Bölüm
7

MYELOM BÖBREĞİ PATOFİZYOLOJİSİ

Sinan KAZAN[1]

GİRİŞ

Multiple myelomada(MM) böbrek birçok şekilde etkilenebilir (Sanders & ark., 1991, Sanders, 1994, Winearls, 1995, Cohen & ark., 1984, Haynes & ark., 2010, Bladé & ark.,1998). MM'deki farklı böbrek patolojileri farklı klinik tablo, tedavi ve prognoza sahiptir (Leung & Behrens, 2012). Bu nedenle, böbrek yetmezliği olan bir MM hastasını değerlendirirken MM'de böbrek hastalıklarının patofizyolojisini bilmek önemlidir. MM'de böbrek hastalığı genellikle plazma hücrelerinden monoklonal immunglobulin veya immünglobulin fragmanları üretimine bağlıdır. MM'de akut böbrek hasarı (ABH) için en sık görülen histolojik tanı myelom Cast nefropatisi (MCN) ve akut tübüler nekrozdur(ATN) (Leung & ark., 2008). Şiddetli ABH'sı olan hastaları değerlendiren başka bir çalışmada MCN en yaygın böbrek histopatolojisi olarak bulunmuştur (Rota & ark., 1987). Yapılan diğer çalışmalarda ise MCN, ATN, AL amiloidoz, monoklonal immünglobulin birikim hastalığı, hafif zincir fanconi hastalığı, membranoproliferatif glomerülonefrit, immünotaktoid glomerülonefrit, renal öneme sahip monoklonal gammopati ve myeloma infiltrasyonunun çeşitli oranlarda myelom hastalarında böbrek tutulumuna neden olabileceği gösterilmiştir (Ivanyi, 1990, Kapadia, 1980, Oshima & ark., 2001, Nasr & ark., 2012a, Solomon & ark., 1991, Leung & ark., 2012). Myelomdaki bu böbrek tutulumları klinikte kendilerini farklı şekillerde gösterebilmektedir. Bu bölümde monoklonal proteinlerin hasar mekanizmaları anlatıldıktan sonra klinik prezentasyon şekillerine göre böbrek hastalığı fizyopatolojileri ele alınacaktır.

[1] Dr. Sinan Kazan, Afyon Sağlık Bilimleri Üniversitesi Hastanesi, sinankazan@hotmail.com

Elektrolit anormallikleri

Hafif zincir proksimal tübülopatisi

Bazı hastalarda hafif zincirler, glomerüler filtrasyon hızında bir azalma olmadan sadece tübül disfonksiyonuna neden olur. Proksimal tübül bu durumdan en fazla etkilenen tübül parçasıdır (Sanders & ark., 1988a). Bu lezyonu üreten hafif zincirlerin, tübüler hücrelerde lizozomlardaki proteazlar tarafından bozulmalara karşı dirençli kılan eşsiz biyokimyasal özelliklere sahip değişken bir alana sahip oldukları görülmektedir (Leboulleux & ark., 1995). Tübüler fonksiyon bozukluğundan muhtemelen değişken alan fragmanlarının sonradan hücre içi kristal formasyonu ile birikmesi sorumludur (Decourt & ark., 1999). Proksimal tübülopatiye sebep olan hafif zincirlerin yaklaşık yüzde 90'ı kappa hafif zincirlerinden oluşmaktadır (Ma & ark., 2004).

Proksimal tübüler fonksiyon bozukluğu ayrıca hafif zincir reabsorbsiyonunu azaltarak hafif zincir Cast nefropatisini şiddetlendirebilir. Bir vaka serisinde 46 hastanın %38'inde Fanconi sendromu olduğu raporlanmıştır (Stokes & ark., 2016).

