Clinical case

doi: http://dx.doi.org/10.22265/acnef.7.1.345

Presence of reactive renal tubular cells in patients with chronic kidney disease

Presencia de células tubulares renales reactivas en pacientes con enfermedad renal crónica

Carlos Martínez-Figueroa[1], Karen Cortés-Sarabia[2], Hilda Guadalupe Catalán-Nájera[1], Micaela Martínez-Alarcón[1]

[1]Emergency Service, Clinical Laboratory, Clínica Hospital ISSSTE, Iguala, Guerrero, Mexico.
[2]Laboratory of Immunobiology and Molecular Diagnosis, Faculty of Chemo-Biological Sciences, UAGro, Chilpancingo, Guerrero, Mexico.

Abstract

In patients with kidney disease, the presence of reactive renal cells has been reported. These cells show severe morphological alterations that difficult their classification and interpretation. Therefore, the knowledge of their morphological characteristics and sediment patterns where they can be found will be helpful for their correct management by medical departments. Here, we reported the presence of renal cells grouped in acinus with abundant cytoplasm, caryomegaly, irregular nuclear contours and prominent nucleoli, accompanied with cylindruria and fatty oval bodies in the urinary sediment of two patients with Diabetes Mellitus, these cells were named as reactive renal cells.

Key words: Urine, chronic kidney disease, diabetes mellitus, proteinuria, hematuria, epithelial cells.

doi:http://dx.doi.org/10.22265/acnef.7.1.345

Resumen

En pacientes con enfermedad renal se ha reportado la presencia de células renales reactivas, cuyas alteraciones morfológicas severas dificultan su clasificación e interpretación. El conocimiento de las características morfológicas y los patrones de sedimentos en donde se presentan pueden ser de ayuda para su manejo en los departamentos médicos correspondientes. Aquí, nosotros reportamos la presencia de células agrupadas en acinos, con abundante citoplasma, cariomegalia, contornos nucleares irregulares y nucléolos prominentes, acompañados de cilindruria y cuerpos ovales grasos en el sedimento urinario de dos pacientes con diabetes mellitus, las cuales fueron sugestivas de células renales reactivas.

Palabras clave: orina, insuficiencia renal crónica, diabetes mellitus, proteinuria, hematuria, células epiteliales.

doi:http://dx.doi.org/10.22265/acnef.7.1.345

Introduction

The urinary tract is lined by a great variety of epithelia among which are the cuboidal epithelium and the squamous and columnar urothelium.[1] The urothelium is located from the minor calyces, which form the largest calyces, passing through the ureters and the bladder to the proximal urethra (prostatic in men) and its main function is to form an impermeable barrier against the toxic urine,[2,3] while the cuboidal epithelium is located in the renal tubules (proximal, distal and collecting) and is essential in the exchange of nutrients and toxins between the urine and the blood.[1] However, the presence of renal cells in the urinary sediment has been associated with tubular and glomerular diseases and in some cases with diabetic nephropathy, severe dehydration and hepatitis.[4] These cells have spherical, cubic and even cylindrical morphology, with a size of 9 to 25 µm and granular cytoplasm; their nucleus is spherical, located centrally or eccentrically with nucleoli.[5] On the other hand, the «reactive renal cells » reach sizes up to 100 µm, with karyomegaly, prominent nucleoli, irregular nuclear membrane and presence of acinar groups. The presence of these cells is erroneously interpreted as a neoplastic process due to the morphological alterations they present; this is mainly caused by the scarce information about them. Therefore, the objective of this article is the diffusion of knowledge

Citation: Martínez-Figueroa C, Cortés-Sarabia K, Catalán-Nájera HG, Martínez Alarcón M. Presencia de células tubulares renales reactivas en pacientes con enfermedad renal crónica. Rev. Colomb. Nefrol. 2020;7(1):130-134. https://doi.org/10.22265/acnef.7.1.345

Correspondence: Carlos Martínez Figueroa, carlos.martinez9411@gmail.com,

Received: 21.04.19 • **Accepted:** 18.09.19 • **Published Online:** 8.02.19

http://dx.doi.org/10.22265/acnef.7.1.345

among the healthcare personnel about the presence of these cells in patients with chronic diseases.[6,7]

