Common Artifacts That Impede Reliable Interpretation and Cause Misdiagnosis

Introduction

A large number of different types of artifacts can be seen with regularity in central nervous system surgical specimens. These can be broadly divided into three categories: 1) those that impede or even prevent diagnostic interpretation, 2) those that may be mistaken for *bona fide* pathological alterations, and 3) extraneous substances introduced into the tissue by physicians (Table 1). Some types of artifact, most prominent cautery and freeze, can either prevent reliable interpretation altogether, or can more subtly mimic pathological change depending on the severity of the artifact.

Table 1. CNS Artifacts

**Artifacts that impede interpretation**

- Postal service artifacts (gross crush, paraffin melting)
- Cautery artifact
- Freeze artifact
- Crush artifact (forceps, embedding bag/sponge/cassette)

**Artifacts that mimic pathological alterations**

- Cavitron ultrasonic aspirator (CUSA) artifacts
- Cautery
- Freeze
- Pseudomineralization
- Delayed fixation artifact
- Air-drying artifact
- Collapsed leptomeningeal vessel artifact
- Formalin pigment ("in situ hybridization" artifact)

**Extraneous iatrogenically-introduced material**

*Preoperative Embolic Agents*
Intraoperative Hemostatic Agents

Gelatin foam (Gelfoam®)
Gelatin Foam with human thrombin (Floseal®)
Oxidized cellulose (Surgicel®, Oxycel®)
Bovine collagen (Avitene®)

**Freeze Artifact**, in particular, can lead to misdiagnosis of diffuse oligodendroglioma as diffuse astrocytoma secondary to the nuclear distortion produced by freezing. An additional contributing factor to this potential pitfall is, paradoxically, the lack of a specific artifact! – the characteristic perinuclear halos, which constitute one of the hallmark diagnostic histopathologic features of oligodendroglioma, are an artifact of FFPE tissue and are lacking in frozen tissue, including frozen tissue that has been processed into paraffin. It is generally sufficient to render a diagnosis of “diffuse glioma” at the time of intraoperative consultation, with precise diffuse glioma classification and grading deferred to permanent sections.

**Cautery artifact** runs the gamut from complete tissue distortion incompatible with any meaningful evaluation at all, to milder, potentially misleading, forms in which nuclear elongation is the subtle result. Thus, with the latter situation, a predominantly round-cell tumor is transformed into a spindle-cell tumor. Careful attention to the vascular morphology usually provides a revealing clue in the form of purplish smudgy blood vessel walls.

**Cavitational Ultrasonic Surgical Aspiration (CUSA, Cavitron) Artifact.** The shearing forces and osmotic stress to which tissue resected by aspiration is subjected lead to several different types of artifact with which the surgical pathologist must be familiar. Nuclear smearing is very common and mimics necrosis. Saline, which is the irrigant used, can induce perinuclear halos and thus mimic
oligodendroglioma. In addition to these two major artifacts, extraneous material in the form of “bone dust” (microscopic fragments of cranial bone introduced into the surgical specimen by the neurosurgeon during craniotomy) and intraoperative hemostatic agents. Thus, CUSA specimens encompass the three major artifact categories of mechanical distortion (crush), osmotic (saline) distortion, and extraneous material introduction. A careful and judicious search of the CUSA tissue section will usually yield scattered well-preserved tissue fragments that are suitable for microscopic evaluation, but caution is the rule when dealing with this specimen type.

**Pseudocalcification.** Several forms of “pseudocalcification” may mislead the pathologist. The most common source, quite ubiquitous in neurosurgical specimens, is “bone dust” mentioned above with respect to its frequent presence in CUSA specimens. These microscopic fragments of cranial bone often become pressed into and surrounded by adjacent tissue fragments, thus mimicking dystrophic tissue mineralization. In re-operated patients, second resection specimens often contain bone dust fragments from the initial operation that have become entombed in a surrounding shroud of dense fibrous connective tissue, sometimes with an accompanying foreign body-type giant cell reaction.

