Manuscript

Introduction

Leiomyomas are smooth muscle tumors of mesenchymal origin that primarily effect organs of the gastrointestinal and genitourinary systems \(^1\), classically manifesting as fibroids within or in close relation to the uterine myometrium \(^2\). Historically, leiomyomas are regarded as benign proliferations of smooth muscle with a low degree of cellular atypia, in contrast to the more ominous and aggressive leiomyosarcoma \(^3,4\). Despite this, leiomyomas have the potential to metastasize \(^2\), with rare involvement of the central nervous system (CNS) having been reported \(^3,5\).

In addition to the consequence of metastatic disease, leiomyomas may also arise intracranially as a primary lesion\(^6\). Such occurrences are exceedingly rare, with less than 25 cases reported, often in a supratentorial intraparenchymal location or in close association with the intracranial dura \(^7-23\). The vast majority of primary intracranial leiomyomas arise in immunocompromised patients \(^6\), predominantly in the setting of Human Immunodeficiency Virus (HIV) \(^13, 14, 16, 17\) or immunosuppressive therapy following transplant \(^20\). Genomic studies of these lesions have demonstrated a strong association the integration of Epstein-Barr virus (EBV) genetic elements \(^21\). Such a finding is ostensibly confounding given the immunocompromised state of the majority of the patient population affected with these tumors, and the relationship of EBV with non-lymphoproliferative neoplasms in the setting of immunodeficiency is not entirely clear and in need of further investigation \(^24\).

Clinically, intracranial leiomyomata tend to imitate meningiomas consequent to their overlapping location in close association with dural elements, slow clinical progression \(^18\) and appearance on cranial imaging \(^21\). Definitive diagnosis is therefore reliant on surgical pathology.

1
Microscopic evaluation of leiomyomata characteristically demonstrate a smooth muscle cytology with positive immunohistochemical (IHC) staining for smooth muscle actin (SMA), desmin, and progesterone receptor (PR) \(^{(22-23)}\). Management is limited surgical resection and post-operative follow up for recurrent disease, as well as further radiological exploration to rule out metastatic components both to and from the cranium. In the context of a primary solitary tumor, gross total resection is often curative \(^{(5)}\).

Here we present a case of primary intraventricular leiomyoma in an immunocompetent adult. To our knowledge, this is the thirteenth report of a primary intracranial leiomyomas in an immunocompetent patient \(^{(6-9, 15, 18, 19, 21-23)}\), and the first report of such a lesion occurring within the ventricular system. We hope that this report provides evidence that these lesions should be considered as a rare etiology in the differential diagnosis of intraventricular masses, and is one that is amenable to curative surgical resection should intraoperative frozen pathology guide surgical strategy.

Case Description
A 30-year-old male with no past medical history presented to our center complaining of a several week history of progressive diplopia and occipital headaches. He reported that these headaches were worse in the early morning and at night, and were accompanied with bilateral retroocular pain. A physical exam on presentation showed no focal symptoms, and the patient was referred to ophthalmology for evaluation. A fundoscopic exam subsequently revealed papilledema, and magnetic resonance imaging (MRI) of the brain was ordered (Figure 1) which showed slightly decrease signal intensity on T1 and increase on T2. T1 weighted MRI with contrast revealed homogeneous avid contrast well circumscribed, enhancing intraventricular mass of 2.15 x 2.11 x
2.32 cm in the left lateral ventricle without calcification. The lesion was accompanied by considerable cerebral edema in the left hemisphere and increased signal as demonstrated by T2 weighted fluid attenuated inversion recovery (FLAIR) and diffusion MRI images showed negative diffusion. A metastatic workup included computed tomography (CT) of the chest and abdomen and failed to demonstrate a primary tumor.

Given the clinical history and findings on MRI, a preliminary diagnosis of a mass radiologically consistent with intraventricular meningioma was made. The patient was scheduled for and underwent diagnostic and therapeutic frontoparietal craniotomy for an interhemispheric transcollosal approach to the second ventricle for tumor resection. Intraoperatively after the corpus callosum was opened, a soft rubbery gray reddish tumor was seen in the lateral ventricle which was adherent to the left wall without parenchymal involvement and was completely resected. The post-operative course was uncomplicated with a stable CT scan demonstrating confirmed complete resection. The patient was discharged home three days following surgery.

Pathological examination of the resected mass demonstrated a smooth muscle tumor with an epithelioid appearance and uncertain biological malignant potential. The mass was noted to be highly vascular and myxomatous, composed of cells with spindle to round nuclei and variable amounts of cytoplasm as well as rare mitotic figures (Figure 2). IHC and special stains performed on paraffin embedded tissue which was positive for smooth muscle actin (SMA) and desmin, and the Masson’s trichrome highlights the presence of a dense as well as loosely arranged fibrous background underlying the tumor which further suggesting smooth muscle differentiation and supporting its mesenchymal nature. The tissue was negative for epithelial
membrane antigen (EMA), PR, glial fibrillary acidic protein (GFAP), neurofilament (NF), S100, synaptophysin, CD34, melanoma antigen (MelanA), and human melanoma black 45 (HMB45). Fluorescent in situ hybridization (FISH) probing for EBV genetic material was negative. Final pathological diagnosis was leiomyoma.

