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CASE REPORT

Multiple pilocytic astrocytomas of the cerebellum in a 17-year-old patient with neurofibromatosis type I

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Abstract
Objective Approximately 10% of patients with neurofibromatosis I (NFI) patients will have central nervous system (CNS) tumors. The most common of these are hypothalamic–optic gliomas, followed by brainstem and cerebellar pilocytic astrocytomas. While isolated pilocytic astrocytomas in NFI are well described, the appearance of multiple pilocytic astrocytomas in an individual patient is less common. The most frequent combination in NFI patients with more than one pilocytic astrocytoma is optic tract/hypothalamic and brainstem. Other combinations are exceedingly rare; multiple pilocytic astrocytomas have only been reported once in the cerebral hemispheres in a patient with NFI. This report presents the first documented case, to our knowledge, of multiple pilocytic astrocytomas in the cerebellum of a patient with NF1.
Methods Case report.
Conclusion The finding of multiple cerebellar pilocytic astrocytomas in a patient with NF1 is important because it expands the spectrum of presentations for patients with NF1 and also highlights specific diagnostic and therapeutic challenges faced by the treating physicians. The genetic and molecular basis of NF1 is reviewed. Strategies of diagnosis and treatment outlined here are relevant to both patients with NF1 and all patients with multiple posterior fossa tumors.

Keywords Neurofibromatosis I · Multiple pilocytic astrocytomas · Brain tumor · Pediatric

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Introduction

Neurofibromatosis I (NFI) predisposes patients to tumors of both the peripheral and central nervous systems (CNS). While peripheral nervous system tumors are more common, up to 5–11% of NFI patients will have CNS tumors [4]. The most common of these CNS tumors are astrocytomas of the optic tract and hypothalamus, followed in frequency by brainstem and cerebellar pilocytic astrocytomas. Despite the benign nature of these tumors histologically, they may, nonetheless, contribute to considerable increases in patient morbidity and mortality.

While isolated pilocytic astrocytomas in NFI are well described, the appearance of multiple pilocytic astrocytomas in an individual patient is less common [3, 6, 8, 10]. The most frequent combination in NFI patients with more than one pilocytic astrocytoma is optic tract/hypothalamic and brainstem [3]. Other combinations, however, are exceedingly rare; multiple pilocytic astrocytomas have only been reported once in the cerebral hemispheres in a patient with NFI [6]. This report presents the first documented case, to our knowledge, of multiple pilocytic astrocytomas in the cerebellum of a patient with NF1. This finding is important because it expands the spectrum of presentations for patients with NF1 and also highlights specific diagnostic and therapeutic challenges faced by the treating physicians.

Case report

A 17-year-old patient with a known history of NFI diagnosed originally by the presence of axillary freckling, multiple café-au-lait macules (>6), an affected first degree relative, and subsequently confirmed by neurogenetic consultation presented with several weeks of progressive nausea, vomiting, and ataxia. His neurologic exam was notable for mild axial instability and bilateral dysmetria. Fundoscopic examination disclosed papilledema. Computed tomography (CT) and magnetic resonance imaging (MRI) disclosed multiple enhancing lesions in the superior left cerebellar hemisphere abutting the tentorium, the vermis, and the left tonsil of the cerebellum, with attendant obstructive hydrocephalus (Fig. 1a–d). Given the unusual presentation of the multiple lesions, a diagnostic angiogram was performed to exclude the possibility of hemangioblastoma and to evaluate the lesions for possible embolization in anticipation of potentially minimizing blood loss with planned surgical resection (Fig. 1e,f).

Given the mass effect of the lesions and the resultant obstructive hydrocephalus, the decision was made to bring the patient to surgery, with the preoperative understanding that total surgical extirpation in a single sitting may not be possible. Goals of surgery included obtaining tissue for definitive pathologic diagnosis; decompression of the posterior fossa; and treatment of obstructive hydrocephalus by resection of presumed tumor tissue occluding the fourth ventricle.

