LUPINE PUBLISHERS

Online Journal of Neurology and Brain Disorders

DOI: 10.32474/OJNBD.2021.06.000227

ISSN: 2637-6628

Review Article

Pineal Parenchymal Tumours

Ana Rita Coelho[1]*, Roberto Silva[1], Jorge Pinheiro[1] and Mrinalini Honavar[2]

[1]*University Hospital Center of São João/ University of Porto, Portugal*

[2]*University Hospital Center of São João, Portugal*

***Corresponding author:** Ana Rita Coelho, University Hospital Center of São João/ University of Porto, Portugal

UAlameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal

Received: September 07, 2021 **Published:** September 21, 2021

Introduction

Pineal region tumours (PRT) are rare, accounting for less than 1% of all Central Nervous System (CNS) neoplasms1. Several distinct tumour types can occur in this location, reflecting the heterogeneity of the various structures of this small region. Pineal parenchymal tumours (PPT) represent approximately 27% of PRT and they are thought to be derived from pineocytes [1], cells with photosensory and neuroendocrine functions associated with melatonin production. According to the World Health Organization (WHO) 2016 classification of CNS tumours, PPT can be divided into three distinct tumour types, that differ in the degree of differentiation and biological behaviour: pineocytomas, pineal parenchymal tumours of intermediate differentiation (PPTID) and pineoblastomas [1].

The clinical presentation is similar across all types of PPT and usually arises from compression of adjacent structures, leading to obstructive hydrocephalus with increased intracranial pressure, neuro-ophtalmological dysfunction and brainstem or cerebellar dysfunction [2]. Age of presentation is variable, with most pineoblastomas occurring in children, whereas pineocytoma and PPTID being more common in adolescent and adult patients1. Treatment options vary according to the type and grade of PPT, and include surgical resection, radiotherapy and chemotherapy. A combination of these treatment modalities seems effective to improve survival in more aggressive cases [3]. Recent molecular research has been highlighting the heterogeneity in the molecular characteristics between these different histotypes. Although pineocytomas and PPTID have no reported syndromic associations or genetic susceptibilities, pineoblastomas have been described in patients with DICER1 [4] and RB1 [5,6] germline pathogenic variants. This review focuses in the current state of the art in PPT, highlighting how new molecular data can improve tumour classification and patient management.

Pineocytomas

Pineocytomas (WHO grade I) account for approximately 20% of all PPT [1]. They occur more frequently in adults (mean age of 43 years) and have a female preponderance [1]. On imaging, they present as well-defined masses localised in the pineal region [7]. They grow locally and are not associated with cerebrospinal fluid seeding or metastasis [8]. The reported 5-year survival rate is up to 100% in some series [8], and the extent of surgical resection is considered to be the major prognostic factor [9]. In the spectrum of PPT, pineocytomas have the highest degree of differentiation. They are composed of moderately cellular sheets of relatively small, uniform, mature cells, resembling normal pinealocytes, with frequent pineocytomatous rosettes. Immunohistochemical profile shows strong reactivity for synaptophysin, neuron-specific enolase and neurofilaments. Mitotic activity is low and Ki67 proliferation index is <1% [10]. Molecular studies on pineocytomas are restricted to cytogenetic studies in single case reports10,11. Numerical alterations involving chromosomes X, 5, 8, 11, 14, 19 and 22 and structural alterations of chromosomes 1, 3, 12 and 22 were described, but further studies are required to establish their association with tumorigenesis.

Pineal Parenchymal Tumours of Intermediate Differentiation

PPTID (WHO grades II or III) account for approximately 45% of all PPT [11]. They occur more frequently in adults (mean age of 41 years) and have a slight female preponderance [1]. On imaging, they present as large, poorly defined masses localised in the pineal region [12]. PPTID present features between pineocytomas and pineoblastoma, with a variable clinical and biological behaviour, from low grade tumours with delayed local recurrences to potentially aggressive neoplasms, with craniospinal dissemination, even after complete surgical resection [8,12].

Histologically, PPTID are moderately to highly cellular neoplasms, composed of diffuse sheets and/or large lobules of cells with mild to moderate atypia, a salt-and-pepper chromatin and distinct cytoplasm. Accordingly to their variable biological and clinical behaviour, mitotic activity, Ki-67 proliferation index, neuronal and neuroendocrine differentiation are also variable. Hence, similarly to pineocytomas, immunohistochemical profile show reactivity for synaptophysin, but variable labelling is seen for neurofilaments and chromogranin-A [1]. Reliable and reproductible grading criteria to define prognosis and treatment response have not been defined yet. Jouvet et al. proposed a grading system regarding mitotic activity and degree of neuronal differentiation. Grade II lesions were defined as having 0-5 mitoses per 10 high-power fields and significant immunostaining for neurofilaments. Grade III lesions were defined as PPT with either 6 or more than 6 mitoses or fewer than 6 mitoses but without immunostaining for neurofilaments [13]. More recently, Wu et al. demonstrated that immunoreactivity for CD24 and PRAME antibodies were significantly higher in PPTID grade III than in grade II, thus proposing the usefulness of these two novel markers for grading PPTID [14].

