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Clinical Study

Primary intracranial fibrosarcoma with intratumoral hemorrhage: Neuropathological diagnosis with review of the literature

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Summary

Primary intracranial sarcomas are rare tumors of mesenchymal origin in the central nervous system (CNS). Spontaneous hemorrhage, while not an uncommon presentation of brain tumors, has not been described in primary cerebral sarcoma. We report the case of a 43 year old woman presenting with spontaneous hemorrhage into a primary cerebral fibrosarcoma, and discuss this case in the context of the diagnostic criterions of these rare tumors, previous reports of intracranial sarcomas and mechanisms of intratumoral hemorrhage.

Introduction

Primary central nervous system (CNS) sarcomas are rare neoplasms accounting for only 1.5% of all intracranial tumors [1, 2]. They are aggressive tumors with a poor prognosis, thought to arise from fibroblastic elements within the brain parenchyma or its meningeal coverings [3, 4]. Spontaneous hemorrhage into brain tumors, be they primary or secondary is not an uncommon event, occurring macroscopically in 5.4% of all intracranial neoplasms [5]. Spontaneous hemorrhage as the presenting event in a primary cerebral fibrosarcoma has not previously been described. We report the case of a 43 year old woman presenting with computer axial tomography (CAT) and clinical evidence of a spontaneous intracerebral hemorrhage, which on further neuroimaging and at craniotomy proved to originate from a primary intracranial fibrosarcoma. This uncommon presentation of a rare tumor underscores the need for appropriate neuroimaging and careful inspection of the hematoma cavity in a young person presenting with spontaneous intracerebral hemorrhage.

Case report

Clinical course

This 43 old previously healthy woman presented to her referring hospital with sudden onset of dizziness, left-sided weakness and focal left leg seizures. On arrival to the neurosurgical service she was opening her eyes to painful stimuli with incomprehensible speech. She was hemiplegic on the left side, but moved her right side to command. The emergency non-enhanced CAT scan revealed a large right parieto-occipital hemorrhage (Figure 1A). Her coagulation screen was within normal limits. An urgent gadolinium enhanced magnetic resonance imaging (MRI) scan showed a focal enhancing solid mass abutting against the falx, at the medial margin of the hemorrhage (Figure 1B). An-

