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Case Report

The Unicorn Mouse: Cranial Lipoma in a B6.Cg Mouse

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Abstract

Intracranial lipomas, also called intracranial lipomatous hamartomas, have been reported in some strains of research mice, but are rare in C57BL6 strains. It is presumed based on current publications that this is the first report of an intracranial lipoma in a mouse with this genetic change (B6.Cg-Cnpy2$^{tm1.2\ Zhli}$ Alb-Cre). Grossly, a fur-covered, soft, cylindrical, exophytic mass on the dorsal midline of the cranium was evident. Upon dissection, a soft, white, tubular structure extended through a 1mm defect in the sagittal suture of the skull to the deep surface of the hypodermis. Histologically, the mass consisted of well demarcated proliferation of mature white adipocytes, each containing one large fat droplet. The mass extended from the cerebrum at the level just caudal to the hippocampus in the third ventricle, between the superior colliculus and the caudal portion of the retrosplenial area and through the sagittal suture to the hypodermis and was surrounded by normal brain tissue.

Key words: Intracranial lipoma, Intracranial lipomatous hamartoma, C57BL/6 mouse.

Introduction

Intracranial lipomas are uncommon but have been reported in a variety of species including laboratory mice and rats, ducks, dogs, pigs, and humans (1,6,15,18,19,21). These masses consist of mainly mature adipose tissue located within the brain, often surrounded by normal tissue, as they often incorporate intracranial vessels and nerves instead of disrupting the tissue (1,6). Intracranial lipomas are synonymously called intracranial lipomatous hamartomas in human medicine; given the widely accepted nature of being congenital malformations, lipomatous hamartoma is thought to be a more accurate term (4,6,15,18). However, since the majority of cited articles referred to the lesion as a lipoma, this report also refers to it as a lipoma to avoid confusion.

Inbred strains of mice are frequently used for research purposes; strains have been sibling mated for at least 20 generations until they are essentially genetically identical (20). Each strain has different phenotypes and disease predispositions, which are used to model different diseases (20). Intracranial lipomas have been reported in BALB/c mice in multiple reports (15,18), and a new line of 3H1 mice exhibiting facial defects and intracranial lipomas was reported in 2012 (6). Few intracranial lipomas have been reported in mice with a C57BL background and even fewer in mice with a C57BL/6 background (7,11-13). The present report describes the first intracranial lipoma found in a C57BL/6 mouse with this genetic change.

Case Description

This seven-month-old experimentally naïve female B6.Cg-Cnpy2 $^{tm1.2\ Zhli}$ Alb-Cre mouse was bred for use in the study of the endoplasmic reticulum heat shock protein gp96. All studies were previously approved by the MUSC Institutional Animal Care and Use Committee. The mouse was reported to the clinical team for an abnormality consisting of a fur-covered, soft, cylindrical, exophytic mass on the dorsal midline of the cranium (Fig. 1). The mouse was submitted to the Medical University of South Carolina (MUSC) veterinary diagnostic lab for further characterization of the observed abnormality.

On physical examination, the mouse was bright, alert, and responsive. Due to the unknown nature of the lesion and to rule out infectious etiologies, the mouse was

euthanized via carbon dioxide asphyxiation followed by a thoracotomy, and a necropsy was performed. Gross external evaluation post-euthanasia showed no abnormalities other than the presenting complaint. Upon dissection, an approximately 1mm defect in the sagittal suture of the skull, caudal to the eyes but rostral to the ears, was observed subjacent to the exophytic lesion. A soft, white, tubular structure extended through the defect in the skull to the deep surface of the hypodermis (Fig. 2). The tubular structure appeared to originate from within the calvarium and extended to the subcutaneous region. All other organs were observed to be grossly normal.

