# HEPATOCYTES IN NAIL-PATELLA SYNDROME

UFUK Ö. METE*
MEHMET KAYA*
EMEL AKOGLU*
SALIH ÇOLAKOGLU*

*SUMMARY: A case of nail-patella syndrome accompanied by oliguria, hypertension and proteinuria in a 25 year old woman is described. She had deformities of the elbows, dystrophic toe nails, iliac horns and renal failure. Electron microscopic examination of the liver biopsy revealed lipid accumulation, glycogen depletion and vacuolar formation both in the cytoplasm and nucleus of the hepatocytes. In this study, the significance of these findings and the possible pathophysiology of the disease are discussed. The liver alterations represent a new manifestation of this syndrome and have never been described previously.*

*Key Words: Nail-patella syndrome, hepatocytes, ultra-structure.*

## INTRODUCTION

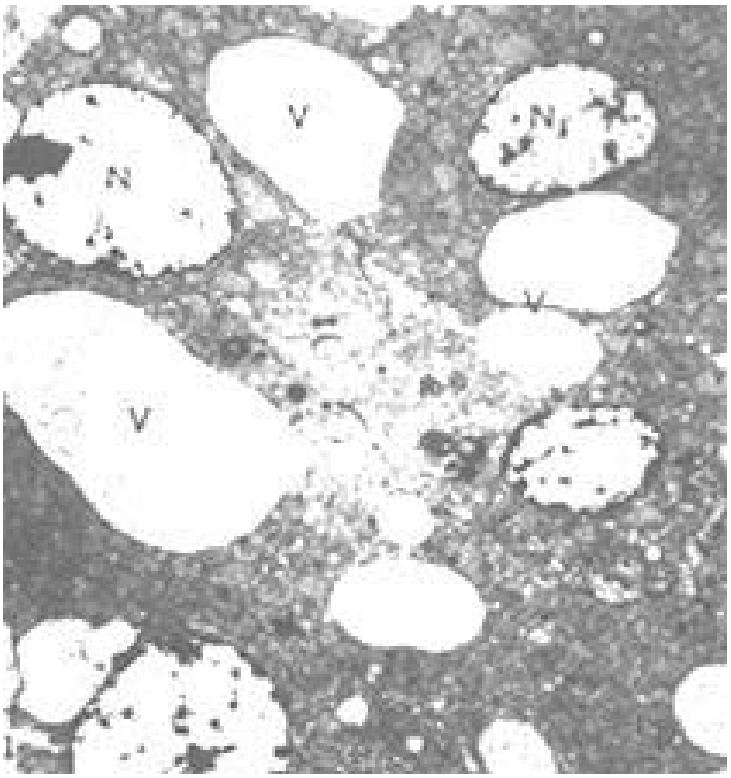
The nail-patella syndrome, an autosomal dominant hereditary disease (3-5, 8,18) is mainly associated with the dystrophy of the nails, absence or hypoplasia of the patella, deformities of elbow joints and iliac horns (3, 4,10,16,17). It can also be accompanied by renal complication and renal manifestations ranging from asymptomatic proteinuria and nephrotic syndrome to end stage renal failure (2-4, 6-8, 12,13,15-18). As a result of electron and light microscopic studies some invaluable structural changes of the kidney, particularly, in the glomerulus have been observed (1-7,12,13,16-18). The structural abnormalities of varying organs have previously been reported in nail-patella syndrome, but have never been described in the liver. The aim of this report is to include the ultrastructural changes in the liver to the present data about the nail-patella syndrome.

## CASE REPORT

A 25 year-old woman was hospitalized for unconsciousness and contraction of her extremities. Nail-patella syndrome was diagnosed 12 years ago as the patient had a history of hypertension with Grade IV retinal papilledema and increased blood urea nitrogen (BUN). The family history revealed that all three of her siblings, her father and the most of the other paternal family members also had nail-patella syndrome. Clini-

* From Department of Histology-Embryology, Faculty of Medicine, University of Çukurova, Balcali, Adana, Türkiye.

