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GATA-3 expression in renal cell tumours: association with oncocytoma and cromophobe renal cell carcinoma diagnosis and other clinicopathologic variables

Renato Campos Bastos
up201807570@icbas.up.pt

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Estudante: Renato Campos Bastos

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Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Endereço de correio eletrónico: up201807570@icbas.up.pt

Orientador: Prof. Doutor Rui Manuel Ferreira Henrique

Professor Catedrático Convidado, Departamento de Patologia e Imunologia Molecular

Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Diretor e Assistente Graduado Sénior do Serviço de Anatomia Patológica

Investigador Sénior do Grupo de Epigenética e Biologia do Cancro, Centro de Investigação

Instituto Português de Oncologia do Porto Francisco Gentil, E.P.E.

Coorientador: Dra. Maria Ana Machado Alzamora

Interno de Formação Específica da de Especialidade de Oncologia Médica

Instituto Português de Oncologia do Porto Francisco Gentil, E.P.E.

Docente Externo

Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

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Assinado por: **Maria Ana Machado de Alzamora**
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DECLARAÇÃO

Júlio Manuel Ramos Maia de Oliveira, Presidente do Conselho de Administração, declara que o Instituto Português de Oncologia do Porto Francisco Gentil, EPE autoriza e acolhe o trabalho académico "GATA-3 expression in renal cell tumours: association with oncocytoma and cromophobe renal cell carcinoma diagnosis and other clinicopathologic variables" do estudante Renato Campos Basto, da componente curricular "Dissertação/Projeto/Estágio", do Mestrado Integrado em Medicina, do Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto, cujo orientador é Rui Manuel Ferreira Henrique.

Ademais, afiança que foram cumpridas as exigências legais em matérias de ética, de proteção de dados e de integridade científica.

Porto, 28 de maio de 2024

Dr. Júlio Oliveira
Presidente do Conselho de Administração
IPO Porto

Resumo

Introdução: São escassos os biomarcadores que auxiliam o diagnóstico diferencial entre diferentes tipos de tumores renais oncocíticos. O GATA-3 é um biomarcador promissor, expresso em múltiplas fases da embriogénese renal, útil para a gestão e determinação do prognóstico de múltiplas neoplasias, tendo sido previamente demonstrado como sendo consistentemente positivo em tumores oncocíticos de baixo grau do rim (LOT).

Objetivos: Procurámos descrever a imunoexpressão de GATA-3 numa coorte de tumores oncocíticos primários do rim, revisto segundo a mais recente classificação da Organização Mundial de Saúde (2022), e determinar a existência de diferenças significativas entre a expressão de GATA-3 em carcinomas de células renais de tipo cromófobo (ChRCC) e oncocitomas renais (RO), bem como em outras entidades pertencentes a este grupo de tumores. Adicionalmente, procurámos outras possíveis associações com variáveis clinicopatológicas e de prognóstico.

Materiais e Métodos: Foram avaliadas 110 amostras de remoção cirúrgica de tumores primários do rim, correspondendo a uma coorte de 109 doentes. A imunoexpressão de GATA-3, foi avaliada recorrendo a um sistema de análise digital de imagens. Os registos clínicos de todos os doentes foram revistos para obter as características clínicas/patológicas de base e a informação do *follow-up*.

Resultados: Nesta coorte, foram identificados, 38 (34,55%) RO, 64 (58,18%) ChRCC, 1 (0,91%) LOT, 2 (1,82%) carcinomas oncocíticos de células renais de tipo não especificado (oRCC-NOS), e 5 (4,55%) tumores renais oncocíticos de baixo potencial maligno (ORNLMP). A média do H-score de imunoexpressão do GATA-3 foi de 6,76, sendo de 5,16 nos RO, 6,94 nos ChRCC, 16,6 nos ORNLMP, e de 0 nos oRCC-NOS. O H-score de imunoexpressão de GATA-3 no caso identificado como LOT foi 19,6, não tendo sido identificada diferença estatisticamente significativa entre as diferentes entidades. Igualmente, não foram encontradas associações clinicamente significativas entre o H-index e as variáveis clínico-patológicas.

Discussão e Conclusão: Os nossos resultados demonstraram a ausência de valor da expressão de GATA-3 para auxiliar no diagnóstico diferencial dos tumores oncocíticos do rim. A elevada imunoexpressão observada nos tumores classificados como ORNLMP e LOT, ainda que não estatisticamente significativa, sugere, contudo, a possibilidade destes elevados níveis conduzirem à sugestão ou favorecimento deste diagnóstico em casos com morfologia dúbia. Estudos de maior escala, envolvendo múltiplas instituições e maior número e variedade de casos, poderão clarificar o potencial valor da utilização de GATA-3 para este fim.

Palavras-chave: Tumores oncocíticos do rim, GATA-3, imunoexpressão, imunomarcador, carcinoma de células renais cromófobo, oncocitoma renal, tumor oncocítico de baixo grau, neoplasia renal oncocítica de baixo potencial maligno, carcinoma de células renais oncocítico de tipo não especificado, diagnóstico diferencial.

