BÖLÜM 67

Radyasyonla İlişkili Kanserlerin Histopatolojik Özelikleri ve Moleküler İmzaları

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GİRİŞ

Radyoterapi (RT), kanser tedavisinde tek başına veya cerrahi ve kemoterapi ile birlikte kullanılmakta olan önemli bir tıbbi uygulamadır (1). RT uygulanan kanser hastalarının çoğunda uzamış sağkalım sağlanmakta, ancak bu hastalarda uzun vadede RT ilişkili morbiditeler ve mortalite görülebilmektedir. RT sonrası beş yıldan daha fazla sağkalıma sahip olgularda hematolojik malignite gelişimi insidansı %1-2, solid tümör gelişimi insidansı ise %2-10 civarıdır (2). Radyasyona maruz kalınan yaş, ışınlanan alanın dozu ve hacmi, organ ve doku tipi, radyasyon tekniği, hastaya ait veya ailesel kanser öyküsü gibi birçok faktör radyasyon ilişkili sekonder malignite gelişimine katkıda bulunur (3). Çocukluk çağı kanserleri, Hodgkin lenfoma, meme, serviks ve testis kanserleri gibi tümörlerde uygulanan RT sonrası meme, akciğer, tiroid kanserleri, sarkomlar ve lösemiler gibi maligniteler gelişebilmektedir (4).

Radyasyon ilişkili kanserlerin belirlenmesinde, Cahan-Woodard ve ark. tarafından tanımlanan ve daha sonra Murray ve ark. (6) tarafından modifiye edilen kriterler kullanılmaktadır. Bu kriterlere göre bir radyasyon ilişkili kanser, a) daha önce ışınlanmış bir alanda gelişmeli; b) histolojik olarak ilk tümör tipinden farklı olmalı, c) RT uygulanma sürecinde yeni tümöre ait bir bulgu olmamalı, d) yeni tümör, RT uygulaması sonrası bir latent periyodun ardından gelişmelidir (5, 6).

İyonizan radyasyon direkt DNA hasarı oluşturarak, DNA'da çift sarmal kırıklarına neden olur. Ayrıca reaktif oksijen radikalleri oluşturarak DNA bazlarında direkt hasar, tek sarmal kırıkları ve çapraz bağlanmalar meydana getirir. Bazı çevresel karsinojenlere (sigara, ultraviyole radyasyon gibi) benzer şekilde, radyasyon ilişkili kanserleri ayırt ettirici moleküler imzalar araştırılmaktadır (7, 8). İleri moleküler incelemelerle elde edilebilen, çok sayıda ve geniş serilerde doğrulanması gereken radyasyon ilişkili moleküler işaretler, radyasyona sekonder gelişen kanserlerin etyopatogenezinin aydınlatılmasında, tanı ve hedef tedavide önemli rol oynayacaktır. Örneğin, bir transkriptom çalışmasında, radyasyon ilişkili sarkomları %96 sensi-

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leer santrali felaketi sonrası yapılan çalışmaların önemli rolü vardır. Bu bölümde yer alan radyasyon ilişkili tiroid, kemik-yumuşak doku (sarkomlar), meme, santral sinir sistemi (gliom ve menenjiyom), mesane ve akciğer kanserleri ile ilgili çok sayıda epidemiyolojik çalışma bulunmasına rağmen histopatolojik çalışmalar son derece kısıtlıdır. Nadir birkaç örnek dışında (ör., Çernobil sistiti) radyasyon ilişkili kanserleri sporadik formlardan ayırt ettirecek karakteristik histopatolojik bir bulgu saptanmamıştır. Bu sebeple radyasyon ilişkili kanserlerde moleküler çalışmalar daha fazla ağırlık kazanmış olup, görece sık görülen histolojik tiplerde sporadik eşdeğerlerinden ayırt edici moleküler değişiklikler gösterilmeye çalışılmıştır. Son yıllarda gelişmiş moleküler tekniklerle radyasyon ilişkili kanserlerin moleküler imzalarını ortaya koymak amacıyla yapılan çalışmaların sayısı artmış olmakla birlikte oldukça kısıtlı veriler elde edilmiştir. Önerilen moleküler imzaların farklı ve daha geniş serilerde doğrulanması gerekmektedir. Tümörlerde histopatolojik bulguların moleküler verilerle harmanlandığı entegre sınıflamalarda çok sayıda yeni tümör tipinin tanımlanmasında çığır açan DNA metilasyon profilleme, transkriptom analizleri gibi ileri düzey moleküler yöntemler, radyasyon ilişkili kanserlerin moleküler patogenezinin aydınlatılmasında umut vadetmektedir (88).

AKILDA TUTULULACAKLAR

- Radyasyon ilişkili tiroid kanserli olgularda öncü çalışmalarda sık gözlenen papiller tiroid karsinomu solid varyant morfolojisi ve agresif biyolojik davranış özelliklerinin, daha sonra yapılan incelemelerde yaş grubu ile ilişkili olduğu bildirilmektedir.
- Radyasyon ilişkili papiller tiroid kanserleri *RET/PTC3* yeniden düzenlenimi ile ilişkili bulunmuştur. Diğer potansiyel moleküler belirteçler arasında 7. kromozomda kazanım (*7q11.22-11.23*), *CLIP2* aşırı ekspresyonu ve *CDKN1A* ekspresyonu yer almaktadır.
- En sık görülen radyasyon ilişkili sarkomlar andiferansiye pleomorfik sarkom, osteosarkom ve anjiyosarkomdur.
- Memenin radyasyon ilişkili anjiyosarkomunun bir diğer radyasyon ilişkili patolojik gelişim olan atipik vasküler lezyondan ayrımı klinik açıdan oldukça önemlidir.
- Memenin radyasyon ilişkili anjiyosarkomunda *MYC* ve *FTL4* amplikasyonlarının varlığı tanıya yardımcı olarak kullanılabilir.
- Radyasyon ilişkili gliomların çoğunda *PDGFRA* amplifikasyonu, *CDKN2A/B* kaybı, sporadik yüksek dereceli pediatrik gliomların aksine histon 3 varyantları veya *IDH1/2* genlerinde hotspot mutasyon yokluğu ile karakterize bir moleküler imza saptanmıştır.
- Radyasyon ilişkili menenjiomlarda sporadik olgularda daha önce saptanmamış *NF2* gen yeniden düzenlenimleri görülmüşken; sporadik menenjiomlarda bilinen *AKT1*, *KLF4*, *TRAF7* ve *SMO* genlerinde rekürren mutasyonlar ise radyasyon ilişkili olgularda saptanmamıştır.
- Radyasyon maruziyeti sonrası mesanede "kronik proliferatif atipik sistit (Çernobil sistiti)" olarak adlandırılan kanser öncüsü histopatolojik gelişim tariflenmiştir.
- Radon maruziyeti ile ilişkili akciğer kanserlerinde tümör mutasyon yükü fazla olup, bu tümörler DNA onarım yolaklarında bozuklukla ilişkilidir.

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