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ARTICLE

Infarction with associated pseudosarcomatous changes mimics anaplasia in otherwise grade I meningiomas

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Abstract

We describe a morphologically distinct pattern of tumor infarction and associated sarcoma-like changes, mimicking focal anaplasia, in otherwise WHO grade I meningiomas. The described cases ($n = 9$) all demonstrated a discrete spindle-cell (pseudosarcomatous) component with brisk mitotic activity (12–14 mitoses/10 HPF), elevated Ki-67 (mean 75.5 ± 25.0%, quantified), absence of PR, SSTR2A, or EMA expression, and potential SMA expression (50%). Despite these high-grade features, all nine patients remained free of progression or recurrence post resection (follow-up mean: 49.8 months). In contrast, among a comparison (control) cohort of consecutive WHO grade II and III meningiomas ($n = 16$), as expected, progression rate was high (68.8%, $P = 0.002$, Fisher's exact, average time to progression = 25 months, follow-up mean: 39.8 months). While necrosis was a frequent feature among atypical/anaplastic meningiomas (12/16, 75%), and elevated mitoses and proliferative index were present consistent with histologic grade, a well-defined zonal pattern with pseudosarcomatous component was not present among these tumors. DNA methylation-based analysis readily distinguished meningiomas by copy number profiles and DNA-based methylation meningioma random forest classification analysis (meningioma v2.4 classifier developed at University of Heidelberg); all pseudosarcomatous cases analyzed (4/9) matched with high level calibrated classifier score to "MC benign-1", with isolated loss of chromosome 22q identified as the sole copy number alteration. In contrast, multiple chromosomal losses were detected among the comparison cohort and classifier results demonstrated good concordance with histologic grade. Our findings suggest that pseudosarcomatous alterations represent reactive changes to central meningioma infarction, rather than focal anaplasia, and further support the use of DNA methylation-based analysis as a useful adjunct for predicting meningioma behavior. These indolent tumors should be distinguished from their atypical and anaplastic counterparts.

Introduction

Meningiomas are the most commonly reported primary intracranial tumor, accounting for almost a third of primary central nervous system neoplasms. The majority are slow-growing, benign neoplasms, corresponding histologically to WHO grade I [1, 2]. Per the latest 2016 WHO Classification of Tumors of the Central Nervous System, atypical or WHO grade II meningiomas are defined by increased mitotic activity (≥4 mitoses per 10 high power fields, HPF), brain invasion, or at least three so-called minor criteria (increased cellularity, high nuclear: cytoplasmic ratio, prominent nucleoli, sheet-like growth, and necrosis); meningiomas displaying frankly malignant cytology and/or markedly elevated mitotic activity (≥20 mitoses per 10 HPF) are designated as anaplastic, or WHO grade III, and carry an extremely poor prognosis [3, 4]. While overall recurrence risk and aggressive

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clinical behavior among meningiomas has been strongly correlated to histologic grade, this is highly influenced by extent of resection and a wide variability in clinical course has been described, particularly among atypical meningiomas [5, 6]. The utility of radiotherapy in postoperative treatment of atypical meningiomas, especially in the setting of complete resection remains unclear [7]. Moreover, the histologic criteria for grading remain somewhat controversial, and their validity continues to be actively studied and debated [8–11]. Molecular alterations underlying meningioma pathogenesis are increasingly well understood [12–14] The increased incorporation of data including copy number alterations [15–17], genetic mutations [18–21], and epigenetic signatures [18, 22, 23] carries the potential for more accurate prognostication and avoidance of diagnostic pitfalls.

We describe the histopathologic features of nine otherwise WHO grade I meningiomas displaying a morphologically distinct zonal pattern of tumor infarction and associated sarcoma-like changes. Despite malignant histologic appearances, extended clinical follow-up demonstrated no evidence of tumor progression or recurrence in these cases, while recurrence rates were high among a comparison cohort of grade II and III atypical and anaplastic meningiomas. We further evaluated the ability of DNA methylation-based analysis to distinguish these pseudosarcomatous tumors from bona fide atypical/anaplastic meningiomas.

