Chapter

Clear Cell Renal Cancer, a Tumour with Neuroendocrine Features Originating from the Erythropoietin-Producing Cell

Helge Waldum and Patricia Mjønes

Abstract

The dominating type of kidney cancer is the clear cell renal cell cancer (ccRCC), hitherto been thought to develop from proximal tubule cells. However, the ability of tubule cells to proliferate is at best controversial. ccRCCs show many peculiarities like erythrocytosis due to erythropoietin overproduction and a combination of early metastases and sometimes apparent dormancy and late recurrence, features in common with neuroendocrine tumours (NETs). We have shown that most ccRCCs express erythropoietin and the neuroendocrine marker neuron-specific enolase, and other neuroendocrine markers in a percentage of the cancers. Missense mutation in von Hippel–Lindau (VHL) factor is rather specific for ccRCC found in familial and sporadic forms. The function of VHL factor is together with other proteins to destroy hypoxia-inducible factors (HIFs), central in adaptation to hypoxia. Lack of functioning VHL factor results in continuous overstimulation of the erythropoietin-producing cell to release erythropoietin and parallelly to proliferate, and in long-term mutations and malignant transformation. Thus, ccRCC occurs about 30 years later in sporadic cases compared with familial von Hippel–Lindau syndrome, reflecting the time necessary for two versus one genetic change. Embryologically, there are many arguments favouring neural crest origin of the erythropoietin-producing cell.

Keywords: classification of kidney cancer, clear cell renal cell cancer, erythropoietin, erythropoietin-producing cell, neural crest, von Hippel–Lindau syndrome

1. Introduction

The kidney is not among the most common locations for cancer development, but kidney cancers often affect middle-aged people, and the mortality is high. Clear cell renal cancer cell (ccRCC) (also called conventional RCC (cRCC)) makes up about 80% of renal malignancies [1] and is accordingly the most important renal cancer. ccRCC may be accompanied by erythrocytosis which has been presumed to be due to production of erythropoietin (EPO) by the erythropoietin-producing cell (EPC) localised in the kidney. Some years ago, we showed that virtually all ccRCC cancer

tumour cells expressed erythropoietin as well as the neuroendocrine marker neuron-specific enolase [2], which may suggest that the cell of origin of ccRCC is the EPC [3]. The present review is a follow-up further discussing the cell of origin of ccRCC.

2. Kidney cancers

Kidney cancers are classified according to presumed cell of origin with renal cell carcinomas making up about 90% [4]. Renal cell cancers consist of subgroups based on histological classification into ccRCC, papillary and chromophobe subgroups. ccRCC and papillary renal cell cancers (pRCCs) have been presumed to originate from proximal tubular cells. However, most cells in the adult kidney do not have the ability to divide and thus replace damaged or dead specialised cells [5]. Therefore, replacement of damaged nephrons does not occur after birth [6]. Generally, it may be noted that it seems strange that nephron cells with absent or at best low reproductive capacity should be the main origin of tumours. Based on gene expressions with similarities between proximal tubular cells and ccRCCs [7, 8], tubular cells have been thought to develop into ccRCC. However, discrepant expressions between normal proximal tubule cells and tumours presumed to originate from proximal tubule cells like ccRCC and pRCCs have been described [9]. In a review in 2012, it was written that the cells of origin RCCs "are far from established and only inferred by accumulated weight of marker similarities" [10]. Similarly, the degree of tubule regeneration and which cell type contributing to this process were discussed in a review in 2016 [11]. Recently, a novel stem cell subtype analysis for ccRCC based on stem cell markers was reported, but apparently not compared to any mature cells of the nephron [12]. It may, therefore, be concluded that there are uncertainties regarding the cell of origin of ccRCCs. Considering the classification of kidney tumours in general, the continuous changes and additions of new types [13, 14] indicate a weakness in the system and may suggest that the classifications are not rooted in biology. Our finding of erythropoietin and neuron-specific enolase expression in virtually all ccRCCs may indicate that the EPC is the cell of origin of ccRCC [2, 3].

3. Erythropoietin (EPO) and the erythropoietin-producing cell (EPC)

In the late part of nineteenth century, French scientists described the association between atmospheric pressure and the concentration of red blood cells [15]. Thus, the concentration of red blood cells increased in members of an expedition to the Andes mountains [16]. A factor in serum was suspected to mediate this effect, and this was shown to be true when serum from anaemic rabbits had erythropoietic activity in normal rabbits [17]. Finnish authors named the postulated substance erythropoietin [18], and the dominating role of the kidneys in the production of EPO was shown by reduced stimulation of erythropoiesis in nephrectomised animals [19]. However, some EPO production also occurs in the liver [15]. Subsequently, EPO was identified as a glycohormone [20]. It stimulates erythropoiesis by interaction with a receptor (REPO) localised on progenitor cells in the red cell line like erythroblasts. The EPC in the kidney was long disputed. However, it seems now that peritubular interstitial cells are established as the EPC [21]. Interestingly, these cells had a neuron-like morphology and expressed neuron genes [21]. In the liver, EPO production was also found in

