Multifocal intracranial astrocytoma in a pediatric patient with Ollier disease

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Abstract

Ollier disease (OD) is a subtype of enchondromatosis. Historically, it has been distinguished from Maffucci syndrome (MS) by the presence of vascular malformations and nonskeletal neoplasms (NSN) in the latter. However, there is an increasing number of reports of NSN in OD, and this categorization is now being questioned. We report a case of OD complicated by multifocal astrocytoma in a young patient, once again pointing to a possible association between OD and NSN. We also review the available literature and examine the similarities between the reported cases.

Key words: Astrocytoma; *IDH1* mutation; multifocal; Ollier disease

Introduction

Enchondromatosis refers to multifocal hamartomatous proliferation of chondrocytes within the metaphyses of bones.[1,2] These cartilaginous masses cause thinning of the overlying cortices, with associated shortening and deformity of the bone. Limb length discrepancies and pathological fractures can also occur.[1,3-5] Enchondromatosis is a rare, nonhereditary condition that was first described by Maffucci in 1881 in association with venous angiomas.[1–3,5,6] In 1899, Ollier described enchondromatosis in a patient with no evidence of vascular anomalies, known as Ollier disease (OD).[1,2]

Historically, these entities have been distinguished based on the presence of vascular malformations and nonskeletal neoplasms (NSN) in Maffucci syndrome (MS).[2,7] With advances in medicine and imaging, more and more cases of OD associated with nonskeletal malignancies are now being discovered. This, coupled with the late discovery of vascular malformations in some of the earlier cases of OD, has led many authors to speculate that these entities are just different manifestations of a common disease process.[1,4,6]

Our case, together with the previously reported cases, supports the association between OD and NSN and once again questions the existence of OD and MS as distinct identities.

Case Report

A 16-year-old male presented to the clinic with a 2-week history of intermittent headaches. There were no localizing signs or motor or sensory symptoms. The past history was significant only for known multiple enchondromatosis, which had been diagnosed at 15 years of age after a pathological fracture of the proximal phalanx of his right index finger. The lesions had been localized to the index and middle fingers of right hand in a ray distribution [Figure 1].

We obtained a noncontrast computed tomography (CT) scan [Figure 2], which showed a nonspecific hypodense lesion in the right insular cortex. There was no hemorrhage, calcification, or significant perilesional edema. The patient was subsequently lost to follow-up and no further investigations could be performed at that point. Three years later, however, the patient was admitted following a road traffic accident. Noncontrast CT scan [Figure 3] was done and showed a subdural hematoma (SDH) over the left cerebral convexity. The previously identified lesion in

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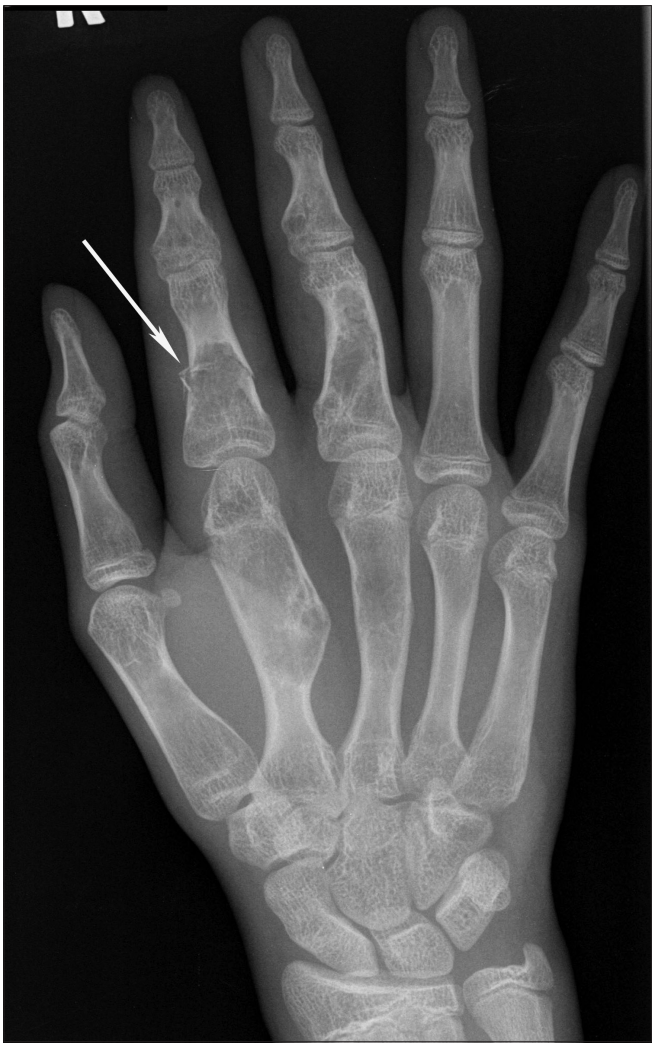