Materials and methods

The described cases ($n = 9$) were collected in the course of clinical consultative practice (MKR). A comparison (control) cohort of consecutive WHO grade II and III ($n = 16$, defined by 2016 WHO classification criteria) was assembled from departmental archives. Tissue was submitted *in toto* for histologic examination. Retrospective chart review, including available radiology reports, was performed for clinicopathological details of these patients under Institutional Review Board approved protocols.

Histopathology

The streptavidin–biotin peroxidase complex method was utilized for immunohistochemical studies with antibodies to epithelial membrane antigen (EMA; Clone E29, Ventana, monoclonal), somatostatin receptor 2 (SSTR2; Clone UMB1, Abcam, 1:500, monoclonal), smooth muscle actin (SMA; Clone 1A4, Cell Marque, 1:200 monoclonal), Ki-67 (MIB-1; Clone MIB-1, Dako,1:200 monoclonal), CD34 (Clone QBEnd-10, Ventana, monoclonal), ERG (Clone EPR3864, Ventana; monoclonal), CD68 (Clone KP1, Ventana, monoclonal). Antibodies were obtained and applied at ready-to-use dilutions unless stated otherwise.

MIB-1 quantification

A quantified labeling index was obtained as follows: MIB-1 stained slides were surveyed to identify regions with highest percentage of stained nuclei. Digital photomicrographs were obtained at 40× power. Positive tumor cells were counted and calculated as a percentage of total cells, ensuring a minimum of 1000 total cells. The procedure was performed by two independent pathologists (TAB, SR) and averaged to calculate the final proliferative index.

DNA methylation-based analysis

DNA methylation analysis was performed at the MSKCC diagnostic molecular pathology laboratory. For each sample, DNA was extracted using standard methods from formalin fixed paraffin embedded tissue (FFPE). Corresponding H&E stained sections were examined to ensure adequate tumor purity in all cases; for the nine pseudosarcomatous cases, H&E sections were used to guide macrodissection for the purposes of avoiding areas of necrosis. For each case, 250 ng of genomic DNA was subjected to bisulfite-conversion (EZ DNA Methylation Kit [Zymo Research, catalog no. D5002]) and FFPE restoration (Infinium HD FFPE DNA Restore Kit [Illumina, catalog no. WG-321-1002]) followed by processing on Infinium HumanMethylationEPIC [850K] arrays and scanning on the Illumina iScan according to the manufacturer's recommended protocol; copy number profiles and meningioma random forest classification results were generated from output data (.idat files) using the brain tumor methylation classifier (vllb4, 82 tumor classes, 9 non-tumorous classes) and meningioma classifier (v2.4) developed at University of Heidelberg [24–26]. Via the meningioma classifier, tumors may be subgrouped into three benign (MC benign-1, 2, 3), two intermediate (MC int-A, B), and one malignant (MC malignant) methylation classes. In short, the classifier generates a predicted tumor class membership probability, or calibrated score. Calibrated scores of >0.9 have been generally proposed as a threshold for a "match," with cut-off scores exceeding 0.5 for tumor subclass prediction. Calibrated scores between 0.3 and 0.9 are frequently encountered a result of low tumor purity among other factors. Scores below 0.5 are recommended to be disregarded, while those above 0.5 are thought to be potentially clinically relevant in an appropriate context with additional supportive evidence [25].

Copy number variation (CNV) analysis

Analysis of CNVs was performed from DNA methylation array data as previously described [25, 27]. Briefly, methylated and unmethylated signal intensities from the