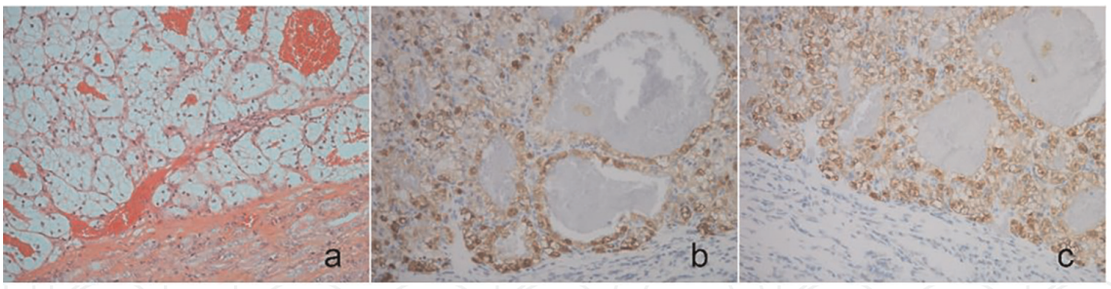

Figure 1.
Clear cell renal cell carcinoma examined by haematoxylin and eosin (a), by immunohistochemistry for erythropoietin (b) and neuron-specific enolase (NSE)(c). From (2) APMIS 2017; 125: 213–222. The figure is reused under the terms of the creative commons public domains declaration and with permission from the publisher.

cells surrounding the central vein in the liver [21], possibly stellate cells which have been shown to express EPO [22]. EPO has also been described in the brain [23].

The main stimulatory mechanism for EPO production and release is by the hypoxia-inducible factors (HIFs). There exist three O2 sensing HIF-α types (HIF-1α, HIF2α, and HIF-3α). HIF-1α and also HIF-2α affect many other processes than stimulation of EPO release including angiogenesis and other functions related to adaptation to hypoxia [15, 24]. HIF-2 seems to be the main regulator of EPO [25]. HIF-1α is ubiquitously expressed, while HIF-2α was initially reported in endothelial cells but has later been shown to be expressed in many other cell types [26].

EPO production in renal cancers, then named hypernephromas [27], was suspected based on erythrocytosis in some of the patients. A case report in 1977 described EPO production in a patient with ccRCC based on a biological mouse assay [28], and there is a report describing EPO production in a cell culture from a renal cell carcinoma [29]. EPO gene expression in ccRCC was reported to be much more common than the occurrence of erythrocytosis [30]. There are also studies evaluating the prognostic significance of EPO expression in renal cell cancers where one study did not find any effect [31], and the other reported reduced survival [32]. We cannot find that anybody had reflected on the EPC as the cell of origin in ccRCC before our paper in 2017 [2], where we found that most ccRCC expressed EPO in contrast to the other renal cell carcinomas which all were negative (**Figure 1**).

Before discussing cell of origin further, we will focus on clinical aspects of ccRCC, which also give strong indications of the central role of EPC in ccRCC carcinogenesis.

4. Clinical aspects of ccRCC

In the past, the classic symptom triad of RCC was haematuria, pain in the kidney area and a palpable tumour. However, nearly half of the patients do not have any symptoms suggesting renal illness [33], and in about half of the cases renal cancers are detected by ultrasonography or other imaging modalities done due to vague symptoms. Paraneoplastic syndromes are also an initial gateway to correct diagnosis. Among these syndromes, hypercalcemia, hypertension, polycythaemia, and Stauffer's syndrome (non-metastatic hepatic dysfunction [34]) are the most prevalent [35]. Hypercalcemia is due to parathyroid-related hormone (PTHrP), polycythaemia due to EPO, hypertension possibly due to renin, whereas the mechanism for Stauffer's

syndrome is unknown. PTHrP elevation has been attributed to vascular endothelial growth factor (VEGF) expression in ccRCC [36].

Elevated erythrocyte sedimentation rate has for long been recognised to be a feature of renal cancer, formerly called hypernephroma, now ccRCC. Rising erythrocyte sedimentation may be an early marker for renal cell cancer [37] and also an independent prognostic factor [38]. C-reactive protein is also a predictive factor for metastasis in patients after potentially curative surgery [39].

