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# Hemorrhage of cavernous malformations during pregnancy and in the peripartum period: causal or coincidence?

## Case report and review of the literature

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✓There is growing evidence to suggest that pregnancy may increase the risk of hemorrhage from cavernous malformations (CMs). In the present case, a 21-year-old primigravida was admitted to the authors' neurosurgical service after a cesarean section. Three weeks before admission she had experienced rapidly progressive bilateral lower-extremity paresthesias. Spinal magnetic resonance (MR) imaging revealed the presence of an intramedullary thoracic lesion. On $T_2$-weighted MR images, heterogeneous signal intensity with a rim of decreased intensity was demonstrated in the spine. The mass was successfully resected, and 1 year later the patient's symptoms had resolved completely. This is the fourth reported case of a spinal intramedullary CM that became symptomatic during pregnancy. The pathogenesis and management of this entity are reviewed.

**Key Words • hemorrhage • intramedullary lesion • spine • cavernous malformation • pregnancy**

There is growing evidence to suggest that pregnancy may increase the risk of hemorrhage from CMs.[1,12,14,26,28,29] However, the literature on the natural history and treatment of CMs during pregnancy is only anecdotal. Whether pregnancy is actually associated with an increased risk of hemorrhage from CMs remains an important question, and neurosurgeons must be prepared to deal with these lesions in patients during pregnancy and the puerperal period.

We report the case of a 21-year-old woman in whom an intramedullary hemorrhage from a spinal CM occurred during the peripartum period. This case appears to be only the fourth report of a spinal intramedullary CM that became symptomatic during the puerperium, and it adds to the knowledge about the pathogenesis and management of this entity.

### Case Report

*History.* This 21-year-old primigravida was admitted to our service 2 weeks after a cesarean section. She reported a 3-week history of rapidly progressive bilateral lower-extremity paresthesias. Her symptoms had developed 3 weeks before her admission, when she noticed a tingling sensation and numbness in her feet. Subsequently she experienced acute paraparesis and required an emergency cesarean section. Admission MR imaging revealed an intramedullary lesion in the thoracic spine. She was transferred to our service for definitive neurosurgical management of the lesion.

*Examination.* On physical examination the patient's upper-extremity motor status was normal, whereas her lower-extremity strength was weakened bilaterally. She had 1/5 strength in the iliopsoas and 3/5 strength in the quadriceps, foot dorsiflexion, and plantar flexion. Lower-extremity hyperreflexia and unsustained cloni were also present bilaterally. Sensation to light touch and pinprick was diminished, and proprioception was diminished in both lower extremities below the T-11 sensory level.

The patient underwent MR imaging of the entire craniospinal axis. Brain imaging revealed no abnormalities, whereas the spinal MR imaging (Fig. 1) confirmed the presence of an intramedullary thoracic lesion at T-10. On $T_2$-weighted MR images, the mass was associated with a heterogeneous signal intensity with a rim of decreased intensity, which made us suspect hemosiderin content. Mild hyperintensity was present on $T_1$-weighted MR images obtained without contrast agents. No significant spinal cord edema or mass effect was associated with the lesion.

*Operation.* The patient underwent a T9–12 laminotomy for resection of the lesion. The dura mater was opened in the midline under the microscope. During microsurgical intradural exploration, an intramedullary multicolored le-

*Abbreviations used in this paper:* bFGF = basic fibroblast growth factor; CM = cavernous malformation; MR = magnetic resonance; VEGF = vascular endothelial growth factor.