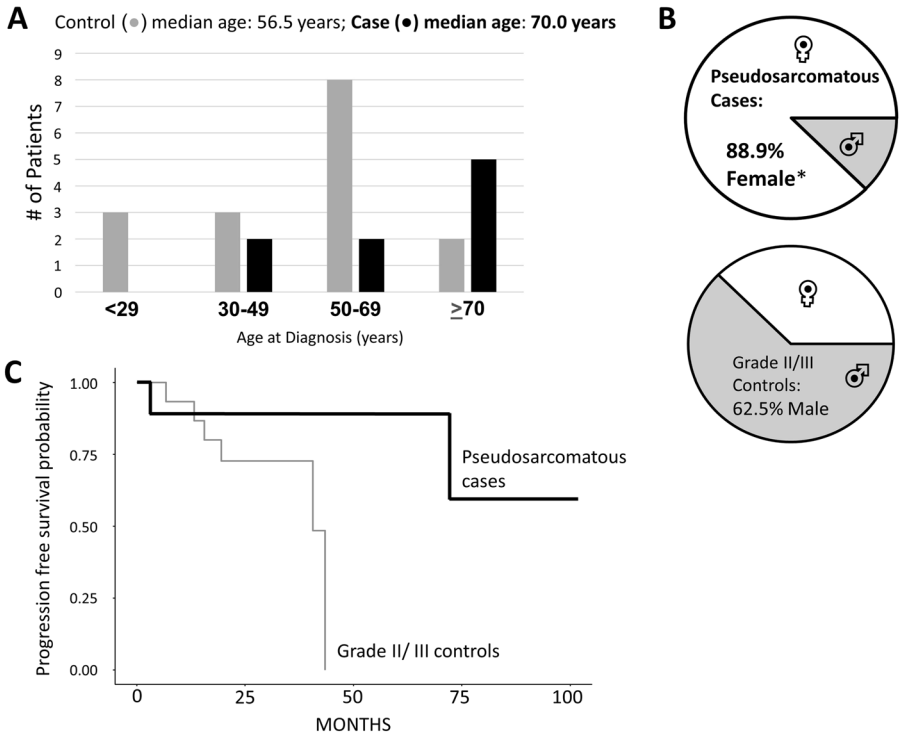

Fig. 1 Clinical features of pseudosarcomatous meningiomas. a Cases (black) tended to occur in older patients as compared with a cohort of grade II/III atypical and anaplastic meningiomas (mean 64 versus 52.25 years, not significant; $P = 0.1164$). **b** Cases occurred in predominately female patients ($P = 0.033$). Despite their malignant histologic appearance, none of the pseudosarcomatous cases progressed over an extended clinical follow-up period, as compared with 68.8% tumor progression among grade II/III controls ($P = 0.002$, average time to progression = 25 months, **c**).

array are added together and a copy-number ratio is generated against healthy reference samples. The resultant ratio is plotted by chromosomal location and graphically represented alongside classifier results. Of note, algorithms used for the classifier are independent of CNV analysis. With the exception of tumor types with significant alterations in baseline chromosomal ploidy, in general high-density methylation arrays have been demonstrated to reliably detect copy number alterations with comparable sensitivity of traditional SNP platforms [28].

Survival analysis

Survival analysis was performed in R version 3.5.2 using the survival (version 2.43-3) and survminer (version 0.4.5) packages.

Results

Clinical features and neuroimaging

Demographically, pseudosarcomatous features were seen in meningiomas occurring in somewhat older patients as compared with atypical/anaplastic cases (median 70 versus 56.5 years, mean 64 versus 52.25 years, not significant; $P = 0.1164$, unpaired t-test). Pseudosarcomatous cases were more likely to occur in female patients (8/9, 88.9% female), as opposed to significantly increased incidence of grade II/III meningiomas among male patients, consistent with previous reports [29, 30] (10/16, 62.5% male, $P = 0.033$, Fisher's exact, Fig. 1).

Five tumors presented in the supratentorial compartment, three in the posterior fossa as tentorium-based lesions and one lesion was a dura-based mass in the thoracic spinal region. While overall features were consistent with meningioma, of note, all five tumors for which additional radiologic description was available were noted to be contrast-enhancing with central non-enhancing, hypodense regions suggesting necrosis or cystic change (cases 1, 3, 5, 6, 8), three of these specifically described as "ring-enhancing" (cases 1, 3, 8). One lesion (case 8) initially imaged as a 1 cm mass on non-enhanced CT was found on MRI eight days later to be a 2 cm, ring-enhancing tumor with conspicuous edema of the neighboring occipital lobe. This is in contrast to grade II/III meningiomas where, while 44% of tumors were noted to have a heterogenous pattern of contrast-enhancement, a central hypodensity, cystic change or ring-enhancement pattern was never encountered (see Table 1).

