Bölüm
12

MONOKLONAL GAMMOPATİLERDE RİSK SINIFLAMASI VE PROGNOZ

Hilmi Erdem GÖZDEN

ANLAMI BELİRLENEMEYEN MONOKLONAL GAMMOPATİ (MGUS) RİSK SINIFLAMASI VE PROGNOZ

Anlamı belirlenemeyen monoklonal gammopati (MGUS) premalign klonal plasma hücre veya lenfoplasmositik proliferatif bir hastalıktır. Elli yaş üzeri genel popülasyonda %3 oranında protein elektroforezi yapılması sonrasında saptanır.

Üç tip klinik alt grubu bulunur ki bunların her biri daha ileri premalign evreye ve devamında malign plasma hücre diskrazisi veya lenfoproliferatif hastalığa progrese olurlar (1-7).

- Non-IgM MGUS (IgG, IgA, veya IgD MGUS) en sık alt tiptir (8). Olguların bir kısmı smoldering multipl miyelom (SMM) veya semptomatik multipl miyeloma (MM) progrese olurlar. Az bir kısım hastada AL tipi amiloidoz, hafif zincir depo hastalığı (LCDD) veya farklı bir lenfoproliferatif hastalığa progresyon saptanır.
- IgM MGUS tüm MGUS hastalarının %15'ini kapsar ve smoldering Waldenstrom makroglobulinemisi (WM) ve semptomatik WM ile non-Hodgkin lenfoma (NHL)'ya progrese olabilir (9). Çok nadir IgM MM progresyon izlenmiştir.
- Hafif zincir MGUS (LC-MGUS) idiopatik Bence jones proteinürisine, hafif zincir MM, AL amiloidoz veya hafif zincir depo hastalığına ilerleyebilen, ağır zincir sekresyonunun olmadığı nadir bir alt tiptir.

Genel olarak MGUS hastalarının daha ileri bir hastalığa progrese olma oranları yıllık %1'dir. Non-IgM MGUS'a kıyasla bu risk IgM MGUS hastalarında biraz daha fazla ve LC_MGUS hastalarında daha azdır. Iki büyük çalışmada MM tanısı alan hastaların %75'inde tanıdan 8 yıl öncesine kadar tetkiklerinde saptanabilir M proteini olduğu görülmüştür (4-5).

Hastalığın biyolojisi ve risk sınıflaması

Tanı anında FISH ile kemik iliğinden bakılan sitogenetik tetkikler ile MM doğal seyri ve agresivitesini tespit edilebilmektedir. Bu sonuçlara gore hastalar yüksek risk veya standart risk olarak ayrılmaktadırlar (Tablo 1)

Tablo 1 . Genetik risk sınıflaması

Yüksek risk	Standart risk
17p13 del t(4;14) t(14;16) t(14;20) Gain 1q LDH değerinin üst limitin 2 katından fazla olması Plasma hücreli lösemi özellikleri Yüksek riskli gen ekspresyon profili	Diğerleri; Trizomiler (hiperdiploidi) t(11;14) t(6;14)

Kaynaklar

1. Rajkumar SV, Kyle RA, Buadi FK. Advances in the diagnosis, classification, risk stratification, and management of monoclonal gammopathy of undetermined significance: implications for recategorizing disease entities in the presence of evolving scientific evidence. Mayo Clin Proc 2010; 85:945.
2. Dispenzieri A, Katzmann JA, Kyle RA, et al. Prevalence and risk of progression of light-chain monoclonal gammopathy of undetermined significance: a retrospective population-based cohort study. Lancet 2010; 375:1721.
3. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003; 78:21.
4. Landgren O, Kyle RA, Pfeiffer RM, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. Blood 2009; 113:5412.
5. Weiss BM, Abadie J, Verma P, et al. A monoclonal gammopathy precedes multiple myeloma in most patients. Blood 2009; 113:5418.
6. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014; 15:e538.
7. Kyle RA, Larson DR, Therneau TM, et al. Long-Term Follow-up of Monoclonal Gammopathy of Undetermined Significance. N Engl J Med 2018; 378:241.
8. Kyle RA, Therneau TM, Rajkumar SV, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med 2002; 346:564.
9. Kyle RA, Therneau TM, Rajkumar SV, et al. Long-term follow-up of IgM monoclonal gammopathy of undetermined significance. Blood 2003; 102:3759.
10. Axelsson U. A 20-year follow-up study of 64 subjects with M-components. Acta Med Scand 1986; 219:519.
11. Neriishi K, Nakashima E, Suzuki G. Monoclonal gammopathy of undetermined significance in atomic bomb survivors: incidence and transformation to multiple myeloma. Br J Haematol 2003; 121:405.
12. Paladini G, Fogher M, Mazzanti G, et al. [Idiopathic monoclonal gammopathy. Long-term study of 313 cases]. Recenti Prog Med 1989; 80:123.

