An unexpected disease course for a patient with diffuse midline glioma

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Abstract

Diffuse intrinsic pontine glioma (DIPG), now reclassified as diffuse midline glioma (DMG), is the most common cause of mortality from paediatric central nervous system (CNS) tumours. Diagnosis is made based on characteristic clinical presentation and neuro-imaging findings. Prognosis is poor, with minimal therapeutic options, reflected in a median survival of under 12 months. We present a patient with Pendred syndrome, diagnosed with DMG at 2-years of age with characteristic presentation and neuro-imaging findings, who remains asymptomatic and well at nearly 4-years post diagnosis despite progression of the primary lesion on serial imaging.

Introduction

Diffuse intrinsic pontine glioma (DIPG) is a rapidly progressive and almost universally fatal diagnosis in children. Now reclassified as diffuse midline glioma (DMG), DIPG comprises approximately 15% of all paediatric central nervous system (CNS) tumour diagnoses and is the most common cause of mortality from CNS tumours in children.[1,2] Diagnosis is often made clinically based on neurological signs, duration of symptoms and specific neuro-imaging findings. Historically biopsy was limited to atypical presentations due to concerns around complications, however recent data demonstrates that biopsy performed at experienced institutions is safe with low morbidity risk.[3,4] Despite numerous clinical trials over the last thirty years to investigate chemotherapeutic options, prognosis remains dismal, with a median survival of less than 12 months and 2-year overall survival less than 10%.[1,5-7] Focal external beam radiotherapy is the only therapy with proven survival benefit,[2,8] shown to increase survival by 3-6 months.[1] Here we present a rare case of a patient with Pendred syndrome, diagnosed with pontine glioma based on classic clinical and radiographic features, with an atypical and unexpected disease course. Pendred syndrome is an autosomal recessive disorder caused by biallelic mutation in the *SLC26A4* gene which encodes for pendrin, and is characterised by the presence of sensorineural hearing loss, goiter and an abnormal organification of iodide.[9]

Case Report

A 2-year-old male with Pendred syndrome and bilateral cochlear implants presented with acute onset ataxia, truncal hypotonia, limb weakness with reduced deep tendon reflexes, dysphagia, weak cry and reduced speech output. Magnetic resonance imaging (MRI) revealed a well-defined mass, approximately 28 x 28 x 21.5mm centred within the pons, with inhomogeneous T2 hyperintensity, limited internal enhancement and extension into the right midbrain and cerebral peduncle (Figs. 1A and 1B), consistent with a pontine glioma. The diagnosis of DMG was made based on the characteristic presentation and imaging features. A short course of dexamethasone was commenced for symptomatic benefit. Given the likely incurable nature of the diagnosis, parents declined radiation therapy and elected to visit family overseas.

Five months later, symptoms had completely resolved with normalisation of speech articulation, swallowing, mobilisation and strength. Examination revealed mild facial weakness with otherwise normal tone, power and reflexes. Repeat MRI revealed the previously described pontine mass of similar size, with diffuse T2 hyperintensity but no enhancement or diffusion restriction. In view of the differential diagnosis of CNS demyelination, further investigations were performed. Weak IgG bands resembling a monoclonal spectrotype of uncertain significance were detected in both cerebrospinal fluid (CSF) and corresponding serum, with otherwise normal CSF findings. Myelin oligodendrocyte glycoprotein and neuromyelitis optica antibodies were negative.

Serial three monthly MRIs revealed interval increase in both size and extent of diffuse T2 hyperintensity, with an increase in size of third and lateral ventricles, despite the patient remaining asymptomatic. Options of biopsy, radiotherapy or surveillance were discussed with the family, who elected to continue imaging surveillance. Clinically, the patient demonstrated mild dystonia and reduction in power in the left upper limb with associated hyperreflexia, however these findings resolved spontaneously. Repeat MRI at twelve months post initial presentation revealed further increase in size and extent of T2 hyperintense pontine mass (now 41 x 29 x 43mm) with ongoing involvement of midbrain, cerebral and cerebellar, with associated increase in mild ventriculomegaly and cerebellar tonsillar herniation (Figs. 1C & 1D). Given the worsening ventriculomegaly and crowding of the foramen magnum, decision was made to proceed to neurosurgical biopsy, 15 months post diagnosis.

