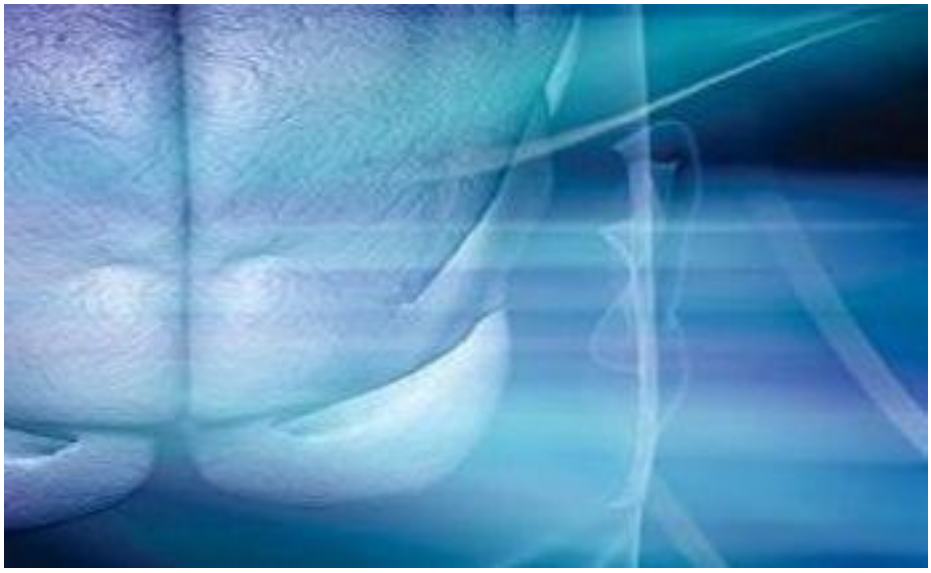

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INSTRUCTIONS FOR AUTHORS

Papers submitted should be original documentation, including photographs. The papers should be single column, double-spaced. The title should be in title case and bold, followed by Authors, degree, organization and city, state.

The papers should contain an abstract and be separated into sections with bold typing of the section title. The page set-up should be 0-6.5 inches. Paragraphs should be indented 0.5 inches. All tables should be submitted separate from the paper. If possible make the tables up to 3 inches wide so that they could fit into a column. This will allow quicker scanning and preparation.

References should be numbered, tab, name of authors. Title of paper. Journal. Year volume:pages.

All papers, correspondence and DUES can be submitted to the:

American Organization of Neurological Surgeons

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EDITOR'S PAGE

Physicians in training, learn and practice research "To formulate, ingrain, and measure, a method of thought, investigation, and evaluation necessary for physicians to have multi-lateral information exchange and communication with experts in areas of scientific and medical discovery, knowledge, and analysis, in order to continuously and efficiently improve human health and patient care." Understanding and performing quality research provides students and residents the tools to propel quality medical care into the community and into the future.

Welcome to the Journal of the American Organization of Neurological Surgeons and the American College of Osteopathic Surgeons Neurosurgical Section. This volume is composed of the Residents' annual papers that were submitted but not published elsewhere. It is therefore dedicated to the future Neurosurgeons and their education. All papers were reviewed by the peer review committee and selected for awards. The papers submitted are excellent, representing some of our talented colleagues. Issues will be published annually. I hope that this issue will spread the knowledge of our residents and our section. We will continue to solicit annual papers and all papers submitted at the annual meeting. This is your Journal paid for by your annual dues. This issue is available on our website AOANeurosurgery.org. This is your organization; please support it as you can.

Thank you,

Dan Miulli, D.O, F.A.C.O.S
Editor

2010 Resident Achievement In Writing Awards

San Francisco at the ACA Saturday October 23, 2010 between 2:00 pm and 3:00 pm presentation of their outstanding works.

The award for the first place paper is $1500. The award for the second place paper is $1000 and the third place winner will receive $500.

The papers were judged based upon original prospective studies in neurosurgery. Case studies and review of the literature are significant contributions and should be combined with retrospective or prospective procedures to qualify as best papers. Papers received up to 100 points in each category for a total of 500 points. The categories judged were: 1. Type of Research Paper (basic science, original clinical research, prospective study, chart review, review of literature, case study), 2. Grammar, 3. Addition to Science, 4. Research Conducted, and 5. Change to Neuroscience Practice. All papers were reviewed by the committee. With corrections non-published papers will be printed in the JAONS.

1st Place
Ripul Panchal, DO
Serum Sodium levels and Optimization of Brain Tissue Oxygenation and Intracranial pressures in Severe Traumatic Brain Injury
Arrowhead Regional Medical Center, Colton CA

2nd Place
Kara Beasley, DO, MBe
The Molecular Pathobiology of Metastasis to the Brain: A Review
Philadelphia College of Osteopathic Medicine, Philadelphia, PA

3rd Place
Michael Verdon, DO
Minimally Invasive Pedicle Screw Instrumentation with PMMA Augmentation for Thoracolumbar Burst Fractures in Osteoporotic Patients
St. John Providence Hospital Medical Centers, Detroit and Southfield, MI

Serum Sodium levels and Optimization of Brain Tissue Oxygenation and Intracranial pressures in Severe Traumatic Brain Injury

Ripul R. Panchal, DO, Department of Neurological Surgery, Arrowhead Regional Medical, Center, Colton CA

ABSTRACT

INTRODUCTION:

Patients with severe traumatic brain injury (TBI) are highly susceptible to secondary insults caused by hypoxemia, systemic hypotension and intracranial hypertension resulting in cerebral hypoxia and ischemia. This is a major source of poor clinical outcome. In these patients, therapy directed at improving brain tissue oxygenation using partial pressure of brain tissue oxygenation ($PbtO_2$) as a dynamic guide and using hypertonic saline to reduce cerebral edema and improving blood rheology has been shown to be effective in improving neurologic outcome. To our knowledge, no clinical data have demonstrated optimal range of sodium levels to maintain in patients with severe traumatic brain injury to optimize intracranial pressure (ICP) and $PbtO_2$. Our study examines the relationship between sodium levels, partial pressure of brain tissue oxygenation, and intracranial pressures in individuals with severe traumatic brain injury.

METHOD

The charts of twenty patients with severe traumatic brain injury (GCS $\leq$ 8) were retrospectively analyzed with institutional review board approval. The mean age was 28.5 years (standard deviation = 23.1) and all but four patients were males. Patients were selected for the study on the basis of initial presentation involving severe traumatic brain injury (TBI) and had undergone placement of ventriculostomy catheter (Integra NeuroSciences, Plainsboro, NJ) and LICOX® catheter (Integra NeuroSciences, Plainsboro, NJ). Neuromonitoring values for ICP, CPP, MAP, and $PbtO_2$ were recorded hourly, and appropriately treated if ICP > 20 mmHg, CPP < 60 mmHg, MAP < 90 mmHg, or $PbtO_2$ < 15 mmHg according to current traumatic brain injury guidelines. Patient's electrolytes were monitored every six hours and serum sodium levels between 140 mEq/L and 150 mEq/L were maintained using hypertonic saline to optimize $PbtO_2$. To describe the nature of the correlation between Na^+, ICP and $PbtO_2$, a quartic regression was performed on the Na^+, ICP, and $PbtO_2$.

RESULTS

A strong correlation was observed between patient's serum sodium with their $PbtO_2$ (R^2 = 0.81) and ICP (R^2 = 0.5). When serum sodium levels are between 145 mEq/L and 147 mEq/L, the $PbtO_2$ values are at their maximum and the average ICP is less than 20 mmHg. Serum sodium levels greater 150 mEq/L may improve $PbtO_2$ and ICP but are observed to be detrimental to adult patients with severe TBI.

CONCLUSION

The data obtained in our study suggest that maintaining patient serum sodium between 145 mEq/L and 147 mEq/L may help optimize partial pressure of brain tissue oxygenation with keeping intracranial pressures less than 20 mmHg in severe traumatic brain injury patients.

KEY WORDS:
Traumatic Brain Injury (TBI), Serum Sodium, hypertonic saline (HTS), brain tissue oxygenation, partial pressure of brain tissue oxygenation ($PbtO_2$, and intracranial pressure (ICP).

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of death among young adults (age < 45 years old) in the United States.[1,13,26,30] Severe TBI is responsible for majority of in-hospital deaths and lifelong disability after trauma in this same population.[13,26,30] Patients with TBI are highly susceptible to secondary insults caused by hypoxemia, systemic hypotension and intracranial hypertension resulting in cerebral hypoxia and ischemia. This is a major source of poor clinical outcome.[7,25,26]

Many monitoring systems have been developed and variables have been evaluated to guide therapies to prevent secondary cerebral hypoxia and ischemia.[28] These monitored parameters include intracranial pressure (ICP), mean arterial blood pressure, cerebral perfusion pressure (CPP), end-tidal CO_2, partial pressure of brain tissue oxygenation ($PbtO_2$), jugular bulb oxyhemoglobin saturation, and metabolic changes via microdialysis.[25,26] The guidelines for the management of severe traumatic brain injury by the Brain Trauma Foundation recommend aggressive attempts to maintain CPP between 50-70 mmHg and treat ICP above 20 mmHg in the adult male.[5] However, continuous monitoring and treatment of changes in ICP values from which CPP values are calculated alone do not predict poor cerebral oxygenation and perfusion.[10,14,17,24,28,30,34,35] Graham observed that 70% of injured brains had evidence of ischemic changes postmortem without previous evidence of clinical, pathological, or radiological changes indicative of increased ICP.[11,28] Presently, continuous monitoring of partial pressure of brain tissue oxygen ($PbtO_2$) is being increasingly used as an adjuvant in the treatment of patients with severe TBI to reduce secondary cerebral injuries and improve clinical outcome.[3,12,29,30,32,33,36] A decrease in $PbtO_2$ less than 15 mmHg is associated with poor outcome for severely head-injured patients.[12,25,26,27,32,33] However, therapy directed at improving brain tissue oxygenation greater than 15 mmHg in severe TBI patients using $PbtO_2$ as a dynamic guide, has been shown to be effective in improving neurologic outcome in these patients.[15,16,18,27,28,30] Intraparenchymal catheterization to measure $PbtO_2$ and brain temperature in real-time has been shown to be a safe and effective methodology and has been granted FDA approval.[12,28] Therapy guided by brain tissue PO_2 from the use of both PbtO2 and ICP monitors is associated with reduced patient death following severe TBI.[16,18,23,30]

Hypertonic saline (HTS) is emerging to be as effective or an even better osmotic and rheologic agent than mannitol to decrease ICP while improving CPP and $PbtO_2$ in patients with severe TBI.[23] The influence of sodium on ICP has been studied extensively in various subfields

of neurocritical care. There exists a therapeutic hypernatremic range of Na^+ concentrations believed to be beneficial to outcome of brain injured patients.[6,9,20,23] However, Na^+ levels above 155 mEq/L has been documented to cause adverse effects and above 160 mEq/L has been associated with increased mortality.[2,9,19,31]

To our knowledge, no clinical data have demonstrated optimal range of sodium levels to maintain in patients with severe traumatic brain injury to optimize ICP, CPP and $PbtO_2$. Our study examines the relationship between sodium levels, partial pressure of brain tissue oxygenation, and intracranial pressures in individuals with severe traumatic brain injury.

METHOD

The charts of twenty patients with severe traumatic brain injury were retrospectively analyzed with institutional review board approval. All patients were admitted to our critical care unit between July 2007 and April 2010. The mean age was 28.5 years (standard deviation = 23.1) and all but four patients were males (Table 1). All patients had an initial Glasgow coma scale (GCS) score of $\leq$ 8 after resuscitation and were managed according to published recommendations for severe TBI.[5]

Patients were selected for the study on the basis of initial presentation involving severe traumatic brain injury (TBI) and had undergone placement of ventriculostomy catheter (Integra NeuroSciences, Plainsboro, NJ) and brain tissue oxygenation monitor (LICOX® catheter by Integra NeuroSciences, Plainsboro, NJ). Both catheters were placed on the ipsilateral side through non-lesioned frontal white matter. The satisfactory positions of both catheters were confirmed with post-insertion head CT scans. All patients were sedated, initially intubated, and mechanically ventilated to maintain PaO_2 greater than 110 mmHg and $PaCO_2$ between 35-40 mmHg. On placement of the ventriculostomy and brain tissue oxygenation monitoring catheters, all patients received a prophylactic antibiotic, cefazolin, and if they were allergic to penicillin, vancomycin was prescribed. None of the patients developed complication of ventriculitis, arachnoiditis, or procedure related hematoma.

Five patients had decompressive craniectomies only, three patients had both decompressive craniectomies and evacuations of mass lesions, and seven underwent evacuations of mass lesions alone. CVP, fluid balance, blood gas analysis, and hemoglobin levels were standardized between patients to eliminate any variability in the data attributable to these factors. These data were recorded in the patients' medical records per the standard critical care nursing protocol. Neuromonitoring values for ICP, CPP, MAP, and $PbtO_2$ were recorded hourly, and treated if ICP > 20 mmHg, CPP < 60 mmHg, MAP < 90 mmHg, or $PbtO_2$ < 15 mmHg according to current traumatic brain injury guidelines. If initial treatment, including patient positioning, sedation, cerebrospinal fluid drainage, and mild hyperventilation failed, 23.4% hypertonic saline (HTS) was administered in 20 ml infusion over 10 min through a large-bore central intravenous access on emergent basis for acute decrease in patient's $PbtO_2$. Continuous drip of 3% NaCl HTS was started at 20 ml per hour and titrated to maintain sodium levels between 140 mEq/L and 150 mEq/L. Patient's electrolytes were monitored every six hours. Patients' chart reviews were

excluded if their GCS was > 8, if they had bilateral fixed and dilated pupils that was consistent with cerebral herniation on initial presentation, had penetrating head injuries, or were dead within 24 hrs after admission.

