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Case Report

Unexpected discovery of a diffuse astrocytoma of the conus medullaris in an elderly NF1 patient☆,☆☆

Takamistu Uchi, MD[a,1], *Tsutomu Inaoka, MD, PhD*[a,1,*], *Noriko Kitamura, MD, PhD*[a], *Rumiko Ishikawa, MD, PhD*[a], *Tomoya Nakatsuka, MD, PhD*[a], *Shusuke Kasuya, MD*[a], *Wataru Tokuyama, MD, PhD*[b], *Nobuyuki Hiruta, MD, PhD*[b], *Hiroshi Takahashi, MD, PhD*[c], *Hitoshi Terada, MD, PhD*[a]

[a] *Department of Radiology, Toho University Sakura Medical Center*
[b] *Division of Surgical Pathology, Toho University Sakura Medical Center*
[c] *Department of Orthopedic Surgery, Toho University Sakura Medical Center*

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ABSTRACT

Neurofibromatosis type 1 (NF1) is one of the most common genetic neurocutaneous disorders, and it is well known to be associated with peripheral or central nervous system malignancies. The most common malignant tumors are malignant peripheral nerve sheath tumors (MPNSTs); MPNSTs are the most common cause of death in patients with NF1. Central nervous system malignancies rarely occur. So far, the occurrence of spinal cord malignancies is exceedingly rare. Herein, we report a rare case of a 69-year-old male with NF1 following tumor resection twice for cutaneous MPNSTs developing intramedullary diffuse astrocytoma in the conus medullaris, which initially presented with traumatic spinal cord injury associated with a compression fracture from fall. Contrast-enhanced magnetic resonance imaging and biopsy of the spinal cord were required to establish the final diagnosis.

Introduction

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease, is one of the most common genetic neurocutaneous disorders with an estimated incidence of 1 in 2500 to 3000 individuals worldwide. Although the autosomal dominant inheritance pattern of NF1 has been confirmed for many years, approx. 50% of NF1 cases arises de novo in individuals with no known family history of NF1. Patients with NF1 are at high risk for peripheral or central nervous system (CNS) malignancies. In fact, relative to the general population, patients with NF1 harbor a 10- to 50-fold increased risk of developing deadly malignancies [1–3].

The most common malignant tumors in NF1 are malignant peripheral nerve sheath tumors (MPNSTs), which occur predominantly in patients who are 20 to 50 years old. MPNSTs are

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* Corresponding author.
E-mail address: tsutomu.inaoka@med.toho-u.ac.jp (T. Inaoka).
[1] Takamitsu Uchi and Tsutomu Inaoka contributed equally to this case report.
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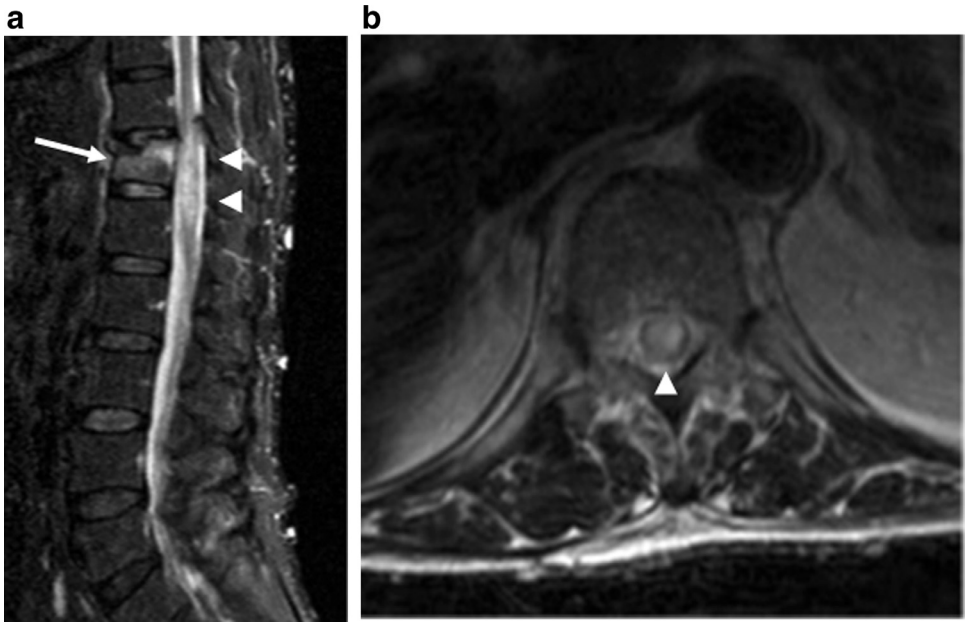

