Bölüm
6

MULTİPL MİYELOMDA KEMİK HASTALIĞI FİZYOPATOLOJİSİ

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Multipl miyelom (MM) seyrinde kemik hastalığı mortalite ve morbiditenin önde gelen komplikasyonudur. Miyelom hücrelerine komşu artmış osteoklastik aktivite ilişkili litik lezyonlar ve bu lezyonlar sonucu gelişen kemik ağrıları, patolojik kırıklar, spinal kord basısı, hiperkalsemi ile karakterizedir(1). Hastaların yaklaşık%80'inde kemik hastalığı (KH) bulunur, patolojik kırık gelişen hastalarda %20 oranında artmış mortalite bildirilmiştir (2,3).

Son yıllarda MM tedavisindeki gelişmelere rağmen hastalıkta henüz kür elde edilememesi nedeni ile yaşam kalitesi ve hastalık ilişkili semptomların azaltılması önem kazanmıştır. Bu sebeplerden dolayı kemik hastalığının tanı ve uygun tedavisi gereklidir.

MM'da kemik hastalığı artan osteoklastik aktivitenin osteoblastlar tarafından yeni kemik oluşumu ile karşılanamaması sonucu oluşur. Osteoklastlar, osteositler, osteoblastlar ve kemik iliği stromal hücreleri arasındaki etkileşimin bozulmasından kaynaklanır. MM hücreleri osteoklast (OK) aktivitesini arttırırken osteoblast (OB) diferansiyasyonunu inhibe eder, kemik iliği stroması da MM hücrelerini destekleyen mikroçevreyi sağlar (4,5). Çalışmalar RANKL/osteoprotegerin yolağı, makrofaj inflamatuar proteinleri gibi çeşitli yolakların osteoklast aktivasyonu ve osteoblast inhibisyonundaki rolünü ortaya koymuştur. Bu yolaklar aynı zamanda MM progresyonu ve tümör yaşamı ile de ilişkilendirilmektedir .

MULTİPL MİYELOMDA KEMİK HASTALIĞI BİOLOJİSİ

KH temelinde uygunsuz "remodeling" yatmaktadır. Artan osteoklastik aktivite nedeni ile oluşan kemik rezorpsiyonu ve buna eşlik eden azalmış kemik formas-

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SFRP-2:

SFRP-2 (secreted frizzled-related protein 2) MM hücrelerinden salgılanır ve BMP-2 tarafından uyarılan OB diferansiyasyonunu ve mineralize nodul oluşumunu inhibe eder (39).

Transkripsiyon Faktörü Runx2/Cbfa 1:

Runx2/Cbfa 1 pre-osteoblastik hücrelerde bulunur. Yokluğunda OB'lar da oluşmaz ve kemik yapımı görülmez (40). MM hücreleri Runx2/Cbfa 1 aktivitesini baskılayarak OB oluşumunu baskılar. IL-7, Runx2/Cbfa 1 düzeyini azaltarak OB diferansiyasyonunu inhibe eder (41).

Osteositlerin Rolü:

Kemik hücrelerinin %95'ini oluşturan osteositler parakrin yolla RANKL ve sklerostin gibi faktörler eksprese ederek OB ve OK aktivitesini düzenler. MM hücrelerinin osteositlerle etkileşimi sonucu oluşan Notch aktivasyonu RANKL/OPG düzeyinin düşmesi ve OK aktivasyonu ile sonuçlanır. Ek olarak sklerostin Wnt sinyal yolağını inhibe ederek OB diferansiyasyonu baskılar(43). MM hastalarında osteosit sayıları azalmış olup hastalığın yaygınlığı ile ilişkilidir (44).

Sonuç:

MM'da kemik hastalığı patogenezi pek çok faktörün etkileşmi sonucu ortaya çıkmaktadır. MM hücreleri, OK ve OB ve stroma arasındaki interaksiyon konusunda yeterince kanıt bulunmaktadır. Mekanizmaların tanımlanması hedefe yönelik tedavileri de beraberinde getirecektir.

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