Statistical analysis of the resultant data was completed using SPSS statistical software version 16.0 (SPSS Inc., Chicago, IL, USA). Charts were generated using Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA, USA). To describe the nature of the correlation between Na^+, ICP and $PbtO_2$, a quartic regression was performed on the Na^+, ICP, and $PbtO_2$ data collapsed over the patients. This permitted identification of the trend and how well they fit the purposed pattern. For the correlations, R^2 was used as a measure of effect size to determine the degree of influence that each independent variable had on $PbtO_2$.

Variable	Number
Total number of Patients	20
Gender	
Male	16
Female	4
Age	
Mean	28.53
Range	13 - 67

Table 1: Basic descriptive features of the patient population analyzed.

RESULTS

A general linear model analysis was performed to evaluate the relationships between Na^+, ICP, and $PbtO_2$. A significant main effect of Na^+ on $PbtO_2$ ($F(26,113) = 16.895$, $p < 0.0005$), ICP on $P_{bt}O_2$ ($F(33,113) = 10.942$, $p < 0.0005$), and a significant Na^+ and ICP interaction effect on $P_{bt}O_2$ ($F(34,113) = 18.109$, $p < 0.0005$) were found. All of these are very strong effects as evidenced by the low p-values in all cases. The effect sizes of Na^+ on $PbtO_2$ and ICP are very strong as evidenced by R^2 values from the quartic regressions of 0.81 and 0.54 respectively (Figures 1 and 2).

In Figure 1, when we examined the pattern of $PbtO_2$ caused by serum sodium, we found that as serum sodium approaches 142 mEq/L, $PbtO_2$ tends to fall. At the point when serum sodium reaches 142 mEq/L, the $PbtO_2$ begins to rise again. $PbtO_2$ continues to rise until a maximum brain tissue oxygenation is reached at 145 mEq/L. Once sodium exceeds 145 mEq/L, $PbtO_2$ trends lower again. At serum sodium of 150 mEq/L, $PbtO_2$ appears to rise again. When

serum sodium levels are between 145 mEq/L and 147 mEq/L, the $PbtO_2$ values are at their maximum. In examining Figure 2 over the range of serum sodium leading to maximal $PbtO_2$ established from the plot in Figure 1 (145-147 mEq/L), the average ICP is stable and within the range of normal.

Furthermore, Figure 1 illustrated that brain tissue oxygen-directed therapy tended to keep ICPs less than twenty five for all severe TBI patients. However, as serum sodium increased beyond 147mEq/L the ICPs trended down but were detrimental to adult patients with severe TBI. Only four patients ever reached serum sodium levels above our purposed serum sodium limit (> 150 mEq/L) with only two of those remaining at that level of hypernatremia for more than a single blood sodium measurement. One of these four patients was a pediatric patient and was the only patient to survive with serum sodium levels this high. The remaining three died within 48 hours of reaching sodium levels above $\geq$ 150 mEq/L.

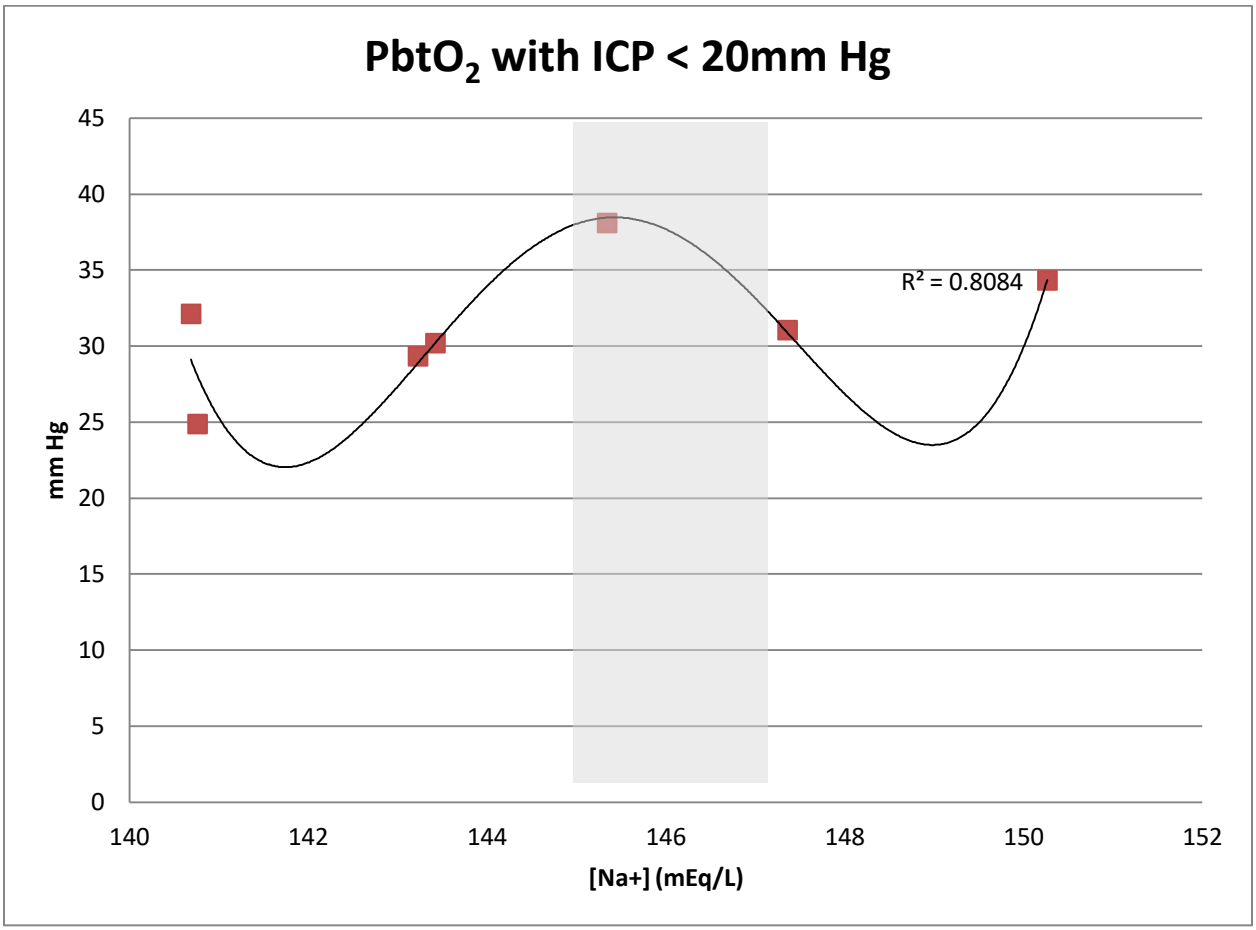

Figure 1: Average $PbtO_2$ with normal intracranial pressure (ICP) plotted against average blood sodium levels. The regression line is quartic. It is evident from the distribution of data that there is a therapeutic range of sodium levels between 145 – 147 mEq/L that will reliably (as predicted

by the high R^2 value) causes a favorably high $PbtO_2$ with normal ICP in severe traumatic brain injured patients.

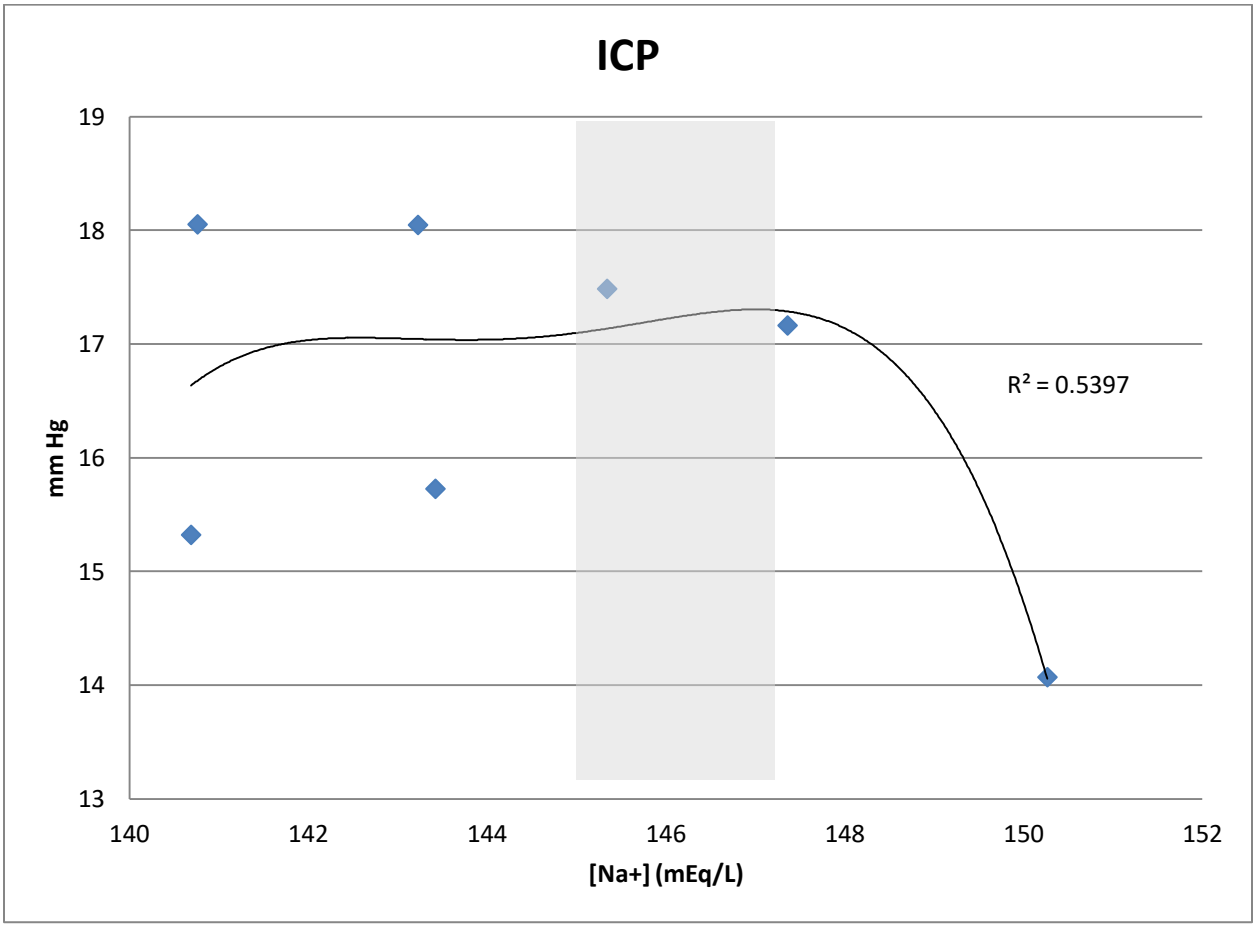

Figure 2: Average ICP plotted against average sodium levels. Again with a quartic regression, we see a very strong R^2 value with relatively stable ICP and serum sodium range, 145 – 147 mEq/L indicated as therapeutic in Figure 1. Although, the ICP is observed to be significantly decreased when serum sodium levels were greater than 150 mEq/L, in three of the four patients in this group the outcome was death and only one to survive was a pediatric patient.

DISCUSSION

Severe traumatic brain injury (TBI) and subsequent secondary injury from hypoxia and ischemia is found to be a major cause of death and disability in the United States.[15,26,30] Despite aggressive monitoring and ventriculostomy directed treatment of intracranial pressures (ICP) and cerebral perfusion pressures (CPP), cerebral hypoxia and ischemia has not been preventable because not all episodes of cerebral ischemia are related to cerebral hypertension.[10,14,34,35] This current gold standard for intracranial monitoring for severe TBI is limited in predicting clinical outcome. Hence, improved technologies such as the brain tissue oxygenation monitoring device (LICOX® catheter by Integra NeuroSciences, Plainsboro, NJ and previously available Codman NEUROTREND™) allows for continuous measure of partial pressure of brain tissue

oxygenation ($PbtO_2$) as an early indicator of the brain tissue's ischemic response to injury and guides therapy accordingly.[1,15,20,25]

A number of studies have illustrated that brain tissue oxygen-directed therapy promotes better outcome. In 2005, Stiefel prospectively observed 53 patients admitted to a Level I trauma center with severe traumatic brain injury (TBI). Twenty-five patients with mean age 44 ± 14 years were treated using an ICP monitor alone and twenty-eight patients with mean age 38 ± 18 years underwent brain tissue oxygen-directed therapy. In both groups mean daily ICP and CPP levels were found to be similar using the goals of maintaining ICP < 20 mmHg and CPP > 60 mmHg. Stiefel concluded that the patient group that underwent brain tissue oxygen-directed therapy there was a decrease in mortality by 19%.[30] In addition, Narotam reported that brain tissue oxygen-directed therapy not only reduced mortality rate after severe TBI, but also resulted in improved six-month clinical outcome over the conventional ICP and CPP-directed therapy. One hundred thirty-nine patients admitted to their institution underwent prospective evaluation. The clinical outcome was recorded as Glasgow outcome score (GOS) and was 3.55 ± 1.75 and 2.71 ± 1.65 ($p < 0.01$) for the patient group that underwent brain tissue oxygen-directed therapy and ICP and CPP-directed therapy respectively.[18]

Furthermore, Rockswold studied the effects of hypertonic saline on ICP, CPP and PbtO2. Twenty-five consecutive patients with severe TBI were evaluated. Hypertonic saline (23.4% NaCl) was infused over fifteen minutes in thirty milliliters volumes for ICP > 20 mmHg. The baseline serum sodium level of 140 to 150 mEq/L was maintained throughout the study. This caused a mean decrease in ICP by 8.3 mmHg ($p < 0.01$) and improved $PbtO_2$ by 3.1 mmHg ($p < 0.0001$). No significant complications were reported from treatment other than electrolyte imbalance.[23] Reily has also concluded that hypertonic saline infusion improved brain tissue oxygenation.[20] However, serum sodium levels greater than 155 mEq/L has been associated with many adverse affects. For example, Froelich retrospectively reviewed charts of 187 patients of neurocritically ill patients, 107 patients had received continuous 3% NaCl hypertonic saline (CHS) and 80 patients had received continuous 0.9% NaCl saline over for at least five days. The observed CHS group had a higher risk of developing increased blood urea nitrogen and creatinine levels.[9] In addition, other reported complications associated with extremely elevated serum sodium levels (greater than 155 mEq/L) range from hypokalemia, renal dysfunction, metabolic acidosis, cardiac complications to death.[2,9,21,22,31]

However, to our knowledge, no clinical data have demonstrated an optimal range of sodium levels to maintain in patients with severe traumatic brain injury to optimize $PbtO_2$ and ICP. Our study examined the relationship between serum sodium levels, partial pressure of brain tissue oxygenation, and intracranial pressures in individuals with severe traumatic brain injury. $PbtO_2$ is highest and ICP values are found to be < 20 mmHg when serum sodium levels are between 145 – 147 mEq/L. Similarly, $PbtO_2$ is observed to increase with serum sodium levels above 150 mEq/L and ICP values to dramatically decrease in Figure 1 and 2, however in these cases, patient outcome worsened. Among the four patients that reached serum sodium levels excessively high (> 150 mEq/L), three patients died. This is likely attributable to the levels of

serum sodium exceeding the body's homeostatic abilities. The only surviving patient was pediatric, suggesting that their physiology may differ from adults.

