplasmic rim. Our findings resembled those of Herpers[12)]. We can provide convincing documentation that these GFAP-positive cells are neoplastic elements. Three main interpretations of these GFAP-positive cells of oligodendrogliomas have been proposed. First, GFAP-positive cells in oligodendrogliomas may be a type of gemistocytic astrocyte in which glial fibrils may not be demonstrated by classical stains for glia (Dearmond *et al.* , 1980, Rubinstein, 1972.) [13)14)]. Second, they may represent an intermediate or transitional tumor cell between the oligodendroglial and astroglial tumor (Van der Meulen *et al.* , 1978) [15)]. The third interpretation suggests the possibility of a bipotential glial precursor cell (Roff *et al.* 1983) [16)]. In 1984. Herpers *et al.* investigated 50 oligodendroglioma and 16 mixed glioma using an anti-GFAP serum in the peroxidase-anti-peroxidase (PAP) method[12)]. The specimen from the removed material in our case consisted of two distant neoplastic cell populations ; that is, oligodendroglioma and astrocytoma. At autopsy, GFAP-positive oligodendrocytes were found in some areas of the classical honey-comb structure with a prominant vascular stroma. We would call the cells gliofibrillary oligodendrocytoma or transitional oligoastrocytoma as subtypes of oligodendroglioma, as Herpers described previously[(12)]. Also, we support the possibility of a bipotential glial precursor cell. GFAP-positive cells with morphological characteristics of oligodendroglia may be considered similar to transient GFAP expression by myelin-forming glia during normal development (Choi and Kim) [17)]. Therefore, our observations suggest a reversion to a fetal behaviour by some neoplastic oligodendrocytes.

In addition, we think that the relation between astroglial and oligodendroglial cells is closer than previously believed, and re-evaluation of the differentiation of glial cells should be performed on the basis of the reported investigations.

Table 1. Immunohistochemical Indirect Method

Antibody	Rt. frontal operation	Vertebrae autopsy
GFAP	+	+
S-100 α	+	+
S-100 β	±	+
MBP	−	−
Leu 7	−	−

List of antibodies and sera used in this study and their optimal dilution.

1) Primary antibodies.
   - # Rabbit anti-human GFAP, 1 : 400, DAKO
   - # Mouse monoclonal anti-bovine s-100 α, 1 : 800, JIMRO
   - # Mouse monoclonal anti-bovine s-100 β, 1 : 400, JIMRO
   - # Mouse monoclonal anti-bovine MBP, 1 : 800, Sero
   - # Mouse monoclonal anti-Leu 7, 1 : 40, BECTON

2) Secondary antibodies.

Swine anti-rabbit/HRP, DAKO, 1 : 40
Rabbit anti-mouse/HRP, DAKO, 1 : 40

3) Others (for reduction of non-specific background staining)
Normal swine serum, 1 : 20, DAKO
Normal rabbit serum, 1 : 20, DAKO

Table 2. Final Pathological Diagnoses

1. Brain tumor, mixed oligo-astrocytoma, rt. frontal lobe
   a) Postoperative state ; bifrontal osteoplastic craniotomy and partial removal of the tumor (June 16, 1982)
   b) Postirradiative state ; 4200 rad
2. Recurrence of mixed oligo-astrocytoma with appearance of anaplastic oligodendroglioma and massive necrosis and hemorrhage, rt. and lt. frontal lobe.
   a) Metastases and/or invasions.
      Cervical, thoracic and lumbar vertebrae, sternum, ribs, subarachinoid space, optic chiasma, cauda equina, spinal cord (C4-8, Th 6-7, Th 9-11)
3. Perforated acute ulcer, duodenum.
   a) Fibrinous peritonitis.
   b) Candidiasis, peritonium.
   c) Ascites, bloody, 1050 ml.
4. Acute pulmonary congestion and edema, lungs.
   a) Pleural effusions, lt. 240 ml, rt. 200 ml.
5. Chronic inactive hepatitis and fatty metamorphosis, liver.
6. Bile stasis, liver.
7. Decubital ulcer, sacro-coccygeal region.