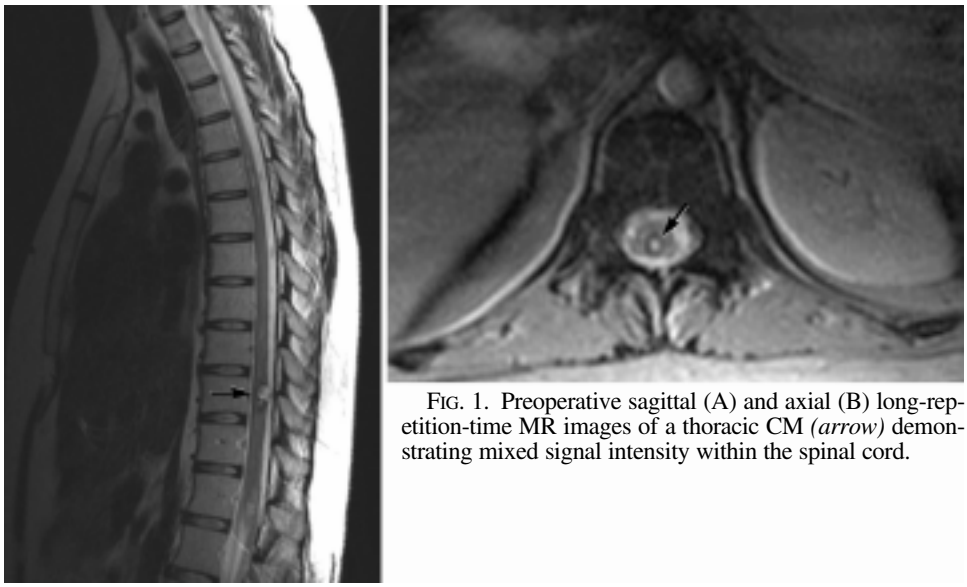

FIG. 1. Preoperative sagittal (A) and axial (B) long-repetition-time MR images of a thoracic CM *(arrow)* demonstrating mixed signal intensity within the spinal cord.

sion with a small exophytic component characteristic of a CM was identified immediately at T-10. The lesion was carefully dissected from the surrounding tissue and excised completely. Decompression of the spinal cord was excellent. The results of pathological examination confirmed the histological features of a CM.

*Postoperative Course.* Postoperatively, the patient recovered well and regained antigravity strength in her lower extremities. She underwent physical therapy and a short stay in a rehabilitation facility. She was discharged on a tapering dose of steroid medications. At a follow-up examination conducted 1 year postoperatively, her symptoms had resolved completely.

## Discussion

*Spinal Intramedullary CMs*

Cavernous malformations are found throughout the central nervous system, and symptomatic lesions have been described in all age groups and both sexes.[43] Histopathologically, spinal cord CMs are indistinguishable from cerebral ones.[5,19] Within the spine they may be located extra- or intradurally and in extra- or intramedullary spaces.[13,21] Most CMs occur in the extramedullary space. Purely intramedullary CMs are rare, with fewer than 200 cases described to date.[8,13,19,24,32–34,40]

The clinical presentation, surgical approaches, long-term outcomes, and complications associated with these uncommon lesions have been emphasized in previous small clinical series.[2,6,13,24,32–34,40] In their review of the literature in 2000, Deutsch and colleagues[8] found 94 reported cases of spinal intramedullary CMs and calculated an overall female/male ratio of 1:1. In previous reports, the lesions have predominated in women.[2,13,19,24] It is therefore assumed that CMs may be found equally in both sexes.

Nevertheless, the hemorrhage rate may be higher in women, who may more often become symptomatic as a result of hormonal stimulation.[8] In fact, in a metaanalysis conducted in 1994, the risk of hemorrhage in 57 reported cases of spinal intramedullary CM was calculated to be 1.6% per year; the highest risk of hemorrhage was in women.[4] That is, in this study almost 70% of the reported intramedullary CMs were in women. Compared with men, the risk of hemorrhage (and development of symptoms) in women harboring CMs at various anatomical locations has been significantly higher in many prospective and retrospective studies.[1,4,22,28,29,38] In other studies, however, no significant differences have been found in the rate and risk of hemorrhage between male and female patients.[8,17,26] The consensus is that hormonal effects may account for the increased growth and higher hemorrhage rate in women.[8,14,29] The available data are inconsistent,[36] however, and this issue remains unresolved.

*Pregnancy, Puerperium, and Symptomatic CMs*

The increasing recognition of de novo formation of CMs in both sporadic and familial cases,[7,22,23,43] and changes in size, number, and imaging characteristics have shown that these lesions are dynamic entities.[43] Furthermore, CMs have been classified as vascular neoplasms[35] because they exhibit vascular proliferation and neoangiogenesis.[36] Moreover, vascular neoplasms can modify their morphological and clinical features as a result of hormonal stimulation.[9,44]

Although it is widely believed that pregnancy and the puerperium are associated with an increased risk of hemorrhage and aggressive behavior in CMs,[1,4,8,10,14,20,25,28,29] quantitative data supporting this assumption are scarce. The size of CMs is known to increase during pregnancy.[14,41,42,44] Exacerbation of other symptoms such as seizures and headaches, symptomatic hemorrhages, and de novo appearance of CMs are also common during pregnancy.[3,28,29] In a series of 100 patients with brainstem CMs treated at our institution, seven (11%) of the 62 women suffered a hemorrhage during pregnancy.[27]

A higher propensity for hemorrhage during pregnancy and the puerperium is also common in other vascular lesions, such as vertebral hemangiomas,[18,37] arteriovenous

malformations, and aneurysms.[10,11,30] In fact, the risk of cerebral hemorrhage is especially increased after delivery, during the puerperium.[16] Several authors have therefore proposed a role for hormonal stimulation in the pathogenesis of symptomatic hemorrhage from CMs.[1,14,27–29]