Histopathologic features of pseudosarcomatous changes in meningioma

All nine cases demonstrated a distinct zonal pattern consisting of (1) a central zone of necrosis having the appearance of infarction, (2) a surrounding atypical spindle-cell proliferation, (3) a predominant background of fibroblastic or transitional-type WHO grade I meningioma (Fig. 2). The

Table 1 Clinicopathological features and meningioma classifier results of pseudosarcomatous cases and atypical/anaplastic controls.

	Age at Dx (years)	Male (M) vs. female (F)	Tumor location	MRI tumor enhancement pattern	Tumor size (greatest dimension, cm)	Histologic grade	Methylation class[a]	Calibrated score	GTR[b]	XRT	Progressed?	Alive?
Case 1	75	F	Left parietal	Heterogeneous[c,d]	3	I vs. III[e]	Benign-1	0.99[f]	✓	x	x	✓
Case 2	58	F	Posterior fossa	–	5	I vs. III[e]	Benign-1	0.99[f]	✓	x	x	✓
Case 3	89	F	Right parietal	Heterogeneous[c,d]	2.5	I vs. III[e]	Benign-1	0.99[f]	✓	x	x	x[g]
Case 4	72	F	Posterior fossa	–	7	I vs. III[e]	Benign-1	0.95[f]	✓	x	x	✓
Case 5	47	F	Thoracic spine (T6-8)	Heterogeneous[c]	1.8	I vs. III[e]	–	–	✓	x	x	✓
Case 6	70	M	Left frontal/ parasaggital	Heterogeneous	5.5	I vs. III[e]	–	–	✓	✓	x	✓
Case 7	72	F	Left posterior fossa	–	2.1	I vs. III[e]	–	–	✓	x	x	✓
Case 8	53	F	Left occipital	Heterogeneous[c,d]	2	I vs. III[e]	–	–	✓	✓[h]	x	x[g]
Case 9	40	F	Left frontal/ parasaggital	–	4.8	I vs. III[e]	–	–	✓	✓	x	✓
Control 1	29	M	Left frontal	Heterogeneous	1.1	II	Intermediate-A	0.55	✓	x	x	✓
Control 2	77	M	Right temporal	Homogenous	1	II	Intermediate-B	0.61	✓	x	x	✓
Control 3	52	F	Left parietal	Homogenous	7.6	II	Intermediate-A	0.67	x	✓	✓	✓
Control 4	62	F	Left parafalcine	Homogenous	4.5	II	Intermediate-A	0.99[f]	✓	✓	x	✓
Control 5	56	M	Parafalcine, bifrontal	Homogenous	1	II	Intermediate-A	0.8	✓	✓	✓	✓
Control 6	82	M	Left frontal /parasagittal	Heterogeneous	3.5	II	Intermediate-A	0.62	x	x	✓	x
Control 7	58	F	Right frontal	Homogenous	7.8	II	Intermediate-A	0.99[f]	✓	x	x	✓
Control 8	42	M	Right frontal	Homogenous	2.5	II	Intermediate-A	0.72	x	✓	x	✓
Control 9	42	F	Right frontotemporal	Homogenous	3.9	II	Intermediate-A	0.91[f]	x	✓	x	✓
Control 10	69	F	Left posterior fossa	Heterogeneous	2.5	II	Intermediate-A	0.83	x	✓	✓	✓
Control 11	60	M	Right frontal	Homogenous	6	II	Intermediate-A	0.38	✓	✓	✓	x
Control 12	13	M	Left fronto-parietal	Heterogeneous	5	II	Intermediate-A	0.99[f]	✓	x	x	✓
Control 13	29	M	Left fronto-parietal	Heterogeneous	2	III	Malignant	0.58	x	✓	✓	✓
Control 14	61	M	Right frontal	Homogenous	8.7	III	Malignant	0.97[f]	✓	✓	✓	x
Control 15	57	M	Right parietal	Heterogeneous	8.5	III	Malignant	0.99[f]	✓	✓	✓	x
Control 16	47	F	Left temporal	Heterogeneous	7	III	Benign	0.59	✓	✓	✓	x

[a]Meningioma random forest classification results were generated using the meningioma v2.4 classifier developed at University of Heidelberg [26–28], to identify predicted tumor class membership (Methylation Class [MC]) and probability, or calibrated score.

[b]Gross total resection (GTR) was achieved in all pseudosarcomatous cases. Radiation therapy (XRT) was rarely used except in case 6, 8, and 9.

