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Rapid Autopsy of a Patient with Recurrent Anaplastic Ependymoma

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Abstract

Objective—To outline a procedure for obtaining a rapid autopsy in order to collect high quality post mortem tissue for genomic analysis.

Methods—This report details a bi-institutional collaborative effort in coordinating a rapid autopsy for a pediatric patient who died at home. We discuss the scientific rationale for offering a rapid autopsy to caregivers of pediatric patients as well as parental perspectives on broaching the subject of autopsy. We then review the logistics and coordination involved with planning a rapid autopsy and sequence of events needed to maximize tissue quality.

Results—We report the successful coordination of a rapid autopsy for a patient who died in the hospice setting at her out-of-state home. The time interval from death to start of the rapid autopsy procedure was 4.5 hours, despite the logistical considerations demanded by the location of the patient. Tumor aliquots and non-neoplastic tissues were successfully snap frozen for downstream genomic studies.

Significance of Results—Physicians should consider trialing a rapid autopsy program at their institution to offer to caregivers of pediatric patients. This report offers a framework to help clinicians develop their own rapid autopsy programs as well as guidelines to help streamline this process for appropriate candidates going forward.

Keywords

Pediatric; Hospice; Autopsy; Communication; Neuro-oncology

Introduction

This report details a bi-institutional experience in coordinating a rapid autopsy for a pediatric patient with anaplastic ependymoma who died at home. The goal was to quickly obtain and freeze tumor samples from multiple predetermined sites, along with non-

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neoplastic tissue, and perform more detailed analysis of the patient's tumor than a traditional autopsy. Tumor tissue was previously collected for analysis at each surgical resection. The procedure was coordinated by the oncology team, pathology department, and Institute for Precision Medicine at two institutions in collaboration with home hospice and the funeral director. We successfully collected high quality tumor and control tissue from multiple central nervous system (CNS) sites, to advance the study of anaplastic ependymoma. We discuss the logistical, scientific, and psychosocial issues that arise in an elective post-mortem procedure and suggest a framework, outlined in Figure 1, for clinicians who wish to streamline this process for appropriate candidates going forward.

Case Review

A previously healthy 3-year-old female presented with fever, emesis, neck pain, and dysarthria. Magnetic resonance imaging (MRI) revealed a 4.9 × 2.6 × 3.0 cm mass occupying the fourth ventricle. A gross total resection was achieved; pathology revealed a glial tumor with prominent true ependymal rosettes and perivascular pseudorosettes, diagnostic of ependymoma. While the tumor was predominantly compatible with a WHO grade II tumor, focal areas with higher grade features were seen. Baseline MRI spine and CSF cytology were negative. She received proton beam radiation therapy (54Gy) to the resection cavity.

Two years after initial diagnosis, MRI spine revealed a new lesion resected via lumbar laminectomy. Pathology was consistent with anaplastic ependymoma. The patient received radiation therapy to the lumbosacral spine followed by 1 year of metronomic chemotherapy (DFCI 04-343). Subsequently she developed several distinct subcentimeter intracranial nodules. Over the course of the next two years she received several chemotherapy agents including sunitinib, lapatinib, bevacizumab, oral etoposide, 5FU and gemcitabine as well as re-irradiation to the left temporal lobe and four surgical resections. Though all surgeries were primarily palliative, tissue obtained was sent for molecular profiling which helped guide further therapy decisions. Finally, the patient received a short course of azacitidine and vorinostat (Mack et al., 2014) but had neurologic decline, at which time her parents transitioned her to home hospice.

