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CASE REPORT

Recurrence myxopapillary ependymoma: A diagnostic challenge

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Abstract

Introduction: Myxopapillary ependymomas are a subset of spinal ependymomas that arise almost exclusively in the conus medullaris and filum terminale, and most commonly affect young adults. However, multifocality has been described, originating in the cervicothoracic spinal cord, the lateral ventricle, the fourth ventricle, and the brain. Spinal myxopapillary ependymomas are associated with a favourable prognosis in children and adults, with 10-year overall survival rates > 90%. Many patients, however, live with persistent disease and require repeated operations and adjuvant therapy, because myxopapillary ependymomas often resist complete removal owing to locally advanced growth and/or cerebrospinal fluid–borne seeding of the thecal sac or more rostral neuraxis. *Case report:* We present a case of a 27-year-old woman who underwent gross-total resection and adjuvant radiotherapy for an L2-L3 spinal tumour, which was diagnosed histologically as ependymoma, but developed a recurrent tumour of myxopapillary ependymoma after a long-term symptom-free period. The recurrent tumour is larger, multifocal, heterogeneously enhancing and extending from the lumbar into the sacrum, resulting in local effects on the bones. Previously, the diagnosis of ependymoma was based solely on histomorphology, with no molecular confirmation of DNA methylation profiling. *Discussion:* This case highlights the importance of diagnostic accuracy when molecular testing is limited, emphasising the crucial role of clinical and histopathological correlation. Hence, a histo-molecular classification is vital for risk stratification and tailored surveillance.

Keywords: myxopapillary ependymoma, ependymoma, spinal tumour, DNA methylation profiling

INTRODUCTION

Ependymomas are primary central nervous system (CNS) tumours derived from the ependymal lining of the ventricular system. These tumours are found in both the paediatric and adult populations. They are found throughout the CNS, including the supratentorial (ST) space, the infratentorial (IT) space and the spinal (SP) compartment. They are most commonly found in the ventricular system, but also in the parenchyma of the brain.[1,2] Spinal ependymomas commonly occur along the cervical or cervicothoracic localisation, in contrast to myxopapillary ependymomas (subset of spinal ependymoma), which nearly always arise in the lumbar region, other than exclusively in the conus medullaris and filum terminale.[3] Primary tumours may be intramedullary (sometimes with an exophytic component extending into the spinal canal) or extramedullary.[4]

Ependymal tumours represent 20.6% of primary spinal tumours in children and adolescents and 17.6% of those in adults aged ≥ 20 years, according to a statistical report from the Central Brain Tumour Registry of the United States (CBTRUS). Across various studies, the median age at diagnosis of patients with spinal ependymoma ranges from 25 to 45 years. The reported M: F ratio ranges from 1:1.3 to 2.16:1.[5] Myxopapillary ependymomas occur at all ages

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but most commonly affect adults; peak case rates were found in patients aged 25–29 years and 45–59 years in one SEER Program analysis.[6]

Spinal ependymomas develop more frequently in patients with neurofibromatosis type 2 with germline nonsense and frameshift mutations in the *NF2* gene.[7] The pathogenesis of myxopapillary ependymomas is unknown. A variety of recurring chromosomal copy-number abnormalities have been described in these tumours, but no consistent structural variants or other driving mutations have been identified.[8]

Spinal ependymomas do not have clinical features specific enough to differentiate them from other spinal cord tumours. Patients often present with back pain and a myelopathy (motor and sensory deficits related to dysfunction of the spinal cord). While lower back pain, often chronic, is an almost constant manifestation of myxopapillary ependymomas, it can be accompanied by sciatica, sensorimotor deficits indicative of myelopathy, impotence, or urinary and faecal incontinence.[4]

Imaging for spinal ependymoma typically shows it as hypointense on T1-weighted images, hyperintense on T2-weighted images, and enhances with contrast. They often include areas of cystic change, haemorrhage, necrosis, and/or calcification that may produce a heterogeneous signal. Approximately 60 % of ependymomas are associated with an intramedullary cyst rostral or caudal to the tumour. Myxopapillary ependymomas have a characteristic appearance on imaging as a heterogeneous lesion with isointense cellular components and hyperintense areas of mucin production or haemorrhage (on T1 and T2). Both are well-delineated tumours.[9]

