Primary intracranial extraskeletal myxoid chondrosarcoma

Pierwotny śródczaszkowy pozaszkieletowy chrzęstniakomięsak śluzowaty

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Abstract

Extraskeletal myxoid chondrosarcomas (EMC) are extremely rare and are usually located in the deep soft tissues of the lower extremities. Less than 10 cases of intracranial EMC have been reported in the literature, making their management and early diagnosis difficult. We present a new case of intracranial EMC occurring in a 70-year-old woman presenting with a right frontal mass initially assumed to be a brain metastasis from breast adenocarcinoma. The optimal management of these tumours is also discussed. Analysis from the literature suggests that complete resection should be recommended, whenever feasible. Although the high risk for relapse after surgery encourages postoperative treatments, relative resistance to both radiotherapy and chemotherapy characterizes EMC. Future perspectives might include multimodal treatments with highly conformal radiotherapy modalities for dose escalation strategies or use of new molecules. Knowledge of these unusual malignant tumours will be the first step for improving patients' outcome.

Key words: intracranial tumour, extraskeletal myxoid chondrosarcoma, brain neoplasm.

Streszczenie

Pozaszkieletowy chrzęstniakomięsak śluzowaty to wyjątkowo rzadki guz, który występuje zwykle głęboko w tkankach miękkich kończyn dolnych. Opisano mniej niż 10 przypadków tego guza umiejscowionych śródczaszkowo, co utrudnia wczesne rozpoznanie i leczenie. W pracy przedstawiono nowy przypadek śródczaszkowego chrzęstniakomięsaka śluzowatego u 70-letniej kobiety z guzem okolicy czołowej prawej, traktowanym początkowo jako przerzut gruczolakoraka sutka do mózgu. Omówiono optymalne leczenie tych guzów. Analiza piśmiennictwa wskazuje, że w miarę możliwości powinno się zalecać całkowite wycięcie. Duże ryzyko wznowy po leczeniu chirurgicznym skłania do podejmowania dodatkowego leczenia, ale guz charakteryzuje się względną opornością na radioterapię i chemioterapię. Przyszłe wielorakie metody leczenia mogłyby wykorzystywać radioterapię konformalną w celu zwiększenia dawki promieniowania lub zastosowanie nowych cząsteczek. Wiedza o tych rzadkich nowotworach złośliwych będzie pierwszym krokiem do poprawy wyników leczenia.

Słowa kluczowe: guz śródczaszkowy, pozaszkieletowy chrzęstniakomięsak śluzowaty, nowotwór mózgu.

Introduction

Cartilaginous tumours represent less than 0.15% of intracranial neoplasms [1]. Intracranial chondrosarcomas are supposed to originate from embryonic rests of the chondrocranium or from metaplasia of meningeal fibroblasts and typically arise from the base of the skull [2]. There is growing biological evidence that skeletal

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chondrosarcoma should be distinguished from extraskeletal myxoid chondrosarcoma (EMC), which is an exceptional entity that accounts for less than 2% of soft tissue sarcoma. While about 75% of cases of myxoid sarcomas are located in the deep soft tissues of the lower extremities, less than ten cases of intracranial EMC have been reported in the literature [2]. Although the management of patients with intracranial EMC remains uncertain, better knowledge of these unusual locations could help neurosurgeons and other physicians to deliver an appropriate treatment.

Here, we present a new case of intracranial EMC occurring in a 70-year-old woman presenting with a right frontal mass initially assumed to be a brain metastasis of a breast adenocarcinoma. The optimal management of these tumours is also discussed through a review of the literature.

Case report

A 70-year-old, right-handed woman presented with a two-month history of behavioural changes and progressive difficulty with walking. Two years before, she had presented a trifocal adenocarcinoma of the breast with three axillary node metastases (pT1c pN1 M0, stage IIA), characterized by no expression of oestrogen or progesterone receptors and no amplification of human epidermal growth factor receptor 2 (HER2/neu). She had been treated with mastectomy with axillary lymph node dissection and had received adjuvant radiotherapy and chemotherapy.