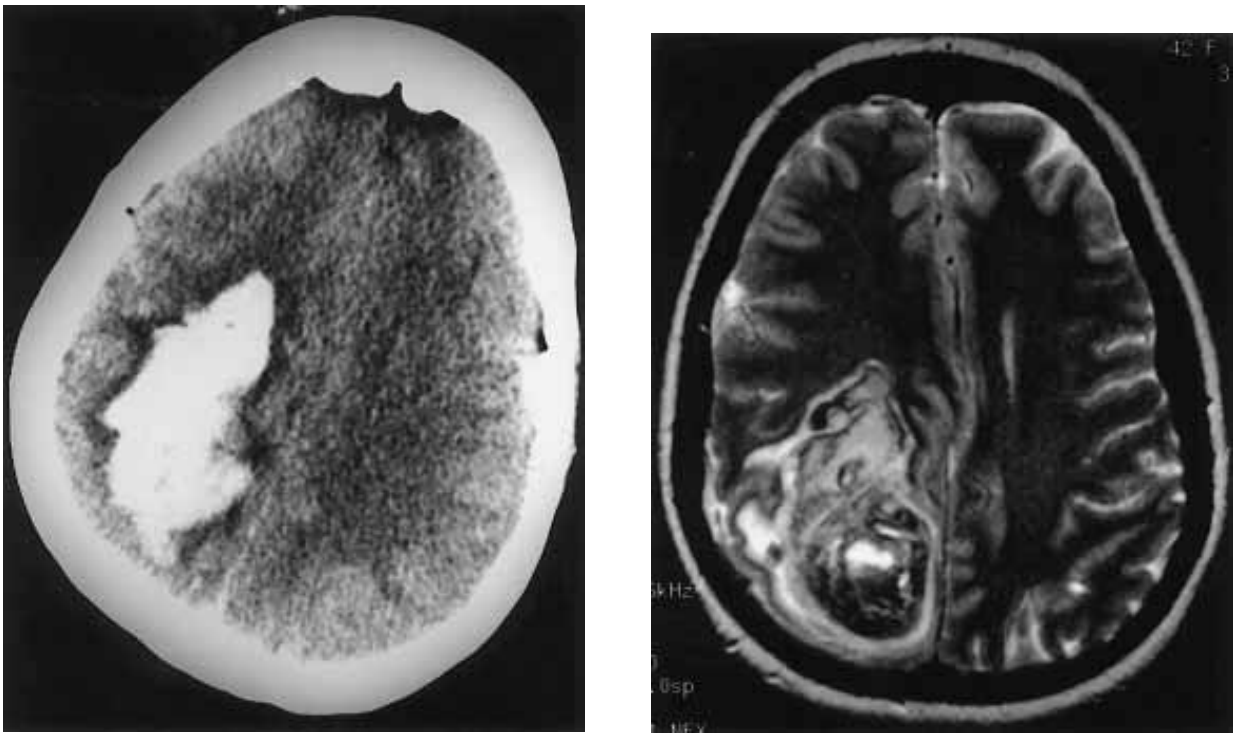

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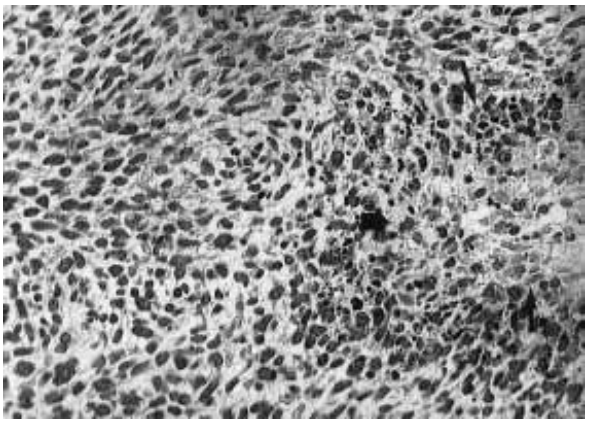
Figure 1. (A) Unenhanced axial CAT scan showing 5 × 4 cm acute intra-axial hemorrhage in the right parieto-occipital lobe. (B) Gadolinium enhanced, T2 weighted axial MRI scan showing varying signal intensities typical of an acute hemorrhagic cavity, with an associated gadolinium enhancing mass adjacent to the falx.

giography (not shown) failed to reveal any abnormal intracranial vasculature including a tumor blush, and demonstrated only mass effect from the hemorrhage.

The patient underwent emergency craniotomy, with evacuation of the intra-axial hemorrhage and associated tumor. The tumor was located at the medial aspect of the hematoma cavity arising from the brain, abutting against but not invading the falx. It was grey in colour, quite soft in consistency with a moderate amount of vascularity. Using ultrasonic aspiration a gross total resection was obtained, with minimal tumor bleeding. Post-operatively, her level of consciousness returned to normal, with power in her left arm improving to grade 3/5, but her left leg remained completely plegic. Her post-operative course was complicated by a left leg deep venous thrombosis two weeks after operation, requiring systemic anti-coagulation. She subsequently underwent a full course of external beam radiotherapy (60 Gy in 30 fractions), and is presently undergoing neuro-rehabilitation with gradual improvement of her left hemiplegia about one year after her presentation.

Neuropathological examination

Hematoxylin and eosin (H&E) sections showed a highly cellular malignant tumor, made up of sheets of spindle-shaped cells in a fascicular pattern with long oval-shaped nuclei which showed atypia and pleomorphism (Figure 2A). The highly malignant nature of the tumor was also reflected by a high mitotic rate (5 mitoses per high power field), and both single-cell and small confluent zones of tumor necrosis. The tumor had a well-demarcated border with the adjacent gliotic brain, however, there were small nests of tumor cells infiltrating along the Virchow-Robin spaces but without direct invasion of



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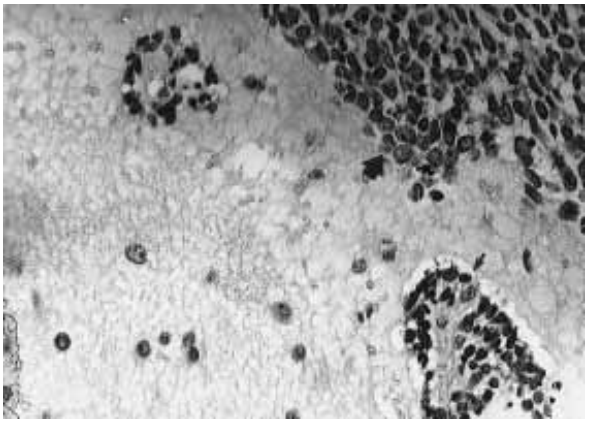

