Pathology - Research and Practice xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

Case report

Chondroblastoma-like tumor of the skull in a patient with cardio-facio-cutaneous syndrome

Danielle Fasciano[a], Shi Wei[a,*], Rong Li[b], Gene P. Siegal[a]

[a] Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama, 35249, United States
[b] Department of Pathology, Children's Hospital of Alabama, Birmingham, Alabama, 35233, United States

ARTICLE INFO

Keywords:
Cardio-facio-cutaneous syndrome
Chondroblastoma
Giant cell-rich lesion

ABSTRACT

Cardio-facio-cutaneous syndrome (CFCS) is a rare genetic disorder characterized by craniofacial deformities and heterogeneous cardiac and cutaneous manifestations. The condition is caused by de novo activating mutations in one of four genes encoding proteins involved in the RAS-MAPK signaling pathway; specifically BRAF, MEK1, MEK2, or KRAS. Variable malignancies have been reported in patients with CFCS. Herein we report a chondroblastoma-like lesion of the skull in a 20-year-old man with a clinical diagnosis of CFCS and a long-standing history of medically intractable epilepsy. Patients with CFCS have previously been noted to have poorly-defined giant cell lesions and this may be one such example.

1. Introduction

Cardio-facio-cutaneous syndrome (CFCS) is a rare genetic disorder caused by de novo activating mutations in one of four genes encoding proteins involved in the RAS-MAPK signaling pathway including BRAF, MEK1, MEK2, and KRAS [1,2]. It belongs to a group of diseases known as "RASopathies," which also include neurofibromatosis, Noonan syndrome, LEOPARD syndrome and Costello syndrome, as these conditions each possess germline mutations in the RAS-MAPK signaling pathway [3]. However, up to 40% of patients with CFCS currently have no molecular diagnosis suggesting other, as yet undefined genes may be involved [4]. Initially described in eight children, the occurrence is sporadic, with men and women equally affected [4]. Clinically, patients with CFCS may demonstrate various phenotypic features but most notably present with craniofacial dysmorphisms, heterogeneous cardiac defects, cutaneous manifestations and intellectual disability. As there is known dysregulation of the RAS-MAPK signaling pathway, it has been suggested that this mechanism may be the driver leading one to develop malignant transformation [5]. We, herein, report an unusual bone tumor in a patient with CFCS.

2. Case report

The patient, a 20-year-old man with a clinical diagnosis of CFCS and a long-standing history of medically intractable epilepsy, presented to the emergency department due to sudden onset of altered mental status, lethargy and vomiting. A chest radiograph, complete blood count, comprehensive metabolic panel, and urinalysis were all within normal limits.

Computed tomography (CT) scan of the head demonstrated a large left temporal parenchymal hematoma demonstrating differential densities. Overall, it measured approximately 7.7 × 6.1 × 4.8 cm in size, along with expansion and soft tissue opacification of the left mastoid temporal bone resulting in a mass effect (Fig. 1). He was immediately taken to the operating room for left temporoparietal craniectomy and debulking of the hemorrhagic mass. Intraoperative consultation revealed a giant cell-rich lesion. Postsurgical magnetic resonance imaging (MRI) revealed residual mass effect in the left mastoid temporal bone with enhancing foci within the adjacent left temporal lobe (Fig. 2).

Further review of the permanent histologic sections revealed a mixed solid and cystic lesion. The more solid areas exhibited sheets of mononuclear cells with eosinophilic cytoplasm, many with nuclear grooves, variably sized multinucleated giant cells and fibrochondroid islands. Adjacent to these zones, blood-filled cystic spaces were seen which lack an endothelial lining but had juxtaposed abundant multinucleated giant cells along the cyst walls characteristic of an aneurysmal bone cyst (Fig. 3). Fluorescence in situ hybridization (FISH) analysis for the Ubiquitin Specific Peptidase 6 (USP6) gene rearrangement was negative. While the collective findings were mostly consistent with a chondroblastoma with secondary aneurysmal bone cyst

* Corresponding author at: Department of Pathology, University of Alabama at Birmingham, NP 3545A, 619 19th St. South, Birmingham, AL, 35249-7331, United States.
E-mail address: swei@uabmc.edu (S. Wei).

https://doi.org/10.1016/j.prp.2018.08.003
Received 25 June 2018; Received in revised form 25 July 2018; Accepted 6 August 2018