Figure 1: Abundant different sized vacuoles (V) markedly large almost reaching to the size of nucleus (N) are seen in the cytoplasm. X 5000.



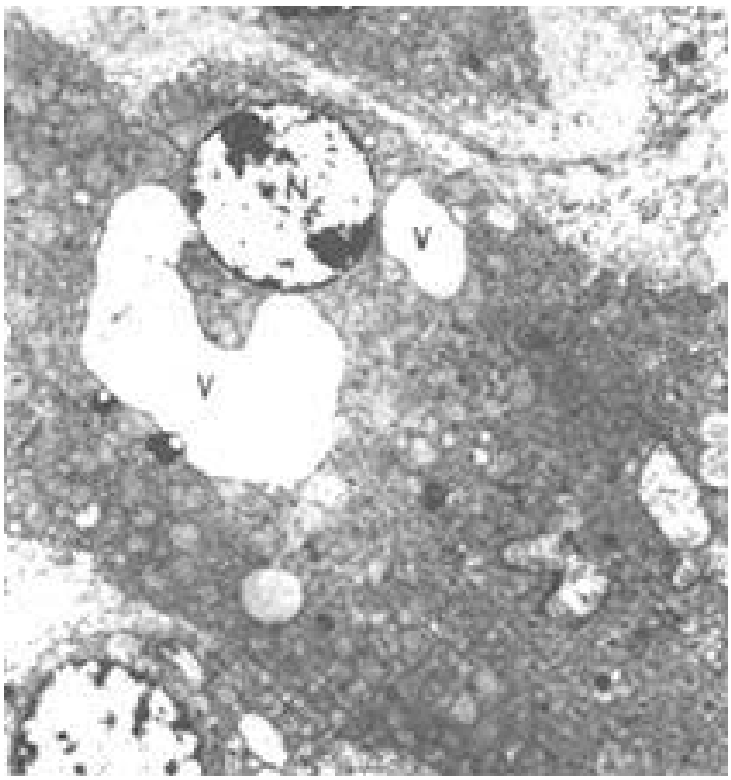

cal progress of this syndrome shows some differences between the family members. Her 68 year-old uncle has severe proteinuria and still alive. However, her sister who is 23 years old had proteinuria and uncontrolled hypertension. There was webbing at the elbow joints and flexion and extension deformities. The nails of both thumbs and index fingers were hypo-plastic and the patellae were bilaterally small. Although she had medical therapy, she died due to relapsing pleural effusion and cardiac failure. Generally, the clinical signs of nail-patella syndrome appear in the second decade and cause death in the third decade, like our patient and her sister.

Table 1

| Hematocrit : 15 % | |
|---|---|
| WBC | : 4200/mm3 |
| BUN | : 180mg/dl |
| Serum creatinine | : 15 mg/dl |
| Serum calcium | : 8.8 mg/dl |
| Serum phosphorus | : 5.6 mg/dl |

On physical examination, the patient's blood pressure was 170/115 with a pulse of 100. She had sacral and pretibial edema and her liver was palpable 3 cm below the right costal margin. The toe nails were dystrophic and there was webbing at the elbow joints. Results of laboratory studies are seen in (Table 1). Roentgenography of the pelvis showed the iliac horns. Although peritoneal dialysis was performed, the

Figure 2: The irregular outlined vacuoles (V) are seen near the nucleus (N). X 5000.