**Pseudonecrosis.** Given the importance of necrosis as a cardinal feature of many CNS diseases, including tumors, it is important that the surgical pathologist be familiar with a number of necrosis mimics (Table 2).

**Table 2. Pseudonecrosis Etiologies**

- Lack of hematoxylin staining (simulates nucleic acid dissolution)
- Hemorrhage and/or fibrin deposition
- The normal cerebellar molecular and granular cell layers (simulate small cell tumor with necrosis on smear preparations and frozen sections)
- Degenerating hemostatic agent (particularly Avitene microfibrillar collagen)

**Preoperative Embolic Agents**
Interventional radiologists routinely introduce foreign substances into blood vessels to create embolic obstruction of flow to highly vascular lesions in order to minimize blood loss and attendant need for replacement during subsequent surgery. Preoperative embolization is typically performed on the day before surgery is scheduled to occur. Embolic agents may then appear on intraoperative cytologic
(smear) preparations and frozen sections, and on permanent FFPE tissue sections. There are several different classes of embolic agent with distinctive morphologic features that are currently in widespread neurosurgical use that the surgical pathologist may encounter. New agents continue to be introduced.

Intraoperative Hemostatic Agents
Neurosurgeons liberally use both non-resorbable and resorbable hemostatic agents to control bleeding during surgery and after closure of the craniotomy. Non-resorbable agents, such as kites and cottonoids, are removed and counted prior to closure, whereas a number of resorbable agents are designed to be left in place to mitigate chances of potentially catastrophic hemorrhage into the resection cavity following closure. Upon subsequent re-operation of recurrent tumor, residual resorbable hemostatic agent is frequently resected with the surgical specimen and thus comes to the attention of the pathologist on frozen or permanent sections in various stages of resorption with an attendant inflammatory response. As with the pre-operative embolic agents, there are several different chemical classes of agent currently employed, and most of these are recognizable by virtue of their unique morphology. One agent class, bovine collagen (Avitene) is notable for its propensity to elicit a robust eosinophilic infiltrate. This reaction is not seen in every case, but may be quite pronounced in some. Any of the various hemostatic agents may be associated with an exceptionally robust host inflammatory response during resorption that may lead to significant edema and even neurologic symptoms. Even in asymptomatic cases, the appearance on scheduled follow-up surveillance imaging studies can be striking, with new contrast enhancement and associated parenchymal vasogenic edema, to the extent that recurrent tumor is suspected and surgical resection performed. Thus the surgical pathologist must keep this type of inflammatory pseudotumor in mind when confronted with a new contrast-enhancing mass lesion arising in a previously treated brain tumor patient. Such iatrogenic inflammatory pseudotumors are referred to as “textilomas” or “gossypibomas”. Their occurrence is by no means confined to the central nervous system and has in fact been widely documented throughout the body, usually in an inadvertent “retained sponge” setting, rather than as a hemostatic agent deliberately left in place to control postoperative bleeding.

Intraoperative therapeutic wafers. Gliadel wafers are synthetic polymer wafers impregnated with a chemotherapeutic agent that are placed into the surgical cavity by the neurosurgeon following tumor (typically glioblastoma) resection to treat local tumor recurrence. The wafers are held in place along the walls of the cavity by a covering layer of hemostatic agent (typically Surgicel and/or Gelfoam). If subsequent local tumor recurrence occurs, resection of the recurrent tumor together with the wafers and hemostatic agent is often performed. Hence the surgical pathologist is likely to see these materials,
which may or may not be readily identifiable grossly, in the frozen and/or permanent tissue sections. Gliadel wafers have a very characteristic rectangular shape, resist staining with H&E, and are refractile when viewed in “tissue sections” under the microscope.

Recommended References


Brat DJ, Schniederjan MJ. Biopsy Interpretation of the Central Nervous System. Philadelphia: Lippincott Williams & Wilkins (coming in 2011)

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