Macroscopically, ccRCCs often are yellowish and small tumours often with an apparent capsule. ccRCCs metastasize at an early stage, and metastases are often present at diagnosis [40]. RCCs may metastasize to uncommon places as a finger [41], the pituitary gland [42], and skeletal muscle [43]. Moreover, first metastasis may manifest itself many years after apparent curative surgery as shown in a case report where a brain metastasis developed 15 years after surgery [44]. Late metastasis has been explained by early dissemination and tumour cell dormancy [45, 46]. Another possibility may be that the cell of origin due to inherent qualities like low expression of factors contributing to cell adhesion may cause metastasis spread at an early phase of malignant development when the proliferation still is rather low. Such a phenomenon may explain the so-called dormancy [47]. As we see it, the possibility that some cancer cells go to sleep and awake after many years does not seem very plausible, although until now it has been the prevailing theory [45]. Production of substances affecting the vascular bed-like dilatation reducing blood flow rate as well as increasing the vascular permeability could also be involved. We have previously described that the enterochromaffin-like (ECL) cell in the oxyntic mucosa of the stomach lacks E-cadherin [48] and also releases histamine which has profound effect on the vasculature [49]. The ECL cell has a very slow proliferation, which made some conclude that this cell did not have the ability to divide [50] which is not correct [51]. There may be an apparent mismatch between the fact that tumours prone to early metastasis are among those with tendency to occurrence of late metastasis many years after other manifestations of malignancy. This is typically found in tumours developed from cells with the capacity to metastasize at an early phase of the malignant process when the proliferation is still slow. Neuroendocrine tumours (NETs) [52–55] and melanomas [56, 57] developed from melanocytes which also are of neural crest origin [58] like the ccRCCs (see later) are among the cancers where late metastasis occur [44]. The dormancy accordingly most probably reflects tumours originating from cells with low proliferation but the ability to metastasize after only minor genetic changes.

Another peculiarity with ccRCCs is the anecdotal spontaneous regression of metastases after surgical removal of the primary tumour, a phenomenon perhaps related to the abscopal phenomenon (regress of tumour metastases outside the area of irradiation of other metastases) [59, 60].

5. Aetiology/pathogenesis

ccRCC is the dominating kidney cancer and is also the most aggressive form. The incidence of ccRCC is nearly the double in men compared with women [4, 61]. An explanation of this sex difference in occurrence is not known. Otherwise, cigarette smoking, obesity, and hypertension have been all associated with a slight increased risk of ccRCC [62], but the exact mechanisms have not been clarified. In Japan, heavy smoking was found to increase the risk [63], but the mechanism for the slight carcinogenic effect on the kidneys have not been clarified. In inhalation studies on rats, we

examined the effect of nicotine added to the air in concentrations giving nicotine in blood exceeding that found in heavy smokers during greater part of 24 h for 24 months [64], or CO in a concentration giving about 15% carboxy-haemoglobin for most of 24 h for 18 months [65]. Although none of these studies were primarily done to explore possible mechanisms for tobacco smoking kidney carcinogenesis, the kidneys were examined macroscopically in both studies without finding any tumours. Thus, the mechanism for the effect of tobacco smoking on renal carcinogenesis is still unknown.

Obesity is an accepted and established role as a risk factor for ccRCC [62], but it is also associated with other types of cancers in other organs [66]. There exists a so-called obesity paradox between ccRCC and obesity, since obesity increases the occurrence and at the same time seems to improve the prognosis of the cancer [67]. Anyhow, a plausible mechanism for the carcinogenic effect of obesity is still not found. Likewise, on the background of the important role by the kidneys in regulation of blood pressure, it is not surprising that hypertension may be elevated in ccRCCs. However, again the mechanism for such a connection is not yet elucidated, although a role of the renin-angiotensin system has been examined.

On the other hand, a central role of the von Hippel–Lindau (VHL) tumour suppressor in pathogenesis of ccRCC is well established causing virtually all familial ccRCCs [68], but also the sporadic ones [69]. The average age at diagnosis of ccRCC as part of VHL syndrome is 37 years compared with 61 years of the sporadic form [40, 70]. Inactivation of VHL gene is only found in ccRCC of kidney cancers [40], and loss of functioning of both alleles of VHL gene may be common to all ccRCCs [40, 71]. VHL gene product (pVHL) binds to elongins making a complex which binds to the hypoxic-inducible factors, HIF-1 and HIF-2, which targets them to ubiquitin-mediated proteolysis [72]. Pathological elongins can also be a factor contributing to lack of proteolysis of HIFs. HIFs are released during hypoxia, and HIF-2 is being the main stimulator of erythropoietin release [25]. Our experience is that it is a close correlation between regulation of function and growth [73], which in this case will indicate that HIF-2 will not only stimulate erythropoietin release but also proliferation of EPC. Lack of proteolysis of HIFs will accordingly lead to chronic overstimulation of proliferation explaining the carcinogenic effect.

