A Rare Cause of Progressive Renal Failure; Karyomegalic Tubulointerstitial Nephritis: Case Report

İlerleyici Böbrek Yetmezliğinin Nadir Bir Sebebi; Karyomegalik Tübülointerstisyel Nefrit

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ABSTRACT Karyomegalic tubulointerstitial nephritis is a rare disorder with unknown etiology which is characterized by excessive enlargement and widening of tubular epithelial cell nuclei. The disease, which is usually presented in the third decade of life, is accompanied by recurrent respiratory tract infections, as well as progressive impairment of renal function. In the light of the available literature, the case that we report is a 32-year-old man who had applied to a thoracic diseases center with complaints of weakness, fever, dyspnea, flank pain and vomiting, and antibiotic treatment had been initiated with preliminary diagnosis of pneumonia. Subsequently, when his urea, creatinine and hepatic enzyme levels were found to be high, the patient was referred to our hospital. The patient was investigated at internal medicine clinics and finally he was diagnosed as karyomegalic tubulointerstitial nephritis.

Key Words: Interstitial nephritis; renal failure

ÖZET Karyomegalik tübülointerstisyel nefrit etiyolojisi bilinmeyen, tübüler epitelyal hücre çekirdeklerinde aşırı büyüme ve genişleme ile karakterize nadir bir hastalıktır. Genellikle yaşamın üçüncü dekadında ortaya çıkan hastalığa renal fonksiyonlarda ilerleyici yetmezlikle birlikte rekürren solunum yolu enfeksiyonları da eşlik eder. Bu çalışmada, mevcut literatür ışığında sunmakta olduğumuz olgu ilk olarak bir göğüs hastalıkları hastanesine güçsüzlük, ateş, solunum güçlüğü, yan ağrısı ve kusma şikayetiyle başvuran ve pnömoni ön tanısı konularak antibiyotik tedavisine başlanan 32 yaşında bir erkektir. Hastanın yapılan biyokimya tetkiklerinde üre, kreatinin ve hepatik enzim seviyelerinin yüksek bulunması üzerine hastanemize yönlendirilmiştir. Hasta iç hastalıkları kliniğinde araştırılarak karyomegalik interstisyel nefrit tanısı konulmuştur.

Anahtar Kelimeler: İnterstisyel nefrit; böbrek yetmezliği

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Karyomegalic tubulointerstitial nephritis (KTN) is a rare disorder which is characterized by excessive enlargement of tubular epithelial cell nuclei. The disease, which is usually presented in the third decade of life, is accompanied by recurrent respiratory tract infections, as well as progressive impairment of renal function. The course of this disease, of which treatment is unclear, progresses to end-stage renal disease.[1]

This disease was first identified in 1974 by Burry and the term "KTN" was first used in 1979 by Mihatsch.[1,2]

In our study, we reported a renal failure case who has typical clinical features.

CASE REPORT

A 32-year-old man had applied to a thoracic diseases center with complaints of weakness, fever, dyspnea, flank pain and vomiting, and antibiotic treatment had been initiated with preliminary diagnosis of pneumonia. Subsequently, when his urea, creatinine and hepatic enzyme levels were found to be high, the patient was referred to our hospital.

