Özgün Klinik Araştırma

Anaplastic Ganglioglioma: Is it a Sign of Better Prognosis?

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✔ **Aim:** Anaplastic ganglioglioma is a rarely seen, high grade malignant glial neoplasm comprising of neoplastic ganglion cells Since gangliogliomas with an anaplastic astrocytic component are reportedly not always clinically aggressive, the significance of these tumors remains uncertain. In this retrospective study 30 consecutive high grade glioma cases within a period of seven years have been re-examined to detect if there were any cases of anaplastic gangliogliomas. The primary goals were to determine overlooked anaplastic ganglioglioma cases, to examine the immunohistochemical staining characteristics and find out if there were any prognostic significance of these cases differing from high grade glial tumors.
Materials and Methods: In this study, 30 documented cases -between 1995 and 2002- with a diagnosis of high grade glial tumor in the Department of Pathology, İnönü University School of Medicine, were reviewed and re-evaluated by immunohistochemical means (glial fibrillary acidic protein -GFAP-, neurofilament, neuron specific enolase -NSE-, and chromogranin A) in order to sort out the anaplastic ganglioglioma cases.
Results: All cases revealed positive staining for GFAP in the glial component. Twenty-two cases revealed positivity for neurofilament, 26 cases were positive for NSE and 22 cases were immunoreactive for chromogranin A in the neuronal component.
In the retrospective analysis of the cases, two of them were rediagnosed as anaplastic ganglioglioma. Both cases were positive for GFAP. Immunohistochemical examinations performed retrospectively including NSE, neurofilament and chromogranin A revealed cells forming tight clusters or discordant arrangement in addition to binuclear, multinuclear and atypical ganglion cells.
Conclusion: Anaplastic gangliogliomas are tumors which can easily be misdiagnosed as high grade glial tumors. In our series, the locations of the tumors were pertinent with the literature. Clinically no patients had an epilepsy history, and one patient with a good follow-up had a longer median survival than the accustomed shorter survival period in high grade glial tumors. It is concluded that anaplastic gangliogliomas might have a better prognosis than high grade glial tumors.

Key words: Anaplastic ganglioglioma, ganglioglioma, immunohistochemistry, prognosis

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Anaplastik Ganglioglioma: Daha İyi Prognoz İşareti mi?

✔ **Amaç:** Anaplastik ganglioglioma, neoplastik ganglion hücreleri ile birlikte yüksek dereceli bir glial tümör içeren nadir sıklıkta habis bir süreçtir. Anaplastik astrositik komponent içeren gangliogliomların her zaman klinik olarak hızlı seyirli olmamaları nedeni ile bu tümörlerin prognostik önemi hala belirsizdir. Bu çalışmada yedi yılı kapsayan bir sürede yüksek dereceli glial tümör tanısı alan 30 olgu, anaplastik gangliogliom olgularının ayırt edilmesi amacıyla immunhistokimyasal yöntemlerle yeniden gözden geçirilip değerlendirilmiştir. Bu çalışmadaki amaç gözden kaçan anaplastik gangliogliomları saptamak, tümörün immunhistokimyasal özellklerini incelemek ve bu vakalarda yüksek dereceli glial tümörlerden farklı prognostik özellikler bulunup bulunmadığını belirlemekti.
Gereç ve Yöntem: Bu çalışmada, anaplastik ganglioglioma vakalarını belirleyebilmek için, 1995-2002 yılları arasında İnönü Üniversitesi Tıp Fakültesi Patoloji Anabilim Dalı'nda yüksek dereceli glial tümör tanısı almış 30 olgu yeniden değerlendirilerek immunhistokimyasal incelemeye (glial fibriler asidik protein -GFAP-, nörofilament, nöron spesifik enolaz -NSE- ve kromogranin A) alınmıştır.
Bulgular: Tüm olgularda glial komponentte GFAP pozitifliği saptanmıştır. 22 olguda nörofilament, 26 olguda NSE ve 22 olguda kromogranin A pozitif bulunmuştur. Olguların geriye dönük incelemesinde, anaplastik gangliogliom kategorisine uygun iki olgu saptandı. Bu olguların her ikisi de GFAP pozitifti. NSE, nörofilament ve kromogranin A'yı içeren immunhistokimyasal incelemelerle sıkışık kümeler ya da düzensiz dağılım gösteren hücreler yanı sıra iki veya daha çok nukleuslu ve atipik ganglion hücreleri görüldü.
Sonuç: Anaplastik gangliogliomlar, yüksek dereceli glial tümörlerle kolayca karıştırılabilen tümörlerdir. Bu seride tümör yerleşim yerleri literatürle uyumlu bulunmuştur. Klinik olarak hastalarda epilepsi öyküsü yoktur. Tatminkar sürede takibi olan bir hastanın yüksek dereceli glial tümörlü olgularda beklenen ortalama yaşam süresinden daha uzun bir yaşam süresi olmuştur. Bu veri anaplastik gangliogliomlu hastaların yüksek dereceli glial tümörlülerden daha iyi bir prognoza sahip olabileceğini düşündürmüştür.

