MEDÜLLER TİROİD KANSERİ VAKASINDA YAKLAŞIM VE TAKİP

25. BÖLÜM

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GİRİŞ

Medüller tiroid kanseri (MTK), tiroidin parafoliküler C hücrelerinden köken alan nöroendokrin bir tümördür. Tiroid maligniteleri arasında yaklaşık %3-5 oranında görülmektedir. Tiroid nodüllü hastaların %0.4-1.4'ünü oluşturmaktadır.[1] Sporadik (%75) veya herediter (%25) olabilir. Sporadik formlar 4-5. dekatlarda tanı alırken, herediter formlar 3. dekattan önce tanı almaktadır.[2,3] Herediter formlar multipl endokrin neoplazi (MEN) sendromları içerisinde sınıflandırılmaktadır. Patogenezde Rearranged during Transfection (RET) mutasyonları rol oynamaktadır.[4] Herediter formlarda sıklıkla germline RET mutasyonları, sporadik formlarda ise somatik RET mutasyonları görülmektedir.[5] Klinik olarak, genellikle spesifik bir semptom olmaksızın, tiroid nodülü ve/veya boyunda lenfadenopati ile tanı almaktadırlar. Tanısında görüntüleme yöntemleri ve patolojik incelemelere ek olarak tümör belirteçleri kullanılmaktadır. Kalsitonin; tanı, tedavi planı ve takipte kullanılan spesifik bir tümör belirtecidir. Tedavisi cerrahidir. Metastatik vakalarda hedefe yönelik tedaviler, sistemik kemoterapi ve radyoterapi gibi tedavi yöntemleri kullanılmaktadır.

Sporadik Medüller Tiroid Kanseri

Sporadik formlar daha çok 4-5. dekatlarda görülürler. Klinik olarak %75-95 oranında soliter, sert bir nodül ile prezente olurlar. Boyunda lenfadenopati eşlik edebilir. Herediter formlara kıyasla daha yavaş büyüme hızına sahip, daha iyi diferensiye tümörlerdir. Genellikle servikal lenf nodu tutulumu evresinde tanı alırlar.[3] Sporadik MTK'lerde yaklaşık %47 oranında somatik RET mutasyonları görülmektedir.[5] Somatik mutasyonu olmayan sporadik vakalarda, somatik Rat Sarkoma (RAS) onkogen mutasyonlarının (HRAS, KRAS, NRAS) olduğu gösterilmiştir.[6]

Herediter Medüller Tiroid Kanseri

Herediter formlar, sporadik formlara göre daha genç yaşlarda ortaya çıkarlar. Bilateral ve multipl olmaya eğilimlidir. Genellikle lokal-rejyonel invazyon veya lenf nodu metastazı evresinde tanı alırlar.[7] MEN2 sendromları içerisinde yer alırlar. Çeşitli endokrin veya endokrin dışı patoloji ile birliktelik gösterebilirler (Tablo-1).

