Review Article

Rosettes and Pseudorosettes and Their Significance

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Abstract

Rosettes are round assemblage of cells found in tumors. They usually consist of cells in a spoke circle, a halo collection surrounding a central or a cellular lumen. Rosettes are so named for their similarity to the rose casement found in gothic cathedrals. There are clusters of different kinds of rosettes in pathology, each with different kind of cells and dissimilar names. Most of them are found in tumors of the nervous system. The detection of rosettes help in diagnosis of different tumors.

Key words: Rosettes; Tumors; Pathology

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What are rosettes?

Rosettes consist of a halo or spoken-wheel arrangement of cells surrounding a central core or hub. The central hub may consist of an empty-appearing lumen or a space filled with cytoplasmic processes. The cytoplasm of each of the cells in the rosette is often wedge-shaped with the apex directed toward the central core: the nuclei of the cells participating in the rosette are peripherally positioned and form a ring or halo around the hub. Named for the flower-like architectural ornament, this pattern resembles the rose windows found in many gothic cathedrals.1

Rosettes may be considered primary or secondary manifestations of tumor architecture. Primary rosettes form as a characteristic growth pattern of a given tumor type whereas secondary rosettes result from the influence of external factors on tumor growth. For example, in the latter instance, regressive cell swelling may centripetally displace the cytoplasm as the nucleus is squeezed to the periphery. Although the presence of primary rosettes may suggest a given diagnosis, usually this finding alone is not considered absolutely pathognomic for one specific tumor type.1

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Rosette are of two types — True rosettes and Pseudorosettes. Pseudorosettes are perivascular radial arrangement of neoplastic cells around a small blood vessel.²

True rosettes are mainly found in neuropathologic disorder and are also present in osteosarcoma, non-Hodgkin lymphoma, fibromyxoid sarcoma, medullary thyroid carcinoma, embryonal tumor with abundant neuropil and true rosettes (ETANTR), rhambdomyosarcoma, chronic cholestasis and chronic active hepatitis, tobacco rosette: complex viral disease, malaria, adenocarcinoma in colon and rectum in the Aghamiri population, hyalinizing spindle cell fused with giant rosette, endometrial stromal sarcoma with hyalinizing giant rosettes, embryonal tumor etc.³-⁶

Where the pseudorosettes occur?
Pseudorosettes are present in neuroblastoma, medulloblastoma, malignant melanoma, ependymoma, Merkel cell carcinoma, neuroendocrine tumor of skin, seborrhic keratosis, dendritic cell neurofibroma, astroblastoma, large cell neuroendocrine tumor of cervix, clear cell ependymoma of spinal cord, celiac disease, nasal tumor of olfactory origin, rosette forming glioneural tumor (RGNT), oncocytoma, Wilm’s tumor, pheochromocytoma of urinary bladder.³,⁵,⁷

Where the true rosettes occur?
True rosettes occur in neuroblastoma, medulloblastoma, malignant melanoma, ependymoma, Merkel cell carcinoma, neuroendocrine tumor of skin, seborrhic keratosis, dendritic cell neurofibroma, astroblastoma, large cell neuroendocrine tumor of cervix, clear cell ependymoma of spinal cord, celiac disease, nasal tumor of olfactory origin, rosette forming glioneural tumor (RGNT), oncocytoma, Wilm’s tumor, pheochromocytoma of urinary bladder.³,⁵,⁷

Significance of rosettes and pseudorosettes
The neuropathologic diagnosis of brain tumors entails the microscopic examination of conventional formalin-fixed paraffin-embedded tissue samples
surgically removed from a radiographically defined lesion. Pathologists rely on visual clues such as pattern recognition when examining the stained tissue with a microscope, much as radiologists rely on gray-scale patterns of densities and intensities on images. Some histologic patterns of cellular architecture are distinctive if not pathognomonic whereas others are less specific, but nevertheless considerably narrow the differential diagnosis. 8,9

The precise biologic bases for some of the observed microscopic patterns are poorly understood though their recognition remains useful nonetheless. One commonly encountered neuropathologic histologic architectural pattern seen within certain tumors is the rosette. The purpose of this report is to review the patterns of rosettes and pseudorosettes in the context of such tumors as medulloblastoma/primitive neuroectodermal tumor (PNET), retinoblastoma, ependymoma, central neurocytoma and pineocytoma. 8,9

Pathogenesis of rosettes and pseudorosettes

Loss or gain of genetic information is the main cause of rosette and pseudorosette formation. The cell populations exhibiting neuronal differentiation are believed to secrete surface glycoproteins and glycolipids which mediate cell-to-cell recognition and adhesion. One hypothesis is that these sticky cell surface markers cause the developing cell bodies to cluster or aggregate and their primitive neurites to tangle. As the cells grow, the neurite tangle remains centrally located and the cell bodies are squeezed to the periphery, thus explaining the rosette pattern.