Anahtar kelimeler: Anaplastik gangliogliom, gangliogliom, immunhistokimya, prognoz

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Anaplastic gangliogliomas are composed of neoplastic, mature ganglion cells and neoplastic glial cells usually of astrocytic nature are referred as gangliogliomas [1-15]. When the glial component is anaplastic, they are called "anaplastic gangliogliomas" [1,13,15,16].

Since gangliogliomas with an anaplastic astrocytic component are reportedly not always clinically aggressive, the significance of these tumors remains uncertain [12,17].

In this retrospective study, 30 consecutive high grade glioma cases within a period of seven years have been re-examined to detect if there were any cases of overlooked anaplastic gangliogliomas. The primary goals were to determine the anaplastic ganglioglioma cases overlooked, to examine the immunohistochemical staining characteristics and find out if there were any prognostic significance of these cases differing from high grade glial tumors.

MATERIALS and METHODS

Thirty consecutive cases of high grade gliomas (Grade IV n=19; Grade III, n=11) were selected from the archives of İnönü University Medical School, Department of Pathology between January 1995 and April 2002.

Following reevaluation of hematoxylin-eosin (H&E.) stained slides, five μm thick sections were cut from formalin fixed, paraffin-embedded blocks and immunohistochemical study was performed by the avidin-biotine-peroxidase complex method to localize antigens in formalin-fixed tissues [18]. The primary antibodies used were as follows: Glial fibrillary acidic protein (GFAP) (DAKO, USA), neurofilament -Clone 2F11- (DAKO, USA), chromogranin A - Ab-3, Clone LK2H10+PHE5 - (Neomarkers, USA), neuron specific enolase (NSE) - Ab-1, Clone E27 - (Neomarkers, USA).

Besides the non-tumoral brain tissue of each case, a normal autopsy brain was also evaluated by immunohistochemical staining for chromogranin A to compare the staining characteristics of the ganglion cells.

RESULTS

Nineteen cases of high grade glial tumors were of male and 11 were of female gender. Age at diagnosis ranged between 7 and 70 years. Tumor sites were as follows: temporal (n=2), parieto-tem-poral (n=4), fronto-temporal (n=1), fronto-temporo-parietal (n=1), temporo-occipital (n=1), parietal (n=3), occipital (n=1) frontal (n=8), third ventricle-sellar-suprasellar (n=1), and unspecified (n=8).

All cases revealed positive staining for GFAP in the glial component. Twenty-two cases revealed positivity for neurofilament, 26 cases were positive for NSE and 22 cases were immunoreactive for chromogranin A in the neuronal component (Table 1). Chromogranin A positivity was also detected in the neurons of all peritumoral brain tissues and partially in the autopsy specimens.

Table 1. Results of immunohistochemical examination.

Immunohistochemical marker	Number of the cases showing positivity
GFAP	30
Neurofilament	22
NSE	26
Chromogranin A	22
Total	30

GFAP= Glial fibrillary acidic protein, NSE= Neuron specific enolase

In retrospective analysis of the cases, two of them were rediagnosed as anaplastic ganglioglioma (Figure 1). Both cases were positive for GFAP (Figure 2a). Immunohistochemical examinations performed retrospectively including NSE, neurofilament and chromogranin A revealed cells forming tight clusters or discordant arrangement in addition to binuclear, multinuclear and atypical ganglion cells (Figure 2b-d).

Table 2. Anaplastic ganglioglioma cases detected retrospectively.

