JOURNAL OF NEUROSURGERY:
Case Lessons

J Neurosurg Case Lessons 9(19): CASE24879, 2025
DOI: 10.3171/CASE24879

Adult H3 K27–altered, H3.3 K27–mutant diffuse midline glioma affecting the conus medullaris: illustrative case

Andrei Sincari, MD,[1] Saif Yousif, MBBS,[1] Thomas Robertson, MBBS,[2,3] Yi-Tung Tom Huang, MBBS,[4] and Hamish Alexander, MBChB[1]

[1]Department of Neurosurgery, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia; [2]Department of Pathology, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia; [3]Faculty of Medicine, University of Queensland, Brisbane, Queensland, Australia; and [4]Lumus Imaging, St. Vincent's Private Hospital Northside, Brisbane, Queensland, Australia

BACKGROUND Diffuse midline glioma (DMG) H3 K27–altered is a rare CNS tumor that predominantly affects midline structures in children. A relatively new subtype of glioma, it was first classified in 2016 and was further expanded in 2021 to include 4 molecular subtypes. While reported on in children, this is the first reported case of an H3.3 K27–mutant subtype of DMG affecting the conus medullaris in adults.

OBSERVATIONS The authors report the case of a 62-year-old man with gradual onset of bladder and lower-limb dysfunction over a 6-month period. Because of the patient's synchronous diagnosis of lymphoma, CSF sampling and positron emission tomography (PET) were initially utilized. Ultimately, an open biopsy was required to yield a diagnosis of H3 K27–altered DMG. After multiple disciplinary team discussions and discussions with the patient, radiotherapy was commenced.

LESSONS H3 K27–altered DMG affecting the conus medullaris is a very rare tumor that can present with gradual-onset lower-limb dysfunction and can be difficult to diagnose on traditional imaging alone. This case emphasized the continued importance of tissue sampling, with further research required on the utility of PET, CSF sampling, and the significance of molecular subtyping on treatment response and prognosis.

https://thejns.org/doi/abs/10.3171/CASE24879

KEYWORDS conus medullaris; spinal cord; diffuse midline glioma; H3 K27–altered; H3.3 K27–mutated; adult

Spinal cord tumors are relatively uncommon, accounting for 5%–12% of all primary CNS tumors.[1] Diffuse midline glioma (DMG) H3 K27–altered is a rare CNS tumor, first classified in the 2016 World Health Organization (WHO) classification of CNS tumors. It was updated in 2021 and is currently known as H3 K27–altered.[2] Classified as a WHO grade 4 tumor, it carries a dismal prognosis, with a mean survival for adults of 16 months.[2] These tumors most often involve the midline structures of the brainstem, spinal cord, and thalamus in children and young adults, with incidence peaking at 6–10 years of age.[2] Reports of these tumors in adults are rare, particularly in the spinal cord and conus medullaris.

There have been around 100 case reports of adult H3 K27–altered DMG affecting the spinal cord; however, only 2 cases involving the conus medullaris have been reported in the literature.[3–5] By nature, these tumors affect midline structures and often have anatomical locations that make obtaining a tissue sample difficult.[6] In addition, the radiological appearances of these tumors are highly variable, resulting in a wide differential diagnosis based on imaging alone.[7]

We present a case of DMG, H3 K27–altered, located in the conus medullaris in a 62-year-old who presented with a 6-month decline in mobility. Our report is the first of its kind to incorporate ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) into the diagnosis of H3 K27–altered DMG in the conus medullaris of an adult and the first to report the diagnosis of the H3.3 K27–mutant subtype DMG in the conus medullaris.

Illustrative Case

A 62-year-old man presented with subacute onset of difficulty initiating micturition on the background of a 6-month gradual worsening of gait. His initial examination revealed a subtle weakness in his left lower limb, but his sensation, tone, and reflexes tested normal. Notably, he had had a recent admission to the hospital with saddle pulmonary embolism, necessitating anticoagulation and malignancy screening. He had a history of chronic lymphocytic leukemia for which he had not had systemic treatment and a pleomorphic dermal sarcoma of the

ABBREVIATIONS DIPG = diffuse intrinsic pontine glioma; DMG = diffuse midline glioma; FDG = F-fluorodeoxyglucose; PET = positron emission tomography; WHO = World Health Organization.