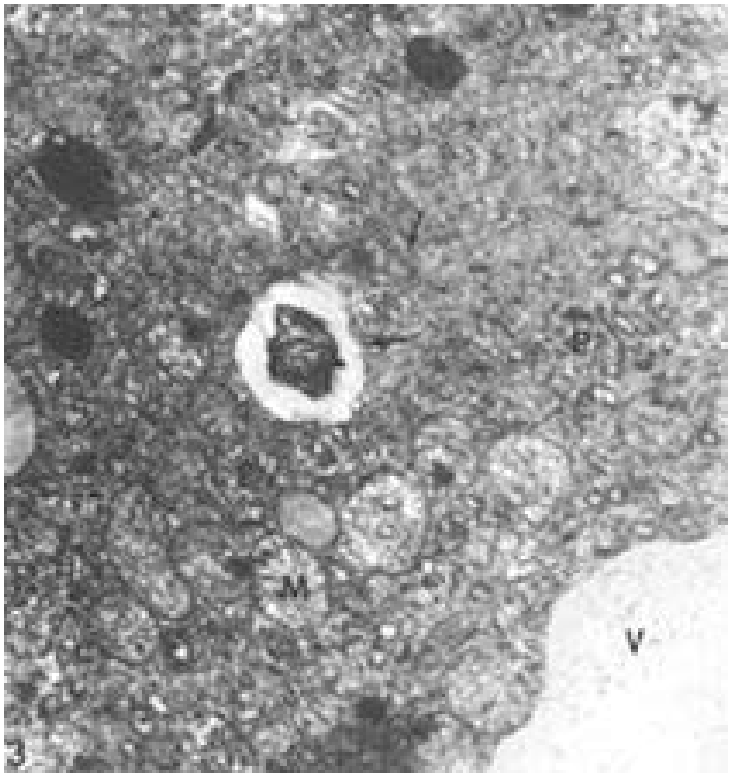

patient died due to the development of uremic pericarditis and cardiac failure.

Postmortem liver biopsy material obtained from the patient with nail-patella syndrome was immediately placed in 5% glutaraldehyde buffered at pH 7,4 with phosphate buffer for 4 hours. The pieces of tissue were subsequently fixed in 1% $O_SO_4$ for 2 hours. They were then dehydrated in graded ethanols and embedded in Araldite. 500 A° thick sections were cut by a Reichart OMU-3 ultramicrotome, double stained with Uranyl acetate and lead citrate and examined with Zeiss EM 10 B electron microscope.

## RESULTS

Electron microscopic examination of the liver biopsy material disclosed distinct ultrastructural alterations. The most prominent feature was occurrence of vacuoles of various size in the cytoplasm of hepatocytes (Figures 1 and 2). Some of the vacuoles contained laminated membranous structures presumably originating from cytoplasmic lysis of hepatocytes (Figure 3). Many vacuoles containing finely granular content, on the other hand, were present in almost all hepatocytes. They were variously sized even some were enormously large, almost reaching to the size of the nucleus or even larger (Figures 1 and 2). This type of vacuoles were present throughout the cytoplasm, but mostly and particularly near the bile canaliculus or perisinusodial spaces (Figure 4). Interestingly, the vacuoles were variously shaped including oval, rounded or irregularly outlined (Figures 1 and 2). Some lipid droplets and lipofuchsin granules were

Figure 3: There were membranous structures (arrows) and peroxisomes (P) with dense, granular matrix. Notice the glycogen depletion. Mitochondria (M), vacuole (V). X 20000.

