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Case Report

Epidermoid cyst in a patient with Alagille syndrome: Coincidence or connection?

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ABSTRACT

Background: Alagille syndrome is a rare genetic syndrome, which arises due to defects in the Notch signaling pathway, resulting in liver, cardiopulmonary, renal, skeletal, and ophthalmologic problems, among others. Epidermoid cysts are rare congenital benign lesions that develop from ectopic ectodermal cell rests formed during neurulation.

Case Description: A 24-year-old Alagille syndrome patient presented with hearing loss and was found to have a sizable posterior fossa mass. He underwent craniotomy for uneventful resection of the lesion, which was found to be an epidermoid cyst.

Conclusion: While our case may represent a coincidental occurrence of two pathologies presenting together, given that epidermoid cysts arise from aberrant neurulation, and in light of the crucial role of the Notch signaling pathway both in normal neurogenesis and in the pathogenesis of Alagille syndrome, we hypothesize a possible association between these entities.

Keywords: Alagille syndrome, Epidermoid cyst, Notch signaling

INTRODUCTION

Alagille syndrome[1,7,12,26] is a rare genetic syndrome which arises due to defects in the Notch signaling pathway, resulting in liver, cardiopulmonary, renal, skeletal, and ophthalmologic problems, among others. Epidermoid cysts[3,6,8,18,22,25,27,28] are rare congenital benign lesions that develop from ectopic ectodermal cell rests formed during neurulation, when the process of neural groove closure separates neurectoderm from surface ectoderm between the 3rd and 5th weeks of embryogenesis. We report an Alagille syndrome patient who presented with a symptomatic epidermoid cyst. Given the low prevalence of each of these conditions and potential overlap in their pathogenetic mechanisms, we propose a pathophysiologic link between the two and perform a brief literature review.

CASE REPORT

History

A 24-year-old male with established Alagille syndrome, complicated by hemodialysis-dependent end-stage renal disease and liver cirrhosis, presented with an 8-month history of headaches

and hearing loss (right worse than left). Brain magnetic resonance imaging (MRI) revealed a 3 cm, extra-axial, diffusion restricting, posterior fossa mass involving the right temporal bone posterior to the mastoid air cells, invading and occluding the transverse/sigmoid sinuses, and distorting the cerebellum [Figure 1] Surgery was recommended for the goals of pathological diagnosis and maximal safe resection.

Procedure

A C-shaped retroauricular incision was made, and the underlying muscle and fascia were reflected to expose the retromastoid region. Drilling was performed to create a quarter-sized retrosigmoid craniotomy; then, dissection under the operating microscope showed an epidural white keratinizing pearly lesion displacing the cerebellum inferomedially. Samples of the lesion were removed and sent for pathological analysis. The lesion was hypovascular and removed completely with suction and microdissection to carefully elevate the capsule of the lesion from the dura. The exposed mastoid air cells were covered with muscle grafts and oxidized cellulose along the superior and anterior aspects. The lesion was further resected to the occluded transverse and sigmoid sinuses, which were filled with thrombus. The surrounding bone was thoroughly curetted, and the surgical cavity was copiously irrigated, then carefully inspected to confirm the absence of gross residual disease. A small myofascial free tissue graft was placed over the resection cavity. There were multiple small rents in the dura, which were covered with a synthetic dural graft. A titanium mesh was used to cover the entire craniectomy defect. The fascia and skin were closed in standard fashion.