Clinical case 1

A 52-year-old male patient with a history of uncontrolled diabetes mellitus, hospitalized for diabetic foot surgery. Preoperative laboratory studies were requested. The results of the blood chemistry tests were: glucose 203 mg/dl, urea 62.5 mg/dl, creatinine 1.9 mg/dl, BUN 29 mg/dl, uric acid 9.8 mg/dl and total cholesterol 160 mg/dl; regarding the hematic cytometry it was found an hemoglobin of 10.7 g/dl, erythrocytes $4.16x10^6$/µl, hematocrit 33.9%, leukocytes $12.06x10^3$/µl and platelets $288x10^3$/µl. The chemical examination of the urinalysis revealed the presence of hemoglobinuria (80 erythrocytes/ml), proteinuria (>300 mg/dl), a pH of 6.5 and a density of 1,020. In the urine sediment it was found microhematuria: 5-10 erythrocytes/field in a strong dry lens, of which 40% were dysmorphic; oval fat bodies (Figure 1, panel d) and cylindruria (hyaline, erythrocytic and lipid) were also observed. In addition, we found spherical cells with granular cytoplasm, a spherical nucleus located eccentrically and a regular or slightly irregular contour, and with one or two nucleoli (Figure 1, panel a, b and c). These cells were found in groups of up to 30 cells of acinar appearance and were classified as reactive renal cells based on the literature consulted.[6,7]

Clinical case 2

A 76-year-old female patient arrived to the emergency department with a hyperglycemic clinical picture. The blood chemistry revealed a glucose of 311 mg/dl, urea 197 mg/dl, BUN 92 mg/dl, creatinine 5.8 mg/dl, uric acid 7.2 mg/dl and total cholesterol of 361 mg/dl; the hematic cytometry showed an hemoglobin of 11.6 g/dl, erythrocytes $4.22x10^6$/µl, hematocrit 35.7%, leukocytes $5.28x10^3$/µl and platelets $205x10^3$/µl. In the chemical examination of the urinalysis it was observed a pH of 7.0 and a density of 1,020, as well as glycosuria (250 mg/dl), hematuria (80 erythrocytes/µl), proteinuria (greater than 300 mg/dl) and leukocyturia (70 leukocytes/µl). These results were corroborated in the urine sediment, where leukocyturia (30-40 leukocytes/field in strong dry lens), cylindruria (waxy and granular) and oval fat bodies were observed (Figure 1, panel h). The chemical analyst (first author) carried out the identification of renal cells with atypical morphology, based on morphological characteristics such as karyomegaly, irregular nuclear contour, presence of prominent nucleoli, nuclei of eccentric or central location, some of them pleomorphic with slightly thick chromatin and increased nucleus-to-cytoplasm ratio. They also presented cytoplasmic vacuolization and acinar groups of up to seven cells; most of them were viable cells (not stained by the Sternheimer-Malbin stain). In both cases the cells were classified based on the morphology and the characteristics of the sediment: presence of casts, microscopic hematuria and oval fat bodies (Figure 1, panel e, f and g).

Discussion

Chronic degenerative diseases such as type 2 diabetes *mellitus* are a major cause of nephropathy that can lead to loss of kidney function.[8] These conditions affect glomerular function and as a consequence, the renal tubules, causing detachment of renal tubular cells and formation of urinary casts.[9] The morphology of renal cells in the urinary sediment of patients with renal diseases tends to be homogeneous; however, in some cases it can be drastically modified and cause false positives for a carcinoma. Reactive or reparative changes in renal cells have been observed in glomerular diseases, drug-induced tubular toxicity, ischemia, and severe tubular damage.[6] Renal cells with abundant vacuolated cytoplasm, poorly defined borders, large oval nuclei, with varying degrees of pleomorphism, chromatin agglutination, and prominent nucleoli were observed in both patients. These cells appeared isolated or in cohesive groups of 7 to 30 and showed an acinar configuration, which is consistent with the characteristics of the reactive renal cells as described by Nguyen & Smith in 2004.[6] This type of cells, due to the morphological alterations they present, are frequently misclassified as urothelial cells of low-grade neoplasms, renal carcinoma and

