Clinical Neuropathological Conference: There's a Child in All of Us

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keywords: Cerebellum, Neuropathology, Neuroradiology, Medulloblastoma

doi:10.1017/cjn.2021.24 Can J Neurol Sci. 2021; 48: 869–873

Case Presentation, Dr Alan Chalil

A 69-year-old man with a history of hypertension, degenerative spine disease and recurrent mononucleosis presented with subacute onset of vertigo, weakness and gait instability over 4 weeks. The patient also experienced a progressive headache over the 3 weeks prior to his presentation. The headache was diffuse, non-positional and associated with photophobia but not phonophobia. Although he did not have definitive infectious symptoms, he was treated with antibiotics for a possible ear infection with no symptomatic improvement. He was noted to have mild cognitive changes in recent weeks by his wife and immediate family. He presented to the emergency department after further deterioration in his gait and multiple falls.

The patient was alert and fully oriented with a Glasgow Coma Scale (GCS) of 15. His pupils were equal and reactive at 3 mm bilaterally. His ocular movements were full and there was no nystagmus in the horizontal or vertical planes. Facial motor and sensory function was intact. There was no dysarthria. He demonstrated some slowness in finger-to-nose movements but no obvious dysmetria. There was mild dysdiadochokinesia, more pronounced on the left. He had normal bulk, tone and strength in all limbs with symmetrical reflexes, graded 2+ to 3+ throughout. Sensation to light touch was intact in all major dermatomes in the upper and lower extremities

Two of the patient's brothers had passed away from liver cancer and colon cancer, and a sister had a history of breast cancer. The patient was retired and lived with his wife. He had a distant history of smoking (5 to10 pack years, quit 45 years ago) and did not consume alcohol or recreational drugs.

Discussion, Dr Greg Cairncross

I will discuss this case in the classic manner: Where is the lesion? What is the lesion? There is an important clue to the diagnosis in the title of the case, but when it comes to "what is the lesion?" I will endeavour to consider a broad range of diagnoses in the first instance.

I have been asked to consider a brief illness in a 69-year-old man. In most areas of clinical neuroscience, and certainly in my field, age matters. It is important to remember that someone who is 69 years old is likely to get a very different illness than someone who is 9 or 29.

Our patient is right hand dominant. I highlight this because we learn later in the case that he has left sided dysmetria and dysdiadokokinesia. These subtle signs may simply reflect the use of his non-dominant hand, especially if drowsy, inattentive, or medicated for pain, or may be of localising value. His first symptom is said to be "vertigo" by the attending physicians, but what word did the patient use – probably not vertigo. Did the patient report "dizziness, light-headedness or a spinning sensation?" Only spinning dizziness has strong localising value. The weakness, as described in the case summary, is non-specific and non-localising. However, he did have an unsteady gait, and worsening headache. At 69, patients do not have new onset headache, unless it is something serious. He also had impaired and worsening cognition. The physical examination did not add a great deal to the localisation of the problem – gait ataxia and mild left sided clumsiness were noted, but there was no papilledema, aphasia, hemiparesis, sensory loss or reflex asymmetry. At this stage, I am thinking that this man has a posterior fossa mass with hydrocephalus. There are alternative localisations such as a supratentorial mass with asymmetric ventricular obstruction, or multifocal supratentorial lesions. Any of these scenarios could explain the constellation of symptoms and signs described in this case. However, I believe the principle symptoms of headache, vertigo and unsteadiness point to a problem in the posterior fossa.

Before considering other aspects of the history, let me expand further on the localisation from the perspective of a neuro-oncologist. This man has a midline syndrome likely complicated by some degree of ventricular obstruction. The differential in this regard would include a mass in the vermis of the cerebellum perhaps extending to the left in view of the subtle dysmetria. A tumour near the foramen magnum is possible, as is a neoplasm in fourth ventricle. He could also have an anterior third ventricle tumor with obstruction of the right (more than left) foramen of

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Received December 14, 2020. Final Revisions Submitted January 29, 2021. Date of Acceptance January 29, 2021.

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Monro. The lesion is unlikely to be in the posterior third ventricle because there are no eye signs.