The patient has continued to do well post-operatively, with no evidence of recurrence at his 2.5-year follow-up MRI scan (Figure 3).

Discussion
Leiomyoma represents a low-grade neoplasm characterized by proliferation of smooth muscle cells with minimal metastatic potential (1). The vast majority of cases are associated either with the female uterine myometrium or along the gastrointestinal tract25, rarely metastasizing to involve the CNS26. Primary intracranial leiomyoma are extremely rare, we reviewed the currently available literature. To date, there are less than 25 reported cases (5-24), and only 13 reported to occur in immunocompetent patients including our case (Table 1). Of the 13 cases, 7 were male (53.8% of cases). The average age at presentation was 30.69 years (range: 4-68). The average age of presentation between males and females was similar (30.66 years female, 30.71 males). Our review reveals that primary intracranial leiomyoma in immunocompetent patients present early in life with 61.5% of cases presenting at or before 30 years of age, including our patient who presented at 30 years of age. The presentation is varies and depends on factors including location and size of the tumor. In our review, we found 30.8% of cases (4/13) located in the cerebral, 30.8% 5(4/13) located in the medial fossa, 30.8 % (4/13) located in sellar, suprasellar and inreassellar, and our case 7.6% located in the ventricle.
Radiologically, these lesions present with features extremely similar to the one encountered in this case \((7,15)\). They tend to be homogenously enhancing on MRI with an iso to slightly hypointensity as compared to the cerebral cortex in non-contrast T1 weighted studies. On T2 they range from being relatively isointense to marginally hyperintense \((7,15)\). The lesion in this case also showed no restriction on diffusion weighted imaging and demonstrated peritumoral edema on FLAIR, as is consistent with past reports \((7,15)\). Unfortunately, these radiographic characteristics happen to be virtually identical to those of the far more common meningioma \((36)\).

As such, primary leiomyoma is an etiology that is often very low in the differential diagnosis of intracranial masses, with a clinical presentation and radiological appearance mimicking that of meningioma \((18, 21)\). Given the presentation, the definitive diagnosis of leiomyoma requires pathology following surgical resection, the latter of which is almost always indicated given a uniformly symptomatic presentation.

The immunological status of the patient in this case is an important distinction, as it suggests the possibility of an alternative pathogenesis. The vast majority of primary intracranial leiomyomas occur in the setting of immune deficiency, either in the context of therapeutic immunosuppression or consequent to uncontrolled HIV infection \((23)\). Concurrent to this, there is a high prevalence of EBV genetic material detected within tumor cells of these patients \((23)\). EBV is a group I carcinogen as determined by the World Health Organization (WHO) International Agency for Research on Cancer \((34)\) with a high association with a number of epithelial, mesenchymal, and lymphoid derivative cancers \((35)\) including leiomyoma \((23)\), where known the relation of the virus to the malignancies varies from primary etiologic agent to necessary or
contributory cofactor \(^{(35)}\). Clonal EBV episomes are found in all the malignant conditions, suggesting that viral infection is an early event in disease pathogenesis \(^{(33)}\). The virus exists ubiquitously in humans as double-stranded DNA virus with most of the malignancies occurring after years of viral dormancy and are accompanied or triggered by viral reactivation, in contrast to infectious mononucleosis, which results from primary infection with EBV \(^{(35)}\). As such, the ostensible pathogenesis in immunocompromised patients with EBV positive leiomyoma would be that an immunodeficient state allowed for the reactivation and proliferation of previously dormant viral elements that triggered a carcinogenic cascade within mesenchymal derivatives located within the central nervous system. For immunocompetent patients, however, the etiology is less clear, and given the reports of intracranial leiomyoma occurring in such patients tend to do so at an early age and without an association of EBV genetic material \(^{(7,15)}\), an alternative pathogenesis is likely responsible.

While the exact mechanism of tumorigenesis in leiomyomas is, as in most neoplasms, unclear, the creation and investigations in the underlying processes of spontaneous reproductive tract neoplasms observed in the Eker rat cell line supports the role of estrogen axis signaling \(^{(30,31)}\). These rats are the only animal model known to develop these lesion spontaneously, and are heterozygous for a germline mutation in the tuberous sclerosis gene 2 (Tsc-2) \(^{(30)}\). Although steroid signaling is not as relevant in the above patient, who is a 30 year old male, it is not unreasonable that cell types that normally undergo marked changes in proliferative rate in concert with hormonal control might become neoplastic in the context of aberrant cellular machinery. That is to say, although it is intuitive to think of how leiomyoma may develop in the estrogen prone female genitourinary tract, it is not unreasonable to assume that such cells are
prone to neoplastic proliferation wherever they might reside given their dependence on extracellular signaling to move back and forth into proliferative and quiescent states. As for the location of the lesion in the lateral ventricle of the brain, such an occurrence is rare, but not devoid of logic, as mesenchymal cells have long been known to reside within the ventricular wall and have been demonstrated at a clonal level to have true multilineage potential towards both, the mesodermal and neuroectodermal phenotype \cite{32}. As such, the substrate for ectopic differentiation of leiomyoma cells is omnipresent, and while the concept of an intraventricular lesion in an immunocompetent male is not intuitive, neither is it outside of the realm of logic.

