Histologic findings of the dura mater at the level of the foramen magnum in 121 CKCS with Chiari-like malformation

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Research Article

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Abstract

Background: To describe histopathologic features found in dural biopsies of Cavalier King Charles Spaniels (CKCS) with Chiari-like malformation (CM) and identify any associations between age, duration of clinical signs, syrinx location or syringomyelia (SM) and quality of life (QOL). The medical records of 121 consecutive client owned CKCS with CM and SM, confirmed by whole body magnetic resonance imaging (MRI), that underwent foramen magnum decompression (FMD) with cranioplasty and durectomy with biopsy from 2006 to 2016 were retrospectively reviewed. Dura biopsies were submitted to a board-certified veterinary pathologist for histopathologic interpretation. The chi-square test was used to analyze associations between diagnosis and categorical variables. For continuous measures, the Kruskal-Wallis non-parametric test was used to compare distributions across pathology categories. A result was considered statistically significant at the $P<0.05$ level of significance.

Results: The mean age, duration of pre-surgical clinical signs, and pre-operative QOL (1-5 scale) were 44.27 months, 44.78 weeks, and 2.72 respectively. Syringomyelia was found in the cervical region only in thirty-nice of one hundred twenty-one (32.23%) of dogs, in the cervical and thoracic region only in seventeen of one hundred twenty-one (14.05%) of dogs, and in the cervical, thoracic and lumbar region combined in sixty-five of one hundred twenty-one (53.72%) of dogs. Sixty-six of one hundred twenty-one (54.55%) dural biopsy specimens had histopathology changes; fifty-five (45.45%) did not. Forty-three of one hundred twenty-one (35.54%) dural biopsy specimens had osseous metaplasia, sixteen of one hundred twenty-one (13.22%) had evidence of fibrosis, four of one hundred twenty-one (3.31%) had arachnoid hyperplasia, and three of one hundred twenty-one (2.48%) had evidence of mineralization.

Conclusions: The majority of dogs with CM were found to have histopathologic changes in the dura at the time of FMD cranioplasty was performed. These dural changes can be observed in dogs experiencing clinical signs for a time period as short as four weeks prior to presentation. Histopathologic changes were not associated with age, breed, duration of clinical signs, the location of syringomyelia or preoperative QOL. The influence of histopathologic changes on long term prognosis in dogs without dural decompression is unknown since all dogs in this study had dural resection.

Background

Chiari-like malformation (CM) has been described in small breed dogs and is especially common among Cavalier King Charles Spaniels [1-6]. Most dogs with CM have syringomyelia (SM) present on imaging at the time of diagnosis [7-18]. Syringomyelia is viewed as a secondary condition, thought to evolve from alteration in cerebrospinal fluid (CSF) flow secondary to chronic compression at the foramen magnum [9-11]. Presenting clinical signs of CM with or without SM, include excessive scratching of the head and neck, air scratching, cervical guarding and pain, and sometimes cerebello-vestibular dysfunction [1, 14, 19, 20].

In addition to osseous compression, thickening of the dura mater at the cervico-medullary region has been reported in human Chiari I malformation (CM-I) [21-25] and in both Cavalier King Charles Spaniels (CKCS) and non-CKCS breeds [1, 26]. Removal of the outer layer of the dura mater (also termed the 'dural band') or duraplasty has been reported as an adjunctive decompression technique for human patients with CM-I. Additionally, there have been several studies describing boney decompression alone versus boney decompression with duraplasty [22, 27-34]. Boney decompression with duraplasty has been associated with a significant reduction in the volume of syrinxes with subsequent improvement of neurologic clinical signs in the human patient [32]. Foramen magnum decompression (FMD) with concurrent cranioplasty and full-thickness removal of the dura called "durectomy" has been reported as a

method of decompression in dogs with CM; with most dogs improving clinically with an overall improvement in quality-of-life score [1].

Although thickening of the dura mater in humans with CM-I has been described, there are only two papers in the human literature discussing the histopathologic changes seen in the dura mater [23, 26, 35]. Gross dural thickening has been described in dogs with CM [14, 19, 26], but no reports of histopathologic findings have been described in the veterinary literature.

The purpose of this study is to describe the histopathologic changes in the dura in dogs with CM and to report any association between age, the location of syringomyelia, the duration of clinical signs prior to surgical intervention, and the quality of life pre-operatively. We hypothesized that dogs with increased age, increased duration of clinical signs and the presence of a syrinx in the cervical, thoracic, and lumbar regions combined will be associated with more severe histopathologic changes.

Methods

Patient Population

One hundred twenty-one consecutive client-owned CKCS from 2006–2016 with CM and SM confirmed by whole body MRI that underwent FMD with cranioplasty and durectomy [36] were included in the study. Informed written consent was obtained from all owners of the animals in this study. Dogs with other known cranio-cervical junction abnormalities were excluded from the current study.

The medical records were retrospectively reviewed. Age, sex, duration of pre-surgical clinical signs, pre-operative quality of life score (QOL), the location of a syrinx, and dura mater histopathology were recorded for all patients.