Fig. 1 – A 69-year-old male with NF1. MRI of the lumbar spine at the first admission just after fall. (A) Sagittal short TI inversion recovery image (STIR), (B) transverse T2WI at the level of Th12. There is a decrease in the height of T12 vertebral body with a bone marrow edema on sagittal STIR, which suggests a fresh compression fracture of Th12 (arrow). In addition, spinal cord swelling with intramedullary edematous change in the conus medullaris is also found at the level of Th12 on sagittal STIR and transverse T2WI (arrow heads). Therefore, the patient was diagnosed as having traumatic spinal cord injury associated with a compression fracture of Th12 from fall. There are multiple skin nodules in the lower back, suggesting multiple tiny neurofibromas.

the most common cause of death in patients with NF1. Most of the CNS tumors in patients with NF1 are optic gliomas and brainstem gliomas, which are usually astrocytomas. These tumors are usually observed in children with NF1 and do not progress to malignancy; however, such CNS tumors do occur in adults with NF1, and these adults are prone to the development of higher-grade gliomas (although they are quite rare) [1,2]. Tumors involving the spinal cord in patients with NF1 are rare, and thus spinal cord astrocytoma in patients with NF1 has not been well described [3–5]. To our knowledge, there are only a few English reports describing a spinal cord astrocytoma in a patient with NF1 [3–5]. Herein, we report a rare case of an elderly patient with NF1 following tumor resection twice for cutaneous MPNSTs developing intramedullary diffuse astrocytoma in the conus medullaris, which initially presented with traumatic spinal cord injury associated with a compression fracture from fall. Contrast-enhanced magnetic resonance imaging (MRI) and biopsy of the spinal cord were required to establish the final diagnosis.

Case report

A 69-year-old Japanese male presenting with severe back pain and mild numbness in the right lower extremity after fall was admitted to our hospital's emergency room. He had a complicated history of illness. He had already been diagnosed as having NF1. His father, 1 brother, and 2 sisters also had multiple skin nodules across their entire bodies, and they were all thus suspected of having NF1 too. The patient had undergone a tumor resection twice for cutaneous MPNSTs in the right shoulder and left buttock 18 months and 8 years earlier, respectively. No evidence of local recurrence had been found. MRI of the lumbar spine was performed and showed spinal cord swelling with intramedullary edematous change in the conus medullaris at the level of Th12 in addition to a compression fracture of Th12 (Figs. 1). Since the patient's neurological symptom was mild, he was diagnosed as having traumatic spinal cord injury associated with a compression fracture of Th12 and had been clinically followed up. Six months later his admission, he presented with acute back pain and severe numbness in the bilateral lower extremities and was again admitted to our hospital's emergency room. The physical examination at his admission to our hospital revealed that the result manual muscle testing of the lower extremities was almost normal. His standing and walking were almost normal. MRI of the lumbar spine was performed again; T2-weighted images (T2WI) showed spinal cord swelling with intramedullary edematous change in the conus medullaris at the levels of Th11 through L1. Compared to the patient's previous MRI of the lumbar spine 6 months earlier, the finding of spinal cord swelling with intramedullary edematous change had become much more severe. Contrast-enhanced T1-weighted images (T1WI) showed good enhancement predominantly at the periphery of the swollen spinal cord (Fig. 2). No evidence of other tumors except for multiple nodules in the skin was found on whole-body CT. No evidence of abnormal-