Stereotactic needle biopsies were taken from the centre of the pontine lesion, via a transpeduncular route, sampling four quadrants. Two pathologists independently reviewed the biopsy and whilst one pathologist's impression was normal brainstem, the other identified very low cellularity tissue showing focal white matter vacuolation, small numbers of infiltrating glial cells exhibiting mild nuclear atypia and one identifiable mitotic figure associated with a focal increase in the Ki67 index (up to 8-10%) (Fig. 2). Immunohistochemistry for BRAFV600E, H3K27M and IDH1 were negative and ATRX and H3K27me3 were both retained on immunohistochemical staining. *BRAF-KIAA1549* and*BRAF-V600E* fusion gene testing was negative and deep sequencing on the tumour specimen did not reveal any abnormalities. Post-operative imaging confirmed biopsy location within the lesion.

Serial three monthly MRIs continued to demonstrate marginal increase in size of the lesion, with stable ventriculomegaly and mild descent of cerebellar tonsils. During this time, the patient remained asymptomatic, progressing with developmental milestones, with an unremarkable neurological examination. MRI just prior to 3 years post diagnosis revealed a new focal syrinx at C4/5, with the pontine lesion measuring 33 x 51 x 59mm, with otherwise stable imaging characteristics (Figs. 1E & 1F). Further assessment was performed with an 18F-fluoro-ethyl-tyrosine positron emission tomography (^{18}FET-PET) scan, which showed minimal diffuse^{18}FET uptake in the pontine lesion, slightly more prominent centrally, however overall activity was less than background brain activity (Figs. 1G and 1H). As there was no evidence of a highly metabolically active lesion further biopsy was not undertaken.

Given these findings, in an otherwise asymptomatic, thriving young boy, decision was made for clinical review and surveillance imaging with treatment to be re-discussed if symptomatic. At most recent review, 46 months post initial diagnosis, the patient remained asymptomatic with normal examination.

Discussion

This case demonstrates a rarely described outcome for a patient with Pendred syndrome and DMG. Several international groups have reported a median survival for DMG of 11 months in the paediatric population.[5,6] However small sub-groups of patients with longer survival have been reported, with 2 and 5-year overall survival rates of 9% and 2% described respectively[6,7]. Favourable clinical prognostic factors described include young age (under 3 years) at diagnosis, prolonged interval between symptom onset and diagnosis, absence of cranial nerve palsies or long tract involvement at presentation[1,6,7]. Our patient meets only meets one of these criteria, diagnosed at age 2 years after a sudden onset of symptoms. Furthermore, our patient remains completely asymptomatic with normal development and neurological examination nearly 4-years

post diagnosis without receiving any treatment.

Given the unexpected disease course, alternate diagnoses were considered at several timepoints and drove the decision for biopsy. However, MRI features of the tumour such as the location within the pons with extension to the midbrain, T2 hyperintensity and limited enhancement, together with the pattern of progression were all highly characteristic of DIPG. Furthermore, histopathology features were consistent with an infiltrating glioma. Given the incongruence between clinical status and findings on neuro-imaging and pathology, functional imaging was utilised to provide dynamic assessment of the tumour to aid in decision making, however was not informative in this patient.

The impact of the concurrent Pendred syndrome in this patient is unclear. Pendrin is known to be expressed in the thyroid gland, kidney, inner ear, airways, mammary gland, testis, endometrium and liver[10], however whether it is expressed in neural tissue is unknown[11]. There have been several reported cases of Pendred syndrome and thyroid carcinoma[12], however no associations with other forms of malignancy have been described. Review of the International DIPG Registry confirmed that there are no reported cases associated with Pendred syndrome in their records (Fouladi M, personal communications).

Our patient will continue to have close clinical and radiographic surveillance with consideration for further invasive investigation in the event of symptom development.

Conflict of Interest

Dr JR Hansford has received funding from Bayer Pharmaceuticals for consulting services for an unrelated project.

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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.

Figure 2. Stereotactic needle biopsy cores showed (A) low cellularity brainstem tissue with focal white matter vacuolation. (B) A rare glial cell showed a mitotic figure (yellow arrow) and apoptosis however there was no hypercellularity, microvascular proliferation or necrosis. (C & D) Immunohistochemistry for Ki67 revealed a focal increase in the Ki67 index at one end of a core, highlighted in (D) of up to 10%. (A) H&E stain, x50 mag, (B) H&E stain, x200 mag, (C) Ki67 immunohistochemistry, x100 mag, (D) Ki67 immunohistochemistry x400 mag.