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Ollier disease with anaplastic astrocytoma: A review of the literature and a unique case

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Abstract

Background: Ollier disease is a rare, nonfamilial disorder that primary affects the long bones and cartilage of joints with multiple enchondromas. It is associated with a higher risk of central nervous system (CNS) malignancies; although the incidence is unknown.

Case Description: Here, we present the case of a 55-year-old woman who developed an anaplastic astrocytoma with a known diagnosis of Ollier disease with a survival time of over 3 years.

Conclusion: This report draws attention to the rarity of this disease and the paucity of information regarding CNS involvement in Ollier disease, as well as reviews the current literature.

Key Words: Astrocytoma, endochondroma, IDH1 mutation, intracranial tumor, Ollier Disease

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INTRODUCTION

Ollier disease is a rare, nonfamilial disorder with a prevalence of 1:100,000, characterized by multiple enchondromatosis, with an asymmetric distribution, and areas of dysplastic cartilage. The condition primarily affects the long bones and cartilage of the joints of the arms and legs, specifically at the metaphysis and is divided into 6 types.[16] Type I consists of multiple, mostly unilateral enchondromas of tubular and flat bones, with hand involvement. Type II is called Mafucci syndrome and is defined by multiple enchondromatosis associated with the soft tissue hemangiomas, typically sparing the spine, is associated with a higher risk of concurrent central nervous system (CNS), pancreatic, and ovarian malignancies. (Maffucci syndrome has been described as a different entity than Ollier, and together with metachondromatosis, these three disease entities are similar but distinct). Type III is characterized by enchondromas and digital osteochondromas. Type IV consists of enchondromas of the bones and spinal dysplasia, without involvement of the hands. Type V is defined by bone and vertebral body lesions, with minimal hand involvement, and Type VI has severe hand and foot lesions and erosion of the iliac crests. A malignant sarcomatous transformation of the lesions has been observed in 25–50% of Ollier patients and 100% of Mafucci patients. It manifests itself as multiple expansible, lytic lesions in the affected limbs, with cortical destruction and invasion into the adjacent bone

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and the local soft tissues.[6] Unique longitudinal lines in the metaphysis are characteristic radiographic findings and are called "sled runner tracks" [Figure 1].[16]

It remains uncertain whether the disorder is caused by a single gene defect or by combinations of (germline and/or somatic) mutations.[16] Cytogenetic analysis of low-grade chondrosarcoma in a patient with Ollier disease (multiple enchondromatosis) revealed an interstitial deletion, del (1) (p11p31.2) as the only chromosome abnormality. Such patients are at a risk of developing chondrosarcoma.[12] Heterozygous mutations in *PTHR1* that impairs receptor function participate in the pathogenesis of Ollier disease in some patients.[4] Ollier disease and solitary enchondromas may have the same signaling pathways involved in tumorigenesis. *JunB* protein expression is significantly higher in grade I chondrosarcomas than in enchondromas, which could be of diagnostic relevance.[14]

Clinical manifestations often appear in the first decade of life and usually start with local pain, bone swelling, and palpable bony masses, which is often associated with bone deformity. Headache and cranial nerve palsy are prominent clinical findings. The only effective treatment is the surgical resection of the lesions and symptomatic treatment of the possible complications such as pathological fractures, growth defect, and neurological symptoms.[5]

Intracranial lesions have been described previously and the most prevalent type of CNS tumors associated with Ollier disease is astrocytoma (low-grade to glioblastoma multiforme) and oligodendroglioma.[9] In this paper, the authors describe a case of an anaplastic astrocytoma in Ollier disease with a survival time of over 3 years, which, to our knowledge, is the first reported case of anaplastic astrocytoma with such a long survival time.