13. Giraldo MP, Rubio-Félix D, Perella M, et al. [Monoclonal gammopathies of undetermined significance. Clinical course and biological aspects of 397 cases]. Sangre (Barc) 1991; 36:377.
14. Gregersen H, Ibsen J, Mellemkjoer L, et al. Mortality and causes of death in patients with monoclonal gammopathy of undetermined significance. Br J Haematol 2001; 112:353.
15. Gregersen H, Mellemkjaer L, Salling Ibsen J, et al. Cancer risk in patients with monoclonal gammopathy of undetermined significance. Am J Hematol 2000; 63:1.
16. Dhodapkar MV, Sexton R, Waheed S, et al. Clinical, genomic, and imaging predictors of myeloma progression from asymptomatic monoclonal gammopathies (SWOG S0120). Blood 2014; 123:78.
17. Kyle RA, Therneau TM, Rajkumar SV, et al. Long-term follow-up of 241 patients with monoclonal gammopathy of undetermined significance: the original Mayo Clinic series 25 years later. Mayo Clin Proc 2004; 79:859.
18. Kyle RA, Therneau TM, Rajkumar SV, et al. Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med 2006; 354:1362.
19. McMaster ML, Caporaso N. Waldenström macroglobulinaemia and IgM monoclonal gammopathy of undetermined significance: emerging understanding of a potential precursor condition. Br J Haematol 2007; 139:663.
20. Gobbi PG, Baldini L, Broglia C, et al. Prognostic validation of the international classification of immunoglobulin M gammopathies: a survival advantage for patients with immunoglobulin M monoclonal gammopathy of undetermined significance? Clin Cancer Res 2005; 11:1786.
21. Varettoni M, Zibellini S, Arcaini L, et al. MYD88 (L265P) mutation is an independent risk factor for progression in patients with IgM monoclonal gammopathy of undetermined significance. Blood 2013; 122:2284.
22. Kyle RA, Greipp PR. "Idiopathic" Bence Jones proteinuria: long-term follow-up in seven patients. N Engl J Med 1982; 306:564.
23. Kristinsson SY, Björkholm M, Andersson TM, et al. Patterns of survival and causes of death following a diagnosis of monoclonal gammopathy of undetermined significance: a population-based study. Haematologica 2009; 94:1714.
24. Baldini L, Guffanti A, Cesana BM, et al. Role of different hematologic variables in defining the risk of malignant transformation in monoclonal gammopathy. Blood 1996; 87:912.
25. Cesana C, Klersy C, Barbarano L, et al. Prognostic factors for malignant transformation in monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. J Clin Oncol 2002; 20:1625.
26. Rosiñol L, Cibeira MT, Montoto S, et al. Monoclonal gammopathy of undetermined significance: predictors of malignant transformation and recognition of an evolving type characterized by a progressive increase in M protein size. Mayo Clin Proc 2007; 82:428.
27. Rajkumar SV, Kyle RA, Therneau TM, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. Blood 2005; 106:812.
28. Rajkumar SV, Kyle RA, Therneau TM, et al. Presence of monoclonal free light chains in the serum predicts risk of progression in monoclonal gammopathy of undetermined significance. Br J Haematol 2004; 127:308.
29. Kyle RA, Durie BG, Rajkumar SV, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. Leukemia 2010; 24:1121.
30. Turesson I, Kovalchik SA, Pfeiffer RM, et al. Monoclonal gammopathy of undetermined significance and risk of lymphoid and myeloid malignancies: 728 cases followed up to 30 years in Sweden. Blood 2014; 123:338.
31. Kumar S, Rajkumar SV, Kyle RA, et al. Prognostic value of circulating plasma cells in monoclonal gammopathy of undetermined significance. J Clin Oncol 2005; 23:5668.