Due to the small number of patients and the small number of data points in serum sodium levels greater than 150 mEq/L, we cannot claim statistical significance. However, with a suggestive trend, it is important to expand the current study to include data from more surviving hypernatremic patients. This will help statistically verify the observed trend toward adverse effects of hypernatremia beyond the therapeutic range established by this investigation on $PbtO_2$.

Our study confirms that a strong relationship between serum sodium levels, partial pressure of brain tissue oxygenation, and intracranial pressures in individuals with severe traumatic brain injury as previously studied by Rockswold and Reily. Furthermore, we observed a therapeutic serum sodium range, 145 – 147 mEq/L, to optimize both the partial pressure of brain tissue oxygenation and the intracranial pressures in patients with survivable outcomes. In the future we would like to evaluate how this finding translates into specific patient outcomes.

CONCLUSION

The data obtained in our study suggest that maintaining patient serum sodium between 145 mEq/L and 147 mEq/L may help optimize partial pressure of brain tissue oxygenation with keeping intracranial pressures less than 20 mmHg in severe traumatic brain injury patients. With only a limited number of case studies published, we believe that a large scale, double blinded, prospective, randomized, controlled study is needed to validate these results. In addition, the efficacy and safety of maintaining such strict serum sodium levels must be further evaluated prior to implementation of such stringent serum sodium levels.

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The Molecular Pathobiology of Metastasis to the Brain: A Review

Kara D Beasley, DO,MBe, PCOM

Introduction

The issue of brain metastasis is an increasing problem for oncologists and neurosurgeons. As the survival rates of patients with systemic cancers increase secondary to improved oncologic therapeutics, there is a need for the discovery of new and different pathobiologic targets to arrest or prevent the metastatic cascade. The actual incidence of brain metastasis is unknown, but estimates range from 140,000 to 170,000 new cases per year. [1] It is well known that certain cancers preferentially metastasize to brain, specifically lung (50-60%), breast (15-20%), melanoma (5-10%, renal and colon (4-6%) [2,3]. Twenty to thirty percent of all breast cancer patients will eventually develop CNS metastasis [1]. Additionally, the prognosis of those with metastasis to the brain from distant sites is poor.

There are several steps in the process by which a tumor is able to escape from its site of origin and lodge in a distant location with continued proliferation. This process is commonly referred to as the "metastatic cascade", and includes escape from the primary site, intravasation, immunologic survival, arrest and extravasation at a secondary site, and finally proliferation. This process is highly selective and dependent upon a multiplicity of factors, each of which must be present and functioning in order for this process to be complete.

Metastasis to the brain in particular, is further complicated by the unique characteristics of the brain. The blood brain barrier (BBB), with its tight junctions and lack of lymphatic drainage, makes the brain particularly difficult to reach via a hematogenous route for most tumors. Unfortunately, it is this same obstacle that makes delivery of chemotherapeutic agents equally as difficult. Additionally, the microenvironment of the brain parenchyma is unique. The interstitial fluid of the brain is high in chloride, which may make the parenchyma a hostile environment to clones of all but neuroepithelial origin, such as lung or melanoma.

The purpose of this paper is to review the known pathobiologic components of the ability of primary tumors to metastasize at each stage of the metastatic cascade. The promoters, contributors, and inhibitors of the cascade are numerous and may become overwhelming without an organizational structure within which to arrange the alphabet soup of chemicals and genes that are involved in this process. By examining the genetic and pathobiologic characteristics of the process in this matter, we hope to create an ultrastucture of understanding that will allow the clinician to create a framework of current therapeutics and possible future research.

Escape/Intravasation

In order for a primary tumor to metastasize to a secondary site, it must possess certain pathobiologic characteristics that predispose clone cells to break free from the primary tumor and enter the vasculature. While many of the molecular processes discussed below are active at both

the escape and extravasation/proliferation stages, they are first encountered within the cascade early on and so will be addressed in this section.

The E-cadherin-catenin complex is vital for the maintenance of both normal and tumoral cytoarchitecture as well as a necessary mediator of cell-cell adhesion. In tumoral metastatic escape, clone cells have reduced intercellular adhesion and disordered cytoarchitecture, and are thus prone to separation from the primary tumor mass. These clones are then free to invade both locally as well as continue to intravasation and further progress in the cascade. [4]. Decreased expression of the E-cadherin-catenin complex has been correlated with invasion, metastasis and unfavorable prognosis [5]. Additionally, Shabani et al established a correlation between expression and an increased MIB-1 index in metastatic adenocarcinoma [6]

Another family of adhesion and signaling receptor proteins are the integrins. They mediate both cell migration and tumor invasion via the triggering of multiple signal transduction pathways. They are therefore vital in the complex cascade of regulation of such processes as gene expression, growth control, cytoskeletal architecture and apoptosis. In an animal model of human non-small cell lung cancer (NSCLC), blocking the $\alpha 3\beta 1$ integrin significantly decreased brain metastasis [7], and researchers at Oxford showed that blockage of $\beta 1$ integrin subunit prevented tumor cell adhesion to the vascular basement membrane (VBM) and attenuated metastasis establishment and growth in vivo. Furthermore, focal adhesion kinase (FAK) is known to be a key mediator of the signaling induced by the integrins and therefore is thought to play a role in metastatic migration and proliferation. Dephosphorylation and therefore inhibition of FAK at the Y397 locus via activated Ras has been shown to promote tumor migration via the facilitation of focal adhesion turnover at the leading edge of tumor cells. [8,9]

Another aspect of a tumor cell's ability to escape the local site is its ability to break down or functionally remodel the extracellular matrix (ECM). Degradation of the ECM via proteolytic enzymes is believed to clear a pathway for invasion. This proteolytic activity has been located on the cell membrane at the advancing edge of invading tumor cells. [10,11] The ECM proteolysis may also release factors that promote cell proliferation and angiogenesis for contribution to later steps in the cascade. Neurotrophins (NTs) are known to promote brain invasion via enhancing the production of the ECM proteolytic enzyme heparinase. Heparinase is an endo-β-d-glucuronidase that cleaves the heparin sulfate chains of the ECM. It is the dominant mammalian heparin sulfate degradative enzyme [12] and is known to destroy both the ECM and the BBB.[4] NT's have been found at the tumor-brain interface of melanoma [13] and there are reports of the p75 NT receptor functioning as a molecular determinant for brain metastasis [14]

Next on the list of molecular degraders of the ECM are the plasminogen activators and their inhibitors. Plasmin is a tumor associated serine protease activated by urokinase-type plasminogin activator (uPA) the production and release of which, has been well documented in human cancers. [14] The uPA binds to the receptor uPA-R (CD87), the activity of which is regulated by the action of plasminogen activator inhibitor type 1 and 2 (PAI-1/2), on the cell membrane and causes urokinase to convert plasminogen to plasmin. The proteolytic activity of plasmin then degrades components of the ECM including fibrin, fibronectin, proteoglycans and laminin.

Plasmin also further activates other proteolytic enzymes with resultant local invasion and migration. [4] As far back as 1994, researchers have found that there are high levels of uPA in metastatic tumors, that uPA correlate with necrosis and edema, and that there is an inverse correlation with tumoral levels of uPA and survival. Additionally, high levels of uPA and absent tPA correlate with aggressiveness and decreased survival. [15]

The matrix metalloproteases (MMPs) are a family of 20 proteolytic enzymes that have also been well established as functioning to degrade the ECM in metastasis. Their expression is regulated via cytokines and the ECM metalloprotease inducer found on the surface of tumor cells. With induction and stimulation, there is ECM breakdown and tumoral migration. MMP activity is known to correlate with invasiveness, metastasis and poor prognosis. [16] MMP-2 has been found in one study to be present in all metastatic brain tumors tested regardless of site of origin and the level of activity was inversely correlated to survival. [17] However, while MMP-9 was found by Arnold et al to be upregulated in all brain metastasis and primary brain tumors, they were unable to correlate upregulation with survival. [17] Finally, tissue inhibitor of metalloprotease 1 (TIMP-1) overexpression in a murine model was shown to reduce the incidence of brain metastasis by 75% compared to wild-type, therefore showing that inhibitors of MMPs are suppressive in brain metastasis. [18]

The actual properties of the tumoral cell membranes themselves may contribute to the local invasiveness and migratory capability of tumor clones. In a study on brain specific breast cancer metastasis, Khaitan et al showed that increased expression of KCNMA1, the gene that encodes for the pore-forming α-subunit of the large-conductance calcium and voltage-activated potassium channel (BKCa) that is known to be upregulated in breast cancer, led to greater invasiveness and transendothelial migration. [19] Furthermore, there has been increased interest in the scientific role of the membrane proteins aquaporins. Among their many functional roles, they are known to facilitate tumor migration as seen in aquaporin-dependent tumor angiogenesis and metastasis via a mechanism if facilitated water transport in the lamellipodia of migrating cells, as well as participate in tissue swelling under stress, as in brain tumors. [20]

There are several known tumor suppressor genes that function at the level of escape and migration/intravasation that are worth exploring. The best known of these is the KISS-1 gene on chromosome 1. KISS-1 encodes metastin, a ligand of the orphan G protein couples receptor hOT7T175. Lee et al found that forced expression of KISS-1 suppressed both melanoma and breast metastasis [21], and other authors have found an inverse correlation between expression and melanoma progression. [22] KAI1 (CD82) is another tumor suppressor gene on chromosome 11p11.2 . KAI1 functions to regulate adhesion, migration, growth and differentiation of tumor cell lines. It has clearly been found to have an inverse correlation with prostate progression [23], as well as breast [24,25] and melanoma metastasis. [26] Additionally, KAI1 is known to be associated with the epidermal growth factor receptor (EGFR), discussed later in this article, and is thought to affect the Rho GTPase pathway, [27] resulting in suppression of lamellipodia and migration. [28] Finally, the tumor suppressor Drg-1 methylated inhibition, has been found to inhibit liver both liver metastasis and colorectal carcinoma invasion. [29] In a murine model of

beast cancer metastasis, the Notch signaling pathway was found to be activated via increased Jag2 mRNA creating a cell line that was both more migratory and more invasive in collagen assays. Additionally, inactivation of the Notch pathway significantly decreased the migratory and invasive activity of the cell lines studied. [30]

Arrest/Extravasation/Proliferation and Growth

The next series of steps in the metastatic cascade involve a complex set of interactions that allow the hematogenously free tumor clones to arrest at a secondary site and extravasate from the vasculature to seed a new organ. The clones must then survive and proliferate at the secondary site. While the exact causes of arrest and proliferation at specific sites have not been completely elucidated, one theory is that there are direct neurotropic interactions between tumor clones and the brain along with as yet undiscovered brain-specific homing capacity within the tumor cells that result in brain metastasis. Carbonell et al described a process termed "vascular cooption" whereby 95% of micro metastasis are observed to grow along the exterior of pre-existing vessels long before any overt metastatic tumor is detected. The VBM tumor cell interaction is adhesive in nature. This interaction implied that the VBM is the "soil" for brain metastasis rather than previously theorized neurotropism. [31] With the VBM as a substrate, the tumor cells are able to infiltrate the brain parenchyma. Saito et al were able to demonstrate that the pia-glial membrane present along the external surface of blood vessels serves as a scaffold for metastatic tumor cells spreading in an angiocentric pattern thus furthering the hypothesis of perivascular "soil". [32]

A biological model for metastatic tumor cells function like macrophages within the vasculature and during extravasation in a mouse model of CNS metastasis was described by Huysentruyt et al in 2008. In this model, the tumor cells expressed multiple properties of macrophages that included morphologic appearance, surface adhesion, phagocytosis, total lipid composition and expression of CD11b, Iba1, F4/80, CD68, CD45, and CXCR (all genes specifically expressed by macrophages). [33]

The exact mechanisms whereby cancer cells pass through the BBB is unknown, however, recently three genes that mediate brain specific breast metastasis have been described. Cyclooxygenase 2 or COX2 (also known as PTGS2) as well as the EGFR ligand HBEGF have been linked to metastasis to lung as well as brain and function to assist extravasation through non-fenestrated capillaries and enhance colonization. The α2,6-sialyltransferase ST6GALNAC5 is normally restricted to the brain and when expressed by breast cancer cells, enhances their adhesion to brain endothelium and their passage through the BBB via cell surface glycosylation. [34]