Sonuç

MM'de böbrek tutulumu olması prognostik bir gösterge olarak bilinmektedir. Myelom hastasında böbrek tutulumunun tipini ve tedavisini iyi bilmek hastalığın patofizyolojisine hakim olmayı gerektirir. Bu bölümde MM hastasında böbrek tutulum mekanizmaları ve klinik prezentasyona göre patofizyolojik mekanizmalar anlatılmıştır

Anahtar Kelimeler: böbrek, fizyopatoloji, multiple myelom, proteinüri

KAYNAKÇA

Akilesh S, Alem A & Nicosia RF. Combined crystalline podocytopathy and tubulopathy associated with multiple myeloma. Hum Pathol 2014; 45:875.

Alpers CE & Cotran RS. Neoplasia and glomerular injury. Kidney Int 1986; 30:465.

Arimura A, Li M & Batuman V. Potential protective action of pituitary adenylate cyclase-activating polypeptide (PACAP38) on in vitro and in vivo models of myeloma kidney injury. Blood 2006; 107:661.

Benabe JE & Martinez-Maldonado M. Hypercalcemic nephropathy. Arch Intern Med 1978; 138:777.

Bhutani G & et al. Hematologic characteristics of proliferative glomerulonephritides with nonorganized monoclonal immunoglobulin deposits. Mayo Clin Proc 2015; 90:587.

Bladé J & et al. Renal failure in multiple myeloma: presenting features and predictors of outcome in 94 patients from a single institution. Arch Intern Med 1998; 158:1889.

Bourke E & et al. Hypocomplementemic proliferative glomerulonephritis with C3 nephritic-factor-like activity in multiple myeloma. Nephron 1989; 52:231.

Bridoux F & et al. Glomerulonephritis with isolated C3 deposits and monoclonal gammopathy: a fortuitous association? Clin J Am Soc Nephrol 2011; 6:2165.

Carstens PH % Woo D. Crystalline glomerular inclusions in multiple myeloma. Am J Kidney Dis 1989; 14:56.

Cohen DJ & et al. Acute renal failure in patients with multiple myeloma. Am J Med 1984; 76:247.
Cohen HJ & Rundles RW. Managing the complications of plasma cell myeloma. Arch Intern Med 1975; 135:177.
Decourt C, & et al. Mutational analysis in murine models for myeloma-associated Fanconi's syndrome or cast myeloma nephropathy. Blood 1999; 94:3559.
DeFronzo RA & et al. Renal function in patients with multiple myeloma. Medicine (Baltimore) 1978; 57:151.
Dimopoulos MA & et al. Pathogenesis and treatment of renal failure in multiple myeloma. Leukemia 2008; 22:1485.
Fattori E & et al. Development of progressive kidney damage and myeloma kidney in interleukin-6 transgenic mice. Blood 1994; 83:2570.
Fogo A, Qureshi N & Horn RG. Morphologic and clinical features of fibrillary glomerulonephritis versus immunotactoid glomerulopathy. Am J Kidney Dis 1993; 22:367.
Gu X & Herrera GA. Light-chain-mediated acute tubular interstitial nephritis: a poorly recognized pattern of renal disease in patients with plasma cell dyscrasia. Arch Pathol Lab Med 2006; 130:165.
Haynes RJ & et al. Presentation and survival of patients with severe acute kidney injury and multiple myeloma: a 20-year experience from a single centre. Nephrol Dial Transplant 2010; 25:419.
Hobeika L, Self SE & Velez JC. Renal thrombotic microangiopathy and podocytopathy associated with the use of carfilzomib in a patient with multiple myeloma. BMC Nephrol 2014; 15:156.
Holland MD & et al. Effect of urinary pH and diatrizoate on Bence Jones protein nephrotoxicity in the rat. Kidney Int 1985; 27:46.
Huang ZQ & Sanders PW. Localization of a single binding site for immunoglobulin light chains on human Tamm-Horsfall glycoprotein. J Clin Invest 1997; 99:732.
Ivanyi B. Frequency of light chain deposition nephropathy relative to renal amyloidosis and Bence Jones cast nephropathy in a necropsy study of patients with myeloma. Arch Pathol Lab Med. 1990;114(9):986-987.
Iványi B. Renal complications in multiple myeloma. Acta Morphol Hung 1989; 37:235.
Jeon YL & et al. Crystalloid podocytopathy with focal segmental glomerulosclerosis in PCM: a case report. Diagn Pathol 2015; 10:213.
Kapadia SB. Multiple myeloma: a clinicopathologic study of 62 consecutively autopsied cases. Medicine. 1980;59(5):380-392.
Kyle RA & Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia 2009; 23:3.
Leboulleux M & et al. Protease resistance and binding of Ig light chains in myeloma-associated tubulopathies. Kidney Int 1995; 48:72.
Leung N & Behrens J. Current approach to diagnosis and management of acute renal failure in myeloma patients. Adv Chronic Kidney Dis. 2012;19(5):297-302.
Leung N & et al. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. Blood. 2012;120(22):4292-4295.
Leung N & et al. Improvement of cast nephropathy with plasma exchange depends on the diagnosis and on reduction of serum free light chains. Kidney Int. 2008;73(11):1282- 1288.
Lin J & et al. Renal monoclonal immunoglobulin deposition disease: the disease spectrum. J Am Soc Nephrol 2001; 12:1482.
Lodhi A & et al. Thrombotic microangiopathy associated with proteasome inhibitors. Clin Kidney J 2015; 8:632.
Ma CX & et al. Acquired Fanconi syndrome is an indolent disorder in the absence of overt multiple myeloma. Blood 2004; 104:40.
Markowitz GS & et al. Collapsing focal segmental glomerulosclerosis following treatment with high-dose pamidronate. J Am Soc Nephrol 2001; 12:1164.
Markowitz GS & et al. Toxic acute tubular necrosis following treatment with zoledronate (Zometa). Kidney Int 2003; 64:281.