[c]Cases were noted to have heterogenous contrast-enhancement, particularly with central non-enhancing, hypodense regions suggesting necrosis or cystic change.

[d]Cases specifically described as "ring enhancing".

[e]Histologic grade of cases at initial clinical evaluation was interpreted to be overall grade I with necrosis and focal severe atypia, possibly representing progression to anaplastic meningioma WHO grade III.

[f]Calibrated scores of >0.9 are generally considered a "match," scores >0.5 may be considered relevant with additional supportive features.

[g]Cases 3 and 8 expired due to unrelated causes with autopsy confirmation of no evidence of meningioma recurrence.

[h]Case 8 did not receive a full course of radiation therapy.

spindle-cell component demonstrated atypical cytologic features including prominent nucleoli and brisk mitotic activity (12–14 mitoses/10 HPF, Fig. 1b, Supplementary Fig. 3; HPF field diameter: 0.45 mm). Ki-67 proliferation indices were markedly elevated (mean 75.5 ± 25.0%, quantified) in this zone (Fig. 2c, d, Supplementary Figs. 1, 3). This pseudosarcomatous zone was consistently devoid of EMA (Fig. 2e), and SSTR2 expression (Supplementary Fig. 3), the expression of which was well-retained in the conventional meningioma component. Although scant SMA expression was present in 50% of cases, desmin, CD34, and ERG immunostains were negative in this atypical spindled component. CD34 highlighted scattered small blood vessels, but did not reveal dense vascular proliferation (Supplementary Fig. 1). Abundant histiocytic infiltration was also noted and highlighted in immunohistochemical studies for CD68. Reticulin staining was performed on a subset of cases ($n = 4$) which demonstrated dense deposition in the pseudosarcomatous zone with variable expression elsewhere in the meningioma. Among the nine cases, there was no history of prior radiation or embolization therapy. Regions of necrosis in the described cases were large, centrally-located, and exceeded 15–20% of the evaluable tissue. Examination of the necrotic central regions demonstrated cellular "ghosts", reminiscent of meningioma. The etiology of the necrosis was unclear, however the overall features were suggestive of central tumor coagulative/ischemic infarction.

Research review of 16 WHO grade II/III meningiomas revealed that while necrosis was a frequent feature (12/16, 75%), these changes were focal and present scattered within the tumor, rather than being central. In general, cellular detail was lost in these necrotic foci. There was no significant difference in tumor size among pseudosarcomatous cases versus grade II/III controls (3.74 cm $\pm$ 1.87 S.D. vs. 4.54 cm $\pm$ 2.76 S.D., $P = 0.45$, unpaired t-test). Elevated mitoses and proliferative index, consistent with histologic grade were present in all comparison cases but were dispersed throughout the tumor rather than being zonal.

Pseudosarcomatous features do not portend aggressive clinical behavior

All nine patients with pseudosarcomatous changes showed no evidence of tumor progression or recurrence (follow-up mean: 49.8 months, range: 3–95 months). Gross total resection was achieved with initial surgery in all cases. Only three patients were treated with subsequent radiation (one with an incomplete course of therapy). At last follow-up, two patients had died of unrelated causes with autopsies demonstrating no evidence of tumor recurrence; the remainder were apparently alive and well (Table 1). In contrast, as expected among the atypical/anaplastic meningioma comparison cases, 68.8% of patients progressed ($P = 0.002$, Fisher's exact, average time to progression = 25 months); with five patients dying of their disease (follow-up mean: 39.8 months, range:13–119 months). Incidence of incomplete resection was high (6/16, 37.5%) with concurrent prevalent treatment with radiotherapy (11/16, 68.8%. Table 1).

