8.BÖLÜM

SANTRAL SİNİR SİSTEMİ TÜMÖRLERİ SINIFLAMASINDA YENİLİKLER

Cevriye CANSIZ ERSÖZ [10]

GİRİŞ

Geçtiğimiz dekatlarda, esasen ışık mikroskobik görünümleri, immünhistokimyasal ve ultrastrüktürel özelliklerine dayanan merkezi sinir sistemi tümörlerinin teşhisine yönelik geleneksel yaklaşım; yapılan çalışmalarla genel ve bazı nadir görülen beyin tümörlerinde tümörogenezin genetik temelinin netleştirilmesiyle moleküler odaklı bir yaklaşıma geçilmesini sağlamıştır. Dünya Sağlık Örgütü' nün (DSÖ) Merkezi Sinir Sistemi (MSS) Tümörlerinin Sınıflandırılması'nın güncellenmiş 2016 baskısı, tümör sınıflandırmasında histolojiye ek olarak moleküler parametreleri de kullanarak "entegre" tanılar oluşturulmasını sağlamaktadır. Majör yeniden yapılanma diffüz gliomalar, medulloblastomlar ve diğer embriyonal tümörler için uygulanırken; hem histolojik hem de moleküler özellikleri ile, izositrat dehidrojenaz (IDH) –wild tip ve IDH-mutant glioblastoma; diffüz orta hat gliomu, H3 K27M-mutant; RELA füzyon pozitif ependimoma; "wingless"(WNT)-aktif medulloblastoma ve "sonic hedgehog"(SHH)-aktif medulloblastoma; çok sıralı rozetli embriyonal tümör, C19MC-değişmiş gibi yeni antiteler tanımlanmıştır. Bunun yanında gliomatozis serebri, protoplazmik astrositom varyantı, fibriler astrositom varyantı; sellüler ependimom varyantı ve primitive nöroektodermal tümor (PNET) terminolojisi gibi bazı antite ve terimler ise sınıflamadan çıkarılmıştır. 2016 DSÖ sınıflamasının hastaların yaşamlarında iyileşmelere neden olacak klinik, deneysel ve epidemiyolojik çalışmaları kolaylaştıracağı düşünülmektedir.

GENETİK ve MOLEKÜLER BİLGİLEr

Tanısal yaklaşımın dönüşümüne yol açan ilk genetik değişikliklerden biri oligodendroglioma'da 1p ve 19q kromozomu kodelesyonunun saptanmasıdır (1). Sentromerler arasındaki dengesiz bir translokasyonun [t(1;19)(q10:p10)] sonucu

[10] Öğretim Görevlisi Doktor, Ankara Üniversitesi Tıp Fakültesi, Tıbbi Patoloji ABD
e-mail: cevriye80@yahoo.com

KAYNAKÇA

1. Reifenberger J, Reifenberger G, Liu L, et al. Molecular genetic analysis of oligodendroglial tumors shows preferential allelic deletions on 19q and 1p. Am J Pathol 145: 1175–1190, 1994.
2. Eckel-Passow JE, Lachance DH, Molinaro AM, et al. Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. N Engl J Med 372: 2499–2508, 2015
3. Brat DJ, Verhaak RG, Aldape KD, et al. Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. N Engl J Med 372: 2481–2498, 2015
4. Cairncross G, Wang M, Shaw E, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. J Clin Oncol 31: 337–343, 2013
5. Jiao Y, Killela PJ, Reitman ZJ, et al. Frequent ATRX, CIC, FUBP1 and IDH1 mutations refine the classification of malignant gliomas. Oncotarget; 3:709-22, 2012
6. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med; 360:765-73; 2009
7. Hartmann C, Hentschel B, Wick W, et al. Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas. Acta Neuropathol 120: 707–718, 2010
8. Balss J, Meyer J, Mueller W, et al. Analysis of the IDH1 codon 132 mutation in brain tumors. Acta Neuropathol, 116: 597–602, 2008
9. Suzuki H, Aoki K, Chiba K, et al.: Mutational landscape and clonal architecture in grade II and III gliomas. Nat Genet, 47: 458–468, 2015
10. Taylor MD, Northcott PA, Korshunov A, et al.: Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol 123: 465–472, 2012
11. Louis DN, Perry A, Burger P, et al. International Society Of Neuropathology-Haarlem consensus guidelines for nervous system tumor classification and grading. Brain Pathol, 24:429–435, 2014
12. Louis DN, Ohgaki H, Wiestler OD, et al. World Health Organization histological classification of tumours of the central nervous system.ed 4, Lyon IARS Press, 2016
13. Louis DN, Perry A , Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary; ; Acta Neuropathol, 131:803–820, 2016
14. Ellison DW, Dalton J, Kocak M, et al. Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups. Acta Neuropathol 121:381–396, 2011
15. Reuss DE, Sahm F, Schrimpf D, et al. ATRX and IDH1-R132H immunohistochemistry with subsequent copy number analysis and IDH sequencing as a basis for an "integrated" diagnostic approach for adult astrocytoma, oligodendroglioma and glioblastoma. Acta Neuropathol 129:133–146, 2015
16. Takashi Komori . The 2016 WHO Classification of Tumours of the Central Nervous System: The Major Points of Revision; Neurol Med Chir (Tokyo) 57, 301–311, 2017
17. Reuss DE, Kratz A, Sahm F, et al. Adult IDH wild type astrocytomas biologically and clinically resolve into other tumor entities. Acta Neuropathol, 2015
18. Ohgaki H, Kleihues P. Population-based studies on incidence, survival rates, and genetic alterations in astrocytic and oligodendroglial gliomas. J Neuropathol Exp Neurol 64:479–489, 2005