The chemokine/receptor system CXCL12/CXCR4 and the recently discovered alternate receptor CXCR7 function in the homing of neoplastic cells from the primary site to the target in metastatic disease. Salmaggi et al , in a study of 56 patients with metastatic lesions to the brain from differing primary sites found that CXCL12 was expressed in tumor cells and tumor vessels and that this expression correlated with shorter survival. Additionally the CXCR7 was expressed by tumor cells as well as adjacent brain and CXCR4 was present in all samples with a nuclear

pattern, but the expression of these receptors was not correlated with survival. Thus the expression of CXCL12 may indicate aggressiveness of brain-specific metastasis. [35] Another recently described mediator of organ-specific breast cancer metastasis is the expression of HSP27. Researchers have been able to associate expression of HSP27 in brain specific breast cancer metastatic cell lines with the 36/67-laminin receptor. HSP27 created clusters of chaperone and cochaperone proteins that facilitate brain specific metastasis. Additionally HSP 27 associated theses chaperone clusters through kinases to a group of filament proteins that may assist in organ-specific homing. [36]

The WNT/TCF pathway and its target genes HOXB9 and LEF1 are mediators of brain specific chemotactic invasion and colony outgrowth in lung adenocarcinoma.. Hyperactivity of this pathway are present in ,metastatic subpopulations of adenocarcinoma cells and decreases in the activity of TCF attenuates the ability of these cells to form brain and bone metastasis indicating their contribution to brain-specific metastatic lung adenocarcinomatous lesions. [37]

Adding to the list of brain specific contributors to metastasis, Zhang et al described another brain-specific molecular determinant for metastasis of melanoma in an elegant murine model. The authors found that transforming growth factor β2 (TGF-β2) was highly expressed in brain specific murine melanoma cell lines and that transfection of the TGF-β2 gene into another cell line resulted in the production of microscopic metastatic lesions to brain parenchyma. [38]

Adhesion of neoplastic cells to the endothelium of secondary sites via a hyaluronate matrix ligand is mediated by CD44 on chromosome 11p11.2. CD44 encodes a membrane glycoprotein that acts as a receptor for hyaluronic acid and osteopontin. [39,40,41] CD44 can be down regulated via DNA methylation [42] and such down regulation has been correlated with increased tumor grade. Additionally upregulation occurs in 48% of brain mets studied, especially thyroid, melanoma, and breast.[43] Primary brain tumors also express CD44, but of the standard form, while metastatic lesions express almost exclusively the splicing variant, providing clinicians with a possible tumor marker for metastatic potential. [44]

Invasion of brain parenchyma is mediated by the tumor suppressor gene phosphate and tensin homologue deleted on chromosome 10 (PTEN) or mutated in multiple advance cancers (MMAC1). The PTEN/MMAC gene product and the cytoskeletal protein tensin are similar and interact with actin filaments at focal cell adhesions inhibiting cell migration in the functioning gene, whereas in an antisense mutation, migration was enhanced. [45,46,47] In lung cancer metastasis, 25% of the genes had an inactivity mutation, suggesting that migration and metastatic progression is inhibited by the normally functioning gene. [48]

Tumor angiogenesis is an important aspect of a neoplastic population's ability to survive and grow at a secondary site. Failure of vascular growth will ultimately restrict the tumor mass to 0.2mm, or the limits of tissue diffusion distance. [49] There appears to be a balanced interplay of proangiogenic and antiangionic factors. [4] Much research has been devoted in recent years to the elucidation of these angiogenic factors as a target for tumor treatment.

The most commonly recognized of these neoplastic angiogenic factors is vascular endothelial growth factor (VEGF). Kim et al found that VEGF expression plays a role in the

ability of breast cancer cells to metastasize and that inhibition of VEGF via a receptor tyrosine kinase inhibitor reduces tumoral angiogenesis and restricted tumor growth. [50] SSecks (Src-suppressed C kinase substrate) is known to decrease the expression of VEGF via reduction of AP-1. It also stimulates the expression of the proangiogenic molecule angiopoietin 1, and may regulate the brain angiogenesis and tight junction formation, therefore regulating BBB differentiation and contributing to angiogenesis. [51]

Yet another angiogenic regulator is a member of the previously mentioned MMP family, the MMP-9/gelatinaseB complex that may contribute to the switch from vascular quiescence to angiogenesis. [4, 52] PAI-1, the aforementioned uPA cell surface receptor is often localized to the proliferating vessels in brain metastasis and therefore may also play an unknown role in angiogenesis. [53] Finally, Plexin D1 expression in tumor versus non-neoplastic vasculature was explored to determine if Plexin D1 is unique to tumor cells and vasculature, and thus participates in tumor angiogenesis. Indeed, Plexin D1 was found to be expressed in neoplastic cells as well as tumor vasculature while its expression in non-neoplastic tissue was restricted to a small subset of activated macrophages, therefore it may play a significant role in tumor angiogenesis. [54]

A significant contributor to secondary site tumor growth potential in breast cancer is overexpression hexokinase 2 (HK2), which plays a key role in glucose metabolism and apoptosis. Researchers at the National Cancer Institute found that both mRNA and protein levels of HK2 were elevated in brain metastatic derivative cell lines compared to the parental cell line in vitro. Additionally, they found that knockdown of expression reduced cell proliferation and therefore the gene and its product must contribute to proliferation and growth of breast ca metastasis. [55] Finally they were able to demonstrate that increased expression was associated with poor survival after craniotomy.

At least two tumor suppressor genes that function at the proliferation level of the cascade have been described. The first is NM23. NM23 regulates cell growth by encoding for a nucleotide diphosphate protein kinase that interacts with menin. [56] NM23 is thought to reduce signal transduction and thereby decrease anchorage independent colonization, invasion and motility. [57] In melanoma, decreased expression is correlated with increased brain metastasis. [58] The second tumor suppressor gene described localizes to chromosome 11 in melanoma and breast cancers. BrMS1 prevents disseminated tumor cell growth by restoring the normal gap junction phenotype and maintaining cell to cell communication in the primary tumor. [59] Seraj et al found an inverse correlation between expression of BrMS1 and metastatic potential in melanoma. [60]

Cascade Nonspecific Metastatic Contributors

Of course, there are certain molecular contributions that cannot be attributed to a specific step in the cascade either because they are active at every level, or as in most cases, their true function is yet to be discovered. These molecular entities are on the forefront of cancer science and are worth mentioning here. Zeb-1, the zinc finger E-box homeobox transcription factor is

over expressed in metastatic cancers This overexpression leads to epithelial-mesenchymal transition and increased metastasis. Mutation of this gene has been shown to decrease proliferation of progenitor cells in mutant mice, perhaps indication a target for metastatic prevention at the progenitor level. [61]

Several other genetic markers have been located that pertain to metastasis in particular. Deletion of 4q arm in lung (both small and non-small cell) metastasis to the brain and bone has been documented. [62] Additionally in NSCLC, the overexpression of three genes CDH2 (N-cadherin), KIFC1, and FALZ were highly predictive of metastasis to the brain in early and advanced lung cancer and thus theses genes may be used to predict high risk of metastasis early in the diagnosis. [63] In prostate cancer, increased expression of KLF6-SV1, the Kruppel-like factor tumor suppressor gene, predicted poorer survival and correlated with increased metastasis to lymph, brain and bone [64] Finally, overexpression of homeoprotein Six-1, a transcriptional regulator increased TGF-β signaling and metastasis in breast cancer with significantly shortened relapse times. [65] Clearly these genes are important in the understanding of the metastatic cascade as well as for further targeting research.

Conclusion

The process by which a tumor cell leaves its primary tumor site and eventually ends up in the brain to proliferate and wreak havoc is clearly quite complex. By understanding as many of the molecular and genetic factors that contribute to the cascade, we as clinicians and researchers will be better equipped to explore and target these tumors from a myriad of angles. Such a multi-faceted approach to metastatic tumor treatment in the brain is not only the future of the field but a necessary advancement in the standard of care.

Keywords

Brain metastasis, molecular biology, genetics, pathobiology

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Minimally Invasive Pedicle Screw Instrumentation with PMMA augmentation for Thoracolumbar Burst Fractures in Osteoporotic patients

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ABSTRACT

Burst fractures are the most common traumatic fractures of the thoracolumbar spine. Treatment options range from non- operative measures (bed rest and bracing) to operative procedures requiring internal fixation with or without spinal canal decompression. When these fractures occur in the elderly they create a challenging balance between mobilization and deformity progression. Osteoporosis begets spinal fractures and ultimately deformity. It also impacts internal fixation strength. PMMA has been used to augment pedicle screw fixation for osteoporotic patients in the past. Conservative treatment in osteoporotic hip fractures results in a 2.5 increase in overall mortality.

Objective: We present a review of the literature and two case reports of a surgical treatment paradigm for burst fractures in osteoporotic patients. We propose a percutaneous technique utilizing kyphoplasty PMMA augmentation of pedicle screw fixation.

Results: Two cases are presented for details of the technique and treatment outcomes. Both of these patients had minimal blood loss, operative time and were discharged to rehabilitation after percutaneous long segment internal fixation.

Conclusion: We describe a safe, effective alternative to provide immediate stabilization using minimally invasive techniques for PMMA augmented long construct pedicle screw fixation of burst fractures in elderly patients.

Key Words: osteoporosis, thoracolumbar burst fractures, pedicle screw fixation, polymethyl methacrylate (PMMA), and minimally invasive spine surgery

INTRODUCTION

Thoracolumbar burst fractures result from high-energy axial loads producing failure of the anterior and middle columns of the spine. The appropriate treatment of these fractures is controversial (3,7,16). Non operative treatment has been utilized in the past, however non-compliance with bracing, the effects of bed rest on bone mass, deep vein thrombosis, infections and increased length of stay has made it a less clinically relevant treatment option (12,22). In elderly patients, we believe these fractures are analogous to osteoporotic hip fractures and they should be treated as such. Early surgical intervention and mobilization of theses patients decreases their overall mortality two fold (12).

When burst fractures occur in older patients they present a unique set of challenges. Surgical treatment options range from posterior instrumentation, anterior approaches alone, anterior and posterior approaches, short segment fusion (two vertebral segments) versus long constructs (greater than 3 spinal segments) an a combined short segment instrumentation and kyphoplasty to the fractured segment (3,6,7,15,18). All of these treatment options assume the patients have bone quality adequate for internal fixation. Osteoporosis plays a significant role in the development of spinal instability and degenerative deformity in the geriatric population (4). Reduced bone mass decreases the ability of the vertebral body to distribute axial loads leading to spinal fractures. The loss of bone mass also limits surgical treatment options by making it more difficult to obtain purchase when placing pedicle screws for the internal fixation and stabilization. (4,9,10,11).

Polymethyl methacrylate (PMMA) has been use to augment pedicle screw fixation strength in osteoporotic patients in the past to increase pullout strength and decrease instrumentation failure (2,4). We propose a percutaneous technique to provide PMMA augmented posterior fixation for osteoporotic patients with burst fractures. This minimally invasive approach limits blood loss; tissue dissection and operative morbidity to hasten the stabilization allow early mobilization of these patients.

CASE REPORT/OPERATIVE TECHNIQUE

All of the patients were admitted through the trauma service with a burst fracture identified on CT imaging with reconstructed images of the thoracolumbar spine. Other non-contiguous fractures where either ruled out clinically or radiographically.

Case 1- 88y/o female diagnosed with a burst fracture at L1 after a fall (see figures 2-4). The patient was neurologically intact with complaints of severe upper lumbar spine pain related to the fracture. There was no radiculopathy, myelopathy or urinary incontinence.

The patient was taken to the operating room, general anesthesia was induced and the patient was placed prone on a Jackson table. Bi- planar fluoroscopy was brought into the field and the appropriate levels were localized. The patient was draped and prepped in the usual fashion. Bilateral paramedian incisions, approximately one inch long were made at T11, T12, L2 and L3. The skin down to the fascia was incised sharply and hemostasis was obtained with monopolor cautery. A standard jamshidi need was used to palpate the cortex over the pedicle. Using bi-planar fluoroscopic guidance the needle traversed the pedicle into the body. Using the standard kyphoplasty technique a cavity was created in the vertebral body. PMMA was then introduced into the cavity through trocars in both pedicles. A long k-wire was introduced down the pedicle into the PMMA filled cavity. Utilizing the Stryker mantis percutaneous screw system a 6.5 mm x 4.5 mm screw was inserted through the pedicle and into body. This same procedure was repeated at each of the three additional levels bilaterally to create two points of fixation above and two points below the level of the fracture. A rod was then introduced through the top incision and passed percutaneously to the bottom of the construct with direct visualization though the tulip of each screw head. A nut was then used to secure the rod in place at each level and all the screws were tighten to product specifications (see figures 5-7).

Case 2- This is an 86 y/o female who suffered a L1 burst fracture after a fall. Again, the patient was neurologically intact without radiculopathy, myelopathy or urinary incontinence. The above procedure was performed as described, without complication.

RESULTS

The average operative time was 135 minutes with a range of 140-130 minutes. The estimated blood loss was 100 cc's for both cases. The average length of hospital stay was 10.5 days with a range of 9 to 11 days. One patient was discharged to inpatient rehabilitation the other one to skilled nursing for rehabilitation. The complications included spontaneous pneumothorax resolved with a chest tube, urinary tract infection treated with antibiotics.

DISCUSSION

Thoracolumbar burst fractures result from high-energy axial loading of the spine producing compression failure of the anterior and middle columns. Classically the posterior column is intact. They account for approximately 15 % of all spinal fractures and are the most common of all thoracolumbar fractures (3,7). There is much controversy over how to properly treat these fractures. It has long been believed that failure of the middle column with retropulsion of the bone into the spinal canal indicates underlying spinal instability and implies likelihood of neurologic compromise without stablization (16). Dai, *etal*, reported in their series of 31cases displaying CT scan evidence of remodeling of retropulsed fractured bone fragments in the spinal canal. The

author's concluded there is no need for surgical decompression of the spinal canal when the patient in neurologically intact.

