THE CUTTING EDGE

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Peer-Reviewed

An Examination of Meningioma

New CE Article

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Fellow members were given the opportunity to apply for a travel grant to attend an upcoming Fall Conference or Spring Meeting of their choice. Fellows were required to write a manuscript, and the four winning entries received a grant valued at up to $1800 (full week registration + $1000 to help cover travel expenses). Congratulations, Tisa, on your winning submission!

Abstract

Meningiomas are a common specimen at the surgical pathology bench, comprising over 36% of intracranial tumors. Arising from the arachnoid cap cell, meningioma is asymptomatic in 75% of cases, benign for 80-85% of diagnoses, and, for locations amenable to surgery, curable in 85% of cases. Meningioma tumors are usually solitary, discrete, and slow-growing. Individuals with neurofibromatosis type 2 are associated with 50% incidence of meningioma, increased incidence of multiple tumors, and higher grade at diagnosis. Meningiomas are more often found in females and more commonly diagnosed in middle age. Treatment options include active surveillance, surgery, and radiation. Meningioma prosection is discussed. The World Health Organization grading system is used for meningioma. While the incidence of meningioma metastasis is rare, the possibility of recurrence increases with grade. Overall five-year survival following meningioma diagnosis is 65% across all grades. A case study, with gross and microscopic photographs, is included.

Keywords: Arachnoid cap cell, intracranial, anaplastic, extra-axial

Introduction

The meningioma is a primary brain tumor that arises from the meninges, the non-neural tissue layers that cover and protect the brain and spinal cord. Meningioma accounts for 38% of all intracranial tumors in females and 20% in males.[1] Females carry a two-fold incidence of meningioma over males; however, men are three times more likely to be diagnosed with malignant meningioma.[2,3] (Primary brain tumors themselves account for 2% of annual US cancer diagnoses.[4]) Around 25,000 US meningioma diagnoses are projected for 2016.[5] Meningioma is more common in Africa than in Europe and North America. In the US, blacks present with meningioma more commonly than whites.[5,6]

Meningioma incidence increases with age[6]; meningiomas are usually diagnosed after age 30 and peak in the 6th decade.[1,5] Pediatric meningiomas are rare, accounting for only 1.5% of cases, and are associated with neurofibromatosis type 2 (NF2) in 25% of diagnoses.[7,2]

Meningiomas are the most common extra-axial, intracranial tumors of the brain.[1,2,4] In adults, 90% of meningiomas are located above the tentorium.[8] Tumors in the pediatric population are more often infratentorial, intraventricular, and intraparenchymal. Meningiomas in children are more aggressive and have a higher incidence of recurrence.[2] Meningiomas tend to be slow-growing, increasing at a rate of 1-2mm/year.[9] Most meningiomas present as solitary tumors, but in 5-40% of cases, multiple tumors are identified.[6] Multiple tumors at presentation are particularly associated with NF2, a genetic disease with 50% incidence of meningioma.[6,4]

The World Health Organization (WHO) grading system is used for meningioma. Incidence of grade at presentation is as follows[1]:

Grade I (benign) – 88-94%
Grade II (atypical) – 5-7%
Grade III (anaplastic/malignant) – 1-2%

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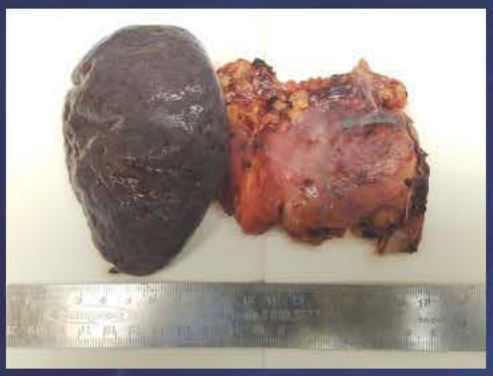

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JOURNAL SUBMISSIONS

The AAPA encourages any AAPA member or interested party to contribute articles, updates, photos or upcoming event announcements for the quarterly edition of *The Cutting Edge*. In particular, articles related to the field of pathology are welcomed. Articles and photos may be submitted electronically. (**Note: photo files must be a minimum of 300 dpi resolution.**)

Use the upload link on the AAPA website or send your contributions directly to journal@pathassist.org. All submitted material is edited for content and clarity. Research articles and case reports are subjected to a peer review process. Please see the AAPA website for complete submission details.

JOURNAL DEADLINES

Issue 1: January 1
Issue 2: April 1
Issue 3: July 1
Issue 4: October 1

AAPA
American Association of Pathologists' Assistants

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Michelle Sok, Executive Director, sitting in front. Not pictured: Jon Bakst.

Mission:

The AAPA is dedicated to providing comprehensive professional support for pathologists' assistants.

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The AAPA will be the premier professional association for pathologists' assistants, supporting the individual practitioners as they serve patients, pathologists, and the profession.

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Letter from the Editor

Dennis Strenk, PA(ASCP)CM
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Dennis Strenk works as Lead PA at Ameripath in Milwaukee, WI. He has been a member of AAPA since 2003, and has been the Managing Editor of The Cutting Edge since 2009. He also serves as the Print Communication Subcommittee Chair for the MarComm Committee.

We have a wide variety of topics covered in this issue. The cover article is by travel grant winner Tisa Lawless, and deals with meningiomas. On page 13 you will find a scholarship winning article, this one by Shelby Currier. In all, we have six original articles in this issue, four of which have an associated CE quiz. And let's not forget the book review, tips and tricks, and gross photo tutorial. By the way, if you are interested in entering to win a travel grant or scholarship you can find more information on page 23.

Another featured article written by a travel grant winner, Kimberly Green, is on page 9, and discusses tissue submission for Zika testing. In the future we are going to have more of these "current events" type of articles. Meghan Pickard has put together a group of staff writers, who will cover such topics that are of interest to PAs. We could still use a few more writers, so if you'd like more information you can contact Meghan.

Of course, none of this would be possible without our group of peer reviewers. They are responsible for critiquing every article that you see here, offering constructive ideas for improvement. We have recently added a couple people to that group, but there is always room for more. Contact me if you are interested.

Starting next year the Board of Trustees (BOT) will conduct quarterly "town hall" style online meetings. You will have the opportunity to submit questions and call in to speak with the board members. See the announcement below for the date and time of the first meeting. More details will follow in future issues.

NEW IN 2018

First Quarterly BOT Online Town Hall Meeting
Sunday, January 21, 2018, 7:00 - 8:00 pm CST
Topic: International Outreach/Advocacy

Tune in to submit questions and to interact with the BOT.
All AAPA members are encouraged to attend.
More details to follow in the next issue of *The Cutting Edge*.

An Examination of Meningioma

> *Continued from cover*

Meningiomas are asymptomatic in 75% of cases.[4] Interestingly, incidental meningioma is diagnosed in 2.3% of autopsies.[6] Symptomatic tumors occur at an annual incidence of 2 in 100,000 persons compared to 7.8 per 100,000 for asymptomatic meningioma.[4] Symptoms are closely associated with tumor location and result from local compression and edema; headaches and seizures are reported most frequently.[2] Tumors in locations amenable to surgery are curable in 85% of cases.[9]

The meninges are composed of three membranes (or maters): the dura, arachnoid, and pia maters. Arachnoid granulations project through the tough outer dura mater and act to regulate flow of cerebrospinal fluid (CSF) from the subarachnoid space into the bloodstream. The arachnoid cap cell, or meningothelial cell, found on the meningeal surface of the arachnoid granulation, is the source cell for meningioma.[2] Arachnoid cap cells are most commonly found within arachnoid villi but may be seeded throughout the craniospinal arachnoid space.[10] Non-neoplastic arachnoid cap cells and meningioma cells express both mesenchymal and epithelial features.[2,6]

Sporadic meningiomas are more common, but significant genetic and environmental factors have been identified. "Genetically, meningiomas can be subdivided into three major genetic groups. The sporadic type, the familial type not related to NF2, and the familial type related to NF2."[2] Chromosome 22 is strongly linked to meningioma development.[10,2] The NF2 gene, which is a tumor suppressor gene, is located on chromosome 22q.[10] All NF2-associated cases of meningioma exhibit chromosome 22q abnormalities. Deletions of chromosome 22 are found in 54-78% of sporadic meningiomas; loss of heterozygosity of chromosome 22 occurs in approximately 60% of meningiomas and loss of NF2 gene function occurs in approximately 30% of meningiomas.[10] This suggests a two-hit model of tumor-suppressor inactivation of the NF2 gene on chromosome 22q.[2,10] "Chromosome 1 abnormalities have been implicated in tumor progression and higher-grade meningiomas."[10] Chromosome 18 has also been associated with meningioma.[2]

Previous radiation exposure to the head and neck, at all doses, increases the chance of developing meningioma. "The implicated radiation exposure range spans from dental radiography, low-dose irradiation to the scalp for tinea capitis, radiation therapy for tumors in the head and neck region, and exposure to atomic explosions in Hiroshima and Nagasaki. The mean interval for tumor development is 35, 26, and 19-24 years, respectively."[2] Radiation-induced tumors tend to present at a younger age, are more aggressive and/or atypical, are more likely to be multifocal, are highly proliferative, and can show a different, more complex karyotype than sporadic meningioma.[2,10] Radiation-induced meningioma is evenly distributed between men and women.[10]

Females have seen an ever-rising incidence of lower-grade meningiomas over the past several decades.[2] Increased meningioma growth rate has been observed in pregnant women.[2] Studies have shown estrogen, progesterone, and androgen receptors on meningioma cell surfaces; these receptors are more prevalent in Grade I tumors.[2] In addition, females have a 10-fold higher incidence of spinal meningioma.[3] A link between widespread oral contraceptive use and meningioma seems likely, but has not yet been proven.[2,3]

Materials and Methods

For its "superior resolution, multiplanar capabilities, and 3-dimensional (3-D) reconstruction abilities," magnetic resonance imaging (MRI) is the single best method for identifying meningioma.[1] "MRI can demonstrate tumor vascularity, arterial encasement, venous sinus invasion, and the relationship between tumor and surrounding structures."[1] Meningioma ordinarily appears as a dural-based, homogeneous, enhancing mass on MRI.[8] A "dural tail" is seen in 65% of meningiomas (and 15% of other intracranial tumors), which is described as a "collar of thickened, enhancing dura that surrounds the tumor's dural attachment."[1]

While MRI is the preferred imaging method, approximately 90% of meningiomas are demonstrable by computed tomography (CT).[10] Contrast-enhanced CT is especially useful for demonstration of adjacent bone changes and in the evaluation of skull involvement and/or calcification within meningiomas.[4,10] Focal calcification is present in 30% of benign meningiomas, but is rare in malignant meningioma.[4]

Meningiomas typically grow along the external surface of the brain or within the ventricular system. Location determines symptoms, if any, and classification. The most common locations include parasagittal, falcine, convexity, intraventricular, skull-based, and spinal.

Parasagittal meningiomas grow along the brain midline. Symptoms include seizures, lower extremity weakness, headache, personality changes, dementia, increasing apathy, flattening of affect, unsteadiness, and tremor. Large parasagittal meningiomas may result in bilateral leg weakness.[7,9]

Falcine meningiomas arise within the falx, the meningeal layer between the brain hemispheres. Falcine and parasagittal meningioma account for 25% of cases. Meningiomas may be both falcine and parasagittal. Symptoms for falcine meningiomas are similar to parasagittal tumors.[7,9]

Convexity meningiomas arise on the surface of the brain away from the midline and account for 20% of cases. Often, convexity meningiomas are asymptomatic until the tumor reaches a large size. Common symptoms include seizures, headaches, extremity weakness, difficulty speaking, and visual field deficit.[7,9]

Intraventricular meningiomas arise within the ventricular system of the brain and account for 2% of meningioma diagnoses. Headaches and dizziness are associated with intraventricular meningioma. Hydrocephalus can result from cases where the tumor blocks CSF flow.[7,9] Intraventricular meningiomas are more commonly seen in children than adults.[2]

Skull-based meningiomas are found within the bones that form the bottom of the skull and the bony ridge in the back of the eyes. Skull-based meningiomas are usually less amenable to surgical resection and often invade adjacent bone, fibrous structures, and brain, leading to symptoms including nerve palsy and dental complaints.[2,6] Tumors of the sphenoid wing, located behind the eyes, account for 20% of cases and can compromise the circulatory system of the brain. Symptoms for sphenoid wing meningioma include eye-bulging, visual problems, seizures, memory problems, personality changes, and headache.[7,9] Olfactory groove tumors grow along the nerves that run between the brain and the nose. Olfactory groove meningiomas comprise 10% of cases and can result in loss of smell, subtle personality changes, mild difficulty with memory, euphoria, diminished concentration, urinary incontinence, and visual impairment.[7,9] Other skull-based meningiomas include posterior fossa (adjacent to the cerebellum), suprasellar, and paranasal.[7,9]

Although spinal meningiomas account for <10% of all cases, up to 90% of spinal meningiomas occur in females.[7,9] Eighty percent of spinal tumors are located within the thoracic spine, followed by the cervical spine; lumbar meningioma is rare.[8] Symptoms include back pain and limb pain.[7,9] Grade I psammomatous subtype meningioma is most frequently located in the spine.[2]

Primary meningiomas can be found outside the central nervous system, in such locations as lung, salivary gland, mediastinum, bone, sinonasal tract, and skin/connective tissue of the head and neck.[2] Primary orbital meningioma must be distinguished from direct extension of brain meningioma.[2]

Results

Grossly, meningiomas are usually rounded masses with a well-defined dural base. Meningioma can compress underlying brain matter, but is easily separated from surrounding tissue. Tumors are generally of rubbery to firm consistency, which is related to collagen content.[2] Typically encapsulated, with polypoid or bosselated external surfaces, the cut surface of meningioma is solid, homogeneous, granular, and tan. Psammoma bodies are common, especially in low-grade tumors, so the cut surface may be gritty due to calcifications.[2] Lipid-rich foci may appear yellow.[2] En plaque meningiomas may show flat, plaque-like growth that blankets the dura[1]; this type of growth pattern may cause dural thickening and is most common in cranial-based locations.[2,11]

Prosection of meningioma is fairly straightforward. Most tumors are received intact, as a discrete tumor mass, often with attached dura. Frozen section is uncommon, as are ancillary studies using fresh tissue. If dura is present, the free dural surface may be inked; the specimen is then serially sectioned perpendicular to the dura, thereby illustrating the tumor-dura interface. For less discrete tumor specimens, the entire external surface should be inked prior to sectioning. Again, the specimen should be sectioned in such a manner as to provide sections that show tumor transition to surrounding non-tumor tissue and surgical margins. Since brain invasion is inextricably linked to meningioma grade and recurrence, all identified brain tissue within the specimen should be submitted.

On occasion, more complicated meningioma resection specimens may be received, especially those including bone. As with other bone-containing specimens, the first and most important step is proper fixation; overnight fixation may be warranted for those specimens containing calvarium. Although bone invasion by meningioma does not change the tumor grade, demonstrating the tumor-bone interface is paramount. Following fixation and gross description, thoroughly sample tumor not directly attached to bone. Afterwards section perpendicular to the tumor-bone interface; use a scalpel to cut through tumor to the bone surface, and then use a bone-cutting device to continue the section through bone. The cut sections are then decalcified. While the process will take longer and cause further decalcification artifact, it may be more appropriate to decalcify the entire tumor-bone interface (or specimen) prior to sectioning.