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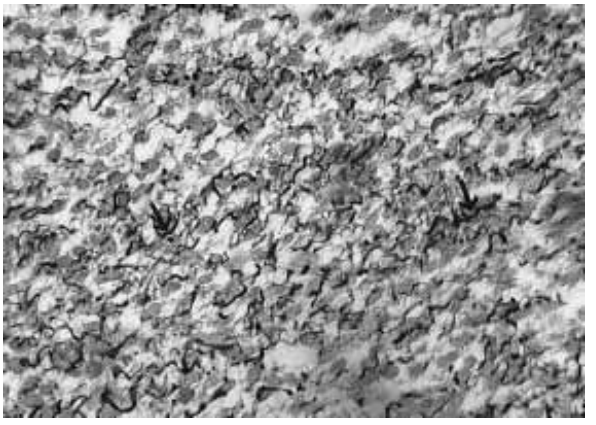

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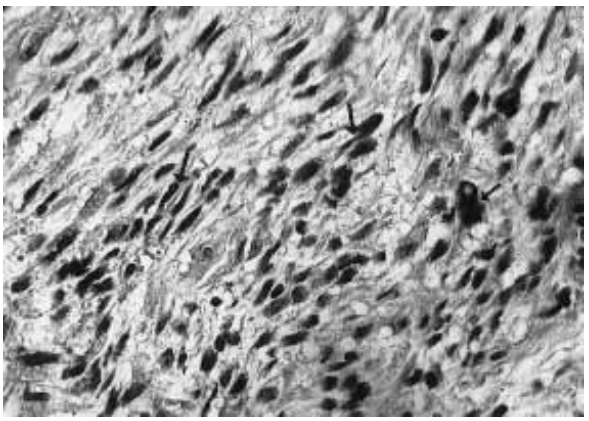
Figure 2. (A) Highly cellular tumor with spindled cells, fascicular architecture and confluent zones of tumor necrosis (arrow) (Hematoxylin + Eosin; 100 ×). (B) Tumor brain interface demonstrating the malignant spindle cells spreading along the Virchow-Robin spaces (small arrow), but not directly invading into the brain parenchyma (large arrow) (Hematoxylin + Eosin; 250 ×). (C) Reticulin stain demonstrating extensive reticulin deposition (arrowheads) around the tumor cells (Modified Gordan + Sweet Reticulin; 250 ×).

the brain parenchyma (Figure 2B). There was evidence of recent hemorrhage, but no tumor invasion into or disruption of the tumor associated vasculature. Reticulin stain revealed a network of reticulin surrounding the tumor cells (Figure 2C) with extensive areas of collagen deposition, characteristics consistent with the diagnosis of a fibrosarcoma. The mesenchymal nature of the tumor was further verified with transmission electron microscopy (not shown), which demonstrated prominent rough endoplasmic reticulum, extracellular collagen and prominent nucleoli, all supportive of the diagnosis of a fibrosarcoma. To determine whether this was a secondary or primary intracranial tumor, chest X-ray, CAT scans of the chest, abdomen and pelvis plus a bone scan was undertaken, the results of which were all negative suggesting this was a primary intracranial fibrosarcoma.

For further pathological characterization of the subtype of sarcoma, a battery of immunohistochemical studies were undertaken. The tumor cells were vimentin positive (Figure 3A), indicative of the diagnosis of fibrosarcoma. In contrast, glial fibrillary acidic protein (GFAP), S100, cytokeratin, epithelial membrane antigen (EMA), synaptophysin, neuron specific enolase, HMB-45 (a melanocytic marker), and myoglobin were all negative. Factor VIII and CD-34 staining revealed moderate tumor vascularity without any endothelial hyper-proliferation or vascular remodelling (Figure 3B). To further investigate tumor angiogenesis, the tumor sections were stained with antisera directed against the N-terminal region of human vascular endothelial growth factor/vascular permeability factor (VEGF/VPF). In many regions of the tumor, the spindle shaped tumor cells stained positively in a diffuse cytoplasmic fashion for VEGF/VPF (Figure 3C).



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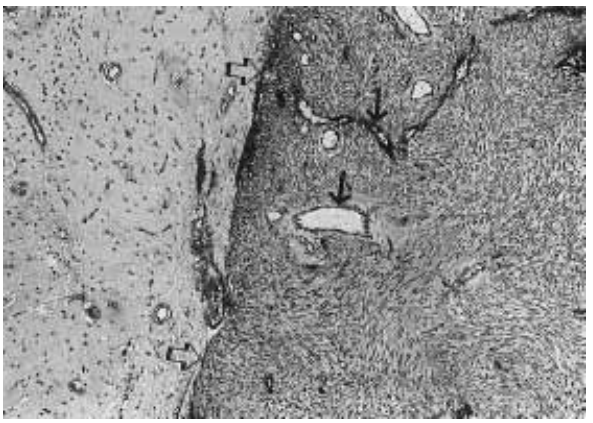