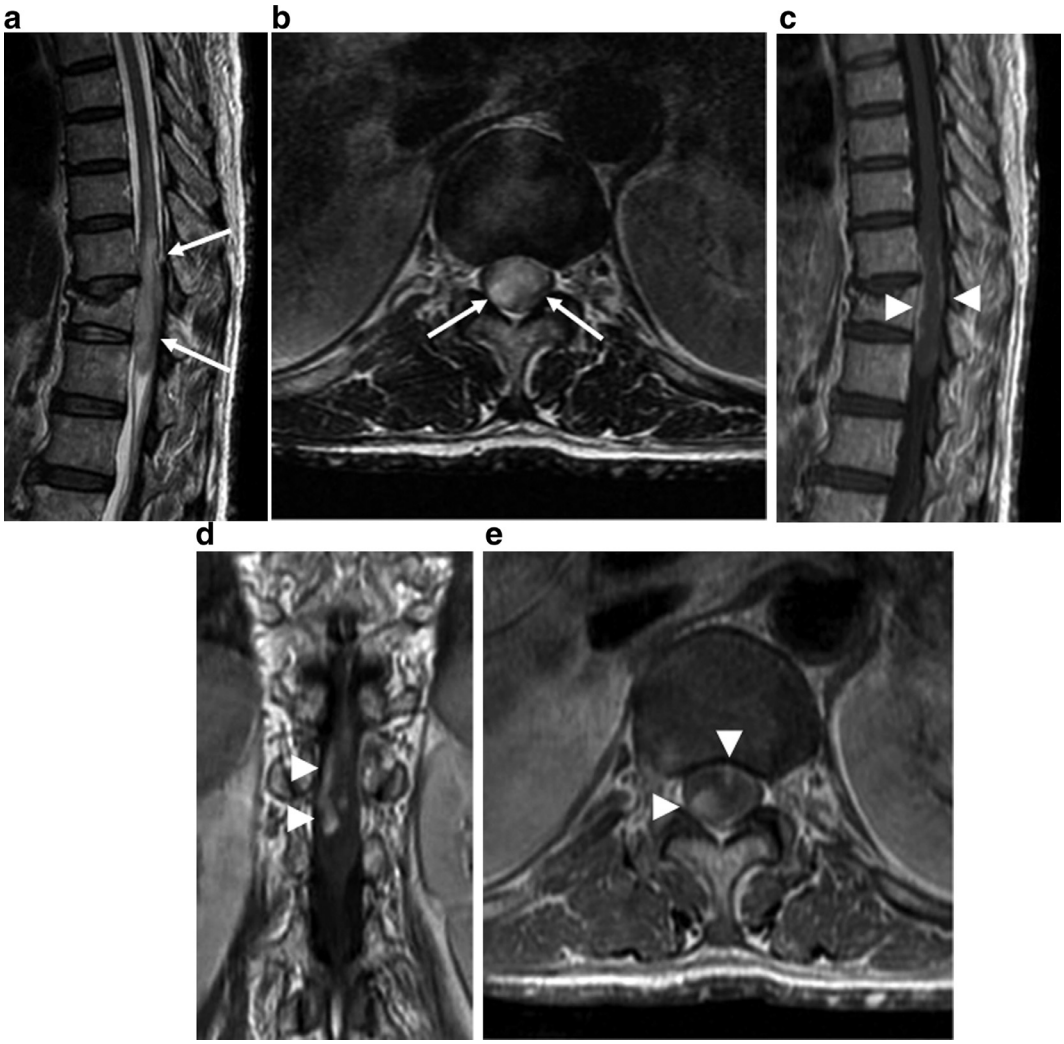

Fig. 2 – A 69-year-old male with NF1. MRI of the lumbar spine 6 months later the first admission. (A) Sagittal T2WI, (b) transverse T2WI, (c) sagittal contrast-enhanced T1WI, (d) coronal contrast-enhanced T1WI, and (e) transverse contrast-enhanced T1WI. There is a decrease in the height of T12 vertebral body without a significant interval change. A healed compression fracture of Th12 is found. Spinal cord swelling with intramedullary edematous change at the levels of T9 through L1 is again found on sagittal and transverse T2WI (arrows), which may increase in size compared to the previous MRI 6 months before. Relatively strong enhancement predominantly at the periphery of the swollen spinal cord at the levels of T11 through L1 on sagittal, coronal, and transverse contrast-enhanced T1WI (arrow heads). Therefore, primary or metastatic spinal cord tumors are suspected.

ity was found on brain MRI. From these findings, primary or metastatic spinal cord tumors were suspected. A Th10–L1 laminectomy and biopsy of the spinal cord were performed. The pathological specimens showed increased cellularity and pleomorphism of the nucleus. Immunohistochemical studies showed positivity for GFAP and S100. Focally, a gemistocytic change was found (Figs. 3). The histopathological diagnosis of diffuse astrocytoma (World Health Organization (WHO) classification, grade II) with a focally gemistocytic change in the spinal cord was thus established. Isocitrate dehydrogenase (IDH) mutations were not tested because the tests were not popular in Japan at the time. The patient underwent radiation therapy with a total of 46.8 Gy. However, the disease progressed, and the patient died 1 year and 10 months after the radiation therapy.