As noted above, most meningiomas display a homogeneous cut surface. Deviations from this expected appearance should be sampled well. Smaller and piecemeal specimens, especially those less than 3cm, are often entirely submitted. For larger specimens, at least one section per centimeter is submitted.[12] Again, all brain tissue should be submitted to rule out invasion.

Microscopically, meningiomas are classified by malignant potential using the WHO grading system (**Table 1**[13]). Fifteen meningioma subtypes are grouped within the three grades. Due to both mesenchymal and epithelial derivation, microscopic heterogeneity is common in these tumors; one feature may predominate, and this aspect is reflected in the wide range of subtypes.[2] For meningiomas, invasion of bone, vascular structures, skeletal muscle, dura, dural sinus, and paranasal sinuses is not indicative of malignancy.[2,11] Frank invasion of brain parenchyma alone is indicative of aggressive behavior, with fingerlike extension of tumor into parenchyma as the classic observation.[2] Mitotic count is also a definitive grading criterion; four or more mitoses per 10 consecutive high-power fields (HPF) is defined as high mitotic count.[2]

WHO Grading of Meningioma[13]

WHO grade I
- Benign meningioma

WHO grade II
- Atypical meningioma
  - Mitotic figures ≥ 4/10 high-power fields (HPF)
    - *or*
  - At least 3 of 5 parameters:
    - Sheeting architecture (loss of whorling and/or fascicles)
    - Small cell formation
    - Macronucleoli
    - Hypercellularity
    - Spontaneous necrosis
      - *or*
  - Brain invasion
    - *or*
  - Clear cell meningioma
    - *or*
  - Chordoid meningioma

WHO grade III
- Anaplastic (malignant) meningioma
  - Mitotic figures ≥ 20/10 HPF
    - *or*
  - Frank anaplasia (sarcoma, carcinoma, or melanoma-like histology)
    - *or*
  - Papillary meningioma
    - *or*
  - Rhabdoid meningioma

Table 1. WHO Grading of Meningiomas[13]

Grade I tumors are typically slow-growing and have distinct borders. Subtypes include syncytial (meningothelial), fibroblastic, microcystic, transitional, psammomatous, angiomatous, and secretory.[2] Microscopically, whorled clusters of spindle cells with psammoma bodies and intranuclear pseudoinclusions may be seen.

A classic syncytial (meningothelial) meningioma, grade I, is presented **(Fig. 1 and 2)**. MRI detected a dural-based, extra-axial, enhancing mass. Craniotomy was performed and a 5.7cm tumor was received in pathology. The external surface is smooth, rounded, and well-circumscribed. Attached dura is present. Upon sectioning, the cut surface is homogeneous, granular, and tan. Microscopically, neoplastic meningothelial cells are arranged in lobules and whorls. The cells are rather uniform, with oval to polygonal nuclei containing a delicate chromatin pattern. Focal nuclear clearing and intranuclear pseudoinclusions are identified. Psammoma bodies are absent and mitoses are sparse. Neither necrosis nor brain invasion is identified. This subtype of tumor displays fuzzy (syncytial) intercellular borders; in fact, well-defined cell borders raise suspicion for more aggressive behavior.[2]

Grade II/atypical meningiomas grow faster than their benign counterparts and tend to recur. While the cells may appear atypical, frank malignant features are absent. Grade II subtypes include clear cell and chordoid.

Less than five percent of meningioma cases are classified as Grade III, displaying frankly malignant/anaplastic features. These are aggressive, fast-growing tumors which exhibit invasive, destructive behavior; "there is a tendency for these aggressive components to become the dominant component in recurrent tumors."[2] Often, Grade III tumors will recur within one year from surgical removal.[14] Rhabdoid and papillary malignant subtypes have been described.

Common differential diagnoses include meningoangiomatosis, hemangiopericytoma, and metastasis, especially dural metastases from primary tumors of the breast and prostate.[2,1]

Immunohistochemistry is useful in the pathologic diagnosis of meningioma. Because arachnoid cap cells may express both epithelial and mesenchymal characteristics, a wide variety of histologic variants and variable immunohistochemical staining occurs.[2] In fact, it is uncommon for meningioma tumors to show complete histologic homogeneity.[2] The most reliable marker for meningioma is epithelial membrane antigen (EMA), but staining is often weak and patchy.[2] Staining for vimentin, when positive, is strong and diffuse.[2] Estrogen, progesterone, and androgen receptors have a higher incidence in grade I meningioma for both males and females.[2] S-100 is focally positive, while keratins are usually negative.[2]

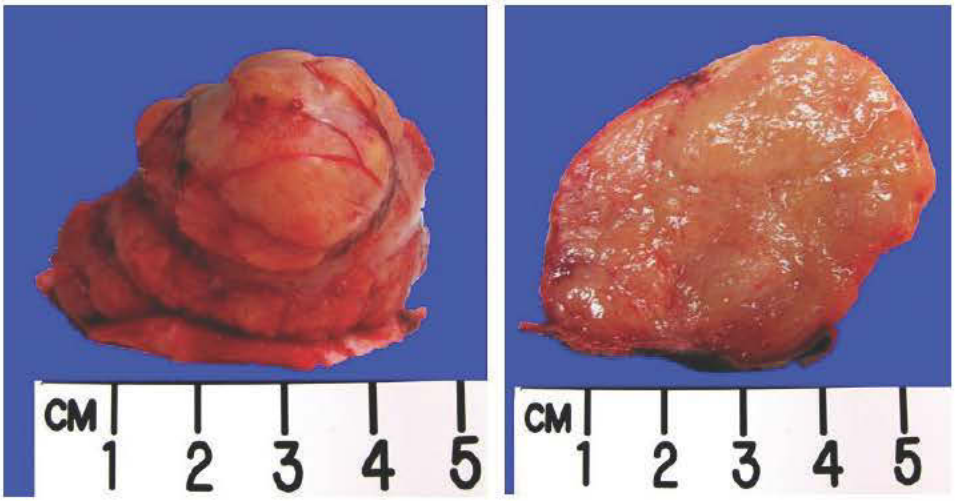

Fig. 1. Gross photographs, external and cut surfaces. Gross photographs of a 5.7cm meningioma from a 64-year-old male. Left image: Intact specimen wi h rounded, well-circumscribed external surface. Right image: The cut surface shows a granular, homogeneous, tan appearance and the attached dura.

Two proliferative markers with significance in meningioma diagnosis are Ki-67 (MIB-1) and anti-phosphohistone-H3 (PHH3). Ki-67 is directly proportionate to tumor grade, whereby increased Ki-67 labeling index correlates to higher tumor grade.[2] An antibody to PHH3 has been used to detect mitotic rates, which has led to some success in distinguishing between meningioma grades I and II.[2]

Discussion

Treatment of meningioma is determined by type, location, growth rate, tumor size, and likelihood of tumor spread and/or recurrence.[9] Other factors include age, health status, medical history, and patient tolerance of the projected treatment. Although alternative treatments for meningioma are available, the three main treatment strategies are active surveillance (i.e. observation), surgery, and radiation.

Patients with small, slow-growing, asymptomatic or minimally-symptomatic tumors, with minimal or no brain swelling, are candidates for active surveillance.[3] Elderly patients or those of poor operative status are also commonly offered observation over more invasive treatments.[3] In a retrospective study published in 2000 (Radhakrishnan et al), 57 patients with asymptomatic meningioma were followed over an average of 29 months; 35 patients showed no growth, 10 patients showed 0.24cm/year tumor growth rate, and none of the patients became symptomatic.[4]

Traditional craniotomy for meningioma offers the best chance of cure and is the treatment of choice.[3] Of course, the surgical goal is to entirely remove the tumor, however, the first priority is to preserve and/or improve the patient's neurologic status.[3] With removal of sufficient tumor, pressure or distortion of normal surrounding brain tissue by tumor is relieved, thus preserving and/or improving neurologic function with possible reduction or elimination of symptoms. Complete tumor removal, including all fibers that attach the tumor to the brain and bone, and with wide dural margin, reduces the possibility of recurrence.[3,8] For those instances in which the tumor cannot be entirely resected due to location or proximity of tumor to major structures and/or organs (e.g. blood vessels, eyes), it is better to leave some tumor tissue behind rather than risk significant morbidity or decrease patient quality of life following surgery.[3]

Surgery also allows for pathologic confirmation of the radiographic meningioma diagnosis. More importantly, microscopic tissue examination determines tumor grade, an important indicator of both prognosis and recurrence.

Preoperative tumor embolization is commonly used for meningioma. In this process, the surgeon fills blood vessels supplying the tumor with a glue-like substance to restrict blood flow to the tumor.[1,9] The embolization itself can cause tumor necrosis and is sometimes the only

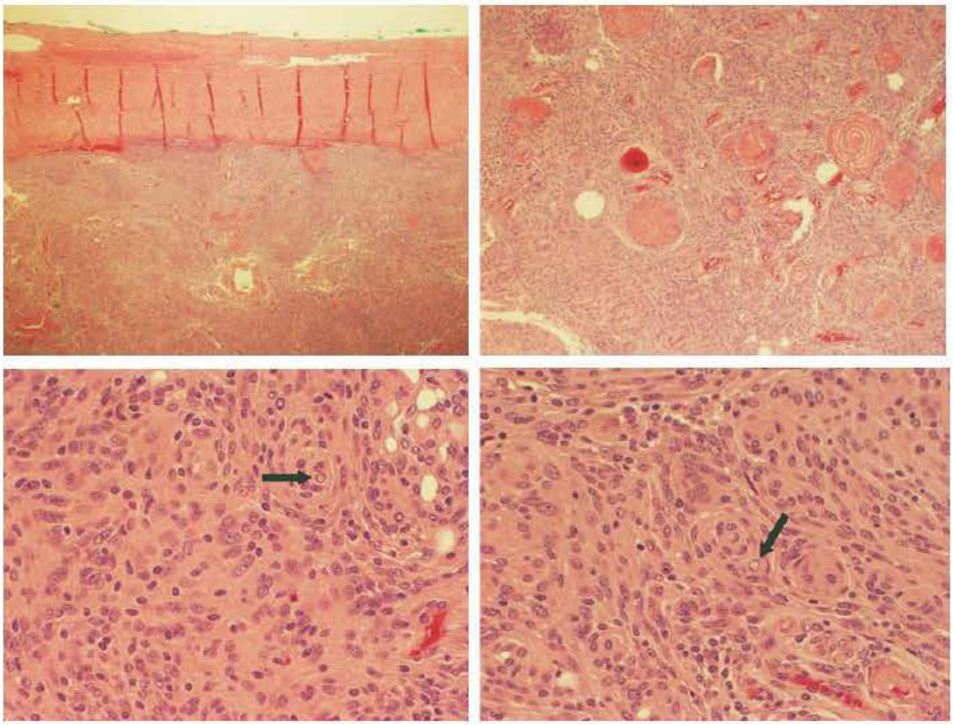

Fig. 2. Photomicrogaphs of Fig. 1 tumor. Top left: Low-power view of tumor with overlying dura (4x). Top right: Medium-power view of meningioma lobules and whorls (10x). Bottom left: High-power view of indistinct cell borders, syncytial appearance at left, and an intranuclear pseudoinclusion indicated by black arrow (40x). Bottom right: High-power view of indistinct cell borders, whorls, and an intranuclear pseudoinclusion indicated by black arrow (40x).

procedure used for meningiomas in high-risk or elderly patients.[1] Embolization reduces blood loss during surgery, can decrease surgery time, and has been associated with better functional outcomes after surgery.[1] It is important for the pathologist to know whether embolization has been performed, however. "Features such as neoangiogenesis (microvessel density), necrosis, and prominent nucleoli should be interpreted with caution in such specimens."[1]

For meningioma tumors in amenable locations, minimally-invasive surgical options are available. Endoscopic removal through the nose is especially useful for olfactory groove and sellar meningioma.[9] Keyhole microsurgical resection using eyebrow incision has been employed for olfactory groove and sphenoid wing meningioma.[9] For intraventricular meningiomas, endoport resection may be used.[9]

Radiation therapy is used for inoperable meningioma tumors, residual tumor following incomplete surgical resection, tumors in elderly patients, or recurrent tumor.[4,9,15,16] External beam radiation utilizes either x-ray or gamma ray photon beams to kill tumor cells by damaging their DNA[17]; conversely proton beam radiation focuses proton beams. Currently, internal radiation treatments (brachytherapy) for meningioma using radioactive pellets or rods are only available in clinical trials.[5]

External beam treatments are generally delivered in daily treatments over the course of several weeks via a machine called a linear accelerator.[17] Advanced types of external beam radiation now in use include 3-D conformal radiation therapy (3D-CRT), intensity-modulated radiotherapy (IMRT), and stereotactic radiotherapy (SRT).

Three-D conformal radiation therapy uses very sophisticated software and advanced treatment machines to deliver radiation to very precisely-shaped target areas.[17] A stationary multi-leaf collimator is used to conform the radiation to the tumor site, minimizing damage to healthy tissue surrounding the tumor.[15]

Intensity-modulated radiotherapy is especially useful for treating tumors near critical parts of the brain, such as the brain stem and areas that control sight.[5] The radiation oncologist assigns radiation doses to different parts of the tumor and the surrounding tissue. Once the doses have been determined, a computer program calculates the required number of beams and angles for treatment.[17] Numerous collimators are used to direct the radiation beams; the collimators may be stationary or moving during treatment, therefore modulating the intensity over the irradiated field.[15,17]

Stereotactic radiotherapy uses concentrated radiation beams from several different angles that overlap at the tumor, thus limiting the radiation dose to non-tumoral tissue.[15] The patient is fitted with a head frame to mobilize the head while undergoing treatment.[15] SRT is delivered over several doses.[15] Fractionated SRT is delivered in smaller fractions over a longer time period and is especially useful to treat tumors in areas that cannot tolerate high doses of radiation, such as tumors adjacent to the optic nerve, major blood vessels, and the brainstem.[5,9]

In contrast to photon beams, protons are charged particles that deposit less energy along the beam's path, theoretically then delivering more direct energy to the targeted site.[17] The main advantage to proton beam radiation is less damage to tissue adjacent to the tumor.[3]

Stereotactic radiosurgery (SRS), while not an actual surgery in the traditional sense, uses radiation rather than a surgical scalpel to resect meningiomas, especially skull-based tumors and those located in inoperable sites. Using "extremely accurate image-guided tumor targeting and patient positioning,"[17] this outpatient radiation treatment focuses high doses of radiation, from multiple angles, to a precise point (the tumor), thus limiting radiation to surrounding, non-neoplastic tissue.[15] A personalized head frame is used to stabilize the patient's head during treatment.[15] SRS has been shown to stop tumor growth in up to 80% of cases.[9] Stereotactic radiosurgery may be limited to one multi-hour procedure or may be given in shorter treatments over a period of time (fractionated).[5] Depending on the delivery system and regimen, different names are used for this technique, such as gamma knife, cyberknife, and Novalis.[3]