McCarthy CS & Becker JA. Multiple myeloma and contrast media. Radiology 1992; 183:519.
Montseny JJ & et al. Long-term outcome according to renal histological lesions in 118 patients with monoclonal gammopathies. Nephrol Dial Transplant 1998; 13:1438.
Morgan C Jr & Hammack WJ. Intravenous urography in multiple myeloma. N Engl J Med 1966; 275:77.
Nasr SH & et al. Dysproteinemia, proteinuria, and glomerulonephritis. Kidney Int 2006; 69:772.
Nasr SH & et al. Proliferative glomerulonephritis with monoclonal IgG deposits: a distinct entity mimicking immune-complex glomerulonephritis. Kidney Int 2004; 65:85.
Nasr SH & et al. Proliferative glomerulonephritis with monoclonal IgG deposits. J Am Soc Nephrol 2009; 20:2055.
Nasr SH & et al. Fibrillary glomerulonephritis: a report of 66 cases from a single institution. Clin J Am Soc Nephrol 2011; 6:775.
Nasr SH & et al. Renal monoclonal immunoglobulin deposition disease: a report of 64 patients from a single institution. Clin J Am Soc Nephrol 2012a; 7:231.
Nasr SH & et al. Clinicopathologic correlations in multiple myeloma: a case series of 190 patients with kidney biopsies. Am J Kidney Dis. 2012b;59(6):786-794.
Oshima K & et al. Clinical and pathologic findings in 52 consecutively autopsied cases with multiple myeloma. Am J Hematol. 2001;67(1):1-5.
Pasquali S & et al. Renal histological lesions and clinical syndromes in multiple myeloma. Renal Immunopathology Group. Clin Nephrol 1987; 27:222.
Pirani CL & et al. Renal lesions in plasma cell dyscrasias: ultrastructural observations. Am J Kidney Dis 1987; 10:208.
Rota S & et al. Multiple myeloma and severe renal failure: a clinicopathologic study of outcome and prognosis in 34 patients. Medicine. 1987;66(2):126-137.
Said SM & et al. Renal amyloidosis: origin and clinicopathologic correlations of 474 recent cases. Clin J Am Soc Nephrol 2013; 8:1515.
Sakhuja V & et al. Renal involvement in multiple myeloma: a 10-year study. Ren Fail 2000; 22:465.
Sanders PW & et al. Mechanisms of intranephronal proteinaceous cast formation by low molecular weight proteins. J Clin Invest 1990; 85:570.
Sanders PW & Booker BB. Pathobiology of cast nephropathy from human Bence Jones proteins. J Clin Invest 1992; 89:630.
Sanders PW & et al. Differential nephrotoxicity of low molecular weight proteins including Bence Jones proteins in the perfused rat nephron in vivo. J Clin Invest 1988a; 82:2086.
Sanders PW & et al. Spectrum of glomerular and tubulointerstitial renal lesions associated with monotypical immunoglobulin light chain deposition. Lab Invest 1991; 64:527.
Sanders PW & et al. Morphologic alterations of the proximal tubules in light chain-related renal disease. Kidney Int 1988b; 33:881.
Sanders PW. Mechanisms of light chain injury along the tubular nephron. J Am Soc Nephrol 2012; 23:1777.
Sanders PW. Pathogenesis and treatment of myeloma kidney. J Lab Clin Med 1994; 124:484.
Sengul S, Zwizinski C & Batuman V. Role of MAPK pathways in light chain-induced cytokine production in human proximal tubule cells. Am J Physiol Renal Physiol 2003; 284:F1245.
Sengul S & et al. Endocytosis of light chains induces cytokines through activation of NF-kappaB in human proximal tubule cells. Kidney Int 2002; 62:1977.
Sepandj F & Trillo A. Dense deposit disease in association with monoclonal gammopathy of unknown significance. Nephrol Dial Transplant 1996; 11:2309.
Sethi S & et al. Crystal-storing histiocytosis involving the kidney in a low-grade B-cell lymphoproliferative disorder. Am J Kidney Dis 2002; 39:183.
Sethi S & Fervenza FC. Membranoproliferative glomerulonephritis--a new look at an old entity. N Engl J Med 2012; 366:1119.
Sethi S & et al. Membranoproliferative glomerulonephritis secondary to monoclonal gammopathy. Clin J Am Soc Nephrol 2010; 5:770.

