Nefropati Epidemika (İdrar Sitolojisindeki Bulguları)

Nephropathia Epidemica (Cytological Findings in the Urine)

*** Gürcan Vural, * Bjorn Hagmar, ** Arne Brantsæter**

* Clinical Cytology, Norwegian Radium Hospital

** Physician, Department of Medicine, Bærum Hospital.

ÖZET

Nefropati epidemika İskandinav ülkeleri ve Rusya'da endemik olarak görülen, Puumala virus tarafından oluşturulan bir zoonozdur. Nefropati epidemika'daki klinik bulgular, Hantaan-virus tarafından oluşturulan renal sendromla giden, hemorajik ateş yapan diğer zoonozların tersine hafiftir.

Bu olgu sunumunda 59 yaşındaki bir kadında görülen nefropati epidemika'ya ait sitolojik bulgular tarif edilmektedir. En önemli bulgu kateter ile alınmış idrarda tubuler hücrelerin görülmesidir. Ayırıcı tanı açısından ise adenokarsinoma en önemli patolojidir.

Anahtar Kelimeler: *Nefropati epidemika, Puumala virüs, idrar sitolojisi, renal tubüler hücreler.*

SUMMARY

Nephropathia epidemica is a zoonosis caused by Puumala virus which is endemic in Scandinavia and Russia. The clinical course of nephropathia epidemica is mild in contrast to the other zoonosis of hemorrhagic fever with renal syndrome (HFRS) caused by Hantaan-virus.

This report describes the cytologic findings nephropathia epidemica in a 59 year-old woman. The main finding was tubular cells in catheter urine and the main differential diagnosis is adenocarcinoma.

Key Words: *Nephropathia epidemica, Puumala virus, Urine cytology, Renal tubular cells.*

INTRODUCTION

In 1934 Zetterholm and Myhrman reported independently a disease occurring in northern Sweden (1). This disease was characterized by an acute onset and the main symptoms were fever, headache, neck stiffness, dizziness, back pain, abdominal pain, nausea, vomiting, loss of appetite, conjunctival irritation, neurological symptoms as well as signs and symptoms of renal failure (2).

In 1945 Myhrman recommended the name nephropathia epidemica (NE) for this disease (3). The name hemorrhagic fever with renal syndrome (HFRS) was suggested by Gajdusek (4).

Yazışma Adresi:

Dr. Gürcan Vural
Cemil Topuzlu Cad. 114/39
Caddebostan/İSTANBUL
Tel: (0216) 353 65 09
(0212) 233 94 48
Fax: (0212) 233 92 46

NE is a Puumalavirus-caused zoonosis and is transmitted to man by inhalation of the virus in desiccated excrement of infected animals. Bank vole (Clethrionomys glareolus) is the most common natural host in the Northern countries. The disease in endemic in forested areas (2).

Diagnosis is made by demonstration of antibody titer to virus (5). Serum creatinine rises and the urine contains albumin and casts.

Treatment includes restitution of fluid and electrolyte balance. Mortality is 0.2-0.5%.

The main histologic finding in NE in an acute interstitial nephritis. Renal biopsies from NE patients have shown deposits of immunglobulins and complement factors in the glomerular basement membrane, along the tubular basement membrane, in the mesangium and in the interstitium (6). Various kinds of deposits are seen in the glomeruli by electron microscopy (3). Tubular casts are frequent (1). Histologically the diagnosis is suggested by interstitial edema, a diffuse but sparse inflammatory infiltrate, dilatation of occasional tubules, and congestion and hypercellularity of the glomeruli.

CASE

A 59 year old woman was admitted to the hospital with a three day history of fever, nausea, abdominal discomfort, generalised muscular pain and gradually increasing headache. Eight years previosly malignant melanoma of the left choroid was diagnosed. She was operated and subjected to regular follow-up but no recurrence had been noted. On presentation, her blood pressure was 130/75 mm Hg, pulse rate was 80/min. and temperature was 38.5°C. We found abdominal tenderness mainly localised to the epigastrium and left lumbar region. The values for initial blood and urine tests were all within the normal range. Cerebral computed tomography scan, X-ray films of the chest and abdominal ultrasound were all normal. On day 6 the patient developed acute oliguric renal failure, with serum creatinine increasing to maximum 819 µmol/L (50-125 µmol/L) and blood urea nitrogen (BUN) to maximum 24.7 mmol/L (3-8.5 mmol/L). She later entered a polyuric phase and was given intravenous fluid to compensate for fluid loss and electrolyte disturbances. Serum creatinine and BUN were within normal range on day 13. Tests for anti-DNase B, anti-streptolysin O, Adenovirus and Mycoplasma complement fixing antibodies, Chlamydia IgG antibody, anti-glomerulus antibody, anti-nuclear antibody, rheumatoid factor and complement C3 and C4 were all negative. Due to abnormal findings in the urine and a suspicion of metastasis from the patient's malignant melanoma, a urine sample was sent for cytological examination.

