Central Neurocytoma: Experience at King Abdulaziz University Hospital Jeddah Saudi Arabia

Shabnum Sultana, Awatif A. Jamal., Dahlia S. Mirdad, Fahad A. Alghamdi

Department of Pathology, Faculty of Medicine, King Abdulaziz University and Hospital, Jeddah, Saudi Arabia
shabnumsultana@yahoo.com

Abstract: Introduction: Central neurocytomas (CNs) are rare neuroectodermal brain tumours with consistent commitment for neuronal differentiation and a potential for additional glial differentiation and that have an origin from bipotential progenitor cells of the periventricular matrix. The overall incidence of CNs is 0.25 to 0.5%. These supratentorial tumours typically found in the lateral or third ventricle and can be detected in young and middle age adults with no sex predilection. **Objectives:** To study the clinical and pathological features of Central neurocytomas in our region and compare the results with the reported literature. **Methods:** We retrospectively studied 5 patients with histological diagnosis of Central neurocytomas at King Abdulaziz University Hospital Jeddah, Kingdom of Saudi Arabia in a period of 18 years. Clinical and pre operative imaging data was obtained from computerized medical records of the patients. Histopathological material was obtained by craniotomy. Haematoxylin and Eosin (H&E) stained slides were examined through light microscope. Data was analysed for age distribution, location, radiological appearance and pathological features. **Results:** Of the 5 patients analysed, 4 were males 1 was female with ages ranging between 23 and 43 years. On pre operative CT scan and MRI, the predominant location of CNs was intraventricular region in 4 out of 5 cases. The tumour showed variable enhancement and appeared as partly cystic with areas of calcification. In all 5 cases, there was evidence of hydrocephalus. Light microscopy revealed characteristic features of neurocytomas with intraventricular location and atypical features with extra-ventricular location that recurred 3 times in the period of seven years. Immunohistochemical studies revealed consistent and uniform expression of synaptophysin in all five cases and negative expression of glial fibrillary acidic protein. **Conclusion:** CNs are rare brain tumours. Although CNs are considered as benign intraventricular tumours but atypical morphological features, high cell proliferation and extra ventricular location has some correlation with recurrence.

[Shabnum Sultana, Awatif A. Jamal, Dahlia S. Mirdad, Fahad A. Alghamdi. **Central Neurocytoma: Experience at King Abdulaziz University Hospital Jeddah Saudi Arabia.** *J Am Sci* 2014;10(3):109-115]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 14

Key Words: Neuroectodermal, neuronal, supratentorial, intraventriculal tumour.

1. Introduction:

Central neurocytomas (CNs) are rare brain tumors with neuronal differentiation. These tumors (CNs) were first described with typical immunohistochemical profile and ultrastructural features of neuronal differentiation by Hassan *et al.* in 1982[1] who reported two cases of central neurocytomas as distinct pathological entity. This report resulted in enhanced recognition of CNs and increased reporting of cases and series of neurocytomas[2-4]. Central neurocytomats are neuroectodermal tumors with consistent commitment for neuronal differentiation and a potential for additional glial differentiation and that have an origin from bipotential progenitor cells of the periventricular matrix [5, 6].

These supratentorial tumors comprising only 0.25-0.5% 0f brain tumors[3], and mainly occur in young or middle aged adults with no sex predilection[2,5-9].The mean age at presentation is 29 years, with an age range from 8 days to 87 years[10].

Central neurocytomas are classically considered as benign intraventricular tumors(3,5,7), with a broad based attachment to the superolateral wall of the ventricle. They are typically found in the lateral or third ventricle, attached to the septum pellucidum or near the foramen of Monro(4,8,10). Tumors with similar macro and microscopic features occasionally been identified in the brain parenchyma and spinal cord and are referred to as extra-ventricular neurocytoma(9,11,12,). Patients with CNs typically present signs and symptoms of increased intracranial pressure secondary to obstructive Hydrocephalus, Visual disturbances and impaired cognitive function may also be present(2, 13).On imaging CNs show heterogeneous enhancement with variable calcification and cystic changes(14).

The clinical course of neurocytomas was initially believed to be benign, more aggressive behavior including disease recurrence, tumor progression, malignant transformation, and craniospinal dissemination has been described with the atypical neurocytomas[15 - 18].

The objective of this study is to review the diagnosed cases of central neurocytoma in our

institute and compare the clinical, radiological and pathological features with the literature.