6. Neural crest origin of erythropoietin-producing cell

Most ccRCCs express erythropoietin as well as neuron-specific enolase [2]. Based on our study, it seems that both clinically (overproduction of EPO in a proportion of the patients), the central and universal role of HIF in the carcinogenesis of familial as well as sporadic ccRCCs and the universal and specific expression of EPO in most ccRCCs, these tumours are of EPC origin. A case report from 1989 also describes EPC expressing cell as the cell of origin of a ccRCC [74]. Moreover, clinically ccRCCs have as outlined above, many similarities to neuroendocrine tumours in general. Furthermore, polycythaemia due to EPO production has been reported together with somatostatinoma, paraganglioma, and phaeochromocytoma [75, 76]. We found not only EPO but also NSE expression in virtually all ccRCCs, but both markers, were mostly negative in the other types of renal cell carcinomas [2]. NSE has had a poor reputation concerning specificity, but when we did a separate study on NSE specificity comparing NSE with many other neuroendocrine markers and applying histochemistry with the highest sensitivity available, we found that NSE was expressed in

all tumours which expressed another neuroendocrine marker [77]. Thus, NSE has unjustly been thought to be nonspecific due to its high sensitivity. Moreover, we detected synaptophysin expression in 6% and CD56, both neuroendocrine markers, in some ccRCCs [2]. It has to be underscored that during the process of malignant transformation, expression of markers from the cell of origin is gradually lost. Therefore, even expression in only a few percent of the tumour cells is of importance.

Interestingly, EPO production in neural and neural crest cells occurs in foetal life [78, 79]. In fact, EPO has been reported to play a role in the brain development [80]. Neural crest-derived cells have typically multipotential properties and play probably a very important role in carcinogenesis not only in the kidney but also for melanomas [81].

7. Conclusion

Evidence suggests that ccRCC is derived from the EPC, which upon hyperstimulation by HIF not only increases its EPO production but also is stimulated to proliferate. Genetic changes in VHL, either familial or sporadic, leading to loss of proteolysis result in increased concentrations of HIF. The EPC expresses markers compatible with neuroendocrine origin. A change in the nomenclature of ccRCC should be considered.

Conflict of interest

The authors declare no conflict of interest.

Author details

Helge Waldum[1*] and Patricia Mjønes[1,2]

1 Faculty of Medicine and Health Sciences, Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

2 Department of Pathology, St. Olav's Hospital – Trondheim University Hospital, Trondheim, Norway

*Address all correspondence to: helge.waldum@ntnu.no

References

[1] Mathers CD, Shibuya K, Boschi-Pinto C, Lopez AD, Murray CJ. Global and regional estimates of cancer mortality and incidence by site: I. application of regional cancer survival model to estimate cancer mortality distribution by site. BMC Cancer. 2002;**2**:36. DOI: 10.1186/1471-2407-2-36

[2] Mjones PG, Nordrum IS, Qvigstad G, Sordal O, Rian LL, Waldum HL. Expression of erythropoietin and neuroendocrine markers in clear cell renal cell carcinoma. APMIS: Acta pathologica, microbiologica, et immunologica. Scandinavica. 2017;**125**: 213-222. DOI: 10.1111/apm.12654

[3] Waldum H, Mjønes P. Time to classify Tumours of the stomach and the kidneys according to cell of origin. International Journal of Molecular Sciences. 2021;**22**:13386. DOI: 10.3390/ijms222413386

[4] Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA: a Cancer Journal for Clinicians. 2009;**59**:225-249. DOI: 10.3322/caac.20006

[5] Li H, Hohenstein P, Kuure S. Embryonic kidney development, stem cells and the origin of Wilms tumor. Genes (Basel). 2021;**12**:318. DOI: 10.3390/genes12020318

[6] Tögel F, Valerius MT, Freedman BS, Iatrino R, Grinstein M, Bonventre JV. Repair after nephron ablation reveals limitations of neonatal neonephrogenesis. JCI Insight. 2017;**2**: e88848. DOI: 10.1172/jci.insight.88848

[7] Lindgren D, Eriksson P, Krawczyk K, Nilsson H, Hansson J, Veerla S, et al. Cell-type-specific gene programs of the Normal human nephron define kidney cancer subtypes. Cell Reports. 2017;**20**: 1476-1489. DOI: 10.1016/j.celrep.2017.07.043

[8] Ishihara H, Yamashita S, Liu YY, Hattori N, El-Omar O, Ikeda T, et al. Genetic and epigenetic profiling indicates the proximal tubule origin of renal cancers in end-stage renal disease. Cancer Science. 2020;**111**:4276-4287. DOI: 10.1111/cas.14633

[9] Lee HW, Handlogten ME, Osis G, Clapp WL, Wakefield DN, Verlander JW, et al. Expression of sodium-dependent dicarboxylate transporter 1 (NaDC1/SLC13A2) in normal and neoplastic human kidney. American Journal of Physiology. Renal Physiology. 2017;**312**:F427-f435. DOI: 10.1152/ajprenal.00559.2016

