Juvenile psammomatoid ossifying fibroma of the parietal bone and review of calvarial presentations: illustrative case

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BACKGROUND Juvenile psammomatoid ossifying fibroma (JPOF) is an uncommon benign fibro-osseous lesion that only rarely presents in the calvaria.

OBSERVATIONS The authors reported a case of JPOF in the left parietal bone of a 20-year-old patient and reviewed the 27 other cases of JPOF occurring in the calvaria as reported in the literature.

LESSONS JPOF rarely presents in the calvaria, and because diagnosis is a histopathologic one, clinicians should consider this entity when presented with a lytic, expansile mass on imaging. Little is known about the molecular mechanisms driving development of JPOF. MDM2 amplification may play a role, although this was not seen in the case presented herein.

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KEYWORDS juvenile psammomatoid ossifying fibroma; JPOF; ossifying fibroma; juvenile active ossifying fibroma

Juvenile psammomatoid ossifying fibroma (JPOF) is a rare, benign fibro-osseous tumor that typically affects the paranasal sinuses/periorbital region and infrequently presents in the skull.1 Treatment of JPOF is primarily surgical, and it should be included in the differential diagnosis for expansile skull lesions so that operative options are considered.2

We report an illustrative case of JPOF in the calvaria with classic histological findings. We also review all previously reported cases of JPOF occurring in the skull as reported in the literature to better understand management and outcomes for this unusual diagnosis.

Illustrative Case

History and Imaging

A 20-year-old woman presented with a focal, left parietal skull protuberance that had been discovered while combing her hair. The lesion was tender to palpation and was not present approximately 1 year earlier. The patient also described increasingly severe headaches during this time. Her past medical history was significant for obesity and generalized anxiety disorder. Physical examination demonstrated a firm nodule on the left parietal aspect of her skull with no other abnormal neurological findings. Her skull radiographs demonstrated a 2.5-cm well-defined lytic lesion of the bone that was suggestive of an indolent, chronic lesion (Fig. 1A). A computed tomography (CT) scan of the head demonstrated a lytic, expansile lesion in the calvaria without obvious meningeal involvement, mass effect, or midline shift (Fig. 1B). Magnetic resonance imaging (MRI) findings demonstrated a well-marginated 2.7-cm expansile mixed cystic and solid lesion with fluid-fluid levels that expanded the outer table and displaced adjacent extracalvarial soft tissue (Fig. 1C and D). The radiographic and clinical findings were interpreted as consistent with a dermoid cyst or eosinophilic granuloma. JPOF was not considered as part of the differential diagnosis before surgery. The options of resection or serial imaging were offered to the patient, and she chose to proceed with surgery.

Operation

A left parietal craniectomy was conducted to remove the lesion en bloc (Fig. 2). The skull was reconstructed with a titanium mesh cranioplasty.

ABBREVIATIONS COF = cemento-ossifying fibroma; CT = computed tomography; EMA = epithelial membrane antigen; FISH = fluorescence in situ hybridization; JPOF = juvenile psammomatoid ossifying fibroma; MRI = magnetic resonance imaging; PR = progesterone receptor.

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Postoperative Course

Postoperative MRI demonstrated complete resection of the expansile lesion and no apparent immediate complications (Fig. 3). She remained neurologically intact and was discharged home on postoperative day 1.

Pathological Findings

On gross examination, cross-sections of the resected specimen revealed a well-demarcated, centrally cystic, soft to rubbery, yellow-white intraosseous lesion (Fig. 4A). The tumor appeared completely excised with negative margins. On microscopic examination, hematoxylin and eosin-stained sections showed a cytologically bland fibro-osseous lesion containing innumerable variably mineralized psammomatoid bodies, consistent with juvenile psammomatoid ossifying fibroma (Fig. 4B and C).

Immunohistochemical stains were also performed, and tumor cells did not stain for MDM2, progesterone receptor (PR), or epithelial membrane antigen (EMA). MDM2 fluorescence in situ hybridization (FISH) analysis was also negative for amplification.

Discussion

Observations

This case illustrates the typical clinical history, radiographic appearance, and classic histological findings of JPOF presenting in the calvaria.

JPOF preferentially affects younger patients, with reported mean age ranging from 16 to 33 years1 (but it has been seen in a 72-
Lessons

We conducted a PubMed search for published cases of JPOF, which produced 117 results. Articles were included for review if they specified occurrence of JPOF in the skull. This search identified a total of 27 unique cases. When combined with the current case, only 28 known instances of JPOF in the calvaria have been reported. We summarize the known clinical features, treatment, and genetic data of these cases in Table 1.