The primary oncology team members who knew the patient and the family best discussed options for post-mortem tissue collection. The family elected to utilize the rapid autopsy program at the Englander Institute for Precision Medicine (IPM) of Weill Cornell Medicine/New York-Presbyterian,(Pisapia et al., 2017) a collaborating institution who would perform post-mortem analysis of the patient's brain and spine with tissue collection for further research. Prior to death, autopsy consent was reviewed with the family. An oncology team member served as the liaison for coordination and communication among the various services. The team contacted the hospice agency and funeral home to explain the family's wish for a rapid autopsy to ensure no delay in pronouncing death; processing the death certificate; and releasing the body to the funeral home for transport to New York-Presbyterian (NYP) Hospital. The team also spoke with the admitting department at the hospital to ensure administrative signoff for autopsy could be processed at all hours. All the

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details were compiled by the liaison and emailed to all services as well as on call staff to ensure that everyone understood the sequence of events and timing required.

When the patient died at home at approximately 1:30AM, her hospice team quickly notified the IPM rapid autopsy team's pathologist on-call, processed the death certificate, and released the body to the funeral home. The body was transferred to NYP for the planned autopsy. The post-mortem interval in this case, from time of death until autopsy procedure start time was 4.5 hours, despite an off-site location of death and the need for third party transportation.

Rationale for offering rapid autopsy

Tumor tissue obtained at autopsy can provide valuable clinical information about the components of a tumor; allow for larger specimens to be collected; and allow for sampling multiple sites of disease. The advantage of performing an autopsy within a shorter post mortem time interval is that the degree of tissue degradation, and in particular RNA degradation, can be reduced and there is a higher probability of obtaining viable tumor cultures for ex vivo assays. Hence, streamlining the process from death to collection of tissue specimens is important to maximize the value of the donation. Tumor tissue can be contributed to research labs and institutions, where examination can reveal molecular mechanisms of tumor progression and resistance, and donations may lead to the creation of tumor banks and development of tumor cell lines. Post-mortem tissue collection is especially helpful in cases where tumors are not often biopsied or resected.(Alabran et al., 2013)

The majority of families of a child with cancer would prefer to be offered some form of autopsy, and none of the families who consented regretted the decision.(Alabran et al., 2013; Baker et al., 2013; Wiener et al., 2014) Among parents the overwhelming reason for consenting to autopsy was the desire to advance knowledge and find a cure for other children with their child's tumor.(Baker et al., 2013; Wiener et al., 2014)

Approaching the family

Broaching the subject of autopsy can be challenging. Clinician's report feeling guilty asking for more from the family after an unsuccessful attempt at cure and have expressed worry that unexpected findings reveal an error in clinical judgment. In addition, clinicians are often unfamiliar with the details and logistics of the autopsy procedure. Families identify lack of educational materials as a barrier to discussion.(Alabran et al., 2013) Overcoming these obstacles by educating the family and the care team is key to initiating the discussion.

Prior to initiating the discussion, clinicians should identify who will accept the tumor tissue for donation and what testing will be performed on the specimens. Hospital administration and the pathology departments can provide information about reimbursement for transportation when funds are available. Having a plan in place prior to discussion allows the family to make an informed decision. Finally, if the family agrees to autopsy, providers should then contact the appropriate members of the team including funeral home/chaplain, hospice team, social worker, hospital pathologists, and researchers to coordinate autopsy and tumor donation.

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The primary clinician who has a consistent and caring relationship with the family should initiate the autopsy discussion.(Alabran et al., 2013; Baker et al., 2013) Parents report that the most appropriate time to raise the subject is when the conversation has turned from curative to initiation of end of life care. The least desirable time is immediately before or after death, when overwhelming emotions hinder clear decision-making.(Alabran et al., 2013; Wiener et al., 2014) Clinicians can improve the autopsy discussion by: 1) being mindful of timing; 2) acknowledging that the discussion is a difficult one; 3) being compassionate during the request; and 4) using layman's terms. Many families want reassurance that the child's body will be presentable after the autopsy. Families may ask when and what information they will receive after the autopsy, and how the findings will benefit others and the medical community.(Alabran et al., 2013; Baker et al., 2013; Wiener et al., 2014)

Pre-Autopsy Coordination

Coordination between clinicians and pathologists prior to autopsy facilitates quick and accurate collection of the desired specimens at the time of autopsy. In the case described herein the patient's primary neurosurgeon coordinated with the IPM rapid autopsy team which included attending and resident pathologists, autopsy technicians, and members of the laboratory team receiving her tissue. Together they reviewed her recent MRI scans, Figure 2, to help guide gross examination during the autopsy procedure and selected seven disease sites as well as uninvolved cortex from which to procure flash frozen samples.