The head was fixed in Cal-Ex II for 24 hours, and a midline sagittal section was routinely processed for histologic examination. The mass consisted of well demarcated proliferation of mature white adipocytes, each containing one large fat droplet (Fig. 3 & 4). The mass extended from the cerebrum at the level just caudal to the hippocampus in the third ventricle, between the superior colliculus and the caudal portion of the retrosplenial area and through the sagittal suture to the hypodermis. The surrounding brain tissue was histologically normal but appeared to be compressed at the margins adjacent to the mass. The dura in the area of the lesion were indistinguishable from a thin connective tissue capsule

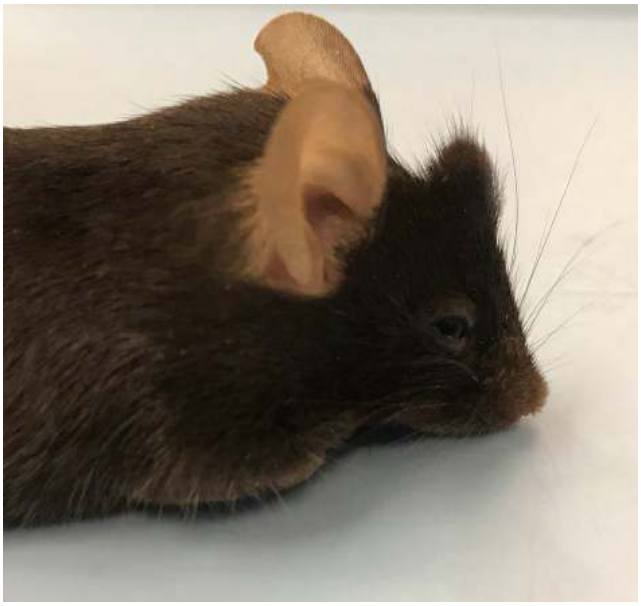

Figure 1. Gross image of mouse with exophytic structure on head.

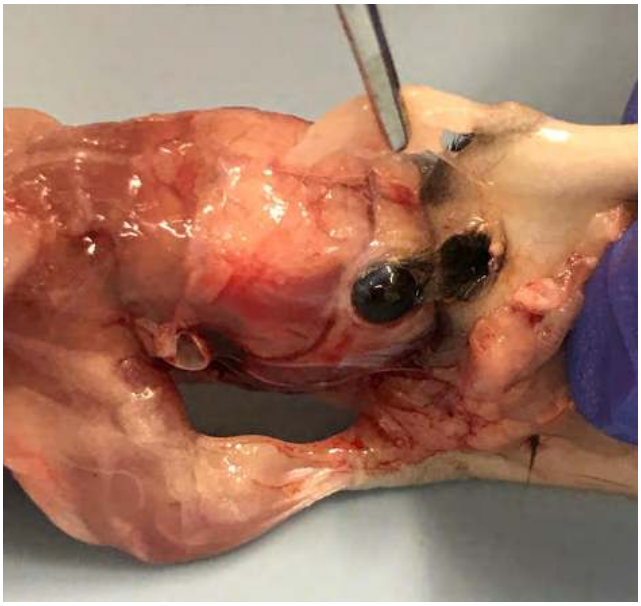

Figure 2. Gross image of dissection. There is pale connective tissue (adipose) extending from exophytic mass through cranial defect.