Preoperative Quality of Life (QOL): Prior to surgery owners were asked to complete a QOL questionnaire. This questionnaire and its components were used in a prior study published in 2007 [1]. Questions related to the pet's quality of life before surgery using a scoring system from 1–5. The scoring system was as follows; 1 = extremely poor, considering euthanasia; 2 = poor, somewhat manageable with medical therapy; 3 = fair - does well overall; 4 = good - minor signs of disease [e.g. occasional scratching, occasionally appears painful]; 5 = excellent - minimal signs of disease [e.g. rarely scratches or appears painful]). The questionnaire also had owners report the level of disease progression prior to pursuing surgical intervention. Progression was categorized as follows: rapidly progressing (i.e. worsening weekly); progressing moderately (i.e. worsening monthly); slowly progressing (i.e. worsening about every 6 months); static/non-progressive (pursued surgery to prevent progression); or improved with medical therapy (pursued surgery to prevent progression) [1].

Anesthetic Protocol

Anesthesia entailed premedication with hydromorphone (0.1 mg/kg subcutaneously) and with atropine (0.02–0.04 mg/kg subcutaneously). Induction was performed with propofol (3–6 mg/kg intravenously), and maintenance with isoflurane in oxygen. Methyl-Prednisolone sodium succinate (30 mg/kg intravenously) and Mannitol (0.5 g/kg intravenously over 10–15 minutes) were also administered at the time of induction of general anesthesia. Cefazolin (22 mg/kg intravenously) was administered at the onset of surgery, and every 2 hours during the surgical procedure until its completion [1].

Surgery: FMD with Cranioplasty – As previously described [37], a dorsal midline approach to the caudal occipital region was performed. A foramen magnum decompression with C1 dorsal laminectomy was performed using a combination of high-speed pneumatic drill and rongeurs. A durectomy was performed using a blunt hook nerve root retractor and number 11 blade along dorsal midline, from the caudal aspect of C1 to the area covering the dorsal cerebellar vermis. Any arachnoid veils or adhesions present between the caudal part of the cerebellar vermis and the dorsal part of the brainstem were broken down via a small blunt-tipped nerve root retractor. A cranioplasty was performed utilizing a titanium mesh covered by a thin layer of polymethylmethacrylate, anchored on 5 titanium screws placed around the widened foramen magnum. A fat graft was placed over the caudal part of C1 (between the caudal part of the cranioplasty/mesh and the cranial part of C2) [37]. The incision was closed routinely in three layers. Samples of dura were placed in 10% neutral buffered formalin and submitted for histopathologic interpretation by a board-certified veterinary pathologist. Samples were trimmed and paraffin embedded. Five micrometer sections cut with a microtome were transferred to slides and stained with hematoxylin and eosin (H&E). All dogs included in this study had surgery performed at Long Island Veterinary Specialists by a neurosurgical team led by one of the authors (DM).

Control Specimens

Histopathology of the canine dura is well understood and described in the veterinary literature [38]. Since the aim of this study was to describe abnormal histopathologic findings of the canine dura in a cohort of CKCS with CM, control samples were not deemed necessary.

Histopathologic Classifications:

No evidence of inflammation or neoplasia

Examined sections of dura mater showed no evidence of inflammation or neoplasia. The samples consisted of normal dense, parallel streams of cellular collagen with small amounts of fibrofatty connective tissue [Figure 1].

Arachnoid Hyperplasia

Dura samples examined showed multiple foci of hyperplastic arachnoid cells lining the inner surface of the dura [Figure 2].

Dural Fibrosis

Dura samples examined showed thickened by hyalinized collagenous tissue of low cellularity within the specimen. The normal thickness of the dura has been distorted due to a moderate expansion of fibrous connective tissue [Figure 3].

Dural Mineralization

Dural mineralization is defined as mild to moderate, multifocal mineralized, basophilic material within the dura mater. Collagen fibers are usually degenerative and still have some level of inflammation present [Figure 4].

Dural Osseous Metaplasia

Dural ossification is defined as foci of osseous metaplasia embedded within the normal connective tissue of the dura mater [Figure 5].

Statistical Analysis

The chi-square test was used to analyze associations between diagnosis and categorical variables. For continuous measures, the Kruskal-Wallis non-parametric test was used to compare distributions across pathology categories. Since only four dogs had arachnoid hyperplasia and three dogs had mineralization, the former category was combined with fibrosis and the latter with osseous metaplasia to form a “collapsed” diagnosis. A result was considered statistically significant at the $P < 0.05$ level of significance.