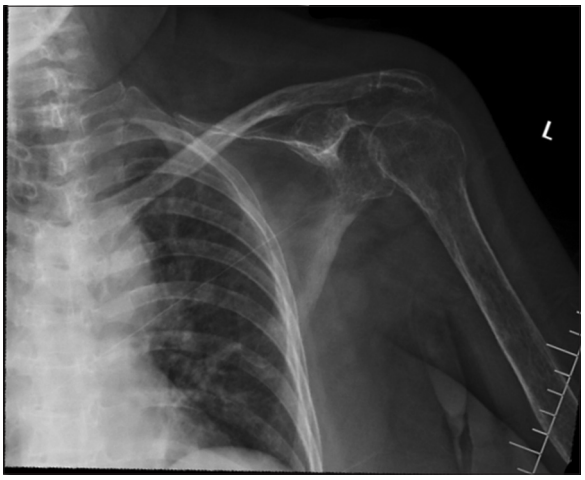

Figure 1: "Sled-track" appearance of the distal humerus and proximal forearm is a characteristic radiographic feature

CASE DESCRIPTION

A 55-year-old woman with Ollier disease and congenital limb deformities presented to our clinic in October 2013. She was originally diagnosed in April 2011 with progressive right hemiparesis and language and memory problems. Imaging studies demonstrated a large left-sided hemispheric mass [Figure 2]. She underwent a craniotomy and subtotal resection of the lesion that was diagnosed as an anaplastic astrocytoma. The postoperative course was complicated by postoperative hemorrhage, extended mechanical ventilation, a tracheostomy, and a percutaneous endoscopic gastrostomy tube placement. The patient had a very gradual and slow recovery but remained densely hemiparetic in the right leg, with facial droop and cognitive dysfunction. She did not receive any postoperative adjuvant treatment such as radiation or chemotherapy; treatment for the brain tumor was offered to the patient but was declined by her and her family. In 2012, she developed a pulmonary embolism and was anticoagulated with fragmin. In 2013, she had an episode of acute pain in the left forearm, and recommendations for more diagnostic tests to rule out a potential malignant transformation of her bony tumors were declined by the patient who also refused any further diagnostic or therapeutic measures.

She was recently seen in the clinic in September 2014 and was remarkably stable despite the lack of any postoperative adjuvant therapy. On examination, she continues to have right facial droop and right hemiparesis but with intact cranial nerves II–XII. Left arm was immobile due to pain but the left leg had full strength. The patient had moderate expressive aphasia but followed requests and answered simple questions easily. There were no spasticity or contractures present. Psychiatric evaluation showed a pleasant, cooperative individual, with poor short-term memory and psychomotor slowing.

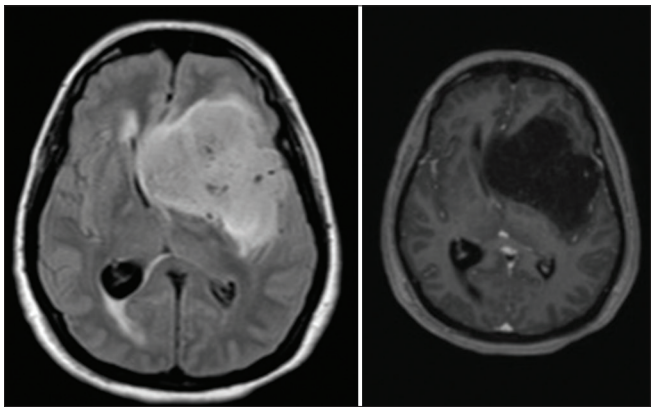

Figure 2: Magnetic resonance imaging: T2-weighted image (left) and T1-weighted image with contrast (right) from 2011 showing a large anaplastic astrocytoma status post-subtotal resection

The husband described typical hypothalamic gelastic seizures episodes, 2–3 brief episodes per month despite the fact that she was on seizure prophylaxis medication. She had an magnetic resonance imaging (MRI) in August 2014 that showed stable disease without any interval [Figure 3]. In addition, we performed an IDH-1 mutation analysis using immunohistochemistry technique that yielded a positive result for the presence of the mutation in the specimen obtained in surgery at 2011 [Figure 4].