Macroscopy findings for spinal ependymomas are generally circumscribed tumours. They appear soft and are mostly grey-white in colour. They can show cystic changes, calcification, and signs of haemorrhage. Similarly, myxopapillary ependymomas are encapsulated and may be grossly gelatinous.[4]

The classic form of spinal ependymoma is composed of isomorphic glial cells with round to oval nuclei and indistinct cytoplasmic membranes. The cells are embedded in a fibrillary glial matrix and have a moderate to high cell density. A characteristic feature is the anucleate perivascular zone (pseudorosette); tumour cells are radially arranged around a blood vessel, with fibrillary processes creating the perivascular anucleate zone. Histology diagnostic criteria of spinal ependymoma have no morphological features of myxopapillary ependymoma or subependymoma. In contrast with myxopapillary ependymoma, where the radial arrangement of cuboidal to elongated tumour cells around hyalinised fibrovascular cores occurs in a papillary fashion, with accumulation of basophilic, myxoid material around blood vessels and in microcysts. Myxoid material, highlighted by Periodic Acid Schiff (PAS) and Alcian blue positivity, is useful in the identification of examples manifesting little, if any, papillary structure and composed of epithelioid cells in confluent sheets.[4] Typically, myxopapillary ependymomas show, at most, only low-level mitotic activity, and the Ki-67 labelling index usually does not exceed 2–3%.[10]

However, tumours with the histopathological features of classic ependymoma, particularly lumbosacral lesions with tanycytic or papillary patterns, may also cluster with myxopapillary ependymomas.[11,12] This reflects the fact that myxopapillary ependymomas can exhibit little myxoid change, form pseudorosettes of the usual ependymal type, and manifest spindle cell (tanycytic) features.[4]

According to the latest WHO tumour classification of Central Nervous System, ependymal tumours are now classified according to a combination of histopathological and molecular features and anatomical site. DNA methylation profiling distinguishes types of ependymal tumours at different levels of the neuraxis, dividing them into molecular groups across the three main anatomical compartments of the CNS: the supratentorial region, posterior fossa, and spine.[5] Two groups of spinal ependymomas are dominated by tumours with either a classic or a myxopapillary morphology.[7,8] A recently described type of aggressive spinal ependymoma with MYCN amplification has also been included. Myxopapillary ependymoma and subependymoma have been retained as histopathologically defined tumour types. While the cIMPACT-NOW group considered that data to inform assignment of grade to molecularly defined ependymomas are insufficiently mature, it recommends assigning WHO grade 2 to myxopapillary ependymoma.[13]

Myxopapillary ependymomas with a typical morphology are easily recognised, but these tumours also have a unique DNA methylation profile.[10,11,12] The prognostic significance of a myxopapillary ependymoma methylation profile in the context of uncharacteristic histopathological features remains to be clarified.

Recurrent gains of chromosome 16 and losses of chromosome 10 have been documented.[11]

Spinal ependymomas are associated with a favourable outcome in children and adults, with progression-free and overall survival rates of 70–90% and 90–100%, respectively, over 5–10 years. However, progression-free survival declines over time, reflecting a large number of late relapses. Extent of resection is a prognostic factor in most studies, with patients' gross total resection having favourable progression-free survival.[14,17] Spinal myxopapillary ependymomas are associated with a relatively favourable prognosis in children and adults, with 10-year overall survival rates > 90%. Many patients, however, live with persistent disease and require repeated operations and adjuvant therapy, because myxopapillary ependymomas often resist complete removal owing to locally advanced growth and/or cerebrospinal fluid–borne seeding of the thecal sac or more rostral neuraxis. Tumours arising in the conus have a poorer prognosis than cauda equina examples because the former adhere densely to the spinal cord and are less amenable to resection. Radiotherapy improves progression-free survival.[15,16]

This case highlights the issues of tumour recurrence of myxopapillary ependymoma after long-term symptom-free gross-total resected histo-morphologically diagnosed 'classical' spinal ependymoma in a setting of lack of clinical correlation and molecular confirmation of methylation profiling.