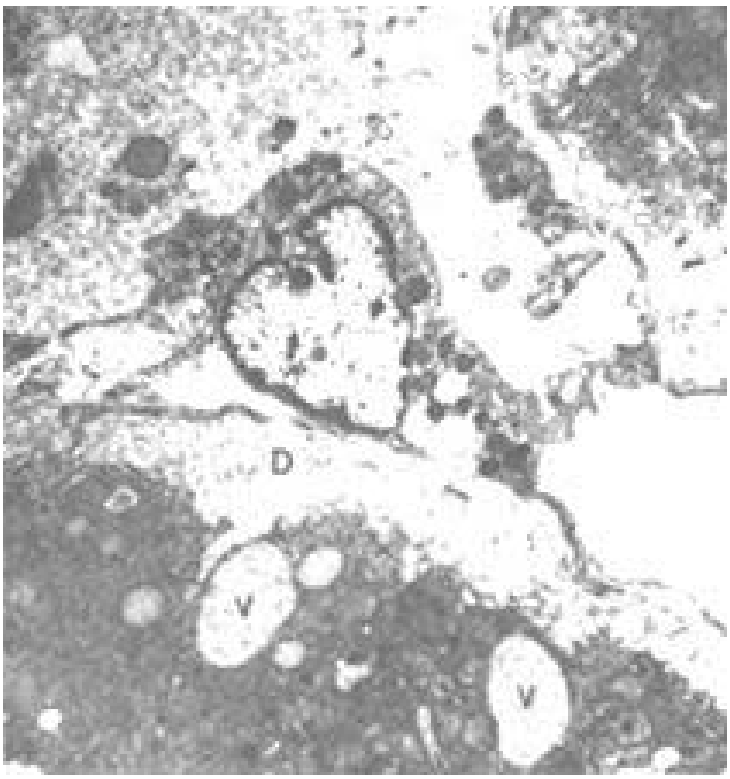



noted to bulge towards the vacuoles, eventually lipid droplets were seen lying freely but membrane bounded within the vacuoles in cross sections (Figures 5 and 6).

Membrane bounded free lipid droplets were also observed frequently in the cytoplasm of hepatocytes. Their sizes were various and some of them were fusing with each other, forming larger lipid droplets (Figures 7 and 8). In some of the micrographs, peroxisomes of various sizes with electron dense, granular matrix were seen (Figure 3). Great number of hepatocytes revealed the existence of abundant lipofuchsin granules (Figure 8). Although glycogen particles in normal hepatocytes can be seen, it is interesting to note that the liver parenchymal cells of the patient did not exhibit any glycogen particles, if present they were ignorable in amount (Figures 3 and 7).

One other significant observation was the presence of lipid droplets in the nucleus; they were either free or surrounded by cytoplasmic rim. On the other hand, there were several cytoplasmic patches without any lipid droplets within the nucleus. Cytoplasmic patches with or without lipid droplets were always surrounded by double membrane, outer areas of which was always delimited by heterochromatin as to be seen at the periphery of the nucleus, just beneath the nuclear membrane. Although the nuclei were usually round in shape, occasional ellipsoid and irregularly outlined nuclei exhibiting cytoplasmic invaginations, were also observed (Figures 5 and 9).

Figure 4: The intracytoplasmic vacuoles (V) are present near the Disse space (D). X 6300.