Challenges and Limitations

A challenge that arose in this review process and in several others was historically inconsistent and involving terminology in the literature for the entity currently described as JPOF. Previous nomenclature and synonyms are further reviewed elsewhere, but names that were included in this search were psammomatous and psammamoid ossifying fibroma, juvenile active ossifying fibroma, psammo-osteoid fibroma, and psammomatoid juvenile ossifying fibroma. Additionally, some reviews of this topic included cases previously classified as psammous desmo-osteoblastoma and cemento-ossifying fibroma (COF), which further complicated this search. We used collated information from prior reviews and closely scrutinized previously published histological images in the related primary literature, when available, to determine which cases were appropriate to include (Table 1) but acknowledge inherent limitations to this approach.

In addition to the limitations discussed above, there are inherent limitations that come with studies that combine data from case reports and case series, such as publication bias and overinterpretation. Publication bias is the tendency for the literature to include more positive outcomes than negative ones, which can lead to the assumption that a particular treatment is more efficacious than it really is. Overinterpretation can arise when outcomes from one case report are assumed to be applicable to other cases. We acknowledge these limitations but also recognize that a more powerful study examining this rare entity would be difficult to conduct.

Clinical Presentation and Treatment Outcomes

The average age of patients presenting with calvarial JPOF is 15 years, and there may be a slight preference for affecting females (16 females:10 males). The most common bone affected in the calvaria is the parietal bone, with nine cases, followed by the frontal bone, with four cases. The clinical history varied, but most patients presented with an enlarging skull mass that was either noticed incidentally on imaging or while grooming their hair. Only one case noted neurological deficits on presentation. Information on outcomes was provided for 10 cases. Complete resection was performed in all of these cases except one. A biopsy for that patient was obtained, but the patient was lost to follow-up. Reconstruction of the skull with titanium mesh, wire-mesh acrylic, or bone replacement material has not shown differences in recovery, although long-term follow-up (>1 year) is only available for four patients. One postoperative complication (meningitis) was reported.

Although the natural history of JPOF is not known definitively, Wehrli et al. reported a case that was observed for 7 years and noted that the mass continued to grow disproportionately to the rate of growth of the child. The tumor was biopsied and continued to grow for another 2 years before it was resected. After resection, the patient's postoperative course was significant for intracranial hypertension that was treated appropriately, and the patient showed no signs of recurrence 16 months later, despite this delay in treatment.

Recommended treatment is complete excision, with some authors arguing that close follow-up should be conducted to monitor for recurrence. Recurrence rates for JPOF in the calvaria are expected to be low but are not known. However, recurrence rates have been reported to be 25% to 32.9% for cases of JPOF in the maxilla or mandible, likely because of the difficulty of complete resection. These rates are within the range for rates of recurrence of ossifying fibroma more generally, which are reported anywhere from 30% to 56%. Recurrence is often attributed to incomplete removal.