2. Material and Methods

A retrospective study identified 5 patients with histological diagnosis of Central Neurocytoma among 267 primary brain tumors diagnosed between Jan1995 to Dec 2013. Data of all primary brain tumors specimen was collected through a computerized search of the Anatomical Pathology archives at King Abdulaziz University Hospital Jeddah, Kingdom of Saudi Arabia. The data was filtered using appropriate morphology, The Systematized Nomenclature of Medicine (SNOWMED) codes indicating following parameters:

a) Date of receiving biopsy
b) Personal Identity (MR number, Age, Sex etc)
c) Clinical diagnosis
d) Morphology
e) Topography

Computerized search was then exported to Microsoft Excel format and used for analysis. Initially we collected all cases of primary brain tumors and then selected the target group which had a confirmatory histological diagnosis of central neurocytoma. The data was rechecked manually to delete the duplications.

Data regarding the age, sex, clinical presentation and radiological reports were obtained from patient records. Material for histopathological examination was obtained through craniotomy which was examined grossly for measurements, color and consistency. Material for histopathological examination was first routinely fixed in 10% formalin, embedded in paraffin and then 5 micron sections were prepared and stained with hematoxyllin and eosin (H &E). All the cases were examined through light microscope to identify the growth pattern of tumor cells, the type of different components of the tumor, morphology of tumor cells (size, shape, nuclear contour and chromatin pattern), mitosis, presence of pseudo rosettes, and ganglion like cells, endothelial proliferation, necrosis and calcification. The presence of mitotic figures was assessed by counting at least 20 randomly chosen high-power fields (approximate area per field, 0.1 mm^2) or, for sections with less than 2 mm^2 of tumor, on the whole section. The presence of pseudo rosettes, ganglion-like cells, endothelial proliferation, and necrosis were assessed on all available material.

Based on light microscopic examination, representative sections were selected for immunohistochemistry (avidin-biotin peroxides method) for synaptophysin and glial fibrillary acidic protein (GFAP). Immunohistochemical staining using an automated stainer with the avidin-biotin-peroxidase complex method was performed using the antibodies.

Data analysis

The evaluation of each case was based on the number of patients with available data. Data were expressed as mean (range) or percentage as appropriate.

3. Results

Clinical findings

There were four male and one female patient in the study group (Table 1). The age of patients at diagnosis ranged from 24 to 43 years. In 4 cases, the tumor was located in the classic location intraventricular (lateral ventricles) and in the fifth case it had an extravenricular location (frontal lobe). All patients presented with signs and symptoms of increased intracranial pressure. All 5 cases shared common presenting clinical features of headaches, nausea, vomiting, dizziness, and visual disturbances. Case number 5, which had an extraventricular location of the tumor, had multiple recurrences with different interval time in the period of seven years, but with similar clinical presentation each time. The Clinical data is summarized in Table1.

Radiological findings

All patients underwent Computerized tomography (CT) and Magnetic Resonance Imaging (MRI) studies. All ventricular tumors were closely related to the septum pellucidum. In the first case the tumor was located in the left lateral ventricle and had a wide-based attachment to the displaced septum pellucidum. In the second case the tumor involved both lateral ventricles and caused symmetrical growth around the septum pellucidum. In the third case the tumor was within the right lateral ventricle body and frontal horn with extension to the region of the upper portion of the third ventricle with associated dilatation of lateral and third ventricles. In the fourth case, the tumor was located in left lateral ventricle extending into the left frontal horn. The fifth case, the tumor had an extra ventricular location in the right frontal lobe (Table 1).

The CT scan and the MRI identified the changes occurring in this tumor, the CT scan of four patients's revealed well defined lesions with mixed density, flecks of calcification and moderate enhancement with contrast, while on MRI imaging, the tumors showed variable enhancement and appeared as partly cystic lesions with areas of calcification in all cases. In all these cases, there was evidence of hydrocephalus.

Table 1: Clinical data of 5 cases of central neurocytoma.