Recent molecular studies have shown that PPTID are distinct from other PPT in their genetic and transcriptomic characteristics. Using whole exome sequencing, Lee JC et al, described unique recurrent somatic small in-frame insertion (p.R313delinsPRR) in the KBTBD4 gene in PPTID, that were absent in other PPT [15]. Thereafter, Pfaff et al validated these results and further demonstrated PPTID as a distinct molecular subgroup according methylation profiling [6]. Additional molecular data regarding PPTID can be found in single case reports. Using a comprehensive NGS panel in two cases of grade III PPTID, Martinez et al. found inactivating ATRX mutations, a gene associated with protein loss and alternative lengthening of telomeres. Since this was the sole pathogenic genetic abnormality identified in this study they suggested that it may represent an important driver in these tumor subset in particular [16].

In a single case study, using targeted exome sequencing, mutations in genes encoding tuberous sclerosis 1 within the hamartin region of the protein and an additional mutation in IKAROS family zinc finger 3 were found. This type of mutation in tuberous sclerosis 1 have been correlated with clinical sensitivity to mammalian target of rapamycin inhibitors, which makes it an interesting candidate for personalized target therapy in these patients [17]. According to cytogenetic studies, the most common chromosomal imbalances found in PPTID are 4q gain, 12q gain and 22 loss [18]. Additionally, Böhrnsen et al. highlighted the gains of 16p in one case of grade II PPTID [19].

Pineoblastomas

Pineoblastomas (WHO grade IV) account for approximately 35% of all PPT [1]. They occur more frequently in children (first two decades of life; mean age of 18 years) and have a slight female preponderance [1]. On imaging, they present as large, multilobulated masses in the pineal region, with frequent invasion of surrounding structures (including the leptomeninges, third ventricle, and tectal plate) [20]. Their locally invasive nature, tendency to disseminate along cerebrospinal fluid pathways and the occasional occurrence of extra-cranial metastasis, brings them to be the most aggressive type of PPT [21]. Prognosis seems to be most affected by the presence of disseminated disease at the time of diagnosis, patient age and extent of surgical resection [1].

In the spectrum of PPTs, pineoblastomas have the lowest degree of differentiation. They are composed of highly cellular patternless sheets of densely packed small cells, resembling other so-called small blue round cell or primitive neuro-ectodermal tumours of the CNS. Tumour cells have a high nuclear-to-cytoplasmic ratio, indistinct cell borders, hyperchromatic nuclei with irregular shapes and occasional small nucleoli, and scant cytoplasm. There are no pineocytomatous rosettes, but occasional Homer-Wright and Flexner-Wintersteiner rosettes may be seen. Necrosis is a common feature, and mitotic activity / Ki-67 proliferation index are generally high. Immunohistochemical profile shows variable positivity for synaptophysin, neuron-specific enolase, neurofilaments and chromogranin-A [1]. Recently, important molecular studies have been showing heterogeneity in the molecular characteristics in pineoblastomas. Concerning cytogenetics, Böhrnsen et al. found that pineoblastomas show frequent gains at 7, 9q, 12q, 16p, 17 and 22q, highlighting gain of 16p as a common alteration in PPT in general [19].

In a recent international collaboration study6, 107 cases of pineoblastoma were characterized by genome-wide DNA methylation profiling, gene panel sequencing and miRNA sequencing. Methylation analysis defined five subtypes of pineoblastoma, with important clinical and genomic heterogeneity. The RB subtype displayed similarities with retinoblastoma, and included cases associated with trilateral retinoblastoma; it occurred in a younger age and was characterised by somatic or germline RB1 alterations; frequent losses on chromosome 16 and gains in chromosome 1q were also found. The MYC subtype displayed similarities with group 3 medulloblastoma; they also occurred at a younger age, and were characterised by MYC activation, chromosome 8p and 10q losses. No germline associations were identified in this group. In the core subtypes (group 1A, 1B and 2) alterations in genes of the miRNA processing pathway (namely DROSHA, DGCR8 and DICER1) were found in about 42% of cases, with all alterations being mutually exclusive. These genetic alterations had been previously reported [15,22]. The most frequent chromosomal alterations found in these subtypes were chromosome 8 gain and chromosome 16 loss for Group 1B and chromosome 14q loss for group 2.

Conclusion

PPT, although rare tumours, have variable prognosis and imply significant morbidity and mortality in young patients. Recent molecular data has been highlighting important differences

between and within PPT histotypes. How to translate these new molecular data in a more precise diagnosis and better patient care is still a challenge.