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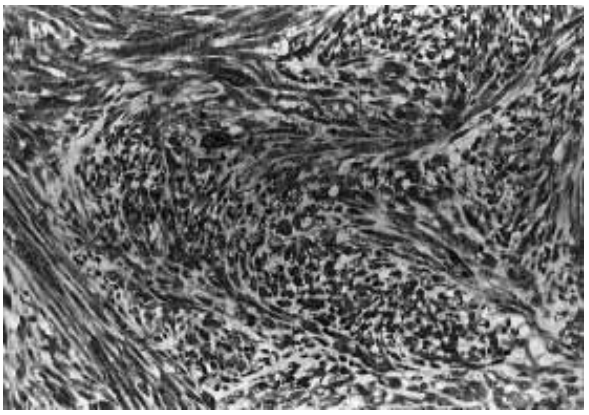

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Figure 3. (A) Immunohistochemistry with anti-sera to vimentin (arrowhead) demonstrating strong cytoplasmic positivity in the malignant tumor cells (Ab-Vimentin: DAKO; ABC method; 250 ×). (B) Factor VIII immunohistochemistry revealing a moderately dense network of intratumoral blood vessels with no endothelial hyperplasia or glomeruli. Note also the well defined border between the tumor and adjacent brain parenchyma (Ab-Factor VIII: DAKO; ABC method, 100 ×). (C) Vascular Endothelial Growth Factor/Vascular Permeability Factor (VEGF/VPF) immunohistochemistry demonstrating strong cytoplasmic immunopositivity (arrowheads) of the malignant fibrosarcoma tumor cells (Ab-VEGF; PAP method, 400 ×).

Discussion

Sarcomas account for up to 1.5% of all intracranial tumors and are more common in the younger age groups [1, 2, 6]. The specific cell of origin remains controversial in these tumors, and nosologic classification has been difficult. At least four categories of CNS sarcoma can be recognized: (1) sarcoma arising from meningeal or peri-vascular mesenchymal cells; (2) sarcomatous transformation of a pre-existing CNS tumor such as meningioma or glioblastoma multiforme (gliosarcoma); (3) radiation induced sarcomas; (4) systemic sarcoma metastatic to the CNS. In our patient, by a process of elimination including a systemic tumor survey and a battery of immunohistochemical examinations, we are left with the diagnosis of primary intracranial fibrosarcoma, corresponding to the first category listed above. Primary intracranial sarcomas are rare, arising from mesenchymal cells in the dura, leptomeninges, vascular adventitia and tela choroidea [1–3, 7, 8]. They are more commonly extra-axial tumors arising from the dura or leptomeninges, although they can arise from within the brain parenchyma such as in the present case, presumably from mesenchymal cells associated with the vascular adventitia.

The histo-pathological diagnosis of a sarcoma is based on the spindle cell nature of the tumor with elongated nucleii (Figure 2A), features that were all prominent in this case. However, prior to the diagnosis of a primary intracranial sarcoma according to the World Health Organization (WHO) classification scheme [9–11], several additional investigations should be undertaken due to its rarity. First, one must exclude metastasis from a pre-existing systemic sarcoma with appropriate imaging studies including a chest X-ray and abdominal and pelvic survey,

as was undertaken in this case. Metastasis to the CNS parenchyma is distinctly uncommon for sarcomas with the exception of the alveolar soft part sarcoma, which occurs in young adults and metastasizes to the brain in 25–30% of cases [12]. Second, sarcomatous transformation from a pre-existing CNS neoplasm such as a meningioma or a glial tumor, which is more common than *de-novo* occurrence must be excluded. In this case the tumor was negative for both EMA and GFAP, thereby helping to exclude a meningeal sarcoma and gliosarcoma respectively. Having established that this was a primary intracranial sarcoma, further pathologic subtyping of these tumors is similar for both CNS and systemic sarcomas [9–11]. The specific diagnosis of primary intracranial fibrosarcoma was indicated by the prominent vimentin positivity (Figure 3A), extensive reticulin (Figure 2C) and collagen deposition, as well as the morphologic features of spindle cells in a fascicular pattern (Figure 2A). In support of the diagnosis of fibrosarcoma, rhabdomyoblastic differentiation or presence of any other mesenchymal elements such as cartillage or bone were not present. The lack of any dural attachment in this tumor, leads us to conclude that this intra-axial tumor arose from peri-vascular mesenchymal cells of the brain. Furthermore, the high cellularity, brisk mitotic activity and areas of necrosis indicated the tumor was a high grade fibrosarcoma (Figure 2A).