[10] Axelson H, Johansson ME. Renal stem cells and their implications for kidney cancer. Seminars in Cancer Biology. 2013;**23**:56-61. DOI: 10.1016/j.semcancer.2012.06.005

[11] Lombardi D, Becherucci F, Romagnani P. How much can the tubule regenerate and who does it? An open question. Nephrology, Dialysis, Transplantation. 2016;**31**:1243-1250. DOI: 10.1093/ndt/gfv262

[12] Wang H, Xu H, Cheng Q, Liang C. Identification of a novel stem cell subtype for clear cell renal cell carcinoma based on stem cell gene profiling. Frontiers in Oncology. 2021;**11**: 758989. DOI: 10.3389/fonc.2021.758989

[13] Delahunt B, Srigley JR. The evolving classification of renal cell neoplasia. Seminars in Diagnostic Pathology. 2015; **32**:90-102. DOI: 10.1053/j.semdp.2015.02.002

[14] Cimadamore A, Cheng L, Scarpelli M, Massari F, Mollica V, Santoni M, et al. Towards a new WHO classification of renal cell tumor: What the clinician needs to know-a narrative review. Translational Andrology and Urology. 2021;**10**:1506-1520. DOI: 10.21037/tau-20-1150

[15] Haase VH. Regulation of erythropoiesis by hypoxia-inducible factors. Blood Reviews. 2013;**27**:41-53. DOI: 10.1016/j.blre.2012.12.003

[16] Viault F. Sur laugmentation considerable du nombre des globules rouges dans le sang chez les inhabitants dans des hauts plateaaux de l` Amérique du Sud. C R Academy Science Paris. 1890;**111**:917-918

[17] Krumdieck N, W.C. Erythropoietic substance in the serum of anemic animals. Proceedings of the Society for Experimental Biology and Medicine. 1943;**54**:14-17

[18] Bonsdorff E, J.E. A humoral mechanism in anoxici erythocytosis. Acta Physiologica Scandinavica. 1948;**16**: 150-170

[19] Peschle C, Sasso GF, Rappaport IA, Condorelli M. Erythropoietin production in nephrectomized rats: Possible role of the renal erythropoietic factor. The Journal of Laboratory and Clinical Medicine. 1972;**79**:950-959

[20] Miyake T, Kung CK, Goldwasser E. Purification of human erythropoietin. The Journal of Biological Chemistry. 1977;**252**:5558-5564

[21] Obara N, Suzuki N, Kim K, Nagasawa T, Imagawa S, Yamamoto M. Repression via the GATA box is essential for tissue-specific erythropoietin gene expression. Blood. 2008;**111**:5223-5232. DOI: 10.1182/blood-2007-10-115857

[22] Maxwell PH, Ferguson DJ, Osmond MK, Pugh CW, Heryet A, Doe BG, et al. Expression of a homologously recombined erythopoietin-SV40 T antigen fusion gene in mouse liver: Evidence for erythropoietin production by Ito cells. Blood. 1994;**84**:1823-1830

[23] Marti HH, Wenger RH, Rivas LA, Straumann U, Digicaylioglu M, Henn V, et al. Erythropoietin gene expression in human, monkey and murine brain. The European Journal of Neuroscience. 1996;**8**:666-676. DOI: 10.1111/j.1460-9568.1996.tb01252.x

[24] Lee JW, Bae SH, Jeong JW, Kim SH, Kim KW. Hypoxia-inducible factor (HIF-1)alpha: Its protein stability and biological functions. Experimental & Molecular Medicine. 2004;**36**:1-12. DOI: 10.1038/emm.2004.1

[25] Kapitsinou PP, Liu Q, Unger TL, Rha J, Davidoff O, Keith B, et al. Hepatic HIF-2 regulates erythropoietic responses to hypoxia in renal anemia. Blood. 2010; **116**:3039-3048. DOI: 10.1182/blood-2010-02-270322

[26] Wiesener MS, Jürgensen JS, Rosenberger C, Scholze CK, Hörstrup JH, Warnecke C, et al. Widespread hypoxia-inducible expression of HIF-2alpha in distinct cell populations of different organs. The FASEB Journal. 2003;**17**:271-273. DOI: 10.1096/fj.02-0445fje

[27] Kazal LA, Erslev AJ. Erythropoietin production in renal tumors. Annals of Clinical and Laboratory Science. 1975;**5**: 98-109

[28] Burk JR, Lertora JJ, Martinez IR Jr, Fisher JW. Renal cell carcinoma with erythrocytosis and elevated erythropoietic stimulatory activity. Southern Medical Journal. 1977;**70**:

955-958. DOI: 10.1097/00007611-197708000-00017

[29] Hagiwara M, Chen IL, Fisher JW. Erythropoietin production in long-term cultures of human renal carcinoma cells. The role of cell population density. Experimental Cell Research. 1984;**154**: 619-624. DOI: 10.1016/0014-4827(84)90187-3

[30] Wiesener MS, Münchenhagen P, Gläser M, Sobottka BA, Knaup KX, Jozefowski K, et al. Erythropoietin gene expression in renal carcinoma is considerably more frequent than paraneoplastic polycythemia. International Journal of Cancer. 2007;**121**:2434-2442. DOI: 10.1002/ijc.22961

[31] Papworth K, Bergh A, Grankvist K, Ljungberg B, Rasmuson T. Expression of erythropoietin and its receptor in human renal cell carcinoma. Tumour biology: the journal of the International Society for Oncodevelopmental Biology and Medicine. 2009;**30**:86-92. DOI: 10.1159/000216844

[32] Michael A, Politi E, Havranek E, Corbishley C, Karapanagiotou L, Anderson C, et al. Prognostic significance of erythropoietin expression in human renal cell carcinoma. BJU International. 2007;**100**:291-294. DOI: 10.1111/j.1464-410X.2007.06978.x

[33] Gibbons RP, Monte JE, Correa RJ Jr, Mason JT. Manifestations of renal cell carcinoma. Urology. 1976;**8**:201-206. DOI: 10.1016/0090-4295(76)90366-6

[34] Tomadoni A, García C, Márquez M, Ayala JC, Prado F. Stauffer's syndrome with jaundice, a paraneoplastic manifestation of renal cell carcinoma: A case report. Archivos Españoles de Urología. 2010;**63**:154-156

[35] Padala SA, Barsouk A, Thandra KC, Saginala K, Mohammed A, Vakiti A, et al. Epidemiology of renal cell carcinoma. World Journal of Oncology. 2020;**11**:79-87. DOI: 10.14740/wjon1279

[36] Feng CC, Ding GX, Song NH, Li X, Wu Z, Jiang HW, et al. Paraneoplastic hormones: Parathyroid hormone-related protein (PTHrP) and erythropoietin (EPO) are related to vascular endothelial growth factor (VEGF) expression in clear cell renal cell carcinoma. Tumour biology: the journal of the International Society for Oncodevelopmental Biology and Medicine. 2013;**34**:3471-3476. DOI: 10.1007/s13277-013-0924-7

[37] Iversen OH, Røger M, Solberg HE, Wetteland P. Rising erythrocyte sedimentation rate during several years before diagnosis can be a predictive factor in 70% of renal cell carcinoma patients. The benefit of knowing subject-based reference values. Journal of Internal Medicine. 1996;**240**:133-141. DOI: 10.1046/j.1365-2796.1996.30195852000.x

[38] Choi Y, Park B, Kim K, Jeong BC, Seo SI, Jeon SS, et al. Erythrocyte sedimentation rate and anaemia are independent predictors of survival in patients with clear cell renal cell carcinoma. British Journal of Cancer. 2013;**108**:387-394. DOI: 10.1038/bjc.2012.565

[39] Johnson TV, Abbasi A, Owen-Smith A, Young A, Ogan K, Pattaras J, et al. Absolute preoperative C-reactive protein predicts metastasis and mortality in the first year following potentially curative nephrectomy for clear cell renal cell carcinoma. The Journal of Urology. 2010;**183**:480-485. DOI: 10.1016/j.juro.2009.10.014

[40] Cairns P. Renal cell carcinoma. Cancer Biomarkers. 2010;**9**:461-473. DOI: 10.3233/cbm-2011-0176

[41] Hopkins DT, Waters D, Manecksha RP, Lynch TH. Isolated soft tissue mass of the finger as the first presentation of oligometastatic renal cell carcinoma. BML Case Reports. 2022;**15**: e248718. DOI: 10.1136/bcr-2021-248718

[42] Öven BB, Demir MK, Çelik S, Moujawaz R, Somay A, Kılıc T. Isolated pituitary metastasis of renal cell carcinoma: A case report and systematic review of the literature. Current Medical Imaging. 2022. DOI: 10.2174/0929866529666220426121245

[43] Sun J, Zhang Z, Xiao Y, Li H, Ji Z, Lian P, et al. Skeletal muscle metastasis from renal cell carcinoma: A case series and literature review. Frontiers in Surgery. 2022;**9**:762540. DOI: 10.3389/fsurg.2022.762540

[44] Choo YH, Seo Y, Choi J. Extremely delayed solitary cerebral metastasis in patient with T1N0M0 renal cell carcinoma after radical nephrectomy: Case report and literature review. Medicine (Baltimore). 2021;**100**:e25586. DOI: 10.1097/md.0000000000025586