Figure 1: Anteroposterior radiograph of the right hand shows multiple expansile, osteolytic lesions involving the metacarpals, proximal and middle phalanges of the right index and middle fingers. There is a pathological fracture (white arrow) involving the proximal phalanx of the right index finger

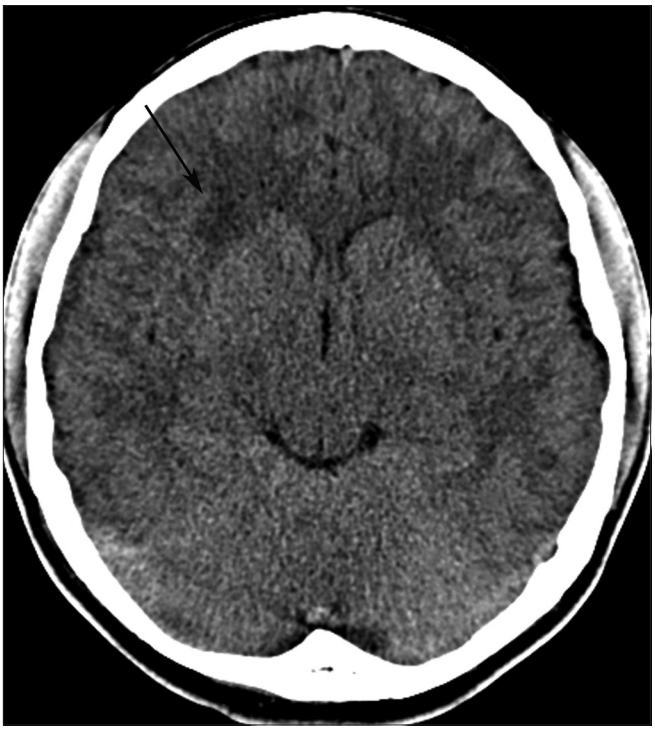

Figure 2: Initial noncontrast CT scan shows an ill-defined lesion (black arrow) in the right frontal lobe. There is no hemorrhage, calcification, perilesional edema, or significant mass effect

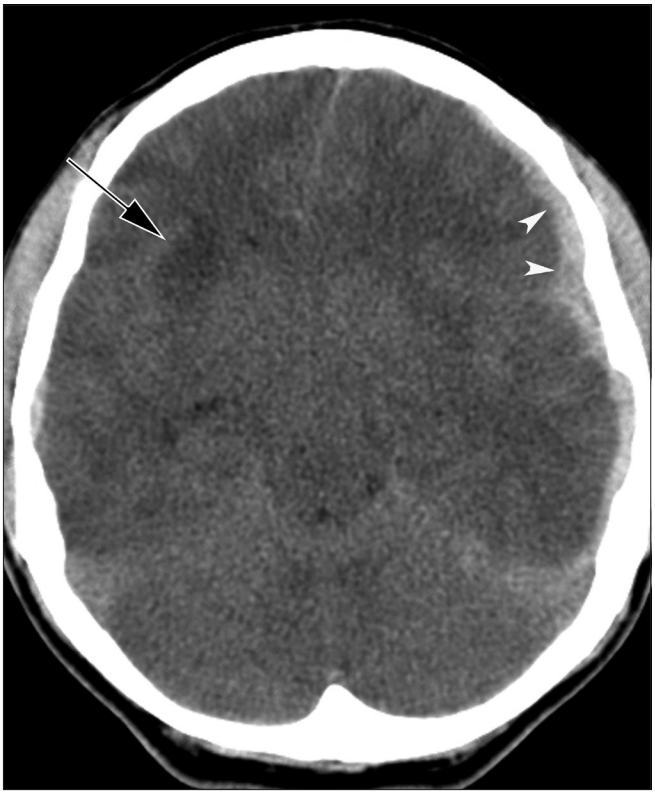

Figure 3: Noncontrast CT scan obtained 3 years later shows subdural hemorrhage (white arrowheads) along the left cerebral convexity, with associated mass effect. The hypodense lesion involving the right frontal lobe (black arrow) has increased in size

the right insular cortex had increased in size. In addition, there were similar hypodense lesions in the left basifrontal region and the left precentral gyrus.