Rapid Autopsy Procedure

Referring to the most recent MRI, the approximate sites of interest were located. Visually, gross tissue abnormalities were evident in all the pre-identified sites, selected areas shown in Figure 3. Using procedures established by the IPM,(Beltran et al., 2015; Faltas et al., 2016; Pisapia et al., 2017) high quality neoplastic and non-neoplastic tissues were obtained.

Discussion

This case report details the process required to perform a rapid autopsy for our patient. There have been previous reports on the feasibility and usefulness of performing autopsy to collect brain tumor tissue for further study.(Broniscer et al., 2010; Kambhampati et al., 2015) Partly as a result of this case, Memorial Sloan Kettering Cancer Center now has an open institutional protocol to streamline the process of autopsy collection.

By sampling the tumor at multiple sites and time points, we are able to characterize the histological and molecular evolution of the tumor in our patient. By increasing the number of patients and samples and eventually consolidating the results in an international registry, we hope to advance our understanding of the pathophysiology of rare tumors like ependymoma. National and international cooperative groups have tumor procurement protocols (ACNS02B3 and ACRN077) and non-therapeutic protocols for living patients, which have contributed valuable data regarding disease subtypes and prognostic indicators. (Carter et al., 2008) Rapid autopsy programs (Broniscer et al., 2010; Kambhampati et al.,

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2015; Spunt et al., 2012) may add similar information but with the advantage of providing multiple high quality samples as well as normal tissue. Tumor registries for a particular disease entity serve as an important resource for consolidating data related to the disease of study.

To that end, repositories in line with tumor registries on a regional scale that are inclusive of autopsy specimens may help circumvent the tissue shortage for pediatric diseases such as ependymomas, diffuse midline gliomas, other low and high-grade gliomas, and CNS embryonal tumors.

We coordinated a rapid autopsy on our patient. The collection of tumor tissue during treatment related resections as well as additional high quality disease and normal tissue at the end of her life is allowing researchers to investigate how her tumor responded to her various therapies over time. Given the significant advances in the understanding of diffuse intrinsic pontine glioma (DIPG) through autopsy specimens, further efforts need to be made in promoting autopsy in all pediatric patients.

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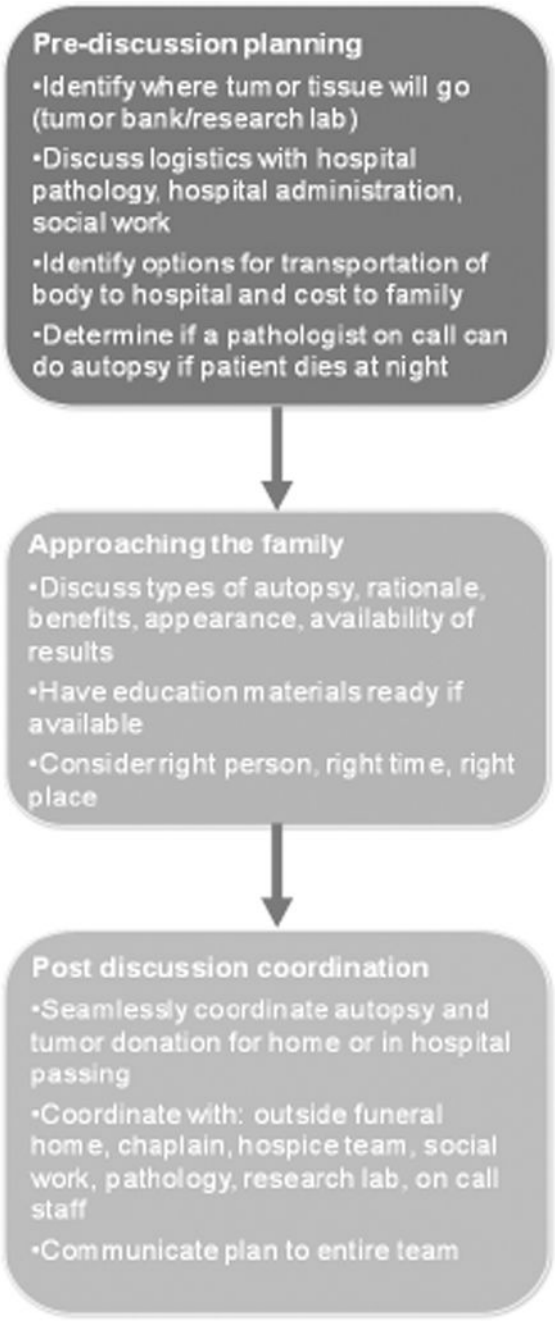

