Case Report

Diffuse midline glioma in Ollier disease: A case report and a brief review of the literature

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ABSTRACT

Ollier disease is a rare condition presenting with enchondromas in an irregular distribution within the medullary cavity of bones. The disease is well known for sarcomatous transformation to chondrosarcomas. It also increases the risk of other malignancies like leukemia, ovarian tumors, and glial tumors. Central nervous system malignancies associated with Ollier disease are thought to arise by somatic IDH mosaicism with their atypical features of distribution, multifocality, and age of onset. We present a case with imaging consistent with diffuse midline glioma in a patient with Ollier disease. We conclude with a brief review of the literature on Ollier Disease with a focus on central nervous system malignancies, tumorigenesis and pathophysiology.

Keywords:
Enchondroma
Enchondromatosis
Glial
Ollier disease

Introduction

Ollier disease is a non-hereditary skeletal disorder characterized by multiple enchondromas in the medullary cavity of bones and usually confined to the metaphyses of the appendicular skeleton in an asymmetric distribution. The disease’s prevalence is 1 in 100,000, and it is the most common subtype of a spectrum called multiple enchondromatosis [1,2]. There are six subtypes of multiple enchondromatosis defined by Spranger et al. based on anatomic site, radiographic appearance, and mode of inheritance; within this classification, Ollier disease is called Spranger type I. Maffucci syndrome or Spranger type II is also a subtype of multiple enchondromatosis and is traditionally distinguished from Ollier Disease with soft tissue hemangiomias [3]. Type III is metachondromatosis, which is characterized by enchondromas along with osteoma and/or osteochondroma like lesions. Spondyloenchondrodysplasia or type IV is enchondromatosis of the long bones and pelvis, combined with vertebral dysplasia (platyspondyly). Type V or dysplasiaenchondromatosis is distinguished with irregularity of the vertebral bodies with segmentation.
abnormalities and secondary deformities. In type IV and V, hands and feet are not usually severely affected. Type VI or chérospondyloenchondromatosis is characterized by evenly distributed enchondromatosis of hands and feet with mild platyspondyly [1,12]. The other subtypes are even rarer when compared with type I and II [1,3].

The onset of Ollier is usually in the first decade of life and can be complicated by cosmetic deformities, angular deformities (i.e., genu varum, genu valgus), pathological fractures, limb-length discrepancy, or swelling of the extremities [4].

Enchondromatosis patients are well known for their predilection of enchondromas to undergo sarcomatous transformation into chondrosarcomas. The incidence of malignant transformation ranges from 5% to 50%. Apart from the sarcomatous transformation, there are different types of tumors associated with Ollier disease such as osteosarcoma, ovarian tumors (Juvenile granulosa cell tumor, Sertoli-Leydig cell tumor), leukemia (chronic myeloid leukemia, acute myelogenous leukemia), breast adenoma, non-small cell lung cancer, extra-abdominal desmoid tumor and finally central nervous system (CNS) tumors [4].

CNS tumors, especially gliomas, accompany Ollier disease as reported in previous case reports and series. Isocitrate Dehydrogenase (IDH) somatic mosaicism (especially IDH1) has been found in recent years in enchondromatosis patients with gliomas [5].

Here we report a case with multiple enchondromatosis with diffuse midline glioma.
Lesions showed similar signal pattern as the phalanges, metacarpal bones and humerus. Biopsy related postoperative changes were demonstrated.

Low NAA and high choline ratio was present.
Case report

A 15-year-old girl presented to the Pediatric Surgery department with complaints about a bump on her posterior chest wall. Her family recognized her problem when she was three years old and had not realized any progression ever since. Plain radiographs revealed mild endosteal scalloping without cortical destruction and small sharply defined lytic lesions with medullary chondroid calcification in the right scapula and humerus (Fig. 1). Bilateral hands and left humerus radiographs were obtained and demonstrated similar lesions consistent with enchondromatosis. Contrast-enhanced MRI showed T1 hypointense, T2 hyperintense enhancing lytic lesions without cortical destruction or surrounding edema in the phalanges, metacarpal bones, and humeral shaft (Fig. 2). Biopsy of one of the lesions with similar signal pattern on MRI in right iliac bone demonstrated enchondroma (Fig. 3). These findings were consistent with Ollier disease, and the patient was followed for eight years at irregular time intervals. All findings were stable during this time, and there was no progression or regression in any of the lesions. Eight years later, when she turned 23-years-old, contrast-enhanced MRI of the brain demonstrated T2-FLAIR hyperintense, non-enhancing diffuse midline glioma in the pons with high choline/NAA ratio on MR spectroscopy (Fig. 4). Biopsy was not obtained due to high post-operative complication risk. The patient was treated with concomitant chemoradiotherapy. Temozolomide cycles with synchronous radiotherapy were delivered, and follow-up with contrast-enhanced MRI exams of the brain at 2-3-month intervals were consistent with stable findings. The last MRI revealed significant regression in the lesion and was considered good response to treatment (Fig. 5).

Discussion

Historically, several theories have been proposed on the pathophysiology of enchondromatosis. The initial focus was on enchondromas, and it was proposed that these benign cartilaginous medullary tumors are just displaced normal physeal cartilage cells. Another proposed theory stated that these lesions resulted from abnormal signaling pathways in organizing the proliferation and differentiation of cartilaginous tissue. Early researchers believed that these tumor-like lesions...
were just hamartomatous growth of chondrocytes due to the failure of enchondral ossification [2].

With the arrival of the molecular era, heterozygous and missense mutations in parathyroid-related peptide type 1 receptor (PTHR1) was thought to be the primary culprit; however, it turned out that this gene was not the cause but a probable contributor to the disease process [6].