Non-operative management of burst fractures has historically been for neurologically intact patients with little loss of vertebral body height or significant canal compromise. Most centers have a wide variety of techniques to handle the fractures ranging from bed rest with "postural reduction " any where from 3 days to 8 weeks, this was followed by external bracing and ambulation (16). These patients require vigilant care to prevent the untoward effects of immobilization, including Roto-Rest beds, aggressive pulmonary toilet, deep vein thrombosis prophylaxis, and skin care to prevent decubitus ulcers (5). Early mobilization with external bracing has also been widely used with patients without significant kyphosis, loss of vertebral body height or canal compromise with minimal incidence of neurological deterioration (7). This is very difficult to justify given the advancement of instrumentation techniques today which allow for safe internal fixation and stabilization of these fracture promoting safe mobilization without the concern of patient compliance with bracing (5,7). Patients with osteoporosis cannot afford to be on prolonged bed rest with postural reduction. Takata *etal* (22) found that 1 week of bed rest in osteoporotic hip fractures resulted in increased bone atrophy and loss. Jain *etal* (12), also noted that bed rest for hip fractures was associated with a 2.5 times higher mortality rate that those treated operatively.

Operative treatment is the most definitive means to achieve immediate spinal stabilization. It is believed that internal fixation allows for restoration of spinal alignment, early mobilization and theoretically improved functional outcomes (7,8). The question then, if surgery is the best treatment options for these patients, what type of surgery is to be performed? The development of the load sharing classification for spinal fractures can be a good resource to guide in determining optimal stabilization procedure (8,13).

The load sharing classification (see figure 1) looks at three variables to establish the extent of injury. They are the amount of communition of the vertebral body, apposition of the fracture fragments and amount of kyphosis If these factors are not accounted for, there is a high likelihood of nonunion and hardware failure. Essentially, this classification system accounts for the spine's ability to accommodate the physiologic load of the patient in weight bearing position (13). There is also a significant correlation between the load sharing classification and loss of sagittal alignment after closed reduction treatment with bed rest and postural reduction.

This scale has been used to determine what patients are at risk for failure from short segment fusion. The most significant factor in the load sharing classification is the extent of vertebral body communition. This reflects the inability of the vertebral body to transfer loads (8). This also can give the surgeon an idea of how extensive a surgery is required to render the spine stable. Do they need posterior stabilization alone or anterior column reconstruction or both (8, 13)?

The main reason for operative treatment is that early stabilization limits the likelihood of late deterioration due to progressive deformity. Internal fixation will also maintain the correction of kyphosis and allow early mobilization and decrease the morbidity associated with bed rest. Published series show complication rates of 1-2 % for decubitus ulcers, 12-20% incidence of deep vein thrombosis and an over all complication rate of 32% with complications ranging from neurological deterioration, pulmonary embolism and spinal cord infarction (16, 21). The benefits of early fixation allow for safe postoperative mobilization in theses patients. Siebenga *etal* (20), found less focal and regional kyphotic deformity in the surgical group. Pain in these patients was greatest at iliac crest harvesting sites, multiple level surgeries and with larger extensive surgeries, (i.e. thoracotomy). Boucher *etal* (3) found that posterior instrumentation alone provided good spinal canal decompression, reduction of kyphotic deformity, and maintence of vertebral body height with positive functional outcomes on SF 36 and Owestry scales. Internal fixation provides immediate segmental stabilization and decreases to need for bracing.

Surgical treatment options for burst fractures range from posterior instrumentation with or without decompression to a 360-degree fusion with corpectomy and posterior supplemental fixation. A more recent treatment option includes short segment instrumentation with open kyphoplasty at the level of the fracture with posterior instrumentation one level above and below the fracture (3,6,7,15,17,18,and 19). Specifically communition of the vertebral body involving the middle column led to early implant failure. Instrumentation failure rates for posterior alone short segment fusion range from 20-50 % (6,17,and 19).

The force vectors producing the burst fracture must be understood in order to attain appropriate spinal alignment and balance. Axial loads compress the spine while it moves into flexion producing failure of the anterior and middle columns producing a burst fractures. Treating these injuries requires reduction and stabilization in extension with distraction. Placing the patient on a surgical spinal frame (i.e. Jackson table) which places the spine in extension will create sufficient lordosis and distraction allowing for fracture reduction and stabilization. Longer constructs, which span at least two levels above and below the fracture, have a 90% fusion rate (15). This is obviously effective at maintaining deformity correction at the cost of additional levels to be fused (21).

Anterior approaches to the spine for thoracolumbar burst fractures provides excellent kyphosis and deformity correction involving minimal number of spinal segments, with a higher fusion rate and less complications of late kyphotic deformity or implant fracture (17,18). However, it is usually supplemented with posterior instrumentation. Anterior surgery also requires a retroperitoneal approach, mobilization of the diaphragm, possible thoracotomy and placement of a chest tube after surgery. Given the larger nature of the exposure carries with it significantly more morbidity and postoperative pain to the patient.

Parker *etal*, in their series of short-segment instrumentation and fusion looked at utilization of the load sharing classification model and fusion rates in constructs, which

spanned one level above, and below the fractured level. The inability to support the anterior column in the first 6 months following instrumentation had a higher incidence on pedicle screw fracture, progression of deformity and pseudoarthrosis (17).

To account for anterior column support in preventing deformity and instrumentation failure Cho *etal*, describes a PMMA vertbroplasty of the fractured level with short segment instrumentation of the adjacent vertebra. They were able to maintain deformity correction with little loss of anterior column height. Instrumentation failure was associated with larger pre-operative kyphotic deformity with significant loss of vertebral body height placing the largest moment arm on the instrumentation producing failure of the construct (614,17).

It is important to distinguish that all of the current literature deals with patients ages 18-65, with good bone quality, and minimal co-morbidities. Treating geriatric patients with burst fractures comes with a unique set of challenges. These patients have multiple co- morbidities and are at high risk for complications due to the effects of immobility including skin break down, deep vein thrombosis, and pneumonia. Osteoporosis and resulting bone mass place these patients at high rest for additional vertebral fractures (11).

Osteoporotic vertebral fractures in and of themselves have a similar effect on the functional impairment of older women with hip fractures. Immobility in this age group has significant impact on the lives of these patients. Bed rest after an osteoporotic hip fracture has a 2.5 greater mortality rate than surgical treatment (12). Bed rest for as little as one week in patients with femoral neck fractures has been shown to result in bone atrophy and demineralization.
(22).

Osteoporosis also produces significant challenges to provide strong fixation for burst fracture treatment. The successful treatment of these fractures requires the spine to be immobilized in extension and distraction (15). Internal fixation through pedicle screw fixation is widely utilized for burst fractures. Transfer of loads across the spine and the implant result in load sharing which facilitates healing of these fractures while spinal alignment can be maintained. Pedicle screw constructs rely on adequate bone mineral density to provide purchase in the vertebral body. Therefore, good bone quality is essential for the instrumentation and stabilization of these fractures (9).

There are methods to enhance pedicle screw purchase and improve the strength of fixation. The pedicle screw diameter has been shown to improve pull out strength. In non- osteoporotic bone use of 7mm diameter screws improves pullout strength. However, this diameter screw will produce pedicle fracture in 20-40% of osteoporotic patients (2,9). Placement of the screw in the pedicle provides 60 % pullout strength, purchase in a vertebral body with good bone density provides an additional 20% pull out strength and bicortical fixation will provide additional 20% pullout strength. Given the risk to vena cava and aorta the practice of bicortical fixation above the sacrum has not been widely adopted (2,9).

Vertebral body bone mineral density is 6 times lower than the pedicle. The cortex of the pedicle is eight times stiffer than the trabecular bone in the vertebral body. Patients with osteoporosis also have loss of bone in the pedicle along with the vertebral body. The pedicle cortical and trabecular bone mass may be reduced by up to 50 % when compared to healthy individuals (2).

PMMA has been used to augment pedicle screw fixation successfully as a salvage technique for poor distal purchase. It has proven effective in increasing the pull out strength in osteoporotic bone. PMMA interdigitates with the surrounding trabecular bone to increase fixation strength and act as an anchor point for the screw (2,9).

Burval *etal* describes the use of a kyphoplasty technique used to augment pedicle screw fixation in the treat osteoporotic compression fractures. This creates a large void in the body and allows larger volumes on PMMA to be instilled at a higher viscosity under lower pressures. Once the void was filled , a pedicle screw was then placed down the pedicle in to the PMMA filled vertebral body. They found a 2-3 fold increase in pullout strength, which is higher then that of a healthy non-osteoporotic spine. The use of the kyphoplasty technique for PMMA augmentation of pedicle screw fixation has 2-3 fold greater pull out strength than non- augmented health spines. This is a safe effective technique, which addresses the challenges of pedicle screw fixation and stabilization with deformity correction in osteoporotic patients.

CONCLUSIONS

Burst fractures in the elderly create a dilemma. Underlying osteoporosis complicates both operative and non-operative treatment options. The orthopedic literate supports early surgery for osteoporotic hip fractures. Surgery for these patients significantly improves survival for these patients. We believe application of this treatment paradigm for the treatment of burst fractures in the elderly.

Minimally invasive spine surgery (MISS) is widely utilized in degenerative conditions of the spine. Traumatic burst fractures are another avenue to provide this type of percutaneous surgery. Minimal blood loss, operative time, and soft- tissue dissection are all added benefits of MISS. The use of kyphoplasty technique to augment percutaneous pedicle screw fixation is a viable treatment option for osteoporotic patients with burst fractures. We have shown that immediate stabilization, minimal blood loss and soft tissue disruption has allowed these patients to be mobilized quickly, decreasing the effects of bed rest without a large open procedure with its inherent operative morbidity.

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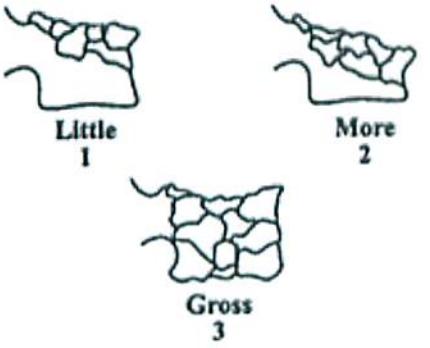
FIGURES

1

Comminution/Involvement



1 Little = < 30% Comminution on sagittal plane section CT

2 More = 30% - 60% Comminution

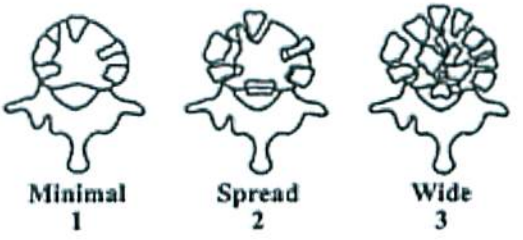
3 Gross = > 60% Comminution

Apposition of Fragments

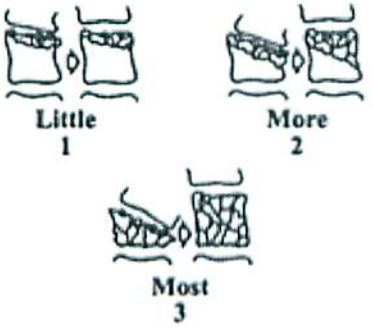
1 Minimal = Minimal displacement on axial CT cut.