On the day of admission, neurological examination revealed right hemiparesis sparing the face and global aphasia. The magnetic resonance imaging (MRI) showed a heterogeneously enhancing rounded mass in the left frontal lobe (Fig. 1), which suggested a primary intracranial lesion. A computed tomography (CT) scan of the chest and abdomen failed to show any other suspicious lesion but indicated a subclinical pulmonary embolism which was a contraindication for intracranial surgery for two months.

After multidisciplinary discussion, it was decided to irradiate the lesion during this period. The patient received a total dose of 60 Gy, in 30 daily fractions. The post-irradiation MRI showed a slight increase in tumour volume. Then, the patient was operated on with neuronavigation. The tumour was totally removed piecemeal. Its dissection was non-haemorrhagic and did not show any signs of former radiotherapy. It was pearly white, with a lobular appearance, firm to slightly hard in consistency. It appeared strictly extra-axial, but was less clearly demarcated at its deep margins during dissection from the cerebral cortex. The perioperative impression was consistent with a meningioma although the lesion had no dural attachment. The postoperative course was eventless, with total recovery of the hemiparesis but persistence of aphasia and mental disturbances.

Microscopic examination of the lesion showed a proliferation of cells in a multilobular arrangement within an abundant myxoid stroma (Fig. 2). Neither haemorrhage nor necrosis was observed. No mitosis was seen. In the periphery, the lesion was more cellular and infil-

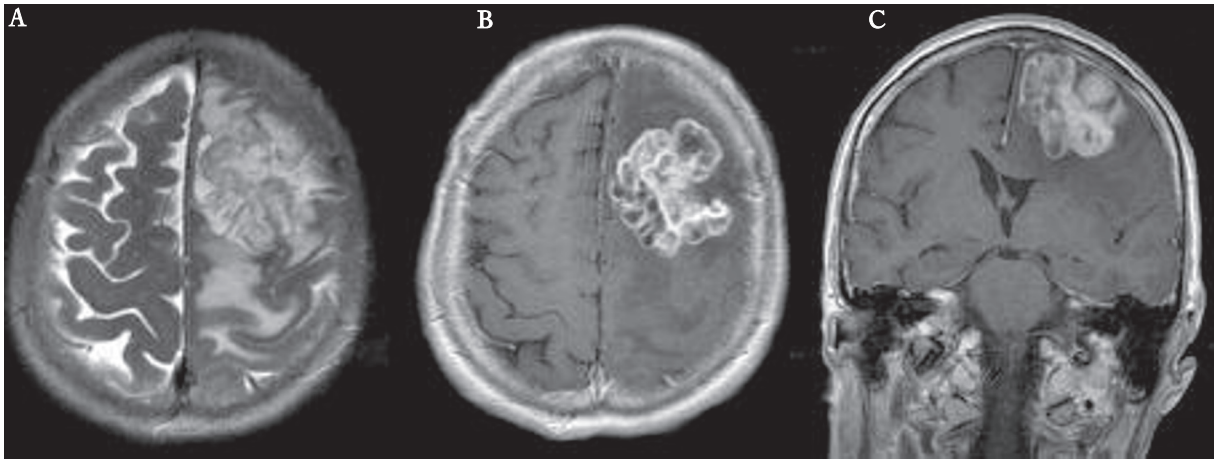

Fig. 1. A) Axial T2-weighted magnetic resonance (MR) image showing hyperintense mass in the left frontal lobe with surrounding oedema; B) axial and C) coronal T1-weighted MR images revealing ring enhancement of the lesion