Cytologic Findings

A catheterized urine specimen was obtained at cystoscopy and was fixed by an equal volume of 50% ethanol. The urinary cells were collected by Millipore filtration and stained with the Papanicolaou stain.

The specimen was relatively cellular (Fig. 1). Tiny cell groups, lying in a background of dissociated polygonal squamous cells were observed. These cells were arranged in tubular structures, and the epithelial cells in these structures had slightly irregular, rounded nuclei and prominent nucleoli (Fig. 2). Some of these nuclei were eccentric. The cytoplasm was rather abundant, sometimes vacuolated. Some tubular structures showed dilated lumina filled with hyaline material (Fig. 3).

Immunocytochemical staining specific for malignant melanoma was negative. Serological tests were positive for anti-nephropathia epidemica virus IgG (IF) and anti-nephropathia epidemica virus IgM (EIA). The patient's temperature gradually subsided, but the polyuric phase was protracted, lasting till day 26. She was discharged from the hospital on day 37.

FIGURE 1: Smear of urine. Tubular structure (Papanicolaou stain, x400)

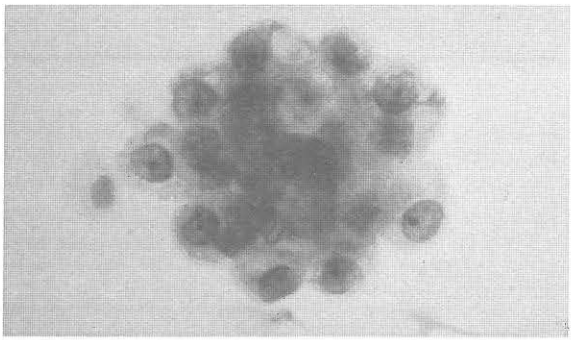


FIGURE 2: Smear or urine. Tubular cells with abundant, vacuolated cytoplasm (Papanicolaou stain, x400)

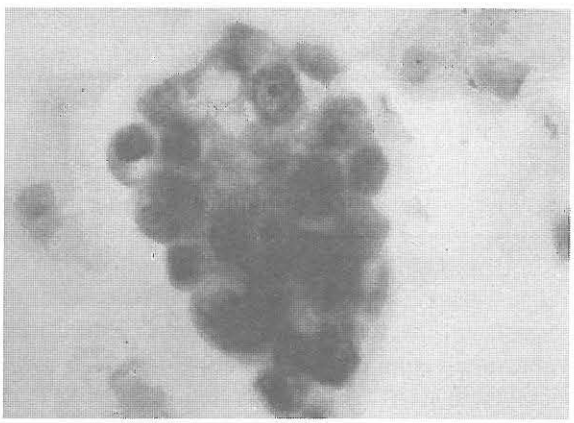
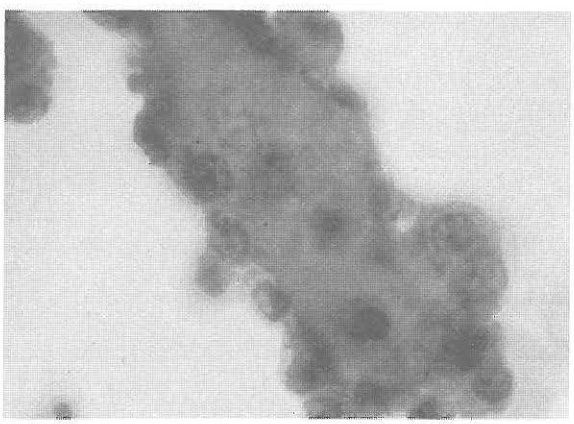


FIGURE 3: Smear or urine. Hyaline in the dilated lumen of renal tubulus (Papanicolaou stain, x400)



DISCUSSION

In the literature there are three microscopic investigations of urine sediments from patients with NE (7, 8, 9). All of them were carried out by phase contrast microscopy and showed that urinary sediments from patients with NE contain many renal epithelial cells, degenerated cells and a few urothelial cells. The authors reported that phase contrast microscopy was useful but not entirely satisfactory because of rapid degeneration of cells in the urine (7, 8, 9). Wahlin and co-workers stated that phase contrast microscopy of urinary sediment may provide pathognomonic evidence for endemic nephropathy (9).

