A solitary calvarial lytic lesion with typical histopathological findings of juvenile hyaline fibromatosis

Case report

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Juvenile hyaline fibromatosis (JHF) is a rare systemic disease characterized by papulonodular skin lesions, gingival hyperplasia, joint contractures, and osteolytic lesions on long bones and the skull. It has recently been reported that the disease is caused by mutations in the gene encoding capillary morphogenesis protein–2 (CMG-2). To date, fewer than 60 cases have been published in the literature. Partial disease expression is common, but no cases featuring a solitary calvarial lesion have been reported.

The authors discuss this 4-year-old boy with a solitary calvarial osteolytic lesion whose histopathological examination exhibited findings characteristic of JHF. Mutational analysis, however, revealed that there were no mutations in the CMG-2 gene. Two years after surgery, he was free of any complaints as well as gingival hyperplasia, joint contractures, and new skull or skin lesions. This patient’s condition may represent clinical or genetic heterogeneity associated with JHF. Whether solitary lesions mimicking JHF can arise from somatic mutation of the CMG-2 gene remains to be proven.

KEY WORDS • juvenile hyaline fibromatosis • juvenile systemic hyalinosis • calvarial lytic lesion • pediatric neurosurgery

Juvenile hyaline fibromatosis is a rare autosomal-recessive disease characterized by papulonodular skin lesions, gingival hyperplasia, joint contractures, and osteolytic lesions on long bones and the skull. The disease maps to chromosome 4q21, and it has recently been reported that it is caused by mutations in the gene encoding capillary morphogenesis protein–2 (CMG-2). Since first described by Murray in 1873 as molluscum fibrosum, fewer than 60 cases have been published in the dermatological, orthopedic, and otorhinolaryngological literature (but not in neurosurgical literature). Despite multiple osteolytic lesions of the skull with other common manifestations of the disease such as skin lesions, gingival hyperplasia, or joint involvement, no case exists in the literature of a patient presenting with a solitary calvarial osteolytic lesion.

In this case report we describe a 4-year-old boy presenting with such a lesion, which on histopathological examination revealed findings typical of JHF; however, mutational analysis revealed that there were no mutations in the CMG-2 gene.

Case Report

Examination and Operation. This 4-year-old boy was admitted to the hospital because of a solitary painless swollen lesion that had gradually grown for 2 years on his right temporoparietal region. He was the only offspring of nonconsanguineous parents. On physical examination, an immobile, painless 3 × 2-cm mass was evident. No other pathological characteristics were found on systemic examination or in routine biochemical investigations.

A lytic lesion with a hyperostotic regular rim was seen on cranigraphy (Fig. 1). Cranial CT scans revealed that the lesion involved the external tabula and the diploe, but the internal tabula remained intact (Fig. 2). The lesion was totally removed with the periosteum on it. The internal tabula was intact as seen on CT scans.

Histological Findings. Histopathological examination of
the lesion revealed an abundance of extracellular matrices that were homogeneous, amorphous, eosinophilic, and collagen-like and that contained spindle-shaped cells (Fig. 3). No mature collagen fibrils were present. The spindle-shaped cells that were thought to be fibroblasts displayed an immunonegative response to S100 protein. On the basis of these typical pathological findings, it was thought that the patient could be suffering from JHF.

For mutational analysis, DNA was extracted from peripheral lymphocytes. The 17 exons of the \textit{CMG-2} gene were amplified using primers flanking the exons and the intron–exon boundaries. Conformation-sensitive gel electrophoresis was used to screen \textit{CMG-2}. Genomic DNA demonstrating mobility shift on CSGE was bidirectionally sequenced using the BigDyeTerminator Cycle Sequencing Kit and a 3100 automated sequencer (ABI; Perkin Elmer, Norwalk, CT), however, no mutations were identified in the \textit{CMG-2} gene.

**Postoperative Course.** The patient was well 2 years after the operation. On his most recent visit, he was free of any complaints, and was not suffering from gingival hyperplasia, joint contractures, or any new skull or skin lesions.

**Discussion**

First described by Murray in 1873 as molluscum fibrosum, JHF is characterized by the production and deposition of an unidentified hyaline material in the skin and other organs. To date, fewer than 60 case reports have been published, and Kitano coined the name currently in use in 1976. Siblings have been affected, and parental consanguinity was noted in several cases; therefore, an autosomal-recessive mode of inheritance is suggested.

The disease particularly involves the skin, gingiva, joints, distal phalanges, long bones, and skull. The skin lesions can be polymorphous, and they can consist of multiple large tumors. Gingival hypertrophy is a common finding and can be severe enough to interfere with feeding. Joint contractures often develop, causing flexion contractures of the fingers, elbows, hips, and knees. A variety of bone lesions have been identified on radiographs and include osteolysis of the distal phalanges, skull, and long bones. Infantile systemic hyalinosis has similar clinical and histopathological characteristics, but those affected die in early childhood. Although it has been a matter of controversy whether JHF and ISH are different entities or part of the same disease spectrum, it has recently been demonstrated by two different groups of researchers that both disorders are allelic and are caused by mutations in the gene encoding \textit{CMG-2}.