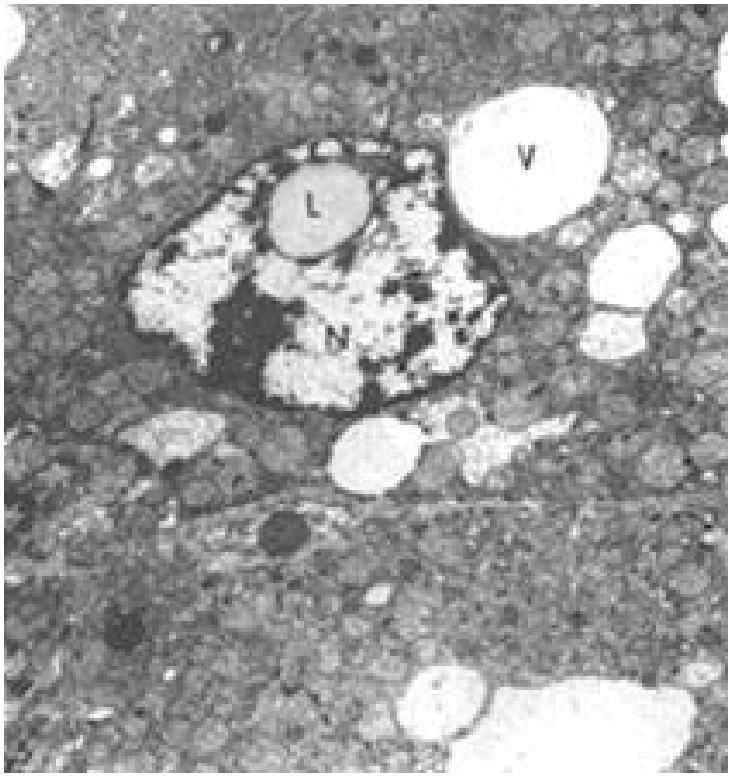

DISCUSSION

Nail-patella syndrome, or hereditary osteo-onychodysplasia is a rare disease characterized by absence or hypoplasia of the patellae, nail dysplasia, skeletal deformities involving the elbow joints and presence of iliac horns (3, 4,10,16,17). But, it is interestingly noted that each case study brought attention to the structural abnormalities of various organs including kidney, skin, blood vessels and eye (3-5, 7-18). Electron microscopic examination of renal biopsy specimens of the patients with nail-patella syndrome revealed irregular thickening of glomerular basement membrane, increased mesangial matrix and deposition of IgM and $C_3$ along basement membrane. Pozo and Lapp (17) and Ben-Bassat *et al.* (3) were the first investigators to report the presence of electron lucent areas, as known moth eaten appearance, in the thickened glomerular basement membrane. This appearance is pathognomonic feature in nail-patella syndrome (24). The epidermal basement membrane in a patient with nail-patella syndrome was thickened as well as having reduplication of the lamina densa.

The patient in this study had typical nail-patella syndrome according to clinical findings, radiology and family history. Electron microscopy of renal biopsy such as glomerular sclerosis, thickened glomerular and capillary basement membrane and multi-lamination of tubular basement membrane had also supported her disease.

Now, it is widely accepted that nephropathy is a recognized component of this syndrome although

Figure 5: Variously sized lipid droplets (L) surrounded by a cytoplasmic rim (arrows) are seen in the nucleus (N). Vacuoles (V). X 8100.

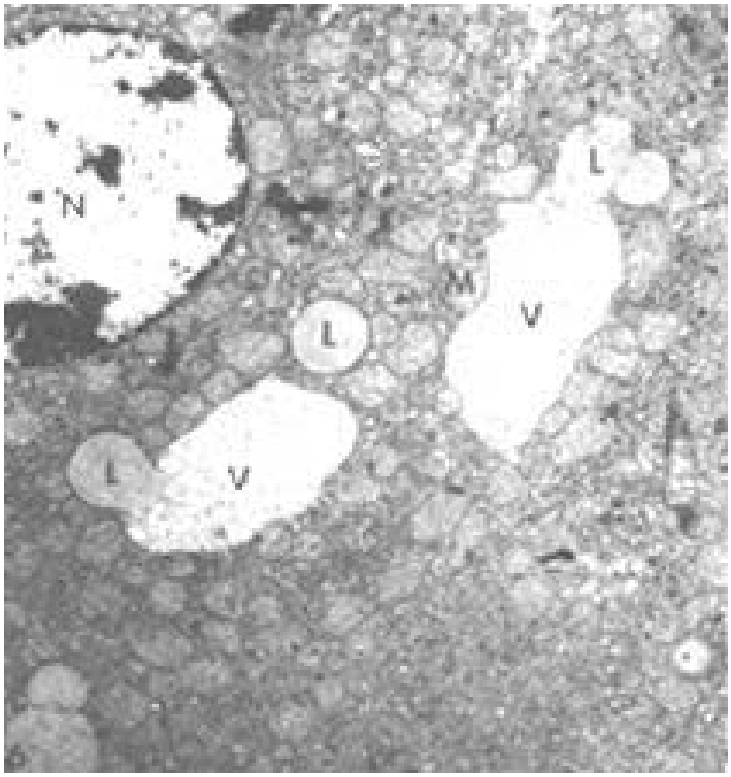



the clinical and pathologic features of this renal involvement still remain ill defined. As the diagnosis of the nail-patella syndrome in this patient is well documented both clinically and by family story supported by renal ultrastructural findings, liver alterations represent a new manifestation of this syndrome and liver pathology have never been described previously.

Electron microscopic examination of the liver biopsy material showed lipid accumulation and peroxisomes with homogenous, electron dense matrix in the cytoplasm of the hepatocytes. Accumulation of the lipid suggest that these inclusions is not able to enter the blood circulation and could be related to the disordered lipid metabolism in the liver. The function of peroxisomes remain obscure. However, peroxisomes abnormalities in association with the lipid accumulation indicate their roles in lipid metabolism. The presence of lipofuchsin granules and membranous structures are considered to be related with severe degeneration in these cells. Accumulation of lipofuchsin granules may represent failure of secretion of end product via biliary system. Glycogen depletion of the liver could be correlated with the disordered glycogen metabolism.