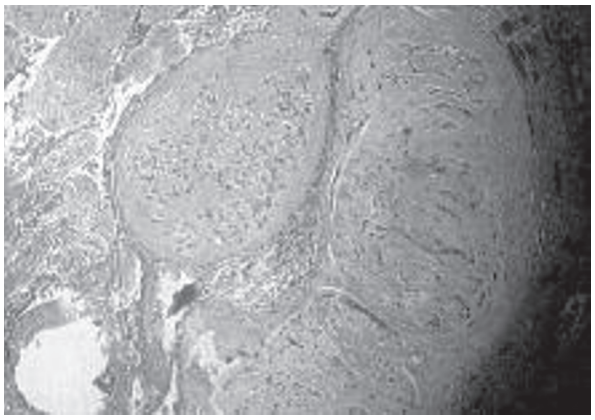

Fig. 2. Light micrograph of the tumour showing lobules and cords of tumour cells embedded within a myxoid stroma (haematoxylin and eosin stain, × 10)

trated into brain parenchyma. Immunohistochemical studies showed that the cells were strongly positive for pancytokeratin AE1 and AE3, EMA, and less positive for anti PS-100. Numerous nuclei of tumour cells were positive for MIB1 staining. The histological diagnosis was myxoid chondrosarcoma.

Unfortunately, the patient presented three months later with a worsening of mental troubles with severe attention deficit hyperactivity disorder and apathy. An MRI scan showed recurrence of the tumour in the same site. Intravenous chemotherapy with ifosfamide was given (1000 mg/m^2 daily for five days every three weeks). After four cycles of this regimen, no clinical benefit was noted and MRI showed moderate progression of the intracranial lesion. Chemotherapy was withdrawn and the patient received the best supportive care. She died ten months after surgery in a palliative care centre.

Discussion

Primary extraskeletal chondrosarcomas are intermediate-grade malignant neoplasms, which are characterized by a high propensity to local recurrence and metastatic evolution [2]. At the time of diagnosis, average age is around 50 years, with a male-to-female ratio of 2 : 1. Since these tumours frequently have an indolent clinical presentation, extraskeletal chondrosarcomas are frequently diagnosed at a late stage, when complete resection has become technically difficult. These tumours are usually classified into two histological subtypes: mesenchymal and myxoid type [3]. The myxoid variant has particular morphological and cytogenetic features and it is the rarest one [4]. Ultrastructural and molecular studies suggested that skeletal myxoid chondrosarcomas and EMC are two separate entities rather than the same entity arising in two different locations: detection of a EWS-CHN gene fusion RNA resulting from the *t* (9;22) mutation would be highly specific to EMC [5,6]. EMC is thought to be a tumour of intermediate malignancy, but with a supposed better prognosis than other types of chondrosarcomas [7,8]. Tumour size, cellular density, presence of anaplasia or rhabdoid features, high mitotic activity, and high Ki67 have been reported

Table 1. Histopathological characteristics of the intracranial extraskeletal myxoid chondrosarcoma cases

First author (year of publication)	Recurrence	Cellularity	Necrosis	Mitotic activity	Tumour size
Scott (1976) [14]	Deceased	Variable	No	NR	NR
Smith (1981) [15]	No	Variable	NR	Low	3.5 × 1 × 0.5 cm
Cybulski (1985) [11]	No	NR	NR	No	NR
Salcman (1992) [8]	Yes	1: moderate 2: higher*	NR	High	1: 7 × 5 × 4 cm 2: NR*
Sato (1993) [13]	No	NR	No	Low	NR
Chaskis (2002) [10]	Deceased	NR	NR	Low	NR
González-Lois (2002) [12]	Yes	1-2: low 3: higher*	NR	1-2: low 3: higher*	NR
Im (2003) [7]	No	Variable	No	Low	1.2 × 1 × 1 cm
Cummings (2004) [6]	NR	Variable	NR	Low	2.4 × 1.8 × 2.3 cm
Current case	Yes	Low	No	No	4 × 4 × 3.5 cm

**1, 2, 3 – number of tumour recurrence*
NR – not reported

Table 2. Review of intracranial extraskeletal myxoid chondrosarcoma cases reported in the literature