CASE REPORT

Clinical Presentation

A 27-year-old lady with a history of spinal ependymoma, WHO Grade 2, diagnosed by histopathological findings in 2015. She was presented with left lower limb weakness for 3 months and lower back pain for 6 months associated with loss of appetite and loss of weight. At that time, the MRI spine showed a spinal tumour at L2-L3. Tumour excision was done, followed by radiotherapy.

In 2023, she was presented again with increasing sacral swelling for 1 year after 8 years free of symptoms. This time, the MRI showed a huge lobulated enhancing intraspinal mass at the level of L4-S2, causing adjacent bone remodelling and erosion. A smaller, similar intraspinal lesion was also seen at the L2 level.

Radiology

MRI disclosed recurrent spinal tumours (Figure 1).

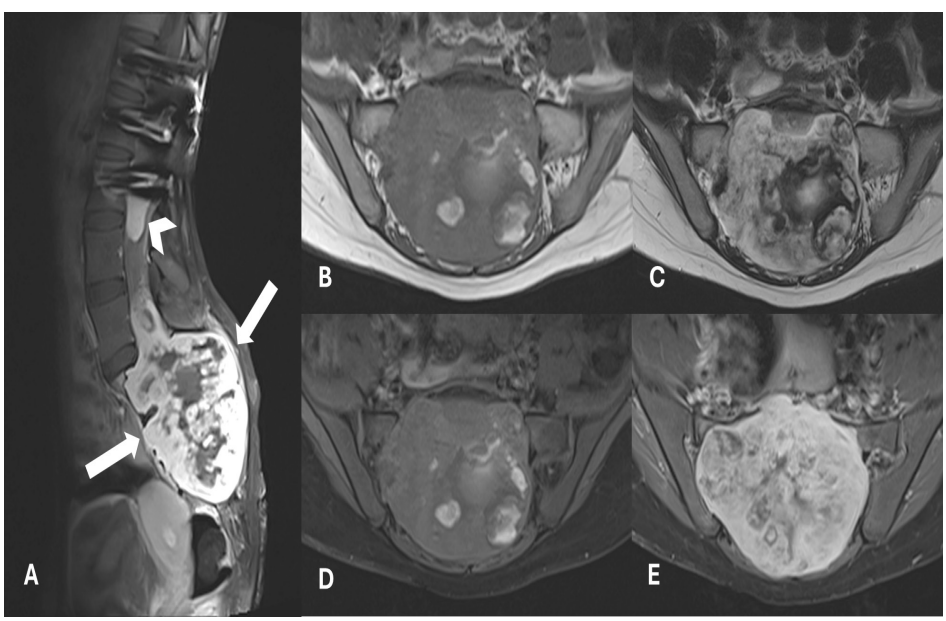

Fig 1. Sagittal T1W- Fat saturated post contrast (A), Axial T1WI (B), Axial T2WI (C), Axial T1W- Fat saturated pre contrast (D), Axial T1W- Fat saturated post contrast (E) demonstrating a large heterogeneously enhancing intraspinal mass (long white arrow) extending from L4 to S2 vertebral level, resulting in erosion and scalloping of the bones. Another enhancing intraspinal lesion is seen at the L2 level (white arrowhead).

Macroscopy
In 2015, the spinal tumour at L2-L3 was sent as multiple fragments of greyish tissue measuring 15 mm in aggregate diameter, which were entirely submitted in 1 block. The intraoperative findings were not available.

In 2023, the tumour in the sacral region measured 10 ×12cm, friable and vascularised, with a clot within, and another tumour at the L3-L4 region measuring 2 × 2cm, friable. It was sent to the laboratory in multiple pieces of brownish tissue measuring 180 mm in aggregate diameter. The tissue ranges from 5 - 80mm in size. Sectioning shows a variegated cut surface with a tan grey to brownish surface and areas of haemorrhage. Representative sections are submitted in 10 blocks. Regrossing was done, and more representative sections were submitted in another 5 blocks.

