Primary intracranial aggressive fibromatosis arising in sella turcica: illustrative case

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BACKGROUND Aggressive fibromatosis is a rare histologically benign but locally infiltrative myofibroblastic tumor. Primary intracranial aggressive fibromatosis (IAF) can exhibit a clinically malignant course.

OBSERVATIONS A 22-year-old otherwise healthy woman presented with left painful ophthalmoplegia. Magnetic resonance imaging (MRI) revealed a left sellar tumor with cavernous sinus invasion. Endoscopic transsphenoidal surgery was performed. The lesion could not be totally resected. An inflammatory myofibroblastic tumor was suspected, so steroid pulse therapy was introduced, but it was ineffective. The tumor recurred after a few months, and she complained of visual acuity loss, abducens nerve palsy, trigeminal neuralgia, and panhypopituitarism. The lesion was diagnosed as primary IAF by a pathological review. Gamma Knife radiosurgery was performed, and chemotherapies were introduced but ineffective. Her consciousness was disturbed, and MRI showed hypothalamic invasion of the tumor, occlusion and stenosis of carotid arteries, and cerebral stroke. Palliative care was introduced, and she died 32 months after the onset. The autopsy revealed tumor invasion to the cavernous sinus, optic nerve, hypothalamus, pituitary, and tonsillar herniation due to massive cerebral stroke.

LESSONS Radical resection can be impossible in patients with IAF. Radiotherapy and chemotherapy are not always effective for residual lesions. Adjuvant therapy for IAF remains to be explored.

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KEYWORDS intracranial aggressive fibromatosis; nonsteroidal anti-inflammatory drugs; radiosurgery; sella turcica; tamoxifen; transsphenoidal surgery

Aggressive fibromatosis is a rare myofibroblastic tumor also known as desmoid tumor, infantile/juvenile fibromatosis, desmoid fibromatosis, deep fibromatosis, grade 1 fibrosarcoma (desmoid type), desmoma, and desmoplastic fibroma of the bone.1,2 It is a histologically benign tumor with no metastatic potential but is locally infiltrative.3 Primary intracranial aggressive fibromatosis (IAF) is described as desmoid-type fibromatosis (International Classification of Diseases for Oncology code 8821/1) in the World Health Organization classification of central nervous system tumours.4 Most patients with aggressive fibromatosis have sporadic cases; they are predominantly female; and their cases are reported to be characterized by a mutation of the catenin β1 (CTNNB1) gene.5,6 The lesions tend to arise in the extraabdominal soft tissue, including the limbs, body trunk, and head and neck regions. Abdominal aggressive fibromatoses tend to be observed in patients with familial adenomatoid polyposis (FAP), which suggests that adenomatous polyposis coli pathway abnormalities can cause

ABBREVIATIONS CTNNB1 = catenin β1 gene; FAP = familial adenomatoid polyposis; IAF = primary intracranial aggressive fibromatosis; ICA = internal carotid artery; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drug; SMA = smooth muscle actin; TKI = tyrosine kinase inhibitor; T1WI = T1-weighted imaging; T2WI = T2-weighted imaging.

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nuclear accumulation of β-catenin and thereby lead to colon cancer and aggressive fibromatosis. IAF is stated to occur on the dura mater and is reported to originate from mesenchymal stem cells. Growth arrest and spontaneous improvement of this tumor have also been observed; however, the local recurrence rate accounts for 27% to 77% of cases, and aggressive therapy is indispensable for refractory cases. Radical curative resection of the tumor is reported to be the gold standard therapy, but this approach may be impossible in cases of IAF due to the proximity of eloquent neurovascular structures. The effectiveness of radiotherapy and chemotherapy have also been described, but IAF can exhibit a clinically malignant course.

In this report, the authors present an autopsy case of intractable IAF arising exclusively in the sella turcica and discuss its therapeutic strategy.

Illustrative Case

A 22-year-old otherwise healthy woman presented to our institute with left painful ophthalmoplegia. No specific family history was reported. Magnetic resonance imaging (MRI) revealed the presence of a left extraaxial sellar tumor (15 × 8 mm in size) with cavernous sinus invasion. The tumor was marked hypointense on T2-weighted imaging (T2WI) and slightly hypointense on T1-weighted imaging (T1WI) relative to the pituitary gland (Fig. 1A–D). At the first examination, no enhancement with gadolinium was noted on T1WI (Fig. 1E and F). No abnormal data were initially observed in endocrine examinations.

Two months after the referral to our department, endoscopic transsphenoidal surgery was performed. The lesion was elastic and hard and had a slightly clear margin between the pituitary and mass, but it was strongly adhered to the left cavernous sinus, hampering resection. As a result, bleeding from the left internal carotid artery (ICA) was encountered, and hemostasis was performed with hemostatic agents. The postoperative course was uneventful, but MRI revealed only partial resection of the tumor (Fig. 1G), and follow-up angiography revealed pseudoaneurysm at the left cavernous portion of the ICA. Coil embolization was additionally performed (data not shown).