2 Spread = At least 2mm displacement of < 50% cross section of body.

3 Wide = At least 2mm displacement of > 50% cross section of body.



Deformity Correction

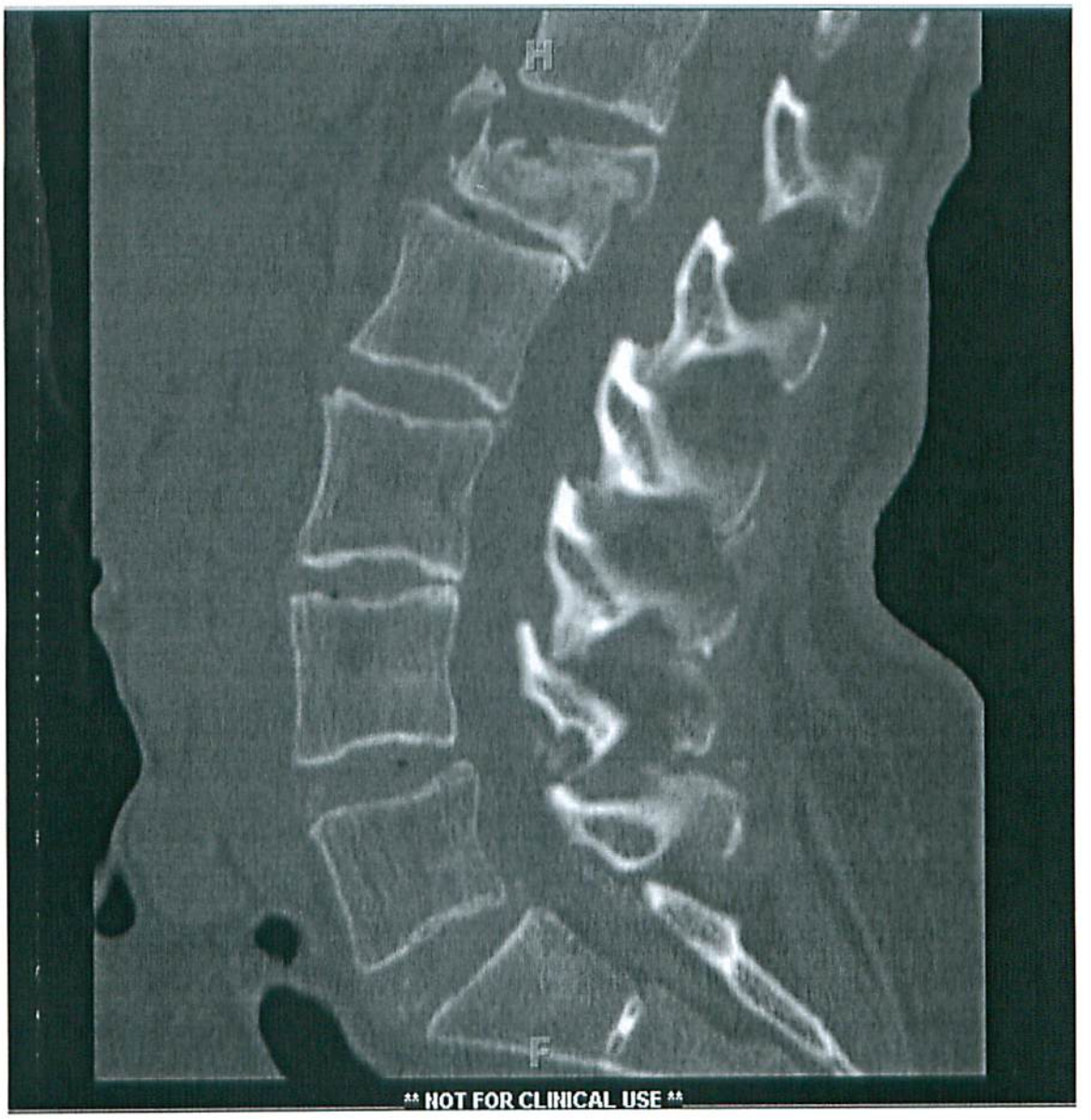


1 Little = Kyphotic correction $\leq 3^{\circ}$ on lateral plain films.

2 More = Kyphotic correction 4° - 9°.

3 Most = Kyphotic correction $\geq 10^{\circ}$.

2



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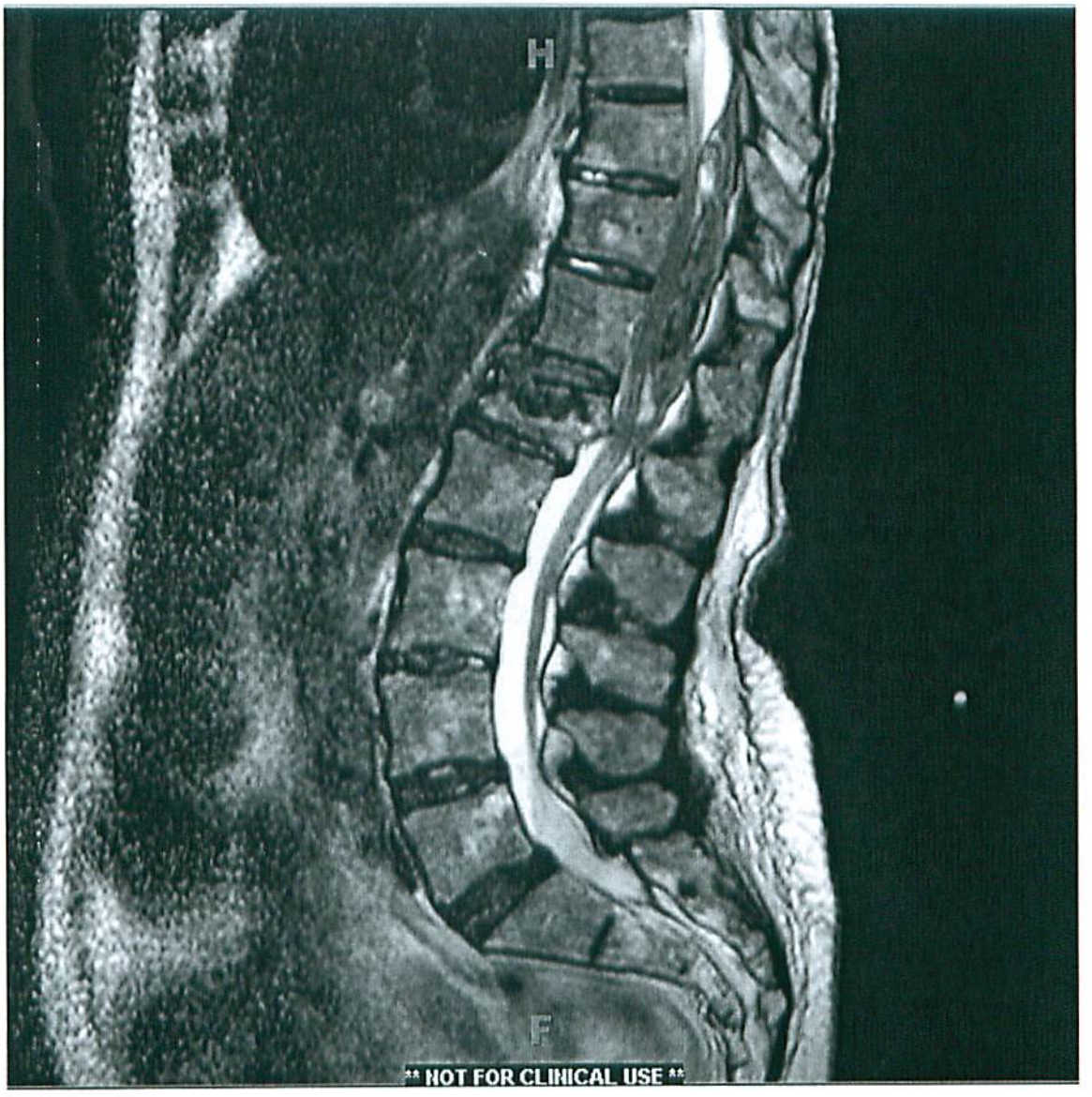

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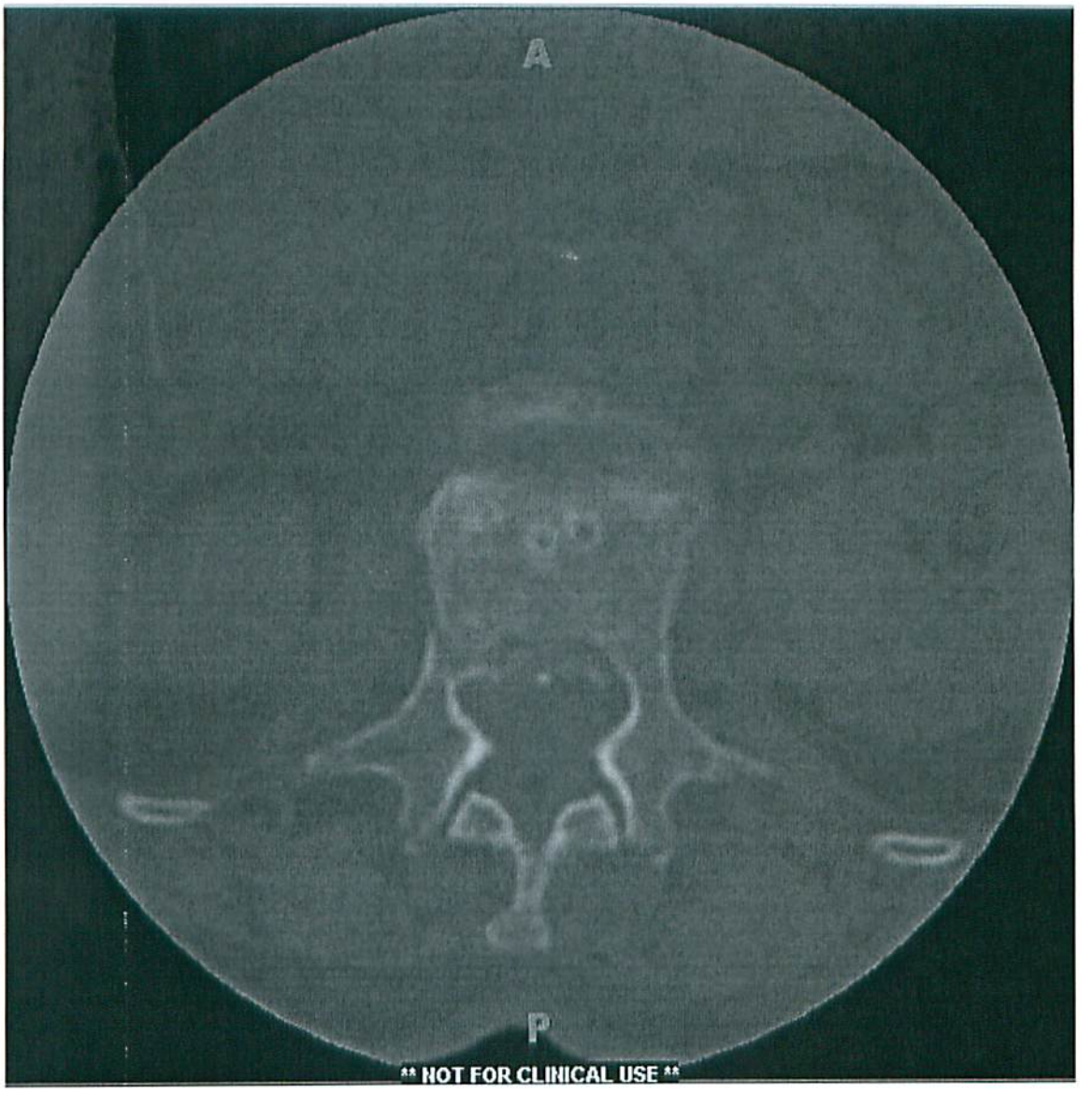

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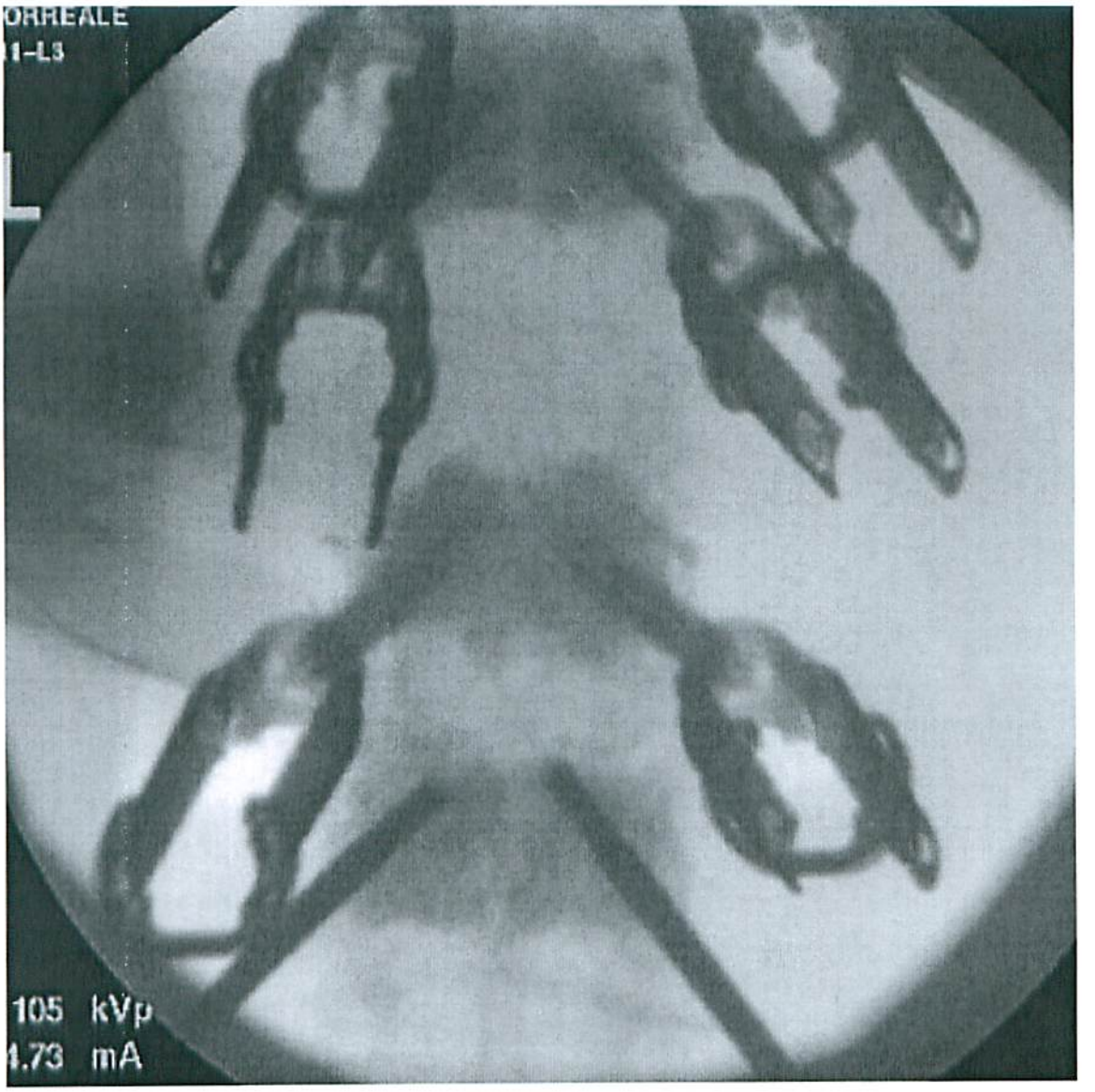