Chemotherapy has not proven effective against meningioma.[3,16] Additional therapeutic options are available and may be used in conjunction with the above conventional treatments or as alternative treatments to alleviate symptoms, treat recurrence(s), or when other more conventional treatments fail. Meningioma medications include steroids and anti-seizure drugs.[5] Physical, occupational, and speech language therapies are often used to round out treatment for meningioma-related symptoms.[5] In

addition, music therapy, acupuncture, hypnosis, massage, meditation, and relaxation exercises have been employed.[16]

Meningiomas can recur, especially following incomplete resection or in direct relation with tumor grade—the higher the grade the more likely the recurrence.[8,9,11] Invasion of adjacent brain tissue is associated with higher recurrence rate.[7] Cranial-based tumors and meningiomas along the anterior visual pathway are more likely to recur; however, recurrence may be more a factor of difficulty in achieving complete resection.[2] Some studies have shown a higher recurrence rate following surgery alone.[4] In 15% of cases, meningioma recurs at a higher grade than the initial tumor.[9] Focal aggressive features may become dominant features in recurrent tumors.[2]

Recurrence rates by grade are as follows[2]:

Grade I – 3%
Grade II – 38-40%
Grade III – 78%

Meningioma metastasis is rare. The most common metastatic sites for meningioma are lung and mediastinum.[11] Metastases from other sources have been reported within a meningioma tumor, most commonly from breast cancer and chronic lymphocytic leukemia.[11]

Prognosis is determined by three main factors: age, grade, and tumor location/accessibility. Younger patients tend to fare better than older patients, including after surgery.[7] Lower grade at diagnosis is predictive of better outcome; patients with Grade I tumors at diagnosis have better outcomes than those with Grade II and Grade III meningioma.[7] Complete tumor resection confers the highest chance of a cure and less chance of recurrence, therefore patients with readily-resectable tumors fare better.[2] Patients with surface-based tumors have an improved prognosis over those with skull-based tumors and tumors adjacent to important brain structures (such as those required for breathing or movement), organs (such as eyes), and major blood vessels.[7]

The overall five-year survival rates for meningioma by grade are as follows[2]:

Grade I – 95%
Grade II – 80%
Grade III – 20%

Sometimes called the neurosurgeon's "friend,"[14] meningioma is a typically-discrete, often readily-resectable, primary brain tumor that is most often benign. For inoperable meningiomas, advanced radiotherapy regimens have reduced symptoms and effected cures. With a 65% five-year survival rate across all grades, meningioma is a tumor like few others. ■

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Peer-Reviewed

A General Overview of Tissue Submission Guidelines for Zika Virus Testing

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University of California, San Francisco

Fellow members were given the opportunity to apply for a travel grant to attend an upcoming Fall Conference or Spring Meeting of their choice. Fellows were required to write a manuscript, and the four winning entries received a grant valued at up to $1800 (full week registration + $1000 to help cover travel expenses). Congratulations, Kimberly, on your winning submission!

Abstract

The Zika virus is making international headlines as it spreads across the globe, mostly due to the severity of birth defects that are seen in infants born to mothers infected with the virus. Affected infants are subject to a range of neurological defects, collectively known as Congenital Zika Virus Syndrome, which includes microcephaly. Tissue testing can be performed on neonatal, fetal, and placental tissues from cases where Zika transmission is suspected. Tissue testing for Zika virus is provided by the Centers for Disease Control and Prevention (CDC). With the rising number of Zika cases within the United States, pathologists' assistants will likely start to see an increase in tissue testing requests. This paper reviews the guidelines for tissue collection and submission set forth by the CDC.

Keywords: Zika Virus, tissue testing, Centers for Disease Control and Prevention Guidelines

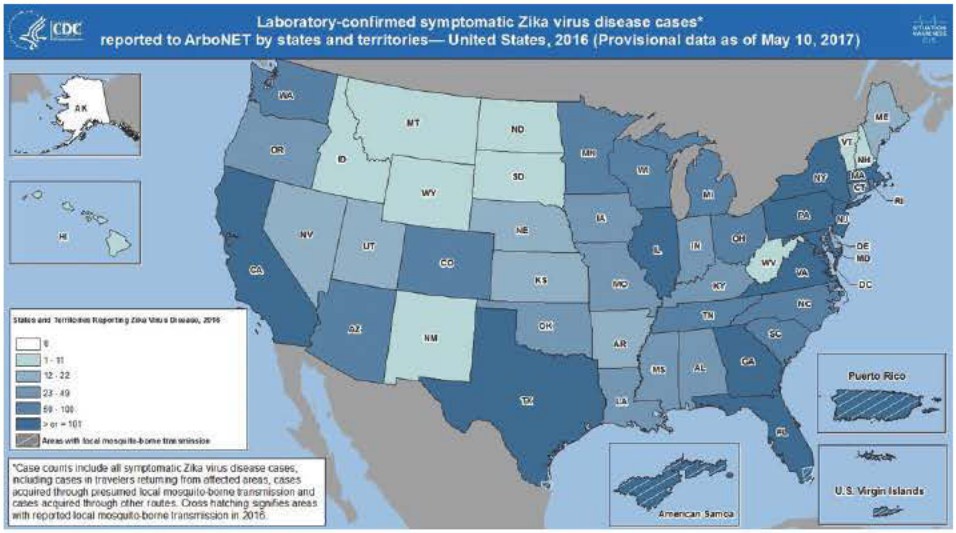

Fig. 1. Map of he United States and US territories showing the number of travel-associated Zika infections and the locations of local vector-born transmission cases as of May 2017. Note: An updated 2017 map reports laboratory-confirmed cases of Zika in Alaska. Reprinted from the CDC.[6]

Background

In February of 2016, the World Health Organization (WHO) held the first International Health Regulations (2005) Emergency Meeting on Zika Virus, and declared that the Zika-associated clusters of microcephaly, and other related neurological disorders, were a public health emergency of international concern. At that time, there was no direct scientific link between the Zika virus and the birth defects; however, the WHO recognized the strong, apparent causal relationship between the two, and agreed that international efforts should be made to better understand the relationship.[1]

By April of 2016, a report was published in the *New England Journal of Medicine*, which stated that there was sufficient evidence to infer a relationship between the Zika virus, microcephaly, and other neurologic anomalies.[2] Through this revelation, scientists and the health care community were able to more intensely focus research efforts, which led to a better understanding about the disease's epidemiology and related birth defects.

First discovered in 1947 in the rhesus macaque monkey in Uganda, the Zika virus was later identified in humans in 1952 in both Uganda and the United Republic of Tanzania.[3,4] Until 2007, confirmed cases of Zika were rare, even in endemic areas (Africa and Southeast Asia). The first major outbreak outside of Asia and Africa was in 2007 in Yap Island Micronesia, and was followed by outbreaks in French Polynesia (2013-2014) and Brazil (2015).[2-4] Since 2016, more than 50 countries have reported evidence of vector-born Zika transmission.[5] By July 2017, all 50 states have confirmed travel-associated disease cases, and Puerto Rico, the US Virgin Islands, American Samoa, Florida, and Texas have confirmed cases of local transmission.[6] **(Fig. 1)**

Zika virus is a member of *Flaviviridae*, a family of viruses that are commonly spread to mammals through arthropod vectors, mainly ticks and mosquitos. Other *Flaviviridae* include Dengue, Chikungunya, Japanese encephalitis, West Nile virus and Yellow Fever.[7] The most common form of transmission of the Zika virus is through the bite of an infected *Aedes* mosquito, particularly *A. aegypti* and *A. albopticus*.[8] However, there are additional documented, and speculated, modes of transmission, including by sexual intercourse, laboratory exposure,[8] and possibly through contact with bodily fluids (e.g., tears, urine, and vomitus).[9] It is likely that transmission through infected blood transfusions could happen, although there are no confirmed cases within the United States as of July 2017.[8]

In adult humans, symptoms related to a Zika infection range from asymptomatic to mild, lasting two to seven days, and may include fever, skin rash, conjunctivitis, muscle and joint pain, general malaise, and headache.[3,10] These symptoms are non-specific to the Zika virus, and as with many other viral infections, there is no specific treatment for a Zika infection. Infected individuals should treat the symptoms they are experiencing, drink plenty of fluids, rest, and take acetaminophen to reduce pain and fever. Non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin should be avoided until Dengue can be ruled out, as these can increase bleeding risk.[11]

Current research suggests that there is also a strong link between Zika and Guillain-Barré syndrome, an autoimmune demyelinating disease that affects the peripheral nervous system, which leads to temporary or long-term paralysis. A large number of recent Guillain-Barré cases have been associated with a concurrent Zika infection; however, only a small percentage of people infected with Zika will go on to develop Guillain-Barré.[12]

Probably the most concerning and potentially devastating form of transmission of the Zika virus is vertical transmission from mother to child in utero. A fetus infected with the virus in utero is susceptible to a range of neurological defects,[13,14] most notably microcephaly. Microcephaly is defined as a head circumference that is two standard deviations below average (median for age and sex), while severe microcephaly is three standard deviations below average.[14] **(Fig. 2)** Affected infants can suffer from a variety of other neurological defects, collectively known as Congenital Zika Virus Syndrome, which can include "craniofacial disproportion, spasticity, seizures, irritability, [and] brain stem dysfunctions, such as swallowing problems, limb contractures, [as well as] hearing and ocular abnormalities…".[14] Radiologically, affected infants can demonstrate "cortical/subcortical calcifications, cortical malformations, simplified gyral pattern/migrational abnormalities, brainstem/cerebellar hypoplasia, and ventriculomegaly."[14] **(Fig. 3)** All of these neurological defects are also associated with various genetic abnormalities as well as other intrauterine infections, specifically the TORCH infections (**T**oxoplasmosis, **O**ther agents [Syphilis, Varicella-zoster virus, and Parvovirus B19,] **R**ubella, **C**ytomegalovirus, and **H**erpes simplex virus).[14]

There is increasing evidence that a Zika infection during pregnancy may be associated with spontaneous abortion,[17] and the severity of Zika-related birth defects is starting a global conversation about abortion access for affected women, particularly in countries where abortion is illegal. With the spread of Zika, pathology laboratories around the country will likely start to see an increase in products of conceptions (POCs), from both spontaneous and therapeutic abortions, as well as placentas related to suspected and confirmed cases of Zika infection. With this increase, it is important pathologists' assistants and other lab personnel are aware of the requirements for tissue collection and submission for Zika testing, as well as safety practices for handling tissue from suspected or confirmed cases.

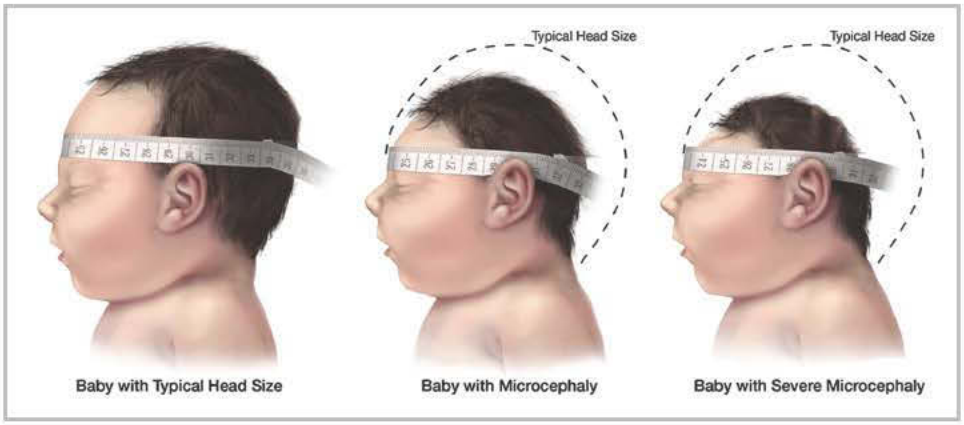

Fig. 2. A normocephalic infant compared to infants with microcephaly and severe microcephaly. Reprinted from the CDC.[15]

Methods

Lab personnel who handle potentially infected tissues should follow universal precautions and Biosafety Level 2 precautions, which include the use of gloves, laboratory gown/coat, and eye protection.[18] Samples can be transported within the US as a Category B Biological substance,[18] meaning the samples are an infectious material not likely to cause permanent disability or cause life-threatening or fatal harm to a healthy individual in the case of accidental exposure.[19] Guidelines for transporting samples can be found on the Centers for Disease and Control and Preventions (CDC) website under Biosafety in Microbiological and Biomedical Laboratories, 5th edition.[18]

The CDC uses a variety of testing modalities to test body fluids and tissue samples for the Zika virus.[20] Urine and serum are the primary diagnostic specimens for Zika virus infections. Other fluids that can be tested include cerebrospinal fluid (CSF), amniotic fluid, and cord blood.[21] If testing on neonatal, fetal, or placental tissues is requested, the types of tissue available for evaluation will depend on the gestational age of the fetus and the type of procedure performed.

It is important to note that all tissue testing for Zika must go through local, tribal, or state health departments prior to submission to the CDC. The health department must have pre-approval from the CDC prior to submitting any tissue samples for testing. When testing of fetal or neonatal tissues is warranted, appropriate consent from the parent or guardian must also be obtained.[22]

Fetal and placental tissue testing is limited to patients who meet the CDC's clinical and epidemiological criteria for testing, which includes a combination of maternal exposure risk and pregnancy outcomes, such as a live birth with anomalies, a live birth which is phenotypically normal, infant death following a live birth, or pregnancy/fetal loss. Additionally, results of maternal Zika testing via blood serum, urine and whole blood testing are a key factor in determining if fetal or placental testing should be considered.[21,23] For example, if a mother definitively tests positive for Zika, then testing of placental tissue is not warranted as it will not provide any diagnostic value. However, if maternal testing is equivocal or the mother has not been tested, then tissue testing can considered.

Determining if a patient qualifies for tissue testing should be decided by the patient's clinical team, the health department, and the CDC; it is not the responsibility of laboratory personnel to determine if tissue

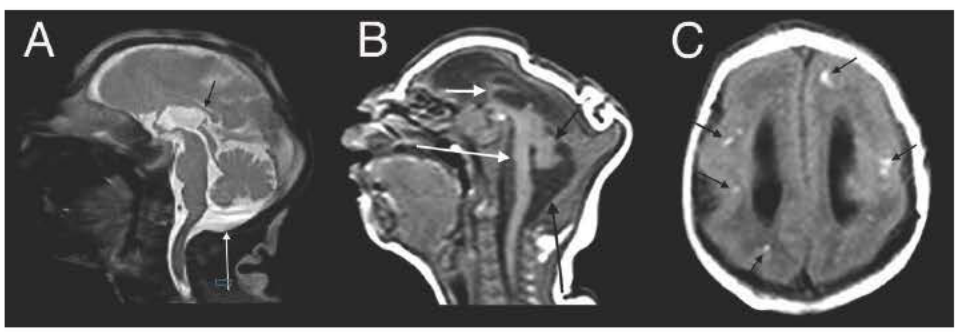

Fig. 3. Sagittal T2 weighted image (A) shows moderate microcephalic brain, a smooth cerebral surface, hypoplasia of corpus callosum (black arrow), and an enlarged cisterna magna (long white arrow). Sagittal T1 weighted image (B) shows profound craniofacial disproportion, hypogenetic corpus callosum (short white arrow), and brainstem (long white arrow), cerebellum hypoplasia (short black arrow), and enlarged cisterna magna (long black arrow). Axial non-contrast CT image (C) shows multiple subcortical calcifications (black arrows). Adapted from The BMJ.[16]

The following chart is a summary of the tissue submission guidelines provided on the CDC's website.[22]

Specimen Type	Fixed Specimens	When to Consider	General Notes
Products of Conception	4 or more sections	Generally less than 12 weeks gestational age	For early pregnancy loss/ miscarriage, send POCs fixed in formalin.
Placenta and fetal membranes	Several full thickness sections (at least 3) from middle third of placental disk, at least 1 cm from the placental disk margin One 12 x 5 cm strip of fetal membranes	Any gestation for which placenta is available	Include sections of the placental disk, fetal membranes and pathologic lesions when possible. Include information about placental weight.
Umbilical cord	At least 4 segments of cord, 2.5 cm each	Any gestation for which placenta is available	Umbilical cord segments should be from the proximal, middle and distal aspects.
Brain and spinal cord	0.5 - 1 cm^3 each 5 or more sections from different parts of the brain and spinal cord	Fetal demise	It is critical to maintain tissue architecture to evaluate viral pathology. Additional fixation time may be required.
Solid Organs	0.5 - 1cm^3 each 1 representative section from each solid organ	Fetal demise	Submission of the eyes is highly recommended.

testing is warranted or meets CDC criteria. Similarly, the CDC will require extensive clinical history on the patient and this should be provided by the clinical team.