The patient in this case presented with a symptomatic, homogenously enhancing, and well-circumscribed lesion within the lateral ventricle with a fair amount of associated cerebral edema. Intraventricular lesions with homogenous enhancement have a relatively short list of possible etiologies in the differential diagnosis, including Meningioma \cite{27}, choroid plexus papilloma (CPP), choroid plexus carcinoma, metastatic disease, and far less common entities such as xanthogranuloma \cite{28}. A CT scan of the chest and abdomen was used to rule out possible sources of metastatic disease, including that of leiomyosarcoma, which can rarely metastasize to the ventricular system with a radiological appearance mimicking that of a meningioma \cite{29}. The possibility of a primary leiomyoma was very low in our differential given the low prevalence of the disease both absolutely and even more so in immunocompetent patients. This notion was accentuated by the intraventricular location of the lesion, as there have been no prior reports of primary leiomyomata arising in this region. The patient therefore underwent transcollosal resection of a symptomatic intraventricular tumor.
Following resection, surgical pathology and IHC reported features consistent with leiomyoma. The absence of disease elsewhere as demonstrated by prior CT scanning indicated that this was a primary leiomyoma of the lateral ventricle. Subsequent FISH studies probing for the presence of EBV within the lesion were negative, as is consistent with past reports of primary lesions found in immunocompetent hosts (7, 15). A post-operative CT scan indicated complete resection, and the patient was discharged from the hospital three days following his surgery, with no evidence of recurrence at 2.5-years on follow-up MRI scan.

Primary intracranial leiomyoma is a very rare condition and as a result data on the diagnosis and management of these lesions is extremely sparse. This is, to our knowledge, the first report of such a mass occurring within the ventricular system, and the thirteenth report of a primary lesion in an immunocompetent patient. We hope this case can serve to supplement the present data and aid in the differential diagnosis, surgical and medical decision making of future patients with intraventricular disease.

Conclusion

To date and to our knowledge, there are fewer than 25 reported cases of primary intracranial leiomyoma, with only 13 occurring in immunocompetent patients including our report. The clinical and radiological features of these lesions are indistinguishable from meningioma, making pre-surgical diagnosis impossible and histological evaluation necessary. Here we report a case of a 30-year-old immunocompetent male diagnosed with a primary intraventricular leiomyoma. We believe this to be the first report of this tumor type involving the ventricles. We hope this case serves to supplement existing data and aid in future surgical and medical decision-making.
Acknowledgment

None

Disclosure and Conflict of Interest

None of the authors have any disclosures or conflicts of interest.

References


**Figure Legends:**

Figure 1: Preoperative magnetic resonance axial views showing intraventricular mass with decrease signal on T1 weighted (a), increase signal on fast relaxation fast spin echo (FRFSE) sequence T2 weighted (B), negative diffusion (c), increased signal on T2 weighted fluid attenuated inversion recovery (FLAIR) (D), and homogeneous avid contrast well circumscribed mass on post-contrast T1 weighted image.

Figure 3: Pathology H&E photomicrographs demonstrating the vascular and myxoid appearance of the tumor at 5X (a), and cells with spindle to round nuclei and rare mitotic figures at 40X (b).

Figure 3: Postoperative magnetic resonance axial views showing complete resection of the tumor at 2.5 years follow-up T1 weighted (a), fast relaxation fast spin echo (FRFSE) sequence T2 weighted (B), diffusion (c), T2 weighted fluid attenuated inversion recovery (FLAIR) (D), and post-contrast T1 weighted image.

**Table legend:**

Table 1: Cases of primary intracranial leiomyoma reported in immunocompetent patients.
<table>
<thead>
<tr>
<th>Authors and Year</th>
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Table 1: Cases of primary intracranial leiomyoma reported in immunocompetent patients.
Highlights

- Leiomyomas may also arise intracranially as a primary lesion and such occurrences are exceedingly rare.
- The majority of primary intracranial leiomyomas arise in immunocompromised patients.
- To our knowledge, this is the thirteenth report of a primary intracranial leiomyomas in an immunocompetent patient.
- The current case is the first report of such a lesion occurring within the ventricular system.
- Definitive diagnosis is therefore reliant on surgical pathology.
Abbreviations list:

MRI: Magnetic resonance imaging
IHC: Immunohistochemistry
CT: Computed tomography
CNS: Central nervous system
EBV: Epstein-Barr virus
FLAIR: Fluid attenuated inversion recovery
SMA: Smooth muscle actin
PR: Progesterone receptor
EMA: Epithelial membrane antigen
GFAP: Glial fibrillary acidic protein
NF: Neurofilament
MelanA: Melanoma antigen
HMB45: Human melanoma black 45
FISH: Fluorescent in situ hybridization
CPP: Choroid plexus papilloma
HIV: Human Immunodeficiency Virus