Figure 1.
Flowchart of major events necessary to coordinate a rapid autopsy

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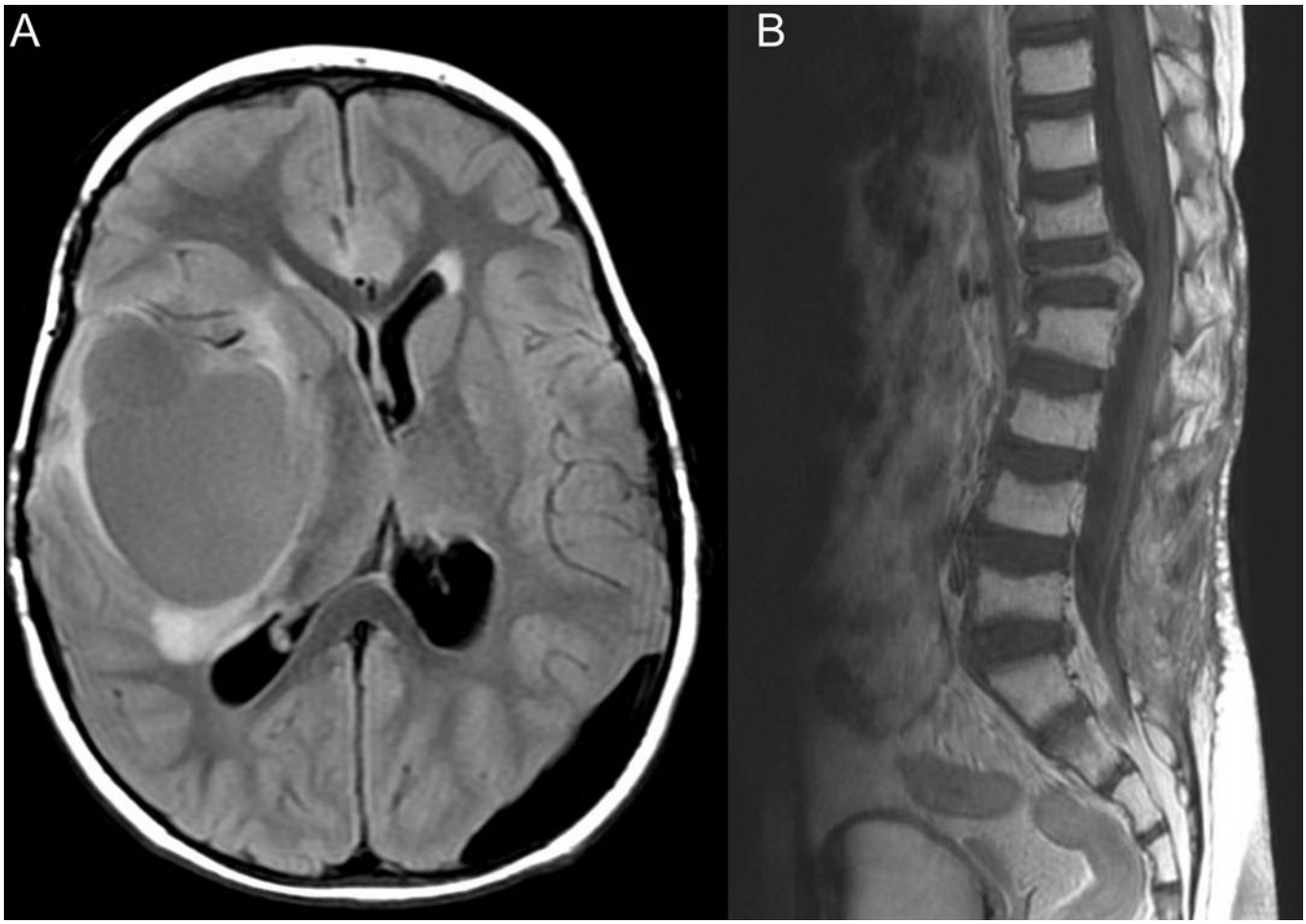