DNA methylation-based classification reliably distinguishes pseudosarcomatous cases from atypical/anaplastic meningiomas

Four out of nine pseudosarcomatous cases and all 16 controls had sufficient material for DNA-based methylation analysis. Using the general brain tumor classifier (v11b4), all 20 cases matched to methylation class (MC) meningioma with calibrated score >0.9. On further analysis using the meningioma classifier (v2.4), all pseudosarcomatous cases matched with high level calibrated classifier score (>0.9) to "MC benign-1", with isolated loss of chromosome 22q identified as the sole copy number alteration (see Fig. 3). In contrast among the comparison cohort of atypical and anaplastic meningiomas, multiple chromosomal losses were detected, most commonly 1p (81.3%), 22q (75%), 14q (43,8%), 18q (43.8%), 10q (37.5%), 19p (37.5%), 6q (31.3%), and 9p (including CDKN2A/B (25%). Methylation classifier results among control cases demonstrated more variability, which may be reflective of tumor purity as a result of inclusion of necrotic zones (avoided by macrodissection in pseudosarcomatous cases). Among controls, classifier results demonstrated generally good concordance with histologic grade (87.5% concordance, calibrated index >0.5). Highest MC probabilities and corresponding calibrated scores are listed in Table 1. No alternative classes were suggested for any of the tumors at a calibrated score >0.3.

In one case with pseudosarcomatous features, adequate material was available for macrodissection of the spindle-cell component and comparison against the fibroblastic-type meningioma background component. While the background meningioma component recapitulated the methylation classifier results for the case as a whole (MC benign-1, calibrated score: 0.97), the spindle-cell component did not classify as any tumor type. Rather it demonstrated closest similarity with "MC control tissue, inflammatory microenvironment," which would be expected for tissue composed of mixed cell types and high mononuclear cell (histiocytic) infiltration (Supplementary Fig. 2). The macrodissected pseudosarcomatous component was negative for detectable copy number alterations including deletion of chromosome 22q (Supplementary Fig. 2).