The patient underwent an emergency craniotomy for the SDH. A subsequent magnetic resonance imaging (MRI) done 1 week later [Figure 4] showed an additional smaller lesion in the right cingulate gyrus. None of these lesions showed contrast enhancement. The possibility of multifocal gliomas was raised. The patient subsequently underwent biopsy of the left high frontal lesion. The initial pathology report, based on hematoxylin and eosin (H&E) staining, showed mild focal increase in cellularity within the sampled tissue [Figure 5]. There was no conclusive evidence of a glioma. Immunohistochemical staining for mutant isocitrate dehydrogenase-1 (IDH1) was subsequently performed and

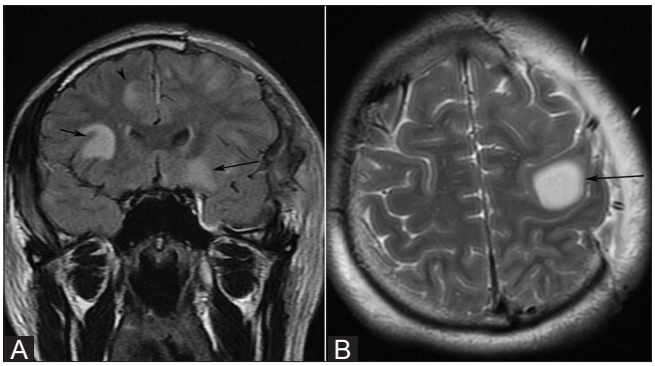

Figure 4 (A, B): MRI done 1 week after evacuation of the subdural hemorrhage. Coronal FLAIR MRI (A) shows areas of signal alteration involving the right frontal lobe (short arrow), cingulate gyrus (arrowhead), and left basifrontal region (long arrow). Axial T2W MRI (B) shows another lesion (arrow) in the region of the left precentral gyrus. Note the interval craniotomy

came back positive in the areas of increased cellularity. The final diagnosis was diffusely infiltrative low-grade glioma.

Follow-up MRI after 6 months did not show any significant change in the lesions. The patient is being planned for radiotherapy.

Discussion

This patient has multifocal low-grade gliomas with associated OD. Together with the previously reported cases, this again points to an association of OD with cerebral glioma [Table 1].

A retrospective analysis of cases of OD with gliomas reveals that the initial age at diagnosis of intracranial gliomas in these patients ranges from 6 to 46 years (cases 9 and 16, respectively), with a mean age of 23.7 years. This is similar to the observation of Hori *et al*., who reported that the median age of diagnosis of glioma was 26.4 years.[8] Including the present case, there were five patients within the pediatric age-group (i.e. <18 years). More significantly, 14 out of 19 (73%) patients were aged between 10 and 30 years.

The gender of case 1 was not available; analysis of the remaining 18 cases reveals a male predominance, with a male:female ratio of 2:1 (12 males and 6 females).

Tissue diagnosis was not obtained in two cases (cases 11 and 12). Out of the remaining 17 cases, 2 cases were reported as astrocytoma, with no further subdivision into low or high grade (cases 4 and 15). Of the remaining, six each were low- and high-grade astrocytomas, two were oligoastrocytomas, and one was an oligodendroglioma.

A total of 6 out of 19 cases (31.5%) were multifocal, with more than one noncontiguous lesion. Based on our review, we speculate that this high rate of multifocality is unlikely

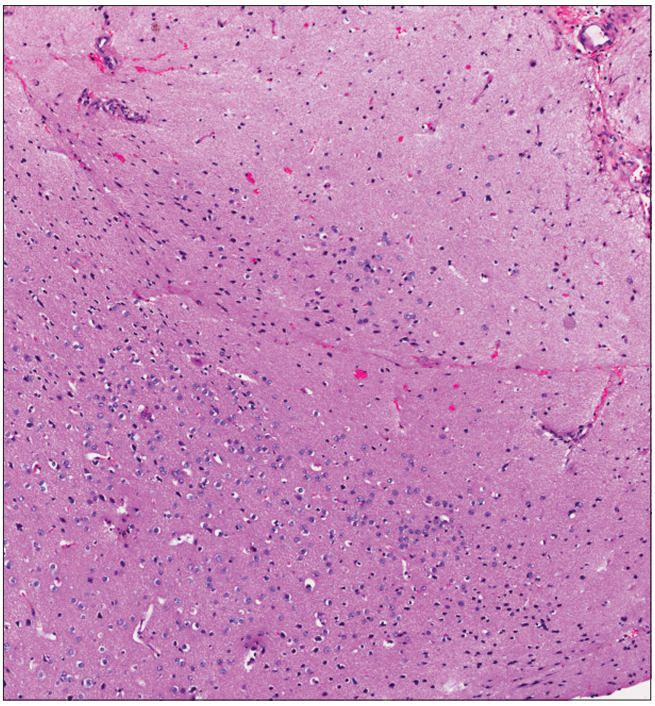

Figure 5: Medium-power view (H and E, ×20) shows areas of mildly increased cellularity composed of astrocytic and oligodendroglial cells (lower part of the image) as compared to normal brain parenchyma (upper part of the image)

to be a chance finding and may point to a widespread astrocyte mutation, predisposing them toward malignant change. This is further supported by the fact that OD is believed to be due to postzygotic somatic mutation, which results in a mosaic cell population. This also helps explain the random distribution of enchondromas in both OD and MS.[17] Occurrence of gliomas in identical twins again points toward an underlying genetic predisposition in these patients to develop gliomas.[2,3]