Case no.	Age	Sex	Clinical symptoms	Duration of the symptoms	Previous diagnosis	Localization	Follow-up (months)
1	65	F	Weakness in the left side of the body	Unknown	Grade IV astrocytoma	Left temporo-occipital lobe	28
2	7	M	Unknown	Unknown	Grade IV astrocytoma	Third ventricle	Perioperative mortality

F = Female, M = Male

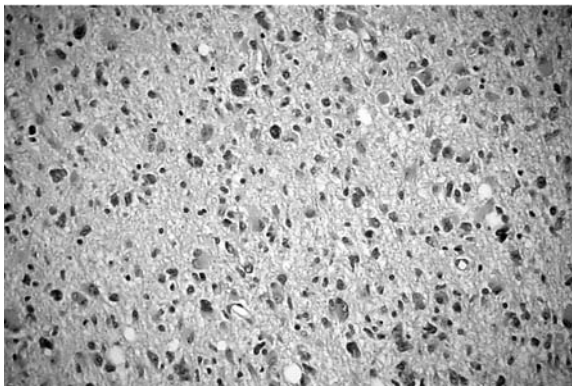

Figure 1. Dysmorphic ganglion cells are interspersed between glial cells in anaplastic astrocytoma supporting a diagnosis of anaplastic ganglioglioma (H.E X 200).

CASE 1: A 65-year-old woman was admitted to the neurosurgery department with a dense left hemiparesis. She had a history of heart failure, pneumonia and cholelithiasis. Computerized brain tomography revealed a 4x4x5 cm mass in the left temporo-occipital region extending to the right side. Total excision of the mass and partial occipital lobectomy were performed. Histologically atypical glial cells in a GFAP positive fibrillary background, high mitotic activity, endothelial proliferation and necrosis were noted and the diagnosis of glioblastoma multiforme was established. Postoperatively the patient was discharged with a slight left hemiparesis. She received radiotherapy as an adjuvant therapy. The patient had a 28 months follow-up with a good Karnofsky Score. Reevaluation of the specimen revealed neurofilament, NSE and chromogranin A positive atypical binuclear and multinuclear cells forming clusters.

CASE 2: A 7-year-old boy presented with a tumor filling the third ventricle and invading sellar, suprasellar regions and left optic nerve. Histologically the tumor was partially cystic and composed of pleomorphic and hyperchromatic cells which were evidenced to be in glial nature by GFAP immunoreactivity against the fibrillary background. Vascular proliferation and necrosis were noted. It was diagnosed as glioblastoma multiforme. Clusters of neurofilament and NSE positive dysplastic neuronal cells were noted in this case but staining for chromogranin was negative. Obvious heterotopic localization of

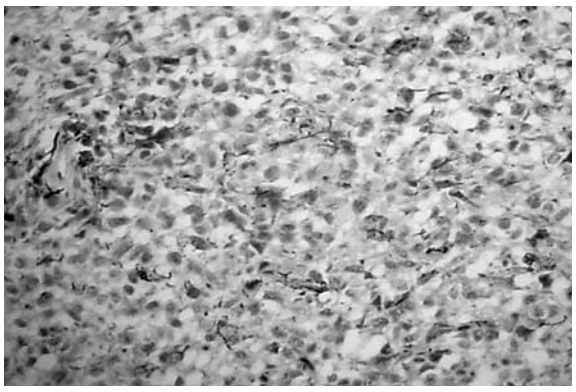

Fig. 2a. GFAP positivity in anaplastic astrocytoma case (GFAP X 200).

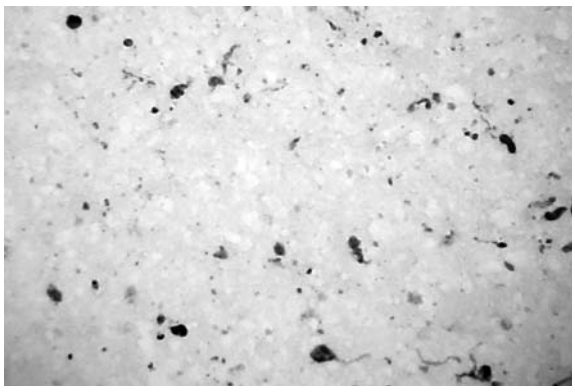

Fig. 2b. NSE positivity in the neuronal cells (NSE X 100).