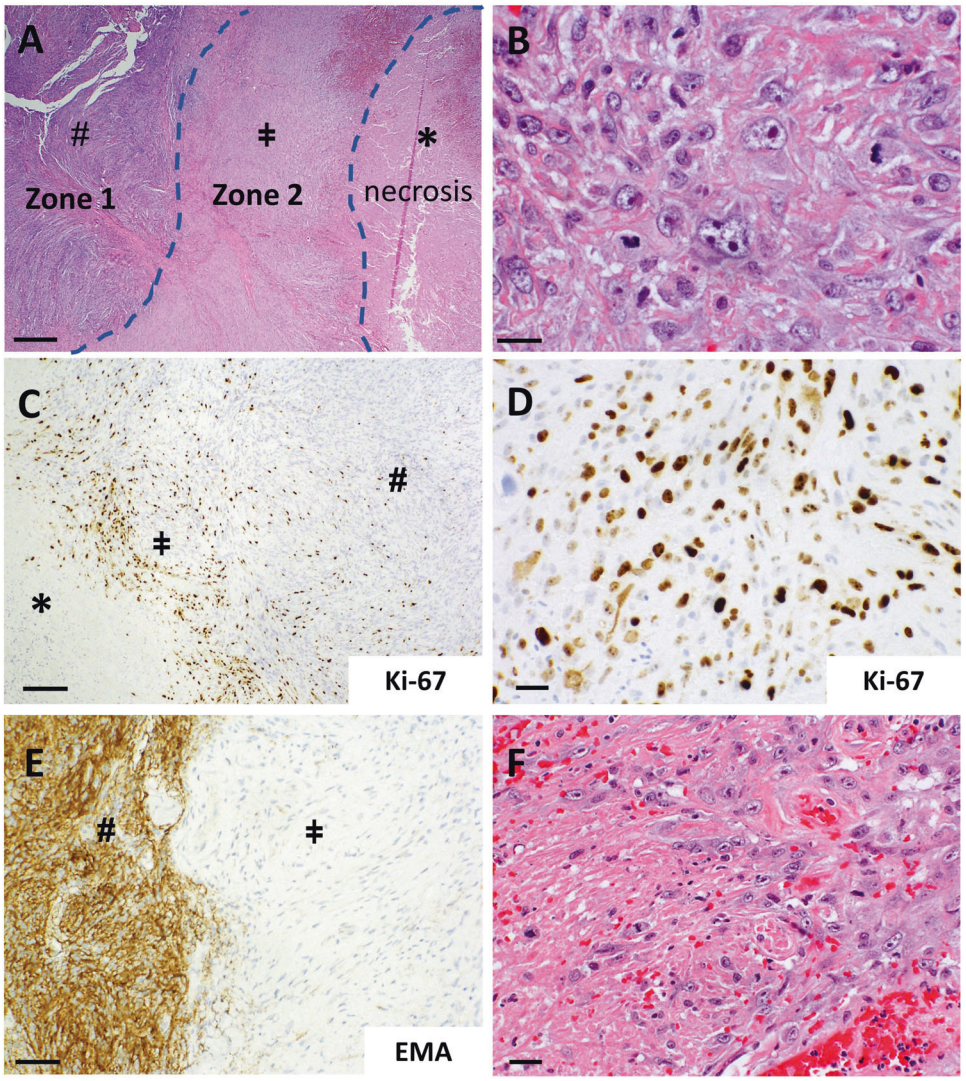

Fig. 2 Histologic features of pseudosarcomatous changes in otherwise grade I meningioma. A reproducible and well-defined zonal pattern consisting of central necrosis (*), which is surrounded atypical spindle cell/pseudosarcomatous proliferation(zone 2, ǂ) within a background of typically fibroblastic WHO grade I meningioma (zone 1, #) defined the nine cases (**a**, scale bar: 200 µm). The pseudosarcomatous zone was composed of spindle cell significant cytologic atypia, prominent nucleoli, abundant mitotic activity and markedly elevated proliferative index (**b**, **c**, scale bars: 20 µm). Note that the Ki-67 labeling highlighted large atypical spindle cells in the pseudosarcomatous zone (**d**, scale bar: 10 µm). The pseudosarcomatous zone consistently demonstrated loss of meningothelial markers otherwise retained in the background meningioma (**e**, scale bar: 20 µm), and surrounded a large central zone of necrosis, suggestive of central infarction (**f**, scale bar: 10 µm).

Discussion

We describe a pattern of necrosis and sarcoma-like changes in otherwise grade I meningiomas that does not appear to denote aggressive tumor biology based on our follow-up data. We are not aware of prior reports documenting the histologic phenomena we describe.

Our findings suggest that pseudosarcomatous alterations may represent reactive changes to tumor infarction, rather than focal progression and anaplasia. While our methylation and immunohistochemical analysis of the spindle-cell component was limited, and we are unable to definitively identify the nature of these atypical cells, we found no copy number alterations or methylation signatures of higher grade meningiomas in these tumors, even when selecting for the pseudosarcomatous proliferation itself. A florid fibroblastic response to tissue infarction, although not previously described in meningiomas, is one possible scenario, a second being a peculiar alteration in tumor cells as a response to tumor necrosis.

We propose that despite meeting high-grade histologic criteria, such meningiomas should be distinguished from their atypical and anaplastic counterparts. The utility of radiation therapy in the setting of grade II meningiomas, particularly after gross total resection, remains under investigation. None of the cases presented here were reported as purely grade I meningiomas. Rather two interpretations were suggested: one (for which there was at the time no supporting literature) being that this was a peculiar reaction to tumor necrosis/infarction, and the other being that this indeed represented sarcomatous tumor progression with loss of meningothelial marker expression. The changes we now describe as pseudosarcomatous were interpreted at the time as possibly suggesting increased biologic potential, for which radiation therapy could be reasonably indicated (and in three cases, treating clinicians did elect to irradiate).