Table 3. Clinical Features of Patients with Extracranial Metastases of Oligodendroglioma

Case	Age (yr)	Sex	Location of primary tumor	Metastases	Operation and/or Radiation	survival
1. James and Pagel[18] 1951	25	F	R parietal	Cervical lymph nodes, lungs, and hilar lymph	Two craniotomies, radiotherapy	84 mo
2. Strang and Nordenstam[19] 1961	30	M	R frontal	Cauda equina	One craniotomy and one laminectomy	unkonwn
3. Spataro and Sacks[20] 1968	7	F	L parietal	Lumbar vertebrae ribs, psoas muscle, liver.	Four craniotomies, radiotherapy	33 mo
4. Smith et al.[21] 1969	45	M	L frontal	L iliac bone.	One craniotomy	17 mo
5. Jellinger et al.[22] 1969	58	F	L frontal	Lumbar vertebrae	One craniotomy	42 mo
6. Kernohan, 1971	3.5	?	R parietal	Lungs, hilar lymph nodes, R adrenal	Four craniotomies.	21 mo
7. Eade and Urich[23] 1971	21	F	Spinal cord	Thoracic vertebrae, sternum	Thoracic laminectomy, biopsy, fossae decompression and radiotherapy.	8 mo
8. Eade and Urich[23] 1971	23	M	L thalamus	Vertebrae	Needle biopsy, radiotherapy, VA shunt.	12 mo
9. Reggiani et al.[24] 1971	43	F	L frontal	Spinal cord. from T3 to T5.	Two craniotomies.	Over 11 yr
10. Cappelaere et al. 1972	57	M	R frontal	R cervical lymph nodes, thoracic vertebrae.	One craniotomy, radiotherapy.	20 mo

11. Cappelaere et al. 1972	22		L temporal	Cervical and thoracic vertebrae, cervical lymph nodes, and parotid gland.	One craniotomy.	25 mo
12. Brander and Turner[9], 1975	30	F	L thalamus	R pleura.	Radiotherapy	13 yr
13. Schuster et al.[25] 1976	58	F	L fronto-parietal	3rd and 5th lumbar vertebrae	One craniotomy.	30 mo
14. Kummer et al.[26] 1977	40	M	R parietal	Lungs and paratracheal lymph nodes, thoracic vertebrae, R femur.	Two craniotomies, and radiotherapy	86 mo
15. Becker et al.[27] 1978	7-weeks	F	R frontal	Peritonium.	Ventriculoatrial and ventricuroabdominal shunt, one craniotomy	18 mo
16. Ordonez et al.[28] 1981	33	F	L frontal	L masseter muscle, L cervical lymph nodes, lumbar vertebrae, R iliac bone	Two craniotomies	50 mo
17. Nakamura et al.[2] 1984	32	F	L frontal	Vertebrae, ribs, iliac bone.	Two craniotomies, radiotherapy, local radiation by afterloading.	80 mo
18. Present case, 1987	44	F	R frontal	Cervical, thoracic, and lumbar vertebrae sternum, ribs, spinal cord (C4-8, Th 6-7, Th 9-11), cauda equina.	One craniotomy and radiotherapy	96 mo

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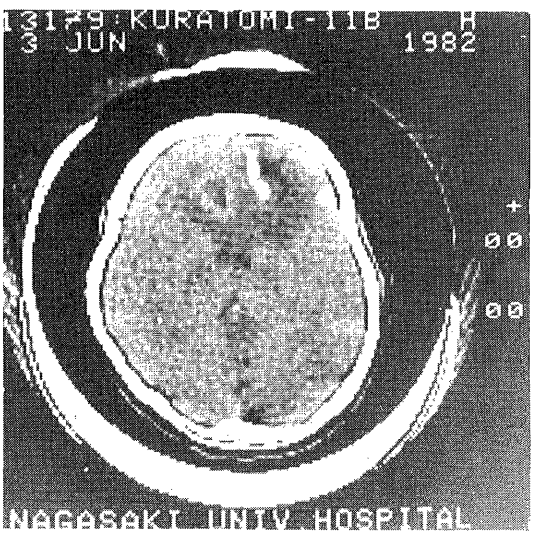

Fig. 1. A plain CT scan of brain shows irregular outline of low density area with calcification in right frontal lobe.

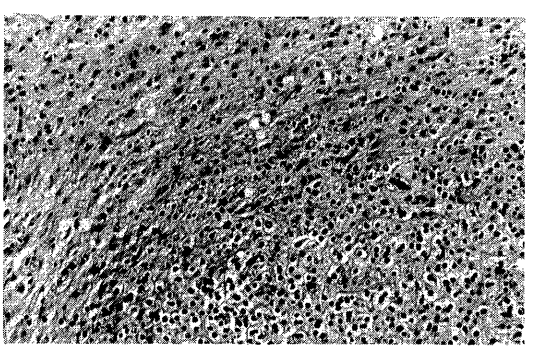

Fig. 2. This surgical specimen shows two sorts of cells with clear perinuclear cytoplasmic halos and eosinophilic cytoplasm. H.E. ×100