Results

Overall Prevalence

There were sixty-nine (57.02%) females and fifty-two (42.98%) males. The mean age, duration of pre-surgical clinical signs, and pre-operative QOL were 44.27 months, 44.78 weeks, and 2.72 (1–5 scale) respectively. Syringomyelia was found in the cervical region only in thirty-nice of one hundred twenty-one (32.23%) of dogs, in the cervical and thoracic region only in seventeen of one hundred twenty-one (14.05%) of dogs, and in the cervical, thoracic and lumbar region combined in sixty-five of one hundred twenty-one (53.72%) of dogs. Sixty-six of one hundred twenty-one (54.55%) dural biopsy specimens had histopathology changes; fifty-five (45.45%) did not. Forty-three of one hundred twenty-one (35.54%) dural biopsy specimens had osseous metaplasia, sixteen of one hundred twenty-one (13.22%) had evidence of fibrosis, four of one hundred twenty-one (3.31%) had arachnoid hyperplasia, and three of one hundred twenty-one (2.48%) had evidence of mineralization.

See Table 1 for a summary of each dural change.

Table 1
Histological diagnosis of dura in 121 dogs with surgically corrected Chiari-like malformation

Diagnosis	n (%)	Age at surgery (months) mean ± SD	Duration of pre-surgery clinical signs (weeks) median (range)	Pre-op QOL (1-5 scale) median (range)
No inflammation or neoplasia	55 (45.45%)	42.5 ± 24.9	13 (1-312)	3 (1-4)
Osseous metaplasia	43 (35.54%)	42.2 ± 30.7	26 (1-339)	3 (1-4)
Fibrosis	16 (13.22%)	57.1 ± 25.2	20 (1-312)	3 (1-4)
Arachnoid hyperplasia	4 (3.31%)	66.0 ± 34.4	21 (2-104)	3 (2-3)
Mineralization	3 (2.48%)	9.0 ± 6.1	7 (3-9)	3 (2-3)

Histopathologic classifications:

No evidence of inflammation or neoplasia:

There were fifty-five of one hundred twenty-one (45.45%) specimens that had no significant findings on dura histopathology. There were thirty of fifty-five (54.55%) females and twenty-five of fifty five (45.45%) males. The mean age, duration of pre-surgical clinical signs, pre-operative quality of life and were 42.45 months, 42.30 weeks, and 2.71 (1–5 scale) respectively. Fifty-five dogs with syringomyelia had normal dura on histology in the following distribution: (cervical region = 15/55 (27.27%), cervical and thoracic region = 10/55 (18.18%), cervical, thoracic & lumbar region =

30/55 (54.55%)). Normal dura was not associated with age, sex, duration of pre-surgical clinical signs, or pre-operative quality of life score (QOL).

Arachnoid Hyperplasia:

There were four of one hundred twenty-one specimens (3.30%) that had evidence of arachnoid hyperplasia on dura histopathology. There were two (50%) females and two (50%) males. The mean age, duration of pre-surgical clinical signs, pre-operative quality of life and were 66.00 months, 36.84 weeks, and 2.75 (1–5 scale) respectively. Four dogs with syringomyelia had arachnoid hyperplasia on histology in the following distribution: (cervical region = 1/4 (25%), cervical and thoracic region = 1/4 (25%), cervical, thoracic & lumbar region = 2/4 (50%)). Arachnoid hyperplasia was not associated with age, sex, duration of pre-surgical clinical signs, or pre-operative quality of life score (QOL).

Dural Fibrosis:

There were sixteen of one hundred twenty-one (13.22%) specimens that had evidence of fibrosis on dura histopathology. There were nine (56.25%) females and seven (43.75%) males. The mean age, duration of pre-surgical clinical signs, pre-operative quality of life and were 57.13 months, 50.00 weeks, and 2.64 (1–5 scale) respectively. Sixteen dogs with syringomyelia had dural fibrosis on histology in the following distribution: (cervical region = 4/16 (25.00%), cervical and thoracic region = 3/16 (18.75%), cervical, thoracic & lumbar region = 9/16 (56.25%)). Fibrosis was not associated with was not associated with age, sex, duration of pre-surgical clinical signs, or pre-operative quality of life score (QOL).

Dural Mineralization:

There were three of one hundred twenty-one (2.48%) specimens that had evidence of mineralization on dura histopathology. There were two (66.67%) females and one (33.33%) male. The mean age, duration of pre-surgical clinical signs, pre-operative quality of life and were 9.00 months, 6.15 weeks, and 2.67 (1–5 scale) respectively. Three dogs with syringomyelia had dural mineralization on histology in the following distribution: (cervical region = 1/3 (33.33%), cervical and thoracic region = 1/3 (33.33%), cervical, thoracic & lumbar region = 1/3 (33.33%)). Mineralization was not associated with age, sex, duration of pre-surgical clinical signs, or pre-operative quality of life score (QOL).

Dural Osseous Metaplasia:

There were forty-three of one hundred twenty-one (35.53%) specimens that had evidence of osseous metaplasia on dura histopathology. There were twenty-six (60.47%) females and seventeen (39.53%) males. The mean age, duration of pre-surgical clinical signs, pre-operative quality of life and were 42.24 months, 49.45 weeks, and 2.77 (1–5 scale) respectively. Forty-three dogs with syringomyelia had dural osseous metaplasia on histology in the following distribution: (cervical region = 18/43 (41.86%), cervical and thoracic region = 2/43 (4.65%), cervical, thoracic & lumbar region = 23/43 (53.48%)). Osseous metaplasia with was not associated with age, sex, duration of pre-surgical clinical signs, or pre-operative quality of life score (QOL).