INCLUDE WHEN CITING Published May 12, 2025; DOI: 10.3171/CASE24879.
SUBMITTED December 27, 2024. **ACCEPTED** February 14, 2025.

scalp treated with resection and adjuvant local-field radiotherapy, with no evidence of recurrence. He had no significant family history.

T1-weighted MRI of the brain and whole spine, including postadministration of gadolinium, was performed initially. The sagittal section at the conus medullaris on a T1-weighted postcontrast sequence demonstrated circumferential contrast enhancement with a bulky spinal cord (Fig. 1). The axial T1-weighted postcontrast sequence demonstrated a subtle enhancing focus measuring 4 mm in diameter within the conus medullaris at T11, with surrounding hyperintensity (Fig. 2). There were no other foci of extradural, dural, or intramedullary enhancement of the brain and spine.

Initial management consisted of interval surveillance via MRI conducted at 3 months, demonstrating slight growth of the contrast-enhancing nodule. In conjunction with the patient's hematologist, a PET scan was obtained from the vertex to the thighs following FDG administration, which demonstrated abnormally high avidity within the region of the conus medullaris (Fig. 3). No other major FDG uptake was noted throughout the body to suggest a primary malignancy.

Given the patient's past medical history of chronic lymphocytic lymphoma, a CSF sample was obtained through a lumbar puncture. The results were normal and not diagnostic. Tests conducted on the CSF included flow cytometry and analyses for protein, myeline oligodendrocyte glycoprotein antibodies, IgG, oligoclonal bands, and anti-neuromyelitis antibodies.

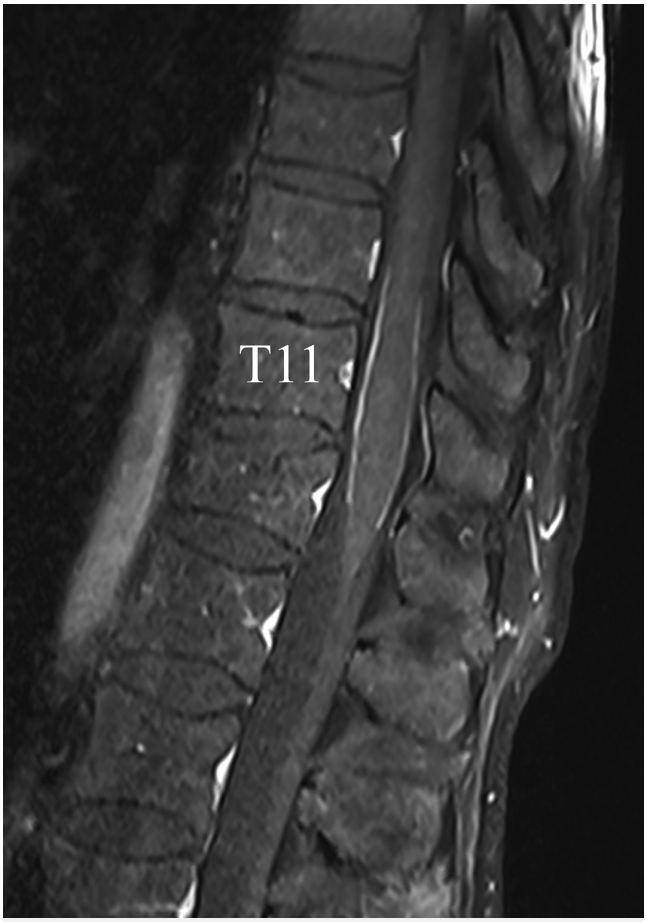

FIG. 1. Sagittal postcontrast T1-weighted MR sequence demonstrating a ring of contrast enhancement of the conus medullaris at the level of the T11 vertebral body.

