Secondary anaplastic oligodendroglioma after cranial irradiation: Case report

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Abstract

Secondary brain tumors rarely arise after cranial irradiation; among them, meningiomas and glioblastomas are the most common and secondary oligodendroglial tumors the most rare. We present a 48-year-old man who developed an oligodendroglial tumor 38 years after receiving 50 Gy of cranial irradiation to a pineal tumor. He underwent gross total removal of a calcified, ring-enhanced mass in the right temporal lobe. The tumor was histologically diagnosed as anaplastic oligodendroglioma. Our review of previously reported secondary oligodendroglial tumors that developed after cranial irradiation revealed that these rare tumors arose after low-dose cranial irradiation or at the margin of a field irradiated with a high dose. We suggest that secondary oligodendroglial tumors arising after cranial irradiation are more aggressive than primary oligodendrogliomas.

Background

The approximate cumulative risk for secondary brain tumors after cranial irradiation is 1 - 3% [1-4]. Radiation-induced secondary oligodendroglial tumors are very rare; to our knowledge, only 7 cases have been reported to date [5-11]. We encountered a patient who developed a secondary anaplastic oligodendroglial tumor after radiotherapy (RT), and discuss the development of secondary oligodendroglial tumors after cranial irradiation.

Case Report

This 48-year-old man was admitted to Hiroshima University Hospital in March 2005 with progressive vomiting, hiccups, and left-sided hemianopsia. In 1967, at the age of 10, he had undergone irradiation with Co-60 at Hiroshima University Hospital to treat a pineal tumor. The radiotherapeutic regimen delivered 2 Gy (200 rad) per day using alternate bilateral side ports every other day; the total dose was 50 Gy (5000 rad). The size of the irradiation field was 6 x 6 cm at the isocenter cross-section. The tumor had completely disappeared and no further events developed until 2005.

Magnetic resonance imaging (MRI) revealed a new mass lesion in the right temporal lobe (Fig. 1*A*). It was ring-enhanced by gadolinium; perifocal edema and a mid-line shift were noted. A computerized tomography (CT) image showed calcification inside the lesion (Fig. 1*B*). We performed craniotomy and removed the mass totally. Histologically, most of the tumor cells were round and uniform with prominent perinuclear halos and a high nuclear:cytoplasmic ratio; there were mitotic activity and microvascular proliferation (Fig. 2A,B). On microsatellite analysis

chromosomes 1p and 19q were intact. Immunohistological examination (Table 1) revealed positivity for S-100, olig-2, glial fibrillary acidic protein (GFAP) (Fig. 2C), phosphatase and tensin homolog (PTEN), and O^6-methylguanine DNA methyltransferase (MGMT) (Fig. 2D). Epidermal growth factor receptor (EGFR), p53, multidrug-resistance (MDR), neurofilament, synaptophysin, and bcl-2 were negative. Most of the tumor cells expressed MGMT. The MIB-1 labeling index was 22.1% (Fig. 2E).

Despite previous extended local irradiation (54 Gy) and chemotherapy based on an alkylating agent (ACNU), his tumor recurred 18 months later at the site of the originally treated tumor bed.

Discussion

Compared to normal cells, cancer cells are highly sensitive to ionizing radiation [12] and the development of radiotherapy (RT) has increased the life span of patients with malignant tumors. However, long-term survivors may experience the sequelae of RT, e.g. vascular occlusion, teleangiectatic dilation, stroke, a decrease in brain weight and size, and hormonal dysfunction after pituitary irradiation [13]. Secondary malignancies are critical post-irradiation complications [1-11,13-16]. Although irradiation destroys cancer cells, it can induce mutations in surrounding normal cells. In some instances the DNA repair mechanisms are incapable of repairing all of the cells with damaged DNA and some cells with damaged DNA may persist [17]. The pathogenesis of secondary post-RT tumors cannot be determined from their spontaneously occurring antecedents because the primary and secondary tumors are

radiographically, pathologically and clinically indistinguishable. Cahan et al. [15] presented diagnostic criteria for secondary sarcomas arising after irradiation. Although their criteria have been modified, fundamental determinants are: 1) tumors arising within a previously irradiated field or its immediate vicinity, 2) a latency period longer than 6 years, 3) absence of a genetic predisposition, and 4) a histological difference between the primary and secondary tumors. Our patient developed a rare secondary oligodendroglial tumor and fulfilled all of these criteria.

Gliomas, meningiomas, and sarcomas are the most frequently investigated secondary tumors that arise after cranial irradiation. Among secondary gliomas, glioblastomas and anaplastic astrocytomas have the highest incidence rate. In a review of 114 secondary gliomas arising after cranial irradiation only 4 were oligodendroglial tumors [14]. We reviewed our and 7 previously reported cases in detail (Table 2); 7 (including our case) were males and 5 had undergone whole cranial irradiation with 24 Gy or less to treat leukemia. The others received more than 50 Gy of cranial irradiation.