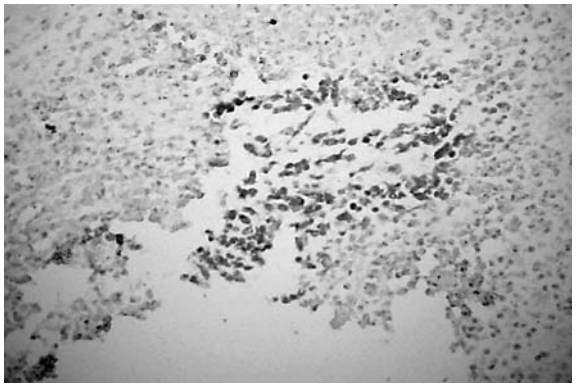

Figure 2c. Ganglion cells showing immunoreactivity for neurofilament (neurofilament X 100).

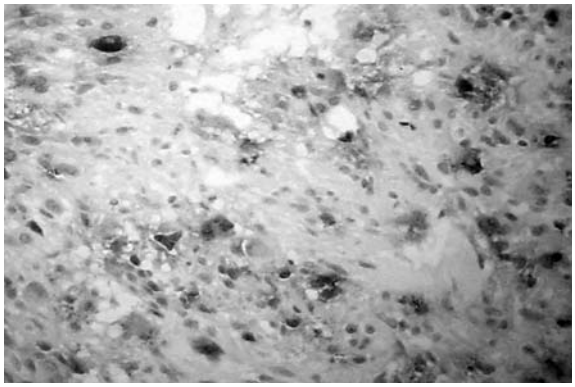

Figure 2d. Chromogranin A positivity in dysmorphic ganglion cells (chromogranin A X 200).

ganglion cells was prominent. Unfortunately this patient deceased within the first two months after surgery due to septisemia.

DISCUSSION

A tumor composed of neoplastic, mature ganglion cells and neoplastic glial cells is known as a ganglioglioma [1-15]. Although it had been a debate if ganglioglioma was a true neoplasm or a previous hamartomatous growth [2,19], because of its biological behavior and histological appearance, recently it is believed that it is a true neoplasm which corresponds to World Health Organization (WHO) grade I or II [2,7,8,10-13,15,20]. Even though glial cells are usually of astrocytic nature, an oligodendroglial component in ganglioglioma has also been described [1,15,19,21,22]. Malignant change can occur in these tumors rarely, being almost invariably in the glial component [2,4-8,10-13,15,22-26]. When the glial component is anaplastic, it is called "anaplastic ganglioglioma" [19,13,15,16] and it corresponds to WHO grade III [9,13,15,16]. Gangliogliomas including grade IV gliomas (glioblastomas)have been also reported [13].

In the present study, depending on the descriptions of neoplastic neurons in gangliogliomas in the literature including WHO definitions [1,2,7,8,10-13,15,24,27], only the ganglion cells showing atypical features (irregular groups of large, hyperchromatic, binucleated or multinucleated, multipolar neurons showing dysplastic features such as variable size, shape and Nissl pattern or heterotopic localizations) were regarded as tumoral (Figure 1). Other cases having neurons in the vicinity of cortex or diffusely distributed neuronal fibrils expressing positivity for neurofilament, NSE and chromogranin A were accepted as entrapment.

Although neurons were discernable with difficulty on H.E. stained slides, immunohistochemical staining properties made them easier to recognize. Ganglion cells are known to be reactive for synaptophysin, neurofilament and less predictably for chromogranin [5,6,9,13,14,17,21,23,24]. In the present study, NSE (the least specific marker) [5], neurofilament and chromogranin A were positive in the tumoral ganglion cells. Chromogranin A positivity was also detected in the neurons of all peritumoral brain tissues and partially in the autopsy specimens, differing from the reports stating the the presence of positivity mainly in the tumoral ganglion cells [9,21]. However, three of the 21 cases in the series of Hirose et al [21], the case reported by Demaerel et al [26], and the second case in the present study demonstrated negativity for chromogranin A in the neoplastic neurons. Relying on the rate of positivity in the normal neurons in the present study, it may be suggested that chromogranin A is not a specific marker for neoplastic neurons.

According to various studies, gangliogliomas represent 0.4-1.7 % of all central nervous system (CNS) tumors [13,19,20] and 0.3-7.6 % of all brain tumors [4,12,28]. The frequency in children is recently reported to be about 7.6-10.7 % of all CNS neoplasms [17,19], while the previous series had stated a lower percentage (4-4.5 %) [24]. In previous studies the frequencies of grade I, II and III tumors diagnosed as ganglioglioma were reported as 85 %, 10 % and 5 %, respectively [15]. Even though the higher frequency of gangliogliomas in the present series (2 in 30-6,6 %) seems challenging, our result indicates the incidence only in high grade glioma group. The relatively small incidences of gangliogliomas in the literature relate to the rates of all brain tumors or all the tumors of CNS.