Testing via reverse-transcription-polymerase chain reaction (RT-PCR), as well as histopathology and immunohistochemical staining, is performed on formalin-fixed and paraffin-embedded tissues. Tissues should be fixed in 10% buffered formalin for a minimum of 72 hours. After 72 hours, tissue should be placed in 70% ethanol for storage and/or shipping. Frozen tissues are considered on a case-by-case basis by the CDC. Fixed tissues should not be subsequently frozen. Each specimen should be separately submitted and clearly labeled with patient identifiers as well as the specific tissue type/location and fixative.[22]

Conclusion

Due to the severity of birth defects related to in utero Zika infections and the overall increase in Zika infections within the US, it is likely that lab personnel will see an increase in requests for Zika testing on neonatal, fetal, and/or placental tissues.

The above information is a general overview of the guidelines set forth by the CDC for testing tissue samples for Zika virus. Local, tribal, and state health departments, as well as the CDC can serve as great resources for anyone who is asked to help facilitate in the tissue collection process. ■

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New CMP Requirements Announced

Beth Obertino-Norwood, PA(ASCP)[CM]
Education Committee Chair

If you were at the AAPA Continuing Education conference in San Antonio this year, you heard that in September the ASCP announced some changes in the CMP requirements for pathologists' assistants. If you weren't able to attend the conference, the following is a brief history and recap of the announcement.

Earlier in the year, the BOT asked the Education Committee to examine the current CMP requirements and determine if they were adequate for a mid-level medical practitioner. As part of this review, two things became apparent. The first was that the number of CE points required was lower for PAs as compared to similar mid-level practitioners (physician's assistants, nurse practitioners, physical therapists, etc.). The second fact that became apparent was that most other mid-level practitioners had a specific number of CE points that addressed the areas of their practice that fluctuated or changed the most. For nurse practitioners and physician assistants, that would be pharmacology. For pathologists' assistants that would be the dissection and staging of complex cancer cases. Our current CMP requirements were not specific and did not address the most dynamic areas of our profession.

After some recommendations by the BOT, and a working weekend for the education committee, a proposal was presented to the ASCP for a new CMP plan that would better align us with similar professions, and require specific CE credits. The ASCP has since contacted us to say that they have approved the plan.

We will remain on the same three year renewal cycle with the new credits required of:

- 1 point in laboratory or patient safety (i.e. quality control, quality assurance)
- 20 points in general anatomic pathology
- 15 points addressing macroscopic examination and staging of cancer cases (i.e. advanced cancer anatomic pathology) **NEW!**
- 1 point in medical ethics **NEW!**
- 23 remaining points in areas of anatomic pathology, management, education, or other clinical specialties

This brings us to a total of 60 credits every three years, compared to our current requirement of 45 credits every three years.

We will have a long time to prepare for the new requirements because they will not go into effect until the three year renewal cycle STARTING on January 1, 2019 (ending on December 31, 2021) and for all current students who take their exam after January 1, 2019.

2017 - 2019:
Certificate maintenance cycle –
Follow current requirements

2018 – 2020:
Certificate maintenance cycle –
Follow current requirements

2019 – 2021:
Certificate maintenance cycle –
Follow **NEW** requirements

The AAPA has already started implementing plans to increase the number of free credits offered with your membership to meet these changes. Currently the AAPA offers 15 credits per year through eblasts and articles in *The Cutting Edge*. They plan on increasing that number to 20 credits per year and will have at least five of those credits fulfill the new "advanced cancer credit". We have already started revising the guidelines for travel grant/scholarship article submissions to make sure they cover all of the requirements to fulfill the advanced cancer credit. We also have a team of speaker liaisons who will help guide speakers with cancer related topics so that our conference lectures will be another great option.

At this point we believe that most hospital Tumor Boards and Cancer conferences will also fulfill the advanced cancer credit. The free credits the AAPA provides will already be PACE approved, but you will have to use your own discretion as to what credits from other sources will work. As always, we will still be subject to audit by the ASCP, so you would need to be able to defend your credit choices.

There is always some associated worry and concern with change. Although we recognize that as normal, we also recognize that ultimately we want to be the best practitioners we can be. Our hope is that the new requirements will make us better informed PAs who offer even better patient care. If you have any questions, please don't hesitate to contact the AAPA or the ASCP. ■

Peer-Reviewed

Giant Lipoleiomyoma of the Posterior Uterus

Shelby Currier, MLSASCP[CM]
Student General Educational Scholarship Winner

Student members were given the opportunity to apply for a $2500 educational scholarship. Congratulations to Shelby as the 2016 winner!

CE Article

Article and CE quiz were originally released in the online CE Store December 2016.

Abstract

Lipoleiomyoma is a rare, benign lesion of the uterus that occurs primarily in obese peri- and postmenopausal patients. Here, a case of lipoleiomyoma of the posterior uterus in a 55 year old is described. The clinical course was complicated by comorbidities of cerebral palsy, pneumonia, and sepsis. Not wanting to risk the spread of potentially malignant cells, physicians decided to remove the huge 24.8 x 20.7 x 25.9 cm mass without biopsy once the patient was stable. Diagnosing the tumor was complicated by its rarity and the unexpected presence of necrosis and atypical lipomatous cells. A murine double minutes (MDM2) mutational analysis was needed to rule out a higher grade lesion, liposarcoma. The debated pathogenesis of lipoleiomyoma and its association with other diseases is also discussed.

Key Words and Phrases:

Lipoleiomyoma, Liposarcoma, Murine double minutes (MDM2), DNA Damage Inducible Transcript 3 (DDIT3), estrogen imbalance

Case Report

A 55-year-old, morbidly obese, African-American female with a clinical history significant for cerebral palsy presented to a community hospital after an anonymous call notified authorities of her weakness and respiratory difficulties. Emergency Medical Services noted that the patient lived with her husband and three adult sons. The patient arrived at the hospital in a state of neglect, but was able to communicate with the health providers. She denied alcohol and tobacco use and reported being bed bound due to increasing weakness in both legs over the past six months. She presented with leukocytosis, aspiration pneumonia and a large, palpable abdominal mass. A computed tomography (CT) scan of her chest and abdomen showed extensive right upper and lower lobe pneumonia, consolidation of the left upper lobe, and a 31 x 21 x 23 cm heterogenous, diffuse soft tissue and fat mass with well-defined macrolobulated margins, likely originating in the right adnexa. The CT also showed findings consistent with uterine fibroids. While waiting for a bed at a larger hospital for a gynecology oncology evaluation, the patient was intubated due to increased respiratory distress. Upon arrival at the larger institution, she was found to be lethargic and was unable to answer questions or follow commands. A second CT measured the abdominal mass at 24.8 x 20.7 x 25.9 cm and noted that the mass appeared to originate from the uterus instead of the previously reported right adnexa. The differential diagnosis based on the scan included liposarcoma, large teratoma, or large lipoleiomyoma. No metastatic disease or enlarged lymph nodes were visualized in the pelvis and abdomen. Excision of the mass, as a biopsy or cyst drainage, was not done due to concern for spillage of potentially malignant contents. Physicians planned to remove the entire mass once the patient was more stable. A month and a half after arriving at the hospital, the patient was still suffering complications from pneumonia, but was stable enough for surgery and underwent a hysterectomy and bilateral salpingo-oophorectomy to remove the mass.

Diagnosis

The anatomic pathology laboratory received her uterus with attached mass, cervix, bilateral fallopian tubes, ovaries and several peritoneal biopsies. The cervix, fallopian tubes, ovaries and peritoneal biopsies were all grossly unremarkable. The uterus measured 13.5 cm from superior to inferior, 7.1 cm from cornu to cornu and 6.6 cm from anterior to posterior. It contained one anterior red-tan polyp, 1.5 x 1.2 x 0.3 cm, consistent with an endometrial polyp, and multiple tan-white whorled nodules, 0.2 to 3.7 cm in greatest dimension, without hemorrhage or necrosis. These nodules were consistent with leiomyomata. A white, whorled nodule in the posterior myometrium appeared to be the origin of the attached

Fig. 1. Cross section of the presumed lipoleiomyoma with attached uterus containing leiomyomata. Grossly, lipoleiomyoma differ from typical uterine leiomyoma by being more yellow and having a softer cut surface.

mass. The mass was 6.3 kilograms, 26 x 25.3 x 19.7 cm, and was surrounded by a tan, shiny serosa. The cut surface revealed soft, yellow fatty areas separated by delicate septae with occasional white and black spots **(Fig. 1)**. Additional areas were more solid and tan. No obvious areas of necrosis or hemorrhage were noted.

Histologic examination of the tumor revealed predominantly mature adipocytes, smooth muscle cells with small areas of necrosis **(Fig. 2)**, and rare atypical lipomatous cells **(Fig. 3)**. The atypical cells had numerous small vacuoles reminiscent of lipoblasts. A murine double minutes (MDM2) mutational analysis was ordered to rule out liposarcoma. The result was still pending at the time of this writing, but the presumed diagnosis was lipoleiomyoma.

Discussion

Lipoleiomyomas are rare lesions of the uterus that occur primarily in obese peri- and postmenopausal patients.[1-3] The age range of reported cases is 34 to 77 years.[2] The incidence of lipoleiomyoma is 0.03-0.2%, compared to 4-11% for uterine leiomyoma.[2-5] No more than two lipoleiomyomas have been reported in one patient.[2] Lipoleiomyomas are often incidental findings in asymptomatic women undergoing scans or surgery for other reasons. When symptoms are present, they are nonspecific and similar to those associated with leiomyomas: abnormal

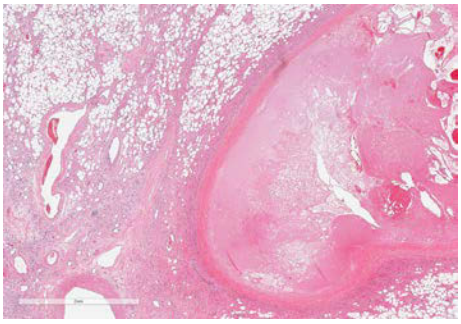

Fig. 2. Micrograph of the tumor showing areas of adipocytes, smooth muscle cells, and necrosis.

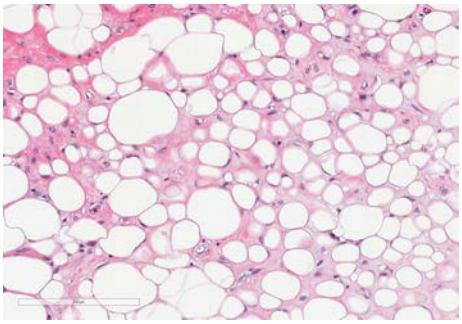

Fig. 3. Micrograph of the tumor showing several atypical lipomatous cells with multiple small vacuoles reminiscent of lipoblasts.

uterine bleeding, pelvic pain or pressure, a palpable pelvic mass, urinary frequency, and incontinence.[1-4,6] Lipoleiomyomas most commonly grow in the uterine corpus in the subserosal or intramural level, but cases have been described in the cervix, ovary, retroperitoneum, and broad ligament.[2-4] There is disagreement in the literature over whether uterine lipoleiomyomas represent a variant of leiomyoma with adipocyte differentiation or a degenerative or neoplastic change in a leiomyoma.[2] Generally, lipoleiomyomas are considered an uncommon and benign variant of uterine leiomyomas, composed of an admixture of mature smooth muscle cells and adipocytes.

Like in this case, uterine lipoleiomyomas are often diagnosed preoperatively as a liposarcoma or teratoma using radiographic scans. Imaging studies play an important role in preoperative localization and diagnosis, but a histologic evaluation is necessary to confirm the diagnosis.[2,4] The differential for a lipomatous pelvic mass includes liposarcoma, lipoleiomyoma, leiomyoma with degenerative change, lipoma, carcinoma with heterologous liposarcomatous differentiation, leiomyosarcoma with degenerative change, ovarian fatty tumors including cystic teratomas, and lipoplastic lymphadenopathy.[1-4,7] Liposarcomas differ from lipoleiomyomas in cellular pleomorphism, the presence of mitotic bodies and lipoblasts, and infiltrative margins.[7] Lipoleiomyomas typically have a benign histological appearance in comparison, but there have been rare cases reported that included atypical smooth muscle cells and lipoblasts.[7] Lipoleiomyomas can be distinguished from leiomyosarcomas by their bland smooth muscle morphology.[3] Scattered lipocytes in a typical leiomyoma are fairly common.[6] Some suggest lipoleiomyoma can be differentiated from leiomyoma with fatty degeneration by the striking number and even distribution of adipose tissue throughout the lesion, but there is no specific defined percentage of adipocytes that would enable a diagnosis of lipoleiomyoma.[4,6]

Grossly, lipoleiomyoma differ from typical uterine leiomyoma by being more yellow and having a softer cut surface.[1] Some lipoleiomyomas can be firm and rubbery, while others are fibro-fatty with pale to yellow irregular soft areas.[2] All lipoleiomyomas are nodular and well circumscribed by a thin connective tissue capsule.[2] As in this case, lipoleiomyomas have been reported to grossly arise from typical leiomyomas.[7] Reported cases have ranged from 0.5 to 55 cm in diameter, with the majority of cases under 10 cm.[2] Necrosis and hemorrhage are thought to never be present, although microscopic areas of necrosis were present in this case.[2-5] Comparatively, liposarcomas do tend to have focal areas of hemorrhage and necrosis present.[7] Liposarcomas can also have a diverse gross appearance, some showing a gelatinous cut surface with others firmer and fleshy tan-white.[7] The well circumscribed mass seen in this case favors the gross description of a lipoleiomyoma vs a liposarcoma, but the presence of microscopic necrosis is concerning.