Location of syrinx:

Syrinx location relative to histopathologic classifications are summarized in Table 2.

Table 2

Histological diagnosis of dura in 121 dogs and associated syrinx location

	HISTOPATHOLOGIC DIAGNOSIS					
SYRNIX LOCATION	NO EVIDENCE OF INFLAMMATION OR NEOPLASIA	ARACHNOID HYPERPLASIA	FIBROSIS	MINERALIZATION	OSSEOUS METAPLASIA	TOTAL
CERVICAL	15	1	4	1	18	39
CERVICAL & THORACIC	10	1	3	1	2	17
CERVICAL & THORACIC & LUMBAR	30	2	9	1	23	65
TOTAL	55	4	16	3	43	121

Discussion

To the authors' knowledge, this is the first study to describe dural histopathologic changes at the cranio-cervical junction in CKCS with CM. In this study, we found that dural histopathology could be classified into five categories based on the predominant histopathological feature (i.e. normal dura, arachnoid hyperplasia, fibrosis, mineralization, and osseous metaplasia). We found pathology in dura in slightly more than half of dogs that underwent a FMD with cranioplasty and durectomy for CM. Of particular interest, dural changes were observed in dogs with only four weeks of pre-surgical clinical signs as noted by the owners at presentation. Disturbances in normal CSF flow, including the formation of high velocity jets, at the cranio-cervical junction have been reported in human and veterinary patients may be the cause of the dural changes observed due to physical insult to the surrounding tissues [39–42]. The phenomenon called the Venturi effect has been proposed to be involved in syrinx formation. The Venturi effect is based on the phenomenon of a jet of cerebrospinal fluid flowing from higher to lower velocity leading to the spinal cord substance being pulled in an outward direction, facilitating the accumulation of fluid in the syrinx cavity. The Venturi effect has been theorized to be responsible for the formation of syringomyelia in veterinary patients[11, 43]. The consequence of histologic changes as it relates to CSF flow is unknown at this time but changes in tissue pliability may impact the movement of CSF.

Age at the time of decompression was not found to be associated with the various changes observed on histopathology. The presumption that older dogs may have more chronic changes was not supported in the study however, the small sample size in some of the classifications may have had an impact on statistical analysis. The syrinx location is consistent with the author's observations in over 350 dogs with CM. Syringomyelia appears to propagate from the initial formation in the cervical region thus the locations were found to begin with the cervical region progressing to the thoracic region and then the lumbar region. Others have reported similar findings [11, 44–49]. The presumption that dogs with more distant syringomyelia (involving cervical, thoracic, and lumbar regions) may have more chronic histopathological changes was not supported in the study however, the small sample size in some of the classifications may have had an impact on statistical analysis. Pre-operative quality of life score was not found to be associated with any of the previously mentioned histopathologic changes. The severity of clinical signs, namely pain and craniofacial pruritus, has been attributed to asymmetrical dorsal horn involvement[50]. while some

of the neck pain may be directly related to constriction at the cervicomedullary junction.[51] The presumption that dogs with more pain and therefore a lower QOL score may have more constriction at the cervicomedullary junction due to more significant changes in the dura in the cervicomedullary junction was not supported in the study however, the small sample size in some of the classifications may have had an impact on statistical analysis.

The authors found no reports of histopathologic findings of full-thickness dura mater in human patients with Chiari malformation having FMD. One study evaluated histopathology of the outer layer of the dura (inner layer and subdural space remain intact) in CM-I patients with SM and compared them to control autopsy specimens [35]. Thickness of the resected dural bands varied from 3–5 mm, which was noted to be three to five times thicker than that of an autopsy specimen. Histopathologic examination focused on the regularity of the collagen arrangements within the dura. Sections of dura examined from CM-I patients with SM showed an irregular collagen patterns and showed degenerative changes such as hyalinosis, calcification and/or ossification. All eight specimens were noted to have irregular collagen arrangements and hyalinosis. One specimen had evidence of calcification only, three showed ossification only, and four showed both calcification and ossification. There were no calcification or ossification noted in any of the control autopsy specimens [35]. Nakamura *et al.* concluded that the thickened dura observed on histopathologic examination seemed to be due to a chronic state and presumed this to be a sequela of dissociation in CSF pressure between the cranial cavity and spinal cord with increased pressure at the cranio-cervical junction [23]. We did not note disruption of the collagen arrangements within our specimens; however similar changes of mineralization and ossification were present in our examined samples. Because of the nature of how our samples were harvested and processed, fiber orientation examination in transverse and longitudinal sections is not possible. Tissues submitted were transferred for embedding making orientation quite variable thereby making an analysis deeply flawed. Because the samples are all embedded in different planes of section resulting in variations in orientation, one cannot acceptably interpret stains for collagen type I, III, reticulin.