The lack of strict diagnostic criteria as outlined, has led to confusion about primary intracranial sarcomas in the literature. Many older reports likely include sarcomatous transformation of meningiomas, hemangiopericytomas, gliosarcomas and also metastatic sarcomas which are impossible to differentiate based on purely pathologic examination. This diagnostic confusion supplemented by their rarity, has led to the varying clinical reports of intracranial sarcomas. For example, early reports by Christensen and Lara [7] suggested a more favourable prognosis for intracranial fibrosarcomas, with occasional long-term survivors and an average survival of 74 months. However, more recent series with stricter diagnostic criteria, indicate a more rapid progression with a mean survival of only 7.5 months despite optimal treatment [3].

The incidence of spontaneous hemorrhage into brain tumors ranges from 1% to 15%, and correlates with the histologic type of tumor [5, 13]. For example only 1.3% of meningiomas, but 5 to 10% of astrocytomas, 29% of mixed oligoastrocytomas, 50% of metastatic melanomas and 100% of choriocarcinomas developed spontaneous intra-tumoral hemorrhage [5]. A large series of 905 intracranial tumors [5] had an overall hemorrhage rate of 14.6%, of which 5.4% were macroscopic. In this series there were three sarcomas of which two developed macroscopic hemorrhage, however, details as to the diagnostic criterions used for the sarcomas were not addressed. Previous series of intracranial fibrosarcomas have all emphasized the poor prognosis and frequent development of multifocal tumors, but make no mention of hemorrhage as either a clinical or pathologic feature [3, 7, 14]. The most recent series of nine primary intracranial fibrosarcomas from a single institution, with a median survival of approximately seven months, does not mention intratumoral hemorrhage as a presenting neuroradiological or neuropathological feature [3]. The two older series, comprised of a large number of intracranial fibrosarcomas with the diagnostic uncertainty as discussed above, describes presenting symptoms characteristic of a progressively growing intracranial mass, but not a single case of an acute neurological deficit (other than seizures as the presentation of some patients) that was associated with intra-tumoral hemorrhage [7, 14]. In summary, this present case is the first fully documented report of a primary intracranial sarcoma presenting with intratumoral hemorrhage.

The mechanism of intratumoral hemorrhage is likely complex and multifactorial, involving both mechanical and biochemical factors. Proposed mechanical factors include vessel distortion due to tumor growth, disruption of friable new tumor vessels perhaps related to angiogenesis and vascular remodeling, vessel wall invasion by tumor cells and venous channel obliteration by tumor or the sequelae of increased intracranial pressure [15–17]. However, in many tumors associated with hemorrhage, such pathological changes in the tumor vascularity has not been observed. Neo-angiogenesis is a prerequisite for the growth of all solid tumors beyond approximately 10 million cells [18, 19]. Angiogene-

sis is a dynamic process resulting from the balance of angiogenic promoting and inhibitory factors [20–22]. Amongst the angiogenic growth factors VEGF/VPF is the dominant angiogenic growth factor responsible for the dynamic angiogenesis seen in malignant astrocytic tumors, with endothelial hyperproliferation leading to a higher incidence of intratumoral hemorrhage associated with the vascular instability and remodeling [23–27]. There are few studies examining the expression of VEGF/VPF in non-glial tumors and none in primary intracranial sarcomas, owing partly of course due to the rarity of the latter tumor. For example, our recent work demonstrated expression of VEGF/VPF at the RNA and protein level in most meningiomas, which correlated with tumor vascularity and peri-tumoral edema (Provias et al.). This case is the first report documenting VEGF/VPF expression by primary intracrnial fibrosarcoma (Figure 3C). However, the expression of VEGF/VPF and its role in angiogenesis and hemorrhage in primary intracranial fibrosarcomas remains unclear, since in most sarcomas including the present case neo-angiogenesis and vascular instability is not a prominent feature.

In summary, this case illustrates the diagnostic issues involved in the accurate neuropathological diagnosis of a primary intracranial sarcoma, an extremely rare tumor. Furthermore, this is the first documented case of gross intratumoral hemorrhage in this tumor, stressing the need of careful pre-operative imaging and intraoperative inspection of the hemorrhagic cavity, especially in younger patients with unexplained intracerebral hemorrhage. The biological basis of the intratumoral hemorrhage in this primary intracranial sarcoma remains uncertain, however, the tumor expressed VEGF/VPF a highly potent angiogenic factor strongly implicated in the neo-angiogenesis and intratumoral hemorrhage associated with malignant astrocytomas.

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