Integrated Genomic Characterization of a Pineal Parenchymal Tumor of Intermediate Differentiation

Yun Jee Kang[1], Wenya Linda Bi[3], Adrian M. Dubuc[4], Louine Martineau[8], Azra H. Ligon[4], Aaron L. Berkowitz[5], Ayal A. Aizer[6], Eudocia Q. Lee[2], Keith L. Ligon[1,7], Shakti H. Ramkissoon[1,7], Ian F. Dunn, MD[3]

■ BACKGROUND: **Pineal parenchymal tumors of intermediate differentiation (PPTIDs) are rare lesions. The differential diagnosis and management strategy for PPTIDs can be challenging because of the variable prognostic and pathologic characteristics of these tumors.**

■ METHODS: **A 24-year-old man presented with progressive headaches, gait abnormalities, and abulia. Magnetic resonance imaging revealed a large T1-hypointense, T2-isointense, contrast-enhancing, partially cystic mass of the pineal and tectal region. Near-total resection was achieved in a 2-stage operation followed by focal and craniospinal irradiation and adjuvant chemotherapy.**

■ RESULTS: **Immunohistochemical analysis including use of pineal lineage marker confirmed a diagnosis of PPTID. Targeted exome sequencing showed mutations in *TSC1*^{L388P} and *IKZF3*^{F206C}, whereas high-resolution array cytogenetics revealed losses in chromosomes 2, 3, 4, 8, 10, 11, 17, and 20, leading to single-copy loss of *PTEN* and *TP53*.**

■ CONCLUSIONS: **Pineal parenchymal tumors reflect a broad spectrum of malignancy potential and prognoses, which mandate better understanding of the disease mechanism for rational therapeutic strategies. We present a case of PPTID and report several mutations and chromosomal abnormalities previously unrecognized in this tumor subtype. Review of the literature highlights a need for surgical resection followed by adjuvant chemoradiation. Further investigation of these novel variants may improve understanding of the pathogenesis underlying pineal parenchymal tumors.**

INTRODUCTION

Pineal parenchymal tumors (PPTs) represent a rare and diverse group of tumors with variable clinical presentation and outcomes. Pineal parenchymal tumors of intermediate differentiation (PPTIDs) bridge the spectrum of disease between slow-growing, well-differentiated pineocytomas and overtly malignant pineoblastomas. PPTIDs can occur at all ages but are observed more frequently in adults (23, 37, 47). They are classified as grade II or III, based on mitotic index, presence of necrosis, and proliferative indices, with a 5-year overall survival of 39%–74% (12, 23, 34). The significant heterogeneity represented by PPTIDs challenges prognostication and management strategies (Table 1) (2, 4, 6, 9, 12-16, 20, 22-25, 27, 28, 30, 32, 35-37, 40, 44, 47-49, 51, 53, 54, 60, 61, 64). We report a case of an aggressive PPTID and its genomic profile and discuss pathologic features and management strategies for this heterogeneous disease entity (2-56, 58-62, 64).

MATERIALS AND METHODS

A 24-year-old man presented with progressive headaches, gait abnormalities, and abulia over the course of 1 year. Physical examination was notable for psychomotor slowing, anisocoria with left-sided mydriasis, restricted upgaze, left pronator drift, dysmetria, intention tremor, hypophonia, limited speech output, and

Key words
- Clinical management
- Genomics
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Abbreviations and Acronyms
PPT: Pineal parenchymal tumor
PPTID: Pineal parenchymal tumor of intermediate differentiation

From the [1]Center for Molecular Oncologic Pathology, Department of Medical Oncology and [2]Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [3]Department of Neurosurgery, [4]Division of Cytogenetics, Department of Pathology, [5]Department of Neurology, [6]Department of Radiation Oncology, [7]Division of Neuropathology, Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; and [8]Hôpital Universitaire de Mirebalais, Mirebalais, Haiti

To whom correspondence should be addressed: Ian F. Dunn, M.D. [E-mail: idunn@partners.org]

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Table 1. Summary of Select PPTID Cases Reported in the Literature