[45] Friberg S, Nyström A. Cancer metastases: Early dissemination and late recurrences. Cancer Growth Metastasis. 2015;**8**:43-49. DOI: 10.4137/cgm.S31244

[46] Hadfield G. The dormant cancer cell. British Medical Journal. 1954;**2**:607-610. DOI: 10.1136/bmj.2.4888.607

[47] Waldum H, Mjønes PG. Correct identification of cell of origin may explain many aspects of cancer: The role of neuroendocrine cells as exemplified from the stomach. International Journal of Molecular Sciences. 2020;**21**:5751. DOI: 10.3390/ijms21165751

[48] Waldum HL, Ringnes E, Nordbo H, Sordal O, Nordrum IS, Hauso O. The normal neuroendocrine cells of the upper gastrointestinal tract lack E-cadherin. Scandinavian Journal of Gastroenterology. 2014;**49**:974-978. DOI: 10.3109/00365521.2014.909275

[49] Waldum HL, Hauso O, Fossmark R. The regulation of gastric acid secretion - clinical perspectives. Acta Physiologica (Oxford, England). 2014;**210**:239-256. DOI: 10.1111/apha.12208

[50] Barrett P, Hobbs RC, Coates PJ, Risdon RA, Wright NA, Hall PA. Endocrine cells of the human gastrointestinal tract have no proliferative capacity. The Histochemical Journal. 1995;**27**:482-486

[51] Waldum HL, Brenna E. Non-proliferative capacity of endocrine cells of the human gastro-intestinal tract. The Histochemical Journal. 1996;**28**:397-398. DOI: 10.1007/bf02331403

[52] Cunningham JL, Janson ET. The biological hallmarks of ileal carcinoids. European Journal of Clinical Investigation. 2011;**41**:1353-1360. DOI: 10.1111/j.1365-2362.2011.02537.x

[53] Tang M, Ai B, Ding L, Du J, Cheng G, Zhang Y. Late recurrence and metastasis of an appendiceal goblet cell carcinoid 24 years after appendectomy. Chinese Medical Journal. 2014;**127**: 591-592

[54] Dello Spedale Venti M, Giannetta E, Bosco D, Biffoni M, Carletti R, Chiappetta C, et al. Metastasis of lung carcinoid in the thyroid gland after 18 years: It is never too late. A case report and review of the literature. Pathologica. 2022;**114**:164-169. DOI: 10.32074/1591-951x-286

[55] Thai E, Gnetti L, Gilli A, Caruana P, Dalla Valle R, Buti S. Very late recurrence of an apparently benign pheochromocytoma. Journal of Cancer

Research and Therapeutics. 2015;**11**: 1036. DOI: 10.4103/0973-1482.154942

[56] Goodenough J, Cozon CL, Liew SH. An incidental finding of a nodal recurrence of cutaneous malignant melanoma after a 45-year disease-free period. BML Case Reports. 2014;**2014**. DOI: 10.1136/bcr-2014-204289

[57] Mansour D, Kejariwal D. It is never too late: Ultra-late recurrence of melanoma with distant metastases. BML Case Reports. 2012;**2012**. DOI: 10.1136/bcr.01.2012.5474

[58] Vandamme N, Berx G. From neural crest cells to melanocytes: Cellular plasticity during development and beyond. Cellular and Molecular Life Sciences. 2019;**76**:1919-1934. DOI: 10.1007/s00018-019-03049-w

[59] Shields LBE, Rezazadeh Kalebasty A. Spontaneous regression of delayed pulmonary and mediastinal metastases from clear cell renal cell carcinoma. Case Reports in Oncology. 2020;**13**:1285-1294. DOI: 10.1159/000509509

[60] Van de Walle M, Demol J, Staelens L, Rottey S. Abscopal effect in metastatic renal cell carcinoma. Acta Clinica Belgica. 2017;**72**:245-249. DOI: 10.1080/17843286.2016.1201614

[61] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a Cancer Journal for Clinicians. 2018;**68**:394-424. DOI: 10.3322/caac.21492

[62] Dhôte R, Pellicer-Coeuret M, Thiounn N, Debré B, Vidal-Trecan G. Risk factors for adult renal cell carcinoma: A systematic review and implications for prevention. BJU International. 2000;**86**:20-27. DOI: 10.1046/j.1464-410x.2000.00708.x

[63] Minami T, Inoue M, Sawada N, Yamaji T, Iwasaki M, Tsugane S. Alcohol consumption, tobacco smoking, and subsequent risk of renal cell carcinoma: The JPHC study. Cancer Science. 2021; **112**:5068-5077. DOI: 10.1111/cas.15129

[64] Waldum HL, Nilsen OG, Nilsen T, Rørvik H, Syversen V, Sanvik AK, et al. Long-term effects of inhaled nicotine. Life Sciences. 1996;**58**:1339-1346. DOI: 10.1016/0024-3205(96)00100-2