If the posterior fossa is the location of the lesion, what might the lesion be in this 69-year-old gentleman? Brain metastasis would be a high frequency diagnosis, especially in a former smoker with a strong family history of cancer. Both brothers had cancer, possibly colon cancer, and his sister had breast cancer. The family history is noteworthy and leads me to muse about inherited cancer syndromes that can lead to brain metastasis, of course, but can also be associated with primary cancers of the central nervous system (CNS). Lynch Syndrome (hereditary non-polyposis colorectal cancer) predisposes to colon cancer and is associated with an increased risk of glioblastoma and Familial Adenomatous Polyposis predisposes to colon cancer and is associated with medulloblastoma. No degree of smoking is safe, which means this man could have lung cancer with a brain metastasis.

The pace of an illness is often helpful diagnostically. This man has a subacute illness. That said, I do not think that he has a brain abscess, prion disease, or inflammatory disorder, categories of neurological illness that might present in a subacute fashion. The pace of his illness excludes a developmental disorder such as a Chiari malformation or degenerative disease. In all likelihood it also excludes a vascular condition such as a subacute hemorrhage from a cavernoma or tumour.

I am left to conclude that he likely has a neoplastic process with an aggressive histology. I cannot fully exclude a rapidly expanding tumour-associated cyst, or quickly worsening hydrocephalus related to an indolent tumour, but I do not think he has a meningioma of the tentorium or large vestibular schwannoma. His tumour is behaving aggressively. In a 69-year-old man, one would think about a metastasis, primary CNS lymphoma, or a rare high-grade glioma. Glioblastomas can occur in the cerebellum but are rare. Additional considerations would include a medulloblastoma although they too are very uncommon at this age. A pilocytic astrocytoma in the vermis with compression of the fourth ventricle is another remote possibility. Pilocytic astrocytomas of the cerebellum in adults are typically more aggressive than in children. More remote still would be a subependymal giant cell astrocytoma or a subependymoma.

Neuroradiology, Dr Andrew Leung

We began with a computed tomography (CT) scan with contrast (Figure 1). There is a 3 cm lesion in the vermis slightly eccentric to the left. The lesion has low density with a slightly enhancing rim. We see parenchymal low density consistent with edema, and superiorly we can see the mass effect on the dorsal pons and fourth ventricle. The differential for this cystic rim enhancing lesion would include metastasis, high grade glioma or abscess.

In the subsequent magnetic resonance imaging (MRI), the T2 sequence demonstrates the same cystic lesion in the vermis with fluid signal extending posteriorly. On the diffusion image, which is very helpful in this case, we can see the lesion has a rim of high signal. There is also a second lesion with high signal in the lateral left cerebellum that cannot be appreciated on the CT or T2 images. On contrast enhanced T1 images, we can see mild enhancement in these areas, but it is not very conspicuous. We can still see some surrounding edema.

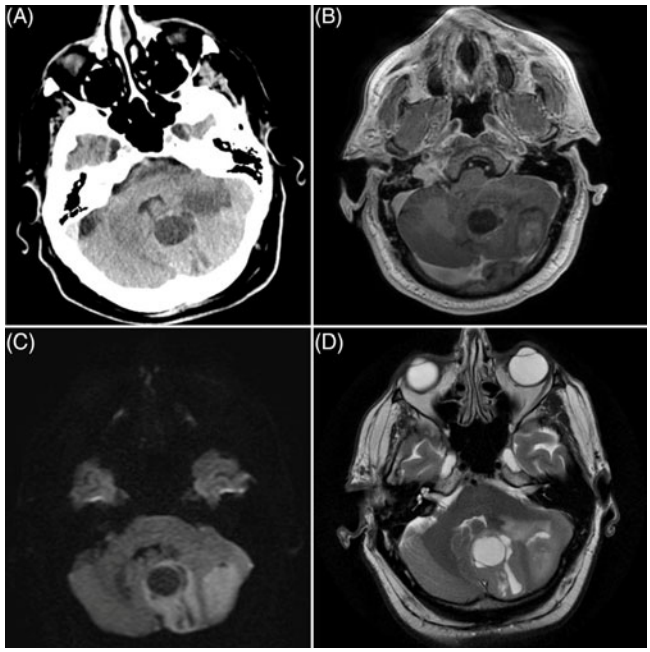

Figure 1. *Neuroradiology. Axial post-contrast CT image demonstrating a solid/cystic left cerebellar mass. Axial post-contrast T1-weighted image demonstrating a solid/cystic mass medially and a solid mass laterally. Axial diffusion trace image showing high signal in the solid component of the mass with low signal on the corresponding ADC map (not shown), indicating hypercellularity. Axial T2-weighted image demonstrating edema around the mass.*

As the fluid component is not diffusion restricting, we can strike abscess off the differential. In terms of neoplastic possibilities, given the diffusion high signal, a hypercellular tumour of some sort is likely, such as glioblastoma multiforme (GBM), metastasis from a small cell lung cancer, or lymphoma.

