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IMAGES IN CYTOLOGY

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Revisiting germinal matrix and ventricular lining cells in cerebrospinal fluid: Potential mimickers of intracranial malignancy

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1 | INTRODUCTION

Morphological evaluation of the cerebrospinal fluid (CSF) is integral in detecting etiological clues for infection, malignancy, and inflammation, and is critical for patient management. While the main purpose of CSF evaluation is to identify the pathological cells/microorganisms, the identification of physiological constituents (germinal matrix [GM] and ventricular lining cells [VC]) is essential, especially to distinguish them from malignant mimics.

2 | CASE 1

An infant born preterm due to placental abruption (gestational age: 25 weeks) developed respiratory distress syndrome and intraventricular hemorrhage (IVH). Magnetic resonance imaging revealed grade IV IVH and no mass lesions. CSF was grossly xanthochromic, and microscopic evaluation revealed numerous histiocytes, hemosiderin filled macrophages, and rare clusters of immature-appearing large cells. The large cells were "blast-like" with a round nucleus, delicate chromatin, inconspicuous nucleoli, high nuclear to cytoplasmic (N : C) ratio, with scant deep basophilic cytoplasm, consistent with GM cells (Figure 1A).

2.1 | Discussion

GM cells are classically described as immature, "blast-like" cells in clusters whose morphological features may pose a potential challenge by mimicking malignant cells like lymphoblasts, neuroblastoma/medulloblastoma, ependymoma, and rarely metastatic tumors.[1] GM supports the development of glial and neuronal precursors at the subependymal layer. These cells are metabolically very active and highly dependent on a rich vascular supply.. These cells are usually not identified after infancy. Lack of adequate perivascular support in preterm infants and hypoxic stress-induced angiogenesis likely increase the risk of GM hemorrhage especially in the early few days of life.[2,3] This pathophysiology helps understand the high likelihood of identifying GM cells in CSF especially in premature infants with intraventricular hemorrhage, Arnold-Chiari malformation, aqueductal-stenosis, traumatic cranial hemorrhage, and hemophilia[1,4-6] and should not be misinterpreted as malignant. For comparison, lymphoblasts also show a high N : C ratio with fine chromatin and potentially mimic GM cells. However, morphological features including occasionally prominent nucleoli, irregular nuclear contours/ nuclear folding and cytoplasmic vacuoles, and lack of clustering help distinguish lymphoblast from GM cells. Also, if needed, lymphoid lineage markers (especially CD3, and CD19) with co-expression of markers of immaturity like TdT help confirm lymphoblasts.[7] On the other hand, the limited studies evaluating the immunohistochemistry (IHC) of GM cells show positive expression of neuron-specific enolase and no reactivity to pan-leukocyte antibodies.[5]

3 | CASE 2

A 6-month-old previously healthy infant born at term via normal vaginal delivery developed an upper respiratory tract infection followed by fever, irritability, and vomiting. A comprehensive microbiology

