Pigmented Renal Cell Carcinoma: A Case with Unusual Findings and Review of the Literature

Ismail Matalka FRCPath[1], Maysa Al-Hussaini FRCPath*[2], Ibrahim Bani Hani FRCS*[3]

Abstract

A few cases of pigmented renal cell carcinoma have been reported in the literature so far. It has been described in both conventional and chromophobe subtypes of renal cell carcinoma. The nature of these pigmentations is consistent with melanin, neuromelanin, and lipochrome granules. We report a rare case of pigmented renal carcinoma due to the accumulation of abnormal phagolysosomal bodies, with histochemical features consistent with neuromelanin. A review of cases of pigmented conventional renal cell carcinoma in literature is also presented. Awareness of pigmentation in primary renal cell carcinoma is important in differentiating it from primary and metastatic malignant melanoma and other malignancies that can show pigmentation. Whether the presence and nature of the pigmentation has any clinical importance has yet to be established.

Keywords: Renal Cell Carcinoma, Pigment, Neuromelanin, Phagolysosomal Granules.

Abbreviations: RCC: renal cell carcinoma, ClRCC: clear cell renal cell carcinoma, CrRCC: chromophobe renal cell carcinoma

(J Med J 2013; Vol. 47 (2):176- 182)

Received	***Accepted***
August 20, 2012	*November 28, 2012*

Case Report

A 27-year-old pregnant lady was incidentally discovered to have a right renal mass during a first trimester ultrasound screening. The other kidney was found to be ectopic (pelvic) with normal function. A biopsy was performed followed by a partial right nephrectomy. A completion nephrectomy was performed once the diagnosis of pigmented type renal cell carcinoma was confirmed. The fetus was lost between the two procedures. She didn't receive chemotherapy or immunotherapy after the nephrectomy. A follow-up CT scan didn't show any evidence of recurrence nor metastasis. The patient is well and alive without evidence of disease 120 months post-nephrectomy. This is the longest follow up for similar types of carcinoma.

1. **Department of Pathology and Microbiology, Faculty of Medicine, JUST**
2. **Department of Pathology and Laboratory Medicine, King Hussein Cancer Center, Amman, Jordan.**
3. **Department of Surgery and Urology, King Abdullah University Hospital, Jordan University of Science and Technology, Irbid, Jordan.**

**** Correspondence should be addressed to:***
Ismail Matalka, FRCPath
Department of Pathology and Microbiology
Jordan University of Science and Technology
Tel/ Fax 00962 2 7200626
E-mail: imatalka@hotmail.com

Pathological Findings

Grossly, the partial nephrectomy consisted of renal tissue measuring 5 x 4 x 4 cm with a smooth outer surface and attached perinephric fat. Cut sections showed a gray trabeculated mass measuring 4.5 x 4 x 3.8 cm with areas of dark pigmentation. Microscopic examination revealed a tumor composed predominantly of clear cells arranged in sheets and pseudoglandular pattern separated by a scanty delicate vascular-rich stroma. The tumor had Fuhrman nuclear grade of 2 / 4.

The striking feature was the presence of scattered individual cells as well as large nests of cells containing an excessive amount of cytoplasmic coarse brown pigment (figures 1A and B). The pigment stained strongly positive with Masson Fontana stain (figure 1C), indicating the presence of melanin pigment. It also stained positively with PAS stain (figure 1D) and negative for acid-fast stain (figure 1E), whereas it was negative for iron and mucicarmine stains.

Neuromelanin are positive with Fontana-Masson stain and they can be bleached. They can be positive for periodic acid-Schiff (PAS) reaction and Ziehl Neelsen stain (acid fast stain). Lipofusin can appear quite dark and mimic melanin pigment. However, they are positive with Ziehl Neelsen stain and sometimes positive for both PAS and Fontana-Masson stain and they are less likely to be bleached. Immunohistochemical markers such as HMB45 would not label these pigments.

The tumor cells in our case are negative for immunohistochemical markers for melanosomes such as HMB45 and showed a positive reaction for CAM5.2 and EMA. On the other hand, S-100, synaptophysin, and chromogranin-A were negative. An electron microscopy showed altered phagolysosomal bodies (figure 1F) that were different from both premelanosomes and hemosiderin.