To assess for cerebrospinal fluid spread of disease, a complete spine MRI was performed which did not show any evidence of further disease.

Discussion, Dr Cairncross

I am pleased that the localisation is correct. An aggressive, hypercellular tumour in the cerebellum would certainly make me think of brain metastasis, primary CNS lymphoma or small cell glioblastoma. But given "there is a child in all of us", medulloblastoma must be a consideration. Adults can get medulloblastomas, but they are much less common than other aggressive hypercellular tumours of the posterior fossa, such as the ones I have mentioned. Brain imaging reveals a cystic lesion with a solid enhancing area, so I would still keep a rare aggressive form of pilocytic astrocytoma on the differential.

Neuropathology, Dr Cynthia Hawkins

This histology is pretty classic for a medulloblastoma, desmoplastic nodular pattern, given a cellular lesion with pale nodules surrounded by hypercellular areas (Figure 2). Reticulin stain was used to ensure that this is indeed a nodular tumour, with reticulin outlining each individual nodule. This feature separates this lesion from other mimickers.

https://doi.org/10.1017/cjn.2021.24 Published online by Cambridge University Press

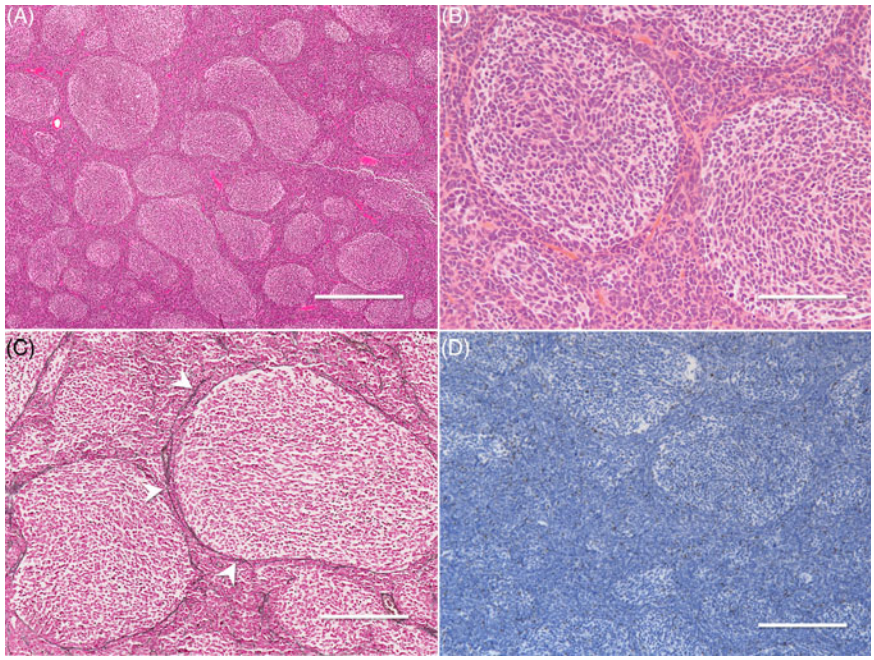

Figure 2. *Neuropathology. (A) The tumour's histology features prominent nodules that appear pale in comparison to dense internodular zones (H & E, bar = 500 μm). (B) Nodules and internodular zones are populated by small, undifferentiated cells that exhibit nuclear molding, high nucleus:cytoplasm ratios and abundant mitotic activity (H&E, bar = 100 μm). (C) Reticulin strands (arrowheads) outline the nodules, formally confirming this histoarchitectural feature (Reticulin stain, bar = 100 μm). (D) Sparse nuclei over-express P53, indicating a non-mutated "wild-type" status (anti-P53 immunoperoxidase, hematoxylin counterstain, bar = 200 μm).*

In general the nodular components tend to be more positive for neuronal markers, with small amounts of glial fibrillary acidic protein (GFAP) in the internodular components, but this lesion is not strongly GFAP-positive. The Ki67 stain shows the high proliferation rate of this lesion where the internodular components are slightly more proliferative than the nodules themselves.

