Title: An unexpected disease course for a patient with diffuse midline glioma

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Abbreviations:

CNS = central nervous system

DMG = diffuse midline glioma

DIPG = diffuse intrinsic pontine glioma

$^{18}$FET-PET = 18F-fluoro-ethyl-tyrosine positron emission tomography

MRI = magnetic resonance imaging
To the editor:

Diffuse midline glioma (DMG) is the most common cause of mortality from paediatric central nervous system (CNS) tumours.\textsuperscript{1,2} Prognosis is poor, with median survival under 12 months.\textsuperscript{1,3} We present a patient with Pendred syndrome, diagnosed with DMG at 2 years, who remains asymptomatic without any treatment, 4-years post diagnosis, noting the unique co-occurrence of Pendred syndrome and DMG.

A 2-year-old male with Pendred syndrome presented with acute onset ataxia, truncal hypotonia, limb weakness, dysphagia, weak cry, reduced speech and deep tendon reflexes. Magnetic resonance imaging (MRI) revealed a well-defined mass, 28 x 28 x 21.5mm centred within the pons, inhomogeneous T2 hyperintensity, limited internal enhancement and extension into right midbrain and cerebral peduncle (Figs. 1A, 1B), consistent with DMG. Given the likely incurable nature, parents declined radiation therapy. Five months later, examination normalised, including articulation, swallowing, mobilisation and strength. Investigations for CNS demyelination were unremarkable. At 15 months, with worsening ventriculomegaly and crowding of foramen magnum (Figs. 1C, 1D), stereotactic transpeduncular biopsies were taken, post-operative imaging confirming biopsy location. Very low cellularity tissue showing focal white matter vacuolation, small numbers of infiltrating glial cells exhibiting mild nuclear atypia, one identifiable mitotic figure associated with focal increase in Ki67 index (8-10%) were identified. Immunohistochemistry for \textit{BRAFV600E, H3K27M and IDH1 were negative and ATRX and H3K27me3 retained on immunohistochemical staining. BRAF-KIAA1549 and BRAF-V600E fusion testing was negative and deep sequencing did not reveal any abnormalities. Serial MRIs demonstrated marginal size increase (Figs. 1E, 1F), whilst our patient remained asymptomatic. 18F-fluoro-
ethyl-tyrosine (\(^{18}\)FET) positron emission tomography at 3-years showed minimal diffuse \(^{18}\)FET uptake in the pontine lesion, however lower than background brain (Figs. 1G, 1H). Decision was made for clinical review and imaging. Our patient remains asymptomatic with normal neurological examination, 4 years post diagnosis, a rarely described outcome for a patient with DMG. Several international groups have reported median survival of 11 months,\(^3,4\) however small sub-groups with longer survival are reported, with 2 and 5-year overall survival rates of 9% and 2%.\(^4,5\) Favourable clinical prognostic factors include age under 3 years, prolonged interval between symptom onset and diagnosis, absence of cranial nerve palsies or long tract involvement at diagnosis.\(^1,4,5\) Our patient meets only one of these criteria. Alternate diagnoses were considered; however, MRI and histopathology were characteristic of infiltrating glioma. Case reports of pontomedullary lesions with spontaneous clinical improvement have been described in neonates and young infants, however unlike our case, have been accompanied by radiographic regression.\(^6\) The impact of concurrent Pendred syndrome is unclear and not previously described. Several cases have been reported of Pendred syndrome and thyroid carcinoma,\(^7\) however no associations with other malignancies have been described. Review of the International DIPG Registry confirmed there are no cases associated with Pendred syndrome (Fouladi M, personal communications). Pendrin is expressed in the thyroid, kidney, inner ear, airways and liver,\(^8\) yet expression in neural tissue is unknown,\(^9\) with potential for future investigation. Our patient will have close clinical and radiographic surveillance with consideration for further invasive investigation in event of symptom development.
References


Legend

Figure 1. Progression of the lesion (arrows) demonstrated on imaging. Axial T2-weighted MRI (A) and sagittal T2-weighted MRI (B) at diagnosis. Axial T2-weighted MRI (C) and sagittal T2-weighted MRI (D) 12 months post diagnosis. Axial T2-weighted MRI (E) and sagittal T2-weighted MRI (F) 3 years post diagnosis. $^{18}$FET-PET imaging, axial (G) and sagittal (H) at 3 years post diagnosis.
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