The ages of patients with ganglioglioma range from 20 days to 80 years [12] but the majority of these tumors appear before age 30 [12,19,23,24,28]. While tumors may occur throughout the CNS including spinal cord, the majority are supratentorial and the most frequent sites are third ventricle, frontal and temporal lobes [2,4-6,8,9,11-14,16,19,23-25,28-31]. However, Garrido et al had found a higher predilection for the IVth ventricle-medulla and spinal cord in their series including 14 children [20]. Localization of the tumors in the present study was concordant with the literature [2,4,6,8,9,11-14,16,19,23-25, 28-31] (Table 2).

The most common clinical presentation of gangliogliomas is seizure [5,6-8,11,12,14,17, 21,23-25,28,29,31] or consequences of increased intracranial pressure [5]. In the series of Chintagumpala et al, rate of the seizure was 78 % [17]. Otsubo et al described that gangliogliomas associated with seizure were located in the temporal and frontal lobes [28,31]. These tumors are known to be the most common with chronic temporal lobe epilepsy [13]. Interestingly, no patients in the present study had had epilepsy in the past contrary to the classical knowledge [6-8,11,12,14,17,21,23-25,28,29,31]. This result may support the conclusion of Aronica et al indicating the association between the malignant progression and absence of epilepsy in gangliogliomas [25].

There is still no strict concensus about the prognosis of anaplastic gangliogliomas. Despite these tumors are often known to show recurrence [8,10,12,15,19,30] and prognosis of them is accepted to be less favorable [6,13,22,29], some authors reported that there was no significant correlation between histological features of anaplasia and clinical outcome [12,17,30,32,33]. Burger and Scheithauer stated that atypia in the form of large, bizarre, or hyperchromatic nuclei was not infrequent in ganglion cell tumors and often appeared to be degenerative in nature [5].

Transformation of gangliogliomas either to anaplastic ganglioglioma [10,30] or to a high grade glioma [8,19] has been also reported. Aronica et al. detected that malignant progression was associated with older age at operation, subtotal resection of the tumor, its extratemporal location and absence of epilepsy [25].

Though some investigators have stated that the tumor site influences the rate of recurrence, some others object this assumption [17,32]. It is also known that these tumors rarely exhibit distant extracranial metastases 4. Interestingly, Chintagumpala et al found in their series that local subarachnoidal involvement does not portend a poorer prognosis [17]. Jay et al. also reported a ganglioglioma which did not include any anaplastic features but was associated with widespread leptomeningeal spread and abnormal karyotypes [11]. In the case reported by Araki et al, there were metastases in the peritoneal and pleural cavities from a cerebral anaplastic ganglioglioma. They stated that all metastatic components were from glial elements rather than ganglion cells, suggesting that the anaplastic components of the tumor had the ability to metastasize along the shunt and survive in a new environment. They also suggested that glial ele-

ments were more aggressive than ganglion cells. Although the route for the tumor metastasis into the peritoneal cavity was through the ventriculoperitoneal shunt, the exact route for the pleural metastasis was not clear in their case. They proposed that it might be through the direct spreading of the tumor cells from the peritoneal cavity where the first metastatic lesions resided or they were disseminated via hematogenous route [4].

While the treatment of choice in gangliogliomas is surgical resection [5-7,12,15,20,25,28,31], the role of adjuvant therapy remains unclear [12,15,17]. Surgery plus radiotherapy is indicated in anaplastic gangliogliomas [6,7,12,20].

This study documents that the evaluation of archival cases of high grade gliomas may reveal a greater number of anaplastic gangliogliomas than anticipated. It can be discouraging and sometimes impossible to distinguish the atypical neurons from atypical glial cells in high grade gliomas especially harbouring giant cells in H.E. stained slides. Therefore the neural markers may help in detection.

Chromogranin A positivity was not detected in tumoral ganglion cells in one of oue cases (Case 2), and it was positive in the neurons of all peritumoral brain tissues and partially in the autopsy specimens. So it may be suggested that chromogranin A is not a specific marker for neoplastic neurons, despite the reports stating the contrary idea [9,21].

Interestingly, no patients in the present study had epilepsy in the history despite the classical knowledge [6-8,11,12,14,17,21,23-25,28,29,31]. So it may be concluded that anaplastic variant of gangliogliomas may not become manifest with clinical seizures.