Case No.	Age(y)Sex	Location	CT/MRI	Surgery
1	42 M	Left lateral ventricle	Enhancing mass with calcification	craniotomy
2	24 F	Both lateral ventricles	Enhancing masses with peripheral cystic changes	craniotomy
3	39 M	Right lateral ventricle body and frontal horn	Marked heterogeneous enhancement, large well-defined mixed signal intensity lesion partly solid and partly cystic,	craniotomy
4	36 M	Left lateral ventricle extending into the left frontal horn	Heterogeneously enhancing, large cystic and enhancing solid component	craniotomy
5	43 M	Frontal lobe	Heterogeneously enhancing cystic mass with calcification	craniotomy

Pathological findings and Immunohistochemistry

Macroscopically, in all five cases, the tumor masses were mainly irregular grayish white to grayish brown fragments with soft to firm consistency. On light microscopy the tumors expressed essentially the characteristic features of neurocytomas in 4 cases (Figure1); sheets of monotonously small-to-medium–sized neoplastic cells with uniform round-to-oval nuclei and inconspicuous nucleoli. The chromatin pattern was regularly distributed and finely granular (salt and pepper). The cytoplasm was clear or eosinophilic with an indistinct border. These tumor cells were embedded in alternating smaller acellular zones of neuropilic matrix. A branching pattern of thin walled capillaries was seen within the tumor in all cases similar to that seen in oligodendrogliomas. All the cases showed areas with perinuclear clearing which imparted a "fried egg appearance" similar to what is observed in oligodendroglial neoplasms. Mitotic figures were rare in case 1 to 4 and there were no areas of necrosis or vascular endothelial proliferation in these four cases, however, calcification was observed. Case 5, the extra-ventricular neurocytoma exhibited nuclear atypia with increased mitotic activity (4 mitosis/10High power fields), endothelial proliferation and coagulative necrosis without tumor cellular pallisading (Figure 2). Ganglion cell differentiation was not observed in any of the cases. The Pathological data is summarized in table 2.

Table 2: Pathological data of 5 cases of central neurocytoma.

Histopathology							
Case No.	Cell morphology	Growth pattern	Peri-nuclear halos	Endothelial proliferation	Necrosis	Mitosis(/10 High power fields)	Calcification
1	Monomorphous Small round to oval	Diffuse	absent	absent	-	0-1	+
2	Monomorphous	Diffuse	absent	absent	-	0-1	-
3	Monomorphous Small round to oval	Diffuse	absent	absent	-	0-1	+
4	Monomorphous Small round to oval	Diffuse	absent	absent	-	0-1	+
5	Atypical nuclear features	Diffuse	Present	Present	+(coagulative)	4	+

Immunohistochemical studies revealed consistent and uniform expression of the neuronal marker proteins with strong positive staining pattern for synaptophysin (Figure3) in all five cases and negative expression of glial fibrillary acidic protein. The proliferative monoclonal antibody Ki-67 was used to stain the tumor in case 5 and it showed high cell proliferation rate (Figure 4). Immno-histochemical results are summarized in Table 3.

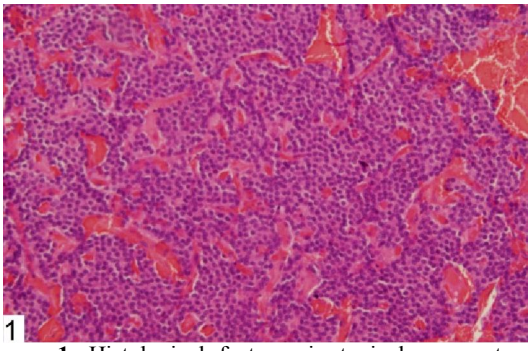

Figure 1. Histological features in typical neurocytoma**:** Densely packed small, monomorphous cells embedded in delicate fibrillary matrix and plexiform capillary arcade.

Table 3: Immunohistochemical results of 5 cases of central neurocytoma

Immunohistochemistry		
Case No.	**Synaptophysin**	**Glial acidic fibrillary protein (GAFP)**
1	+	-
2	+	-
3	+	-
4	+	-
5	+	-