Many cardiovascular, hemodynamic, and hormonal changes occur during pregnancy. Vascular proliferation and expansion are critical components of placental development. Consequently, interference with vascular growth is a physiological response in pregnancy and may occur anywhere in the maternal body. In general, the angiogenic process is initiated by growth factors such as VEGF, bFGF, or placental growth factor.[45] Complex signal transduction machinery increases the permeability of the maternal vessels to permit growth and invasion of endothelial cells.[45] Interestingly, angiogenic growth factors such as VEGF, bFGF, and transforming growth factor–α are expressed in CMs.[15,31,39]

In fact, VEGF and bFGF are abundantly expressed during embryonic development but are absent in normal adult vascular beds, including the cerebral vasculature. Therefore, the expression of these growth factors may promote angiogenic processes and proliferation of new vessels in CMs, which are normally dormant in adult brain tissue.[15,31] The same physiological mechanisms and angiogenic factors that prepare for and promote pregnancy-related vasculogenesis may also promote growth, thrombosis, and hemorrhage of vascular lesions. Venous obstruction and engorgement related to the enlarged uterus, and the aggravation of preexisting spinal cord ischemia by pregnancy-associated hemodilution and anemia are other mechanisms proposed to explain the pathogenesis and hemorrhage of spinal CMs.[20]

To our knowledge, this is the fourth reported case of a symptomatic spinal intramedullary CM. In 1990 Lopate and coworkers[20] reported the first case, which occurred in a 19-year-old patient with a cervical CM; this woman had an uneventful vaginal delivery and experienced a postpartum development of symptoms. In 1994 Canavero, et al.,[4] reported on a woman with a thoracic CM who became symptomatic during pregnancy. Initially, however, the lesion was not diagnosed, but was discovered on MR imaging and treated surgically almost 15 years later. In their series of 12 patients with intramedullary CMs, Cristante and Hermann[6] described a young woman with a cervical spinal intramedullary CM who had experienced symptoms during her pregnancy 5 years before the lesion was diagnosed. Our patient became symptomatic in her last trimester and underwent surgery 2 weeks after her baby was delivered via cesarean section. Regardless of the underlying mechanisms of the pathogenesis of these lesions during pregnancy, neurosurgeons should be prepared to manage CMs in the puerperal period.

### *Management of Spinal Intramedullary CMs During the Peripartum Period*

Until we know more about the natural history of these lesions in pregnant women, the risk of hemorrhage and life-threatening maternal and fetal complications must be weighed against the risk related to individual surgery. Resection may lead to transient worsening of symptoms. Nevertheless, most patients eventually improve and the incidence of permanent deficits has been low.[34,40] Delayed complications such as tethering of the spinal cord[40] or subsequent hemorrhage and recurrence of symptoms result from incomplete resection.[24,32,40] These facts must be considered when the decision is made to perform surgery for a CM in a young woman during or soon after pregnancy.

The management of CMs during pregnancy and the peripartum period is based on when the symptoms developed during the course of pregnancy. The need for emergency neurosurgical therapy during pregnancy has been rare.[12] Most cases have been treated neurosurgically after a cesarean section or vaginal delivery, and these procedures have been associated with good outcomes.[6,20,28] Thus, the method of delivery should be based on obstetrical considerations, unless an emergency cesarean section is needed. If the symptoms are severe, occur early in the course of the pregnancy, and endanger maternal and fetal life, neurosurgical therapy may precede delivery, as has been reported in the case of a brainstem CM.[12]

Surgical management in asymptomatic patients with incidental intramedullary spinal CMs is not recommended.[2] Some authors, however, consider performing resection of accessible lesions in women contemplating pregnancy.[29] Given the low risk of permanent deficits and the potentially higher risk of hemorrhage during pregnancy, it is tempting to suggest aggressive surgical management. Yet, in the case of pregnant women with asymptomatic or minimally symptomatic lesions, the high risk that new symptoms will develop or existing ones will deteriorate after surgery, even transiently, may have devastating consequences and must be considered on an individual basis.

## Conclusions

This article adds to the body of literature in which pregnancy is implicated as a potential promoter of growth and hemorrhage of CMs. As with any rare condition in which guidelines are lacking, medical decision making requires careful deliberation. Management must be tailored to each individual based on the specific circumstances. Symptomatic lesions should be removed totally to avoid recurrence and rebleeding of the residue. In most cases neurosurgical therapy can be performed after delivery. In some cases, however, emergency neurosurgical intervention may be required prior to term.

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