Amary et al. and Pansuriya et al. discovered that mutant IDH pathways contribute to the tumorigenesis in enchondromatosis patients with giomas [1,7]. IDH1 (affecting arginine 132) and IDH2 (affecting arginine 172) hotspot mutations were found in enchondromas of Ollier Disease and Maffucci syndrome. Chondrocytes along with the normal blood and bone marrow cells surrounding the tumor also have these mutations, which eventually led to the conclusion that this is a post-zygotic event that results in somatic mosaicism. Moreover, even in the same tumor, there is mosaicism among tumor cells. This finding explains the multifocality of gliomas and the irregular distribution of enchondromas in these patients [1,7,8,9].

IDH1R132H, followed by IDH1R172S, are the most common mutations in gliomas seen within Ollier disease and Maffucci syndrome patients [5]. However, the other types of tumors tend to have different mutations, such as chondrosarcomas with IDH1R132C [9]. Tan et al. found IDH2M131I mutation in a focus of multifocal infiltrating glioma in a patient with Ollier disease, supporting the tendency of multifocality [10]. Ollier disease patients are susceptible to malignancies developing in different sites of the body due to somatic IDH mosaicism. Our patient had diffuse midline glioma associated with multiple enchondromatosis. The tumor was responsive to concomitant chemoradiotherapy and was found to gradually regress after two years of therapy. Given that the five-year survival is less than 3% in diffuse midline glioma patients without Ollier disease, we can speculate that our patient has a more favorable prognosis. Nevertheless, the mean survival of

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### Table 1 - Ollier disease and intracranial tumors.

| Patient | Author | Age/Gender | Site | Histology |
|---------|--------|------------|------|-----------|
| 1       | Becker and Thron (1979) [16] | 26/F | Right frontal lobe | Grade 2 oligoastrocytoma |
| 2       | Rawlings et al. (1987) [17] | 29/M | Right frontal lobe | Anaplastic astrocytoma |
| 3       | Mellon et al. (1988) [18] | 34/M | Right frontal lobe | Grade 2 astrocytoma |
| 4       | Schwartz et al. (1987) [19] | 38/M | Temporal/parietal lobe | Astrocytoma |
| 5       | Patt et al. (1990) [20] | 24/M | Brainstem | Low grade astrocytoma |
| 6       | Bendel and Gelmer (1991) [21] | 29/F | Left frontal | High grade astrocytoma |
| 7       | Chang et al. (1994) [22] | 23/M | Left temporal, left occipital, right frontal and right parietal lobes | Anaplastic astrocytoma |
| 8       | Chang et al. (1994) [22] | 25/M | Right frontal | Oligodendroglioma |
| 9       | Chang et al. (1994) [22] | 46/M | Bilateral frontal lobes, crossing midline | Oligoastrocytoma |
| 10      | Hofman (1998) [23] | 28/M | Left temporal lobe and brainstem | Low grade astrocytoma (biopsy from left temporal lobe lesion) |
| 11      | Balcer et al. (1999) [24] | 23/F | Pons | No biopsy. Imaging consistent with astrocytoma |
| 12      | Frappaz et al. (1999) [25] | 16/M | Brainstem | No biopsy. Imaging consistent with astrocytoma |
| 13      | Simsek et al. (2002) [26] | 7/F | Right frontal lobe | Low grade astrocytoma |
| 14      | Mahafza et al. (2004) [27] | 21/F | Right frontal lobe and brainstem | Low grade astrocytoma |
| 15      | Koc and Koc (2006) [28] | 28/F | Cerebrum | Astrocytoma |
| 16      | Ranger (2009) [29] | 6/F | Left thalamus | Glioblastoma multiforme |
| 17      | Wald and Troup (2008) [30] | 14/M | Posterior fossa | Anaplastic astrocytoma |
| 18      | Hori et al. (2010) [31] | 19/M | Extensive supra- and infratentorial disease | Anaplastic astrocytoma |
| 19      | Bathla et al. (2012) [8] | 16/M | Multiple lesions in both frontal lobes | Low grade astrocytoma |
| 20      | Pearce et al. (2012) [13] | 19/M | Bilateral frontal, temporal, parietooccipital region | Low grade astrocytoma |
| 21      | Gajavelli et al. (2016) [14] | 55/F | Left frontal, temporal and parietal lobes | Anaplastic astrocytoma |
| 22      | Achiha et al. (2017) [15] | 32/M | Left frontal lobe | Oligodendroglioma |
| 23      | Current case | | | |
patients with Ollier disease and a CNS malignancy is unclear since there have been only 23 cases described, including our current case (Table 1).

Retrospective analysis of Ollier disease cases with gliomas by Bathla et al. found that these patients’ age range from 6 to 46 years, have a male-to-female ratio of 2:1, and 31.5% of cases are multifocal. Bathla et al. reported that 50% of patients have a tumor in the frontal lobe, and 37.5% occur in the brainstem [8].

Subsequently, three more cases were published by other authors, and three of these lesions were in the frontal lobe [13–15]. The fourth case (our current patient) has a brainstem lesion. Of these four cases, there were two males and two females, and the mean age was 27.2 years. The age of onset of non-Ollier-associated diffuse midline gliomas is nine years old, and the prognosis is very poor [5]. However, our patient was diagnosed at the age of 23, and the disease seems to be under control after treatment with chemoradiotherapy.

The risk of malignancy in enchondromatosis patients increases the need for screening with the aim for early diagnosis and treatment. Since gliomas, like most malignancies, may have better outcomes when diagnosed early, screening these patients with MRI at regular intervals may be necessary. A retrospective evaluation of clinical and radiological data of Ollier disease and Maffucci syndrome by Mandonnet et al. showed that follow-up of these patients with brain MRI at regular intervals is helpful since the rate of glioma in Ollier disease and Maffucci syndrome may be close to 5% [11].

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