When RT is applied via two or more sources, the highest possible dose is delivered to the target lesion at the crossing of the sources. In patients treated with Co-60, tissues at the periphery of the target site are exposed to lower doses [12]. Our study of published images from 2 patients who had received more than 50 Gy [5,7] revealed that their secondary tumors arose from the margin of the irradiated field. At his first treatment, our patient had received alternating doses of Co-60 from both sides; the total delivered dose was 50 Gy. Therefore, based on our calculations, his secondary tumor developed in an area that had been exposed to approximately 20 Gy. This finding strengthens our hypothesis that secondary oligodendroglial tumors tend to develop after low-dose irradiation or in the immediate vicinity of a field exposed to high-dose

radiation treatment.

Clinically, oligodendroglial tumors are sensitive to RT [18] whereas astrocytic tumors are resistant. In rats, high-dose irradiation selectively induced apoptosis in oligodendroglial- but not astrocytic cells and led to optic neuropathy [19]. This suggests that astrocytic cells that survive high-dose irradiation can develop into high-grade astrocytoma over the long term and that oligodendroglial tumors may develop after the delivery of lower doses (<24 Gy) of irradiation.

It remains unknown whether the features of primary and secondary oligodendroglial tumors are identical. Histologic analysis showed that radiation-induced meningiomas tended to behave more aggressively [16]. The course of 4 previously reported secondary oligodendroglial tumors was aggressive and the prognosis of the 3 other patients was not described (Table 2). Studies of patients with oligodendroglial tumors indicated that a loss of chromosome 1p and 19q was indicative of high sensitivity to chemo- and radiotherapy and that these patients had a better probability of survival [20-22]. Reports of secondary oligodendroglial tumors after cranial irradiation did not address allelic loss. Chromosomes 1p and 19q were intact in our patient; this may explain why his secondary oligodendroglial tumor recurred within 18 months of adjuvant therapy. In addition, our immunohistological examination revealed increased MGMT expression, which reduces the toxicity of alkylating agents by rapidly reversing the formation of adducts at the O^6 position of guanine, thereby averting the formation of lethal cross-links. Thus, MGMT activity is a major mechanism of resistance to alkylating drugs [23,24].

The presence of intact chromosome 1p and 19q and the increased expression of MGMT in our patient suggest that his type of secondary oligodendroglial tumors was

more aggressive than the primary type. The level of MGMT expression should be investigated not only in secondary oligodendroglial tumors but also in secondary astrocytic tumors and glioblastomas.

Conclusion

We described a patient with a secondary oligodendroglial tumor that developed after cranial irradiation. We postulate that these tumors develop after low-dose cranial irradiation or at the margin of a radiation field exposed to high-dose treatment. As secondary oligodendroglial tumors tend to be highly aggressive, optimal treatment strategies must be developed.

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Figure Legends

Figure 1. MRI- and CT brain scans.

A. T1-weighted gadolinium-enhanced axial MRI shows a mass lesion in the right temporal lobe. The presence of perifocal edema produced a right-to-left midline shift.

B. Plain CT scan shows calcification inside the lesion.

Figure 2. Histological findings on the anaplastic oligodendroglioma.

A., B. Most of the tumor cells are round and uniform with prominent perinuclear halos and a high nuclear:cytoplasmic ratio. Note the mitotic activity and microvascular proliferation.

Immunostaining for ***C.*** GFAP ***D.*** MGMT **E.** MIB-1

Table 1: Materials and methods of immunostaining.

Antibody	Dilution	Manufacture	Method	Result
EGFR (M)	x40	Novo castra	LSAB	negative
p53 (M)	x150	Novo castra	LSAB	negative
MDR (M)	x200	Santa-cruz	LSAB	negative
Neurofilament (M)	Prediluted	Immunotech	ENVISION	negative
Synaptophysin (R)	x50	DAKO	ENVISION	negative
bcl-2 (M)	x50	DAKO	LSAB	negative
MIB-1 (M)	x150	DAKO	LSAB	22.1%
PTEN (M)	x150	Santa-cruz	LSAB	positive
MGMT (M)	x150	Santa-cruz	LSAB	positive
GFAP (M)	x150	DAKO	LSAB	positive
Olig-2 (R)	x100	IBL	LSAB	positive
S-100 (R)	x500	DAKO	ENVISION	positive

(M): mouse anti-human

(R): rabbit anti-human

EGFR: epidermal growth factor receptor

MDR: multidrug resistance

PTEN: phosphatase and tensin homolog

MGMT: O6-methylguanine DNA methyltransferase

LSAB: Labeled StreptAvidin-Biotin

Table 2: Secondary oligodendroglial tumors after cranial irradiation.