First author (year of publication)	Age (years), gender	Duration of symptoms before treatment	Location/ origin within brain	Surgery extent	Postoperative treatment	Time to recurrence	Treatment of recurrence	Survival	Follow-up duration
Scott (1976) [14]	39, M	5 months	Fourth ventricle	Partial	No	NA	NA	13 days	13 days
Smith (1981) [15]	12, M	4 days	Posterior cranial fossa	Complete	No	NA	NA	NR	13 months
Cybulski (1985) [11]	58, M	1 week	Falx	Complete	No	NA	NA	NR	18 months
Salcman (1992) [8]	28, F	2 months	Left parafalcine area	Complete	No	10 months	Total removal and BT	NR	22 months
Sato (1993) [13]	43, F	2 months	Pineal region	Partial	RT and chemotherapy	NA	NA	37 months	37 months
Chaskis (2002) [10]	69, M	3 months	Right frontal lobe	Complete	No	NA	NA	1 month (septic shock)	
González-Lois (2002) [12]	17, F	> 3 years	Right, fronto-parietal	Complete	No	16 months	Total removal and RT	NR	20 months
Im (2003) [7]	43, M	2 months	Left parietal lobe	Complete	RT	NA	NA	36 months	36 months
Cummings (2004) [6]	63, M	1 year	Right cerebello-pontine angle	Complete	NR	NR	NR	NR	NR
Current case	70, F	2 months	Left frontal lobe	Complete	RT before surgery	3 months	Chemotherapy	5 months	5 months

BT – brachytherapy, F – female, M – male, NA – not applicable, NR – not reported, RT – radiotherapy

to be adverse pathological prognostic factors, but the rarity of intracranial locations does not allow for validation of those factors as significant prognostic factors for survival (Table 1) [9].

In order to highlight optimal strategies for management of intracranial EMC, we conducted a search in the literature using the Medline database (PubMed, http://ncbi.nlm.nih.gov/PubMed) for the keywords 'extraskeletal myxoid chondrosarcoma', 'brain neoplasm', and 'intracranial tumour', between 1970 and 2010. The manuscripts were reviewed and their bibliographies scanned for additional articles. Nine previously reported cases of intracranial extraskeletal myxoid chondrosarcoma were found [6-8, 10-15]. Their features are reported in Table 2. Age at the time of diagnosis ranged from 12 to 69 years. The duration of symptoms depended on the location of the tumour (four days for the patient with cerebellar EMC, more than three years for the patient with right frontoparietal location).

No definitive conclusion could be drawn from the literature regarding the exact site of tumour origin in intracranial extraskeletal cases. In the unique case of chondrosarcoma of the fourth ventricle, the tumour was thought to arise from the stroma of the choroid plexus [14]. For the cases in which the tumour is attached to or infiltrates the falx, tentorial or dural sinuses, it is usually assumed that the tumour could derive from meningeal fibroblasts. In our case, however, neither dural attachment nor dural invasion by the tumour was found. The tumour was characterized by the absence of a true cleavage plane

Table 3. The magnetic resonance imaging characteristics of intracranial extraskeletal myxoid chondrosarcomas cases reported in the literature

First author (year of publication)	T1-weighted	Contrast enhancement	T2-weighted	Oedema
Salcman (1992) [8]	Hypointense	NR	Homogeneous hyperintense	No
Chaskis (2002) [10]	NR	Strong and homogeneous	NR	Yes
González-Lois (2002) [12]	Hypointense	Strong and heterogeneous	NR	NR
Im (2003) [7]	Hypointense	Strong and homogeneous	Slightly hyperintense	Yes
Cummings (2004) [6]	NR	Strong and heterogeneous	NR	NR
Current case	Hypointense	Strong and heterogeneous	Homogeneous hyperintense	Yes

NR – not reported

deep within the operating field and the presence of histological signs of parenchymal infiltration. The site of origin in this case could be the leptomeningeal sheath around vessels or the vessel walls in the depth of a sulcus, as was hypothesized for other patients with intraparenchymal locations reported in the literature.

Regarding radiological features, intracranial EMC usually present as hypointense well-demarcated lesions with strong enhancement after contrast injection on T1-weighted sequences and high intensity on T2-weighted sequences (Table 3). In the case of our patient with a previous history of breast carcinoma, the heterogeneously enhancing lesion could mimic a metastatic brain tumour, which should be considered as a differential diagnosis. Histological confirmation of the diagnosis should be a priority whenever feasible, since radiological features are not specific.