Figure 2.
MRI images, A (brain) and B (spine) used to plan autopsy tissue sampling sites

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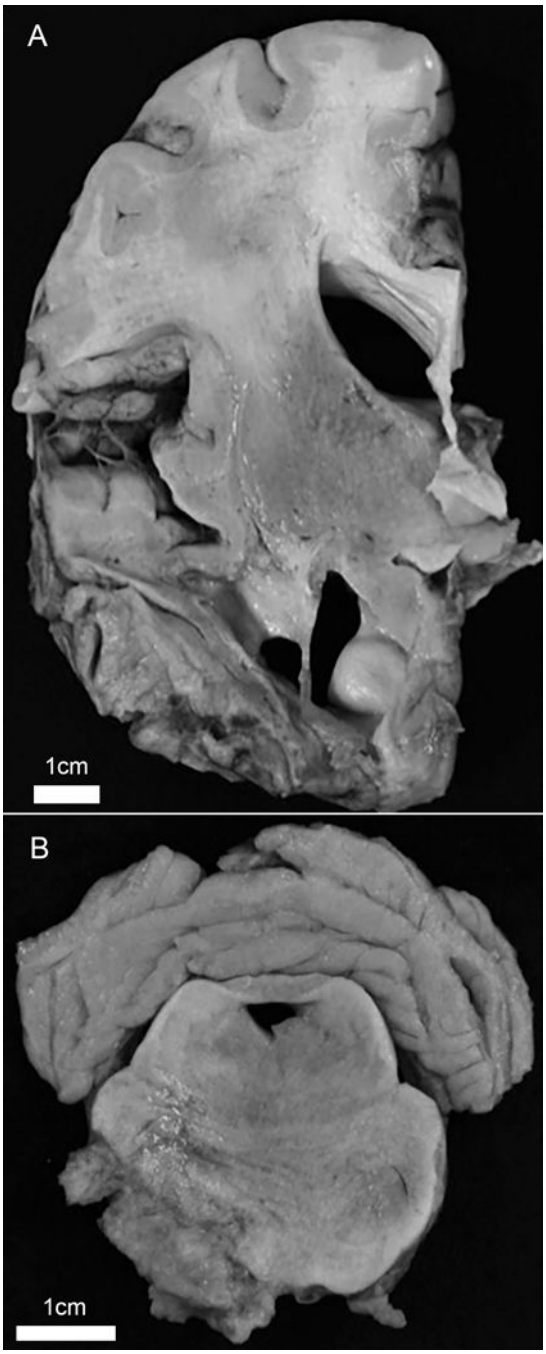

Figure 3.
Gross anatomy images, A (brain) and B (spine) from patient's autopsy