Histologically, lipoleiomyomas are encapsulated tumors with interlacing bundles of spindle-shaped smooth muscle cells in a whorled pattern admixed with lobules of mature adipocytes and fibrous tissue.[1,3-5] The ratio of smooth muscle to fat cells is inconsistent. One study found no significant correlation between amount of adipocytes and other clinical and pathological features, none between the proportion of lipomatous and leiomyomatous components and the tumor size, and none between the amount and distribution of the lipomatous component and the age of the patient.[2] Characteristically, the nuclei of the elongated smooth muscle cells show no atypia and have even chromatin, and the adipocytes are entirely mature.[3] Some cases of lipoleiomyoma show massive lymphocyte infiltration and, in separate cases, angiomatous hyperplasia.[2] No mitoses, cytologic atypia, immature lipoblasts, necrosis, calcifications, or other degenerative changes are typically present in lipoleiomyomas, but there have been rare cases reported that included atypical smooth muscle cells and lipoblasts.[2,7] This case showed rare atypical lipomatous cells, prompting the pathologist to order additional studies to rule out liposarcoma. Liposarcomas also contain a non-malignant smooth muscle component, but lipoblasts are present in all tumors.[7] Liposarcomas can show multinucleated cells and bizarre nuclei.[7] Several cases of liposarcomas that appeared to originate in a lipoleiomyoma have been reported, including liposarcomas imperceptibly merged with a lipoleiomyoma and a liposarcoma that contained a well-demarcated, infarcted lipoleiomyoma.[7]

Cytogenetics and immunohistochemistry are used to characterize soft tissue tumors. Well-differentiated and dedifferentiated liposarcomas are characterized by amplification of the 12q13-15 region, causing overexpression of multiple genes including those coding for high-mobility glycoprotein (HMAG2), cyclin-dependent kinase (CDK4), and MDM2.[7] Immunohistochemistry is often utilized to test for these and other proteins instead of performing the expensive and time-consuming genetics studies. Immunohistochemically, the adipose tissue of lipoleiomyoma tests positive for vimentin and S100 protein and the smooth muscle element for vimentin, desmin and α-smooth muscle actin.[2,6] Both test positive for estrogen (ER), progesterone (PR), and the Ki-67 protein and negative for pancytokeratins (AE1/3, CAM5.2) CEA, CA19-9, CA125, CD34, HMB45, p53, MDM2, CDK4, and CD117.[2,6] The markers of well-differentiated liposarcoma, MDM2 and CDK4, are negative in lipoleiomyomas. These markers are particularly important in cases, such as the one reported here, of large lipomatous tumors. Tumors suspicious for liposarcoma can also be tested for the DNA damage inducible transcript 3 (DDIT3) rearrangement characteristic of liposarcomas.[7] The liposarcoma translocation is t(12;16)(q13;p11) or more rarely t(12;22)(q13;q12).[7]

The pathogenesis of adipocytes present in the myometrium remains unclear. Proposed mechanisms include lipomatous degeneration, multipotential undifferentiated mesenchymal cells, fatty differentiation or metaplasia of muscle or connective tissue, perivascular entrance of fat cells into the uterus, and misplaced embryonic fat cells.[1-3,5,6] Uterine smooth muscle cells have divergent differentiation potential and can become adipocytes or skeletal muscle cells.[2] Numerous immunohistochemical studies affirm the complex pathogenesis of lipoleiomyoma, providing evidence that at least some cases result from lipomatous metaplasia of leiomyomas, like the gross description from this case hints at, and others from multipotential undifferentiated mesenchymal cells.[2,3] The presence of

ER and PR in the lipoleiomyomas implies that the tissue is specific to female genital organs.[2] Both elements in lipoleiomyomas are positive for Ki-67, suggesting that both have the capacity for cell proliferation and are neoplastic, evidence against proposed degeneration mechanisms.[2,6] In one study, adipocytes from a lipoleiomyoma were positive for desmin, aiding the theory of direct transformation of muscle cells into adipose cells.[2]

Altered lipid metabolism related to estrogen imbalance in menopausal women may also contribute to the development of lipoleiomyomas.[1,3,4,6] Lipoleiomyomas have been associated with lipid metabolic diseases like hyperlipidemia, hypothyroidism, and diabetes and have been described in patients with leiomyomata, ovarian follicular cysts, adenomyosis, endometriosis, endometrial hyperplasia, and polyps.[1-4,6] Although not associated with many, lipoleiomyoma have also been identified in a few cases of malignancy.[2,4,7] In most cases there was no gross or histologic contiguity between the lipoleiomyoma and the malignancy, but there have been multiple uterine liposarcomas arising in lipoleiomyoma reported.[7] In the largest study with a cohort of 70, 17% of patients with lipoleiomyomas had a noncontiguous gynecologic malignancy and 76% had different types of lesions associated with hyperestrogenic status such as adenomyosis, endometriosis, endometrial hyperplasia, polyps, complex atypical endometrial hyperplasia, and gynecologic carcinomas, providing evidence that estrogenic manifestations may be an important factor in the development of lipoleiomyomas.[2] Additional studies are needed to elucidate any association of lipoleiomyomas with malignancy, estrogenic status or metabolic disorders, but if estrogenic status does prove to be a true correlation, it follows that the presence of adipocytes in otherwise normal leiomyoma should instigate an evaluation in search of a coexistent gynecological neoplasm.[2]

Although the pathogenesis and association with other conditions remain unclear, all studies agree that lipoleiomyomas are benign and, if asymptomatic, require no treatment. No recurrences have been reported after hysterectomy for lipoleiomyoma.[4] At the time of writing, the MDM2 result in this case is still pending and the diagnosis remains unclear. The well encapsulated, predominantly mature adipocyte and smooth muscle tumor strongly favors a lipoleiomyoma. The immunohistochemistry test will reveal if the scant necrosis and rare atypical lipomatous cells were signs that the tumor is actually a liposarcoma. If so, the patient will need adjuvant therapy and closer follow-up. ■

Member Spotlight

Travis Rinehart, PA(ASCP)^{CM}

Travis has been a PA for seven years and works at the University of Nebraska Medical Center in Omaha, NE.

Favorite travel destination?
A small public lake in western Nebraska called Merritt Reservoir.

Embarrassing story from clinicals?
An orchiectomy with seminoma that completely effaced the seminiferous tubules, and I couldn't find "the tumor."

Where were you born and raised?
A small farming community called Franklin, NE.

Do you do any volunteer work?
I volunteer monthly at Open Door Mission, a local homeless shelter.

Favorite movie?
Ferris Bueller's Day Off – *I can still probably recite 70 percent of the movie.*

Best advice you ever got?
Tell the truth.

Best advice you ever gave?
Tell the truth.

If you weren't a PA, what other line of work would you enjoy?
Farming

What's your favorite hobby?
Fishing . . . both freshwater and saltwater.

What would your super power be and why?
Time travel would be wicked awesome to catch Woodstock in 1969.

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Peer-Reviewed

Plasmacytoid Variant Urothelial Carcinoma: Diagnostic and Grossing Challenges

Kailyn Gibson MS, PA(ASCP)CM, Congli Wang, MD

Johns Hopkins Hospital Department of Surgical Pathology

Fellow members were given the opportunity to apply for a travel grant to attend an upcoming Fall Conference or Spring Meeting of their choice. Fellows were required to write a manuscript, and the four winning entries received a grant valued at up to $1800 (full week registration + $1000 to help cover travel expenses). Congratulations, Kailyn, on your winning submission!

Article and CE quiz were originally released in the online CE Store December 2016.

Abstract

Plasmacytoid variant urothelial carcinoma (PUC) is a rare variant form of urothelial carcinoma that typically presents with macroscopic hematuria, and tends to present late, with metastasis, and is associated with a poorer prognosis compared to nonvariant urothelial carcinoma. Presented here is a case of PUC, outlining the diagnostic and grossing challenges associated with this rare bladder neoplasm. The gross appearance of the tumor can mimic the classic wall thickening seen in cystectomies treated with neoadjuvant therapy, leading to oversampling. The tumor cells themselves have abundant cytoplasm, with an eccentric nucleus, closely resembling plasma cells. Due to the variable presentation of the tumor, the differential diagnosis can be wide. Immunohistochemistry plays a crucial role in diagnosis, specifically to rule out plasma cell derived tumors and demonstrating the presence of an epithelial component. This case is a well-rounded example of many facets of pathology working together to make an accurate diagnosis, ultimately providing the best patient care. It is important for everyone at the grossing bench to be aware of rare, variant types of tumors because it has potential to lead to more efficient grossing and submission.

Patient History

A 62 year-old male presented to his primary care physician with dysuria and a burning discomfort during urination, with increased frequency and urgency, specifically during the night. He was advised to alter his nighttime fluid intake, and was treated for overactive bladder symptoms; however, the treatment was discontinued due a lack of improvement and unpleasant side effects. After two months of worsening symptoms, he underwent an abdominal ultrasound, revealing mild left hydronephrosis with irregular thickening of the bladder wall. The patient is a nonsmoker with no known industrial exposure to carcinogenic agents.

Diagnosis

Following failed therapeutic attempts to alleviate the patient's symptoms, and an abnormal ultrasound, a cystoscopy was performed, with transurethral resection of the bladder tumor. The biopsy slides were sent to our institution for consultation, and a diagnosis of a T2, poorly differentiated urothelial carcinoma, plasmacytoid variant, was made. The following immunostains were positive, supporting this diagnosis: pankeratin, CK7, CK20, monoclonal CEA, and MOC-31. The patient completed four cycles of neoadjuvant chemotherapy and was scheduled for a cystoprostatectomy.

Upon receipt, the specimen consisted of an intact cystoprostatectomy specimen. The bilateral ureter margins were submitted for frozen section diagnosis and were negative for tumor. The specimen was inked and opened along the anterior aspect to reveal a 5.0 x 4.5 cm pink-red, flattened, and slightly ulcerated area involving the anterior and left lateral bladder walls **(Fig. 1)**. This area did not appear to involve the ureteral orifices or distal urethral margin. The bladder wall was diffusely thickened, particularly at the anterior and left lateral wall, corresponding to the lesion **(Fig. 1)**. The prostate was unremarkable.

This case presented a specific grossing challenge, in that the lesion was ill-defined and the patient had a history of neoadjuvant chemotherapy. At our institution, treated nonvariant urothelial carcinomas are generally submitted entirely. Because this lesion presented as a slight ulceration with associated diffuse bladder thickening, I was advised to submit the lesional area entirely, along with additional sections of each bladder wall. The routine sections of right and left ureteral orifices, prostatic urethra, and prostate were also submitted.

Microscopic examination revealed mitotically active tumor cells exhibiting a large amount of eosinophilic cytoplasm with an eccentrically located nucleus **(Fig. 2)**, similar in appearance to plasma cells. The tumor cells display both a nesting and cord-like dispersal pattern into and through the smooth muscle of the bladder wall **(Fig. 3)**. **Fig. 4** displays the classic appearance of the tumor in a background of fibrofatty soft tissue, representing tumor extension into the perivesicular soft tissue. The case was signed out as T3 high-grade invasive urothelial carcinoma, plasmacytoid variant with extension into the perivesicular fat. Tumor was identified diffusely throughout the bladder, present at the right lateral, left lateral, anterior, and posterior walls, dome, and right and left ureteral orifices. The final margins were negative for tumor, and metastasis was present in four of 20 lymph nodes. No recurrence has been reported in the six months following the surgery.

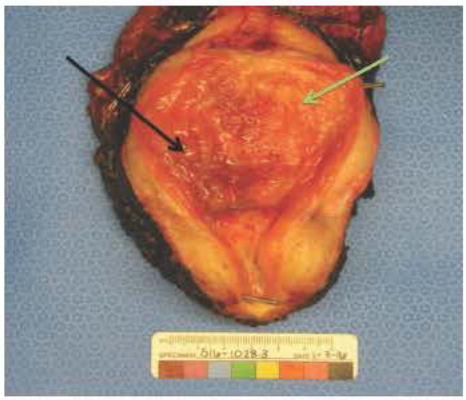

Fig. 1. The slight mucosal ulceration (green arrow) and adjacent edema (black arrow).

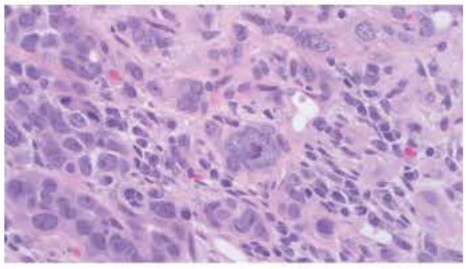

Fig. 2. Plasmacytoid urothelial carcinoma cells wi h abundant eosinophilic cytoplasm, eccentric nuclei and mitotic figures.

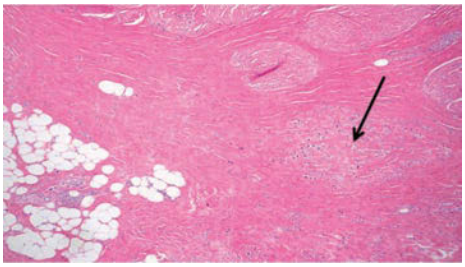

Fig. 3. A nest of tumor cells (arrow) within the muscularis of the bladder wall.

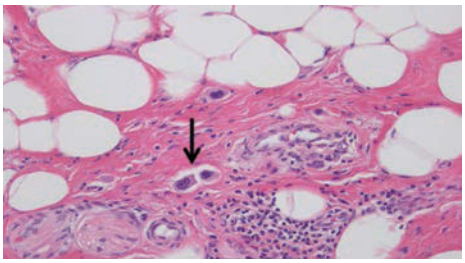

Fig. 4. Tumor cells (at arrow) in a background of fibrofatty tissue, representing tumor extension into the perivesicular soft tissue.

Discussion

Plasmacytoid variant urothelial carcinoma (PUC) was first described by Zuckerberg et al. in 1991, as a tumor either presenting with a marked lymphoid infiltrate, obscuring the invasive nature of the bladder cancer, or as a diffuse pattern of lymphoid-like cells with a histologic similarity to malignant lymphoma or plasmacytoma.[1] The case presented here demonstrates the latter, posing one of the specific challenges in diagnosing PUC. Because the tumor cells so closely resemble plasma cells, the differential diagnosis for PUC can be wide, especially in small biopsy cases, or in cases with abnormal presentation. It is of utmost importance to be aware of variant types of urothelial carcinoma, to avoid an initial misdiagnosis. Sahin et al. discussed a case of PUC initially misdiagnosed as multiple myeloma due to presentation with multiple lytic bone lesions of the skull and ribs, displaying cells with a distinct plasmacytoid appearance.[2] The differential diagnosis in cases like these, and the one presented here, ranges from benign diagnoses such as cystitis with plasma cell infiltration, to plasma cell derived neoplasms including plasmacytoid-type lymphoma, multiple myeloma, and large B-cell lymphoma.[3] The overall clinical picture, including the patient's initial presenting symptoms, is helpful in narrowing the differential diagnosis.

PUC generally cannot be diagnosed from histology alone. CD138, an immunohistochemical marker for plasma cells, can be initially employed if the differential diagnosis is wide, to rule out a plasma cell derived lesion.[3] CD138 is positive in both plasmacytoma and PUC, with kappa and lambda light chain markers differentiating the two. PUC is positive for CD138, but negative for light chains.[3] Once a primary plasma cell tumor can be ruled out, the identification of an epithelial component via immunohistochemistry solidifies the diagnosis of PUC.[3,4] CK and CK7 will confirm the epithelial origin of transitional cells[3]. In this case, both the bladder biopsy and tumor from the cystoprostatectomy specimen stained positive for CK7. This demonstrates the valuable role that immunohistochemistry plays, in conjunction with histology, to diagnose PUC.