Previous studies in dogs with CM have proposed that the concurrent diagnosis of syringomyelia occurs from altered CSF flow at the level of the foramen magnum [7, 11, 26]. The objective of surgery in both human and veterinary medicine is restoration of normal CSF flow, by decompression which includes removal of bone and in the opinion of some, the dura. There remains significant debate regarding the merits of osseous decompression alone (leaving the dura intact) versus osseous and soft tissue decompression (removing the outer layer of the dura and performing a duraplasty) versus osseous decompression and soft tissue decompression (full-thickness durotomy and addressing arachnoid pathology)[22, 27–30]. Meningeal pathology has been suspected to play a role in the pathophysiology of CM-I and subsequent syrinx formation [52–54]. Tubbs *et al.* was the first report of arachnoid pathology, also termed arachnoid veils and/or adhesions, at the foramen Magendie. The finding of arachnoid pathology was significantly more common in patients with CM-I with SM than in those without.

Although we note the majority of dogs had dural pathology present at the time of decompression, we do not yet know the significance of this pathology as it relates to the development of SM. All dogs with CM at our practice undergo a full thickness durectomy at the time of surgery, making it difficult to assess the effectiveness of leaving the dura intact (control group of dogs with osseous decompression only, without durectomy). We do not know the implications of leaving the dura intact or what the previously described histopathologic changes have on clinical outcome.

Limitations of the Study

Due to the nature of a retrospective study, having a control cohort of dogs without craniocervical junction disease for dural histopathology evaluation was not possible, thus previously described dural histopathology in normal dogs was

relied on. Although some dogs had significant dural histopathology changes, the effect on patient outcome could not be determined because the dura was removed in all cases.

Conclusions

Varying classifications of dural histopathology were observed in a majority CKCS with CM having FMD with cranioplasty. These dural changes can be observed in dogs with only four weeks of pre-surgical clinical signs. No association was found between the different histopathologic classifications and age, duration of clinical signs, syrinx location, and the QOL before surgery. Future studies evaluating CSF flow before and after decompression, as well as intraoperatively could help classify and investigate associations between thickening of the dura mater and arachnoid veils/adhesions with restoration of CSF flow through the foramen magnum and its relation to SM. Biomechanical testing of abnormal resected dura could be performed in order to assess structural compliance of the dura and if the dura plays a role in altering CSF flow at the level of the foramen magnum.

List Of Abbreviations

Chiari-like malformation (CM), syringomyelia (SM), magnetic resonance imaging (MRI), foramen magnum decompression (FMD), Cavalier King Charles Spaniels (CKCS), cerebrospinal fluid (CSF), Chiari I malformation (CM-I), quality-of-life (QOL), Statistical Analysis System (SAS).

Declarations

Ethics approval and consent to participate:

Ethical approval was obtained from the Ethics Review Committee of Long Island Veterinary Specialists. Privately owned dogs were recruited to the study and informed written consent was obtained from all owners of the animals in this study. All methods were carried out in accordance with relevant guidelines and regulations and followed the ARRIVE guidelines.

Consent to publish:

Not applicable.

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests:

The authors declare no competing interests.

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Authors' Contributions:

JPH, DJM, CAL were the major contributors to the writing of the manuscript. JJS, MOD & MLL contributed the statistical analysis of all histopathologic data in the manuscript. ADM reviewed all the histopathologic specimens. All authors read and approved the final manuscript.