http://dx.doi.org/10.22265/acnef.7.1.345

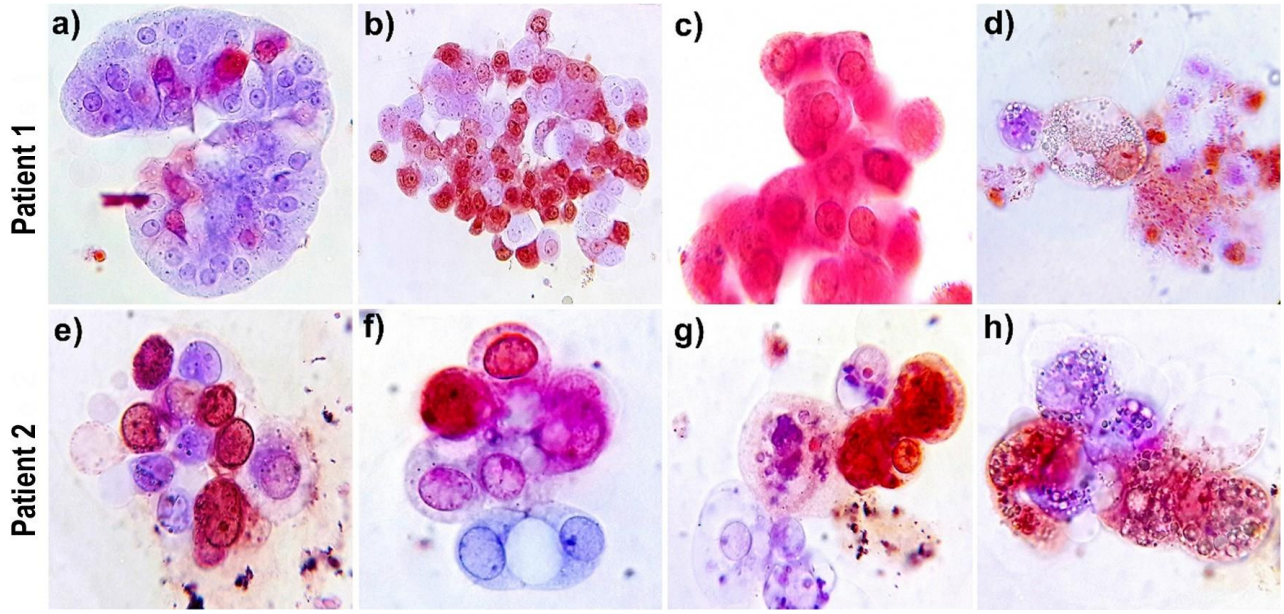

Figure 1. Reactive renal cells in patients with diabetic nephropathy. Patient 1: groups or acinar cells (a) and of large size (b and c) with cells of eccentric nuclei, prominent nucleuli, karyomegaly and granular cytoplasm and oval fat bodies with their birefringent intracytoplasmic lipids (d). Patient 2: acinar groups of cells with karyomegaly, eccentric nuclei and slight nuclear pleomorphism with slightly thick granular chromatin and cytoplasmic vacuolization (e, f and g) and presence of oval fat bodies with a large amount of intracytoplasmic lipids (h). Bright field microscopy, 40x objective, Sternheimer-Malbin stain. Source: Own elaboration.

adenocarcinomas. For the differential diagnosis between the reactive renal cells and the carcinoma cells, is important to look for the presence of renal casts associated with the tubular alterations generated by the glomerular disease and the dysmorphic microhematuria, which support the renal origin of the cells, in contrast with the neoplastic processes in which isomorphic hematuria is found.[6,7,10-12] Casts were found in both patients and in one dysmorphic microhematuria of 40%. In 2008, Fogazzi *et al*. established that dysmorphic hematuria greater than 40% is associated with glomerular diorders.[13] In addition, we reported the presence of fatty oval bodies in both subjects, which are an unequivocal sign of severe kidney disease and are frequently associated with nephrotic syndrome.[5,14]

The confirmation of the presence of reactive renal cells can be carried out by a positive immunocytochemical staining for the vimentin protein, in contrast with the urothelial cells of low-grade tumors. However, the immunocytochemical staining has the disadvantage of not being able to differentiate between a renal carcinoma and reactive renal cells, which can be done based on the type of hematuria and the presence or absence of casts.[7,15] Due to the aforementioned, a series of morphological criteria has been proposed to give greater importance to cytological interpretation in order to be able to differentiate these types of pathological processes based on these criteria.[7]

Conclusion

Reactive renal cells are present in diseases that severely affect the renal tubules; the knowledge of their morphology and their adequate interpretation can guide the clinical diagnosis of kidney disease or neoplastic processes, with which they are commonly confused. This article describes the presence of these cells in patients with type 2 diabetes *mellitus*; but it is still necessary to continue analyzing the importance of the presence of these cells in the diag-

http://dx.doi.org/10.22265/acnef.7.1.345

nosis and prognosis of chronic diseases, as well as the establishment of morphological patterns that can be used by the clinical analyst.