On the electron microscopic level it is clearly evidenced that the cytoplasmic rim around the intranuclear lipid derived from the cytoplasm of hepatocytes. The authors are indeed aware of the fact that portal hypertension could cause invagination of intercellular space towards the cytoplasm of hepatocytes (14); this phenomenon eventually will force

Figure 6: The lipid droplets (L) and mitochondria (M) are bulged towards the vacuoles (V). Nucleus (N). X 8100.

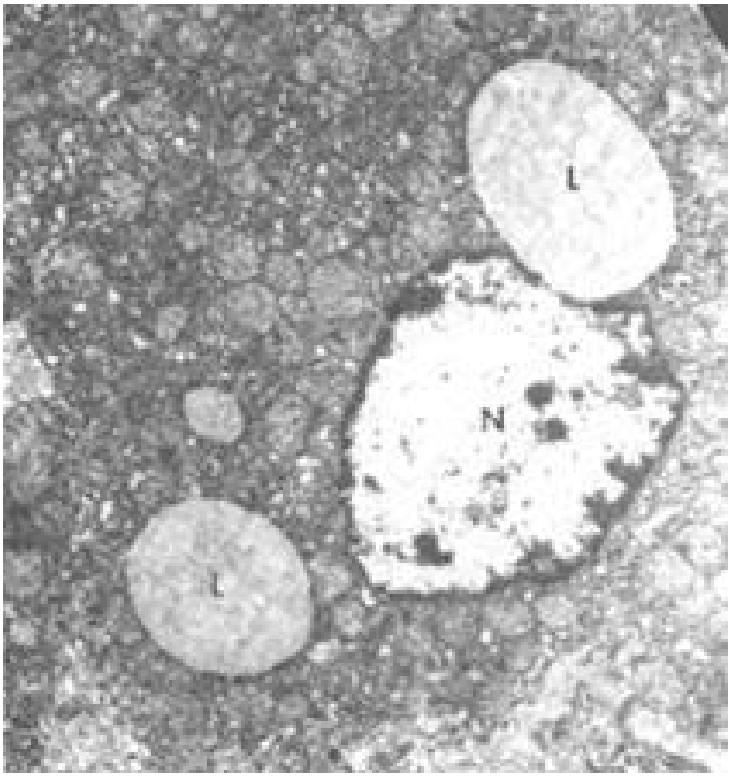



the cytoplasm to introduce the nucleus. In cross sections of hepatocytes, cytoplasmic invaginations frequently appear as intra-nuclear vacuoles containing cytoplasmic patches with lipid droplets. It should be remembered that increased blood pressure causes the appearance of vacuoles in hepatocytes. One reason for the development of these vacuoles could well be the hypoxia which could be expected in the hypertensive patients. Failure of the renal function undoubtedly will cause the accumulation of toxic material in the body. This of course would effect the metabolic organs in the body causing ultrastructural alterations such as vacuoles in the cytoplasm of the hepatocytes, which has also been reported by Meiss *et al*. (14) in rat and mice after experimental intoxication. These authors noted a vacuolation and widened intercellular spaces in liver parenchymal cells and supposed that these vacuoles derived from the intercellular spaces.

Limpaphayom *et al*. (12) suggest that the common cause of such diverse abnormalities, in bones, joints, ligaments, muscles, nails and kidney could be related to connective tissue disorders. It has been considered by some investigators that the fibrinoid necrosis of arterioles, thickening of the wall of the larger arterioles, the presence of many collagen fibrils in the thickened basement membranes and mesangial matrix are specific abnormalities possibly representing a congenital metabolic disorder of connective tissue (12,16).

Waste products accumulates in the body due to renal failure which in turn will effect the hepatocytes as

Figure 7: There were enormous sized lipid droplets (L) in the cytoplasm of hepatocyte. Nucleus (N). X 12400.




the liver is the major organ for detoxification. Furthermore, it should be remembered that nail patella syndrome is a metabolic disorder and the liver is the largest metabolic organ in the body. Above mentioned findings clearly suggest that the nail-patella syndrome also effect the liver as the other organs such as kidney, skin, blood vessel and eye.

