HOW IS TUMOUR TISSUE MICROARCHITECTURE LINKED WITH CEREBROSPINAL FLUID SPREAD?

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Essay submitted for the consideration of the Sir Hugh Cairns Essay Prize

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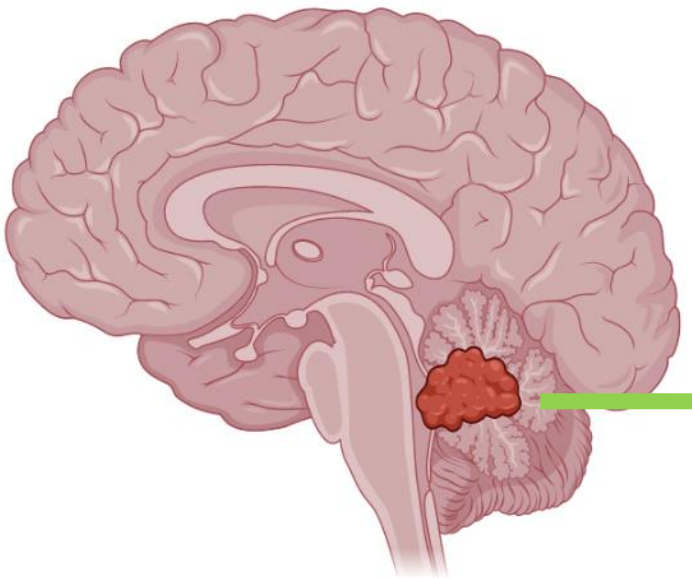
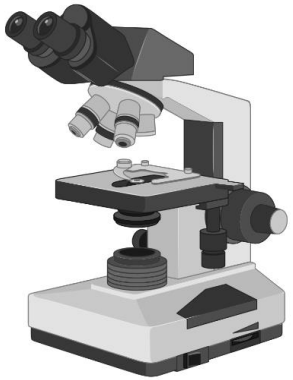
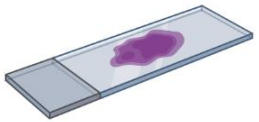
2800 words
38 references

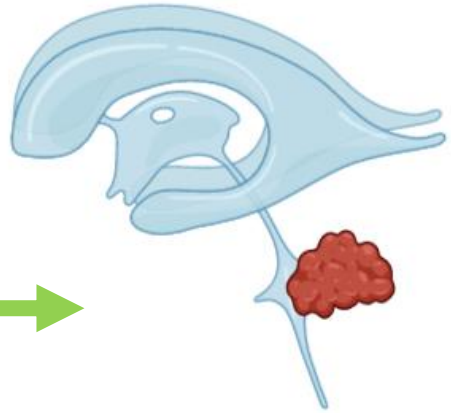






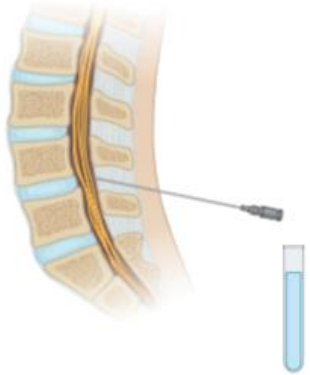
Paediatric Posterior Fossa Tumour
(e.g. Ependymoma, Medulloblastoma)

Tropism to interstitial fluid spaces
(e.g. True ependymal rosette)

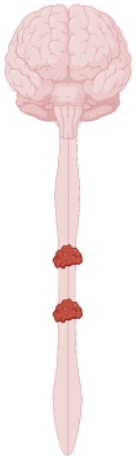


Hydrocephalus

Communicating in addition to obstructive



Tumour cells in CSF



Drop metastases

Leptomeningeal spread

Graphical abstract caption:

Rosette-like tumour cell arrangements may be related with extracellular cues in interstitial fluid which is contained in their lumens. Tumour cell affinity to interstitial fluid and resulting tropism may result in tumour cells appearing in CSF and tumour spread along CSF pathways, including drop metastases and leptomeningeal spread. The glymphatic system provides a framework for a continuum between interstitial fluid and CSF spaces and tumour cell presence in glymphatic/CSF pathways could contribute to hydrocephalus.