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Figures

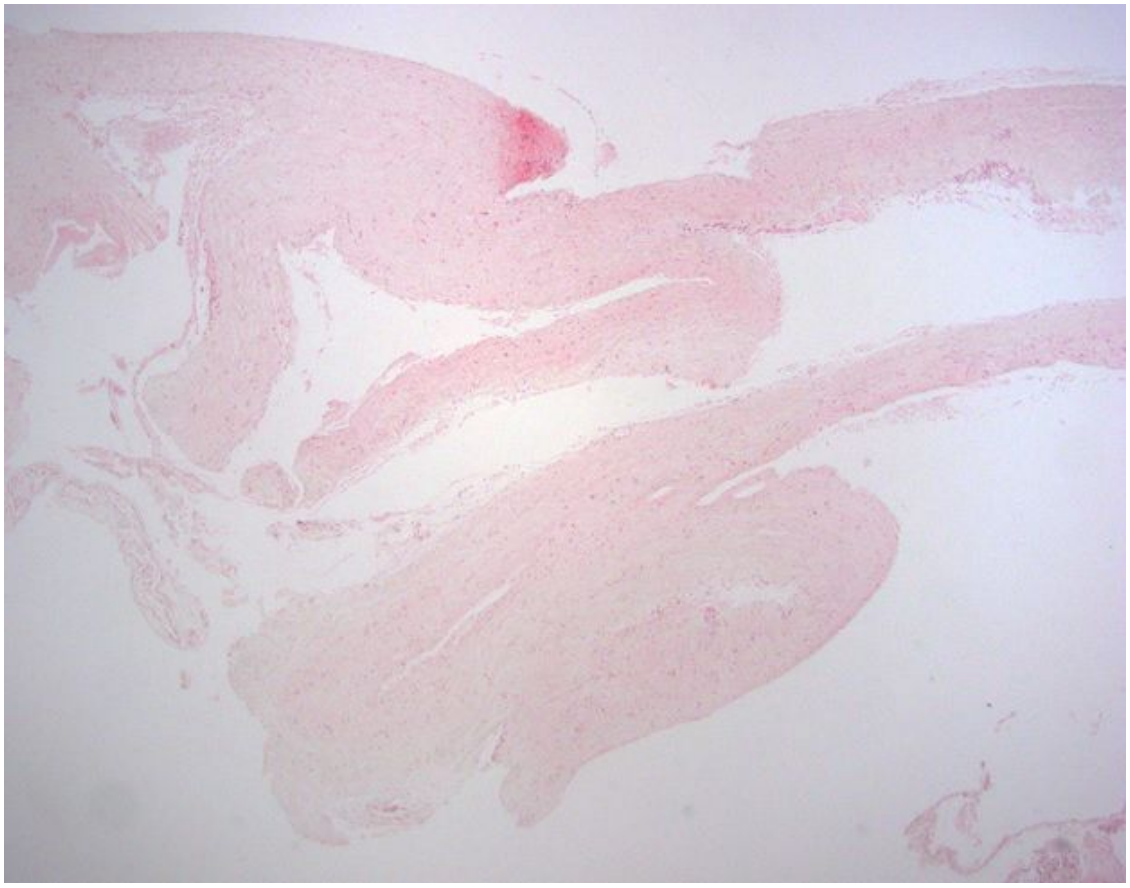

Figure 1

Normal Dura

