Case Report

Natural history of spinal ganglioglioma in neurofibromatosis type 1: a 10-year follow-up

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Abstract: The presence of gangliogliomas in combination with a diagnosis of neurofibromatosis type 1 (NF1) is extremely unusual. Here, we present a case of spinal cord ganglioglioma of a child who also had NF1 and attempt to describe the natural history and treatment course of this tumor. Ten years prior to this report, a 16-year-old boy affected by NF1 was diagnosed with an enhancing tumor of the spinal cord that extended from C3 to T1. After radiotherapy was applied, he chose a follow-up of conservative observation. Ten years later, the patient underwent a subtotal resection. A pathological examination revealed a ganglioglioma. We are of the opinion that the malignant transformation of the ganglioglioma in this patient was more likely a natural occurrence rather than a result of radiotherapy. Due to its favorable survival rate, ganglioglioma should be considered when differentially diagnosing an NF1 patient who presents with a spinal cord tumor.

Keywords: Ganglioglioma, natural history, neurofibromatosis type 1, radiotherapy, treatment strategy

Introduction

Neurofibromatosis type 1 (NF1) is one of the most commonly inherited autosomal dominant genetic disorders in humans, with a frequency of one in every 3000 live births [1]. The NF1 gene, which has been mapped to 17q11.2, directs the synthesis of the neurofibromin protein. This protein exhibits GTPase-activating activity towards Ras, such that a loss of neurofibromin expression leads to a high accumulation of activated Ras, which can increase cell proliferation and possibly enhance tumor formation [2]. The clinical course of NF1 is generally progressive but highly variable. The primary characteristics of patients presenting with NF1 include neurofibromatosis and the presence of café-au-lait spots [3, 4]. Additional benign and malignant tumors also develop in these patients; the most common tumors are astrocytomas, malignant peripheral nerve sheath tumors (MPNST), and sarcomas [5]. Gangliogliomas (GGs) are characterized by a biphasic morphologic pattern composed of neuronal and glial cells, and they vary from having a predominantly neuronal phenotype to having prominent glial populations. They occur mainly in children and young adults and account for approximately 1-4% of all central nervous system neoplasms in pediatric patients [1, 3, 4]. Spinal cord gangliogliomas are rare. The concurrent presentation of a spinal ganglioglioma and NF-1 is very unusual.

In this report, we present the case of a 16-year-old male who presented with concurrent NF1 and spinal gangliogliomas. To the best of our knowledge, there are only two case reports that document a similar presentation: one in a 4-year-old and one in a 5-year-old patient [6, 7]. In both cases, follow-up was only conducted for 2 years. Our report therefore represents the third documented case of this type of concurrence, and the innovation of our study is that we conducted follow-up of the patient for 10 years to initially summarize the natural history of spinal ganglioglioma in neurofibromatosis type 1.

Case summary

History and examination

A 16-year-old right-handed male began experiencing symptoms of seizures and weakness in
Figure 1. MRI revealed a long tumor that extended from C3 to T1 and had partial contrast. The patient was imaged when he was 6 years old, 8 years old, 13 years old, and 16 years old, as well as before (A-D) and 1 week and 3 months after (E, F) surgical intervention. Over a course of 10 years, the tumor expanded slowly and spinal deformity worsened.

his right upper extremity when he was 6 years old. Magnetic resonance imaging revealed a long tumor, which extended from C3 to T1 and had partial contrast (Figure 1). An intramedul-
lary glioma was suspected. Due to a fear of complications, the patient’s parents refused surgery and instead opted for Photon Knife radiotherapy in another hospital. The dose of the applied radiation was not recorded. Following radiotherapy, no symptomatic improvement was noted, and the patient’s right extremities slowly weakened. One month prior to being admitted to our department, the patient developed neck pain. On examination, he was found to have multiple café-au-lait spots on his face, abdomen and arms, and multiple neurofibromas were found in his skin. His father and grandfather also had multiple café-au-lait spots covering their skin. A contracture deformity was noted in his right hand, and obvious muscular atrophy was affecting his right limbs. A manual muscle test performed using his right hand was scored as grade 0. Tests of his right upper and lower limbs were scored as grade 3, and his left upper and lower limbs were scored as grade 4. Touch sensation was decreased in the right limbs. There were negative Babinski signs on both sides. Magnetic resonance imaging revealed a long tumor that spanned from the medulla oblongata to the third thoracic level.