Because the tumor cells tend to form nests, with cords of malignant cells extending deep into the musculature of the bladder wall[3], the appearance of the tumor can make grossing more challenging. Several of the case reports in the literature document an ill-defined, diffuse lesion, affecting multiple areas of the bladder, with associated rigidity of the bladder wall.[3,5,6] In cases like this, and the one presented here, it is difficult to approximate the overall size of the lesion. We followed the same grossing guidelines that we use for nonvariant urothelial cancers, and submitted the grossly obvious lesional area entirely, but this arguably may have been over submission. At sign-out, tumor cells were identified throughout the bladder, within the described area of ulceration, but also in the areas of what appeared to be associated edema. Because neoadjuvant therapy can lead to morphology changes of the bladder itself, such as fibrosis of the bladder wall[7], treatment effect may look strikingly similar to the tumor itself. We are no longer hunting for residual tumor in a bladder wall thickened by treatment effect. Armed with the understanding that PUC presents as a diffuse, infiltrative tumor, representative sections of each area of the bladder may be a more prudent approach than attempting to block out a single solitary lesion.

PUC is commonly diagnosed at an advanced stage and is associated with a poorer prognosis than that of other urothelial neoplasms. The most common presenting symptom is hematuria, commonly with accompanying urgency and frequent micturition, as seen in this case. An associated tendency for peritoneal recurrence is also a factor in the overall survivability of this neoplasm.[8] A retrospective look into the Indiana University Bladder Cancer Database, at all patients undergoing curative cystectomy revealed that 80% of the 30 patients with PUC on TURBT were upstaged at cystectomy to ≥pT3, and 60% had lymph node involvement[9], as seen in this case. The standard treatment for muscle-invasive PUC is cystectomy with lymph node dissection. In the case presented here, the patient underwent four rounds of neoadjuvant therapy prior to the cystoprostatectomy. While individual cases of complete response of PUC to neoadjuvant chemotherapy exist in the literature[10,11], broader studies suggest that PUC may show an initial response to neoadjuvant therapy, but long-term survival is limited to a few patients.[9]

This case is noteworthy on two levels. Not only is PUC an interesting, rare variant of bladder cancer, it can pose a challenge at the grossing bench, and histologically. Upon first look at the bladder mucosa, it may resemble inflammation, rather than a discrete, readily identifiable mass. Under the microscope, the tumor cells may be misidentified as plasma cells, thus leading to misdiagnosis of a benign inflammatory process or plasma cell derived neoplasm. Understanding the gross presentation of a case diagnosed as PUC on biopsy will help guide sectioning and submitting decisions. Further study into the effect of neoadjuvant therapy on PUC is necessary to solidify a specific grossing protocol for PUC. This is an excellent example of a complex case requiring multiple levels of analysis in the grossing room and beyond. A complete clinical history, a pathologists' assistant with a keen eye and understanding of the urothelial carcinoma variants, in combination with the appropriate immunohistochemical stains will lead to accurate diagnosis and ultimately the best level of patient care. ■

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Peer-Reviewed

Case Report: Unicornuate Uterus; An Unusual Variant of Mullerian Duct Anomalies

Rosie Falcon, PA(ASCP)CM
Contract PA

Members are encouraged to submit articles for The Cutting Edge. *An upload link can be found on the Publications page of the website. Earn 5 CMP points for authoring journal articles for peer-reviewed publications. Published articles are also eligible for the annual Journal Award with cash prizes!*

Patient History and Hospital Course

A 39-year-old female underwent laparoscopic abdominal hysterectomy with bilateral salpingo-oophorectomy for transgender dysphoria. The surgery and subsequent hospital course were uneventful.

Gross Findings

The uterus had a single cornu with a fallopian tube and ovary attached near the fundus. Parametrium was only present on one side of the uterine corpus; the remaining anterior, lateral, and posterior surfaces were entirely covered by serosa. The endometrial cavity was spindle-shaped, and the cavity communicated with the fallopian tube that was attached near the fundus. A second short, apparently incomplete fallopian tube with attached ovary was attached to the soft tissue inferior to the uterine corpus, near the cervix, by a band of fibrovascular or smooth muscle tissue. The lumen of the inferior fallopian tube showed no communication with the endometrial cavity. The ovaries were unremarkable. **(Fig. 1 and 2)**

Diagnosis

Cervix: atrophy and focal squamous atypia (cannot exclude CIN1). Endometrium: inactive. Myometrium: No histopathologic change. Ovaries: simple follicular cysts. Fallopian tubes: No histopathologic change.

Discussion

Anomalous development of the Mullerian ducts fall into seven major categories. According to the American Society of Reproductive Medicine, the major classes are:

Class Anomaly

I. Uterovaginal hypoplasia and agenesis
II. Unicornuate uterus
III. Uterus didelphys
IV. Bicornuate uterus
V. Septate uterus
VI. Arcuate uterus
VII. Uterine anomalies related to diethylstilbestrol exposure

Class II anomalies of the Mullerian duct (Unicornuate uterus) result from the incomplete development of one of the ducts or failure of one of the ducts to develop. The unicornuate (Class II) type of anomaly can be further divided into four subtypes. In all four subtypes the uterine corpus is somewhat pear or banana shaped, showing only one cornu, and often leans to the side corresponding to the single cornu within the pelvic cavity. A fallopian tube and ovary are attached at the cornu. Peritoneum or serosa will cover the remaining uterine corpus, and a vertical margin of transected parametrium will be evident on only one side of the uterus (corresponding to the single cornu).

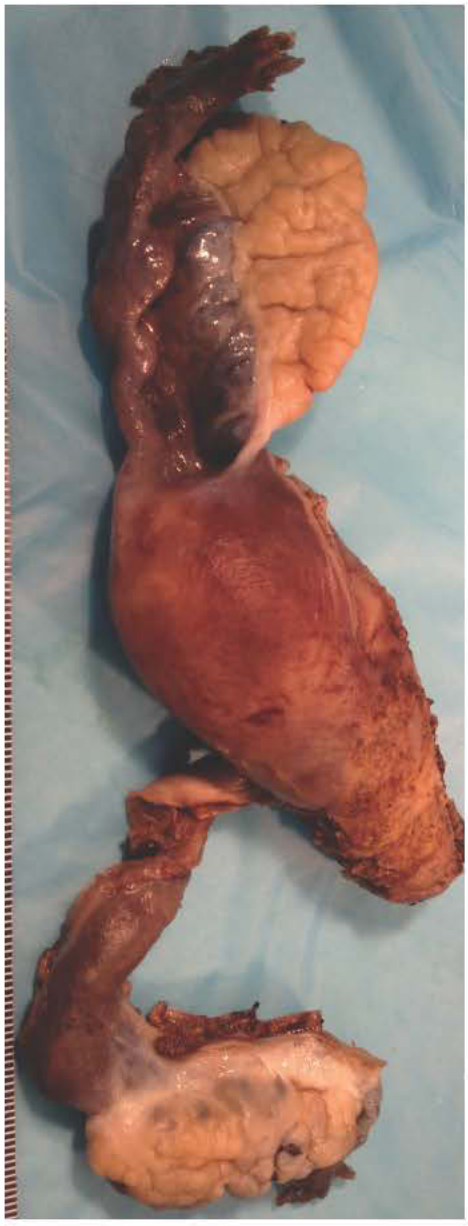

Fig. 1

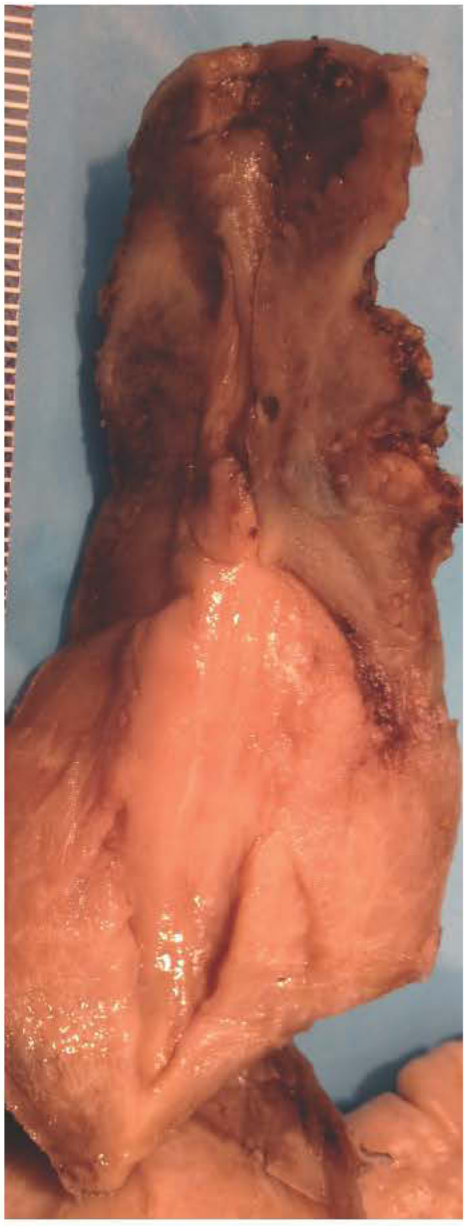

Fig. 2

In the first subtype of unicornuate uterus there is complete agenesis of the second Mullerian duct, with no second fallopian tube present. This is referred to as "isolated unicornuate" or "unicornuate – no horn". **(Fig. 3)**

The second subtype is unicornuate with no cavity. In this type there is a rudimentary horn emanating from the inferior uterus near the peritoneal reflection. The rudimentary horn has an attached at least partly developed fallopian tube but the lumen of the tube is present only in the distal part of the horn and does not communicate with the endometrial cavity. The rudimentary horn located between the main body of the uterine corpus and the second fallopian tube has no endometrial cavity. **(Fig. 4)**

The third variant of unicornuate uterus is non-communicating. In this variant there is a rudimentary horn with an attached fallopian tube, and a small second endometrial cavity. The second endometrial cavity does not communicate with the larger endometrial cavity in the main body of the uterus, and has no outlet to the cervical canal. This variant, due to the isolation of the second endometrial cavity, is often associated with hematometra and endometriosis. **(Fig. 5)**

The fourth and last variant is unicornuate communicating. A rudimentary horn with an endometrial cavity is present, and the endometrial cavity communicates with the endometrial cavity of the main body of the uterus. The appearance of this anomaly can be similar to that of a bicornuate uterus but is distinguished by the fact that the two endometrial cavities are not symmetrical in size or location, with one cavity fully formed and the second displaced and incompletely formed (without a cornu). **(Fig. 6)**

The prevalence of a unicornuate uterus (including all four of the subtypes) is estimated at approximately 0.1 % of the unselected population. This number may not reflect the true incidence since some cases may remain undiagnosed in the absence of complications. Additionally, the unicornuate uterus comprises approximately 10% of all uterine or Mullerian duct anomalies.

The prevalence of the various subtypes of unicornuate uterus are as follows:

Isolated or no horn:
35% of all unicornuate uteruses

No Cavity:
33% of all unicornuate uteruses

Non Communicating:
22% of all unicornuate uteruses

Communicating:
10% of all unicornuate uteruses

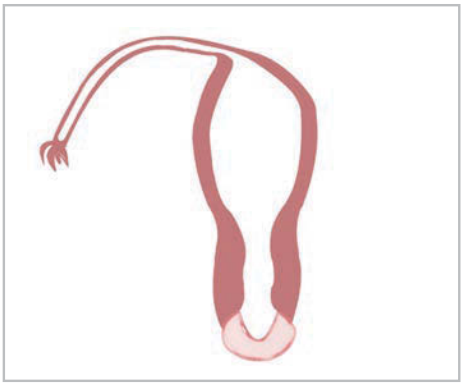

Fig. 3. No Horn

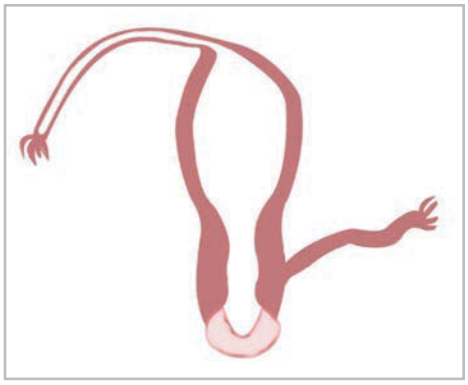

Fig. 4. No Cavity

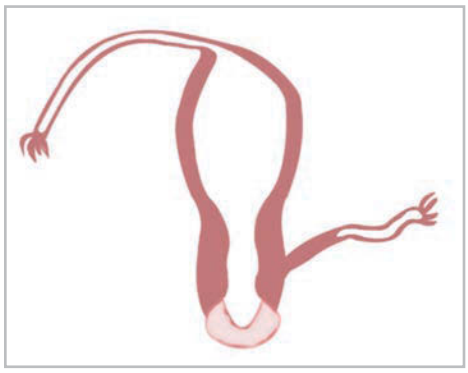

Fig. 5. Non Communicating

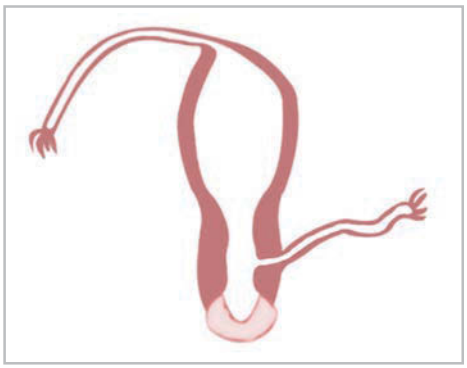

Fig. 6. Communicating

Unicornuate uteruses are often asymptomatic until menarche or until the patient becomes pregnant. Symptoms associated with a unicornuate uterus include chronic pelvic pain, dysmenorrhea, hematometra, hematosalpinx, and endometriosis. Unicornuate uterus is associated with an increased incidence of abnormalities of the urinary tract, most commonly renal agenesis on the side contralateral to the main (fully developed) uterine horn. Procedures useful in detecting and classifying a unicornuate uterus include hysterosalpingography, sonography, and MRI.

Patients with a unicornuate uterus demonstrate a significantly increased risk of complications of pregnancy. Although these patients can carry a pregnancy through to a live birth, fetal survival is estimated at around 40% of these pregnancies. Preterm deliveries in the first two trimesters, intrauterine fetal demise, spontaneous abortions, and ectopic pregnancies are common in this condition. The only Mullerian duct anomaly that has a worse outcome for pregnancy than a unicornuate uterus is a septate uterus. In the case of pregnancy in the rudimentary horn, uterine rupture is a very high risk. Interestingly, a pregnancy in a non-communicating rudimentary horn, although rare, can occur if sperm or a fertilized ovum migrate across the peritoneal cavity from the communicating (fully formed) horn to the non-communicating horn.

Unfortunately few therapeutic options are available for this condition. A number of experts recommend surgical removal of a rudimentary horn while the patient is not pregnant. When a patient with a unicornuate uterus becomes pregnant, strict increased monitoring of the pregnancy is indicated.

Special thanks to the Department of Anatomic Pathology, Kaiser Permanente South Sacramento Hospital, 6600 Bruceville Road, Sacramento, CA 95823 for permission to reproduce images and information related to this case.