Some authors believe that the lesions will regress with age. In the generally accepted opinion, however, the prognosis for patients is not good, and most of them are left...
with deformities and joint contractures. Some patients are followed up for long periods, such as 8, 15, 19, or even 30 years.15,22

Gilabarte, et al., reviewed 33 cases in the literature along with their case and reported diagnostic criteria for JHF as follows: major criteria are cutaneous lesions (including nodules, tumors, and plaques) and gingival enlargement; minor criteria are joint contractures, osteolytic lesions and/or cortical erosions, and family history for JHF. They also stated that histological confirmation is necessary.

The patient presented with a solitary calvarial lytic lesion only, with no other skin, gingival, or bone and joint involvements. The parents were nonconsanguineous healthy adults. The patient underwent an operation with the suspicion that the lesion was Langerhans cell histiocytoma; however, histological features were typical of JHF. These include an abundance of homogeneous amorphous ground substance in which spindle-shaped tumor cells with elliptical nuclei are embedded.23 The bone, muscle, and joint involvement is characterized by interstitial deposition of amorphous eosinophilic material similar to that observed in the skin.4 Our case also featured an abundance of homogeneous eosinophilic extracellular matrices that contained spindle-shaped cells.

The differential diagnosis of such a lesion includes localized infantile myofibromatosis, cranial fasciitis, and neurofibroma. In investigating myofibromatosis, microscopically one finds fascicles containing myofibroblastic cells, primitive areas composed of smaller rounded cells, and necrotic areas. In cranial fasciitis, a loose myxoid area is populated by nonpleomorphic myofibroblasts loosely arranged with a tissue-culture appearance. The background stroma shows variable myxoid change.5,18 The presented tumor was different from these two lesions, having no myofibroblastic cells, no necrotic areas, and different stroma. Neurofibroma is characterized by hyperchromatic tumor cells with serpentine nuclei in a fibrillar eosinophilic stroma, but these cells display an immunopositive response to S100 protein.24 In the presented tumor, however, cells were immunonegative to −100.

Expression variability is not unusual in JHF, and partial disease expression has been described.13,15 De Rosa, et al., posited two clinical variants of JHF: 1) the localized form, characterized by limited cutaneous involvement only and by small, very slow-growing skin tumors; and 2) the diffuse form, in which cutaneous involvement is wide, with large and rapidly growing tumors. If it is true that two distinct forms of JHF exist, then it appears that in belonging to the “localized form,” our patient may represent an extreme example of clinical heterogeneity associated with JHF. No new skin or locomotor lesions appeared in this patient 2 years after the operation; however, localized disease can in time evolve into the diffuse form. In a patient in whom JHF was diagnosed at 29 years of age, widespread locomotor involvement had occurred 5 years after removal of a scalp tumor when he was 9 years of age.11 Therefore, regular follow up of a patient with JHF is necessary.

Several pathogenetic mechanisms for JHF have been proposed. According to recent research, the formation of the hyaline ground substance seems to be caused by a focal mesenchymal cell proliferation followed by an abnormal production and accumulation of glycosaminoglycans and glycoproteins.19 A defect in collagen synthesis has been demonstrated.14 Some investigators have suggested that the abnormal collagen fibers result from an underlying defect in glycosaminoglycan formation.17 Characterization of the gene and the protein it encodes now provides fresh data that is expected to allow a better understanding of the pathogenesis of JHF. Capillary morphogenesis protein–2 was originally identified as a gene upregulated in endothelial cells induced to undergo capillary formation in three-dimensional collagen matrices.1

The lack of mutations in the CMG-2 gene in the present case also deserves attention. On a theoretical ground, it is possible that JHF is associated with genetic heterogeneity and that other genes, especially those interacting with CMG-2, may also be responsible for the disease. Another possible explanation could be the somatic mutation of the CMG-2 gene, which can only be demonstrated in the DNA extracted from the biopsy specimen. Unfortunately, we were not able to perform mutational analysis of DNA isolated from the biopsy sample. In the absence of additional clinical findings other than the calvarial lytic lesion and a demonstrable mutation of the CMG-2 gene, we suggest that the present case represents an atypical and localized form of JHF.

Treatment of JHF consists of excision of the tumors, mainly for cosmetic reasons, but recurrences are common.13 If surgical treatment is not performed promptly, the nodules can continue to grow and may become very large.3 In the patient presented here, surgery was performed because of the misdiagnosis of Langerhans cell histiocytoma.

Conclusions
Although JHF is a rare and peculiar systemic disease, the solitary calvarial lesion in the present case suggests that it may be associated with clinical and genetic heterogeneity. Further molecular and clinical studies are necessary, however, to document whether a distinct, localized form of JHF exists. We also suggest that JHF be remembered in the differential diagnosis of a solitary calvarial osteolytic lesion.

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References

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