Author, year	Age at RT, yr	Sex	Primary Diagnosis	Chemo-therapy	Radiation Dose, Gy	Latency, yr	Secondary Diagnosis	Surgery	Post Operative Irradiation, Gy	Chemo-therapy	Prognosis
Zuccarello et al, 1986	32	M	Meningioma	No	56	10	Oligodendroglioma/ Glioblastoma	total	No	—	Died. Postoperative complication
Fontana et al, 1987	6	M	Leukemia	Yes	24	11	Glioblastoma/ Oligodendroglioma multifocal	biopsy	30.5	—	Died. 7 months after RT
Huang et al, 1987	26	M	Pituitary adenoma	No	66	12	Anaplastic oligodendroglioma	subtotal	No	—	No data
Palma et al, 1988	3	M	Leukemia	Yes	24	11	Oligoastrocytoma	subtotal	40	—	Died. 13 months after surgery
Corn.B et al, 1993	12	F	Leukemia	Yes	20	16	Malignant oligodendroglioma	subtotal	No	Lumustine/ procarbazine/ vincristine	Died. 16 months after surgery
Panigrahi et al, 2003	7	M	Leukemia	Yes	5.4	7	Anaplastic oligoastrocytoma	Tumor resected	No	Palliative	2 years with minimal neurodeficiency
Tanrioveret al, 2006	5	M	Leukemia	Yes	18	9	Anaplastic oligoastrocytoma	total	No	—	No data
Present Case, 2008	10	M	Pinealoma	No	50	38	Anaplastic oligoastrocytoma	total	54	ACNU/ Vincristine	Recurrence. 18 momths after surgery