Microscopy
Both tumours in 2015 and 2023 show similar findings of moderately cellular tumour cells in a sheet pattern. The neoplastic cells show radial arrangement around hyalinized fibrovascular cores. The neoplastic cells are uniform with round to oval nuclei, fine chromatin, smooth nuclear membrane, inconspicuous nucleoli and eosinophilic cytoplasm. However, neoplastic cells in 2015 had elongated nuclei, and some of the cells had clear cytoplasm. Ependymal rosettes and perivascular pseudorosettes were present in the previous histopathological examination (HPE) in 2015. Mitosis is hardly seen. No necrosis or identifiable myxoid component. The slides in 2015 were not traceable for image capture.

However, neoplastic cells are overtly arranged in a papillary pattern in 2023, with increased mitotic figures up to 2/10 hpf in 2023, and prominent myxoid material (highlighted by alcian blue) is seen around the blood vessels, and some are in a microcyst pattern. Areas of haemorrhage and a large area of ischaemic necrosis are noted. No microvascular proliferation or spontaneous tumour necrosis is appreciated.

Immunohistochemistry
The immunohistochemistry in 2015 was not available.

Immunohistochemistry studies in 2023: The neoplastic cells are diffusely positive for Glial Fibrillary Acidic Protein (GFAP) and vimentin with patchy S100 staining. Very focal Epithelial Membrane Antigen (EMA) positivity is seen in the neoplastic cells. Ki-67 proliferative index is generally less than 1% with focal increased Ki-67 proliferation labelling up to 5% (Figure 2).

Molecular Findings
Fluorescence in situ hybridisation (FISH) analysis for the *MYCN* gene using N-MYC/CEP2 probe (ZytoLight) was done in 2023, showing non-amplified signals, i.e, consistent with Normal *MYCN* gene status.

Interpretation
The diagnosis of ependymoma, WHO grade 2, was made in 2015 based on histopathological assessment. In view of tumour recurrence at the same location as the previous tumour with extension into the sacrum, similar histomorphology and supported by the immunoprofile findings, the diagnosis was given as consistent with tumour recurrence, ependymoma WHO grade 2. After discussion with a neuropathologist, and a revised diagnosis of Myxopapillary Ependymoma, WHO Grade 2, was made.

DISCUSSION

This case highlights a recurrent tumour with non-classical morphology in the previous tumour, which led to a different diagnosis. Retrospectively, limited clinical information is available for a better correlation. The tumour sampling may not be representative of the actual tumour. There is no tumour size stated in the radiology report, and no intraoperative findings available for confirmation. The tissue sample was received in 2015, only 15mm in aggregate diameter and was only submitted in 1 block, even though the tumour has been claimed to be totally excised. In the microscopy findings, it was mentioned that the neoplastic cells have elongated nuclei arranged radially at the perivascular, but no myxoid component was identified. No higher-grade element is noticeable. Therefore, the diagnosis was given as 'classical ependymoma' at that time.

The recurrent tumour showed classical morphology, supporting a diagnosis of myxopapillary ependymoma with the presence of ischemic necrosis and increased mitotic activity. These findings support a local advanced disease, as described in the radiology report of tumour extension into the sacrum and larger tumour size, up to 10 cm and multiple tumours. In view of those tumour advanced findings, the possibility of a newly molecularly classified