Placement of an external ventricular drain was performed as part of the operative procedure, and a midline suboccipital craniectomy and C1 laminectomy were performed. A significant subtotal resection was performed, achieving the goals outlined preoperatively with resection of the vermian, tonsillar, and superior hemispheric lesions. The patient tolerated the procedure well without requiring a transfusion.

Pathologic analysis was consistent with pilocytic astrocytoma, with standard features of elongated cells and Rosenthal fibers identified (Fig. 2a,b). Despite restoration of normal cerebrospinal fluid (CSF) pathways, with decompression of the fourth ventricle and posterior fossa, the patient ultimately required placement of a ventriculoperitoneal shunt several weeks after craniotomy for communicating hydrocephalus.

His perioperative course was otherwise remarkable for a mild posterior fossa syndrome, and he was discharged to rehabilitation. He recovered well and was independent at school at his appropriate grade level and performing well academically without detectable deficits. Eighteen months later, he returned to our institution with 3 weeks of increasing ataxia and intermittent diplopia, with examina-

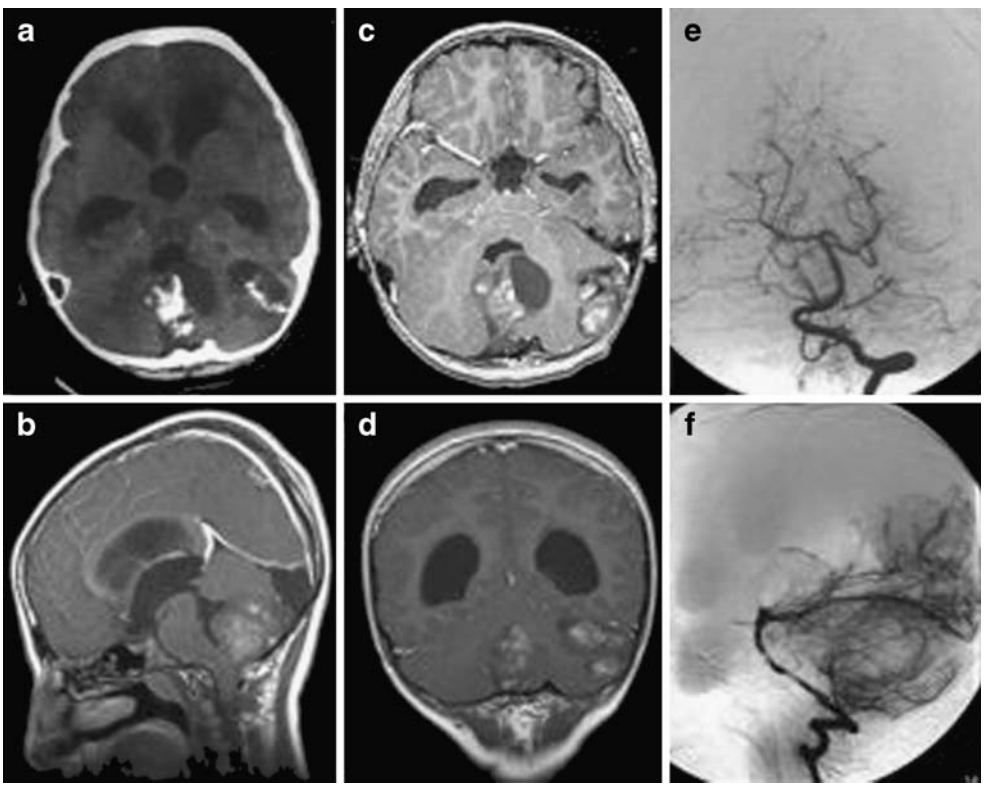

Fig. 1 a–f. **a** Axial CT with contrast demonstrating enhancing, cystic lesions in the cerebellum and hydrocephalus. Sagittal (**b**), axial (**c**), and coronal T1-weighted MRI images with gadolinium demonstrating multiple lesions of the cerebellum. Anteroposterior and lateral angiograms of left vertebral artery injection showing multiple hypovascular lesions in the cerebellum