DISCUSSION

A retrospective analysis published by Bathla *et al*. shows cases of Ollier disease with gliomas diagnosed at a mean age of 23.7 years.[3] The incidence of CNS malignancies in Ollier disease is unknown because it is a rare entity, with only 19 cases described in the literature [Table 1].[3] The mean survival of the 19 patients with Ollier disease and CNS malignancy reported in the literature is not clear, but undoubtedly the prognosis for such patients is poor.[9] In patients with non-Ollier disease astrocytomas, the median progression free survival (PFS) is 4.6 months and the overall survival (OS) is 20.5 months.[6]

Interestingly Bathla reported that 50% of the patients had a distinct frontal lobe lesion, followed by 37.5% with brainstem lesions.[3] This is different from non-Ollier astrocytomas, which most commonly involve the temporal lobe.[9] Our patient is a 55-year-old woman with a large left-sided frontotemporal lesion. Her age at presentation was almost twice the median age at diagnosis for gliomas in Ollier disease, as cited in the literature.[9] In addition, the disease seems to be well-controlled after her subtotal resection even without postoperative adjuvant therapy, as shown in the second MRI image from 2014 [Figure 3]. The patient continues to survive without postoperative treatment 3 years from diagnosis, and after subtotal resection, compared to an observed 27% 5-year survival in untreated non-Ollier astrocytomas, where despite implementation of intensive therapeutic strategies and supportive care, the median survival of glioblastomas has remained at 12 months over the past decade.[7]

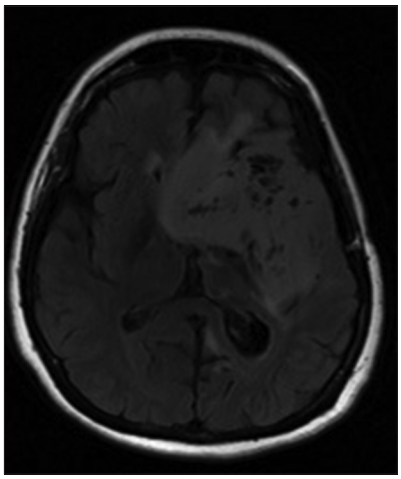

Figure 3: Magnetic resonance imaging: T1-weighted image without contrast in 2014 demonstrating a stable lesion. Immunocytochemistry of the specimen with IDH-1 demonstrates strong positivity

A potential explanation could be a difference in the tumor genotype; in patients with anaplastic astrocytomas without any association with Ollier Disease, isocitrate dehydrogense 1 (*IDH1*) has been demonstrated to be the single, most prominent prognostic factor for survival, followed by age, diagnosis, and methylguanine-DNA-methyltransferase (MGMT) status.[10] Somatic mutations in *IDH1* and *IDH2* occur in gliomas that are not associated with Ollier disease.[1] *IDH*-mutated astrocytomas have been shown to duplicate *8q24*. Single nucleotide polymorphisms (SNPs) mapped to *8q24* have been shown to be associated with glioma development, and recent data suggest that carrying the risk allele for rs55705857 predisposes to the development of gliomas that subsequently duplicate *8q24*.[15] Studies have shown that chromatin-remodeling pathways including *ATRX* aberrations were detected in 46% of grade III gliomas, as well as in 80% of secondary gliomas and glioblastomas in adults.[11] Data show that *ATRX* alterations are frequent in adult diffuse gliomas and are specific to astrocytic tumors carrying IDH1/2 and TP53 mutations.[11]

These genetic variations have been correlated with outcome and the sequence from most to least favorable prognosis is as follows: (1) Anaplastic astrocytoma with *IDH1* mutation, (2) glioblastoma with *IDH1* mutation, (3) anaplastic astrocytoma without *IDH1* mutation, and (4) glioblastoma without *IDH1* mutation.[8] The prognostic value of *IDH1 R132H* mutation in glioblastoma patients has been established, and patients with mutation had significantly longer PFS and OS than patients with wild-type *IDH1*.[13] Ollier disease and Maffucci syndrome have been shown to have a mutation in *IDH1* or *IDH2*.[2] These mutations may be the reason why the natural history and prognosis of gliomas associated with Ollier disease is more favorable. We did the *IDH1* mutation analysis using immunohistochemistry technique and found that