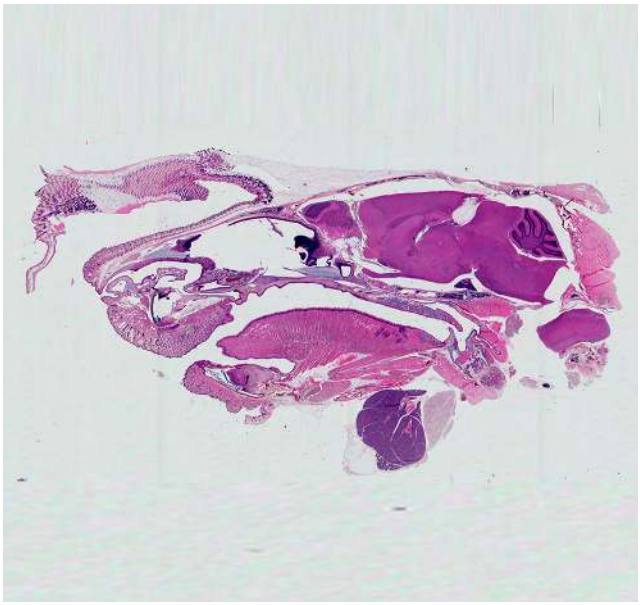

Figure 3. Subgross image of histology slide showing intracranial lipoma extending from brain through calvarium into exophytic structure.

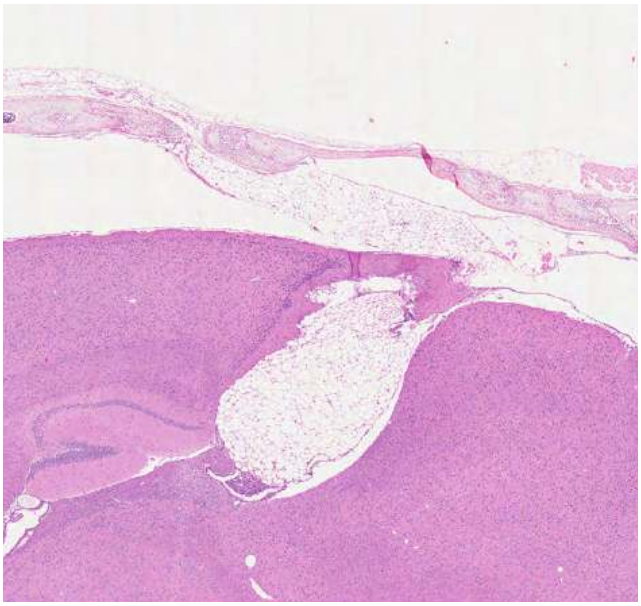

Figure 4. Increased magnification of figure 3 showing the structure of the lipoma and location more clearly.

around the mass. For further examination, the remaining hemisphere of fixed tissue was cut into coronal hemi-sections and routinely processed for further histologic examination. Deeper cuts were made into the lateral sagittal section of the previously processed block. None of these subsequent sections revealed any abnormalities.

The differential diagnoses were encephalocele, meningocele, or other intracranial mass. Encephaloceles are congenital cranial defects allowing brain tissue and meninges to protrude through a defect in skull (2,5,9,14,17). Meningoceles are similar to encephaloceles with the exception that only the meninges, often filled with cerebrospinal fluid, are herniated through the skull (5,14). While it is estimated that 70-90% of encephaloceles in humans occur in the occipital region, they normally occur in the frontal regions of animals as was the case for the mass in the mouse of the present report (4,5,14). The postmortem diagnosis confirmed that the lesion in the mouse of the present report was not encephalocele as, on histologic examination of the lesion, brain tissue did not protrude through the opening in the sagittal suture. The diagnosis of intracranial lipoma (as opposed to a true neoplasm) was made based on the monocellular population of abundant adipocytes within the mass and the normal appearance of the surrounding brain tissue. We were unable to determine the presence or absence of a concurrent meningocele due to the indistinguishable nature of the dura in the area of the lipoma. If the dura also protruded through the defect in the skull and surrounded the lipoma, a concurrent meningocele would have also been diagnosed.

Discussion

An investigation into the prevalence of encephaloceles, meningoceles, and intracranial lipomas in mice of various backgrounds was performed. The Jackson Laboratory Mammalian Phenome Ontology database listed 14 references of mouse strains with encephaloceles, 5 with wide sagittal sutures, 6 with increased lipoma incidence, and 8 with increased hibernoma incidence (11-13). Of these, 9 of 14 strains with encephaloceles, 3 of 5 with wide sagittal sutures, 2 of 6 with increased lipoma incidence, and all 8 with increased hibernoma incidence were on a C57BL/6 background, as was the mouse of the present report (11-13). The *Cnpy2* gene that was altered in the mouse of the present report was not included in any of the strains (11-13). Given this information, it is presumed that this is the first report of an intracranial lipoma in a mouse with this genetic change; however, this does not rule out the lesion being a change consistent with the C57BL/6 background.