HOW IS TUMOUR TISSUE MICROARCHITECTURE LINKED WITH CEREBROSPINAL FLUID SPREAD?

Several brain tumours are associated with metastasis along cerebrospinal fluid (CSF) pathways. Typical manifestations include drop metastases along the neuraxis and leptomeningeal spread. Further, CSF cytological analysis may demonstrate tumour cells in some tumour types, for example in medulloblastoma and primary CNS lymphoma.

Tumours with a propensity for spread along CSF pathways include ependymoma, medulloblastoma, primary CNS lymphoma, atypical teratoid/rhabdoid tumour (AT/RT), malignant pineal region tumours and other primitive tumours. Autopsy data suggests that upwards of a quarter of patients with ependymoma have spinal metastases (Ernestus and Wilcke, 1990). Conversely, glioblastoma and astroglial tumours, oligodendroglioma, most cerebral metastatic deposits, meningioma and solitary fibrous tumours are not typically associated with spread along CSF pathways. This holds true despite close anatomical proximity to subarachnoid spaces and ventricles (e.g. glioblastoma, diffuse midline glioma).

Trends may be observed in tumour types with propensity for CSF spread and those without. Types of brain tumours associated with childhood (e.g. ependymoma and medulloblastoma) frequently spread along CSF pathways (Lin and Riva-Cambrin, 2015). In these tumours, increasing grade correlates with propensity for spread along CSF pathways. For example, drop metastases occur more frequently in grade 3 ependymomas than grade 2 ependymomas (Ernestus and Wilcke, 1990). Furthermore, medulloblastoma (grade 4, by definition) has greater CSF spread than ependymoma. Some observations and trends are hereby presented.

Firstly, the association of hydrocephalus in tumours with CSF spread is evident. Potential for CSF spread appears to correlate with hydrocephalus risk, with medulloblastoma and ependymoma associated with the highest risk as such (Lin and Riva-Cambrin, 2015). Obstructive hydrocephalus as a result of macroscopic tumour blocking CSF pathways is often found. That hydrocephalus often persists despite gross total resection (relief of macroscopic obstruction) is not readily explained (Dewan et al., 2023). The possibility of a superadded communicating hydrocephalus, in addition to obstructive hydrocephalus, in these tumours is conceivable.

The glymphatic system is a recently described system of aquaporin expressing perivascular channels which allow the flow of CSF from the subarachnoid space and brain interstitial fluid into dural sinuses and onwards. In essence, the glymphatic system allows for the conceptual framework of a continuum between CSF and interstitial fluid (Rasmussen et al., 2018). The existence of the glymphatic system has been validated through advanced MRI techniques and its physiological roles may include waste clearance, fluid/ionic homeostasis, inflammatory and immunological roles. In pathological states infiltration of glymphatic channels is found, for example in haemorrhagic and neuroinflammatory pathologies such as multiple sclerosis (Kumaria et al., 2022). While the interaction between tumour tissue and interstitial fluid/glymphatic channels remains to be fully understood, we have previously suggested that primary CNS lymphoma metastasis involves the glymphatic system, including spread along Virchow-Robin spaces (Kumaria, 2021). Cellular tropism to glymphatic perivascular spaces is supported by findings of perivascular cuffing which is found in primary CNS lymphoma (Kumaria, 2021). An affinity for CSF and interstitial fluid spaces may be associated with tumour spread along CSF pathways (Kumaria, 2021).

Indeed, a number of other tumours have been shown to infiltrate Virchow-Robin/perivascular spaces. This includes tumours that are associated with spread along CSF pathways such as medulloblastoma, ependymoma, pineoblastoma, retinoblastoma and AT/RT. Aquaporin-4, the principal regulator of CNS water homeostasis, has been linked with leptomeningeal dissemination of medulloblastoma (Pollo et al., 2014) and we believe this underscores the importance of the glymphatic system of which aquaporin-4 is an essential feature. Interestingly, the desmoplastic/nodular histological subtype of medulloblastoma has less expression of aquaporin-4 (Pollo et al., 2014) and this may contribute to the finding that this histological subtype has less leptomeningeal spread. Aquaporin-4 expression has also been documented in infratentorial ependymoma (Wang and Owler, 2011). Indeed, aquaporins including aquaporin-4 is thought to be involved in tumour cell migration and growth in human brain tumours; antagonising aquaporin activity is thought to represent an a potential therapeutic approach (Nico and Ribatti, 2011; 2012; Chen et al., 2022). Furthermore, aquaporin-4 has been linked with the development of hydrocephalus (Filippidis et al., 2012; Peng et al., 2023) and several studies report a linkage between peri-tumoral aquaporin-4 expression and hydrocephalus in humans and animals (McAllister and Miller, 2006; Saadoun et al., 2002; Saadeh et al., 2018).