19. Olar A, Wani KM, Alfaro-Munoz KD, et al. IDH mutation status and role of WHO grade and mitotic index in overall survival in grade II–III diffuse gliomas. Acta Neuropathol 129:585–596, 2015
20. Reuss DE, Mamatjan Y, Schrimpf D, et al. IDH mutant diffuse and anaplastic astrocytomas have similar age at presentation and little difference in survival: a grading problem for WHO. Acta Neuropathol 129:867–873, 2015
21. Killela PJ, Pirozzi CJ, Healy P, et al. Mutations in IDH1, IDH2, and in the TERT promoter define clinically distinct subgroups of adult malignant gliomas. Oncotarget 5:1515–1525, 2014
22. Herrlinger U, Jones DT, Glas M, et al. Gliomatosis cerebri: no evidence for a separate brain tumor entity. Acta Neuropathol, 2015
23. Ohgaki H, Kleihues P. The definition of primary and secondary glioblastoma. Clin Cancer Res 19:764–772, 2013
24. Chen L, Voronovich Z, Clark K, et al. Predicting the likelihood of an isocitrate dehydrogenase 1 or 2 mutation in diagnoses of infiltrative glioma. Neurooncology 16:1478–1483, 2014
25. Broniscer A, Tatevossian RG, Sabin ND, et al.Clinical, radiological, histological and molecular characteristics of paediatric epithelioid glioblastoma. Neuropathol Appl Neurobiol 40:327–336, 2014
26. Kleinschmidt-DeMasters BK, Aisner DL, Foreman NK. BRAF VE1 immunoreactivity patterns in epithelioid glioblastomas positive for BRAF V600E mutation. Am J Surg Pathol 39:528–540, 2015
27. Alexandrescu S, Korshunov A, Lai SH, et al. Epithelioid glioblastomas and anaplastic epithelioid pleomorphic xanthoastrocytomas— same entity or first cousins? Brain Pathol, 2015
28. Perry A, Miller CR, Gujrati M, et al. Malignant gliomas with primitive neuroectodermal tumor-like components: a clinicopathologic and genetic study of 53 cases. Brain Pathol 19:81–90, 2009
29. Joseph NM, Phillips J, Dahiya S, et al. Diagnostic implications of IDH1-R132H and OLIG2 expression patterns in rare and challenging glioblastoma variants. Mod Pathol. 26:315–326, 2013
30. Giannini C, Scheithauer BW, Weaver AL, et al. Oligodendrogliomas: reproducibility and prognostic value of histologic diagnosis and grading. J Neuropathol Exp Neurol 60:248–262, 2001
31. van den Bent MJ. Interobserver variation of the histopathological diagnosis in clinical trials on glioma: a clinician's perspective. Acta Neuropathol 120:297–304, 2010
32. Huse JT, Diamond EL, Wang L, et al. Mixed glioma with molecular features of composite oligodendroglioma and astrocytoma: a true "oligoastrocytoma"? Acta Neuropathol , 2015
33. Ramkissoon LA, Horowitz PM, Craig JM, et al. Genomic analysis of diffuse pediatric low-grade gliomas identifies recurrent oncogenic truncating rearrangements in the transcription factor MYBL1. Proc Natl Acad Sci USA, 2013
34. Zhang J, Wu G, Miller CP, et al. Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas. Nat Genet 45:602–612, 2013
35. Suri V, Das P, Pathak P, et al. Pediatric glioblastomas: a histopathological and molecular genetic study. Neuro Oncol;11:274-80, 2009
36. Fontebasso AM, Schwartzentruber J, Khuong-Quang DA, et al. Mutations in SETD2 and genes affecting histone H3K36 methylation target hemispheric high-grade gliomas. Acta Neuropathol;125:659-69, 2013