32. Rossi F, Petrucci MT, Guffanti A, et al. Proposal and validation of prognostic scoring systems for IgG and IgA monoclonal gammopathies of undetermined significance. Clin Cancer Res 2009; 15:4439.
33. Pérez-Persona E, Vidriales MB, Mateo G, et al. New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. Blood 2007; 110:2586.
34. Paiva B, Vidriales MB, Mateo G, et al. The persistence of immunophenotypically normal residual bone marrow plasma cells at diagnosis identifies a good prognostic subgroup of symptomatic multiple myeloma patients. Blood 2009; 114:4369.
35. Mateo G, Montalbán MA, Vidriales MB, et al. Prognostic value of immunophenotyping in multiple myeloma: a study by the PETHEMA/GEM cooperative study groups on patients uniformly treated with high-dose therapy. J Clin Oncol 2008; 26:2737.
36. Pérez-Persona E, Mateo G, García-Sanz R, et al. Risk of progression in smouldering myeloma and monoclonal gammopathies of unknown significance: comparative analysis of the evolution of monoclonal component and multiparameter flow cytometry of bone marrow plasma cells. Br J Haematol 2010; 148:110.
37. Raja KR, Kovarova L, Hajek R. Review of phenotypic markers used in flow cytometric analysis of MGUS and MM, and applicability of flow cytometry in other plasma cell disorders. Br J Haematol 2010; 149:334.
38. Pecherstorfer M, Seibel MJ, Woitge HW, et al. Bone resorption in multiple myeloma and in monoclonal gammopathy of undetermined significance: quantification by urinary pyridinium cross-links of collagen. Blood 1997; 90:3743.
39. Mailankody S, Mena E, Yuan CM, et al. Molecular and biologic markers of progression in monoclonal gammopathy of undetermined significance to multiple myeloma. Leuk Lymphoma 2010; 51:2159.
40. Katzmann JA, Clark R, Kyle RA, et al. Suppression of uninvolved immunoglobulins defined by heavy/light chain pair suppression is a risk factor for progression of MGUS. Leukemia 2013; 27:208.
41. Larsen JT, Kumar SK, Dispenzieri A, et al. Serum free light chain ratio as a biomarker for high-risk smoldering multiple myeloma. Leukemia 2013; 27:941.
42. Kyle RA, Remstein ED, Therneau TM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. N Engl J Med 2007; 356:2582.
43. Kristinsson SY, Holmberg E, Blimark C. Treatment for high-risk smoldering myeloma. N Engl J Med 2013; 369:1762.
44. Kyle RA, Larson DR, Therneau TM, et al. Clinical course of light-chain smouldering multiple myeloma (idiopathic Bence Jones proteinuria): a retrospective cohort study. Lancet Haematol 2014; 1:e28.
45. Pérez-Persona E, Vidriales MB, Mateo G, et al. New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. Blood 2007; 110:2586.
46. Mateos MV, Hernández MT, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. N Engl J Med 2013; 369:438.
47. Bianchi G, Kyle RA, Larson DR, et al. High levels of peripheral blood circulating plasma cells as a specific risk factor for progression of smoldering multiple myeloma. Leukemia 2013; 27:680.
48. Dispenzieri A, Stewart AK, Chanan-Khan A, et al. Smoldering multiple myeloma requiring treatment: time for a new definition? Blood 2013; 122:4172.
49. Rajkumar SV, Gupta V, Fonseca R, et al. Impact of primary molecular cytogenetic abnormalities and risk of progression in smoldering multiple myeloma. Leukemia 2013; 27:1738.
50. Neben K, Jauch A, Hielscher T, et al. Progression in smoldering myeloma is independently determined by the chromosomal abnormalities del(17p), t(4;14), gain 1q, hyperdiploidy, and tumor load. J Clin Oncol 2013; 31:4325.

51. Dhodapkar MV, Sexton R, Waheed S, et al. Clinical, genomic, and imaging predictors of myeloma progression from asymptomatic monoclonal gammopathies (SWOG S0120). Blood 2014; 123:78.
52. Russell SJ, Rajkumar SV. Multiple myeloma and the road to personalised medicine. Lancet Oncol 2011; 12:617.
53. Fonseca R, Bergsagel PL, Drach J, et al. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. Leukemia 2009; 23:2210.
54. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003; 78:21.