The patient, who was hospitalized with preliminary diagnosis of pneumonia and acute renal failure, did not have recurrent upper respiratory tract infections and impaired renal function in his anamnesis. In physical examination, it was observed that his skin was pale and he had dyspnea. His arterial blood pressure was 90/60 mmHg and axillary body temperature was 37.7°C. On auscultation, coarse crackles and rhonchi were audible in lung bases. Hepatomegaly of 3 cm and splenomegaly of 1 cm were present. The patient had diuresis of 3000 mL/day. In laboratory examinations, sedimentation was found to be 109 mm/hour, and density 1012, protein 100 mg/dL in urinalysis. In microscopic examination of urine sediment, 3-4 epithelia, 2-3 erythrocyte casts and rare leucocytes were observed per high-power field. Urea and creatinine levels and hepatic enzyme levels were high (urea 157 mg/dL, creatinine 7.24 mg/dL, ALT 142 U/L and AST 104 U/L). Creatinine clearance was found to be 15 mL/min. A 24-hour urine sample was collected and in this analysis, a proteinuria of 2 grams a day was determined. In other biochemical investigations, some of the test results were found to be high; total bilirubin 2.6 mg/dL, direct bilirubin 1.5 mg/dL, GGT 550 IU/L, ALP 775 IU/L, globulin 4.8 g/dL, phosphorus 6.5 mg/dL, K 6.2 mEq/L, INR 1.4, PT 16.4 sec, aPTT 51.5 sec, and some were found to below; albumin 2.6 g/dL, calcium 8.5 mg/dL and Na 136 mEq/L. In protein electrophoresis, a reduced albumin band and increased alpha 1 (8.3%), alpha 2 (16.3%) and gamma (23.2%) bands were observed. Immunological investigations revealed high levels of CRP (15.2 mg/dL), IgA (579 mg/dL), IgG (1200 mg/dL), IgM (64.4 mg/dL), C3 (164 mg/dL) and C4 (45.5 mg/dL). Hematological investigations revealed anemia, leukocytosis and thrombocytosis (Hb 8.2 g/dL, Hct 24.6%, WBC 12.600/mL, PLT 619.000/mL). Parathyroid hormone level was found to be high (241.1 pg/mL). Hepatitis and HIV serological screening tests were found to be negative. No growth was detected in urine culture.

ANA, anti ds-DNA, c-ANCA and p-ANCA were found to be negative.

PA chest X-ray graphy revealed a bullous lesion with a diameter of 4 cm in the upper lobe of the left lung, and a non-homogenous consolidation area in the upper zone of the right lung (Figure 1). Computerized tomography images revealed multiple bullouse formations in various sizes in the lateral of the upper and the mid zones of both lungs (Figure 2a and 2b). Whole abdominal ultrasonography revealed a marked corticomedullary border, and increased parenchymal echogenity consistent with grade 1 nephropathy, in both kidneys. MR cholangiography was found to be normal.

In histopathological examination of renal biopsy, 12 glomerular structures were observed. 5 global sclerotic glomeruli were noticed (Figure 3). Collagenous material occupying Bowman's space was noticed in the sclerotic glomeruli, whereas the capillary basal membranes of the non-sclerotic glomeruli were observed as normal and lumens were in normal appearance. A quite large and pleomorphic appearance showing evident nucleolus in epithelial cell nuclei was noticed (Figure 4). In the

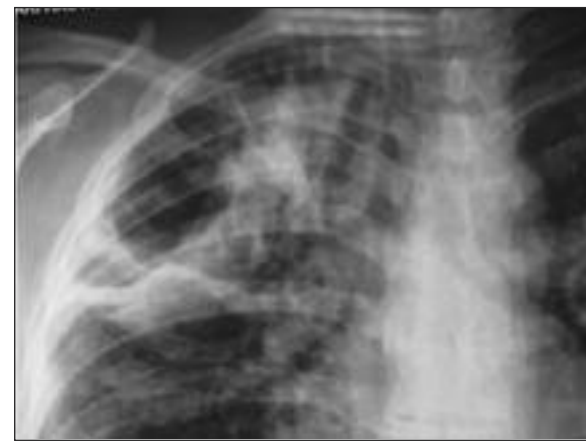
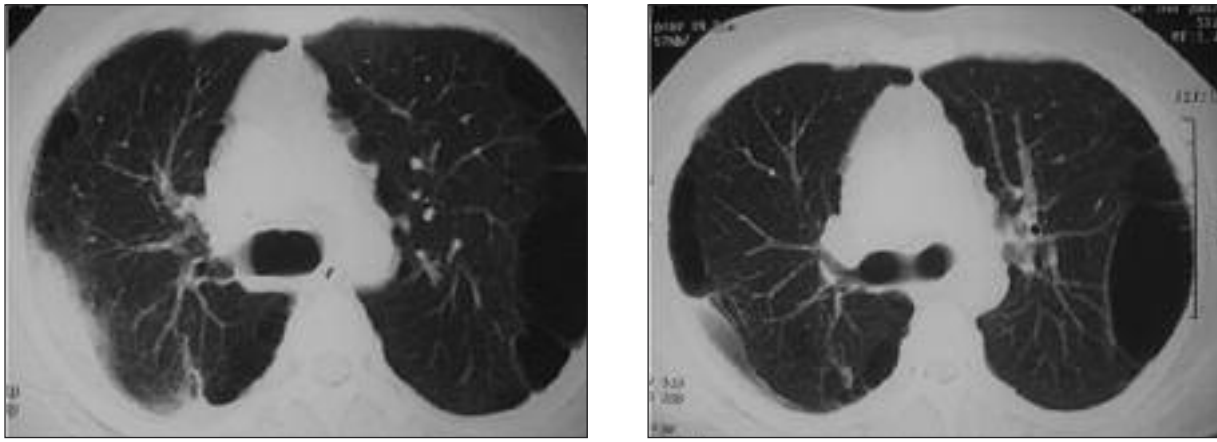