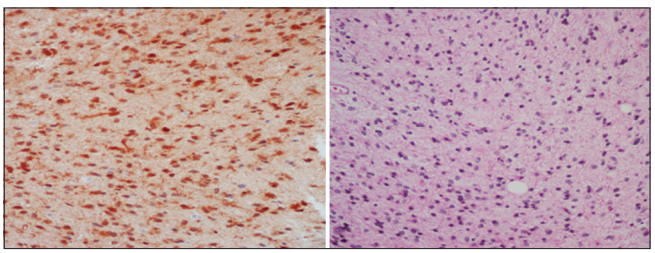

Figure 4: Small anaplastic astrocytes with dark oval nuclei and very scant cytoplasm overrun pre-existing brain tissue. Magnification: ×200

Table 1: All the published cases of Ollier's disease

Patient	Author	Age/Gender	Site	Histology
1	Becker and Thron (1979)	26/???	Right frontal lobe	Grade 2 oligoastrocytoma
2	Rawlings *et al*. (1987)	29/M	1. Right cerebellum 2. Right frontal lobe and corpus callosum	Anaplastic astrocytoma
3	Mellon *et al*. (1988)	34/M	Right frontal lobe	Grade 2 astrocytoma
4	Schwartz *et al*. (1987)	38/M	Temporal/parietal lobe	Astrocytoma
5	Patt *et al*. (1990)	24/M	Brainstem	Low grade astrocytoma
6	Bendel and Gelmer (1991)	29/F	Left frontal	High grade astrocytoma
7	Chang *et al*. (1994)	23/M	Left temporal, left occipital, right frontal, and right parietal lobes	Anaplastic astrocytoma
8	Chang *et al*. (1994)	25/M	Right frontal	Oligodendroglioma
9	Chang *et al*. (1994)	46/M	Bilateral frontal lobes, crossing midline	Oligoastrocytoma
10	Hofman (1998)	28/M	left temporal lobe and brainstem	Low grade astrocytoma (biopsy from left temporal lobe lesion)
11	Balcer *et al*. (1999)	23/F	Pons	No biopsy. Imaging consistent with astrocytoma
12	Frappaz *et al*. (1999)	16/M	Brainstem	No biopsy. Imaging consistent with astrocytoma
13	Simsek *et al*. (2002)	7/F	Right frontal lobe	Low grade astrocytoma
14	Mahafza *et al*. (2004)	21/F	Right frontal lobe and brainstem	Low grade astrocytoma
15	Koc and Koc (2006)	28/F	Cerebrum	Astrocytoma
16	Ranger (2009)	6/F	Left thalamus	Glioblastoma multiforme
17	Walid and Troup (2008)	14/M	Posterior fossa	Anaplastic astrocytoma
18	Hori *et al*. (2010)	19/M	Extensive supra- and infratentorial disease	Anaplastic astrocytoma
19	Bathla *et al*. (2012)	16/M	Multiple lesions in both frontal lobes	Low grade astrocytoma
20	Present Case	55/F	Left frontal, temporal, and parietal lobes	Anaplastic astrocytoma

???: Unknown

the tumor cells expressed *IDH1*. The mean survival of the 19 patients with Ollier disease and CNS malignancy reported in literature is unclear, but undoubtedly low in comparison to our patient who has been progression free for the last 3 years. The importance of this disease lies in the high risk of sarcomatous transformation of the skeletal lesions, as well as the increased risk of developing extraosseous malignancies. Only a limited number of studies address systematic screening for early diagnosis. However, early diagnosis of a brain tumor would improve the prognosis of patients. Because the signs and symptoms of a brain tumor may initially be vague, a neurological examination and MRI, if necessary, should be conducted during the follow-up period.[9] In addition, immunohistochemistry for *IDH1* should be performed whenever a specimen is available.