The median survival of case 1 in this study was longer than the median survival of ordinary patients with high grade glial tumors [16]. Neither intracranial, nor extracranial metastasis were detected in these two patients. Although there is a trend to suggest that a tumoural ganglion cell component in a high grade glial tumor may have a better prognostic value, no such conclusion can be derived due to the scarce number of patients in this study. In addition, re-evaluation of the high grade glial tumors showing a better course than expected may lead to detect undiagnosed anaplastic ganglioglioma cases in larger series which may yield a better understanding of the tumoral behaviour for both groups.

REFERENCES

1. **Adams JH and Graham DI.** Chapter 18: Nervous Systems: Voluntary Muscles: The Eye (The Central Nervous System). In: McSween RMN and Whaley K, eds. Muir's Textbook of Pathology. 13th ed. Frome and London: Buttler and Tanner Ltd., 1992: 804-90.
2. **Allegranza A, Pileri S, Frank G, Ferracini R.** Cerebral ganglioglioma with anaplastic oligodendroglial component. Histopathology 1990; 17(5):439-41.
3. **Arai Y, Ackerley CA, Becker LE.** Tuberin expression in ganglioglioma. Ultrastruct Pathol 2000; 24:93-8.
4. **Araki M, Fan J, Haraoka S, Moritake T, Yoshii Y and Watanabe T.** Extracranial metastasis of anaplastic ganglioglioma through a ventriculoperitoneal shunt: A Case Report. Pathol Int 1999; 49:258-63.
5. **Burger PC and Scheithauer BW.** Chapter 4: Neuronal and Glio-Neuronal Tumors. In: Atlas of Tumor Pathology, 3rd Series, Fascicle 10, Tumors of the Central Nervous System. Washington, DC: Armed Forces Institute of Pathology, 1994: 163-92.
6. **Hakim R, Loeffler JS, Anthony DC, Black PM.** Gangliogliomas in adults. Cancer 1997; 79(1):127-31.
7. **Hall WA, Yunis EJ, Albright AL.** Anaplastic ganglioglioma in an infant: Case report and review of the literature. Neurosurgery 1986; 19(6):1016-20.
8. **Hayashi Y, Iwato M, Hasegawa M, Tachibana O, von Deimling A, Yamashita J.** Malignant transformation of a gangliocytoma/ganglioglioma into a glioblastoma multiforme: A molecular genetic analysis. J Neurosurg 2001; 95(1):138-42.
9. **Hirose T, Kannuki S, Nishida K, Matsumoto K, sano T, Hizawa K.** Anaplastic ganglioglioma of the brain stem demonstrating active neurosecretory features of neoplastic neuronal cells. Acta Neuropathol 1992; 83:365-70.
10. **Jay V, Squire J, Becker LE, Humphreys R.** Malignant transformation in a ganglioglioma with anaplastic neuronal and astrocytic components. Cancer 1994; 73(11):2862-8.
11. **Jay V, Squire J, Blaser S, Hoffman HJ, Hwang P.** Intracranial and spinal metastases from a ganglioglioma with unusual cytogenetic abnormalities in a patient with complex partial seizures. Child's Nerv Syst 1997; 13:550-5.