We see an infiltrative pattern of tumour cells in the sub-pia in the cerebellum. In the GFAP-stained slide, we have neoplastic cells within a glial layer immediately below the pial surface. We can also see some evidence of tumour cells in the Virchow-Robin spaces. This is different from what is seen in gliomas, which tend to have cells that spread directly through the parenchyma.

The current classification of medulloblastoma is based on molecular subgroups and histology. The molecular subgroups were described by multiple groups including the Taylor group in Toronto.

At SickKids, we use a nanoString (RNA)-based medulloblastoma subgrouping assay. This assay is robust on formalin-fixed, paraffin-embedded (FFPE) tissue, with good concordance with the original gene expression-based subgrouping and has relatively low cost and rapid turn-around time. The nanoString algorithm results indicate a 100% confidence that this tumour belongs to the SHH subgroup, which is expected based on the desmoplastic nodular pattern seen earlier.

The p53 stain was negative. In a child, this would be a strong consideration, but in an older adult, it is much less likely to be a P53-mutant medulloblastoma.

In a layered diagnosis fashion, the final diagnosis is:

Resection, left cerebellar tumour:

- Medulloblastoma, SHH-activated and TP53-wildtype
- WHO grade 4
  - Desmoplastic/nodular histology
  - SHH subgroup (nanoString)
  - P53 wildtype (IHC)

Comment, Dr Cairncross

The molecular subtyping of medulloblastoma has been one of the great stories to emerge in neuro-oncology over the past decade. I think the next major advance in the care of children and adults with medulloblastoma will be highly effective molecular-subtype-specific treatments. Indeed, this is already beginning. We have learned, for example, that the WNT subtype has a very good prognosis with standard therapy. This realisation has led to studies that seek to deescalate treatment-intensity for WNT cases. Guided by the results of these trials it may be possible to reduce the dose of radiation to nervous system, or delay it safely, while still maintaining excellent tumour control and longevity for patients with WNT medulloblastomas. Future treatment of the more aggressive forms of medulloblastoma will be science-based and hopefully more effective and much less toxic than current one-size-fits-all treatment approaches.

Comment, Dr Hawkins

Checkpoint inhibitors are used in tumours with high mutational burden, and that does not usually apply to medulloblastoma, with only rare cases associated with underlying mismatch repair deficiency. Most of the phase one trials are aimed at gliomas. There was a trial that aimed at eliminating radiation

https://doi.org/10.1017/cjn.2021.24 Published online by Cambridge University Press

Table 1. Summary of reported cases of medulloblastoma in patients above the age of 60 in the literature

Study	Age	Sex	Tumour location (medial vs. lateral)	Treatment
Seitz and Operschall, 1978[8]	88	Female	Medial	Surgery + RT
Kepes et al., 1987[9]	73	Female	Lateral	Surgery + RT
Cervoni et al. 1994[10]	71	Male	Lateral	Surgery + RT
Cervoni et al. 1994[10]	67	Male	Lateral	Surgery + RT + CT
Ramsay et al. 1995[11]	66	Male	Lateral	Surgery + RT
Ramsay et al. 1995[11]	65	Female	Lateral	Surgery + RT
Salvati and Cervoni, 2000[12]	68	Male	Medial	Surgery + RT + CT
Jaiswal et al., 2000[13]	65	Male	Medial	Surgery + RT
Yong et al., 2006[14]	71	Male	Medial	Surgery + RT
Huppmann et al., 2009[15]	66	Male	Lateral	Surgery only
Snuderl et al. 2015[16]	62	Female	Lateral	Surgery + RT
Liang et al., 2016[3]	72	Female	Lateral	Surgery + RT
De et al., 2016[17]	72	Male	Not reported	Surgery + RT + CT
Murase, et al. 2018[18]	63	Female	Medial/suprasellar	Surgery + RT + CT
Sajko et al. 2004[19]	62	Male	Midline	Surgery*
Maslehaty et al. 2018[20]	71	Male	Medial	Surgery*
Maslehaty et al. 2018[20]	72	Male	Medial	Surgery*
Present case	69	Male	Lateral	Surgery*

*Patients passed away in the post-operative period before initiation of oncological treatment.

therapy for WNT medulloblastomas, but that failed. As far as we know, the good outcome for WNT is still dependent on the children receiving radiation, although they may need less than non-WNT medulloblastoma patients.