CONCLUSION

We present the case of a patient with Ollier disease and anaplastic astrocytoma who had a very favorable natural history of the CNS malignancy despite the lack of any adjuvant treatment after subtotal tumor resection. Analysis for *IDH1* gene mutations in this patient was positive and *IDH1* mutation in the tumor cells compared to wild type seems to have some protective effects in Ollier disease patients with anaplastic astrocytoma. An early genetic analysis after diagnosis can help in the prognostication of the illness and help the patients and their families to realistically deal with such a life-threatening cancer.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Amary M. IDH1 and IDH2 mutations are frequent events in central chondrosarcoma and central periosteal chondromas but not in the other mesenchymal tumors. J Pathol 2011;224:334-43.
2. Amary M. Ollier disease and Maffucci syndrome are caused by somatic mosaic mutations of IDH1 and IDH2. Nat Genet 2011;43:1262-5.
3. Bathla G, Gupta S, Ong CK. Multifocal intracranial astrocytoma in a pediatric patient with Ollier disease. Indian J Radiol Imaging 2012;22:58-62.
4. Couvineau A, Wouters V, Bertrand G, Rouyer C, Gerard B, Boon LM, *et al*. PTHR1 mutations associated with Ollier disease result in receptor loss of function. Hum Mol Genet 2008;17:2766-75.
5. D'Angelo L, Massimi L, Narducci A, Di Rocco C. Ollier disease. Childs Nerv Syst 2009;25:647-53.
6. Elens I, De Vleeschouwer S, Pauwels F, Van Gool S. Resection and Immunotherapy for Recurrent Grade III Glioma. ISRN Immunol 2011;2012:9.
7. Furnari FB, Fenton T, Bachoo RM, Mukasa A, Stommel JM, Stegh A, *et al*.

Malignant astrocytic glioma: Genetics, biology, and paths to treatment. Genes Dev 2007;21:2683-710.
8. Hartmann C, Hentschel B, Wick W, Capper D, Felsberg J, Simon M, *et al*. Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: Implications for classification of gliomas. Acta Neuropathol 2010;120:707-18.
9. Hori K, Matsumine A, Niimi R, Maeda M, Uchida K, Nakamura T, *et al*. Diffuse Gliomas in an adolescent with multiple enchondromatosis (Ollier's disease). Oncol Lett 2010;1:595-7.
10. Kloosterhof NK, Bralten LB, Dubbink HJ, French PJ, van den Bent MJ. Isocitrate dehydrogenase-1 mutation: A fundamentally new understanding of diffuse glioma? Lancet Oncol 2011;12:83-91.
11. Liu XY, Gerges N, Korshunov A, Sabha N, Khuong-Quang DA, Fontebasso AM, *et al*. Frequent ATRX mutations and loss of expression in adult diffuse astrocytic tumors carrying IDH1/IDH2 and TP53 mutations. Acta Neuropathol 2012;124:615-25.
12. Ozisik YY, Meloni AM, Spanier SS, Bush CH, Kingsley KL, Sandberg AA. Deletion 1p in a low-grade chondrosarcoma in a patient with Ollier disease. Cancer Genet Cytogenet 1998;105:128-33.
13. Polivka J, Polivka J Jr, Rohan V, Pesta M, Repik T, Pitule P, *et al*. Isocitrate Dehydrogenase-1 Mutations as Prognostic Biomarker in Glioblastoma Multiforme Patients in West Bohemia. Biomed Res Int 2014;2014:735659.
14. Rozeman LB, Hameetman L, van Wezel T, Taminiau AH, Cleton-Jansen AM, Hogendoorn PC, *et al*. cDNA expression profiling of chondrosarcomas: Ollier disease resembles solitary tumours and alteration in genes coding for components of energy metabolism occurs with increasing grade. J Pathol 2005;207:61-71.
15. Rynearson AL, Schowalter KA, Fink SR, Kollmeyer TM, Halder C, Sarkar G, *et al*. Abstract 4207: The germline rs55705857 risk allele is not preferentially gained in gliomas with 8q24 duplication. Cancer Research 2013;73(8 Suppl):4207.
16. Silve C, Juppner H. Ollier disease. Orphanet J Rare Dis 2006;1:37.