Discussion

Renal cell carcinoma (RCC) is the most common renal tumor, accounting for 2-3% of all malignancies.[1] It has the highest incidence in the 6th decade of life and occurs twice as often in men as compared to women.[2] The tissue of origin for renal cell carcinoma is the proximal renal tubular epithelium. Several histological variants have been recognized depending on morphology, histochemistry, clinical behavior, and genetic alterations.[3] The most common is the clear cell, followed by the papillary carcinoma type. Other less common types include chromophobe renal cell carcinoma (CRCC) and collecting duct carcinoma. However, it is not infrequent to find a mixture of those distinct types.[4]

Non-hemosiderotic pigmentation in renal cell carcinoma has been described primarily in 2 variants, the chromophobe [5] and the clear renal cell carcinoma.[6] The first report of pigmentation in clear cell carcinoma came from Kamishima et al,[7] in which he attributed the pigments to abnormal lysosomes, with histochemical features consistent with neuromelanin. This was followed by more cases from the same group of authors. Fukuda et al reported Neuromelanin in 3 out of 5 cases; a finding that suggested the lysosomal origin of granules in those three cases, one of these three cases was chromophobe renal cell carcinoma(CrRCC).[8] Hirokawa et al described the cytological findings of another case of pigmented clear renal cell carcinoma with

features of neuromelanin.[9] Lei et al [10] reported a peculiar case of pigmented renal cell carcinoma where the pigment exhibited characteristics of melanin. They also proposed the melanocytic differentiation of the tumor cells containing the pigment due to their expression of HMB-45 in addition to S-100. In a more recent article, a heavily pigmented conventional clear cell carcinoma was described [11] where pigmentation was attributed to lysosomes (table 1).

Reference	Age (yrs)/gender	Diagnosis	Type of pigment	Special stains	IHC	EM	Outcome
Kamishima/ 1995 7	38/F	ClRCC	Neuromelanin/ intracytoplasmic	PAS/PASD+ MF+/Bleached ZN+	HMB45-/S100- Chromogranin -	Round granules No melanosomes No NSG	A/W-8mon
Fukuda/ 1997 8	37/F*	ClRCC	Neuromelanin/ intracytoplasmic	PAS+/PASD+ MF+/Bleached ZN+	HMB45-/S100-** Chromogranin -	Dense granules No melanosomes No NSG	A/W-8mon
	46/M	CrRCC					A/W-15mon
	61/M	ClRCC**					A/W-52mon
	54/M	ClRCC	Slender or irregular shaped brown pigment/ intracytoplasmic	PAS+/PASD+ MF- ZN-	HMB45- /S100+ Chromogranin-	Angulated lysosomes	A/W-17mon
	41/M	ClRCC	Granular tumor-like		HMB45-/S100- Chromogranin -	Electron dense myelinated like areas	A/M=42mon
Hirokawa/ 1998 9	40/F	ClRCC	Neuromelanin/ intracytoplasmic	***PAS+/PASD+ MF+/Bleached ZN /NA	***HMB45- /S100-	N/A	N/A
Lei/ 2001 10	26/F	ClRCC	Melanin /intracytoplasmic	MF+	HMB45+ S-100+	N/A	A/M-15mon
Rossi/ 2009 11	48/M	ClRCC	Neuromelanin	PAS+/PASD+ MF+/Bleached	HBM 45- /S100-/melanA- Chromogranin -	No premelanosomes	A/W-4mon

A/W: alive and well, A/M: alive with metastasis, ClRCC: clear cell renal cell carcinoma, CrRCC: chromophobe renal cell carcinoma, F: female, M: male, PASD: periodic acid Schiff with diastase, MF: Masson Fontana, N/A: not available, ZN: Zeil-Nelson stain, NSG: neurosecretory granules.
** same case reported in Kamisaki*
*** case showed some positivity with S-100 immunostain*
**** performed on paraffin embedded sections*

The pigmentation in our case is similar to that described in some of reported cases in the literature.[7,8,11] Our case showed abnormal phagolysosomal granules, the morphology of which is similar to 3 of the 5 cases described by Fukuda; granules showed a fine or coarse granular matrix with or without dense homogenous areas. This is different from the

angulated lysosomes filled with parallel microfilaments shown in case 4 in that series, or from the granules in the fifth cases with granular cell tumor morphology. The granules are also clearly different from premelanosomes.

Pigmentation in chromophobe renal cell carcinoma (CrRCC) was first described by Bonsib,[12] who identified the presence of lipochrome in a case of chromophobe renal cell carcinoma by electron microscopy. The tumor appeared macroscopically yellow tan, and in light microscopy didn't demonstrate the pigmentation. In contrast, Michal [13] identified the pigmentation at the light and electron microscopic level in CrRCC cases . He described dark electron-dense pigment granules, the exact nature of which was not identified. More recently, Dundr [14] described an additional case with clusters of pigmented cells in a 60-year-old female. Of note is that the brown pigment associated with CrRCC is seen mostly in extracellular locations [5] and not intracellular as in cases of clear RCC.