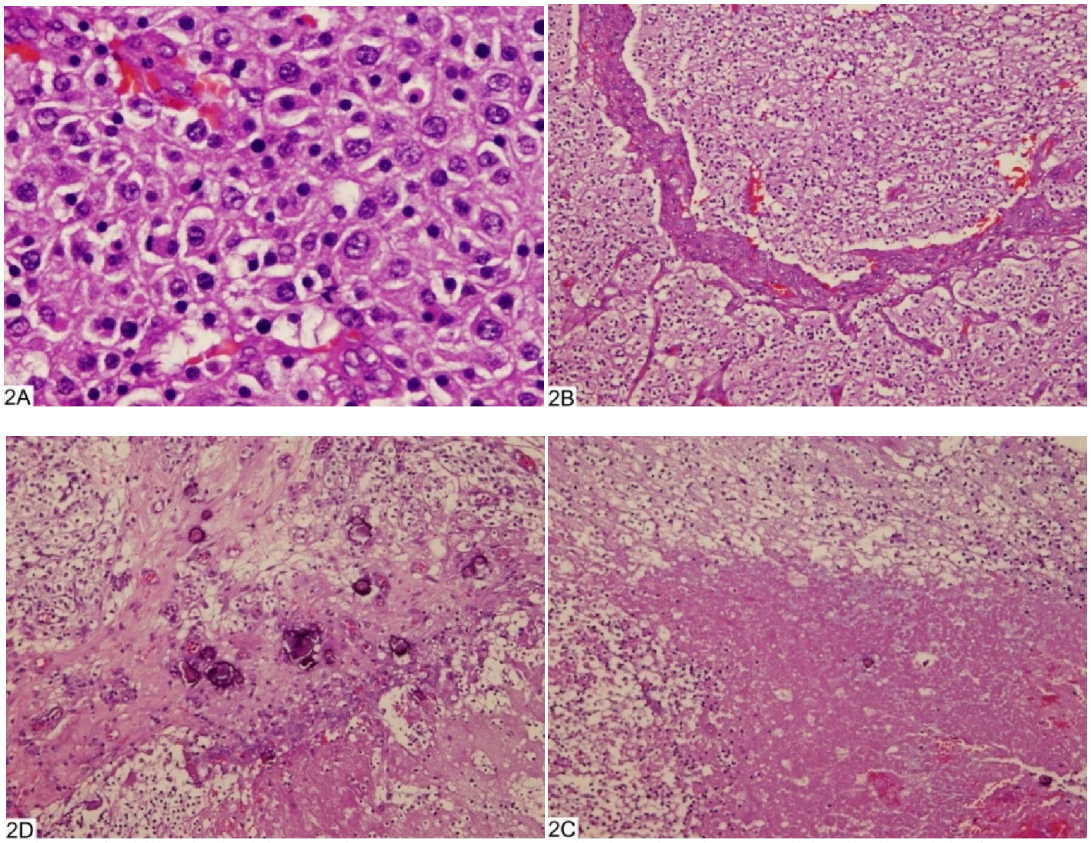

Figure 2. The atypical histological features in neurocytoma. **A: a**typical nuclear features with mitotic activity in neurocytoma. **B:** endothelial cells proliferation in neurocytoma. **C:** necrosis in neurocytoma. **D:** neurocytoma with focal microcalcification.

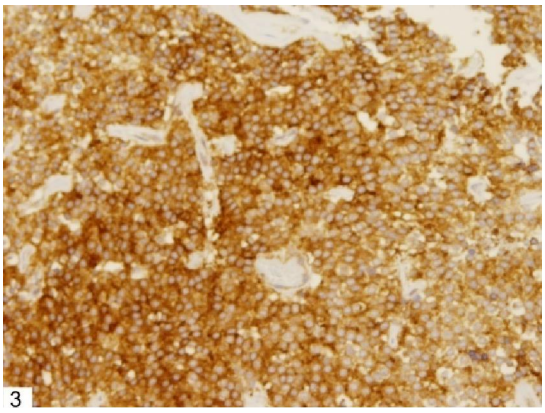

Figure 3: Tumour cells consistently express synaptophysin

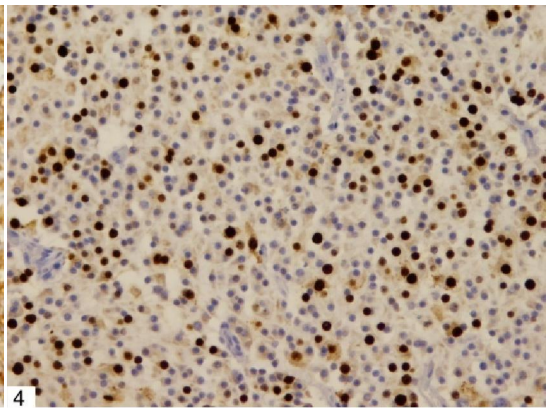

Figure 4: Strong immunostaining of tumour cells for KI-67.