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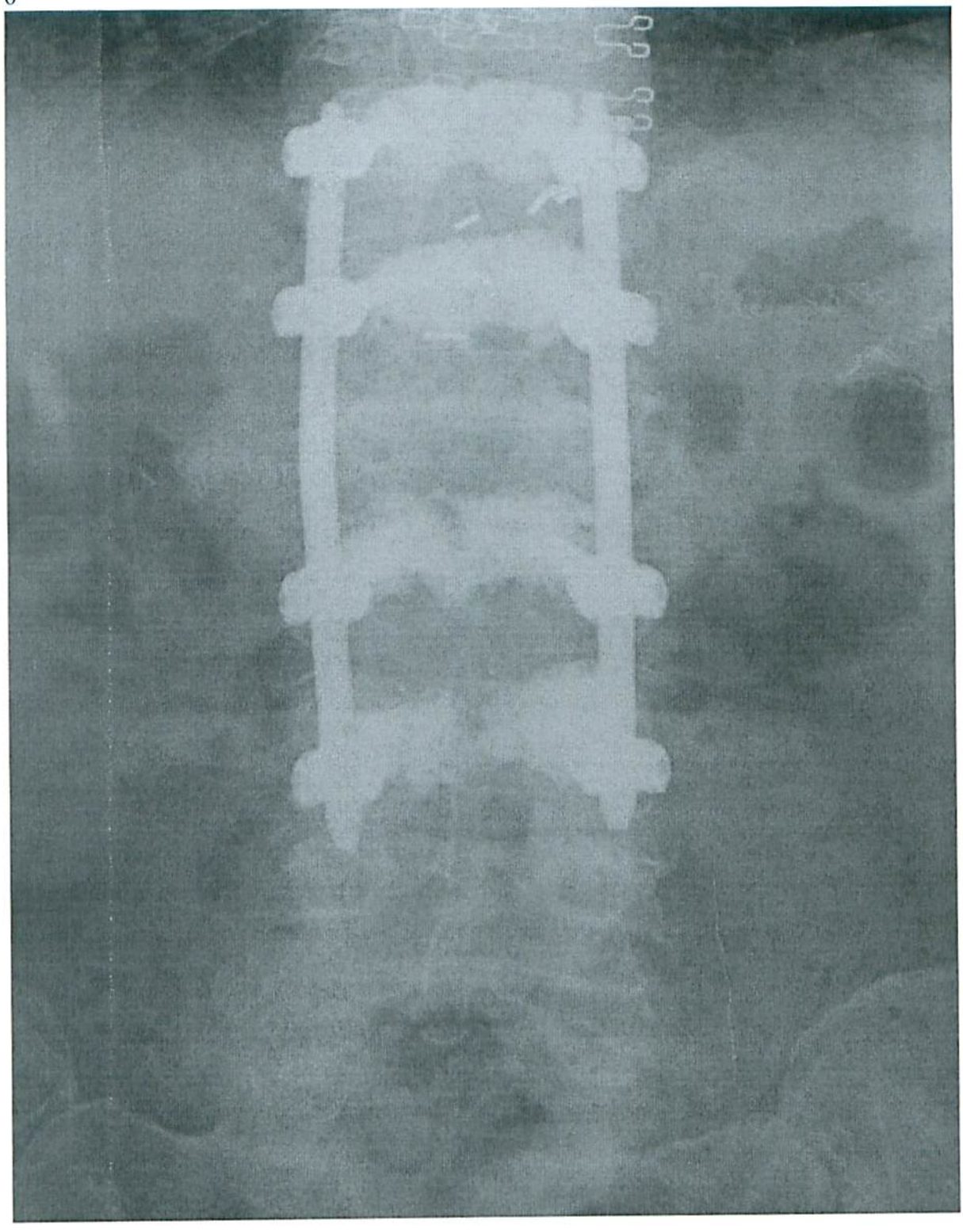

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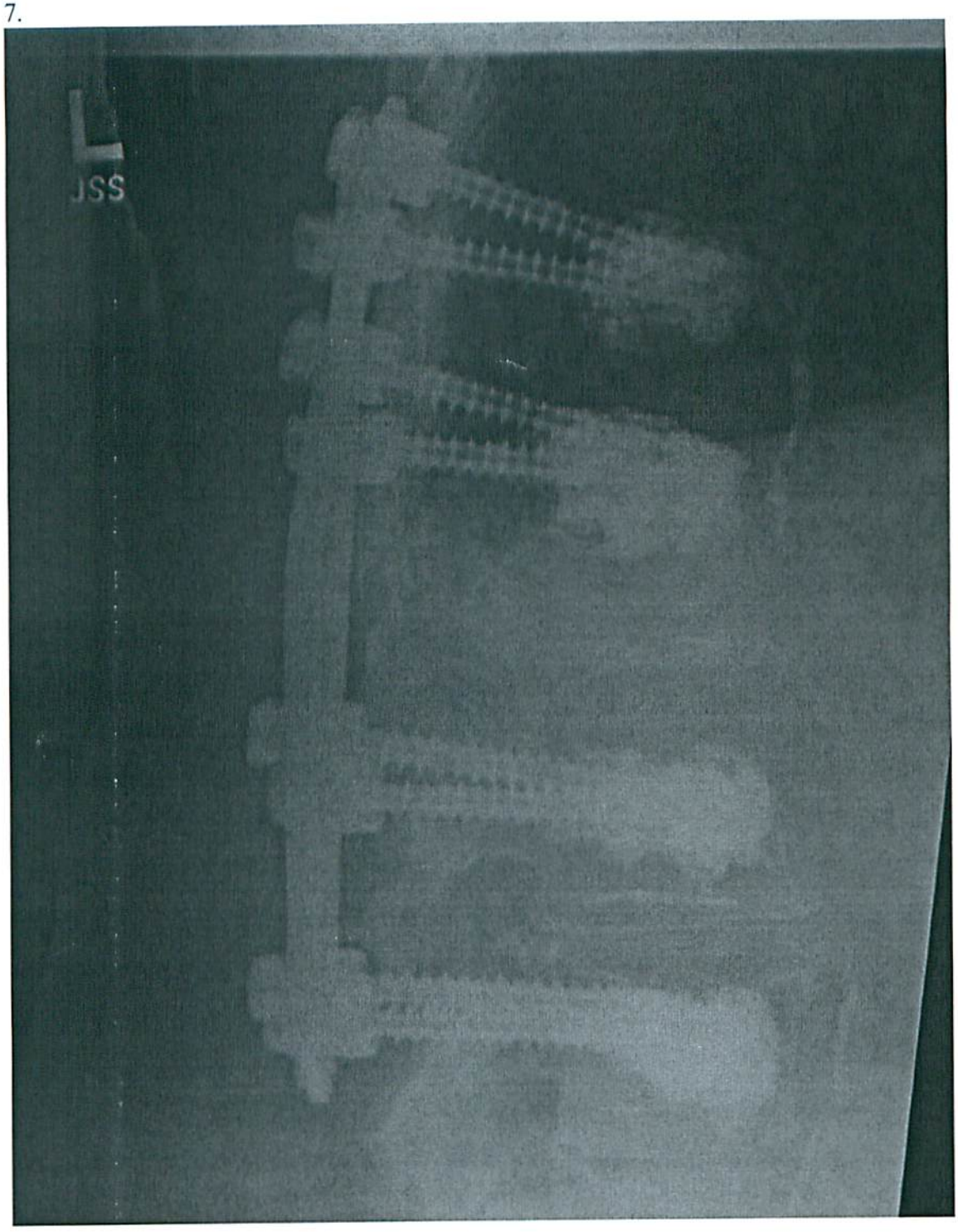

Neuroenteric Cyst

Bryan D. Bolinger, DO,

Case Report

A 52-year-old male presented to our facility with two months of low back pain associated with intermittent bladder and bowel incontinence. He indicated that the onset of his symptoms was not associated with any traumatic event. He also denied having fevers, chills, night sweats, and/or a profound weight loss over the past several months. Furthermore he stated that he has been in his usual state of "good health." Review of systems was positive for wheezing as well as chronic hip pain. His medical history was positive for hypertension, asthma, a left-sided breast mass, and left-sided hip pain. He has undergone excision of his left-sided breast mass (malignant) and has had a left-sided hip replacement. His family history is positive only for coronary artery disease. He admits to 30 pack year smoking history and drinking anywhere from 15 to 18 cans of beer per day over the past 20 years. He denied any illicit drug usage. His medications include oxycodone and albuterol. Physical exam revealed an ill appearing adult male in a mild amount distress. He had normal gait and demonstrated having good ability at performing heel walk, toe walk, as well as squat to rise. His straight leg raise was negative bilaterally. He demonstrated no tenderness to palpation over his spinous processes, sacroiliac joints, or greater trochanters bilaterally. Motor strength testing reveled that all stations were full strength (5/5) except for his left sided iliopsoas (4+/5). Sensory exam was positive for decreased perianal sensation. His reflexes were 2/4 throughout. There was no clonus and his toes were down going. He had poor rectal tone. Relevant imaging studies are provided below. After the risks, benefits, and alternatives to surgical resection we're explained, the patient decided to undergo resection of this lesion via a posterior approach. His operative and postoperative course was uneventful. Formal pathology results returned with the lesion being consistent with a neurenteric cyst.

Epidemiology

Neurenteric cysts make up approximately 0.3 to 1.3% of all spinal "tumors" (1). They are, in fact, not tumors, which differentiates them from teratomas; instead, they are hamartomas – displaced nests of endodermally derived tissue. They are known by a variety of names such as enterogenous, neurogenic, neurenteric, foregut, bronchogenic, respiratory, epithelial, epithelial-lined, teratomatous cysts, and gastrocytoma. They are also considered to be a form of occult spinal dysraphism (OSD), as are the following entities: lipoma, lipomyelomeningocele, meningocele manqué, dermal sinus tract inclusion cysts (dermoids and epidermoids), terminal syringohydromyelia, and myelocystocele.

Lesion Location, Morphologic and Histological Features

In a large literature review conducted by Lippman et al, greater than 90% of spinal neurenteric cysts were found in the intradural extramedullary compartment. They found that 54% of reported spinal neurenteric cysts occurred in the cervical region; between 12% and 21% were found in the thoracic spine; between 15% and 20% of neurenteric cysts were located at the thoracolumbar junction; and the remainder were located more caudally (2). In Agnoli and associates' review of 32 published cases of neurenteric cysts, the most common cyst location was at the level of the conus medullaris (3). The gross appearance of neurenteric cysts may vary from thin to thick walled, with the color being grayish-white to creamy. Cyst contents may be clear, mucinous, whitish, or turbid liquid. Histologically, there may be great variation in microscopic appearance. The most common finding is a thin wall, lined by a layer of pseudostratified or stratified cuboidal or columnar epithelium, lying on a basement membrane and supported by a connective tissue wall of varying vascularity. Wilkins-Odom classified intraspinal neurenteric cysts into three types: Type A cysts are lined by a single pseudostratified or stratified cuboidal or columnar epithelium with or without cilia lying on a basement membrane. Type B cysts have some of the other elements found in the gastrointestinal or respiratory tracts (such as mucous gland, serous gland, smooth muscle, and striated muscle). Type C cysts have ependymal and glial elements (4). The World Health Organization classifies neurenteric cysts under the category of "other malformative tumors and tumor-like lesions."

Clinical Presentation

Neurenteric cysts are congenital lesions that can present at any age from newborn through the fifth decade. There is a three-to-two male predominance (5). The malformations of the split notochord syndrome (6, 7) have been diagnosed prenatally by ultrasound and are apparent at birth; the complex association of intestinal protrusion, cloacal/bladder exstrophy and renal dysgenesis may be fatal. Mediastinal and intra-abdominal cysts are usually symptomatic during the first decade of life; symptoms may include abdominal distention, dyspnea, hoarseness, and chronic pulmonary infections with partial bronchus obstruction (8, 9, 10). The presentation of intraspinal cysts is more common during adulthood. The symptoms of spinal cord or nerve root compression may mimic other space occupying lesions of the spinal canal, including disc herniation. Pain is the most common symptom and localizes to spinal level of the malformation. When a long history of episodic paresis and dysesthesia is elicited, multiple sclerosis is considered in the differential diagnosis (3, 11, 12). This is commonly due to periodic rupture of the cyst contents. Bacterial meningitis can also occur when the cyst is associated with a dorsal sinus tract (10, 11). Certainly children with recurrent bouts of bacterial meningitis need be further examined to see if they posses a dorsal sinus tract of the spine.

Development

The embryogenesis of endodermal cysts is not known with certainty however a number of hypotheses have been postulated. The predominant proposal has been that endodermal cysts originate from the faulty separation of ectodermally derived spinal cord and endodermally derived foregut during closure of the neurenteric canal during the third week of embryonic life (12).

Imaging Characteristics

Magnetic resonance (MR) imaging reveals neurenteric cysts to be typically isointense to hyperintense relative to cerebrospinal fluid (CSF) on long-relaxation sequences. On T1-weighted MR imaging they appear isointense or slightly hyperintense to CSF. Based on reports in the literature, these signal characteristics are typical and correlate with the high-protein content fluid within the cyst (14, 15, 16). Two features, the lack of contrast enhancement of the cyst wall and the absence of a mural nodule, help to differentiate these lesions from neoplastic processes. Other nontumor, cystic entities, such as teratomas, teratoid tumors, and syrinx, may appear radiographically similar to neurenteric cysts, and likewise, do not necessarily enhances following contrast administration. Additional use of computerized tomography scanning is useful to help rule out any concurrent vertebral abnormality prior to treatment.

Treatment

In order to prevent reoccurrence, every attempt at complete surgical resection should be made during the primary operation. This might not be possible if vital neural structures are involved and because of that, some authors advise to avoid overaggressive removal of the lesion because of the benign course following subtotal excision (17-21). With regards to surgery the question remains of which approach to utilize. Although most cysts are approached posteriorly, significant cord manipulation may be necessary to completely excise ventral lesions. An endoscope may be used to visualize the ventral spinal cord in adherent cyst wall tissue (22). An anterior approach may provide one with better visualization and safer removal of ventral lesions however this approach is more complicated and technically difficult (23, 24, 25). Some authors report using a lateral approach to excise lesions of the cervical spine (26). It gives excellent cranial-caudal access to the thecal sac, spinal cord, and the lesion to be resected.

Recurrent Cysts

The risk of recurrence of neurenteric cysts is very difficult due to the uncommon nature of these lesions. Despite long duration of symptomatic relief, these lesions can recur after several years, especially in patients with partial excision (22). Long-term follow up is recommended. Several authors have provided their experience with

recurrent neurenteric cysts. Holmes et al. had noticed only 1 cyst recurrence in their series of 26 patients (28). Over a 38-month period, Kim et al., reported no recurrence in any of their 8 patients (21). Chavda et al. reported a 37% recurrence in their 8 patients over a period of 30 years. They also reported recurrence between 4-14 years out from their initial surgeries (29). The excision of recurrent neurenteric cysts can be technically difficult due to the reaction caused by epithelial secretions from the masupialized cyst. In rare cases, incomplete resection of a neurenteric cyst cause cranio-spinal dissemination and multiple recurrences.