Pigments other than melanin or neuromelanin can also be found in clear cell RCC, the most common of which is hemosiderin.[15] Hemosiderin is easy to recognize because of its characteristic variably sized, reflective, golden yellow brown granules that can be confirmed with Pearl's stain.[10,16] Hemosiderin is usually secondary to hemorrhage and necrosis and is common in RCC.[17] Melanocytic colonization or phagocytosis of melanosomes of tumor cells has been detected in breast and colon carcinoma.[18-20] These mechanisms are unlikely in our current case of RCC because the pigmented cells lacked melanin.

Because of the presence of pigment and the morphologic features of the tumor, it is important to recognize the lesion as a primary renal tumor and not a metastasis from other tumors that might show pigmentation. Metastatic melanoma, neuroendocrine neoplasm, neuroectodermal tumors, pigmented perivascular epithelioid clear cell tumor (PEComa), and pigmented pheochromocytoma are the most important considerations in the differential diagnosis. The negative staining of tumor cells for synaptophysin and Chromogranin A ruled out the diagnosis of pheochromocytoma as well as neuroectodermal and neuroendocrine tumors. The absence of S-100 and HMB-45 expression ruled out primary and metastatic melanoma as well as PEComa.[21,22] The histological features of the tumor in this study are clearly different from that of the schwannoma and small cell carcinoma of the lung, which might occasionally show pigmentation.

The presence and nature of pigmentation in RCC appears not to have any clinical effect.[6] Of all the cases of pigmented clear cell RCC reported so far, only one showed distant metastasis.[10] The other cases didn't show metastasis neither in the pre- nor postoperative state. Of note is that the age of presentation in all cases was younger compared with the usual age of conventional non-pigmented RCC.[2] Apparently, more studies are needed to support this observation.

In conclusion; we are reporting a case of pigmented clear RCC in a young adult female. The pigmentation is attributable to phagolysosomes with histochemical characteristics of neuromelanin. Whether pigmented RCC behave differently from the more common non-pigmented variant is difficult to ascertain due to the rarity of the condition. Further molecular and cytogenetic studies are needed on these types of pigmented

renal cell carcinoma.

Acknowledgment

The authors would like to thank Professor Stewart Fleming for his help in providing the electron microscopy for the case.

Figure legends

1A and B: admixture of clear cells and groups of cells with coarse intra-cytoplasmic brown granules (H&E X20 and X40, respectively). C: the pigment was intensely positive with Masson Fontana. D: PAS stain was positive. E: ZN stain was negative. F: electron microscopy revealed altered phagolysosomal bodies.

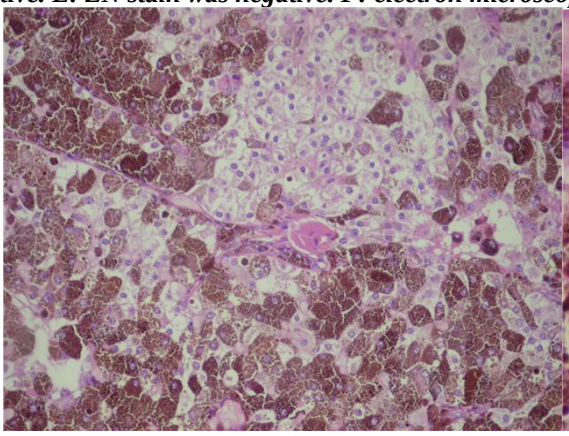

Figure (1-A)

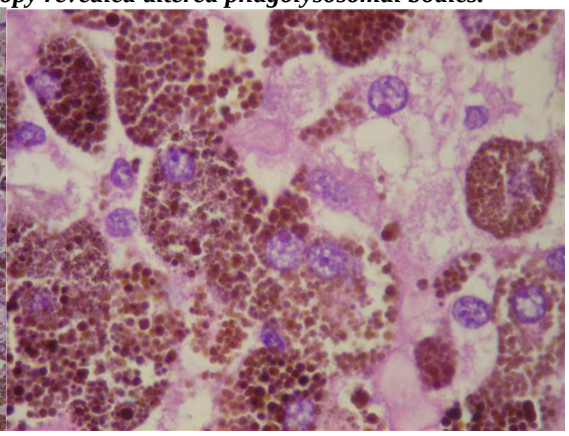

Figure (1-B)