Pathologic Findings and Differential Diagnosis

JPOFs generally present with nonspecific imaging and clinical findings that encompass a broad differential diagnosis, including fibrous dysplasia, meningioma, aneurysmal bone cyst, eosinophilic granuloma, dermoid cyst, certain subtypes of osteoma, and low-grade central osteosarcoma. JPOF can be distinguished from these other skull lesions based on histopathological analysis. The characteristic histology of JPOF demonstrates a hypercellular spindle cell stroma composed of bland stellate to spindle-shaped fibroblasts with numerous admixed rounded, mineralized collagenous ossicles (i.e., psammomatous bodies). Other benign fibro-osseous lesions may enter the differential diagnosis, most notably juvenile trabecular ossifying fibroma, which demonstrates longer, interconnecting strands of osteoid matrix, and COF, which harbors cementum-like material and is associated with tooth-bearing regions of the jaw. Fibrous dysplasia may also be a consideration, and the diagnosis can be confirmed by detection of activating GNAS mutations, which are absent in JPOF. The mineralized psammomatous bodies in JPOF may raise the possibility of meningioma; however, true psammoma bodies as seen in meningioma are smaller than the ossicles in JPOF, more sharply defined, and lamellar. Additionally, the stromal component usually contains areas in which the lesional meningothelial cells have a more epitheliod, whorled appearance. By immunohistochemistry, the lesional cells in meningioma are typically positive for EMA and PR (both are negative in JPOF), although ancillary staining is neither necessary nor sufficient to make the diagnosis of JPOF. Low-grade central osteosarcoma may be a diagnostic consideration, particularly in small biopsies. Thorough study usually reveals foci of distinct, albeit mild, cytological atypia and infiltration of preexisting bone. MDM2 and CDK4 immunohistochemistry positivity support the diagnosis of low-grade osteosarcoma. MDM2 amplification is generally lacking in
| Case No. | Author, Year | Age (Yr), Sex | Location | Clinical/Imaging Features | Pathologic Description (Initial Diagnosis, If Applicable) | Treatment/Genetics |
|----------|--------------|--------------|----------|--------------------------|----------------------------------------------------------|-------------------|
| 1        | Willis, 1949 | 5, F         | Temporal region | Not available | (Hamartoma) | — |
| 2        | Katzer, 1969 | 28, F        | Parietal | Incidentally discovered nonpainful lump in the roof of skull | (Psammo-osteoid fibroma) Spherical psammoma-like structures embedded w/in spindle-shaped base tissue | Not provided |
| 3        | Lichtenstein, 1972 | 9, F | Temporal region | Not available | (Osteoblastoma) | — |
| 4        | Seitz et al., 1980 | 33, M | Right parietal bone | Presented as a hard, nontender mass that grew over the course of 20 yrs; no history of trauma; radiograph showed a poorly demarcated, partially lucent lesion | (Ossifying fibroma) “… areas of high cellularity, irregular trabeculations & other areas with densely mineralized cementsites.” | Resection w/ mesh-acrylic cranioplasty reconstruction, no recurrence at 18 mos postop |
| 5        | Makek, 1983 | 13, F        | Temporal region | Not available | Not provided | Not provided |
| 6        | 6, M         | Parieto-occipital | Imaging showed a seam of sclerotic matter & delicate, thorn-like extensions in the peripheral area w/ a central area of lucency & multiple cystoid structures | Cell-dense stroma w/ islands of immature osteoid | Not provided |
| 7        | 23, F        | Frontal      | Not available | Not provided | Not provided | Not provided |
| 8        | 10, F        | Parietal     | Incidentally discovered; imaging showed sclerotic border, heterogeneous area of cystoid radiolucency, septum formation, & trabeculated spongiosa-like thickening | (Monostotic fibrous dysplasia) Whirled & cellular stroma w/ spherical trabeculae of bone | Biopsied but lost to follow-up |
| 9 & 10   | Johnson et al., 1991 | Not available | Not available | Not available | — | — |
| 11       | 3, F         | Lambdoid     | Not available | — | — |
| 12       | 5, M         | Fronto-temporal | Not available | — | — |
| 13       | 8, M         | Calvaria     | Not available | — | — |
| 14       | 9, M         | Calvaria     | Not available | — | — |
| 15       | 15, F        | Skull        | Not available | — | — |
| 16       | 13, F        | Skull        | Not available | — | — |
| 17       | 13, F        | Fronto-parietal | Not available | — | — |
| 18       | 19, F        | Skull        | Not available | — | — |
| 19       | 11, F        | Mastoid      | Not available | — | — |
| 20       | 18, F        | Mastoid      | Not available | — | — |
| 21       | El-Mofty, 2002 | 27, M      | Left parietal bone | “Expansive, painless, & of several months duration” Imaging showed expanded bone, w/ mixed radiolucent, radiodense regions & ground-glass appearance | Small, uniform, spherical osteoid distributed throughout stroma | Complete resection & acrylic cranioplasty w/o recurrence 7 yrs postop |
| 22       | Hasselblatt et al., 2005 | 24, M | Fronto-parietal junction | Presented 5 yrs after discovery w/ a well-defined, expansive, intraosseous lesion on imaging | Fascicles w/ whirling patterns w/in the fibrous stroma. Ki-67/ MIB-1 index low & EMA stain absent | Resection w/ no sign of recurrence 6 mos postop |

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JPOF, although rare cases of MDM2 and RASAL1 coamplification have been reported (see below). In the current case, negativity for MDM2, EMA, and PR immunoreactivity as well as absent MDM2 amplification by FISH further supported the already classic morphological diagnosis of JPOF.

Two other entities were considered consistent with the imaging findings in this case: eosinophilic granuloma and dermoid cyst. However, these findings are histologically distinct from JPOF and were no longer considered upon histological analysis of the lesion in this case. Eosinophilic granuloma is a well-demarcated intraosseous form of Langerhans cell histiocytosis that demonstrates ovoid histiocytic cells with characteristic grooved, folded nuclei and admixed inflammatory cells, including eosinophils. Dermoid cysts are benign intraosseous squamous epithelial-lined cysts with adnexal structures such as hair follicles, sebaceous glands, and sweat glands and are thought to arise from embryologic tissue of ectodermal origin.