## REFERENCES

*l. Akoglu E, Kaya M, Tuncer I, Tunali C, Sagliker Y, Gürçay A : Nail-Patella syndrome. Bulletin of the Çukurova Medical Faculty, 1:46-54, l987.*

*2. Angelov A, Boykinov B, Ragiev M : Electron microscope study of renal lesions in nail-patella syndrome. Fol Med, 11:41-46, 1981.*

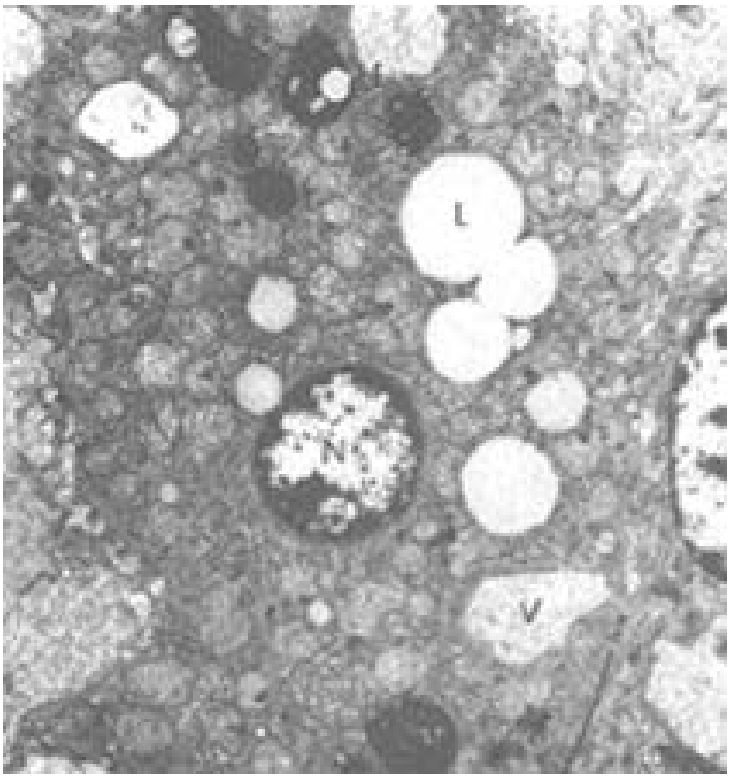
*3. Ben-Bassat M, Cohen L, Rosenfeld J : The glomerular basement membrane in the nail-patella syndrome. Arch Path, 92:350-355, 1971.*

*4. Bennet WM, Musgrave JE, Campbell RA, Elliot D, Cox R, Brooks RE, Lovrien EX, Beals RK, Porter GA : The nephropathy of the nail-patella syndrome. Clinicopathologic analysis of 11 kindred. Am J Med, 54:304-319, 1973.*

*5. Bhatnagar LK, Goyal VK, Sethi JP, Abbas SG, Agrawall GR : Hereditary onycho-osteodysplasia syndrome (Hoods). JAPI, 30:623-625, 1982.*

*6. Browning MC, Weidner N, Lorentz Jr WB : Renal histopathology of the nail-patella syndrome in a two-year-old boy. Clin Nephrol, 29:210-213, 1988.*

Figure 8: The intra-cytoplasmic vacuoles (V) filled by finely granular material and variously sized lipid droplets (L) are seen. Nucleus (N), lipofuchsin granules (Lf). X 10000.