Smolens P, Barnes JL & Kreisberg R. Hypercalcemia can potentiate the nephrotoxicity of Bence Jones proteins. J Lab Clin Med 1987; 110:460.

Solomon A, Weiss DT & Kattine AA. Nephrotoxic potential of Bence Jones proteins. New Engl J Med. 1991;324(26):1845-1851.

Stokes MB & et al. Light Chain Proximal Tubulopathy: Clinical and Pathologic Characteristics in the Modern Treatment Era. J Am Soc Nephrol 2016; 27:1555.

Wanchoo R & et al. Renal Toxicities of Novel Agents Used for Treatment of Multiple Myeloma. Clin J Am Soc Nephrol 2017; 12:176.

Wang PX & Sanders PW. Immunoglobulin light chains generate hydrogen peroxide. J Am Soc Nephrol 2007; 18:1239.

Winearls CG. Acute myeloma kidney. Kidney Int 1995; 48:1347.

Yamamoto T & et al. Crystal-storing histiocytosis and crystalline tissue deposition in multiple myeloma. Arch Pathol Lab Med 1991; 115:351.

Ying WZ & et al. Mechanism and prevention of acute kidney injury from cast nephropathy in a rodent model. J Clin Invest 2012; 122:1777.

Ying WZ & et al. Immunoglobulin light chains activate nuclear factor-κB in renal epithelial cells through a Src-dependent mechanism. Blood 2011; 117:1301.

Zand L & et al. C3 glomerulonephritis associated with monoclonal gammopathy: a case series. Am J Kidney Dis 2013; 62:506.