However, tumours that are not typically associated with spread along CSF pathways can also infiltrate Virchow-Robin/perivascular spaces, for example malignant gliomas and central

neurocytoma. It follows that other phenomena including cellular morphology, growth patterns (including metastatic potential) and extracellular signalling (e.g. chemotactic ligands and extracellular cell adhesion molecules) may predispose tumours with recognised extension into the glymphatic space to spread along CSF pathways.

An association between tumour tissue architecture and propensity for spread along CSF pathways may be observed. Rosettes, a histological feature of several paediatric brain tumours, consist of a halo or spoke-wheel arrangement of tumour cells surrounding a central core or hub. The central hub may be empty (filled with interstitial fluid) or also contain cytoplasmic processes (Wippold and Perry, 2006). Rosette like patterns of tumour tissue architecture are in contrast to palisades or sheet-like tissue growth where tumour cells are parallel to one another. Homer Wright rosettes, found in medulloblastoma, PNET and pineoblastoma, consist of a halo of tumour cells surrounding a central hub containing neuropil (Wippold and Perry, 2006). Flexner-Wintersteiner rosettes, found in retinoblastoma, pineoblastoma and medulloepithelioma, consist of a halo of tumour cells surrounding a largely empty central hub with cytoplasmic processes projecting into the lumen (Wippold and Perry, 2006). True ependymal rosettes are found in a subset of ependymoma (especially posterior fossa ependymoma) and are characterised by a halo of tumour cells surrounding an empty tubule-like lumen (Wippold and Perry, 2006). The tubule-like lumens of true ependymal rosettes are thought to represent an attempt by the tumour to recapitulate ventricles with ependymal linings (Wippold and Perry, 2006).

For the purposes of this paper, the rosettes discussed are limited to those whose lumen consists of interstitial fluid, with or without cytoplasmic processes, i.e. Homer Wright, Flexner-Wintersteiner and true ependymal rosettes. For completeness, two further types of rosette-like structure exist. Perivascular pseudorosettes are characterised by tumour cells forming a halo around a blood vessel as opposed to a central lumen formed by the tumour itself (Wippold and Perry, 2006). A non-specific finding, perivascular pseudorosettes are found in ependymoma, medulloblastoma, PNET, central neurocytoma, less commonly in glioblastoma and monomorphous pilomyxoid astrocytoma. Lastly, pineocytomatous and neurocytic rosettes, found in pineocytoma and central neurocytoma respectively, are similar to Homer Wright rosettes but are much larger and irregular in contour; the lumen is a large fibre-rich neuropil island (Wippold and Perry, 2006). These forms of tumour tissue architecture are excluded for the purposes of this paper because they do not represent a circular arrangement of tumour cells around an interstitial fluid containing space. Additionally, pineocytoma being a grade 1 tumour does not metastasise.

The significance of rosette formation is unclear and rosettes may either be primary or secondary manifestations of tumour tissue architecture (Wippold and Perry, 2006). Primary rosettes appear as a characteristic growth pattern of a tumour type (e.g. ependymoma recapitulating CSF spaces in forming true ependymal rosettes). Secondary rosettes appear as a result of external factors influencing tumour growth (e.g. regressive cell swelling displacing neuropil towards the central lumen) (Wippold and Perry, 2006). Nonetheless, why a circular – halo-like or spoke-wheel shape – is adopted remains unclear. Furthermore, the mechanisms underlying the formation of the rosette shape are poorly understood.