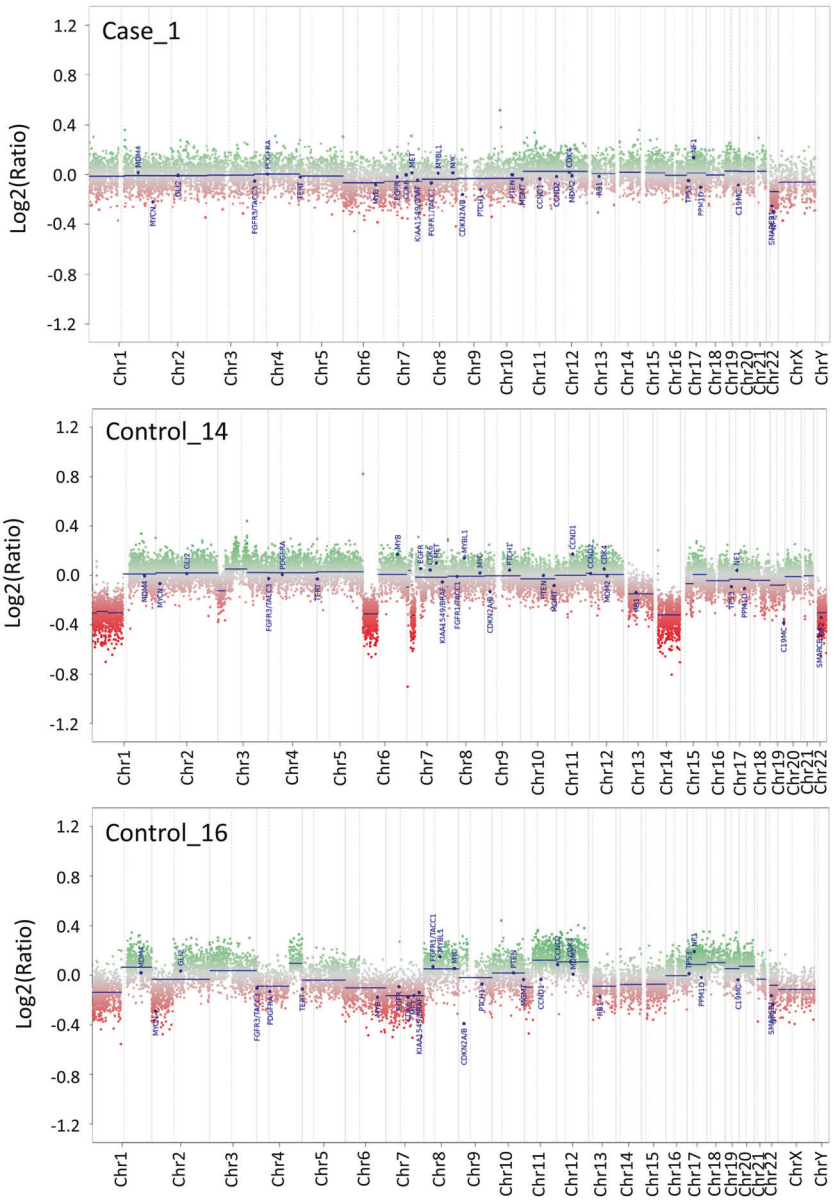

Fig. 3 Copy number variation (CNV) plots calculated from DNA methylation array data. Examples of CNV plots from a pseudosarcomatous case, and 2 malignant (grade III) meningiomas. Note that while the classifier results were discordant with histologic and clinical features in Case_16 (see Table 1), the multiple chromosomal losses seen on CNV plot are in keeping with aggressive tumor biology [12, 32].

Our data now suggest that for tumors with this distinct zonation pattern and reassuring molecular features, a conservative approach should be considered, particularly after complete resection.

Our findings further support the use of DNA methylation-based analysis as a useful adjunct for predicting meningioma behavior, and for distinguishing pseudosarcomatous changes from true anaplasia. While DNA methylation-based analysis is rapidly becoming more commonplace across practice settings, its clinical utility in meningioma is only just emerging and appears to be of greatest value when integrated with other molecular findings and clinical features, particularly in cases with calibrated scores <0.9, as frequently encountered among grade II and III meningiomas presented here [23, 31]. The pseudosarcomatous cases described here provide evidence of a role for ancillary testing in meningiomas. In the absence of additional testing, when encountering this rare but distinctive constellation of findings, (i.e., having an atypical, hyperproliferative, and meningioma marker-negative cellular component restricted to the perimeter of a central region of tumor necrosis/infarction), the possibility of a reactive process rather than focal progression, should be raised. The immunohistochemical expression pattern described may be of diagnostic utility when seen in the zonal pattern observed in our cases, (though this does not exclude the possibility that meningiomas undergoing bona fide anaplastic change could lose EMA and SSTR2

expression). However, given our follow-up data, we suggest practicing pathologists who may not have access to methylation array methodology report tumors conforming to those we have described as meningiomas, with reference to our experience as indicating the pseudosarcomatous nature of such changes, in addition to reporting the grade of the background conventional meningioma. We hope the identification of additional cases with adequate follow-up will support our interpretation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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