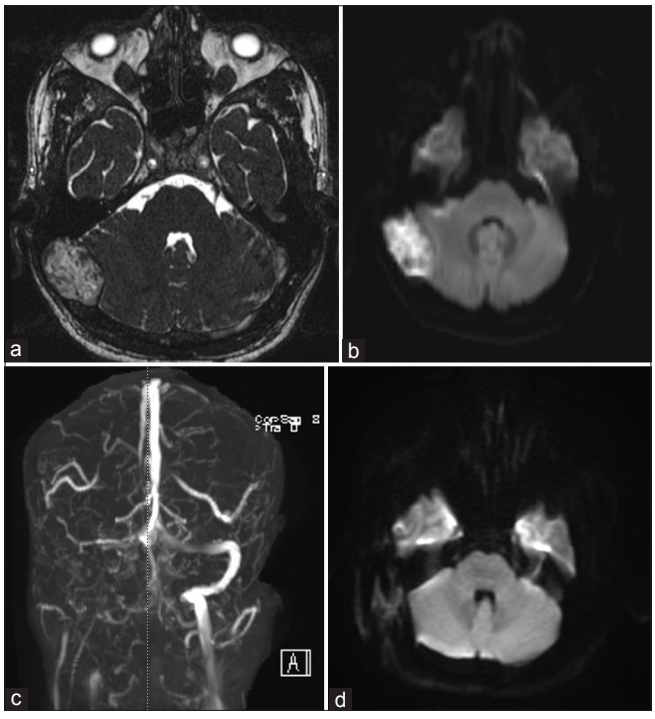

Figure 1: Preoperative (a) T2 magnetic resonance imaging (MRI), (b) diffusion-weighted imaging (DWI) MRI, and (c) magnetic resonance venography demonstrating right posterior fossa mass causing transverse sigmoid sinus occlusion with cerebellar distortion. (d) Postoperative DWI MRI showing resection of the mass.

Pathology

On microscopic examination, permanent sections showed multiple portions of tumor wall containing acellular keratin debris. The tumor was lined by keratinizing stratified squamous epithelium with a granular layer. This was most consistent with an epidermal inclusion cyst with dystrophic calcification [Figure 2].

Postoperative course

Postoperative brain MRI demonstrated gross total resection of the lesion. Postoperatively, he received hemodialysis while hospitalized and was quickly weaned off of steroids and restarted on his home antihypertensive medications. He made an uneventful recovery and was discharged on postoperative day 3, and was doing well when evaluated at 3 months postoperatively.

DISCUSSION

In this report, we highlight the case of a young man with two uncommon conditions: Alagille syndrome and a posterior fossa epidermoid cyst. Based on a review of the literature, we hypothesize that the importance of Notch signaling in neural tube development and in the pathogenesis of Alagille syndrome may implicate a role for this signaling pathway in the pathogenesis of epidermoid cysts as well.

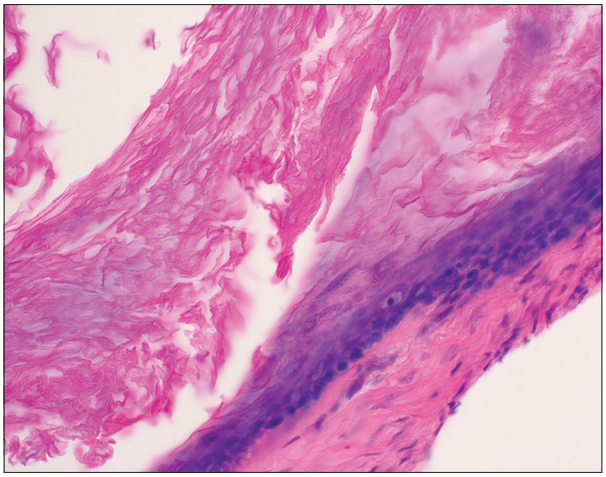

Figure 2: Histopathologic image demonstrating epidermoid tumor cyst wall with acellular keratin debris. The cyst is lined by keratinizing stratified squamous epithelium with a granular layer.

Alagille syndrome

Alagille syndrome is a genetic disorder, transmitted in an autosomal dominant fashion, characterized by liver, heart, lung, kidney, skeletal, and eye problems, among others.[1,7,26] [Table 1] It is often diagnosed in childhood.[12] Due to its variable expressivity, the management of Alagille syndrome addresses the particular problems of each patient. Many patients can lead normal lives with normal life expectancy, whereas others experience several life-threatening complications or life-limiting sequelae.