Importantly, rosette formation appears to correlate with tumour dissemination in CSF. As above, grade 3 ependymomas are associated with more CSF dissemination (Ernestus and Wilcke, 1990), and lower grade ependymal tumours may have fewer ependymal rosettes. True ependymal rosettes are present in 44% of all ependymomas, but are present to a lesser extent in lower grade ependymal tumours (Kawano et al., 1998). For example, true ependymal rosettes are found in 10% of myxopapillary ependymoma (Engelhard et al., 2010), and are absent in tanycytic ependymoma (Kawano et al., 2001; Kumaria et al., 2022) and subependymoma (Prayson and Suh, 1999). Furthermore, desmoplastic/nodular medulloblastoma – the histological subtype of medulloblastoma least associated with CSF dissemination – is not typically associated with rosette formation (McManamy et al., 2007). These observations may support a correlation between tumour tissue architecture and CSF spread.

We present novel observations that may explain why rosette-like tissue architecture in brain tumours with metastatic potential may involve CSF pathways. These are presented in turn.

Firstly, in ependymoma, the interstitial fluid containing, empty appearing lumen of true ependymal rosettes has been postulated to be an attempt by tumour cells to recapitulate the formation of ventricles with ependymal linings (Friede and Pollak, 1978). True ependymal rosettes provide strong evidence of ependymal differentiation on light microscopy and can develop into elongated structures known as ependymal canals. Ependymal canals are three dimensional structures that can be visualised in different planes and aquaporin channels are likely to be associated with their formation. Ependymal cells have been described to display two cell poles – one projecting to the ventricular surface/CSF interface and the other "submesenchymal pole" projecting in the opposite direction, towards the surface of the brain (Friede and Pollak, 1978). Ependymoma cells may also

bear polarity such that recapitulated ventricular poles may form the luminal or inwards pointing aspect of true ependymal rosettes and the submesenchymal poles form the abluminal or outer aspect (Friede and Pollak, 1978). As such, the polarity of ependymal cells to CSF is recapitulated by the affinity to interstitial fluid spaces of ependymoma cells. We hypothesise that tropism to interstitial fluid/CSF may be a substrate by which tumour cells organised in a rosette-like architecture could spread along interstitial fluid and CSF pathways. This may manifest as the finding of tumour cells in CSF, hydrocephalus, and drop metastases as a result of tumour spread along CSF pathways.

In medulloblastoma, the presence of rosettes is believed to indicate neuronal differentiation according to one theory (Katsetos et al., 1988). Indeed, although medulloblastoma in general is considered a primitive tumour, variable degrees of neuronal differentiation are nearly always found on microscopic, ultrastructural and immunohistochemical levels (Katsetos et al., 1988). Markers of neuronal differentiation such as synaptophysin, neuron-specific enolase, and neurofilament protein are very commonly found in medulloblastoma (Katsetos et al., 1988). Furthermore, organelles and subcellular processes including microtubules, neurosecretory and synaptic processes reminiscent of neuroblasts (i.e. migratory immature neurons) and mature neurons may be found (Herman and Rubinstein, 1984). Experimental studies of neurogenesis have shown that the neurogenic niches in the post-natal brain contain rosette-like repeating units which are key to the formation and differentiation of new neurons (Mirzadeh et al., 2008). Further, new neurons in the post-natal brain have been shown to follow the flow of CSF (Sawamoto et al., 2006; Kaneko and Sawamoto, 2018). In the context of medulloblastoma, where tumour cells recapitulate neuroblasts and mature neurons, rosettes may promote and/or facilitate tumour cell migration along interstitial fluid/CSF pathways. As described above, this may result in the finding of tumour cells in CSF, hydrocephalus and drop metastases.

While it remains unclear why rosette-like patterns form in certain brain tumours, recent mathematical modelling studies provide insights (Boman et al., 2023). Asymmetric cell division and rotation in a centripetal pattern at a tissue level, resulting in rosette formation, has been demonstrated as such (Boman et al., 2023). We offer a further and perhaps simpler explanation. Rosettes are by definition a polarised structure – with one pole orientated towards the central lumen and the other pole orientated externally (Harding et al., 2014). As above, these have been referred to as the “ventricular” and “submesenchymal” poles of the cell respectively, with the ventricular pole demonstrating affinity for interstitial fluid in the rosette lumen (Wippold and Perry, 2006). It is conceivable that tumour cells organise themselves in rosette-like structures based on their affinity

for extracellular paracrine cues within interstitial fluid. Indeed, similar associations between rosette formation and extracellular signalling are well-recognised in developmental biology (Harding et al., 2014).