Depending upon their location, ependymal cells may display 2 cell poles. A luminal pole projects to the ependymal lining of a ventricle and a “submesenchymal pole” projects toward the surface of the brain demonstrating glial processes and peripherally situated footplates. Frieda and Pollak conceptualize the architecture of ependymomas as a primitive neural tube turned inside out with the submesenchymal poles converging toward a central vessel, thus forming a pseudorosette rather than projecting centrifugally toward the pia. 8,10,11

Methods for diagnosis of rosettes and pseudorosettes

More advanced methods of tissue examination such as histochemical and immunohistochemical profiling, genetic analysis, and electron microscopy have been developed, the microscopic review of H&E-stained material remains a critical component of tumor diagnosis. Immunohistochemical evidence of neuronal differentiation is found in nearly all cases with neuronal markers such as synaptophysin, neuron-specific enolase, and neurofilament protein.

Some medulloblastomas may also display other forms of differentiation as demonstrated by the presence of the astrocytic marker glial fibrillary acidic protein. Skeletal muscle and melanocytic differentiation are considerably less common and define the medulomyoblastoma and melanotic medulloblastoma variants, respectively. 4,8
Types of different important rosettes and pseudorosettes with diagrammatic and histopathological pictures

A. True rosettes

a) True ependymal rosettes

The empty-appearing lumen of the true ependymal rosette resembles a tubule lumen and contains no fiber-rich neuropil or central cytoplasmic projections. These tubule-like structures, as well as more elongated versions known as ependymal canals, may represent an attempt by the tumor cells to recapitulate the formation of ventricles with ependymal linings. This rosette provides strong evidence of ependymal differentiation at the light microscopic level.1,3

b) Flexner Wintersteiner rosettes

Simon Flexner (1863–1946) noted that the cell clusters resembled rods and cones. Several years later, in 1897, Austrian ophthalmologist Hugo Wintersteiner (1865–1946) agreed with Flexner’s observations. These cellular aggregates were termed rosettes and were subsequently recognized as important features of retinoblastomas. The tumor cells that form the Flexner-Wintersteiner rosette circumscribe a central lumen that contains small cytoplasmic extensions of the encircling cells; however, unlike the center of the Homer Wright rosette, the central lumen does not contain the fiber-rich neuropil.1,11,12

B. Pseudorosettes

a) Homer Wright rosette

The Homer Wright rosette is named for James Homer Wright (1869–1928), the first director of the Massachusetts General Hospital Pathology Laboratory and developer of the Wright stain. He recognized a group of adrenal and sympathetic nervous system tumors, which became known as neuroblastomas, and described within these lesions characteristic ball-like arrangements of cells that enclosed meshworks of fibers. These fibers did not stain like those associated with neuroglia, and he postulated that they represented primitive neuronal processes resembling those in the developing sympathetic nervous system.
The typical Homer Wright rosette with its central lumen or hub filled with fiber-like processes can also be found in medulloblastomas and histologically similar tumors occurring outside the cerebellum, designated PNETs. The delicate fibrillary material found within the central lumen of the Homer Wright rosette is composed of neuropil, which contains primitive neuronal processes or neurites.

b) Perivascular pseudorosette

Another type of rosette is the perivascular pseudorosette. In this pattern, a spoke-wheel arrangement of cells with tapered cellular processes radiates around a wall of a centrally placed vessel. The modifier “pseudo” differentiates this pattern from the Homer Wright and Flexner-Wintersteiner rosettes, perhaps because the central structure is not actually formed by the tumor itself, but instead represents a native, non-neoplastic element. Also, some early investigators argued about the definition of a central lumen, choosing “pseudo” to indicate that the hub was not a true lumen but contained structures.

Nevertheless, this pattern remains extremely diagnostically useful and the modifier unnecessarily leads to confusion. Perivascular pseudorosettes are encountered in most ependymomas regardless of grade or variant.

As such, they are significantly more sensitive for the diagnosis of ependymomas than true ependymal rosettes. Unfortunately, perivascular pseudorosettes are also less specific in that they are also encountered in medulloblastomas, PNETs, central neurocytomas, and less often in glioblastomas, and a rare pediatric tumor, monomorphous pilomyxoid astrocytomas.1,3

c) Pineocytomatous and neurocytic rosettes

Histologic features of these two tumors are virtually identical, including their tendency to form neuropil-rich rosettes, referred to as pineocytomatous rosettes in pineocytomas and neurocytic rosettes in central neurocytoma. Both are quite similar to the Homer Wright rosette, but they are generally larger and more irregular in contour. The cells of the pineocytomatous and neurocytic rosettes are also considered to be much more differentiated than the cells forming Homer Wright rosettes in that the nuclei are slightly larger,
more rounded, much less mitotically active, and paler or less hyperchromatic. In rare cases, these rosettes may aggregate in a sheet of back-to-back clusters resembling field stone pavement.1,5,7

Conclusion

In summary, rosettes and pseudorosettes represent a histologic architectural pattern seen within specific nervous system tumors. The rosette pattern consists of a halo or spoke-wheel arrangement of cells surrounding a central core or hub which may be empty or contain fibers, cytoplasmic processes, or a blood vessel. Although the significance of the presence of rosettes is not always understood, most authorities agree that they represent various forms of tumor differentiation. The presence of rosettes is rarely if ever pathognomonic of a specific tumor, though identification of rosettes is often helpful in the histologic diagnosis of medulloblastoma/PNET, retinoblastoma, ependymoma, central neurocytoma, and pineocytoma.

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