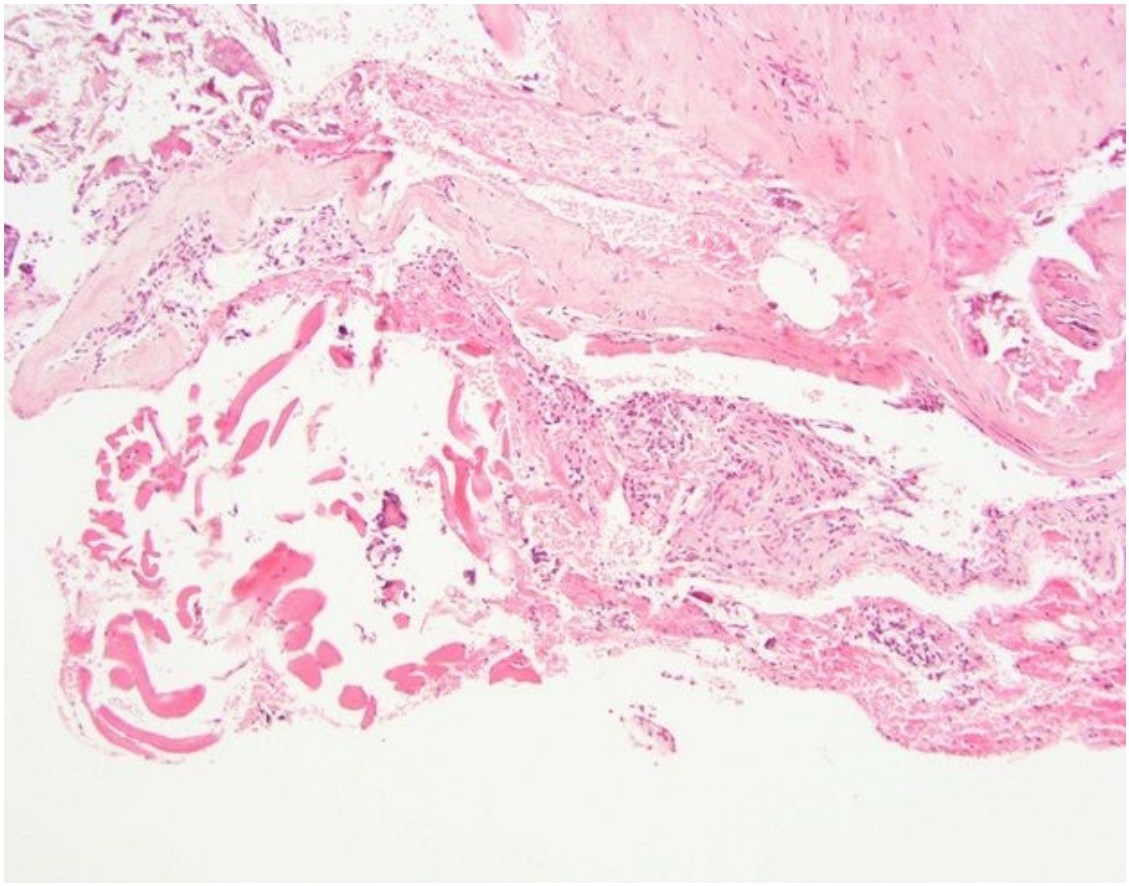

Figure 2

Dural Arachnoid Hyperplasia

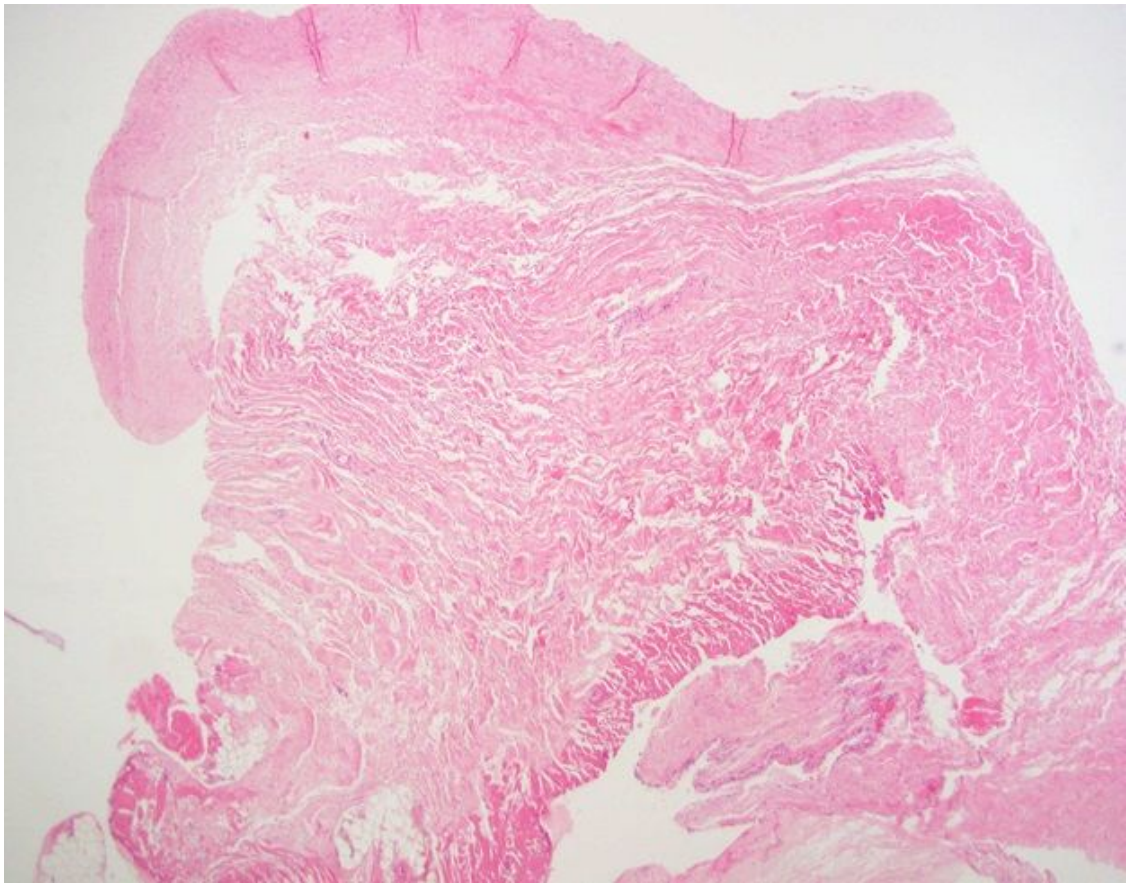

Figure 3

Dural Fibrosis