In summary, we hypothesise that rosette-like tumour cell arrangements may be related with extracellular cues in interstitial fluid which is contained in their lumens. Tumour cell affinity to interstitial fluid and resulting tropism may result in tumour cells appearing in CSF and tumour spread along CSF pathways (including drop metastases and leptomeningeal spread); the glymphatic system provides a framework for a continuum between interstitial fluid and CSF spaces. Furthermore, tumour cell presence in glymphatic/CSF pathways would contribute to hydrocephalus. Finally, in medulloblastoma we hypothesise that neuronal differentiation recapitulates neurogenesis, including rosette-like features which are found in neurogenic niches. As CSF flow is a key component of neurogenesis, medulloblastoma cells may recapitulate this phenomenon to metastasise in CSF and contribute to hydrocephalus. Further studies are indicated.

Further studies may evaluate further the associations between CNS tumours associated with rosettes and the glymphatic system. This is of particular relevance as immunotherapy has demonstrated success in malignant gliomas in adults (Liau et al., 2023) and there may be scope to increase its indications in other brain tumours. There are merits in deciphering the cell-signalling mechanisms of tumour cell tropism because blocking these may attenuate metastasis along CSF pathways. In neurogenesis, the epithelium sodium channel (ENaC) has been shown to act as a mechanosensor which regulates neural stem cells by translating CSF flow to cell proliferation and migration (Petrik et al., 2018). This channel, which can be inhibited with the drug amiloride, is expressed on malignant brain tumours including medulloblastoma (Bubien et al., 1999). Pharmacological modulation of ion channels in general (Simon et al., 2015), and amiloride in particular (Hegde et al., 2004), have shown some promise as anticancer agents in malignant brain tumours. Indeed, modulation of the glymphatic system may attenuate dissemination of tumour cells along interstitial fluid/CSF pathways.

Shortcomings of this paper include its theoretical nature. Nonetheless, it is hoped that the novel observations presented here are the starting point for future research. Caveats herein are that observations relevant to one particular tumour type (e.g. ependymoma or medulloblastoma) may not apply to all tumours. As neuro-oncology is increasingly trending towards detailed molecular profiling, it is ultimately the molecular features of a tumour (even within the same tumour subtype)

that predict its behaviour. Further, for the purposes of this paper not all rosette-like structures appearing in tumour histology have been included - conspicuously perivascular pseudorosettes and neurocytic rosettes. Neurocytic rosettes are found in tumours with low grade and therefore low metastatic potential (pineocytoma and central neurocytoma) and their lumen is a much larger, primarily neuropil containing island, as opposed to interstitial fluid. Perivascular pseudorosettes too were not included as their lumen is a blood vessel, even though they feature in tumours with CSF spread such as ependymoma and primary CNS lymphoma. To this we counter that the perivascular space is a defined glymphatic pathway, containing interstitial fluid, and that in tumours with tropism to the perivascular space (as opposed to the blood vessel) there may be affinity for spread along interstitial fluid/CSF pathways. We have previously proposed this mechanism in primary CNS lymphoma (Kumaria, 2021).

An assumption in this paper is that there is some continuum between interstitial fluid and CSF, as described by the glymphatic system. It is important to emphasise that although the glymphatic system is increasingly accepted, this is not universal (Kumaria et al., 2023). Cushing referred to CSF as the "third circulation" and the glymphatic system has been called the "fourth circulation" (Kumaria et al., 2021). Interstitial fluid and CSF are not interchangeable – in an allusion to water bodies they have been referred to as rivers and oceans respectively, albeit with significant similarities. Nonetheless, contemporary research increasingly demonstrates a role for glymphatic pathophysiology in hydrocephalus and glymphatic spread of tumour – not unlike haemorrhagic and inflammatory pathologies – remains highly plausible.

In conclusion, we believe there may be an association between rosette-like tissue microarchitecture, hydrocephalus and tumour spread along CSF pathways. Interactions between certain tumours, particularly paediatric posterior fossa tumours, and the glymphatic system require further study as there may be roles for immunological and pharmacological interventions.

Acknowledgements:
AK is supported by the Society for Research into Hydrocephalus and Spina Bifida Integra

Travelling Award.
No other conflicting interests.

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