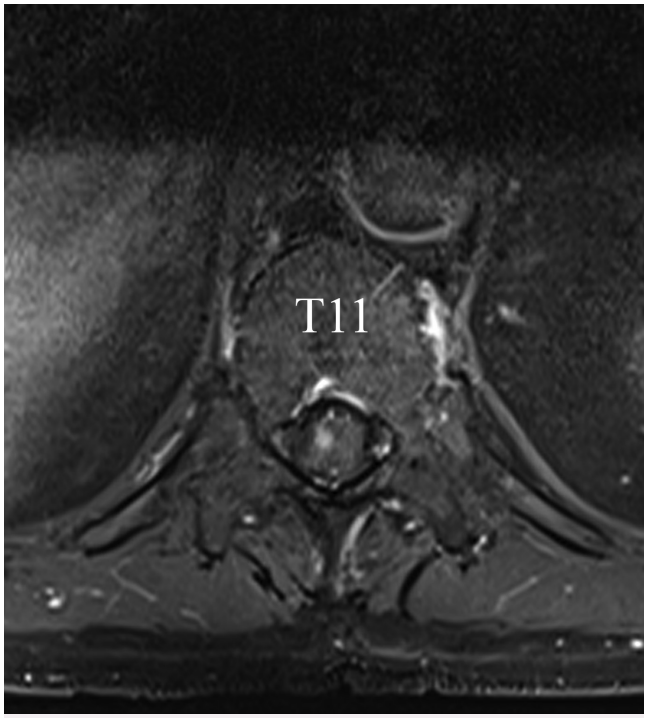

FIG. 2. Axial postcontrast T1-weighted MR sequence demonstrating a small contrast-enhancing nodule within the right anterior quadrant of the conus medullaris.

With radiological progression, the decision was made to proceed with an open biopsy. The patient underwent a T10–12 laminectomy and open biopsy targeting the contrast-enhancing component. Multimodal neuromonitoring was used throughout the operation, without a significant change in motor evoked potentials intraoperatively. Intraoperative ultrasound was utilized to help guide the biopsy. Four biopsies were taken for a frozen section, which demonstrated lesional tissue, with 2 further biopsies taken for formal histopathology. The biopsies were visibly abnormal, with a creamy appearance that was paler than the normal spinal cord. Paraffin sections confirmed a diffusely infiltrating astrocytic glioma (Fig. 4) without discernible mitotic activity and without vascular proliferation or necrosis.

The lesion was positive for the H3 K27M mutation by immunohistochemistry (Fig. 5) and demonstrated loss of the H3 K27me3 trimethylation epitope, diagnostic of a DMG, H3 K27–altered. The tumor was positive for the H3.3 K27–mutant subtype. Normal staining for ATRX was retained, and staining for p53 was in a wildtype pattern. Immunohistochemistry for the *IDH1*-R132H and *BRAF*-V600E mutations were negative.

The patient recovered well from the operation, with no further changes to his baseline neurological function; his bladder function remained altered but preserved. Unfortunately, given the rarity of this disease, there are no treatment protocols.[4] Postdiagnosis, multidisciplinary involvement with both the medical and radiation oncology teams, along with an informed decision by the patient, led to the choice to proceed with radiotherapy. The patient received 30 fractions of targeted radiotherapy at the site. Follow-up imaging demonstrated

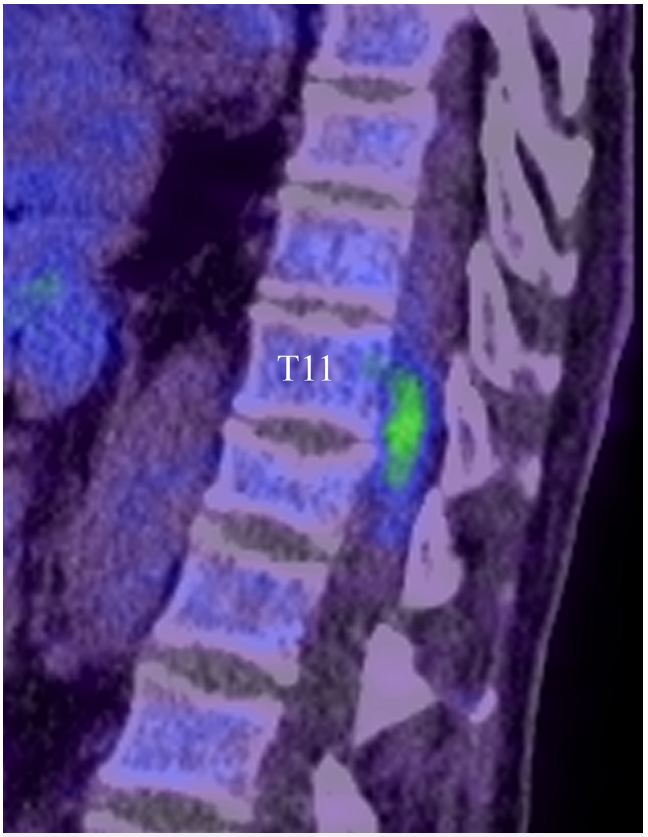

FIG. 3. Sagittal PET scan post-FDG administration demonstrating a 27 × 8–mm region of moderate avidity within the conus medullaris thought not to be physiological.

disease progression at T11–12, with a new focus on intramedullary enhancement at the level of T9. It has been more than 12 months since the initial symptom onset and index imaging. The patient continues to maintain functional independence and has been referred to palliative care.