References

1. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Ellison DW, et al. (2016) WHO Classification of Tumours of the Central Nervous System. (4th edition), IARC Lyon.
2. Smirniotopoulos JG, Rushing EJ, Mena H (1992) Pineal region masses: Differential diagnosis. Radiographics 12(3): 577-596.
3. Mallick S, Benson R, Rath GK (2016) Patterns of care and survival outcomes in patients with pineal parenchymal tumor of intermediate differentiation: An individual patient data analysis. Radiother Oncol 121(2): 204-208.
4. de Kock L, Sabbaghian N, Druker H, Evan Weber, Nancy Hamel, et al. (2014) Germ-line and somatic DICER1 mutations in pineoblastoma. Acta Neuropathol 128(4): 583-595.
5. de Jong MC, Kors WA, de Graaf P, Castelijns JA, Kivelä T, Moll AC (2014) Trilateral retinoblastoma: A systematic review and meta-analysis. Lancet Oncol 15(10): 1157-1167.
6. Pfaff E, Aichmüller C, Sill M, Stichel D, Snuderl M, et al. (2020) Molecular subgrouping of primary pineal parenchymal tumors reveals distinct subtypes correlated with clinical parameters and genetic alterations. Acta Neuropathol 139(2): 243-257.
7. Chiechi MV, Smirniotopoulos JG, Mena H (1992) Pineal parenchymal tumors: CT and MR features. J Comput Assist Tomogr 19(4); 509-517.
8. Fauchon F, Jouvet A, Paquis P, Saint Pierre G, Mottolese C, et al. (2000) Parenchymal pineal tumors: A clinicopathological study of 76 cases. Int J Radiat Oncol Biol Phys 46(4): 959-968.
9. Clark AJ, Sughrue ME, Ivan ME, Aranda D, Rutkowski MJ, et al. (2010) Factors influencing overall survival rates for patients with pineocytoma. J Neurooncol 100(2): 255-260.
10. Rainho CA, Rogatto SR, de Moraes LC, Barbieri Neto J (1992) Cytogenetic study of a pineocytoma. Cancer Genet Cytogenet 64(2): 127-132.
11. Dario A, Cerati M, Taborelli M, Finzi G, Pozzi M, et al. (2000) Cytogenetic and ultrastructural study of a pineocytoma case report. J Neurooncol 48(2): 131-134.
12. Komakula S, Warmuth Metz M, Hildenbrand P, Loevner L, Hewlett R, et al. (2011) Pineal parenchymal tumor of intermediate differentiation: imaging spectrum of an unusual tumor in 11 cases. Neuroradiology 3(8): 577-584.
13. Jouvet A, Saint Pierre G, Fauchon F, Privat K, Bouffet E, et al. (2000) Pineal parenchymal tumors: A correlation of histological features with prognosis in 66 cases. Brain Pathol 10(1): 49-60.
14. Wu X, Wang W, Lai X, Zhou Y, Zhou X, et al. (2020) CD24 and PRAME Are Novel Grading and Prognostic Indicators for Pineal Parenchymal Tumors of Intermediate Differentiation. Am J Surg Pathol 44(1): 11-20.
15. Lee JC, Mazor T, Lao R, Wan E, Diallo AB, et al. (2019) Recurrent KBTBD4 small in-frame insertions and absence of DROSHA deletion or DICER1 mutation differentiate pineal parenchymal tumor of intermediate differentiation (PPTID) from pineoblastoma. Acta Neuropathol 137(5): 851-854.
16. Haydee Martínez, Michelle Nagurney, Zi Xuan Wang, Charles G Eberhart, Christopher M, et al. (2019) ATRX Mutations in Pineal Parenchymal Tumors of Intermediate Differentiation. Journal of Neuropathology & Experimental Neurology 78(8): 703-708.
17. Kang YJ, Bi WL, Dubuc AM, Martineau L, Ligon AH, et al. (2016) Integrated Genomic Characterization of a Pineal Parenchymal Tumor of Intermediate Differentiation. World Neurosurg 85: 96-105.
18. Rickert CH, Simon R, Bergmann M, Dockhorn Dworniczak B, Paulus W (2001) Comparative genomic hybridization in pineal parenchymal tumors. Genes Chromosomes Cancer 30(1): 99-104.
19. Bohrnsen F, Enders C, Ludwig H, Bruck W, Fuzesi L, et al. (2015) Common molecularcytogenetic alterations in tumors originating from the pineal region. Oncology Letters 10(3): 1853-1857.
20. Nakamura M, Saeki N, Iwadate Y, Sunami K, Osato K, et al. (2000) Neuroradiological characteristics of pineocytoma and pineoblastoma. Neuroradiology 42(7): 509-514.
21. Villà S, Miller RC, Krengli M, Abusaris H, Baumert BG, Servagi Vernat S, et al. (2021) Primary pineal tumors: outcome and prognostic factors-a study from the Rare Cancer Network (RCN). Clin Transl Oncol 14(11): 827-834.
22. Snuderl M, Kannan K, Pfaff E, Wang S, Stafford JM, et al. (2018) Recurrent homozygous deletion of DROSHA and microduplication of PDE4DIP in pineoblastoma. Nat Commun 9(1): 2868.

DOI: 10.32474/OJNBD.2021.06.000227