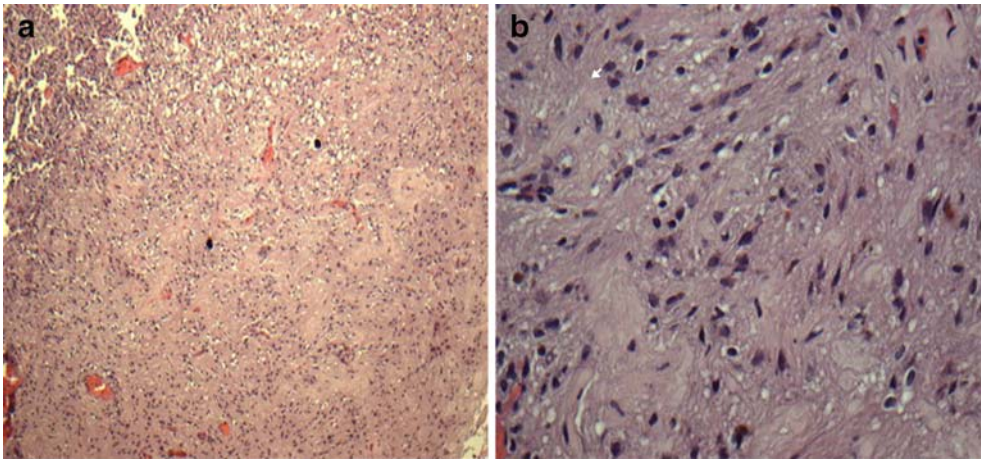

Fig. 2 **a** and **b**.×100 Hematoxylin and eosin (H and E) slide (**a**) of specimen from resection demonstrating pilocytic astrocytoma; ×400 H and E slide (**b**) of same specimen. *White arrow* shows representative Rosenthal fibers

tion notable for mild horizontal nystagmus and left-sided dysmetria. MRI showed a 6.7×4.5 cm cystic mass centered in the left cerebellum with an enhancing mural nodule inferiorly (Fig. 3a–c). He was taken to surgery for gross total resection; tissue was consistent with pilocytic astrocytoma and likely represented a recurrence of the left tonsillar lesion. He did well postoperatively and was discharged home where he has continued to recover well. His most recent MRI scan has shown a recurrence of the left superior cerebellar lesion, which has slowly increased in size on prior scans performed over a 2-year period since his initial resection (Fig. 3e–f). He is currently clinically stable and will be followed closely.

Discussion

Multiple CNS tumors in a single patient have been described in the setting of NF1 [1, 3, 5, 8, 9]. In Guillamo's series of 104 patients, multiple tumors in NFI patients were likely to be located in the optic tract and brainstem [3], although pathology was not confirmed in all cases in this series. Bilaniuk et al. reported a similar propensity for optic tract tumors to be associated with brainstem fibrillary astrocytomas. Multiple pilocytic astrocytomas, however, are rare. This phenomenon has only been reported twice before—in a patient without NF1 [2] and in association with NF1 [6]—and has not been reported in the cerebellum. This case describes multiple cerebellar pilocytic astrocyto-