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Book Review

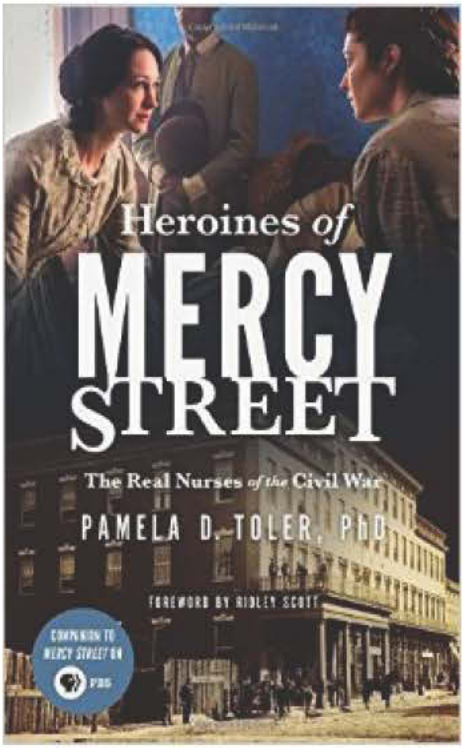
Heroines of Mercy Street
The Real Nurses of the Civil War

Written by Pamela D. Toler, PhD
Review by Chet Sloski, PA(ASCP)[CM]

When it comes to war and American casualties, the Civil War stands alone. The number of Americans killed in World War I was 116,516. In World War II the count was 405,399. The Civil War claimed an estimated 625,000 American lives. While deaths from weapons such as the Gatling gun and musket were many, diseases such as typhoid, pneumonia, yellow fever, malaria, dysentery and gangrene accounted for two-thirds of all Civil War deaths. When the war started in 1861, the Union army's Medical Bureau was blindsided by the carnage that would follow. American medicine was not up to the task. As the war raged on, the North's estimate of a ninety-day war was quickly forgotten.

In her new book, *Heroines of Mercy Street, The Real Nurses of the Civil War*, author Dr. Pamela D. Toler explores the fledgling profession of nursing as seen through the eyes of the nurses who cared for Union soldiers during the Civil War. Dr. Toler focuses on one particular Union hospital, and the nurses who passed through it. She sources the nurses' letters and diaries which affords us a first-hand glimpse into our nation's most seminal event. And although we see the war through the eyes of Union nurses, many of their general experiences almost certainly paralleled those of their Confederate counterparts.

Before the Civil War, nursing was largely an unrecognized profession in the United States. The entire state of American medicine could be described as archaic at best. Europe, however, was in the midst of a medical revolution. Although illegal in America, France enjoyed unfettered access to corpses for dissection, affording physicians a thorough understanding of the relationship between nerves, blood vessels, muscles, and organs. European physicians were amongst the best trained in the world. But in the United States, neither a medical license nor a medical degree was required to practice medicine. Many learned medicine as apprentices to older doctors. If nursing was not considered a recognized profession, medical doctors were not far ahead. Toler tells us that the American medical schools that did exist were often



more concerned with generating fees than training doctors. Those who were serious about medicine, and who could afford it, often went to study in Europe. It would be ten years after the end of the Civil War that Joseph Lister would introduce carbolic acid as the first antiseptic, and Louis Pasteur would pioneer the germ theory of disease. None of this was available to Civil War doctors. Before the Civil War, doctors relied on emetics, purgatives, bloodletting, and the painkilling properties of whiskey, which they administered in the absence of anesthesia. True, ether and chloroform were used as anesthetics for twenty years, but dosages were still a hunch and it was difficult to secure the necessary supplies on a reliable basis during wartime.

Hospitals, too, were far from the respectable institutions they are now. At the time, hospitals were basically charity institutions that served the abject poor and existed only in the largest cities. Instead, doctors often visited patients at their houses. If surgery was needed, the kitchen table was used, which, Toler tells us, was probably cleaner than a hospital operating room.

With the fall of Fort Sumter, the Civil War began on April 12, 1861. By the time the Civil War began, Dorothea Dix had spent twenty years crusading for the rights of the mentally ill. In the eighteen months before the war, she spent much of her time on the road, touring mental health facilities, lobbying state legislatures for capital appropriation and needed reform. When she heard the news that Sumter had fallen, she left for Washington. She offered to form an army corps of female nurses, which was prescient since the Union army had not even organized its own medical corps for the coming war. Dix envisioned a nursing corps similar to that pioneered by Florence Nightingale during the Crimean War.

From the beginning, Dix's vision faced the requisite misogyny of the era. The army's Medical Bureau objected to female nurses on the grounds of female modesty and lack of upper-body strength. On top of that, the army had never employed women before; nursing duties were performed by other wounded soldiers during their convalescence.

But Dix was undeterred. Her own requirements for her nurses were also somewhat misogynistic and included a preference for the middle-aged, matronly, and physically plain (homely), all of which was intended to discourage candidates from romancing wounded soldiers as well as to shield nurses against the charges of immorality or husband hunting; both of which were grounds for immediate dismissal. Such were the pressing concerns of the antebellum United States, both north and south.

Dix never controlled all the nurses in Union hospitals. Surgeons had the right to hire their own, and often did so. Some volunteer nurses bypassed the system altogether and nursed without official sanction, such as Clara Barton, who traveled to the battlefield as an independent nurse. Scores of men Barton helped would later name their daughters after her. Barton

Book Review continued on page 26 >

Board of Trustees Chair's Report

Jana Sovereign, MHS, PA(ASCP)CM
botchair@pathassist.org

The Board of Trustees is composed of nine members, each of whom serves a term of three years. The terms are staggered with three members rotating off each year. Most years one or two of the members whose terms are up choose to run for an additional term and are typically re-elected. This year, that is not the case. Our three board members with terms ending this year have chosen not to run for an additional term, and will be stepping down from the board after each serving two or more terms. During her time on the board, **Karen Riviello** has been actively involved with the Membership Committee, the new Student Subcommittee, Student Delegate Program, and organization of the annual calendar. In addition to his regular Tips and Tricks article in *The Cutting Edge* AAPA Journal, **Bill Ahlfield** has been actively involved with the *Grossing Guidelines*, and has worked closely with the Marketing and Communications Committee (MarComm) in his oversight role. **Jonathan Bakst** has been responsible for financial oversight for the AAPA during his time as the Chief Financial Officer (CFO), previously held the position of Vice Chair of the board, and served as the Public Relations (PR) Committee Chair prior to his time on the board. It has been a true honor serving with these three inspiring individuals during their time on the board, and it is with great sadness that I have to say goodbye to Karen, Bill, and Jon, and wish them well in their future endeavors. Thank you for your time served, dedication to the advancement of our profession and association, and for your friendship.

With every farewell comes a welcome, at least with regard to the AAPA Board of Trustees. In contrast to the sadness I feel saying goodbye to those departing their seats, I joyfully welcome the new, incoming board members.This year I am particularly excited as I have also worked closely with each of them over the past several years, during their time serving at the committee level. **Beth Obertino-Norwood** has been the Education Committee Chair for the past several years, with direct responsibility for CE and Conference. **Lindsay McCarley** was our Administration Committee Chair for a number of years, and **Dennis Strenk** has been involved with the *Grossing Guidelines* as a Managing Editor, in addition to his role of Editor of *The Cutting Edge* AAPA Journal. These three individuals exemplify the volunteer spirit that keeps our organization moving forward and evolving to the next level. I am excited to see where they take us! Welcome to Beth, Lindsay, and Dennis.

I would also like to thank Jennifer Perez, Mark Anderson, and Darryl Kinnear, the three additional candidates who ran in this year's election, but will not be joining the board this time around. It takes a bit of gumption and a strong commitment to run for the Board of Trustees. I encourage each of you to run again in the future and I look forward to welcoming you on to the board after one of our upcoming election cycles in the next year or so. ■

Jana Sovereign, MHS, PA(ASCP)CM works in the UCLA David Geffen School of Medicine Pathology Department as a PA. She has been a member of AAPA since 1999 and is currently serving as the Board of Trustees Chair.

Thank you to the current Board of Trustees members with terms ending at the end of 2017


Bill Ahlfeld


Jonathan Bakst


Karen Riviello

Congratulations to the new 2018-2020 Board of Trustees members announced at the San Antonio Fall Conference


Lindsay McCarley


Beth Obertino-Norwood


Dennis Strenk

Peer-Reviewed

Not an Average Bump on the Head

Joseph Pociopa, PA(ASCP)[CM]
Bronson Methodist Hospital

Members are encouraged to submit articles for The Cutting Edge. *An upload link can be found on the Publications page of the website. Earn 5 CMP points for authoring journal articles for peer-reviewed publications. Published articles are also eligible for the annual Journal Award with cash prizes!*

Patient History

A 23-year-old male presented to neurosurgery for the evaluation of a rapidly growing, non-tender, non-mobile mass on the central upper forehead. The patient's history included mild mental retardation, hypothyroidism, and anemia secondary to a duodenal ulcer. A temporal lobe resection was performed nine years prior to treat non-retractable epilepsy. The patient's mother first noticed the mass two months earlier and became concerned due to a recent dramatic change in size. The rapid growth corresponded with a decrease in appetite and slight weight loss.

Hospital Course

An MRI demonstrated a subgaleal soft tissue mass along the frontal midline. Intracranial involvement was not seen. Images showed scattered calcified foci within the lesion and underlying bony changes were evident. Specifically, small erosions were noted within the corresponding diploic space. Radiology reported a differential diagnosis that included eosinophilic granuloma, metastatic tumor, and primary bone tumor. The patient was scheduled for a bifrontal craniotomy to excise the mass and underlying calvarium. Pathology received an 8.0 x 6.0 x 1.5 cm portion of skull bone with a central 5.2 x 4.5 cm dome-shaped, soft red mass on the external surface, measuring 1.6 cm thick **(Fig. 1)**. The cut surfaces were pale tan-pink and gritty with interspersed pinpoint spaces that exuded necrotic appearing material. The underlying bone was grossly suspicious of tumor involvement. Multiple sections were submitted following decalcification.

Diagnosis

Histologic sections revealed metastatic colonic adenocarcinoma. The infiltrating neoplasm was arranged solely in tubules that extensively involved the subjacent bone and soft tissue immediately surrounding the mass. Immunostains for CDX 2 and cytokeratin 20 were strongly positive within the neoplastic cell population while an immunostain for cytokeratin 7 was negative — an immunophenotypic pattern consistent with colonic adenocarcinoma

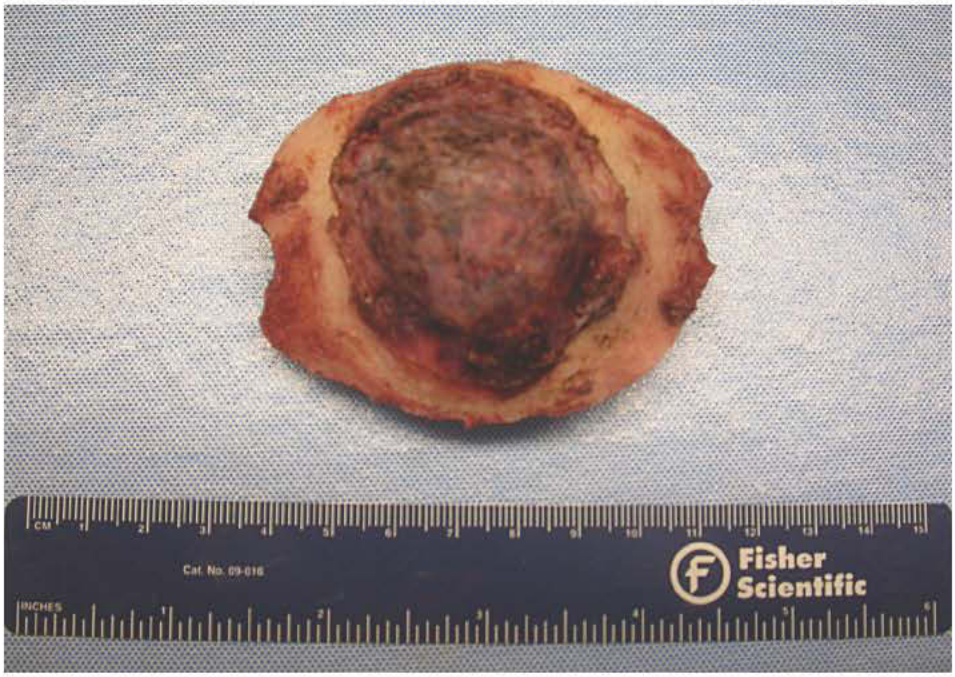


Fig. 1.

(Fig. 2). Mismatch repair proteins were evaluated immunohistochemically to establish a low probability of microsatellite instability. Additionally, NRAS, KRAS, and BRAF gene mutations were not detected. Follow-up radiologic scans revealed a perihilar mass within the left lower lobe, multiple small liver nodules and sigmoid thickening consistent with colon cancer.

Discussion

In the United States, overall rates of colorectal cancer (CRC) in patients 50 years and older have been declining consistently since the 1980s.[1] Screening colonoscopies in high risk groups are thought to be primarily responsible.[1,2] CRC is most prevalent between the sixth and seventh decades of life while less than 20% of cases are diagnosed in patients less than 50 years of age.[3] This case is undoubtedly an exception, and one that draws attention to a troubling trend: CRC is becoming more common in young adults. Multiple retrospective studies analyzed data collected between 1992 and 2010 in patients ranging from 20-49 years old. Variable annual increases in CRC were observed based on age group, sex, race and anatomic site.[1,4] The most striking inclines were noted in the youngest age group, 20-29 years, which showed a 5.2% per year increase in men and a 5.6% per year increase in women.[1] Between 1985 and 2004, rectal cancers alone rose by 3.8% per year in adults under 40 years old.[4] Perhaps the most unsettling feature of early onset CRC is the often dismal clinical outcome. In young patients, the disease tends to present at an advanced stage and, as such, is much less likely to be cured.[2,4] The tumors commonly develop in the distal colon, show poor differentiation, and usually exhibit both signet ring and mucinous features.[4] Unfortunately, the presented case exemplifies these aggressive characteristics. Metastatic bone lesions are observed in only 4-6% of CRCs and almost always signify poor prognosis.[5] Of note, hands, feet, and skull involvement account for just 17% of total bone metastases seen in advanced CRC.[5] Through an Italian based retrospective study that analyzed data from 1985-2009, Santini et al. established an 11.00 month