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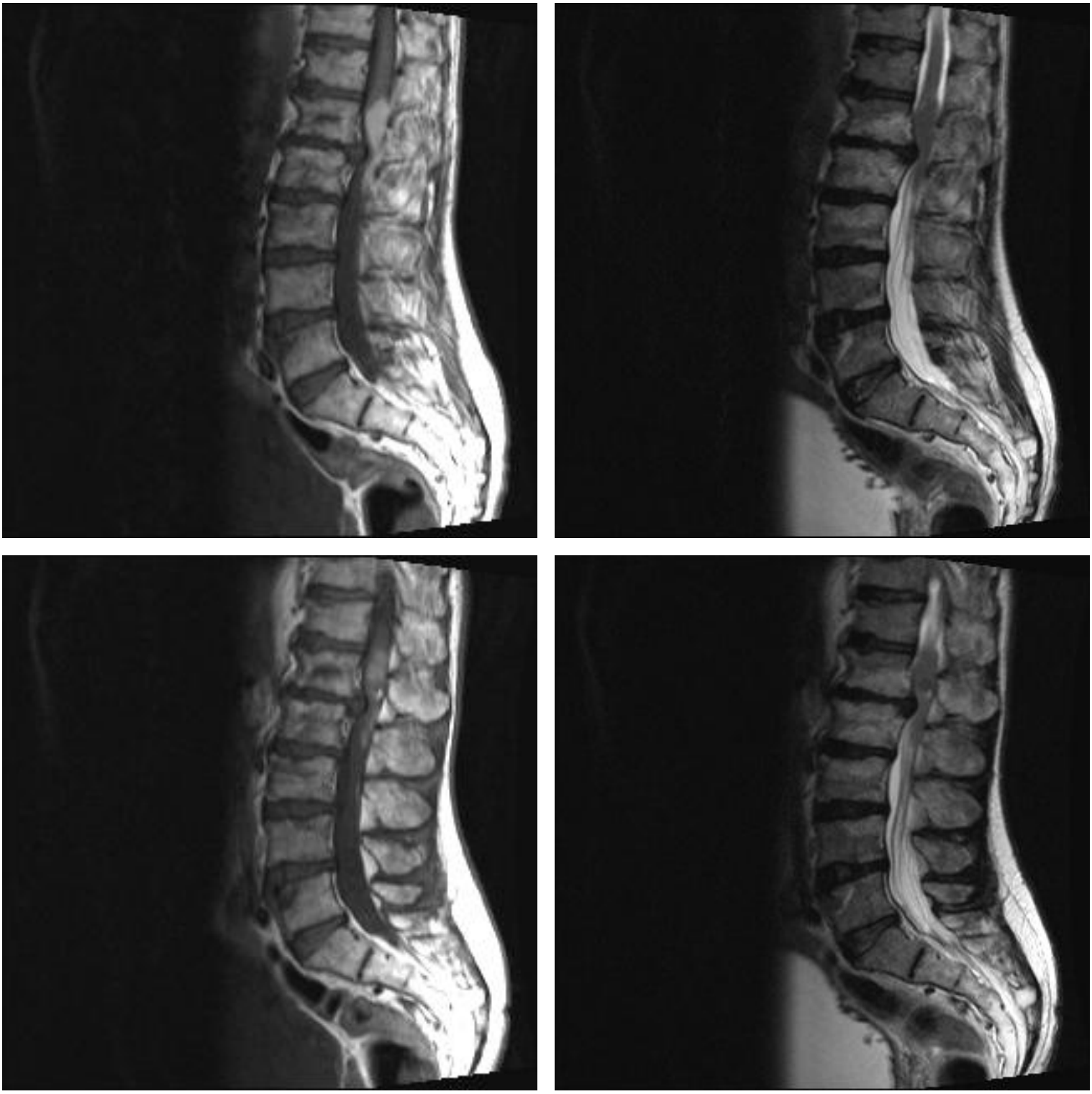
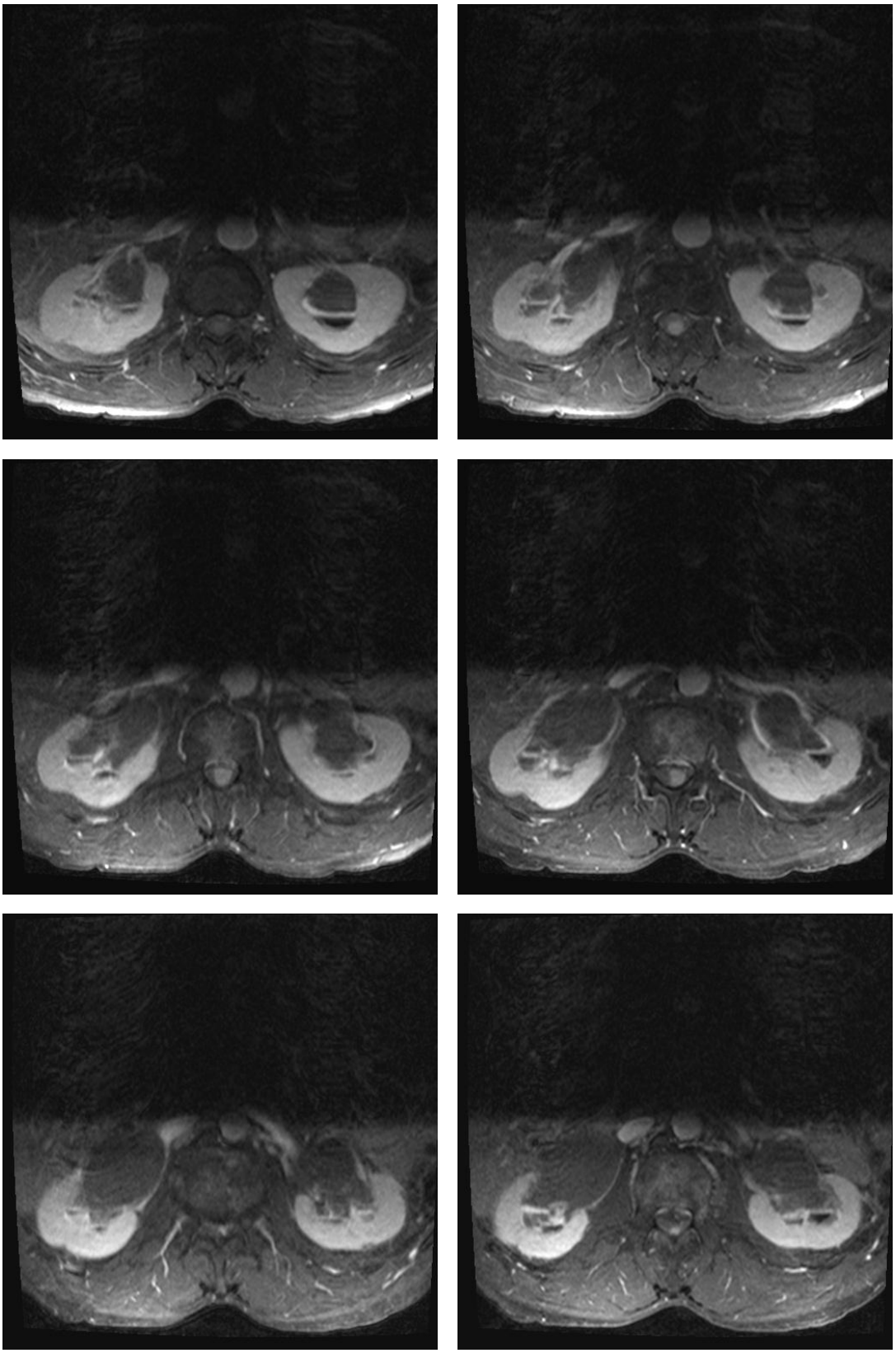
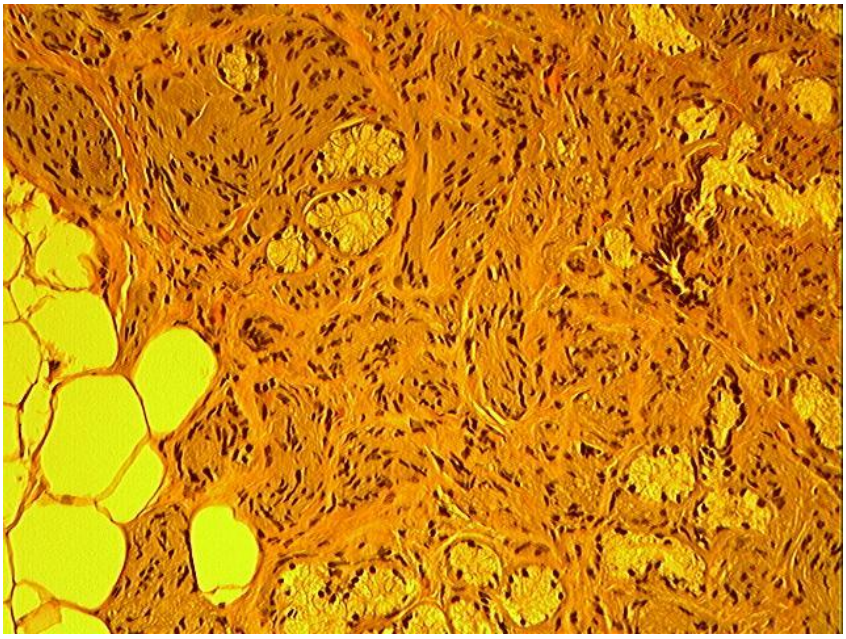
The column on the left demonstrates the T1+Contrast weighted sagittal MRI images. The column on the left demonstrates the corresponding T2 weighted sagittal MRI images of the patient provided in the case report.

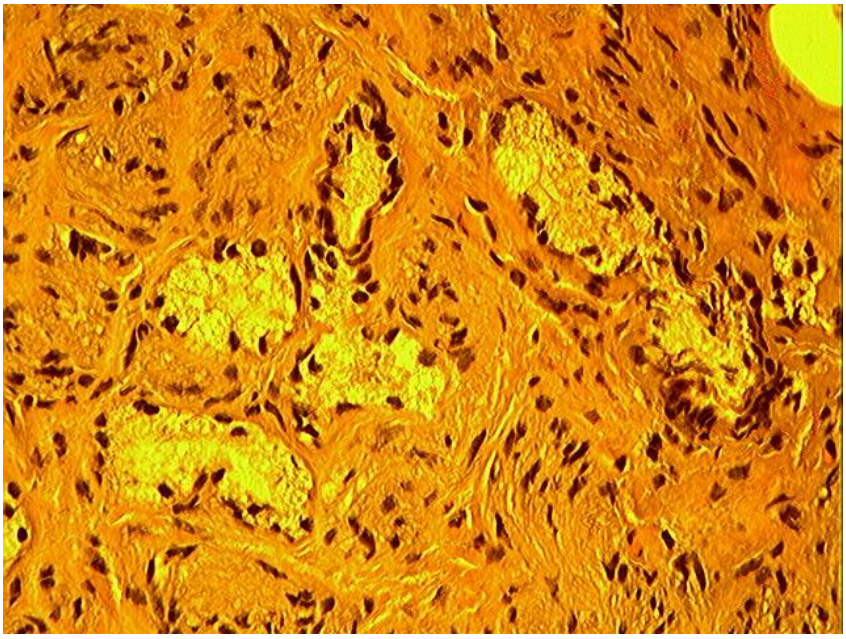


The column on the left demonstrates the T1 weighted axial MRI images. The column on the left demonstrates the corresponding T1+Contrast weighted axial MRI images of the patient provided in the case report.

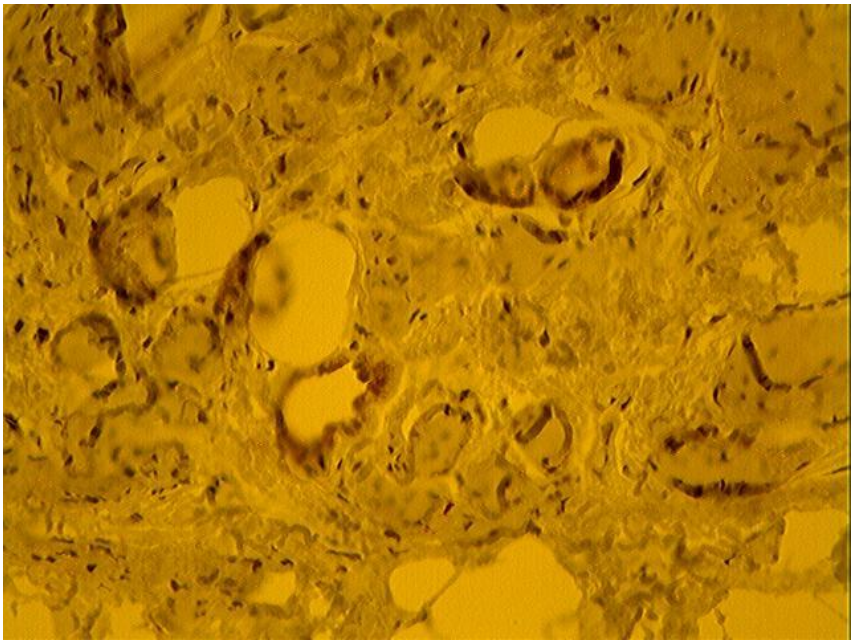




Hematoxylin and Eosin Stain (H + E Stain) f.rom a permanent section of the patient provided in the case report



Hematoxylin and Eosin Stain (H + E Stain) f.rom a permanent section of the patient provided in the case report



Demonstrates + staining for Epithelial Membrane Antigen which is uniquely positive in endodermally derived tissue of the GI tract. This specimen was also taken from the patient provided in the case report.