Remal tubuler cells can be present in the urine in CMV infection (10). In this infection, however, the tubular cells have viral inclusions, which are surrounded by individual halos, in the nucleus and in the cytoplasm. The presence of tubular cells in the urinary sediment is also one of the important features of renal allograft rejection (11). Other characteristics of renal allograft rejection are: red blood cells, lymphocytes, "dirty" background and mixed cells clusters.

The diagnosis of NE is mainly serologic. Lately Hedman and co-workers have developed a test, which measures the avidity (functional affinity) of IgG antibodies against Puumala virus, for rapid and better serodiagnosis of NE (5).

In spite of this, we believe that cytology can be useful to help clinicians establish the diagnosis at the onset of the infection. Exfoliative cytology will serve a different purpose other than for tumor diagnosis. But hematuria, as seen in NE, may mislead the clinicians initially to suspect a tumor of the urinary tract. Tubular cells, as described here can be mistaken for cancer cells. In fact, in our case, the urine specimen was submitted because the registar receiving the patient observed large cells in the urine suspicious for tumor. Consequently, the cytological findings of NE need to be differentiated from adenocarcinoma and urothelial carcinoma. In adenocarcinoma, the malignant cells often have large, hyperchromatic nuclei and vacuolated cytoplasm. In urothelial carcinoma, the nuclei of cancer cells are large, sometimes bizarre in shape, with large nucleoli, and the cytoplasm in often cyanophilic.

We saw mild irregularity in the tubular cells but the lack of significant cytologic atypia argues against carcinoma. Renal tubular cells are rounded, with eccentric light-gray nuclei in which the nucleoli are clearly visible. The cytoplasm is homogenous, without granules. The presence of tubular structures sometimes even with hyaline material in lumina should rule out the cancer diagnosis. Cytology consequently can be useful in supporting the diagnosis of NE.

REFERENCES

1 Collan Y., Mihatsch MJ., Lahdevirta J., et al.: Nephropathia epidemica: Mild variant of haemorrhagic fever with renal syndrome. Kidney Int, 40, Suppl. 35: 62-71, 1991.

2 Lahdevirta J.: Nephropathia epidemica in Finland. Ann Clin Res. 3: 1-154, 1971.

3 Collan Y, Lahdevirta J., Jokinen EJ.: Electron microscopy of nephropathia epidemica. Virchows Arch A Path Anat Hist. 377: 129-144, 1978.

4 Gajdusek DC.: Virus haemorrhagic fevers. Special reference to haemorrhagic fever with renal syndrome. J Pediatr 60: 841-857, 1962.

5 Hedman K., Vaheri A., Brummer M.: Rapid diagnosis of hantavirus disease with an IgG-avidity assay. Lancet 338: 1353-56, 1991.

6 Billheden J., Settergren B., Stegmayt B., Juto P.: Detection of serum IgM antibodies to glomerular basement membrane in two cases of nephropathia epidemica. J Int Med 232: 91-93, 1992.

7 Lindqvist B., Wahlin A.: Differential count of urinary leucocytes. Acta Med Scand 198: 505-509, 1975.

8 Settergren B.: Nephropathia epidemica in Scandinavia. Reviews Infect Dis. 13: 736-44, 1991.

9 Wahlin A., Lindqvist B., Nyström K.: The urinary sediment in endemic benign nephropathy. Acta Med Scand 202: 51-54, 1977.

10 Koss LG.: Diagnostic Cytology and Its Histopathologic Bases. 3. edition, JB Lippincott, Philedelphia, 1979, 728.

11 Schumann GG., Burleson RL., Henry JB., Jones DB.: Urinary cytodiagnosis of acute renal allograft rejection using the cytocentrifuge. Am J Clin Pathol. 67: 134-140, 1977.