4. Discussion

Neurocytomas constitute nearly one half of supratentorial intraventricular tumors in adults but amount to less than 1% of all tumors of the central nervous system and its coverings[7,19]. Other studies claim an incidence of 0.25-0.5 %[3]. Despite the increased recognition of central neurocytomas, they remain rare neoplasms of the central nervous system that require and dictate a careful evaluation. A number of studies of central neurocytomas in the literature represent case reports or small retrospective series, often of patients with previous diagnosis of intraventricular oligodendrogliomas, ependymomas, or menengiomas who underwent re-evaluation in the light of the diagnostic criteria for central neurocytomas[6,17] Seven cases of central neurocytomas were reported in a 15 –year survey in Kuwait [18, 20]

These tumors are mainly found within the ventricular system (third and lateral) in close relationship with the septum pellucidum and formen of Monro. They do not usually occur in the occipital or temporal horns. Other less common sites of location are in the corpus callosum, in the fornix, in the basal ganglia and within the brain parenchyma [9, 11, 21]. Intracerebral central neurocetomas has been reported in all four lobes [16]. Recently, neurocytoma of the cerebellum has been reported [22]. In the present study we encountered the tumor in the classical location of the lateral ventricles in four cases and in the frontal lobe in the fifth case which is in agreement with what was reported in the literature.

Most reports delineate the prominence of central neurocytomas in the young adults age group without predilection for either sex, and emphasize that intraventricular neurocytoma should be considered in any young patient with symptoms of raised intracranial pressure with radiological evidence of an intraventricular lesion[4, 10, 13, 18], a notion supported also by the present study.

The common presenting symptoms in our patients were headache associated with nausea, vomiting, and visual problems. Chien *et al.* [23] analyzed presenting symptomsof 27 patients with central neurocytoma. Ninety-three percent (25/27) of patients had headache, 37 % (10/27) had visual problems, and 30 % (8/27) had nausea and vomiting. These symptoms are mainly due to raised intracranial pressure which is related to the hydrocephalus [2].

The CT and MRI imaging of the study were consistent with the literature reports, neurocytomas appeared as heterogeneously enhancing masses. This due to the calcification and cystic degeneration [14], approximately 50% of central neurocytomas demonstrate calcification on CT [2, 5,13].

The era prior the characterization of neurocytoma by neuronal immunohistochemical markers and by ultra structural studies, neurocytomas were diagnosed as an *intraventricular oligodendroglioma* or an *ependymoma of the foramen of Monro*. This was due to the artificial characteristic perinuclear halo that give a" fried egg appearance" to the neoplastic cells creating a remarkable resemblance to oligodendrogliomas[13,22,23,]. The present study is contributing another small series (5 cases) to the literature reflecting the rarity of this tumor, but confirming the similar histological features and neuronal differentiation by immunohitochemistry. Al the five cases revealed fried egg appearance and had fine capillary network with no tendency to form pseudo- rosettes and or ganglion cells differentiation. Neuronal differentiation confirmed by the positive neuronal marker synaptophysin[5] which is the most reliable immunohistological marker for central neurocytomas (Figure 1E).

The correlation of central neurocytomas histology with their biological behavior is not clear from the published reports [13]. Although neurocytomas were initially believed to be benign

tumor, approximately 25% of the central neurocytomas are more aggressive [3, 10, 18] and have an MIB-1 labeling index > 2% or atypical histological features such as variable degree of mitotic activity, vascular endothelial proliferation and tumor necrosis: these features qualify these types of neurocytomas as atypical neurocytoma[24, 25]. The atypical neruocytoma, case 5, in this study was extra ventricular in location and exhibited endothelial proliferation, coagulative necrosis, pleomorphism with increased mitosis (Figure 2). This case had multiple recurrences with different interval time in the period of seven years with similar pathological features, supporting the notion that atypical histological features and high cell proliferation rates correlate with clinical behavior and recurrence [26-29].

Conclusion:

The results of our study are concordant to the literature. Central neurocytomas are rare tumors as only 5 cases were diagnosed in a period of 18 years. Although neurocytomas are considered as benign intraventricular tumor but atypical morphological features, high cell proliferation and extra ventricular location has some correlation with recurrence. This is a single institutional study; however further multi-institutional studies are required to pursue the biological behavior of this disease.

Correspondence:
Dr Shabnum Sultana,
Lecturer and Specialist Pathologist
King Abdulaziz University Hospital, Pathology Department, Room B/5165
P.O. Box 80215, Saudi Arabia, Jeddah, 21589
E-mail: shabnumsultana@yahoo.com

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