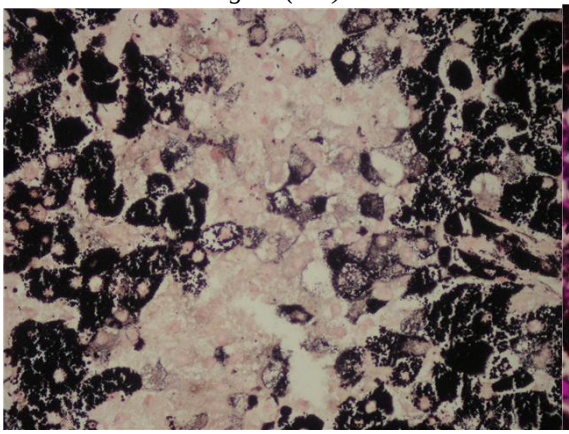

Figure (1-C)

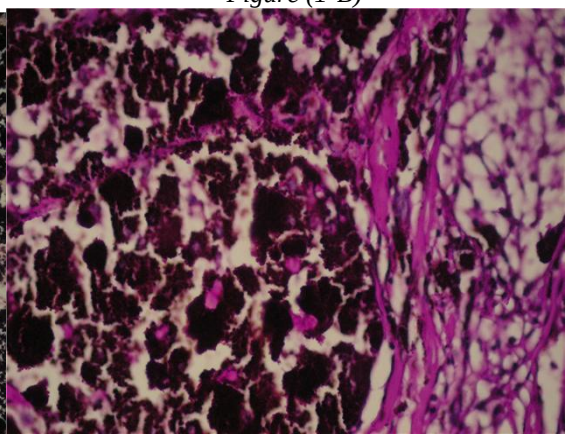

Figure (1-D)

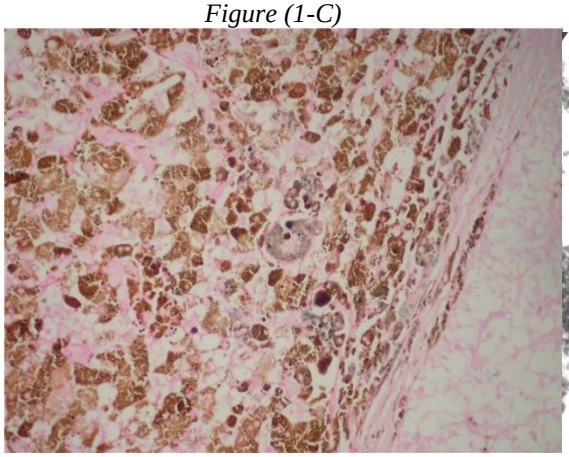

Figure (1-E)

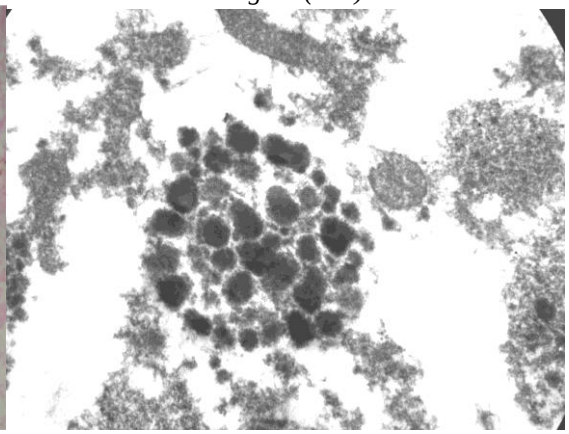

Figure (1-F)