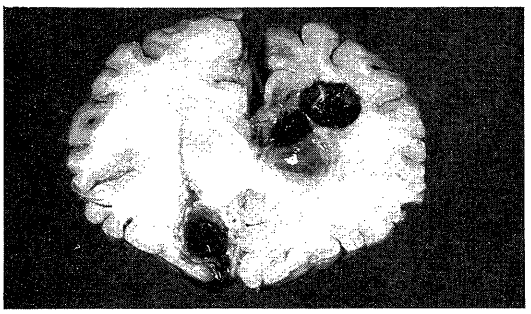

Fig. 3. There is a cystic space with a hemorrhagic lesion in the right frontal lobe. This lesion ruptures in the lateral ventricle.

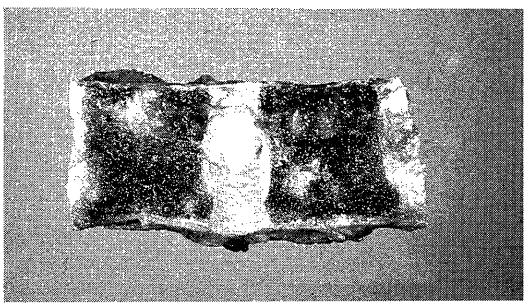

Fig. 4. Gross appearance of lumbar spine. It shows some gray nodules with irregular border.

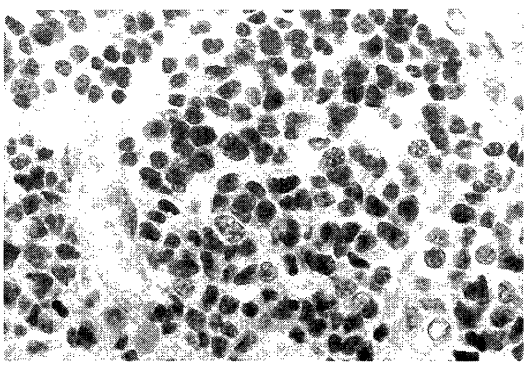

Fig. 5. Microscopic finding of optic chiasma shows rapid anaplastic transformation. H.E. ×400

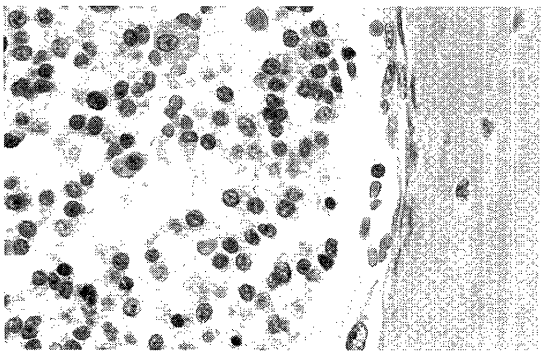

Fig. 6. This spine specimen shows solid cellular area with round hyperchromatic nuclei and cytoplasm. (lumbar spine) H.E. ×400

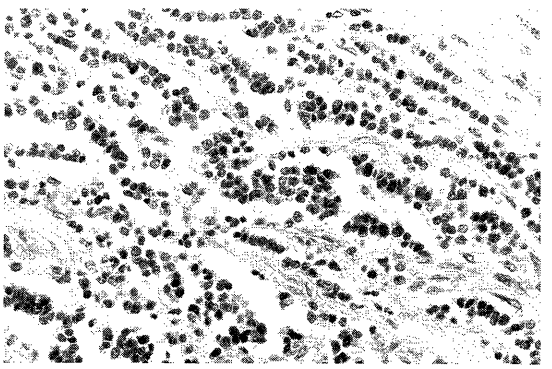

Fig. 7. Alveolar pattern in meninges of spinal cord. H.E. ×200

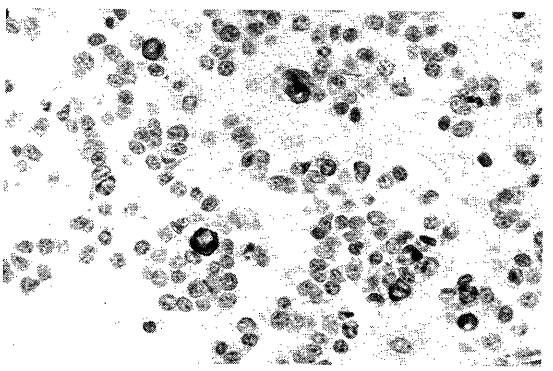

Fig. 8. GFAP stain showing positive findings. (lumbar spine) ×400