The optimal treatment of intracranial EMC remains uncertain. In the previous cases of intracranial EMC, complete removal was achieved for all but two patients. Two patients died during the month following surgery. One patient with complete removal and another patient with partial surgery received postoperative external beam radiotherapy then chemotherapy was delivered for the latter. For six patients, follow-up was reported (duration: 13-37 months). Three of them experienced tumour relapse, treated either with salvage surgery ($n = 1$), radiotherapy ($n = 1$), or brachytherapy ($n = 1$). Five patients were alive at the last follow-up. Altogether, these observations suggest that surgery should be the first-line treatment. It also allows the determination of the final diagnosis. However, total removal of the tumour does not seem to be sufficient to prevent short-term recurrence as in the case of our patient. Probably, useful information could be obtained through analysis of literature on EMC from other sites. In their experience, Kawaguchi *et al*. reported on 20 males and 22 females with histologically confirmed EMC. Mean age at diagnosis was 52.1 years. Univariate analysis revealed that inadequate initial surgery was a significant prognostic factor for local recurrence. After wide excision, only 14% patients had relapsed, supporting the role of complete excision in the local control of the disease [16]. Unfortunately, such functionally safe wide excision is usually not possible for patients with intracranial EMC, and their prognosis remains particularly poor [10].

Combined with the very low number of patients, the relative resistance to ionizing radiation of chondrosarcoma could explain the lack of marked benefit demonstrated for adjuvant radiotherapy in patients with EMC. However, this treatment is usually proposed after surgery if recurrence occurs or when the lesion is inoperable or only partially removed. Since most patients with intracranial EMC cannot be offered microscopically complete resection, delivering irradiation could be logically proposed as adjuvant therapy. However, the risk of relapse is important when surgery is marginal, and this risk will not be counterbalanced by postoperative radiotherapy [12]. Although not demonstrated, new highly conformal irradiation modalities such as helical tomotherapy and gamma knife could be potentially used for treatment of tumour relapse or management of inoperable patients. By sparing critical organs from irradiation, dose escalation strategies could potentially overcome this intrinsic resistance to ionizing radiation.

Few data have been reported regarding the place of chemotherapy for management of unresectable disease. Therapeutic agents used for other locations of EMC are the same as those used for soft-tissue sarcomas and include doxorubicin, dacarbazine, beta-interferon, and ifosfamide, but these drugs lack significant evidence of efficacy in this setting [17,18]. Drilon *et al*. reported a retrospective review on 87 patients with EMC from two referral centres. The authors found that 37% of patients

presenting with a local disease developed distant metastases within a median time of 3.3 years. The 5-year, 10-year, and 15-year overall survival rates were 82%, 65%, and 58%, respectively. However, the progression-free survival at 9 months was only 26%, with no significant responses noted in 21 patients receiving chemotherapy. This analysis highlighted that aggressive control of localized disease should be the first-line treatment [2]. Although no data have been reported on the place of chemotherapy for the management of patients with intracranial EMC, its efficacy will probably be limited by intrinsic drug resistance of the tumour and by the additional theoretical obstacle of the blood-brain barrier. New molecules and targeted agents are being developed for the treatment of soft tissue sarcoma. By targeting specific molecular alteration, those could significantly improve the outcome of patients.

In conclusion, EMC is a neoplasm only rarely encountered intracranially, and thus defining an optimal therapeutic strategy is difficult. Altogether, our clinical presentation and analysis from the literature suggest that these rare locations are associated with a poor prognosis despite total removal of the tumour. Moreover, it is difficult to extrapolate the treatment outcome of patients with EMC located elsewhere, since surgical conditions are substantially different here. Further improvements in the management of patients with EMC could be achieved with the area of targeted agents and new irradiation modalities. In all cases, multidisciplinary management should be strongly recommended for those rare tumours. Better knowledge of these unusual tumours will reduce diagnostic delays and hopefully improve patients' outcome.

Disclosure

Authors report no conflict of interest.

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