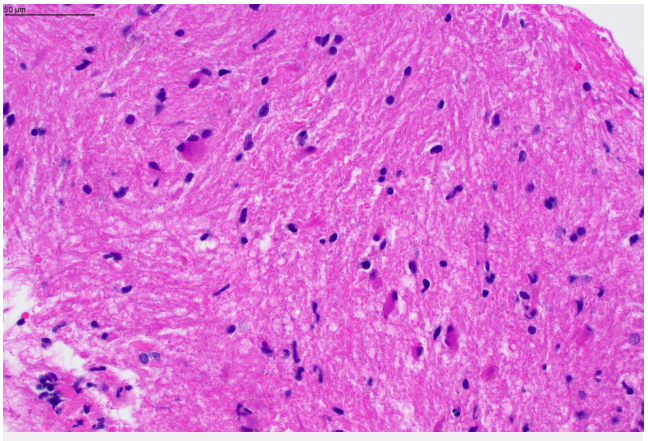

FIG. 4. H&E stain, original magnification ×400, demonstrating atypical astrocytic cells that are diffusely infiltrating the spinal cord white matter.

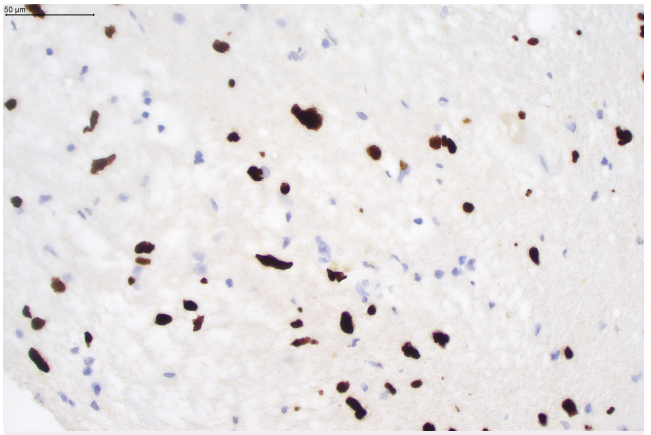

FIG. 5. Immunohistochemical stain, original magnification ×400, using the K27M mutation-specific antibody, showing strong aberrant staining of the tumor cell nuclei.

Informed Consent

The necessary informed consent was obtained in this study.

Discussion

Observations

We describe the case of a 62-year-old male presenting with bladder dysfunction and gait disturbance over 6 months, who, after a period of diagnostic uncertainty, was confirmed to have an H3 K27–altered DMG affecting the conus medullaris. Because of the tumor's relatively new classification and rarity in adults, its demographics are poorly understood. Pediatric DMGs are more commonly located within the brainstem, whereas, in adults, their reported incidence within the spinal cord could be higher.[8] A retrospective analysis of adult DMGs using an institutional glioma database demonstrated that 22% of these tumors were located within the spinal cord, with common presenting symptoms including ataxia, headache, and cranial nerve deficit.[7] The median age of these patients was 38 years, with a range of 23–68 years[7] and with only 1 of these patients being older than 55 years. The location of the tumor specifically within the conus medullaris is also extremely rare, with only a few cases being reported in the literature.[5]

As of the 2021 WHO classification of CNS tumors, there are 4 molecular subtypes of H3 K27–altered DMG, which include H3.3 K27–mutant and H3.1 or H3.2 K27–mutant, H3-wildtype with EZHIP overexpression, or DMG, EGFR-mutant.[9,10] The molecular subtype for this patient is H3.3 K27–mutated. The molecular markers include ATRX being retained, p53 wildtype, and *IDH1*-R132H negative, which appear to be typical for intramedullary astrocytoma.[11]

The radiological appearance of these tumors is also variable on MRI.[12] In a study of 61 cases of adult H3 K27–altered DMG, 8 of which involved the spinal cord, 11 had no enhancement, 25 had partial enhancement, and 25 had either diffuse or irregular peripheral enhancement. The enhancement patterns observed included ring-like, patchy, homogeneous, and cystic with nodules of contrast enhancement. In the series of Qiu et al., 8 patients had lesions within the spinal cord, with the lesions demonstrating either no enhancement or irregular peripheral enhancement.[13] The 1 case affecting the conus medullaris with a similar appearance of peripheral enhancement and

bulkiness was in a 41-year-old woman.[13] These findings are consistent with our case, which revealed a nodule of enhancement and peripheral enhancement.