FIGURE 1: PA chest X-ray graphy reveals a bullous lesion in the upper lobe of the left lung, and a non-homogenous consolidation area in the upper zone of the right lung.



a b

FIGURE 2a, b: Computerized tomography images reveal multiple bullouse formations in various sizes in the lateral of the upper and the mid zones of both lungs.

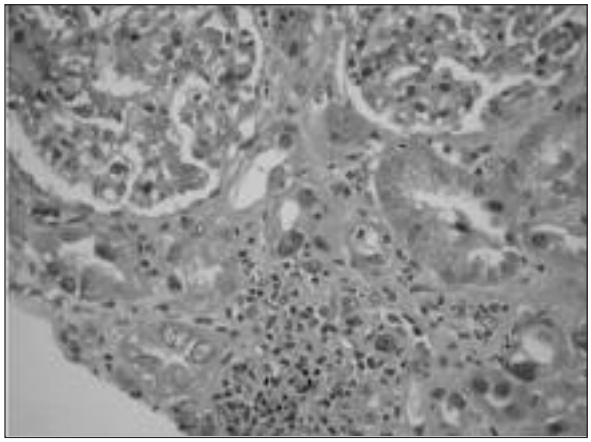


FIGURE 3: Glomerular structures in normal appearance and bulky, hyperchromatic appearance in tubuler epithelial cells (HEx125).

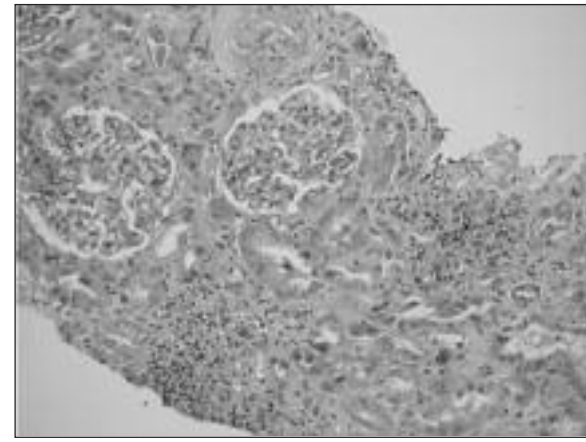


FIGURE 4: Hyperchromatic tubuler epithelial cells with nucleomegaly, sclerotic glomerular structure (HEx310).

epithelial cell cytoplasms, a vacuolar appearance, flattened and swollen in parts, was observed. In the tubular lumens, degenerated desquamous cells, and sparsely, granulated or hyaline casts were observed. Focal mononuclear cell infiltration and a slight fibrosis were detected in the interstitium. The patient was diagnosed with KTN according to the biopsy results. No features were observed in urine cytology.