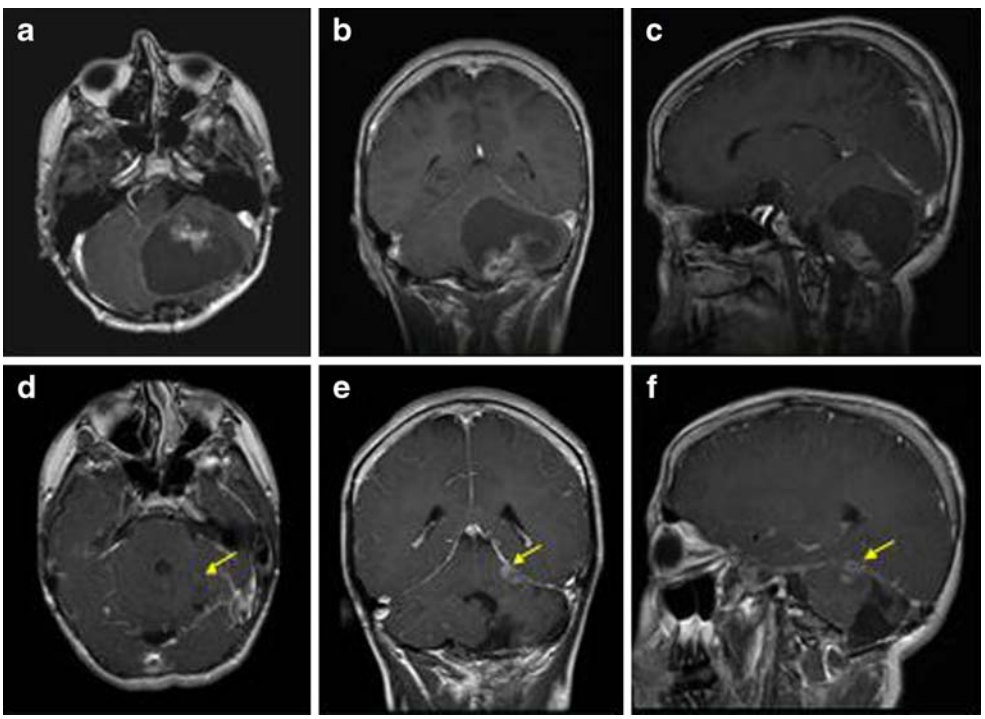

Fig. 3 **a–c**: T1 with gadolinium axial (**a**), coronal (**b**), and sagittal (**c**) MRI views show recurrent left inferior cerebellar cystic tumor with enhancing nodule resected during second surgery. A left superior cerebellar tumor is not seen; **d–f** left superior cerebellar nodule (*yellow arrow*) on follow-up MRI 8 months after MRI shown in **a–c**

mas in a patient with NFI, a presentation that has not previously been reported in association with this disease.

The genetic background in which these tumors arose may help explain the presence of multiple tumors. Neurofibromatosis type I is a common inherited disease with an autosomal dominant pattern in which the NF1 gene, encoding the protein neurofibromin, is mutated [7]. Neurofibromin is a tumor suppressor as a member of the Ras-GTPase activating protein (RasGAP) family, and its loss results in hyperactivation of the Ras pathway; activation of Ras family members of Ras superfamily members is a central event in a wide range of human cancers. Children with NF1 are, thus, at high risk of developing tumors of the central and peripheral nervous systems, including optic nerve gliomas, intraspinal tumors, and peripheral nerve tumors. While NF1 loss may help explain the appearance of multiple tumors in this particular case, it is unclear why this patient's phenotypic manifestation of NF1 is rare.

The variable phenotypic expression of the NF1 genotype, as exemplified by this patient, leads the discussion from the molecular mechanism of disease to the clinical management of these patients. Because of the genetic background of these children, they are prone to the development of multiple tumors over their life span. The practical outcome of this genetic defect is that there is a strong impetus to manage these growths conservatively. Unless a lesion exhibits rapid growth, symptomatic progression, or malignant degeneration, there is often a clinical consensus to observe them with serial imaging and clinical exams.

This case is important because it highlights two issues relevant to the underlying genetic defect in NF1—namely, treating only symptomatic lesions and formulating strategies to manage multifocal disease. For those patients presenting with multiple symptomatic tumors, complete surgical extirpation may be difficult, and clear surgical goals need to be formulated. The complex nature of this constellation of tumors mandates execution of hierarchical objectives in the operating room-tissue diagnosis, decompression of vital neural structures, restoration of CSF pathways, and if possible, gross total excision. Tumor progression may result in the need for further resection or consideration of adjuvant therapies. In all settings, long-term dedicated follow-up is of primary importance in maximizing the probability of optimal outcomes in these complex patients.

Conclusion

We here add to the literature describing CNS manifestations of NFI, reporting the first case to our knowledge of multiple cerebellar pilocytic astrocytomas in a patient with NFI. This case not only expands the scope of presentations reported in association with NFI but also highlights treatment strategies that can be applied to a broader range of clinical scenarios involving pediatric tumor patients, including the need for clear surgical objectives, ongoing communication of these objectives to family members, and the importance of long-term clinical and radiographic follow-up.

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