Discussion

The molecular mechanisms of NF1 tumorigenesis remain unclear. However, NF1 gene is known as a tumor suppressor gene mapped to chromosome 17q11.2 and is expressed in almost all tissues but most highly in brain, spinal cord, and the peripheral nervous system. NF1 gene encodes the cytoplasmic protein neurofibromin, which is found mainly in neurons, astrocytes, oligodendrocytes, microglia, and Schwann cells in adults, and is also expressed in other cell types such as keratinocytes, adrenal medulla, and white blood cells. To date, it appears that a decreased production of the intracellular neurofibromin protein is caused by mutations of the NF1 tumor suppression gene in NF1. Neurofibromin is reduced or

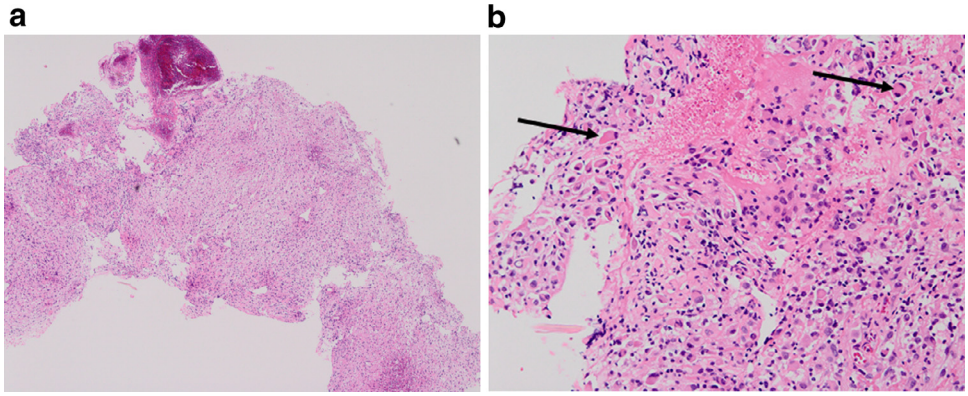

Fig. 3 – A 69-year-old male with NF1. Pathological specimens of the swollen spinal cord show the proliferation of tumor cells with small to medium round nuclei in the matrix. There are slightly increased cellularity and pleomorphism of the nucleus (A). Focally, hypertrophic cells with abundant cytoplasm and 2 eccentric nuclei are found, suggesting gemistocytic cells (arrows) (B). The histopathological diagnosis of diffuse astrocytoma (WHO grade II) with a focally gemistocytic change in the spinal cord was thus established.

absent in neurofibroma cells, which are composed principally of Schwann cells without functional neurofibromin. In addition, it is also speculated that additional molecular cascades may be involved in the tumorigenesis of malignant tumors in NF1 [1,2,6,7].

The most common malignant tumors in NF1 are MPNSTs. Approximately 5% to 10% of patients with NF1 develop MPNSTs, which are highly aggressive sarcomas and cause potentially fatal complications in NF1 patients. The development of MPNST in NF1 has been examined. MPNSTs are typically transformed from pre-existing neurofibromas in NF1. This malignant transformation may be the result of additional mutations in one or more genes controlling cell growth and differentiation. Subsequent genetic alterations of benign neurofibromas result in progression toward MPNST development. A number of genetic changes (including losses of TP53, RB1, and CDKN2A) as well as several oncogenes and cell-cycle genes, have been implicated in the development of MPNSTs [1,2,6,7].