At the first pathological examination, an inflammatory myofibroblastic tumor (allergic granulomatosis) was suspected, and steroid pulse therapy was introduced but was ineffective. After a few months, the patient complained of headache, impaired left visual acuity, painful ophthalmoplegia, trigeminal neuralgia, diabetes...
insipidus, and panhypopituitarism. MRI revealed the tumor recurrence, with the lesion now gradually enhanced with gadolinium on T1WI (Fig. 1H and I). Hormone replacement therapy was started. Kaufmann treatment had been introduced for hypophysial amenorrhea but was stopped due to tumor progression.

A pathological consultation and review were performed. A histopathological examination showed fibrous connective tissue with collagen fibers (Fig. 2A and B). Immunostaining revealed positive reactivity of vimentin and α-smooth muscle actin (SMA) (Fig. 2C and D). The patient’s Ki-67 index was 5%. No immunostaining was observed for β-catenin, estrogen, or progesterone. The tumor was diagnosed as IAF.

Gamma Knife radiosurgery (marginal dose 15 Gy, maximum dose 30.1 Gy) was performed, and chemotherapy with tamoxifen and sulindac was introduced 17 and 18 months, respectively, after the onset; however, the lesion progressed thereafter. Her visual acuity was lost, and her activities of daily living gradually decreased. Psychological palliative care was introduced.

She was admitted due to a syncope attack caused by ventricular tachycardia (torsades de pointes), but the definite cause was unclear. Transiently, tamoxifen was stopped, and an antiarrhythmic drug was introduced.

Thirty-one months after the onset, she was referred to our department due to consciousness disturbance. MRI revealed hypothalamic invasion of the tumor and perifocal edema, which were suspected of being the cause of her consciousness disturbance (Fig. 3A and B). Right ICA stenosis, left ICA occlusion, and stroke in cerebral hemispheres were observed on serial MRI.
Autopsy care was applied, and she died 32 months after the onset.

**Autopsy Report**

A grayish white hard tumor, 22 × 20 × 13 mm in size, was observed from the optic chiasm and sella turcica to the cavernous sinus (Fig. 4A–C). It involved the optic nerve and compressed the pituitary gland (Fig. 4B–D). Histopathologically, the tumor showed bundles of spindle cells with apparent collagenous fiber deposition (Fig. 4D). Immunostaining demonstrated positive reactivity of vimentin and partial positivity for αSMA. Immunostaining of S100 protein and CD34 was not observed. At the margin, the tumor had invaded the surrounding structures. Tumor cells were found to have infiltrated the pituitary gland and the submucosa of the sphenoid sinus. The optic nerves had been almost completely replaced by the tumor. The ICAs were compressed and suspected of having stenosis and/or occlusion (Fig. 4E). The final diagnosis was as follows: (1) aggressive intracranial fibromatosis in the sella turcica, optic nerve, pituitary gland, sphenoid bone, cavernous sinus, and sphenoidal sinus; (A) cavernous sinus syndrome; (B) panhypopituitarism; (C) diabetes insipidus; (D) occlusion or stenosis of left and right ICAs; (a) ischemic brain and multiple small infarctions, cerebrum and cerebellum; (E) cerebellar tonsillar herniation; (a) cerebral softening, midbrain and brainstem; (2) acute bronchopneumonia, left lower, right middle, and right lower lungs; (3) steroid-induced cortical atrophy of adrenal glands; and (4) steroid-induced hypocellular bone marrow.

**Discussion**

**Observations**

IAFs involving the sella turcica are extremely rare; the available cases are summarized in Table 1. The MRI features of IAF were first described by Flacke et al. Marked hypointensity on T2WI and slight hypointensity on T1WI were described in that report. Many authors have similarly reported well-enhanced radiological images; however, some authors have reported hypoenhanced lesions on angiography. In our case, the tumor...
had not been enhanced on initial T1WI with gadolinium, but enhancement was later found in a serial MRI examination, suggesting that neoangiogenesis gradually occurred during the tumor growth. Changes in the enhancement profile on radiological images can happen in IAF. The tumor also arose exclusively in the sella turcica and cavernous sinus in the present case, supporting the dural origin of this myofibroblastic tumor. When IAFs arise in this region, resection is anatomically limited, and endocrinological consideration should be practiced when testing abnormalities of the hypothalamic–pituitary axis.