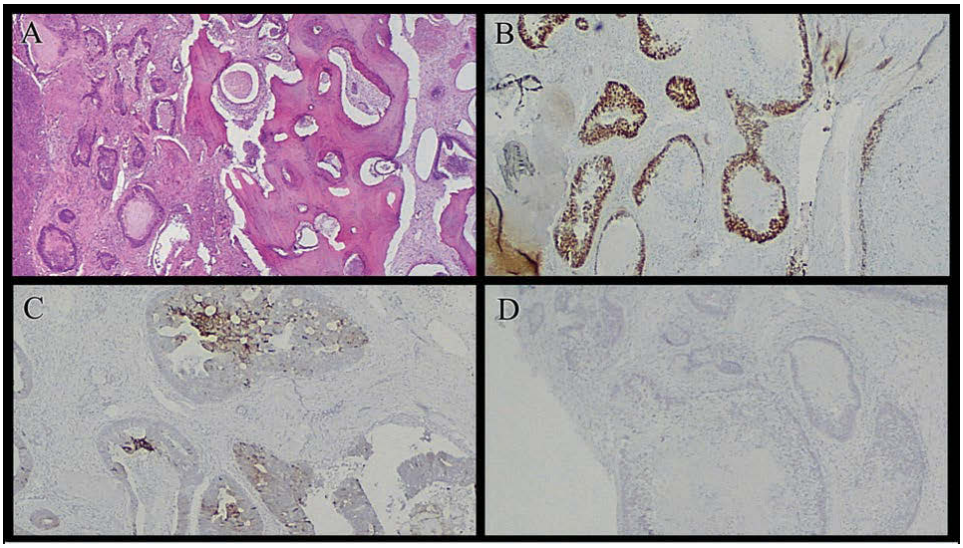


Fig. 2. A) H&E x2—Tumor involving subjacent cranial bone. B) CDX 2 x4—Positive Immunostain. C) CK20 x4—Positive Immunostain. D) CK7x4—Negative Immunostain.

median between primary CRC diagnosis and the discovery of bone metastasis.[6] The group also examined variables including tumor site, histology, stage, tumor grade, lymph node status, and use of adjuvant chemotherapy. Interestingly, tumor grade alone showed a direct correlation with the rate of bone metastasis.[6] Beginning at the time when metastatic bone lesions were first established, the same study revealed a median survival of seven months.[6]

Multiple theories have been proposed, but it seems the etiology of early onset CRC remains unclear. Surprisingly, it is estimated that known familial syndromes (e.g. Lynch, FAP) account for only 20% of the neoplasms in question.[4] Many researchers acknowledge that undiscovered forms of genetic predisposition likely play a role in these seemingly sporadic cases, and molecular data comparing early versus late onset tumors is currently scarce.[4] The most widely accepted explanation at this time points to an environmental component and suggests that sedentary lifestyle, obesity and poor diet may be largely responsible.[2,4] Consumption of processed meats, in particular, has faced much scrutiny in regard to the development of CRC and many other cancers. Occupational exposure, air pollution, and increasing pesticide use are also thought to contribute to tumorigenesis.[4]

Regardless of the cause, the discovery of early onset CRC seems to be the most significant hurdle in many cases. Due to lack of awareness and low clinical suspicion in younger patients, CRC may not be included in the differential diagnosis even when alarming symptoms are present.[2] Additionally, no early screening protocols are currently in place unless a strong family history or known condition warrant the use of colonoscopy.[2] As data compiles, research will hopefully help further identify high risk groups to enhance early onset CRC detection. In the meantime, it's difficult to speculate how we might be impacted in Pathology. Perhaps we can expect an increase in GI biopsies from patients less than 50 years old. Maybe the change we observe will be minimal or not even noticeable. However this plays out, I'm sure we can agree that everyone involved would benefit from fewer surprise metastatic tumor resections — especially such young, unsuspecting patients.

Acknowledgement

I would like to thank Dr. Kevin Herzog for his assistance with this case, and also for the use of his microscopic description included in the diagnostic section of this case study.

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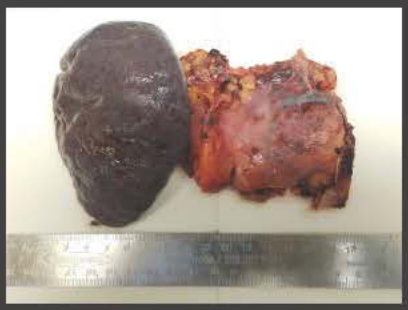
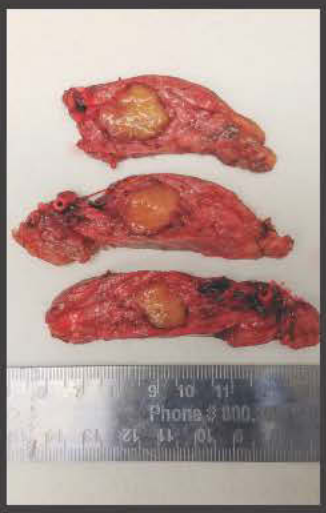
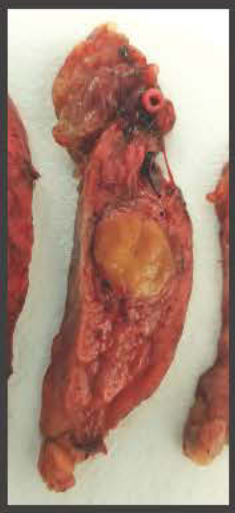
Gross Photo Unknown

A female patient presents with increasing confusion, frequent sweating, and an irregular heartbeat. The patient undergoes various blood tests and a CT scan, which shows a lesion within her pancreas.







Quiz

1. **All of the following are in the differential diagnosis, except:**
   a. Pseudocyst
   b. Adenocarcinoma
   c. Insulinoma
   d. Lipoma

2. **Pancreatic endocrine neoplasms are defined based primarily on _____?**
   a. Potential to metastasize
   b. Clinical features and associated hormonal syndromes
   c. Size alone
   d. None of the above

3. **What is the most common pancreatic endocrine neoplasm?**
   a. Insulinoma
   b. Adenocarcinoma
   c. Glucagonoma
   d. Gastrinoma

Answers found on page 27 >

Pathology Tips & Tricks

Teamwork

Bill Ahlfeld, PA(ASCP)CM

Do you have a special tip or technique that has helped you with your workday? Care to share it with your fellow PAs? Members can email their suggestions to tipsandtricks@pathassist.org. If photos will help the clarity or briefness of your tip, please include these with your message. Remember: a picture is worth a thousand words.

I have not received any tips recently and was at a loss for what to contribute to the column. Following a very timely conversation with a manager at another laboratory about our work experiences, I found my topic. *Disclaimer: The views expressed below are personal or based on my experiences and the aforementioned conversation. They do not represent any specific employer or the AAPA in any fashion.*

Since we've all been asked to define teamwork or have been asked in an interview how we function as a member of a team, what personal responsibility do we have as a member of that team? Whether the team consists of members of your gross room staff or a volunteer organization, the team's success is only as good as the individual effort and commitment put in by each member.

Many of us are familiar with the gross room example, so let's examine this a little deeper. As a member of the gross room team, do you decide to:

- Suggest ideas that would make processes more efficient or do things "the way we have always done them" just because it is easier?
- Volunteer for special projects or new tasks or do you "duck and hide" hoping you won't be asked?
- Share the caseload or look for ways to avoid taking that next specimen?
- Work at a consistent productive pace or hope that doing "just enough" will get you by?

Of course, these are just a few possibilities. Besides the clear, best choices in the examples above, what are the costs associated with making the wrong decision? Is the team affected? Do the patients suffer? Are lab issues ignored? We are all aware that any delay affects OUR patients who are anxiously awaiting their results. Each of the items in the list above contributes to this delay, but may not be as obvious as that specimen left until the next day. And what are the indirect costs to the team, to your department? Who is really being hurt by your actions? The other members of your team will have to pick up your "slack". Will they do the same to you next time? The department expenses increase without efficiency, putting staff positions or even the lab or hospital at risk of failure/closure. Will this lack of effort sustain you for a long period or is your own position in jeopardy? While I suspect the readers will see these words as blatantly obvious, my hope is that it will stimulate personal reflection or discussion on how individual effort (or lack thereof) affects more than just you. ■

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tipsandtricks@pathassist.org

Bill Ahlfeld, PA(ASCP)CM works for Health Network Laboratories as a Surgical Pathology Manager in Allentown, PA. Ahlfeld has been a member of AAPA since 2012 and is currently serving on the Board of Trustees. He has been the editor of The Cutting Edge *Tips & Tricks section since 2009.*

Mark your calendar for upcoming AAPA meetings!

7th Annual Spring Meeting
Embassy Suites by Hilton
Portland Downtown
March 12-14, 2018

44th Annual Continuing Education Conference
New Orleans Marriott
September 23-28, 2018

8th Annual Spring Meeting
Embassy Suites by Hilton
Phoenix Scottsdale
April 8-10, 2019

45th Annual Continuing Education Conference
Hyatt Regency Chicago
August 25-30, 2019

46th Annual Continuing Education Conference
Westin Fort Lauderdale Beach Resort
September 13-17, 2020

> Book Review continued from page 20

would later go on to form the American Red Cross. All in all, Dix had a hand in selecting, training, and appointing more than 3,000 nurses to serve in the Union army.

With the war in full swing, nurses had their hands full. By June 1861, 30 percent of the Union army was on sick call on account of outbreaks of infectious diseases, mostly typhoid and dysentery. The Medical Bureau requisitioned buildings throughout the Washington area, primarily hotels and schools, for use as general hospitals and medical shelters. Many of the structures were rundown, and most suffered from inadequate ventilation and flawed toilet facilities, which enlarged the problems of infectious disease. Later, the army would requisition churches, temples, the top floor of the US Patent Office, and hundreds of private homes.

As the Union casualties mounted and the realization of a protracted war became apparent, a second wave of nurses volunteered. Many had no training other than taking care of a sick family member. Many served out of patriotism or religious conviction, and looked down on those nurses who drew a salary (12 dollars a month.) Nurses served everywhere from battlefields to hospitals to transport ships that ferried the wounded to hospitals. The nurses became experts at dressing wounds, and in a pre-antibiotic era, many a soldier's arm or leg was spared amputation due to a nurse's meticulous technique. They took the time that doctors were unable or unwilling to take. In addition to their medical duties, the nurses made a point to learn the soldier's names and often helped them write to family members. Female nurses were a comfort to the soldiers, and a welcome reminder of home; even more so to those soldiers who realized they would not be going home.

Toler tells us that nurses also initiated the concept of the special-diet kitchen first introduced by Florence Nightingale in Crimea. Illnesses, such as those that affected the gastrointestinal tract, made it impossible for patients to tolerate the common diet served to active soldiers, which were often heavy, greasy, and coarse. One medical officer described it as "death from the frying pan." As was often the case with improvements put forth by women, surgeons resisted the change at first, but relented once they soon saw the positive effects of the new system.

So, what were some of the more common battlefield wounds doctors and nurses treated? Exploding cannon balls shattered soldier's arms and legs. Falling horses crushed them. They received an occasional bayonet or saber stab. But, according to Toler, musket balls caused the majority of wounds, at roughly 94 percent. The soft lead bullets known as Minnie balls caused worse damage than a modern steel-jacket cartridge might; they flattened when they met flesh, tearing through muscle and bone. Bones would splinter and shatter into hundreds of spicules. They almost always left an infected wound that would not heal and often led to amputation. Amputations, of course, were commonplace. Nurses would tell of literal piles of arms and legs stacked in corners.

Toler tells us that nurses fell into two camps on the question of caring for the enemy. Those driven by a religious need for service were generally willing to nurse the enemy. Those who enlisted out of patriotic zeal were less sympathetic to wounded Confederates. According to some nurse's writings, this amounted to nothing more than perhaps handling a Confederate patient a little rougher than normal, but even this did not last long once an empathetic nurse got to know the patient, perhaps coming to the conclusion that what side you were on was largely an accident of birth.

As Toler tells us, the longer the nurse was on the job, the more likely she was to conquer the prejudice of the doctors she worked with. Signs of progress and professionalism leisurely appeared as the war went on, one doctor and nurse at a time. Clara Barton said that as a result of the Civil War women had advanced at least 50 years beyond the position they would have been had the country remained at peace.

In 1868, the American Medical Association (founded in 1847) recommended that general hospitals open schools to train nurses. The AMA both acknowledged the value of skilled nursing in hospitals, and hoped to avoid another run of untrained volunteer nurses in future wars. The first nursing school in America actually opened during the Civil War. The New England Hospital for Women and Children was founded in 1862, and had its own nurses' training program.

For those interested, there is a new PBS series titled *Mercy Street* which is now filming its second season. The series is historical fiction set in the Civil War, and the book just reviewed is a companion to the series. ■

Chet Sloski PA(ASCP)CM works as a PA at North Coast Pathology in Oceanside, CA. He has been a member of AAPA since 1993, and he has been reviewing books for The Cutting Edge *since 2001.*

AAPA Calendar

December 1
- San Antonio Recorded Lectures

December 15
- Spring Meeting Registration Opens

December 29
- Annual CE Award Certificate Submission Deadline

January 1, 2018
- Journal Submission Deadline

January 2
- CE Article Release

January 21
- Town Hall Meeting

January 31
- Membership Renewal Deadline

February 1
- CE Article Release
- General Student Scholarship Submission Opens
- Membership Renewal Late Fee Begins

February 28
- Fellow Conference Travel Grant Deadline (moved from 1/1/18)

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Peer reviewers read through articles that have been submitted to the AAPA for various publications.

They review the articles for relevancy and accuracy. If you're interested, contact Dennis Strenk at journal@pathassist.org

Gross Photo Tutorial

Michelle Proctor Johnson, PA(ASCP)CM

Our patient was diagnosed with insulinoma, which is a predominantly benign tumor causing the increased secretion of insulin. Excess insulin decreases blood sugar, and can cause an irregular, increased heartbeat. An insulinoma is a well-differentiated pancreatic endocrine neoplasm, and can look like an invasive cancer on gross inspection. Pancreatic endocrine neoplasms are defined primarily on their clinical features, with associated hormonal syndromes. The histologic features are evaluated with the clinical findings of the patient, including looking at the serum peptide levels and immunohistochemical marking of the cells. Insulinomas demonstrate B-cell differentiation, and are the most common functional pancreatic endocrine neoplasm. These tumors present as circumscribed, soft, and red to brown. Surgical removal is the usual treatment, with patients doing well post surgery.

Gross Photo Unknown

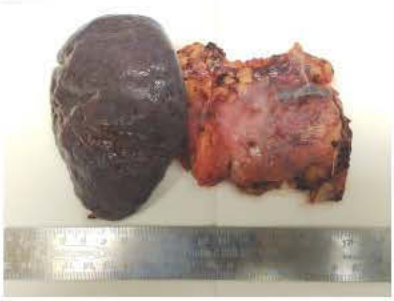
> Continued from page 24

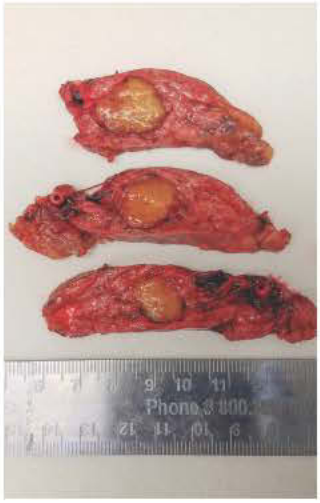
Quiz Answers:

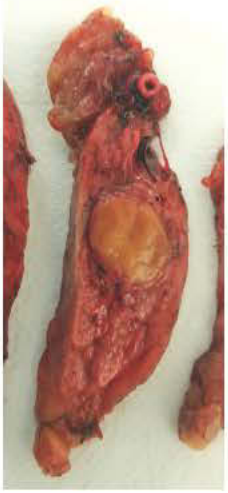
1.) A

2.) B

3.) A







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See more San Antonio Conference photos in Issue 4. Coming soon!

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