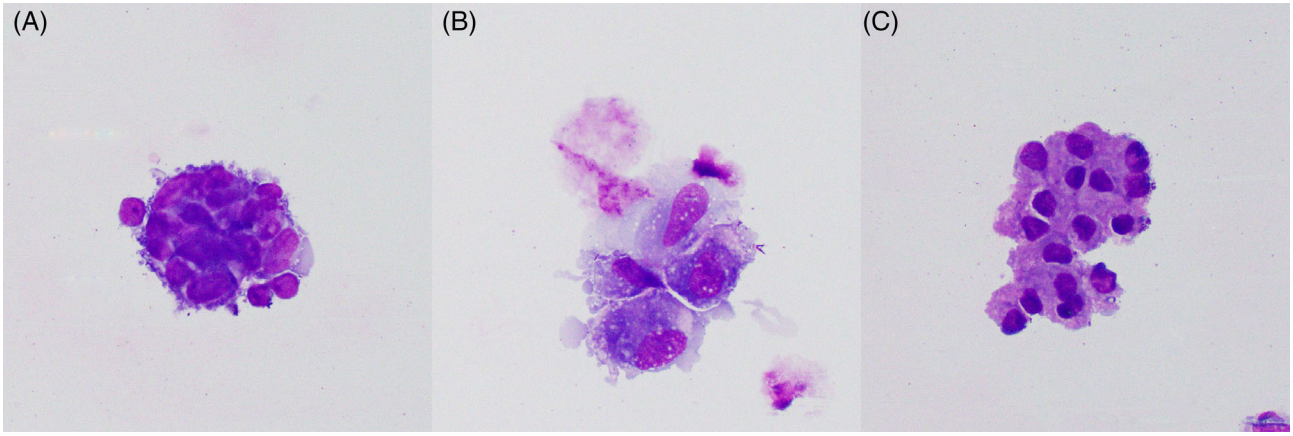

FIGURE 1 Cerebrospinal fluid (CSF) original magnification ×500; modified Wright-Giemsa stain. A, The image shows a cluster of cells with round to oval nucleus, delicate chromatin, and scant basophilic cytoplasm (germinal matrix cells). Occasional cells within the cluster show cytoplasmic projections and may represent ventricular lining cells. B, The image highlights the choroid plexus cells as a cluster of large cells with a round nucleus, and abundant basophilic granular cytoplasm with cytoplasmic projections. C, The image shows ependymal cells highlighting their bland appearance as clusters of large cells, with an eccentrically located nucleus and amorphous granular cytoplasm with not so prominent cell membranes and rough edges

workup was performed, and the patient was transferred to our facility on empiric antibiotics for critical care. Lumbar puncture and CSF evaluation performed at our institute revealed clumps of large cells and occasional mature granulocytes. These large cells in clumps showed round to oval nuclei with granular cytoplasm and indistinct cell borders. While some of the cells had amphophilic cytoplasm with occasional microvilli-like projections compatible with choroid plexus cells (Figure 1B). Other clusters showed cells with bland, eccentrically located nucleus with ruffed cytoplasm edges, compatible with ependymal cells (Figure 1C). Peripheral blood, sputum, and CSF specimens were all positive for the growth of *Escherichia coli*. The patient improved on antibiotic treatment and supportive care and was subsequently discharged in stable condition.

3.1 | Discussion

Choroid plexus and ependymal cells line the ventricles in the central nervous system (ventricular lining cells). Ventricular lining cells are commonly shed into the CSF, especially due to trauma, ventricular shunt, prematurity, hydrocephalus, recent CNS surgery, infection, and brain infarction. Ventricular lining cells present as scattered or frequently clumps of large cells with an eccentrically located round nucleus, with smooth contours, inconspicuous nucleoli, and granular amphophilic cytoplasm with indistinct borders. Microvilli-like processes are common in choroid-plexus cells. These cells may mimic other non-malignant cells, including neurons, chondrocytes, leptomeningeal cells, monocytes/macrophages, and rarely malignant nonhematopoietic cells.[1] The lack of hyperchromatic nuclei, prominent/multiple nucleoli, irregular nuclear contours, and pleomorphism are features that distinguish them from most overt malignancies.

There is also a potential overlap between these physiological cells and intracranial malignancies including medulloblastoma and ependymoma.

A 6-year-old boy presents with headache, vomiting, and ataxia and was noted to have a 5.6 cm intracranial mass in the fourth ventricle diagnosed as medulloblastoma on biopsy. CSF analysis revealed clusters of atypical cells with predominantly round nucleus with occasional indentations, speckled "dusty" chromatin, with some cells showing prominent nucleoli, and scant cytoplasm (Figure 2A) morphologically compatible with medulloblastoma. Medulloblastomas may show a spectrum of morphological features, with classic medulloblastomas at one end of the spectrum showing uniform round bland cells with syncytial arrangement potentially mimicking GM cells. Morphological features like speckled chromatin, rosette formation, and also predominantly seen in other subtypes of medulloblastomas, prominent nucleoli, hyperchromatic pleomorphic nuclei, nuclear molding, and lobular architecture, helps distinguish these from GM cells. Also, synaptophysin expression by IHC is characteristic.[8]