Most of the CNS tumors in patients with NF1 are optic gliomas, seen in 15% to 20% of NF1 patients. Other CNS tumors are brainstem and cerebellum gliomas. These intracranial gliomas in NF1 patients are usually astrocytomas. Chromosomal abnormalities at the NF1 gene have been reported in patients with astrocytomas who do not have NF1. Therefore, the NF1 gene may play some role in astrocytoma tumorigenesis, but this association has not been clearly defined as it has in other nervous system neoplasms that are typically associated with NF1. These tumors are usually observed in children with NF1. Although the tumors in children with NF1 do not progress to malignancy, adults with NF1 are prone to the development of high-grade gliomas. Such malignant CNS tumors are uncommon, affecting fewer than 1% of all individuals with NF1 [1,2]. A relationship between traumatic events and tumorigenesis of gliomas reportedly remains controversial [8].

Interestingly, spinal tumors can be detected by MRI in 40% to 60% of patients with NF1, but these tumors may cause neurological symptoms in approx. 2% of NF1 patients [5]. Spinal tumors in NF1 causing symptoms are mainly in adults. In fact, most of the tumors involved in the spinal canal of NF1 patients are definitely neurofibromas, rarely astrocytomas. Therefore, spinal canal involvement in NF1 is typically from the extramedullary growth of spinal nerve root tumors [3,5]. The development of an intramedullary spinal cord astrocytoma in NF1 patients remains unclear because of the rarity of intramedullary spinal cord astrocytomas [3–5]. To our knowledge, only seven cases of patients with NF1 and pathologically proven intramedullary spinal cord astrocytomas have been reported [3]. There is a trend for spinal cord astrocytomas to occur in the patients with NF1, while for spinal cord ependymomas to occur in the patients with NF2 [4].

In general, the most common site of spinal astrocytoma involvement is the thoracic cord, followed by the cervical cord. Isolated conus medullaris involvement is exceedingly rare, seen in approx. 3% of cases [9]. MRI is the diagnostic modality of choice; the tumors show poorly defined margins and are iso- to hypointense relative to the spinal cord on T1WI and hyperintense on T2WI. The length of spinal cord involvement is relatively long. Cysts are a common feature, with both polar and intratumoral types being observed. Nearly all spinal cord astrocytomas show at least some enhancement following the intravenous administration of contrast material. Because astrocytomas arise from the spinal cord parenchyma and not from the central canal, they are usually eccentric within the spinal cord [3–5,9]. Although rare, these findings may mimic traumatic spinal cord injury when the patients had traumatic events. Therefore, clinical histories and symptoms are very important for differentiating spinal cord tumor from traumatic spinal cord injury. A close follow-up including contrast-enhanced MRI is also needed.

The prognosis for high-grade astrocytomas is poor. Gross total resection is not possible because of the infiltrating nature of these lesions. Gemistocytic astrocytomas are a distinct variant of astrocytomas, generally classified as WHO grade II, and are associated with an aggressive biological behavior and unfavorable prognosis as in our patient's case. Recently, IDH mutations have been tested. Clinical and molecular features

of diffuse astrocytomas with or without IDH mutations have been further investigated [10]. Unfortunately, malignant transformation cannot be predicted on the basis of laboratory data. Further studies are necessary, including molecular analyses to clarify the mechanisms of tumorigenesis in NF1 [11]. MRI is helpful for assessing the malignancy based on the findings such as progression in size, heterogeneity in signal intensity, and progression and heterogeneity in contrast enhancement [5].

Approx. 40% to 65% of MPNSTs lead to local recurrence after surgery, and approx. 30 to 60% of MPNSTs develop distant metastasis, with pulmonary metastasis being the most common. Cutaneous MPNSTs usually have a better prognosis than their deep-seated form [7]. In our patient's case, tumor resections for cutaneous MPNSTs in the right shoulder and left buttock had previously been performed twice, and no local recurrence was identified. Initially, as for the conus medullaris lesion, we suspected traumatic spinal cord injury associated with Th12 compression fracture from fall. Six months later the first admission, the conus medullaris lesion was getting larger and showed heterogeneous contrast-enhancement on lumbar spine MRI. Therefore, we had a suspicion of primary or metastatic spinal cord tumors. At first, we considered a primary MPNST involving the spinal canal. However, as we noted above, MPNSTs must show extramedullary growth features. We next considered the possibility of distant metastasis of MPNSTs or other tumors into the spinal cord. In addition to its exceedingly rare nature, the finding of a solitary lesion in the conus medullaris is quite atypical as distant metastasis from previous cutaneous MPNSTs in the shoulder and buttock. No other tumor or lymphadenopathy was identified in our patient's whole body. Therefore, although rare, primary spinal cord tumors (in this case, intramedullary spinal cord astrocytomas) should be considered.