HLA tissue group determination revealed A2, B40, B49, DRB1-07, DRB1-11.

The patient's urea and creatinine levels decreased during his hospitalization, and after a conservative treatment was arranged, he was planned to be followed as an outpatient. The patient remained in outpatient follow-up approximately 3 months and was prepared to hemodialysis in the meantime. Because his urea and creatinine levels increased and uremia symptoms started, the patient was planned to be treated by hemodialysis. His hemodialysis program is currently ongoing.

DISCUSSION

Systemic karyomegaly associated with KTN was first identified in 3 patients by Mihatsch et al.[1] The disease, which is characterized by dramatic enlargement of tubular epithelial cell nuclei, leads to chronic renal failure with progressive interstitial

fibrosis and tubular atrophy. In our case, histopathological examination of renal biopsy revealed focal global glomerulosclerosis, focal interstitial fibrosis and marked diffuse nucleomegaly in the tubular epithelia.

The pathogenesis of the disease is unclear and controversial. However, it was suggested that numerous environmental factors, toxins or viral pathogens might be responsible in the etiology of the disease. These include intensive analgesic use and exposure to heavy metals and a fungal toxin, Ochratoxin A. Ochratoxin A is a nephrotoxic and carcinogenic compound produced as a secondary metabolite by fungi.[3,4] Godin et al. demonstrated that Ochratoxin A has a role in the pathogenesis of this disease.[5] In our patient, there was no exposure to the environmental factors which are suggested that might be responsible from the pathogenesis. Although the mechanism is not clear, some genetic liabilities also lead to the disease.

In our patient, albumin/globulin ratio was decreased. We thought that this result was due to hypoalbuminaemia caused by 2 grams per day proteinuria which was revealed by 24-hour urine sample analysis.

The patient had an anemia with laboratory findings of Hb 8.2 g/dL and Hct 24.6%. This was probably due to chronic renal failure which caused decreased serum levels of hematopoietin which had an important role in hematopoesis.

In the preliminary laboratory analysis of the patient, we also noticed a high sedimentation rate of 109 mm/hour. This was simply thought to be because of the respiratory tract infection that the patient suffered from at the time of the application.

Spoendlin et al. mention the effect of a defect in the 6th chromosome associated with cellular major histocompatibility complex on the pathogenesis. It was found that some of the patients in this study commonly carry the HLA A9 and B35 types.[6] In our patient, HLA type is identified as A2, B40, B49, DRB1-07, DRB1-11. Spoendlin et al. also conducted a study on tissues of 4 patients to assess proliferation markers Ki-67, PCNA and cellular cycle control molecule p53, and they concluded that a mitotic block causes karyomegaly.

Most of the cases in the literature have a history of past respiratory tract infection that required antibiotic therapy. Similarly, our patient was admitted to our hospital with respiratory tract infection.

Atypical cytology was detected in urine in a series of 4 patients in the study conducted by Spoendlin et al.[6] In our case, we could not detect any atypical cells in urine. Although the position of urine cytological examination in KTN diagnosis is unclear, it is thought that it can be used in the asymptomatic family members. But it must be remembered that epithelial cells shed into urine may imitate carcinoma. However, cells with expanded vesicular nuclei of different appearance can help diagnosis.

Karyomegaly may not be limited with renal tubular epithelium. Moch et al. reported that karyomegaly was also detected in intestinal smooth muscle cells, vascular endothelium, alveolar epithelium cells, astrocytes, and Schwann's cells of peripheral nerves.[7]

In conclusion, the common characteristic in KTN cases is that they have a history of recurrent respiratory tract infections as well as chronic renal failure. Similarly, our patient admitted to the clinic with respiratory tract infection, findings consistent with chronic renal failure were identified and he was diagnosed with KTN according to the renal biopsy results. It is seen that histopathology plays the main role in diagnosis of this disease, of which etiopathogenesis is yet unclear.

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