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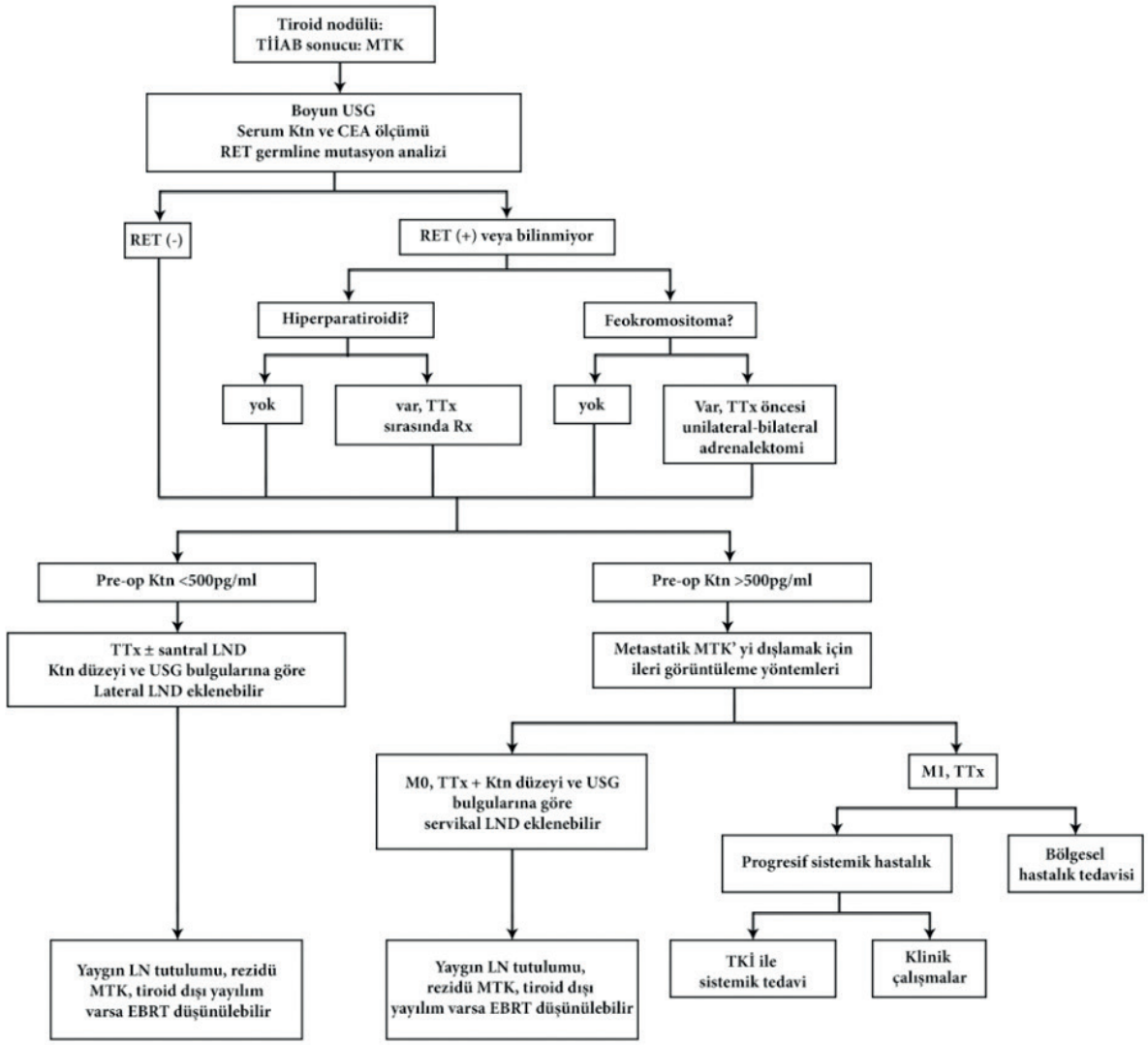

Şekil 1. Tiiab İle Medüller Tiroid Kanseri Tanısı Alan Hastalarda Değerlendirme ve Yönetim Algoritması
CEA: Karsinoembriyojenik Antijen, EBRT: Eksternal Beam Radyoterapi, Ktn: Kalsitonin, LND: Lenf nodu Diseksiyonu, M0: Uzak metastaz yok, M1: Uzak Metastaz var, MTK: Medüller Tiroid Kanseri, Rx: Rezeksiyon, TİAAB: Tiroid İnce İğne Aspirasyon Biyopsi, TKİ: Tirozin Kinaz İnhibitörleri, TTx: Total Tiroidektomi, USG: Ultrasonografi
Wells Jr SA, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 2015; 25:567. den modifiye edilmiştir.

KAYNAKLAR

1. Wells SA Jr, Asa SL, Dralle H et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma: The American Thyroid Association Guidelines Task Force on medullary thyroid carcinoma. Thyroid 2015; 25: 567–610. Doi:10.1089/thy.2014.0335.
2. Randle RW, Balentine CJ, Leverson GE et al. Trends in the presentation, treatment, and survival of patients with medullary thyroid cancer over the past 30 years. Surgery. 2017 Jan;161(1):137-146. Doi: 10.1016/j.surg.2016.04.053.
3. Viola D, Elisei R. Management of Medullary Thyroid Cancer.Endocrinol Metab Clin North Am. 2019 Mar;48(1):285-301.
4. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab. 2001 Dec;86(12):5658-71. Doi:10.1210/jcem.86.12.8070
5. Dvorakova S, Vaclavikova E, Sykorova V, et al. Somatic mutations in the RET proto-oncogene in sporadic medullary thyroid carcinomas. Mol Cell Endocrinol. 2008 Mar 12;284(1-2):21-7. Doi: 10.1016/j.mce.2007.12.016.
6. Fussey JM2, Vaidya B, Kim D et al. The role of molecular genetics in the clinical management of sporadic medullary thyroid carcinoma: A sys-