Epidermoid cysts

Epidermoid cysts develop from displaced ectodermal cell rests that become trapped in the neural tube during closure. These lesions grow over time by accumulating keratin and cholesterol, which are breakdown products from desquamating epithelial cells and give it a characteristic pearly appearance. Within the cranium, they have a predisposition for the cerebellopontine angle and the parasellar region.[18] However, epidermoid cysts are typically discovered extra-axially, as in this case, due to migration following the path of the otic vesicles or burgeoning neurovasculature.[6,28] Epidermoid cysts can contain an inner tumor fluid, which can secondarily become infected. These tumors are commonly symptomatic during adulthood due to compression of adjacent neural structures. The most common presenting symptoms include hemiparesis, abducens and facial cranial nerve palsy, gait ataxia, and increased intracranial pressure.[20] MRI is the preferred imaging modality for diagnosis for epidermoid cysts. These lesions appear hypointense on T1-weighted imaging, hyperintense on T2-weighted imaging, and exhibit restriction on diffusion-weighted imaging. Surgery is the mainstay of treatment for these lesions; however, total resection is not always possible because the cyst capsule is often adherent to important surrounding neurovascular structures.[20] A rare but important complication of surgical removal of these lesions is aseptic meningitis due to rupture of the cyst contents into the subarachnoid space.[22] In addition to careful surgical technique, irrigation with hydrocortisone combined with perioperative steroid administration has been reported to reduce the incidence of perioperative aseptic meningitis.[3,25,27] The recurrence rate of epidermoid cysts varies widely (1-54%)[3,27,28] and is likely related to lesion location, size, surgical goals, and extent of resection, among other factors. Malignant transformation of recurrent epidermoid cysts is very rare.[25]

Table 1: Clinical features of Alagille syndrome.

Organ system	Pathological features
Facial features	Broad forehead, deep-set eyes with upslanting palpebral fissures, straight nose with a bulbous apex, pointed chin
Visual	Posterior embryotoxon, among other anterior chamber defects
Cardiac	Peripheral pulmonic stenosis, tetralogy of Fallot, atrial septal defect, ventricular septal defect
Hepatic	Paucity of intrahepatic bile ducts, chronic cholestasis, liver failure
Renal	Ureteropelvic anomalies, congenital tumors, renal tubular acidosis
Skeletal	Vertebral anomalies such as butterfly vertebrae and hemivertebrae, metabolic bone disease
Vascular	Cerebrovascular accidents from neurovascular malformations, moyamoya, renovascular malformations, middle aortic syndrome

Notch signaling

The Notch signaling system is a highly conserved developmental signaling pathway in many tissues, organisms, and diseases. It plays important roles in cell fate determination and differentiation.[2] Activation of a Notch receptor by its ligand causes proteolytic cleavage of the Notch intracellular domain (NICD). NICD enters the nucleus and associates with CBF1 Suppressor of Hairless-LAG1 and Mastermind to promote gene transcription. About 90% of cases of Alagille syndrome are caused by a 20p12 mutation in JAG1, one of the proteins in the Notch signaling pathway, 5–7% are caused by deletion mutations in JAG1, and 1% of patients with Alagille syndrome have a mutation in the NOTCH2 gene.[17,19] Alagille syndrome displays allelic and locus heterogeneity, with variable expressivity. However, there are two distinctive phenotypes of Alagille syndrome: Types 1 and 2. Type 1 Alagille syndrome is associated with mutations in JAG-1, whereas Type 2 is associated with mutations in NOTCH2. Among its roles in cell differentiation, Notch signaling determines neurogenesis during neural tube closure. Cells that have decreased Notch signaling increase activation of neurogenic genes that determine their fate as neuronal cells.[24] Experimental manipulations that suppress Notch signaling increase the density of neurons in neuron-competent regions of the neural plate.[9] During neural tube closure, special morphologically round cells at the border of the two ends extend cellular processes across the gap.[16] It is likely that the Notch signaling pathway combines with apoptotic programmed cell death to also play an important but still poorly understood role in the above process. Furthermore, Notch signaling maintains apical/basal polarity, which is necessary for proper folding of the neural tube.[15] Mice that lack Notch pathway components also show neural tube defects such as wavy or kinked appearance, closure defects, or shortening of the neural axis.[4,5,10,11,13,14,21,23] Given its importance in neurogenesis, it is not inconceivable that Notch signaling may play a role in the formation

of heterotopic ectodermal tissue in the neural tube, the pathogenesis of epidermoid cysts. A possible connection between Alagille syndrome and epidermoid cysts has not yet been explored in the literature to our knowledge.

CONCLUSION

While our case may represent a coincidental occurrence of two pathologies presenting together, given that epidermoid cysts arise from aberrant neurulation, and in light of the crucial role of the Notch signaling pathway both in normal neurogenesis and in the pathogenesis of Alagille syndrome, we hypothesize a possible association between these entities. This report may prove useful for heightened clinical awareness for epidermoid cysts in Alagille syndrome patients.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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