References

1. Curti BD. Renal cell carcinoma. JAMA 2004; 292; 97-100.
2. Murai M, Oya M. Renal cell carcinoma: etiology, incidence and epidemiology. Curr Opin Urol 2004; 14; 229-233.
3. Storkel S, Eble JN, Adlakha K et al. Classification of renal cell carcinoma: Workgroup No. 1. Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Cancer 1997; 80; 987-989.
4. Renshaw AA, Zhang H, Corless CL, Fletcher JA, Pins MR. Solid variants of papillary (chromophil) renal cell carcinoma: clinicopathologic and genetic features. Am J Surg Pathol 1997; 21; 1203-1209.
5. Hes O, Vanecek T, Perez-Montiel DM et al. Chromophobe renal cell carcinoma with microcystic and adenomatous arrangement and pigmentation--a diagnostic pitfall. Morphological, immunohistochemical, ultrastructural, and molecular genetic report of 20 cases. Virchows Arch 2005; 446; 383-393.
6. Fleming S. Recently recognized epithelial tumours of the kidney. Curr Diagn Pathol 2005; 11; 162-169.
7. Kamishima T, Fukuda T, Emura I, Tanigawa T, Naito M. Pigmented renal cell carcinoma. Am J Surg Pathol 1995; 19; 350-356.
8. Fukuda T, Kamishima T, Emura I, Takastuka H, Suzuki T. Pigmented renal cell carcinoma: accumulation of abnormal lysosomal granules. Histopathology 1997; 31; 38-46.
9. Hirokawa M, Sakurai T, Shimizu M, Manabe T, Kanahara T. Cytology of pigmented renal cell carcinoma. A case report. Acta Cytol 1998; 42; 788-790.
10. Lei JY, Middleton LP, Guo XD et al. Pigmented renal clear cell carcinoma with melanocytic differentiation. Hum Pathol 2001; 32; 233-236.
11. Rossi G, Cadioli A, Costantini M, Grazia Del Buono M, Oleari G. Heavily pigmented renal cell carcinoma: a case report, with review of the literature and differential diagnosis. Int J Surg Pathol 2009; 17; 167-169.
12. Bonsib SM, Bray C, Timmerman TG. Renal chromophobe cell carcinoma: limitations of paraffin-embedded tissue. Ultrastruct Pathol 1993; 17; 529-536.
13. Michal M, Hes O, Svec A, Ludvikova M. Pigmented microcystic chromophobe cell carcinoma: a unique variant of renal cell carcinoma. Ann Diagn Pathol 1998; 2;149-153.
14. Dundr P, Pesl M, Povysil C et al. Pigmented microcystic chromophobe renal cell carcinoma. Pathol Res Pract 2007; 203; 593-597.
15. Perez-Montiel MD, Suster S. An unusual renal cell carcinoma, unclassified. Adv Anat Pathol 2003; 10; 291-295.
16. Medina Perez M, Valero Puerta JA, Valpuesta Fernandez I, Perez Martin D. [Pigmented renal carcinoma, rich in hemosiderin]. Arch Esp Urol 2000; 53; 70-72.
17. Murphy WM BJ, Farrow GM. Atlas of Tumor pathology: Tumors of Kidney, Bladder and Related Urinary structure. Washington D.C., 1994; 92-131.
18. Chumas JC, Lorelle CA. Melanotic adenocarcinoma of the anorectum. Am J Surg Pathol 1981; 5; 711-717.
19. Azzopardi JG, Eusebi V. Melanocyte colonization and pigmentation of breast carcinoma. Histopathology 1977; 1; 21-30.
20. Nobukawa B, Fujii H, Hirai S et al. Breast carcinoma diverging to aberrant melanocytic differentiation: a case report with histopathologic and loss of heterozygosity analyses. Am J Surg Pathol 1999; 23; 1280-1287.
21. Argani P, Aulmann S, Karanjawala Z, Fraser RB, Ladanyi M, Rodriguez MM. Melanotic Xp11 translocation renal cancers: a distinctive

neoplasm with overlapping features of PEComa, carcinoma, and melanoma. Am J Surg Pathol 2009; 33;609-619.

22. Adachi S, Hanada M, Kobayashi Y et al. Heavily melanotic perivascular epithelioid clear cell tumor of the kidney. Pathol Int 2004; 54; 261-265.

سرطان الخلايا الكلوية المصطبغة: حالة بنتائج غير عادية ومراجعة الأدبيّ

إسماعيل مطالقة،[1] ومبساء الحسيني،[2] وابراهيم بني هاني[3]

1- قسم علم الأمراض والأحياء الدقيقة، كلية الطب، جامعة العلوم والتكنولوجيا، اربد، الأردن
2- قسم علم الأمراض والطب المخبري، مركز الملك حسين للسرطان، عمان، الأردن
3- قسم الجراحة، مستشفى الملك عبد الله الجامعي، جامعةالعلوم والتكنولوجيا، اربد، الأردن

الملخص

يوجد عدد قليل من حالات سرطان الخلايا الكلوية المصط بغة في الأدب النظري حتى الآن. تشتمل هذه الدراسة حالة نادرة من سرطان الكلى المصطبغة بسبب تراكم أجسام ***phagolysosomal*** غير طبيعية، ذات ميزات نسيجية قريبة من الميلانين العصبي. تم تقديم أيضا استعراضا للحالات سرطان الخلايا الكلوية التقليدية المصطبغة في الأدب . أكدت الدراسة أن للوعي الصبغ في حالة سرطان الخلايا الكلوية المصطبغية أهمية في التفريق بينه وبين الأنواع الابتدائيّ والنقيليّ من سرطان الجلد والأورام الخبيثة الأخرى التي يمكن أن تظهر صبغ.

الكلمات الدالة: سرطان الكلى الخلية؛ الصباغ؛ ميلانين عصبي؛ حبيبات ***phagolysosomal***.