Evaluation based on the site of lesions showed that in 8 of the 16 cases (50%) there was a distinct frontal lobe lesion, followed by 6 out of 16 cases (37.5%) with brainstem lesions. This is different from non-Ollier astrocytomas, which most commonly involve the temporal lobe. Two cases showed involvement of multiple lobes/extensive disease (cases 7 and 18), while no exact site of involvement was specified in case 15; these three cases were not included in this analysis.

Our patient is the first case where a mutation within the glioma has been identified in a patient with known OD. The *IDH1* mutation is seen in up to 75% (range: 50–80%) of grade II and grade III diffuse gliomas and secondary glioblastoma multiforme (75%) and is most common in young patients.[18] Very recently, mutations in the *IDH1* gene were also detected in conventional cartilaginous tumors of patients having both single and multiple enchondromas.[19] *IDH* mutations may provide a common link between

Table 1: Intracranial neoplasms in patients with Ollier disease

Reference no.	Authors	Age/gender	Site	Histology
[9]	Becker and Thron (1979)	26/not specified	Right frontal lobe	Grade 2 oligoastrocytoma
[10]	Rawlings *et al*. (1987)	29/M	1) Right cerebellum 2) Right frontal lobe and corpus callosum	Anaplastic astrocytoma
[6]	Mellon *et al*. (1988)	34/M	Right frontal lobe	Grade 2 astrocytoma
[11]	Schwartz *et al*. (1987)	38/M	Temporal/parietal lobe	Astrocytoma
[12]	Patt *et al*. (1990)	24/M	Brainstem	Low-grade astrocytoma
[13]	Bendel and Gelmer (1991)	29/F	Left frontal	High-grade astrocytoma
[3]	Chang *et al*. (1994)	23/M	Left temporal, left occipital, right frontal, and right parietal lobes	Anaplastic astrocytoma
[3]	Chang *et al*. (1994)	25/M	Right frontal	Oligodendroglioma
[3]	Chang *et al*. (1994)	46/M	Bilateral frontal lobes, crossing the midline	Oligoastrocytoma
[2]	Hofman (1998)	28/M	Left temporal lobe and brainstem	Low-grade astrocytoma (biopsy from left temporal lobe lesion)
[7]	Balcer *et al*. (1999)	23/F	Pons	No biopsy. Imaging consistent with astrocytoma
[5]	Frappaz *et al*. (1999)	16/M	Brainstem	No biopsy. Imaging consistent with astrocytoma
[14]	Simsek *et al*. (2002)	7/F	Right frontal lobe	Low-grade astrocytoma
[15]	Mahafza *et al*. (2004)	21/F	Right frontal lobe and brainstem	Low-grade astrocytoma
[16]	Koc and Koc (2006)	28/F	Cerebrum	Astrocytoma
[1]	Ranger (2009)	6/F	Left thalamus	Glioblastoma multiforme
[17]	Walid and Troup (2008)	14/M	Posterior fossa	Anaplastic astrocytoma
[8]	Hori *et al*. (2010)	19/M	Extensive supra- and infratentorial disease	Anaplastic astrocytoma
	Present case	16/M	Multiple lesions in both frontal lobes	Low-grade astrocytoma

Figures in square brackets are the corresponding reference numbers

gliomas and enchondromas in patients with OD, though this remains speculative at this point.

Mutations involving the parathyroid hormone-related peptide (PTHrP) type 1 receptor (*PTHR1*) have also been described in patients with OD, but are seen in only about 10% of cases.[20] In the central nervous system (CNS), *PTHrP* overexpression has been described in normal embryonic and human glial tumors.[21] These findings may point to another common link involving enchondromas and gliomas in patients with OD. Considering the multifactorial etiology of enchondromatosis, we speculate that *IDH1* mutations may also account for another subset of OD patients. However, further studies on a larger scale are needed to establish the pathophysiology of OD and associated tumors.

Conclusion

This is the first case report of a multifocal glioma in a pediatric patient, where the underlying genetic mutation was identified. The analysis of available literature shows that patients with OD develop gliomas at a relatively younger age and there is a high rate of multifocality. In addition, involvement of the frontal lobe and brainstem is more common.

The relatively asymptomatic presentation in our case may argue in favor of routine screening of these patients for intracranial gliomas.

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