Molecular Mechanisms of Disease

Although the etiology of JPOF is unknown, Johnson et al. speculated that deranged production of bone formation at the sutures or in sinuses may contribute to this process. This hypothesis is supported by the six cases that presented at skull sutures and the

### TABLE 1. Imaging and histopathologic findings in JPOF in the calvaria

| Case No. | Author, Year | Age (Yr), Sex | Location | Clinical/Imaging Features | Pathologic Description (Initial Diagnosis, If Applicable) | Treatment/Genetics |
|----------|--------------|---------------|----------|---------------------------|-----------------------------------------------------------|-------------------|
| 23       | 27, F        | Right parietal bone | Discovered in diagnostic workup for vertigo; imaging as above | As above | Complete resection w/o recurrence 18 mos postop (−) GNAS1 |
| 24       | Chang et al., 2009 | 14, M | Right parietal bone | 3 yrs of growth before resection; imaging showed cystic transformation, fluid levels, & calcification; history of trauma | Dense fibrous stroma w/ osteoid psammoma-like ossicles interspersed w/in spindle-shaped mesenchymal cells | Complete resection |
| 25       | Wehrli et al., 2012 | 11, F | Right frontal bone | First noticed at 30 months old & continued to enlarge until treatment at 11 years; imaging revealed expansive lesion w/ subacute bleeding into cyst; history of trauma | Osteoid matrix & hemosiderin deposition, w/ cystic & solid parts; latter composed of monomorphic spindle cells | Resection, w/ hydroxyapatite ceramic implant; recovered from postop intracranial hypertension 16 mos postop (−) GNAS |
| 26       | Barrena López et al., 2016 | 6, M | Left fronto-parietal bone | Time to presentation not provided, developed aneurysmal bone cyst; history of trauma; imaging revealed expanding lytic, well-circumscribed lesion w/ linear trabeculation & no peripheral sclerosis | Multiple round psammoma body-like ossicles w/in spindle cell stroma growing in fascicle w/ whorl formation; demonstrated some aneurysmal cystic degeneration; no IHC performed | Complete resection w/ bone replacement matrix w/o recurrence 6 mos postop |
| 27       | Cotúa Quintero et al., 2016 | 18, M | Left parieto-occipital bone | Presented w/ 6-wk history of headache & blurred vision, CN VI palsy w/ diplopia, & bilateral papilledema on exam Imaging showed 6 × 4-cm enhancing lesion, producing mass effect over the lt cerebellum & obliterating the cisterna magna | Extensive osteoid production w/in a fibrous cellular stroma w/ round calcifications | Total resection, w/ bacterial meningitis that was addressed w/ no sequelae; no recurrence in 4 yrs of follow-up |
| 28       | Present case, 2020 | 20, F | Left parietal bone | Discovered incidentally; evaluated a few months after discovery; w/ well-defined lytic lesion w/ mixed cystic & solid components on imaging | Psammomatoid bodies w/in a whorled, fibrous stroma; IHC for EMA, PR, MDM2 was negative | Complete resection w/ titanium mesh replacement (−) MDM2 amplification |

CN VI = cranial nerve 6; IHC = immunohistochemistry; − = “negative for expression of” a gene product (MDM2 or GNAS1).

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frequency with which this entity affects the sinuses of facial bones. Curiously, three reported cases note a history of minor trauma to the region before the lesion appeared, but no clear link between trauma and the development of JPOF has been established. It may be worth noting that one case in the literature describes the development of COF after major trauma.

Although chromosomal or genetic alterations in benign tumors such as ossifying fibromas are less well described than in malignant tumors, several genetic changes have been noted. Tabareau-Delalande et al. report that there is broad amplification, but not overexpression, of MDM2 and RASAL1 in ossifying fibromas. Additionally, alterations in the HRPT2 gene, which has been identified in cases of hyperparathyroidism–jaw tumor syndrome, have been seen in sporadic cases of COF but do not seem relevant to JPOF. Sawyer et al. propose that chromosomal translocations may be relevant to the pathogenesis of COF, but this area still needs further research. Currently, no underlying genetic mutations that might drive pathogenesis have been identified in JPOF.

Summary
We present a case of JPOF arising in the left parietal bone and review 27 other instances in the literature regarding JPOF in the calvaria. JPOFs are rare, benign, slowly enlarging skull tumors best treated with complete resection. JPOF should be considered in the differential diagnosis when a lytic, well-demarcated skull lesion is seen on imaging.

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Author Contributions

Conception and design: Hong, Montejo, Kerr. Acquisition of data: Hong. Analysis and interpretation of data: Hong, Kerr. Drafting the article: Hong, Chung. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Hong. Administrative/technical/material support: Hong. Study supervision: Hong, Montejo.

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