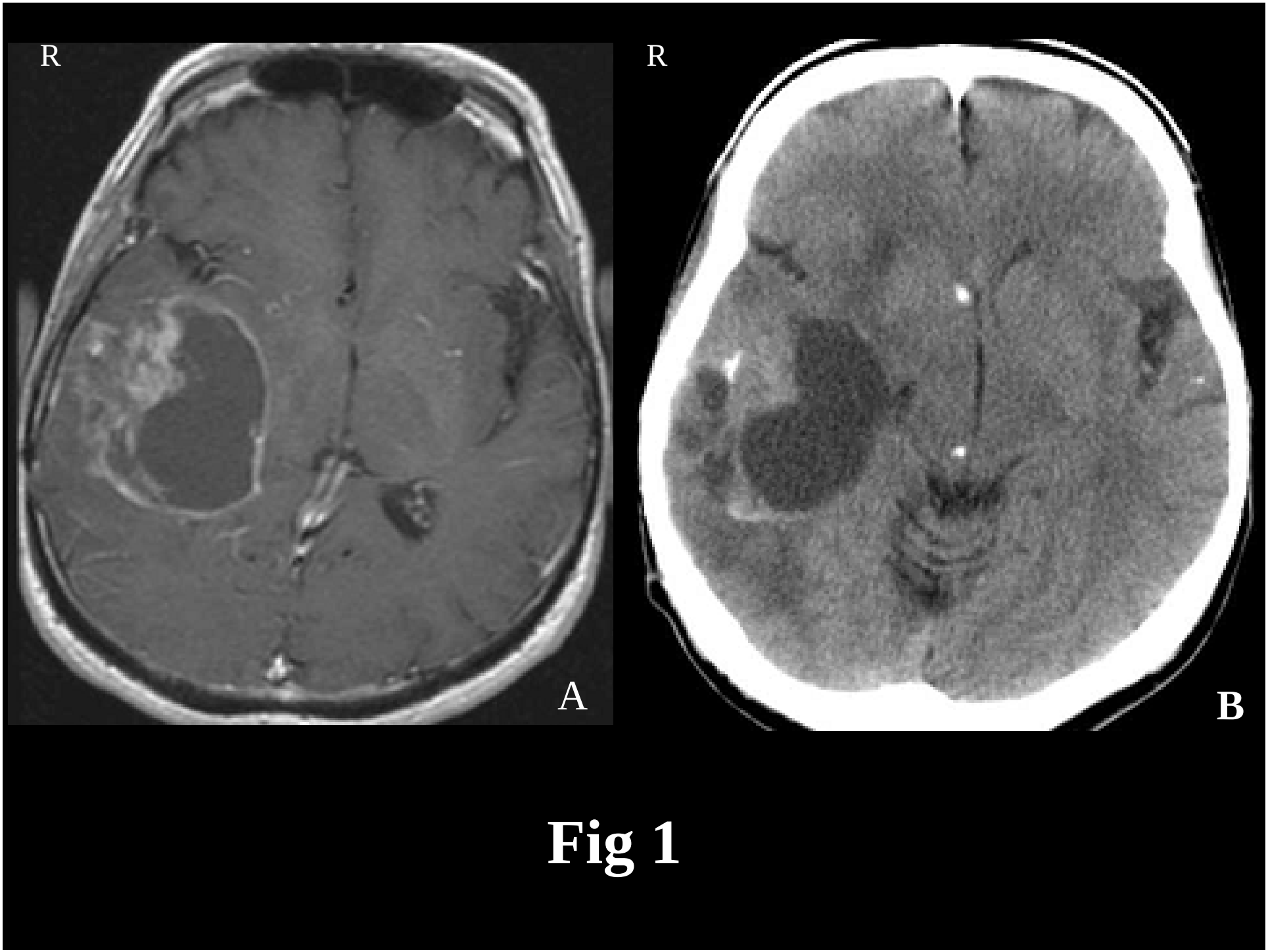

Fig 1

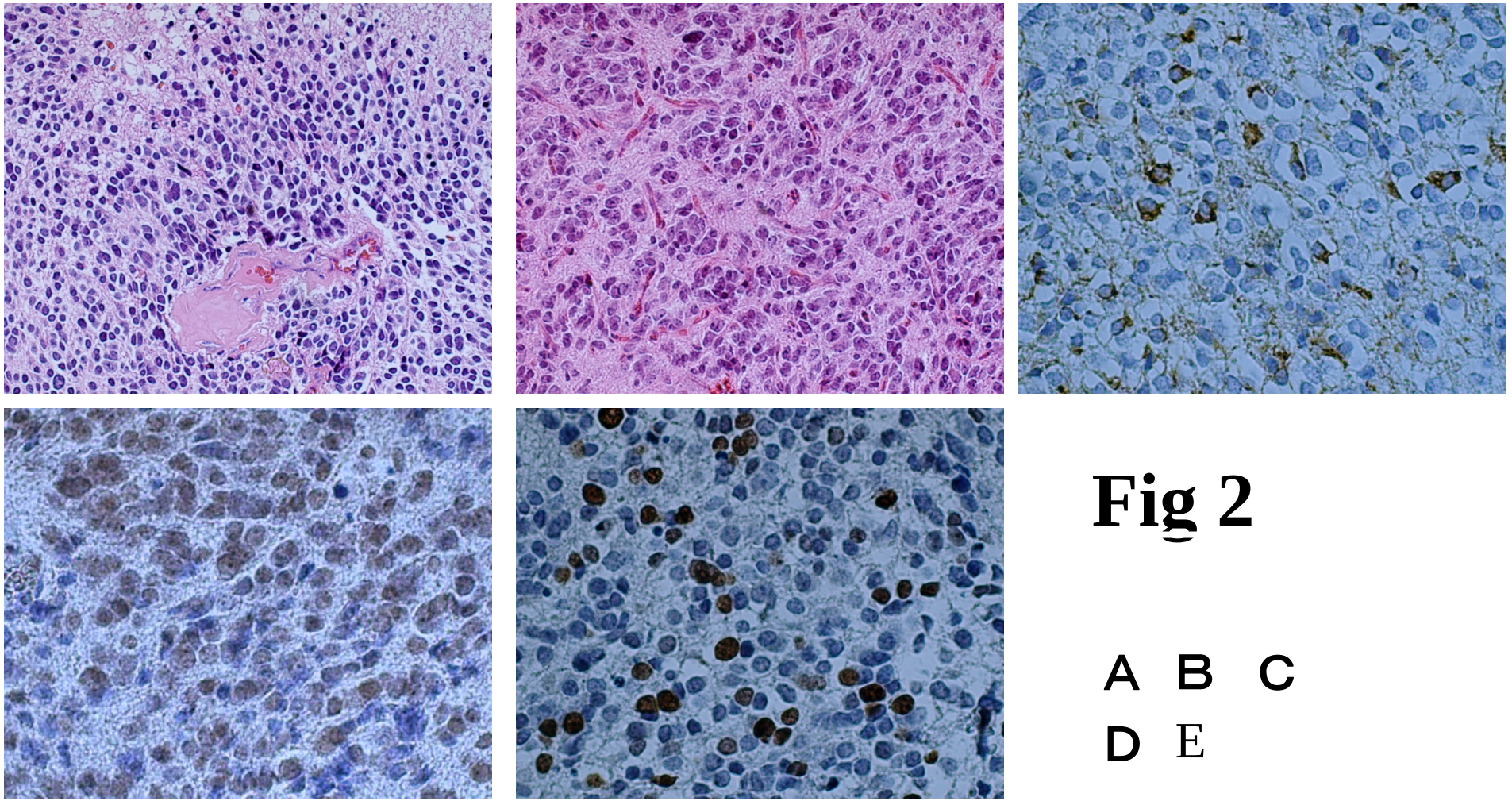

Fig 2

A B C

D E