In addition to traditional MRI, attempts have been made to use PET.[2] Although evidence is lacking, it appears as though DMGs are commonly FDG avid; however, the utility of this imaging is not clear as these tumors often present in regions of the CNS, and tumor FDG avidity is, therefore, masked by physiological cerebral glucose metabolism.[6] There have been several case reports of the use of FDG-PET imaging for spinal cord gliomas. One such case described a 40-year-old female with MRI equivocal but FDG-PET avidity that aided in the diagnosis of recurrent spinal ependymoma.[14] The use of FDG-PET avidity to guide biopsy location has also been investigated, with suggestions that its use improves diagnostic yield. Furthermore, increases in FDG avidity in gliomas are attributed to increased anaplasia.[6,7,15,16]

Although the use of CSF sampling, otherwise termed "liquid biopsy," was not beneficial in our case, it has been described as having both diagnostic and prognostic utility for both adults and children with primary CNS tumors,[17,18] with a potential role in DMGs. At present, there is 1 clinical trial for pediatric H3 K27–altered DMG incorporating frequent CSF sampling to monitor levels of tumor DNA as well as novel treatment agents. This trial can also help to shed light on the utility of CSF sampling for the purpose of diagnosis.[18]

The prognostic significance of the molecular subtype of DMG of the spinal cord is not well understood at this stage. However, it has been suggested that H3 K27–altered gliomas in adults can carry an improved prognosis when compared with glioblastoma at midline locations. One retrospective study of adult H3 K27–altered DMG observed that these patients demonstrated longer overall survival (17.6 months) when compared to patients with high-grade DMGs at midline locations that were K27-wildtype (7.7 months).[19] Most of the K27-wildtype midline gliomas in this study were also IDH-wildtype. There are no studies investigating the response to treatment and prognosis between different subtypes of adult DMG within the spinal cord. However, for diffuse intrinsic pontine glioma (DIPG) within the mutated (H3.3 and H3.1) subtype, an observational retrospective study of 91 patients found that tumors with the mutation in H3.1 responded better to radiotherapy than those with an H3.3 mutation, with the patients having a longer overall survival of 15 months, compared to 9.2 months for those having tumors with the H3.3 mutation.[20] Our case has shown the rapid progression of disease within the conus medullaris and surrounding spinal cord despite radiotherapy, which is consistent with the findings reported in DIPGs.

Lessons

Adult H3 K27–altered DMG affecting the spinal cord and conus medullaris is a rare entity. This is the third case of adult DMG localized to the conus medullaris described in the literature and the first to describe the H3.3 K27–mutant subtype. While PET and CSF sampling can provide utility, our case demonstrates the diagnostic uncertainty presented by this radiologically variable tumor and highlights the ongoing importance of tissue sampling. The significance of molecular subtyping for this tumor in the conus medullaris remains to be seen, and further research is needed to understand treatment responses based on the molecular subtypes.