tematic review. Clin Endocrinol (Oxf). 2019 Dec;91(6):697-707. Doi: 10.1111/cen.14060.
7. Pappa T, Alevizaki M. Management of hereditary medullary thyroid carcinoma. Endocrine. 2016 Jul;53(1):7-17. Doi: 10.1007/s12020-016-0873-1.
8. Makri A, Akshintala S, Derse-Anthony C et al. Pheochromocytoma in Children and Adolescents With Multiple Endocrine Neoplasia Type 2B. J Clin Endocrinol Metab.2019 Jan 1;104(1):7-12. Doi: 10.1210/jc.2018-00705.
9. Elisei R, Tacito A, Ramone T. Et al. Twenty-Five Years Experience on RET Genetic Screening on Hereditary MTC: An Update on The Prevalence of Germline RET Mutations. Genes (Basel). 2019 Sep 10;10(9). pii: E698. doi: 10.3390/genes10090698.
10. Larouche V, Akirov A, Thomas CM, et al. A primer on the genetics of medullary thyroid cancer. Curr Oncol. 2019 Dec;26(6):389-394. Doi: 10.3747/co.26.5553
11. Aydoğan Bİ, Yüksel B, Tuna MM, et al. Distrubution of RET Mutations and evaluation of Treatment Approaches in Hereditary Medullary Thyroid Carcinoma in Turkey. J Clin Res Pediatr Endocrinol. 2016 Mar 5;8(1):13-20. Doi: 10.4274/jcrpe.2219.
12. Türkiye Endokrinoloji ve Metabolizma Derneği (2019), Tiroid Hastalıkları Tanı ve Tedavi Klavuzu, (1. Baskı). Ankara: Orta Doğu Yayıncılık
13. Abe K, Adachi I, Miyakawa S, et al. Production of calcitonin, adrenocorticotropic hormone, and betamelanocyte-stimulating hormone in tumors derived from amine precursor uptake and decarboxylation cells. Cancer Res 37:4190–4194.
14. Choi N, Moon WJ, Lee JH, et al. Ultrasonographic Findings of medullary thyroid cancer: differences According to tumor size and correlation with fine needle Aspiration results. *Acta Radiol* 2011;52:312–16. Doi: 10.1258/ar.2010
15. Liu MJ, Liu ZF, Hou YY, *et al.* Ultrasonographic characteristics Of medullary thyroid carcinoma: a comparison with papillary Thyroid carcinoma. *Oncotarget* 2017;8:27520–8. Doi: 10.18632/oncotarget.15897
16. Chang TC, Wu SL, Hsiao YL. Medullary thyroid carcinoma: Pitfalls in diagnosis by fine needle aspiration cytology and Relationship of cytomorphology to *RET* proto-oncogene Mutations. *Acta Cytol* 2005;49:477–82.
17. Trimboli P, Treglia G, Guidobaldi L, *et al.* Detection rate of fna Cytology in medullary thyroid carcinoma: a meta-analysis.*Clin Endocrinol (Oxf)* 2015;82:280–5. Doi: 10.1111/cen.12563.
18. Haddad RI, Nasr C, Bischoff L, et al. NCCN Guidelines Insights: Thyroid Carcinoma, Version 2.2018. J Natl Compr Canc Netw. 2018 Dec;16(12):1429-40. doi: 10.6004/jnccn.2018.0089.
19. Giraudet AL, Vanel D, Leboulleux S, et al. Imaging medullary thyroid carcinoma with persistent elevated calcitonin levels. J Clin Endocrinol Metab. 2007 Nov;92(11):4185-90
20. Machens A, Dralle H. Biomarker-based risk stratification For previously untreated medullary thyroid cancer. J Clin Endocrinol Metab. 2010 Jun;95(6):2655-63. doi: 10.1210/jc.2009-2368
21. Ceolin L, Duval MADS, Benini AF, et al. Medullary thyroid carcinoma beyond surgery: advances, challenges, and perspectives. Endocr Relat Cancer. 2019 Aug 1;26(9):R499-R518. doi: 10.1530/ERC-18-0574.
22. Hoff AO1, Hoff PM. Medullary thyroid carcinoma.Hematol Oncol Clin North Am. 2007 Jun;21(3):475-88.
23. Moley JF1, DeBenedetti MK. Patterns of nodal metastases in palpable medullary thyroid carcinoma: recommendations for extent of node dissection. Ann Surg. 1999 Jun;229(6):880-7.
24. Scollo C, Baudin E, Travagli JP, et al. Rationale for central and bilateral lymph node dissection in sporadic and hereditary medullary thyroid cancer. J Clin Endocrinol Metab. 2003 May;88(5):2070-5.
25. Bae SY, Jung SP, Choe JH, et al. Prediction of lateral neck lymph node metastasis according to preoperative calcitonin level and tumor size for medullary thyroid carcinoma. Kaohsiung J Med Sci. 2019 Dec;35(12):772-777. Doi: 10.1002/kjm2.12122.
26. Perros P, Boelaert K, Colley S, et al. British Thyroid Association. Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf) 2014; 81 (Suppl 1): 1–122. Doi: 10.1111/cen.12515
27. Prete FP, Abdel-Aziz T, Morkane C, et al. MEN2 in Children UK Collaborative Group. Prophylactic thyroidectomy in children with multiple endocrine neoplasia type 2. Br J Surg. 2018 Sep;105(10):1319-1327. Doi: 10.1002/bjs.10856.
28. Filetti S1, Durante C1, Hartl D2, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019 Dec 1;30(12):1856-1883. doi:10.1093/annonc/mdz400.
29. Park SY, Cho YY, Kim HI, et al. Clinical Validation of the Prognostic Stage Groups of the Eighth-Edition TNM Staging for Medullary Thyroid Carcinoma. J Clin Endocrinol Metab. 2018 Dec 1;103(12):4609-16. Doi: 10.1210/jc.2018-01386.
30. Barbet J, Campion L, Kraeber-Bodéré F et al. Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. J Clin Endocrinol Metab. 2005 Nov;90(11):6077-84.
31. Romero-Lluch AR, Cuenca-Cuenca JI, Guerrero-Vazquez R, et al. Diagnostic utility of PET/CT with 18F-DOPA and 18F-FDG in persistent or recurrent medullary thyroid carcinoma: the importance of calcitonin and carcinoembryonic antigen cutoff. Eur J Nucl Med Mol Imaging. 2017