The SHH subtype has some specific inhibitors, and these were available even before subgrouping was proposed. The hardest to treat tend to be the MYC amplified group 3 and *TP53* mutant cases, the latter are linked to germline cancer mutations. Currently, all paediatric SHH patients are offered germline testing to look for such mutations.

Conclusion and Review of Topic, Dr Alan Chalil

The patient underwent uncomplicated, gross total resection of the posterior fossa mass through a sub-occipital craniectomy. His postoperative neurological status was unchanged and the management plan was to undergo cranio-spinal radiation once the surgical site was healed. The patient was reluctant to undergo further treatment. Unfortunately, he developed a wound infection requiring operative care 5 weeks after the tumour surgery and eventually succumbed to sequalae of pulmonary emboli 3 months after his initial presentation.

Medulloblastoma is the most common malignant primary central nervous system tumour in childhood, accounting for up to 20% of all intracranial masses.[1] Most patients are between 4 and 15 years of age at the time of diagnosis. Medulloblastoma is rare in adulthood, where it comprises 0.4%–1% of all CNS neoplasms.[2,3] Most adult patients with medulloblastoma are 40 years of age or younger, while a medulloblastoma diagnosis above the age of 60 is exceedingly rare.[2,3]

On reviewing the literature, 17 cases of medulloblastoma in patients above the age of 60 were identified between 1978 and 2020 (Table 1). Medulloblastomas in adults tend to take a slow, progressive course; the previously reported cases had a relatively long duration of symptoms, ranging between 1 and 18 months. This subacute presentation is consistent with the time course of the case presented in this report.

Medulloblastoma is quite heterogeneous in its histology and genetics, which is reflected in the 2016 WHO sub-classification of medulloblastoma into four subtypes: 1- WNT activated 2- SHH activated and TP53 wildtype; 3- SHH activated and *TP*53 mutant (Type 3); and 4- non WNT/no-SHH (type 4). In adults (patients above the age of 18), SHH activated/*TP*53 wildtype medulloblastomas tend to be the most common subtype. The SHH subtype can make up to 50% of all adult medulloblastoma as suggested in a recently published analysis.[4] However, in all reported medulloblastoma cases in the literature of patients above the age of 60, only four tumours were molecularly subtyped according to the 2016 WHO CNS tumour classification; all tumours were found to be type 4 (non WNT/non-SHH).

Imaging characteristics of adult medulloblastomas tend to differ in comparison to tumours diagnosed in paediatric and adolescent cases. Adult medulloblastomas tend to centre around the cerebellar hemisphere or the peduncle, and less often along the midline. These tumours also tend to have varying levels of enhancement, in contrast to the paediatric tumours which tend to be avidly enhancing.[1,5]

Two main considerations should be given when treating adult patients with medulloblastoma: first, the adult patient is more

https://doi.org/10.1017/cjn.2021.24 Published online by Cambridge University Press

likely to tolerate higher doses of radiation compared to paediatric patients, as adults are theoretically less susceptible to the side effects of higher radiation doses. Second, adults are more likely to suffer side effects of chemotherapeutic agents in comparison to paediatric patients. These side effects may also be more severe with increasing age.

Overall, previous reports demonstrate that post operative chemotherapy and radiation tend to produce the best prognostic outcomes in adult medulloblastoma patients with survival ranging from 5 to 15 years after diagnosis.[6,7]

The present case and discussion broaden the usual differential for a cerebellar mass in an older adult. This is particularly true when features on MRI suggest a primary hypercellular lesion. Our literature review confirms the rarity of the diagnosis and identifies commonalities on imaging and histopathology to our case. As additional cases accrue, clinical, radiographic, pathological and molecular correlates will optimise the future diagnosis and management of these rare tumours.

Acknowledgement

The authors wish to thank Ashley Shaw for coordinating the live interactive online version of this clinical neuropathological conference.

Conflicts of Interest

The authors claim no conflict of interest with the present publication.

Author Contributions

Author contributions toward the manuscript are as follows:
Case Presentation: AC and RRH.
Discussions: JGC.
Neuroradiology: AEL.
Neuropathology: CH.
Comments: JGC and CH.
Conclusion and Review of Topic: AC and RRH.
Preparation and Review of Manuscript Drafts: AC, JGC, CH, AEL, MH, and RRH.

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