To our knowledge, there are no reports of naturally occurring encephaloceles in rodents, although in research settings subtle encephaloceles are likely to be overlooked unless the research focuses on cranial morphology and defects as outwardly abnormal research rodents are likely to be euthanized early. Several strains have been developed as mouse models of human syndromes in which encephaloceles may be present (9). We found more reports of intracranial lipomas than of encephaloceles. In 2012, a BALB/c mouse with a lipoma in the third ventricle was reported (18). This report and a similar study which surveyed both mice and rats both found that mice had a higher incidence of intracranial lipomas than rats (10,18). Another study also surveyed brain tumors in several strains of inbred mice, determining that lipomas were the most common type of brain tumor; all of the lipomas found in this survey were in BALB/c backgrounds, and 14 of the 15 were in females (15). A different study surveyed C57BL mice for brain tumors and found a prevalence of 21 lipomas out of 16,200 mice surveyed (7). We attempted to determine if these were C57BL/6 or C57BL/10 mice, but the study in question had referred to the animals as just C57BL mice and had not disclosed the specific line examined (7). Also in 2012, a lab from the University of Hawaii published the development of a new line of 3H1 mice presenting with intracranial lipomas and midline craniofacial defects that arose spontaneously (6). The lab called this mutation the tuft trait (6). Their description of the intracranial lipomas associated with this trait is very similar to what we observed, excepting that the lipoma in the mouse of the present report did not invade the brain parenchyma and was located in the third ventricle, as opposed to being located anterior to the corpus collosum (6). The lipomas in the tuft mice also included bone spicules, which were not present in this case (6). This new mutation was traced to chromosome 10, which is the same chromosome that the *Cnpy2* gene altered in the mouse of the presence report is located (6,16). The range given for the location of the *tuft* gene on chromosome 10 did not overlap the location of the *Cnpy2* gene; however, there are other genes that result in abnormal cranial morphology along chromosome 10, such as the *Alx1* and *Apaf1* genes (6,8,16,20,22,23). To our knowledge there are no reports of these two genes resulting in intracranial lipomas.

Defects in embryogenesis have been implicated in the development of both encephaloceles and intracranial lipomas (5,6,9,14,15,17). Unfortunately, the pathogenesis of encephaloceles is less understood than that of other neural tube defects (5,9,17). There are very few studies examining whether the lesion occurs due to defects in primary neural tube closure or post-closure abnormalities such as a herniation through a skull defect (9,17). A mouse model of encephaloceles indicated that a post-closure anomaly was the most likely pathogenesis, and other papers also indicate that they occur after closure of the neural tube (9,17). The most widely accepted theory of pathogenesis is that encephaloceles result due to incomplete separation of the surface ectoderm from the neuroectoderm after the neural tube closes (5,14). Similarly, the pathogenesis of intracranial lipomas is not well understood, but there are implications that defects with neural tube development may be involved (6,15). One study suggested failure of migration or differentiation of the rostral neural crest cells, while another suggested defects with neural tube closure (6,15). Interestingly,

intracranial lipomas do not seem to disrupt the formation of cerebral tissue, as they often incorporate intracranial vessels and nerves instead of disrupting the tissue (6). Since these lipomas are widely accepted to be congenital, many argue that these are not true neoplasms and should instead be referred to as lipomatous hamartomas (3,6,15,18).

Since intracranial lipomas are congenital malformations that do not displace neural tissue or vessels, they are often benign and asymptomatic (3,6). This was the case in the mouse of the present report. It is speculated, therefore, that had euthanasia not been performed, the mouse of the present report likely would have had a good prognosis.

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