12. **Krouwer HGJ, Davis RL, McDermott MW, Hoshino T, Prados MD.** Gangliogliomas: A clinicopathological study of 25 cases and review of the literature. J Neurooncol 1993; 17:139-54.
13. **Nelson JS, Bruner JM, Wiestler OD, Vanderberg SR.** Ganglioglioma and Gangliocytoma. In: Kleihaues P and Cavenee WK, eds. WHO Classification of Tumors, Pathology and Genetics of Tumours of the Nervous System. Lyon, France: IARC Press (International Agency for Research on Cancer), 2000: 96-98.
14. **Parisi JE and Scheithauer BW.** Chapter 7: Glial Tumours. In: Nelson JS, Parisi JE and Schochet, Jr SS, eds. Principles and Practice of Neuropathology, St. Louis: Mosby-Year Book, Inc., 1993: 123-83.
15. **Sasaki A, Hirato J, Nakazato Y, Tamura M, Kadowaki H.** Recurrent anaplastic ganglioglioma: Pathological characterization of tumor cells. J Neurosurg 1996; 84(6):1055-9.
16. **McKeever PE.** Chapter 10: The Brain, Spinal Cord and Meninges. In: Sternberg SS, ed. Diagnostic Surgical Pathology, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 1999: 389-480.
17. **Chintagumpala MM, Armstrong D, Miki S, Nelson T, Cheek W, Laurent J, Woo SY, Mahoney, Jr, DH.** Mixed Neuronal-Glial Tumors (Gangliogliomas) in Children. Pediatr Neurosurg 1996; 24:306-13.
18. **Hsu Su-Ming, Raine L, and Fanger H.** Use of Avidin-Biotin-Peroxidase Complex (ABC) in immunoperoxidase techniques: A comparison between ABC and Unlabeled Antibody (PAP) Procedures. Am J Clin Pathol 1981; 75(6):816-21.
19. **Mittler MA, Walters BC, Fried AH, Sotomayor EA, Stopa EG.** Malignant Glial tumor arising from the site of a previous hamartoma/ganglioglioma: Coincidence or malignant transformation? Pediatr Neurosurg 1999; 30(3):132-4.
20. **Garrido E, Becker LE, Hoffman HJ, Hendrick EB, and Humphreys R.** Gangliogliomas in children. Child's Brain 1978; 4:339-46.
21. **Hirose T, Scheithauer BW, Lopes MBS, Gerber HA, Altermatt HJ, Vanderberg SR.** Ganglioglioma, an ultrastuctural and immunohistochemical Study. Cancer 1997; 79(5):989-1003.
22. **Johnson MD, Jennings MT, Toms ST.** Oligodendroglial ganglioglioma with anaplastic features arising from the thalamus. Pediatr Neurosurg 2001; 34(6):301-5.
23. **Powers JM and Horoupian DS.** Chapter 77: Central Nervous System. In: Damjanov I and Linder J, eds. Anderson's Pathology, 10th ed. USA: Mosby-Year Book Inc., 1996: 2693-798.
24. **Russell DS and Rubinstein LJ.** Chapter 3: Tumours of Central Neuroepithelial Origin. In: Pathology of the Nervous System. 5th ed. Frome and London: Edward Arnold, 1989: 83-350.
25. **Aronica E, Leenstra S, van Veelen CWM, van Rijen PC, Hulsebos TJ, Tersmette AC, Yankaya B, Troost D.** Glioneuronal tumors and medically intractable epilepsy: A clinical study with long-term follow-up of seizure outcome after surgery. Epilepsy Res 2001; 43(3):179-91.
26. **Demaerel P, Droessaert M, Lammens M, Menten J, Nuttin B, Verbeeck R, Wilms G, Baert AL.** Anaplastic (malignant) ganglioglioma arising from heterotopic grey matter nodules. J Neurooncol 1996; 30:237-42.
27. **Esiri M and Oppenheimer DR.** Chapter 12: Tumours Arising in the Brain and spinal Cord. In: Diagnostic Neuropathology. Great Britain: Blackwell Scientific Publications, 1989: 171-97.
28. **Otsubo H, Hoffman HJ, Humphreys RP, Hendrick EB, Drake JM, Hwang PA, Becker LE, and Chuang SH.** Detection and Management of Gangliogliomas in Children. Surg Neurol 1992; 38:371-8.
29. **Dash RC, Provenzale JM, McComb RD, Perry DA, Longee DC, McLendon RE.** Malignant supratentorial ganglioglioma (ganglion cell-giant cell glioblastoma). Arch Pathol Lab Med 1999; 123:342-5.
30. **Lindboe CF, Cappelen J, Kepes JJ.** Pleomorphic xanthoastrocytoma as a component of a cerebellar ganglioglioma: Case Report. Neurosurgery 1992; 31(2):353-5.
31. **Otsubo H, Hoffman HJ, Humphreys RP, Hendrick EB, Drake JM, Hwang PA, Becker LE, and Chuang SH.** Evaluation, surgical approach and outcome of seizure patients with gangliogliomas. Pediatr Neurosurg 1990; 16:208-12.
32. **Jaffey PB, Mundt AJ, Baunoch DA, Armstrong DL, Hamilton WJ, Zagaja VG, Grossman RG, and Wollmann RL.** The clinical significance of extracellular matrix in gangliogliomas. J Neuropathol Exp Neurol 1996; 55(12):1246-52.
33. **Jay V and Greenberg M.** Unusual cerebellar ganglioglioma with marked cytologic atypia. Pediatr Pathol Lab Med 1997; 17(1):105-14.