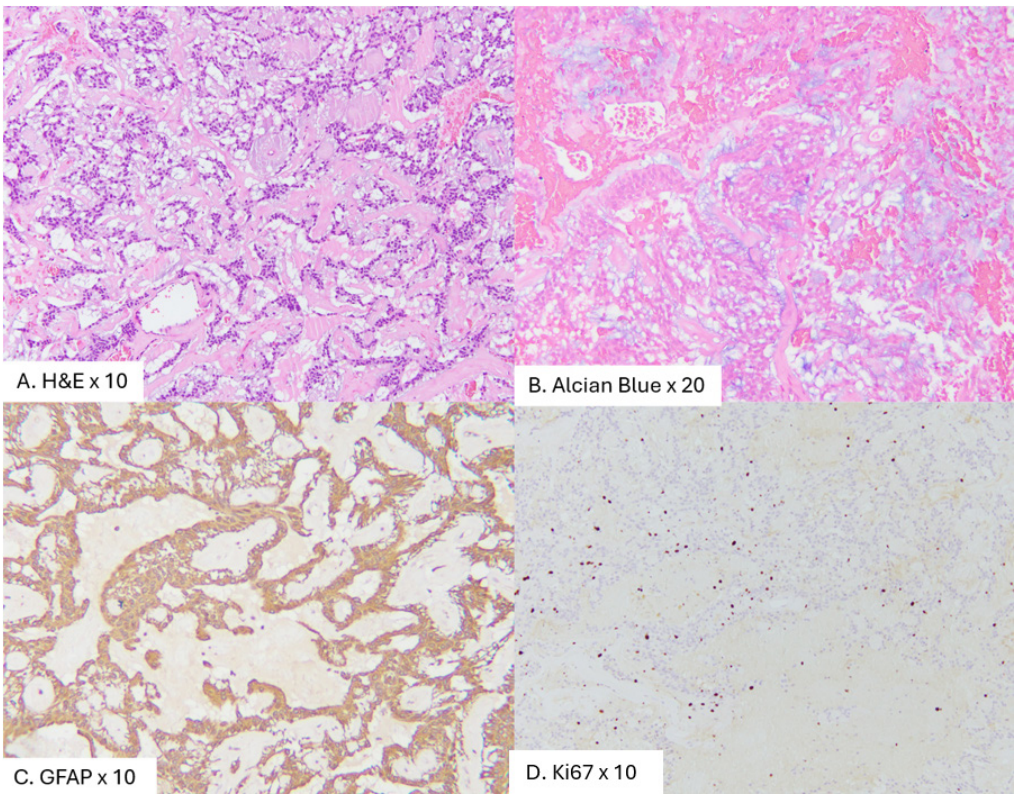

Fig 2. Uniform glial cells surround hyalinised fibrovascular cores (A), embedded in an Alcian-Blue positive myxoid stroma (B). Immunohistochemically, the tumour showed diffuse GFAP positivity (C) and focal increased Ki-67 proliferative index (~5%)(D).

spinal tumour, *MYCN* amplified, was anticipated. A molecular test was performed and showed no *MYCN* amplification. Therefore, the diagnosis of recurrent myxopapillary ependymoma was given.

Myxopapillary ependymomas with a classic morphology are easily recognised, but these tumours also have a unique DNA methylation profile. However, tumours with the histopathological features of classic ependymoma, particularly lumbosacral lesions with tanycytic or papillary patterns, may also cluster with myxopapillary ependymomas. This reflects the fact that myxopapillary ependymomas can exhibit little myxoid change, form pseudorosettes of the usual ependymal type, and manifest spindle cell (tanycytic) features. The prognostic significance of a myxopapillary ependymoma methylation profile in the context of uncharacteristic histopathological features remains to be clarified. Recurrent gains of chromosome 16 and losses of chromosome 10 have been documented.

The limited clinical information, with a lack of molecular profiling in this case, may contribute to a misleading diagnosis of the previous HPE. Thus, a possible future research direction is encouraged in anticipation of these histopathology diagnostic challenges.

CONCLUSION

Molecular examination is an important tool to diagnose a CNS tumour, especially in this molecular era. Hence, the recent WHO classification of CNS tumours included molecular findings in the diagnostic criteria, integrated with histo-morphological findings for a final diagnosis. This is to anticipate the higher rate of tumour heterogeneity in CNS tumours, for example, in the event of non-classical histomorphology findings. In the developing countries or countries which have limitations in the availability of those molecular tools, a correlation with clinical, radiology, and intraoperative findings is essential to narrow down the possible differential diagnoses. An

appropriate immunoprofile is important to support the tumour lineage and give the most possible final diagnosis.

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