In another case, a 1.5-year-old boy who presents with hydrocephalus due to a 6.4-cm intracranial mass in the fourth ventricle was diagnosed as anaplastic ependymoma on surgical resection. CSF analysis revealed clusters of cells with a round nucleus, inconspicuous nucleoli, and abundant cytoplasm (Figure 2B,C) with projections. Perivascular pseudorosettes with a perivascular anuclear zone and true ependymal rosettes or tubules around a central lumen is characteristic of ependymomas and may reminisce on fluid cytology. While these cytological features may overlap with ventricular lining cells, the presence of rosetting is certainly helpful in distinction. Ependymoma is a slow-growing tumor arising from radial glial cells and is positive for glial fibrillary acidic protein (GFAP), along with cytokeratin and epithelial membrane antigen (EMA) in a subset of cases.[9,10]

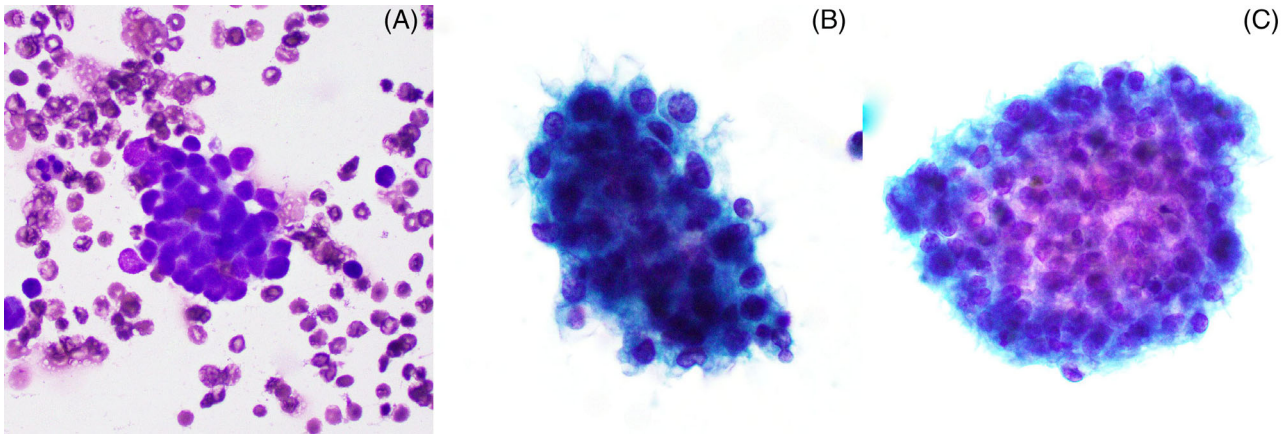

FIGURE 2 A, Image shows cerebrospinal fluid (CSF; modified Wright-Giemsa stain; original magnification ×500) with medulloblastoma showing clusters of atypical cells with "dusty/speckled chromatin," round to polygonal nucleus with some molding effect with the neighboring cells, and scant cytoplasm forming a syncytial arrangement. Focal rosetting is also appreciated. B,C, Both these images represent CSF (Papanicolaou stain; original magnification ×500) revealing an anaplastic ependymoma as clusters of atypical cells with round to occasionally irregular nuclei, inconspicuous nucleoli, and abundant cytoplasm with projections (best visualized in B). Characteristic rosetting is well appreciated (especially in C)

4 | CONCLUSION

We reviewed the cytomorphological details of GM and ventricular lining cells to highlight their distinct-benign yet potentially misleading features, especially for the education of the next generation of pathologists. While critical evaluation of cytomorphological features is indispensable, correlations with clinical presentation and if available, radiological studies significantly help in confirmation.

CONFLICT OF INTEREST

The authors have no potential conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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