References

1. Spinal Cord Tumor—an overview. ScienceDirect Topics. Accessed July 13, 2024. https://www.sciencedirect.com/topics/neuroscience/spinal-cord-tumor
2. Lovibond S, Gewirtz AN, Pasquini L, Krebs S, Graham MS. The promise of metabolic imaging in diffuse midline glioma. *Neoplasia*. 2023;39:100896.
3. Cheng R, Li DP, Zhang N, et al. Spinal cord diffuse midline glioma with histone H3 K27M mutation in a pediatric patient. *Front Surg*. 2021;8:616334.
4. Yabuno S, Kawauchi S, Umakoshi M, et al. Spinal cord diffuse midline glioma, H3K27M-mutant effectively treated with bevacizumab: a report of two cases. *NMC Case Rep J*. 2021;8(1):505-511.
5. Saluja S, Razzaq B, Servider JA, Seidman R, Mushlin H. Diffuse midline glioma, H3K27-altered, of the conus medullaris presenting as acute urinary retention: illustrative case. *J Neurosurg Case Lessons*. 2023;5(16):CASE22529.
6. Tomura N, Ito Y, Matsuoka H, et al. PET findings of intramedullary tumors of the spinal cord using [18F] FDG and [11C] methionine. *AJNR Am J Neuroradiol*. 2013;34(6):1278-1283.
7. Dono A, Takayasu T, Ballester LY, Esquenazi Y. Adult diffuse midline gliomas: clinical, radiological, and genetic characteristics. *J Clin Neurosci*. 2020;82(A):1-8.
8. Roux A, Pallud J, Saffroy R, et al. High-grade gliomas in adolescents and young adults highlight histomolecular differences from their adult and pediatric counterparts. *Neuro Oncol*. 2020;22(8):1190-1202.
9. Auffret L, Ajlil Y, Tauziède-Espariat A, et al. A new subtype of diffuse midline glioma, H3 K27 and BRAF/FGFR1 co-altered: a clinico-radiological and histomolecular characterisation. *Acta Neuropathol*. 2023;147(1):2.
10. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol*. 2021;23(8):1231-1251.
11. Lebrun L, Bizet M, Melendez B, et al. Analyses of DNA methylation profiling in the diagnosis of intramedullary astrocytomas. J Neuropathol Exp Neurol. 2021;80(7):663-673.
12. Huang RY, Guenette JP. Non-invasive diagnosis of H3 K27M mutant midline glioma. *Neuro Oncol*. 2020;22(3):309-310.
13. Qiu T, Chanchotisatien A, Qin Z, et al. Imaging characteristics of adult H3 K27M-mutant gliomas. *J Neurosurg*. 2019;133(6):1662-1670.
14. Singhal A, Sharma P, Karunanithi S, et al. ^{18}F-FDG PET-CT for detection of recurrent spinal ependymoma. *Nucl Med Mol Imaging*. 2013;47(1):63-64.
15. Park YW, Vollmuth P, Foltyn-Dumitru M, et al. The 2021 WHO classification for gliomas and implications on imaging diagnosis: Part 2—Summary of imaging findings on pediatric-type diffuse high-grade gliomas, pediatric-type diffuse low-grade gliomas, and circumscribed astrocytic gliomas. *J Magn Reson Imaging*. 2023;58(3):690-708.
16. Pirotte BJM, Lubansu A, Massager N, Wikler D, Goldman S, Levivier M. Results of positron emission tomography guidance and reassessment of the utility of and indications for stereotactic biopsy in children with infiltrative brainstem tumors. *J Neurosurg*. 2007;107(5 suppl):392-399.
17. Li D, Stellpflug W, Romanski K, Kilgallon M, Speck S, Saratsis AM. Ventricular cerebrospinal fluid sampling in pediatric diffuse midline glioma patients: institutional experience and review of the literature. *Front Pediatr*. 2020;8:556802.
18. ONC201 in *Pediatric H3 K27M Gliomas*. NCT03416530. *ClinicalTrials.gov*. Accessed July 16, 2024. https://clinicaltrials.gov/study/NCT03416530
19. Schreck KC, Ranjan S, Skorupan N, et al. Incidence and clinicopathologic features of H3 K27M mutations in adults with radiographically-determined midline gliomas. *J Neurooncol*. 2019;143(1):87-93.
20. Castel D, Philippe C, Calmon R, et al. Histone H3F3A and HIST1H3B K27M mutations define two subgroups of diffuse intrinsic pontine gliomas with different prognosis and phenotypes. *Acta Neuropathol*. 2015;130(6):815-827.

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Sincari, Yousif, Robertson, Alexander. Acquisition of data: Robertson, Huang, Alexander. Analysis and interpretation of data: Robertson, Huang, Alexander. Drafting the article: Sincari, Robertson. Critically revising the article: Sincari, Yousif, Robertson, Alexander. Reviewed submitted version of manuscript: Sincari, Yousif, Robertson, Alexander. Approved the final version of the manuscript on behalf of all authors: Sincari. Administrative/technical/material support: Sincari, Huang. Study supervision: Yousif, Alexander.

Correspondence

Andrei Sincari: Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia. andrei.sincari@outlook.com.