Because of the scarcity of cases and diversity of differential diagnoses, the histopathological diagnosis of IAF is extremely difficult. The differential diagnosis of IAF should include meningioma, schwannoma, cranial fasciitis of childhood, cranial infantile myofibromatosis, nodular fasciitis, low-grade fibrosarcoma of bone or meninges, solitary fibrous tumor/hemangiopericytoma, ossifying fibroancoma, fibrous dysplasia, and granulomatous hypophysitis. At first, we accepted the initial diagnosis of the inflammatory myofibroblastic tumor but later ruled it out due to the progressive clinical course. Retrospectively, the uniform myofibroblastic cells in the abundant collagogenous stroma and bundle-like arrangement indicated IAF. The Ki-67 index of 5% implied the serial progression of the abundant collagenous stroma and bundle-like arrangement indicating schwannoma, cranial fasciitis of childhood, cranial infantile myofibromatosis. The Ki-67 index of 5% implied the serial progression of the abundant collagenous stroma and bundle-like arrangement indicating schwannoma, cranial fasciitis of childhood, cranial infantile myofibromatosis. The Ki-67 index of 5% implied the serial progression of the abundant collagenous stroma and bundle-like arrangement indicating schwannoma, cranial fasciitis of childhood, cranial infantile myofibromatosis.

Radiotherapy is not always effective for residual lesions. Nuytens et al. reported a meta-analysis of radiation therapy. They found that resection and irradiation yielded the best results and that irradiation alone was superior to resection alone. The current recommendation is 56 Gy in 28 fractions, based on data from the European Organisation for Research and Treatment of Cancer. Stereotactic radiosurgery for IAF was described in the present report but was ineffective. The optimum method for the adequate delivery of irradiation remains to be determined.

Medication and chemotherapy are not always effective for residual lesions. We selected a nonsteroidal anti-inflammatory drug (NSAID) and an antihormonal drug as chemotherapeutic agents. The epidemiological female predominance implies a link between aggressive fibromatosis and sex hormones, and such therapy has been applied to this tumor. NSAIDs have been described as anti–β-catenin drugs. A systematic review by Bocale et al. described an overall response rate of 51%, and Quast et al. reported long-term local control with estrogen receptor modulators and NSAIDs in 81% of cases. This therapy was ineffective for the present patient. In this context, Kaufmann therapy might have been harmful to our patient, although this is mere anecdotal speculation and requires further inspection.

Other chemotherapeutic agents have been anecdotally applied to treat IAF, but no reports have yet described their efficacy.

Radiotherapy can be impossible. Radiotherapy and chemotherapy are not always effective for residual lesions. The appropriate adjuvant therapy for refractory IAF remains to be determined.

Several limitations to this study warrant mention. First, the definite cause of the patient’s ventricular tachycardia was not determined by the autopsy. Second, other chemotherapeutic agents, including melphalan, vinblastine, and TKIs, might have been effective in our patient; however, we were unable to administer these agents due to their toxicity and/or lack of availability. Furthermore, the timing of additional chemotherapy was lost due to the unexpectedly rapid progression of the disease. Third, tamoxifen and sulindac should not have been used for the patient, based on her

### Table 1: Primary intracranial aggressive fibromatosis involving sella turcica

| Authors & Year          | Age (yrs), Sex | Onset Symptoms          | Surgery                        | Rx (Gy) | Chemo               | Outcome                      |
|------------------------|---------------|-------------------------|--------------------------------|---------|---------------------|------------------------------|
| Jenny et al., 2002     | 48, F         | Headache, Trigeminal neuralgia | TS/partial resection           | None    | None                | Unknown (watch and wait policy) |
| Gursoy et al., 2005    | 34, M         | Panhypopituitarism, Diabetes insipidus, Facial palsy | Transcranial/partial resection | None    | None                | Unknown (watch and wait policy) |
| Inácio de Tella et al., 2006 | 20, F | Proptosis, Nasal obstruction | Craniofacial/partial resection | None    | None                | Relapse in 8 mos TS partial resection Unknown (not described) |
| Present case           | 22, F         | Painful ophthalmoplegia  | TS/partial resection           | SRS, 15 Gy | Tamoxifen, Sulindac | Dead in 32 mos               |

Chemo = chemotherapy; Rx = radiation; SRS = stereotactic radiosurgery; TS = transsphenoidal.

**Lessons**

Radical curative resection of IAF can be impossible. Radiotherapy and chemotherapy are not always effective for residual lesions. The appropriate adjuvant therapy for refractory IAF remains to be determined.

Several limitations to this study warrant mention. First, the definite cause of the patient’s ventricular tachycardia was not determined by the autopsy. Second, other chemotherapeutic agents, including melphalan, vinblastine, and TKIs, might have been effective in our patient; however, we were unable to administer these agents due to their toxicity and/or lack of availability. Furthermore, the timing of additional chemotherapy was lost due to the unexpectedly rapid progression of the disease. Third, tamoxifen and sulindac should not have been used for the patient, based on her...
negative findings on immunostaining of estrogen and progesterone and the negative nuclear accumulation of β-catenin, but there were no other available options for therapy. Finally, IAF is an off-label use of tamoxifen and sulindac in Japan.

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