Acknowledgments

To the laboratory staff of the Clinic of the Institute of Social Security and Services, and to the State Workers (ISSSTE) of Iguala, Gro., for their support in the realization of the work.

Conflict of interest

The authors did not declare conflict of interest.

Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Data confidentiality

The authors declare that they have followed the protocols of their workplace on the publication of patient data.

Right of privacy and informed consent

The authors declare that patient data do not appear in this article.

Funding

No funding source was obtained for this work.

Contribution of the authors

All authors contributed to the analysis, literature research, writing and revision of this work.

References

1. Ross MH, Pawlina W. Histología. Texto y Atlas. 7 ed. Barcelona, España: Wolters Kluwer; 2015.
2. Koss LG, Hoda RS. Koss's cytology of the urinary tract with histopathologic correlations. Springer; 2012.
3. Khandelwal P, Abraham SN, Apodaca G. Cell biology and physiology of the uroepithelium. Am J Physiol Renal Physiol. 2009;297(6):1477-501. Available from: https://doi.org/10.1152/ajprenal.00327.2009
4. JCCLS. Urinary Sediment Examination. Japanese J Med Technol. 2017;66:51-85. Available from: https://doi.org/10.14932/jamt.17J1-2e
5. Fogazzi GB. The urinary sediment. An integrated view. 3 ed. Italia: Elsevier; 2010.
6. Nguyen GK, Smith R. Repair renal tubular cells: A potential false-positive diagnosis in urine cytology. Diagn Cytopathol. 2004;31(5):342-6. Available from: https://doi.org/10.1002/dc.20139
7. Ohsaki H, Hirakawa E, Kushida Y, Yokoshita S, Nakamura M, Kiyomoto H, et al. Can cytological features differentiate reactive renal tubular cells from low-grade urothelial carcinoma cells? Cytopathology. 2010;21(5):326-33. Available from: https://doi.org/10.1159/000325510
8. Cruz Abascal RE, Fuentes Flebes O, Gutiérrez Simón O, Garay Padrón R, Águila Moya O. Nefropatía diabética en pacientes diabéticos tipo 2. Rev Cuba med. 2011;50(1):29-39.
9. González Álvarez MT, Mallafré Anduig J. Nefrología. Conceptos básicos en atención primaria. 1a ed. Barcelona, España: MARGE MEDICA BOOKS; 2009.
10. Ohsaki H, Haba R, Matsunaga T, Nakamura M, Kiyomoto H, Hirakawa E. Cytomorphologic and inmmunocytochemical characteristics of reactive renal tubular cells in renal glomerular disease. Acta Cytol. 2008;52(3):297-301. Available from: https://doi.org/10.1159/000325510
11. Caleffi A, Lippi G. Cylindruria. Clin Chem Lab Med. 2015;53(s2):1471-7. Available from: https://doi.org/10.1515/cclm-2015-0480
12. Muto S, Sugiura S, Nakajima A, Horiuchi A, Inoue M, Saito K, et al. Isomorphic red blood cells using automated urine flow cytometry is a reliable method in diagnosis of bladder cancer. Int J Clin Oncol. 2014;19(5):928-34. Available from: https://doi.org/10.1007/s10147-013-0623-9
13. Fogazzi GB, Edefonti A, Garigali G, Giani M, Zolin A, Raimondi S, et al. Urine erythrocyte morphology in patients with microscopic haematuria caused by a glomerulopathy. Pediatr Nephrol. 2008;23(7):1093-100. Available from: https://doi.org/10.1007/s00467-008-0777-2
14. Quinn JR, Zimmerman HJ. Significance of Oval Fat Bodies in Urinary Sediment. Am J Clin Pathol. 1954;24(7):787-95. Available from: https://doi.org/10.1093/ajcp/24.7.787
15. Strojan M, Srebotnik I, Gutnik H. Use of Vimentin Immunocytochemical Staining for Evaluation of Atypical Cells in Voided Urine Samples. Diagn Cytopathol. 2016;45(2):85-90. Available from: https://doi.org/10.1002/dc.23645