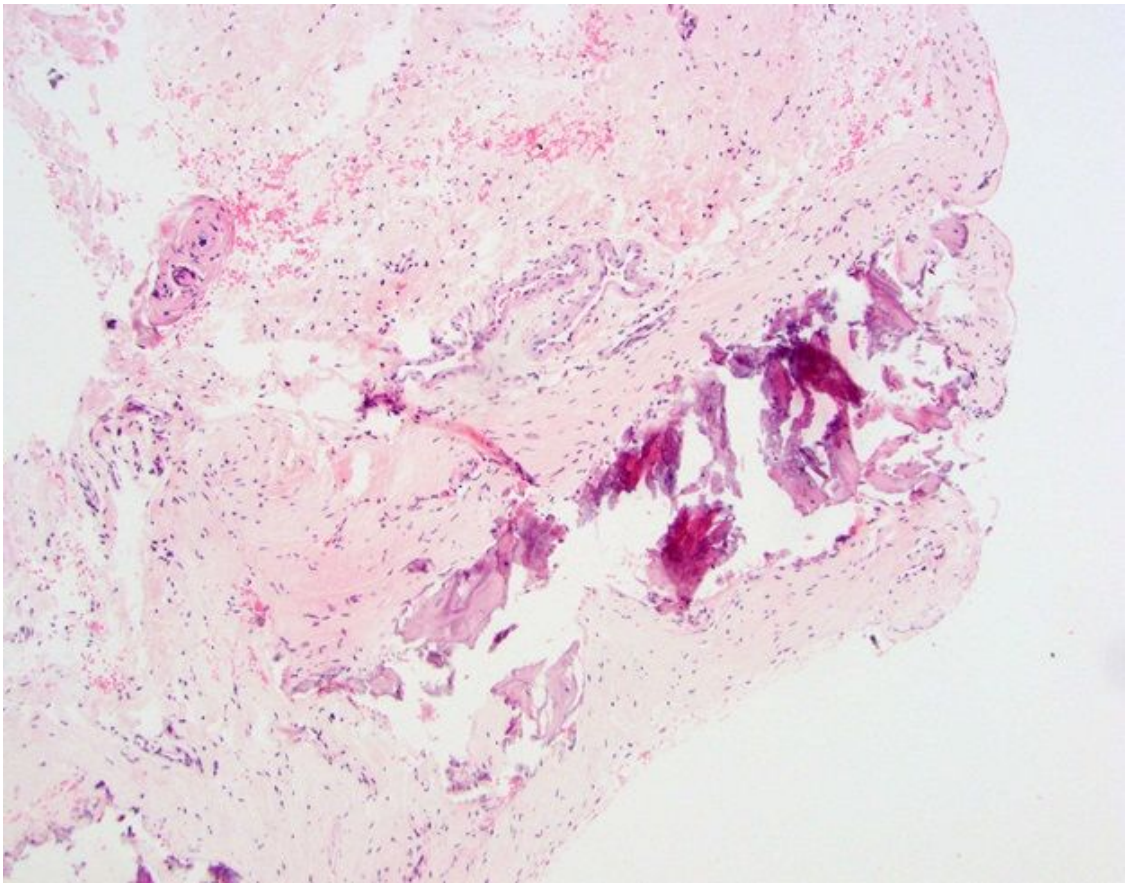

Figure 4

Dural Mineralization

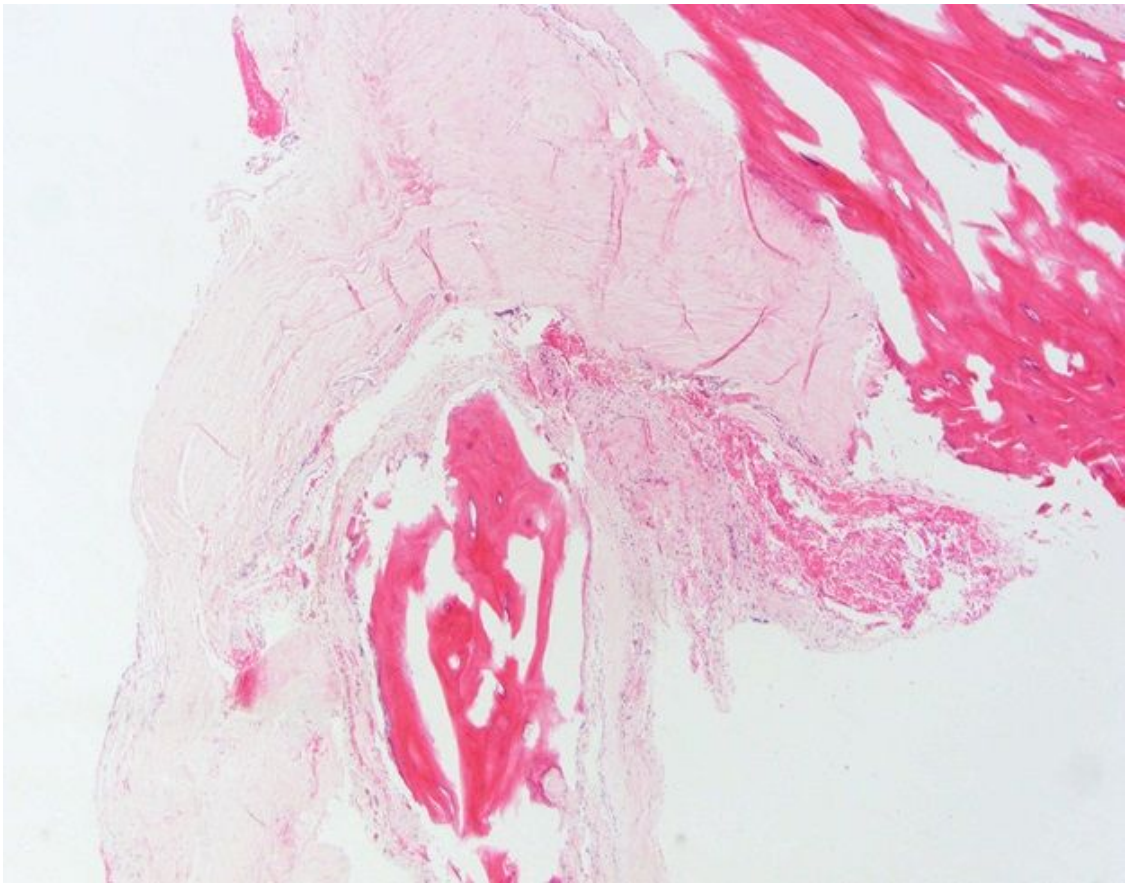

Figure 5

Dural Osseous Metaplasia