Nov;44(12):2004-2013. Doi: 10.1007/s00259-017-3759-4
32. Castroneves LA, Coura Filho G, de Freitas RMC, *et al*. Comparison of 68Ga PET/CT to other imaging studies in medullary thyroid cancer: superiority in detecting bone metastases. J Clin Endocrinol Metab. 2018 Sep 1;103(9):3250-3259. doi: 10.1210/jc.2018-00193.
33. Brierley J, Sherman E. The role of external beam radiation and targeted therapy in thyroid cancer. Semin Radiat Oncol. 2012 Jul;22(3):254-62. Doi: 10.1016/j.semradonc.2012.03.010.
34. Fromigué J, De Baere T, Baudin E, et al. Chemoembolization for liver metastases from medullary thyroid carcinoma. J Clin Endocrinol Metab. 2006 Jul;91(7):2496-9.
35. Wexler JA. Approach to the thyroid cancer patient With bone metastases. J Clin Endocrinol Metab. 2011 Aug;96(8):2296-307. Doi: 10.1210/jc.2010-1996.
36. Mahler C, Verhelst J, de Longueville M, et al. Long-term treatment of metastatic medullary thyroid Carcinoma with the somatostatin analogue octreotide. Clin Endocrinol (Oxf) 33:261–9.
37. Barbosa SL, Rodien P, Leboulleux S, et al. Ectopic adrenocorticotropic hormone-syndrome in medullary carcinoma of the thyroid: a retrospective analysis and review of the literature.Thyroid.2005 Jun;15(6):618-23.
38. Nella AA, Lodish MB, Fox E, et al. Vandetanib successfully controls medullary thyroid cancer-related Cushing syndrome in an adolescent patient. J Clin Endocrinol Metab. 2014 Sep;99(9):3055-9. doi: 10.1210/jc.2013-4340
39. Wells SA Jr, Robinson BG, Gagel RF et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2012 Jan 10;30(2):134-41. doi: 10.1200/JCO.2011.35.5040
40. Schlumberger M, Elisei R, Müller S et al. Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma. Ann Oncol. 2017 Nov 1;28(11):2813-2819. doi: 10.1093/annonc/mdx479.
41. Hadoux J, Schlumberger M. Chemotherapy and tyrosine-kinase inhibitors for medullary thyroid cancer. Best Pract Res Clin Endocrinol Metab. 2017 Jun;31(3):335-347. doi: 10.1016/j.beem.2017.04.009
42. Iten F, Muller B, Schindler C et al. [(90)Yttrium-DOTA]-TOC response is associated with survival benefit in iodine-refractory thyroid cancer: long-term results of a phase 2 clinical trial. Cancer. 2009 May 15;115(10):2052-62. doi: 10.1002/cncr.24272.