**Operation and postoperative course**

The patient underwent a midline laminaplasty from C2 to T2. The tumor was filled with blood and contained obvious calcified plaques, and it was closely adhered to normal spinal cord tissue. Thus, the resection of the tumor was difficult. It was partially removed to protect spinal cord function. Histopathological examination revealed an aplastic ganglioglioma. Immunostaining results for glial fibrillary acidic protein (GFAP), synaptophysin and Ki-67 were all positive (Figure 2). The patient recovered after surgery and was of stable clinical status after 6 months.

**Discussion**

**Association of NF1 with CNS lesions**

NF1, formerly known as von Recklinghausen disease after the researcher (Friedrich Daniel
Clinical behavior of spinal ganglioglioma in NF1

von Recklinghausen) who first documented the disorder, is a human genetic disorder [8]. Benign and malignant tumors can develop in NF-1 patients, such as malignant peripheral nerve sheath tumors (MPNST), optic gliomas, other gliomas, leukemias, and sarcomas [5]. The most common type of central nervous system tumor that is observed in these patients is pilocytic astrocytoma of the optic nerve. Cerebellar astrocytoma or ependymoma, third-ventricle astrocytoma, cerebral astrocytoma, brain stem glioma, and spinal cord tumor have also been found in NF-1 patients [9]. In rare cases, NF-1 may be associated with a medulla oblongata glioblastoma. Tumors in NF-1 patients undergo malignant transformation at a higher frequency than tumors at comparable sites in patients without NF1 [10]. However, brain stem gliomas in individuals with NF1 may have a more indolent course and often do not require treatment.

Ganglioglioma

Ganglioglioma (WHO I) is a rare type of tumor, accounting for only 0.4% to 1.3% of intracranial tumors and 1.1% of intramedullary tumors. These tumors mainly occur in children and people under the age of 30 [11]. Gangliogliomas are biphasic tumors consisting of neuronal and glial cells, and they range from having a predominantly neuronal phenotype to having a prominent glial population [12]. Patients with supratentorial ganglioglioma have a good prognosis and a 93.5-year-survival rate. Intraspinal cord gangliogliomas are relatively rare. Lang et al. reported 30 cases of intraspinal cord ganglioglioma, and 29 of the 30 cases underwent near-total resection, which led to favorable long-term outcomes [13].

Naturally occurring malignancy versus malignancy caused by radiotherapy

Anaplastic ganglioglioma is a rare disease and is WHO grade III [14]. Malignant progression usually occurs in the glial cell populations of these tumors but has also been reported in their neuronal cell populations. Anaplastic ganglioglioma can be divided into primary and secondary anaplastic ganglioglioma [15]. When reviewing the literature, Demarchi et al. found only two cases of anaplastic ganglioglioma out of 184 documented supratentorial gangliogliomas: one case was primary and the other exhibited malignant change that was caused by recurrence after surgery [4]. Based on 58 cases of anaplastic ganglioglioma taken from the Surveillance, Epidemiology, and End Results (SEER) library-based cancer registry, Selvanathan et al. found that the majority of cases of anaplastic ganglioglioma resulted from the malignant transformation of low-grade gangliogliomas [16].

The mechanism of malignant transformation in ganglioglioma remains unclear. The patient in our study had received radiotherapy, which suggests that the malignant transformation of his tumor was driven by a complex mechanism. Therefore, it is difficult for us to distinguish whether this transformation was a product of natural events or radiotherapy. As there was no indication of a sudden change in his lesions in the imaging data that was acquired during 10 years of follow-up, we are of the opinion that the malignant transformation of his lesions was more likely a result of natural events.

Treatment therapy

Anaplastic ganglioglioma has a favorable prognosis after total resection [4, 16]. As calcification of these tumors is common, total resection is difficult. The need for radiotherapy after resection remains controversial. Karabekir et al. described the case of a 2-year-old presenting with a naplastic ganglioglioma [17]. In this case, despite the use of an ultrasonic aspirator to remove the calcified tumor, only partial resection could be achieved. Postoperative radiotherapy was performed, and the tumor was finally stabilized after 22 months of follow-up. However, the effectiveness of using radiotherapy to control tumor growth is controversial, as radiotherapy can also induce malignant transformation. A retrospective study conducted by Selvanathan et al. evaluated a patient cohort comprised of 21 cases that received adjuvant radiotherapy and 37 cases that did not and concluded that adjuvant radiotherapy did not influence overall survival [16].

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Disclosure of conflict of interest

None.

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