*7. Burkhart CG, Bhumbra R, Iannone AM : Nail-patella syndrome. A distinctive clinical and electron microscopic presentation. J Am Acad Dermatol, 3:251-256, 1980.*

*8. Croock AD, Kahaleh MB, Powers JM : Vasculitis and renal disease in nail-patella syndrome: A case report and literature review. Ann Rheum Dis, 46:562-565, 1987.*

*9. Daniel CR, Osment LS, Noojin RO : Triangular lunulae. A clue to nail-patella syndrome. Arch Dermatol, 116:448-449, 1980.*

*10. George S, Narasimhan P, Banerjee MK, Basha SA : Nail-patella syndrome. JAPI, 33:304-305, 1985.*

*11. Kouskoukis C, Tousimis A, Minas D : The nail-patella syndrome. J Dermetal Surg Oncol, 7:715-718, 1981.*

*12. Limpaphayom M, Pochanugool C, Pathmanand C, Chitinand SP, Bhongsvej S, Supapidhayakul S : The nail-patella syndrome. J Med Ass Thailand, 59:36-42, 1976.*

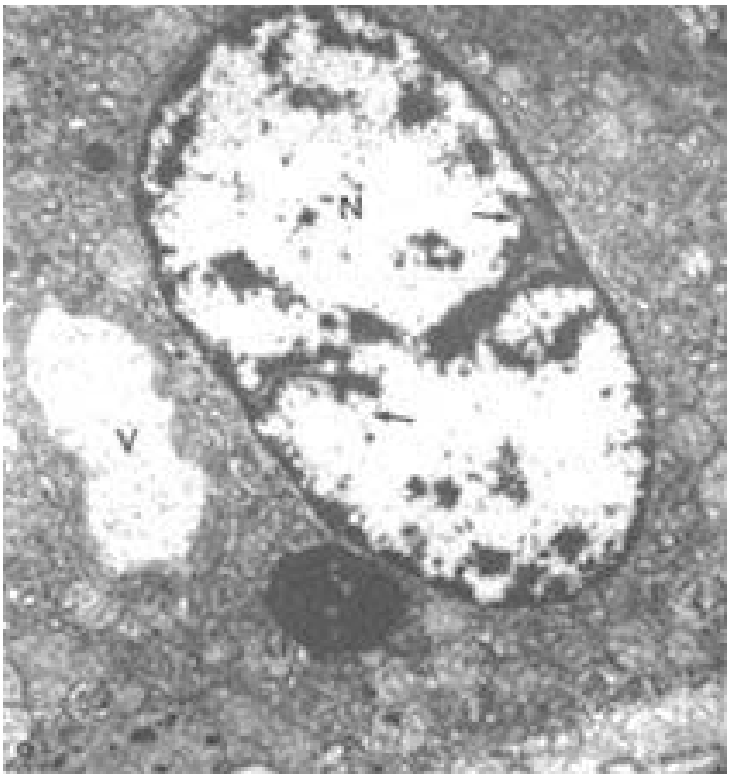
*13. Mackay IG, Doig A, Thomson D : Membranous nephropathy in a patient with nail-patella syndrome nephropathy. Scott Med J, 30:47-49, 1985.*

*14. Meiss R, Robenek H, Rassat J, Themann H : New aspects of the origin of hepatocellular vacuoles. An ultrastructural study on rat and mice liver after different intoxications. Exp Path, 19:239-246, 1981.*

*15. Melnick A, Berger R, Lisgar H : Nail-patella syndrome: Report of three Cases in the same family. Journal AOA, 74:99-61, 1974.*

*16. Morita T, Laughlin LO, Kawano K, Kimmelstiel P, Suzuki Y, Churg J : Nail-patella syndrome. Light and electron microscopic studies of the kidney. Arch Intern Med, 131:271-277, 1973.*

Figure 9: The cytoplasmic pathces with or without lipid droplets (arrows) are seen with in the nucleus (N). Lipofuchsin granules (Lf), vacuole (V). X 12400.




*17. Pozo ED, Lapp N : Ultra structure of the kidney in a nephropathy of the nail-patella syndrome. AJCP, 54:845-851, 1970.*

*18. Taguchi T, Takebayashi S, Nishimura M, Tsuru N : Nephropathy of nail-patella syndrome. Ultra-structural Pathology, 12:175-183, 1988.*

Correspondence:
Ufuk Ö. Mete
Çukurova Universitesi,
Tip Fakültesi,
Histoloji-Embriyoloji,
01330, Balcali, Adana,
TÜRKIYE.