Reference	Number of Patients	Histology Observed (*n*)	Positive Immunostain (*n*)	Primary Treatment (*n*)			Recurrence (n)/Mean Time to Recurrence	Secondary Treatment	Survival (months)—Mean, Median, Range
				Surgery (EoR)	Chemotherapy	Radiation			
Schild et al., 1993 (47)	6	NA	NA	5 (2 GTR, 1 STR, 2 Bio)	2 (1 VCR/CCNU/PRD, 1 VCR/CCNU/CDDP)	6 (4 WBRT + local; 2 CSI)	1 (NA)	NA	NA
Jouvet et al., 1994 (22)	9	Clublike processes (2), Homer-Wright rosettes (2), interstitial cells (2), neurite processes (8), pineocytomatous rosettes (3)	CGA (5), GFAP (3), NF (4), SYP (4), S100 (2)	9 (7 GTR, 2 STR)	NA	6 (NA)	NA	NA	70.2, 48, 8—168+
Mena et al., 1995 (37)	3	Flexner-Wintersteiner rosettes (3), Homer-Wright rosettes (3)	NA	2 (1 Bio, 1 NA)	0	2 (NA)	1 (9 months)	NA	24, 24, 2—46+
Matsumoto et al., 1995 (36)	1	NA	NA	1 (Bio)	0	1 (local/36 Gy)	NA	NA	8+
Chang et al., 1995 (6); Lutterbach et al., 2002 (35)*	2	NA	NA	2 (2 STR)	1 (CCNU/CDDP/VCR)	2 (1 CSI + local/72 Gy; 1 CSI + local/102 Gy)	1 (21 months)	0	58.5, 58.5, 55—62+
Kurisaka et al., 1998 (30)	2	NA	NA	2 (NA)	2 (CDDP/VLB/BLEO)	2 (local/25 Gy; GKRS/20 Gy)	1 (25 months)	1 (chemo—CDDP/VLB/IFO; RT—25 Gy)	30, 30, 25—35+
Tsumanuma et al., 1999 (54); Tsumanuma et al., 2009 (53)*	4	Atypia (1), Homer-Wright rosettes (2), necrosis (1), neurite processes (2)	CGA (2), NF (3), SYP (3)	3 (3 GTR)	0	4 (NA)	2 (55 months)	Bio, RT; RT, chemo	140.8, 135.5, 124—168
Jouvet et al., 2000 (23)	33	Diffuse (13), lobulated (11), mixed (2), transitional (7)	CGA (22), GFAP (12), NF (17), NSE (27), SAg (3), SYP (30), S100 (12)	32 (16 Bio, 9 GTR, 7 STR)	NA	NA	9 (51.9 months)	0	55.0, 39.6, 0—246
Fauchon et al., 2000 (12); Lutterbach et al., 2002 (35)*	28	NA	NA	27 (5 GTR, 10 STR, 12 Bio)	6 (2 ETO/CDDP, 3 M7, 1 ETO/CBCDA, 1 ETO/DBD/5-FU, 1 MTX)	23 (NA)	15 (54.3 months)	9 (8 chemo; 1 chemo, RS, Sx)	67.0, 40.5, 4—246+
Lutterbach et al., 2002 (35)	1	NA	NA	1 (Bio)	0	1 (CSI + local/96.0 Gy)	0	0	38+

NA, not available; CGA, chromogranin A; GFAP, glial fibrillary acidic protein; NF, neurofilament; SYP, synaptophysin; S100, S-100 protein; NSE, neuron-specific enolase; SAg, retinal S-antigen; MAP2, microtubule-associated protein 2; PP1—PPI7, protein phosphatase 1—7; TUBB3, class III beta tubulin; VIM, vimentin; AE1/AE3, cytokeratin AE1/AE3; MGMT, O^6-methylguanine DNA methyltransferase; NeuN, neuronal specific nuclear protein; CD56, neural cell adhesion molecule; EoR, extent of resection; GTR, gross total resection; STR, subtotal resection; Bio, biopsy; NTR, near-total resection; VCR, vincristine; CCNU, lomustine; PRD, prednisone; CDDP, cisplatin; VLB, vinblastine; BLEO, bleomycin; ETO, etoposide; M7, 8-drug treatment; CBCDA, carboplatin; DBD, dibromodulcitol; 5-FU, 5-fluorouracil; MTX, methotrexate; ICE, ifosfamide, etoposide, carboplatin; CTX, cyclophosphamide; ACNU, nimustine; VDS, vindesine; IFN, interferon; WBRT, whole-brain radiation therapy; CSI, craniospinal irradiation; GKRS, Gamma Knife radiosurgery; LINAC, linear accelerator; WVI, whole-ventricular irradiation; IFO, ifosfamide; RT, radiotherapy; Chemo, chemotherapy; RS, radiosurgery; Sx, surgery; PCB, procarbazine.

*Information updated as available in second study; overlapping cases not tabulated.