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Review article

Tumour stem cells in meningioma: A review

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ABSTRACT

Meningioma is a common intracranial and intraspinal neoplasm accounting for 25–30% of all primary neurological tumours. It is associated with high rates of recurrence especially in higher-grade tumours and lesions located at the skull base. Cancer stem cells are increasingly recognised as the origin of cancer and are attributed to loco-regional recurrence, metastasis and treatment resistance. This review presents the accumulating evidence of the presence of tumour stem cells within meningioma and the stem cell markers being used to characterise this putative primitive population within this common tumour.

1. Introduction

Meningioma (MG) is a common intracranial and intraspinal neoplasm accounting for 25–30% of all primary neurological tumours [1,2]. MGs are presumed to arise from the arachnoid cap cells of the brain and spinal cord, based on histological and ultrastructural similarities between arachnoid cap cells and MG cells [3]. MGs are typically attached to the dura mater [4] but may also enter the ventricular spaces via folds of arachnoid mater known as tela choroidea [5]. Arachnoid cells are thought to be of neural crest neuroectodermal origin, differentiated from pluripotent stem cells [6].

The incidence of MG is 6/100,000 with a female preponderance (8/100,000) [7]. Most MGs are asymptomatic with autopsy studies demonstrating a 2.8% incidental MG rate [7]. The majority of MGs are benign WHO grade I lesions with approximately 8% considered atypical (grade II) and 2% anaplastic/malignant (grade III) [8]. A genetic predilection for MG is seen in patients with neurofibromatosis type 2 (NF2) [7], and other risk factors include ionising radiation exposure [7].

MGs typically present with headaches, seizures and focal neurological symptoms, determined by their intracranial location. Radiological features of MG include slight hyper-attenuation on CT (Fig. 1A and B), sometimes associated with calcification and surrounding cerebral oedema with homogeneous enhancement [9,10]. MG typically appears hyper-intense on T2-weighted MRI (Fig. 2A) and iso-intense on T1-weighted sequence with homogeneous Gadolinium enhancement (Fig. 2B and C) [9,10].

Most MGs have a convexity dural base to which they are attached (Fig. 3) and derive their blood supply from meningeal arteries [11,12], with a minority being entirely intraventricular [5].

Current management of MG involves neurosurgical resection as the first-line treatment [13–15]. Up to 30% of MGs are located at the skull base, often adherent to cranial nerves, arteries of the Circle of Willis, dural venous sinuses and the brainstem [16], making complete surgical excision impossible due to the risk of neurological sequalae and vascular injury [17]. The residual disease from these MGs cause significant morbidity and requires multiple interventions [17,18]. Atypical and anaplastic MGs have reported recurrence rates of 40% and 80%, respectively [19,20]. In cases of recurrent and residual MG, further surgery is often attempted and/or radiotherapy is used, although radiotherapy resistance is not uncommon [19,21].

Unlike glioblastoma (GB) there has been limited investigation into the presence of stem cells within MG, with the first report by Hu et al. [22], who described a 62-year-old male with GB who subsequently developed an aggressive grade III MG following radiotherapy. The authors demonstrate cells within both the GB and MG that stained positively for the stem cell marker CD133.

In this report, we review the literature on tumour stem cells in MG, highlighting the putative role of tumour stem cells in the patho-aetiogenesis of MG. We also review the stem cell markers currently used to identify this primitive population.

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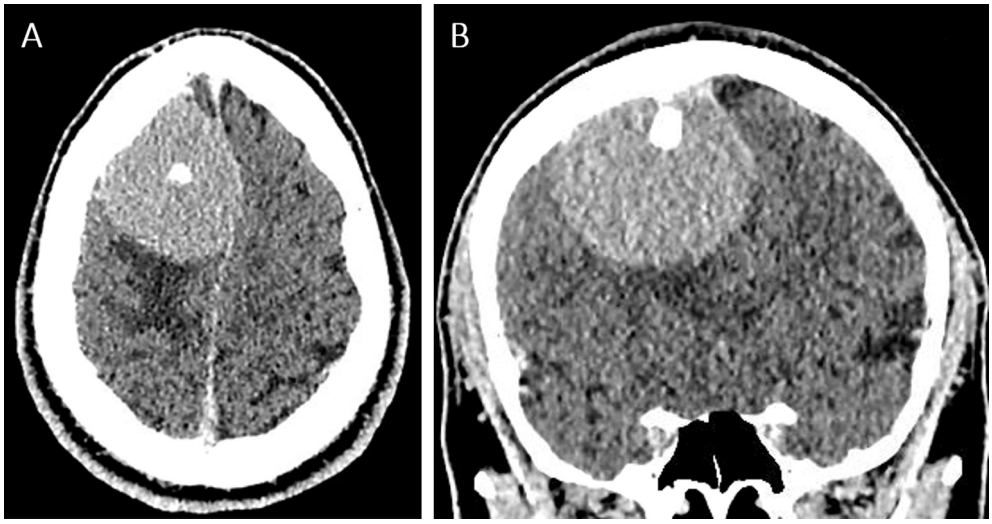

Fig. 1. Axial (A) and coronal (B) non-contrast CT scans demonstrating a right frontal meningioma with calcification and mass effect.