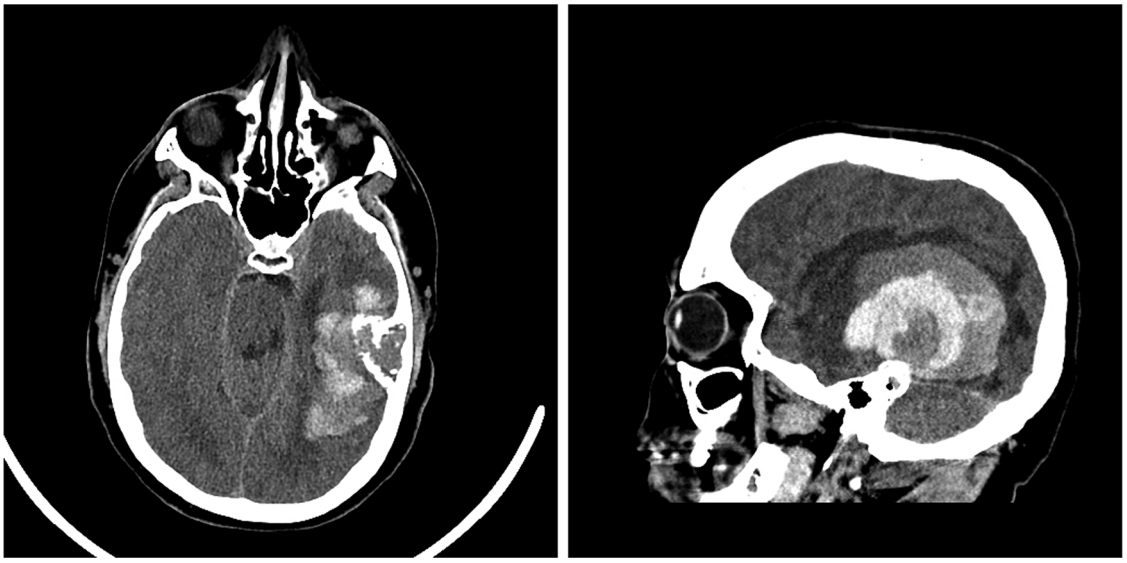

Fig. 1. Axial (left) and sagittal (right) CT without contrast demonstrate a large left temporal parenchymal hematoma of differential densities. There is expansion and soft tissue opacification of the superior portion of the left mastoid temporal bone which causes a mass effect on the temporal lobe. There is "dehiscence" of the bone along the medial aspect.

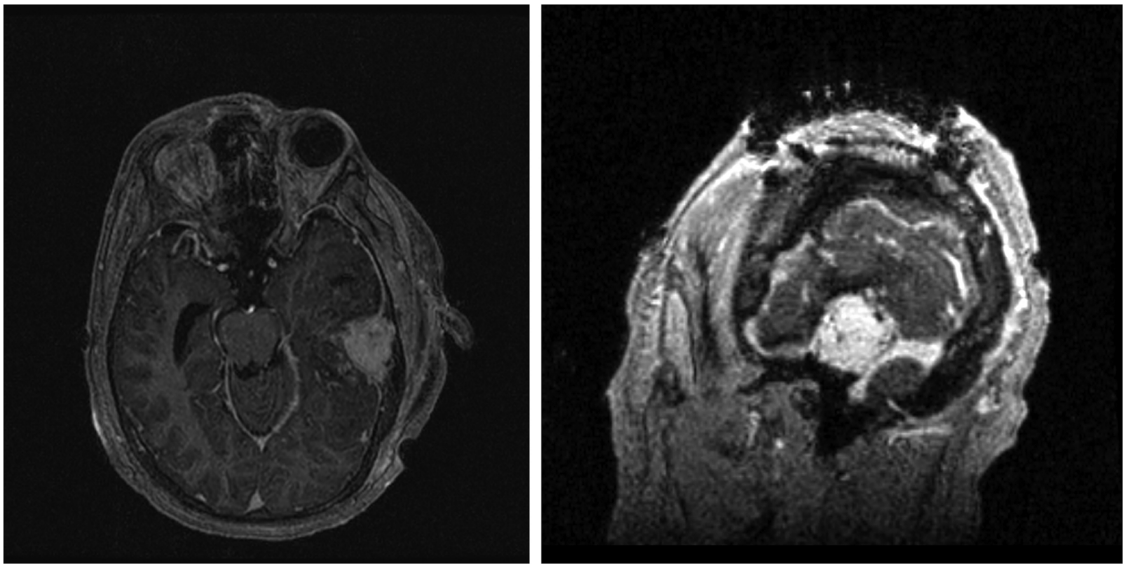

Fig. 2. Postsurgical magnetic resonance imaging (left: neuronavigation; right: sagittal T1) revealed a residual mass effect in the left mastoid temporal bone with enhancing foci within the adjacent left temporal lobe.

formation, subsequent next generation sequencing studies of the lesional tissue revealed no mutations in either the H3F3A or H3F3B gene, respectively. However, a p.Q257R alternation located on exon 6 of the BRAF gene, characteristic for CFCS, was identified.

The patient's postoperative course was uneventful. CT scan 3 months after the initial surgery demonstrated an expansile osseous lesion with a central soft tissue component arising from the left mastoid temporal bone with destruction of the inner table. MRI studies revealed a stable enhancing soft tissue lesion and nodular enhancement within the left temporal resection cavity. The patient therefore underwent a left transpetrosal resection of the tumor. His seizures stabilized and his general condition returned to baseline 6 months after the initial presentation.

3. Discussion

As the name implies, CFCS is characterized by craniofacial deformities and heterogeneous cardiac and cutaneous manifestations. The condition is caused by a gain-of-function mutation in either the BRAF gene (75–80%), MEK1 and MEK2 gene (10–15%) or KRAS gene (< 5%) [1,2]. CFCS has been previously reported to predispose an individual to malignant neoplasms including embryonal rhabdomyosarcoma, urothelial carcinoma and neuroblastoma [5]. Furthermore, poorly-defined giant cell lesions have been rarely reported in patients with CFCS [6]. These lesions, however, were all located bilaterally within the mandible and initially classified as syndromic multiple giant cell lesions prior to identification of mutations in genes causal for CFCS. Moreover, multiple giant cell lesions of the jaw also rarely accompany patients with Noonan syndrome [7]. Importantly, all mutations detected in the patients with syndromic multiple giant cell lesions in the English language literature had previously been reported in subjects with Noonan syndrome and CFCS, respectively, without apparent multiple giant cell lesions [7]. These observations suggest that dysregulation of the RAS-MAPK pathway may represent the common