37. Phillips JJ, Aranda D, Ellison DW, et al. PDGFRA amplification is common in pediatric and adult highgrade astrocytomas and identifies a poor prognostic group in IDH1 mutant glioblastoma. Brain Pathol; 23:565-73, 2013
38. Bax DA, Mackay A, Little SE, et al. A distinct spectrum of copy number aberrations in pediatric high-grade gliomas. Clin Cancer Res;16:3368-77, 2010
39. Khuong-Quang DA, Buczkowicz P, Rakopoulos P, et al. K27M mutation in histone H3.3 defines clinically and biologically distinct subgroups of pediatric diffuse intrinsic pontine gliomas. Acta Neuropathol 124:439– 447, 2012
40. Wu G, Broniscer A, McEachron TA, et al. Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. Nat Genet 44:251–253, 2012
41. Ida CM, Rodriguez FJ, Burger PC, et al. Pleomorphic xanthoastrocytoma: natural history and long-term follow-up. Brain Pathol, 2014
42. Giannini C, Scheithauer BW, Burger PC, et al. Pleomorphic xanthoastrocytoma: what do we really know about it? Cancer; 85:2033-45, 1999
43. Ellison DW, Kocak M, Figarella-Branger D, et al. Histopathological grading of pediatric ependymoma: reproducibility and clinical relevance in European trial cohorts. J Negat Results Biomed 10:7, 2011
44. Parker M, Mohankumar KM, Punchihewa C, et al. C11orf95-RELA fusions drive oncogenic NF-kappaB signalling in ependymoma. Nature 506:451–455, 2014
45. Gessi M, Giagnacovo M, Modena P, et al. Role of Immunohistochemistry in the Identification of Supratentorial C11ORF95-RELA Fused Ependymoma in Routine Neuropathology Am J Surg Pathol. Jan;43(1):56-63, 2019
46. Rodriguez FJ, Perry A, Rosenblum MK, et al. Disseminated oligodendroglial-like leptomeningeal tumor of childhood: a distinctive clinicopathologic entity. Acta Neuropathol 124:627–641, 2012
47. Rodriguez FJ, Schniederjan MJ, Nicolaides T, et al. High rate of concurrent BRAF-KIAA1549 gene fusion and 1p deletion in disseminated oligodendrogliomalike leptomeningeal neoplasms (DOLN). Acta Neuropathol 129:609–610, 2015
48. Kavneet K, Aanchal K, Anupam K, et al. Integrating molecular subclasssification of medulloblastomas into routine clinical practice: a simplified approach; Brain Pathology 26; 334-343, 2016
49. Korshunov A, Ryzhova M, Hovestadt V, et al. Integrated analysis of pediatric glioblastoma reveals a subset of biologically favorable tumors with associated molecular prognostic markers. Acta Neuropathol 129:669–678, 2015
50. Jakobiec FA, Kool M, Stagner AM, et al. Intraocular medulloepitheliomas and embryonal tumors with multilayered rosettes of the brain: comparative roles of LIN28A and C19MC. Am J Ophthalmol;159(6):1065-74, 2015
51. Korshunov A, Ryzhova M, Jones DT, et al. LIN28A immunoreactivity is a potent diagnostic marker of embryonal tumor with multilayered rosettes (ETMR). Acta Neuropathol;124(6):875-81, 2012
52. Biegel JA. Molecular genetics of atypical teratoid/rhabdoid tumor. Neurosurg Focus 20:E11, 2006
53. Hasselblatt M, Gesk S, Oyen F, et al. Nonsense mutation and inactivation of SMARCA4 (BRG1) in an atypical teratoid/rhabdoid tumor showing retained SMARCB1(INI1) expression. Am J Surg Pathol 35:933–935, 2011

54. Schweizer L, Koelsche C, Sahm F, et al. Meningeal hemangiopericytoma and solitary fibrous tumors carry the NAB2-STAT6 fusion and can be diagnosed by nuclear expression of STAT6 protein. Acta Neuropathol 125:651–658, 2013
55. Bouvier C, Metellus P, de Paula AM, et al. Solitary fibrous tumors and hemangiopericytomas of the meninges: overlapping pathological features and common prognostic factors suggest the same spectrum of tumors. Brain Pathol 22:511–521, 2012