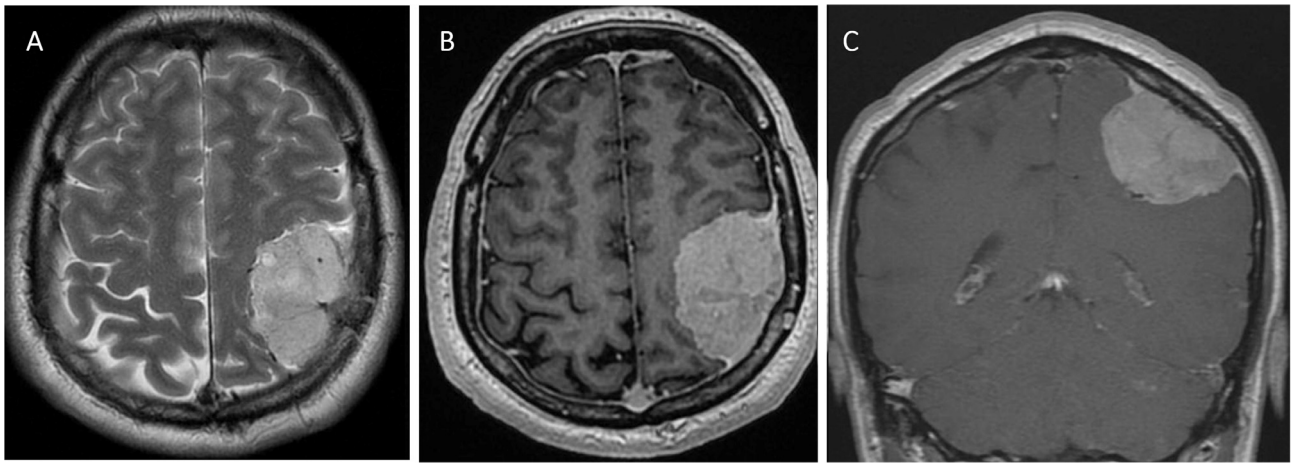

Fig. 2. Left temporal meningioma showing hyper-intensity on T2-weighted axial MRI (Fig. 2A) with homogeneous Gadolinium enhancement on axial (B) and coronal (C) T1 sequences.

2. Genetics

The most common genetic changes reported in MG relate to the loss of chromosome 22, deletion of the short arm of chromosome 1, and the loss of chromosome 14 [23,24]. A number of tumour suppressor genes have been implicated in the formation of MG including *NF2, DAL-1*, various tissue inhibitors of matrix metalloproteinases (TIMPs) and genes associated with the short arm of chromosome 9 including *CDKN2A, CDKN2B* and *p14ARF* [25,26]. The *NF2* gene on the long arm of chromosome 22 is commonly involved in the development of MG with approximately 60% of patients with sporadic MG possessing a loss of the *NF2* gene [25,27]. Bi-allelic inactivation of the *NF2* gene results in loss of the merlin protein and may be associated with NF2, which is associated with multiple MGs and schwannomas [25,28,29]. *DAL-1* which is found at chromosome 18p11.3 has been reported in 60% of sporadic MGs [30,31], and has been reported to play a role in the progression rather than initiation of MG [25,32]. TIMP and the chromosome 9 tumour suppressor genes *CDKN2A, CDKN2B* and *p14ARF* are proposed to play a crucial role due to their association with the higher grade MGs [25,33]. The chromosome 9 tumour suppressor genes have been identified in 46% of anaplastic MGs and 3% of atypical MGs [34]. Oncogenes c-Myc and STAT3 have also been implicated in the pathogenesis of MG, especially in higher-grade lesions [25,35,36]. Lastly, the Wnt signalling pathway, implicated in the development of a number of types of cancer, has also been implicated in the progression of MG especially in clinically aggressive lesions [25,37,38].

2.1. Tumour stem cells in meningioma

MGs displaying one of the following morphological characteristics: meningothelial, fibrous, microcystic, psammomatous, transitional, secretory, angiomatous, metaplastic or lymphoplasmacytic-rich, are considered grade I lesions (Fig. 4A) [39,40]. Importantly these lesions do not demonstrate any features of higher grade lesions (Fig. 4B), being more than 4 mitotic figures per 10 high-powered field, brain invasion, or three out of the five following histological features: spontaneous necrosis, prominent nucleoli, high nucleus to cytoplasm ratios, increased cellularity or patternless sheet-like growth [39,41,42].

Cancer stem cells (CSCs) have been proposed to be the origin of many types of cancer, including GB [43], oral cavity squamous cell carcinoma (OCSCC) affecting different subsites [44–46] and leukaemia [47]. The CSC concept proposes that cancer originates from a small population of CSCs, which possess the capacity for

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