Conclusion

Most of the tumors involving the spinal canal of NF1 patients are reportedly neurofibromas, or understandably MPNSTs from neurofibromas, which typically show the extramedullary growth of spinal nerve root tumors. However, although rare, for intramedullary spinal cord tumors in patients with NF1, astrocytomas should be considered first. Particularly in adult cases, furthermore, clinicians should be aware that intramedullary astrocytomas may have a potential to transform into high-grade astrocytomas. Although rare, the MRI findings of spinal cord tumors may mimic traumatic spinal cord injury when the patients have vertebral fractures and spinal cord abnormalities at the same level of the spine after traumatic events as in the present case. In our case, contrast-enhanced MRI and biopsy of the spinal cord were required to establish the final diagnosis. Therefore, a close follow-up including contrast-enhanced MRI is very important in addition to clinical histories and symptoms.

REFERENCES

[1] Cimino PJ, Gutmann DH. Neurofibromatosis type 1. Handb Clin Neurol 2018;148:799–811. doi:10.1016/B978-0-444-64076-5.00051-X.
[2] Peltonen S, Kallionpaa RA, Rantanen M, Uusitalo E, Lahteenmakl PM, Poyhonen M, et al. Pediatric malignancies in neurofibromatosis type 1: a population-based cohort study. Int J Cancer 2019;145(11):2926–32. doi:10.1002/ijc.32187.
[3] Hong JT, Lee SW, Son BC, Kim MC. A case of intramedullary spinal cord astrocytoma associated with neurofibromatosis type 1. J Korean Neurosurg Soc 2004;36(1):69–71. https://www.jkns.or.kr/upload/pdf/0042004133.pdf.
[4] Lee M, Rezai AR, Frred D, Epstein FJ. Intramedullary spinal cord tumors in neurofibromatosis. Neurosurgery 1996;38(1):32–7. doi:10.1097/00006123-199601000-00009.
[5] Thakkar SD, Feigen U, Mautner VF. Spinal tumours in neurofibromatosis type 1: an MRI study of frequency, multiplicity and variety. Neuroradiology 1999;41(9):625–9. doi:10.1007/s002340050814.
[6] Gottfried ON, Viskochil DH, Couldwell WT. Neurofibromatosis type 1 and tumorigenesis: molecular mechanisms and therapeutic implications. Neurosurg Focus 2010;28(1):E8. doi:10.3171/2009.11.FOCUS09221.
[7] Hataya Y, Komatsu Y, Osaki K, Fukuda Y, Sato T, Morimoto T. A case of neurofibromatosis type 1 coinciding with bilateral pheochromocytomas, multiple gastrointestinal stromal tumors, and malignant peripheral nerve sheath tumor. Intern Med 2012;51(12):1531–6. doi:10.2169/internalmedicine.51.6385.
[8] Siminska D, Kojder K, Jezewski D, Kojder I, Skorka M, Gutowska I, et al. The pathophysiology of post-traumatic glioma. Int J Mol Sci 2018;19(8):2445. doi:10.3390/ijms19082445.
[9] Koeller KK, Rosenblum RS, Morrison AL. Neoplasms of the spinal cord and filum terminale: radiologic-pathologic correlation. RadioGraphics 2000;20(6):1721–49. doi:10.1148/radiographics.20.6.g00nv151721.
[10] Hasselblatt M, Jaber M, Reuss D, Grauer O, Bibo A, Terwey S, et al. Diffuse astrocytoma, IDH-wildtype: a dissolving diagnosis. J Neuropathol Exp Neurol 2018;77(6):422–5. doi:10.1093/jnen/nly012.
[11] Avninder S, Sharma MC, Deb P, Mehta VS, Karak AK, Mahapatra AK, et al. Gemistocytic astrocytomas: histomorphology, proliferative potential and genetic alterations-a study of 32 cases. J Neuro Onco 2006;78(2):123–7. doi:10.1007/s11060-005-9077-x.