[65] Sørhaug S, Steinshamn S, Nilsen OG, Waldum HL. Chronic inhalation of carbon monoxide: Effects on the respiratory and cardiovascular system at doses corresponding to tobacco smoking. Toxicology. 2006;**228**:280-290. DOI: 10.1016/j.tox.2006.09.008

[66] Vucenik I, Stains JP. Obesity and cancer risk: Evidence, mechanisms, and recommendations. Annals of the New York Academy of Sciences. 2012;**1271**: 37-43. DOI: 10.1111/j.1749-6632.2012.06750.x

[67] Hakimi AA, Furberg H, Zabor EC, Jacobsen A, Schultz N, Ciriello G, et al. An epidemiologic and genomic investigation into the obesity paradox in renal cell carcinoma. Journal of the National Cancer Institute. 2013;**105**: 1862-1870. DOI: 10.1093/jnci/djt310

[68] Latif F, Tory K, Gnarra J, Yao M, Duh FM, Orcutt ML, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. Science. 1993;**260**: 1317-1320. DOI: 10.1126/science.8493574

[69] Gnarra JR, Tory K, Weng Y, Schmidt L, Wei MH, Li H, et al. Mutations of the VHL tumour suppressor gene in renal carcinoma.

Nature Genetics. 1994;**7**:85-90. DOI: 10.1038/ng0594-85

[70] Pavlovich CP, Schmidt LS, Phillips JL. The genetic basis of renal cell carcinoma. The Urologic Clinics of North America. 2003;**30**:437-454, vii. DOI: 10.1016/s0094-0143(03)00023-5

[71] Dalgliesh GL, Furge K, Greenman C, Chen L, Bignell G, Butler A, et al. Systematic sequencing of renal carcinoma reveals inactivation of histone modifying genes. Nature. 2010;**463**: 360-363. DOI: 10.1038/nature08672

[72] Clifford SC, Astuti D, Hooper L, Maxwell PH, Ratcliffe PJ, Maher ER. The pVHL-associated SCF ubiquitin ligase complex: Molecular genetic analysis of elongin B and C, Rbx 1 and HIF-1alpha in renal cell carcinoma. Oncogene. 2001; **20**:5067-5074. DOI: 10.1038/sj.onc.1204602

[73] Waldum H, Mjønes P. Towards understanding of gastric cancer based upon physiological role of gastrin and ECL cells. Cancers (Basel). 2020;**12**:3477. DOI: 10.3390/cancers12113477

[74] Furukawa A, Kanda K, Yokozeki H, Maebayashi K, Kagawa S. A case of erythropoietin-producing renal cell carcinoma with a skin metastasis. Nihon Hinyokika Gakkai Zasshi. 1992;**83**:247-250. DOI: 10.5980/jpnjurol1989.83.247

[75] de Herder WW, Zandee WT, Hofland J. Somatostatinoma. In: chrousos G, de Herder WW, Dhatariya K, Dungan K, Hershman JM, Hofland, J, Kalra S, et al. Endotext. South Dartmouth (MA): MDText.com, Inc.; 2000

[76] Williams ST, Chatzikyriakou P, Carroll PV, McGowan BM, Velusamy A, White G, et al. SDHC phaeochromocytoma and paraganglioma: A UK-wide case series. Clinical Endocrinology. 2022;**96**:499-512. DOI: 10.1111/cen.14594

[77] Mjones P, Sagatun L, Nordrum IS, Waldum HL. Neuron-specific enolase as an Immunohistochemical marker is better than its reputation. The Journal of Histochemistry and Cytochemistry. 2017;**65**:687-703. DOI: 10.1369/0022155417733676

[78] Suzuki N, Hirano I, Pan X, Minegishi N, Yamamoto M. Erythropoietin production in neuroepithelial and neural crest cells during primitive erythropoiesis. Nature Communications. 2013;**4**:2902. DOI: 10.1038/ncomms3902

[79] Hirano I, Suzuki N. The neural crest as the first production site of the erythroid growth factor erythropoietin. Frontiers in Cell and Development Biology. 2019;**7**:105. DOI: 10.3389/fcell.2019.00105

[80] Yu X, Shacka JJ, Eells JB, Suarez-Quian C, Przygodzki RM, Beleslin-Cokic B, et al. Erythropoietin receptor signalling is required for normal brain development. Development. 2002;**129**: 505-516. DOI: 10.1242/dev.129.2.505

[81] Liu J, Rebecca VW, Kossenkov AV, Connelly T, Liu Q, Gutierrez A, et al. Neural crest-like stem cell transcriptome analysis identifies LPAR1 in melanoma progression and therapy resistance. Cancer Research. 2021;**81**:5230-5241. DOI: 10.1158/0008-5472.Can-20-1496