Abstract

Background: Presently, biomarkers which might aid the diferential diagnosis among oncocytic renal cell tumors are of limited value. GATA-3 is a promising biomarker, expressed in multiple stages of renal embryogenesis, previously reported to help in the management and prognosis of multiple neoplasms, being consistently positive in low grade oncocytic tumours of the kidney (LOT).

Objectives: We aimed to characterize GATA-3 immunoexpression in a cohort of patients with primary oncocytic tumours of the kidney, recoded according to the most recent World Health Organization classification (2022), looking for significant diferences in GATA-3 expression between chromophobe type renal cell carcinoma (ChRCC) and renal oncocytoma (RO), as well as other entities belonging to this group of tumours. Additionally, we researched other possible associations with clinicopathologic and prognostic variables.

Materials and Methods: Surgical specimens of 110 primary renal tumours, corresponding to a cohort of 109 patients, were evaluated for GATA-3 immunoexpression using a digital image analysis system. Clinical records of all patients were reviewed for baseline clinical/pathologic characteristics and follow-up.

Results: Of the individual tumor components, 38 (34,55%) were identified as RO, 64 (58,18%) as ChRCC, 1 (0,91%) as LOT, 2 (1,82%) as oncocytic renal cell carcinoma not otherwise specified (oRCC-NOS), and 5 (4,55%) as oncocytic renal neoplasm of low malignant potential (ORNLMP). Average H-score for GATA-3 immunoexpression was 6,76, corresponding to 6,94 in ChRCC, 5,16 in RO, 16,6 in ORNLMP, and 0 in oRCC-NOS. The H-score for GATA-3 immunoexpression corresponding to the single case identified as LOT was 19,6. No statistically significant difference in GATA-3 expression was disclosed among the different entities. Furthermore, no statistically significant associations with clinicopathologic parameters were depicted.

Discussion & Conclusions: Our results show that GATA-3 immunoexpression does not help to discriminate among oncocytic renal cell tumours. HIgh GATA-3 immunoexpression observed in ORNLMP and LOT suggests, nonetheless, that this biomarker may be useful to favour that diagnosis in cases with dubious morphology. Larger scale, multi-institutional studies involving a greater number and variety of cases may help validate the use of GATA-3 to this end.

Keywords: Oncocytic tumour of the kidney, GATA-3, immunoexpression, immunomarker, chromophobe renal cell carcinoma, renal oncocytoma, low-grade oncocytic tumour, oncocytic renal neoplasm of low malignant potential, oncocytic renal cell carcinoma not otherwise specified, differential diagnosis.

List of acronyms

WHO: World Health Organization

ChRCC: Chromophobe Renal Cell Carcinoma

RO: Renal Oncocytoma

LOT: Low-Grade Oncocytic Tumours

EVT: Eosinophilic Vacuolated Tumours

HOCT: Hybrid Oncocytic Tumours

ORNLMP: Oncocytic Renal Neoplasm of Low Malignant Potential

oRCC-NOS: Oncocytic Renal Cell Carcinoma- Not Otherwise Specified

CK7: Cytokeratin 7

IPO-Porto: Portuguese Institute of Oncology of Porto

AJCC: American Joint Comittee on Cancer

IHC: immunohistochemistry

H-score: Histo-score

H-index: Histo-index

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Introduction

Adult renal tumours have been classified into various types by the World Health Organization, and, within this classification, lies the group of oncocytic renal tumours, the hallmarks being well-recognized entities, such as chromophobe renal cell carcinoma (ChRCC) and renal oncocytoma (RO). However, recent updates to the WHO classification[1] have seen the recognition of new and emergent entities such as Low-Grade Oncocytic Tumours (LOT) and Eosinophilic Vacuolated Tumours (EVT), collectively themed "*other oncocytic tumours of the kidney*". This particular category also includes Hybrid Oncocytic Tumours (HOCT) and Oncocytic Renal Neoplasm of Low Malignant Potential (ORNLMP) Not Otherwise Specified, which designate, respectively, hereditary and sporadic oncocytic tumours with borderline features between RO and ChRCC, and which do not fit the diagnosis of LOT or EVT[14].

The group of oncocytic renal tumours encompasses a spectrum of different entities which share certain morphologic and immunohistochemical characteristics, that make differential diagnosis challenging, especially in the preoperative (biopsy) setting[2]. The ability to discriminate between RO and ChRCC is especially important, given that, despite their similarities, RO is a benign tumour, while ChRCC is malignant, and the treatment which a patient must undergo may differ. This justifies the need for the investigation and discovery of new histological and immunohistochemical features that might help in discerning between these two entities.

While there is a scarcity of serum and immunohistochemical markers which might aid in diferentiating between those entities, CD117 (KIT) and vimentin have long been recognized as helpful markers in discerning RO and ChRCC from other renal cell tumours. Cytokeratin 7 (CK7) is useful in the diferential diagnosis between RO and ChRCC, however, some eosiniphilic examples of ChRCC may exhibit less prominent CK7 labelling, which makes the establishment of a positive staining threshold more complicated[3].

GATA-3 belongs to a family of transcription factors that bind to WGATAR sequences, a specific sequence of nucleotides found in the transcriptional regulatory region of many genes. Each member of this family has a distinct distribution in human tissue and different developmental profiles, which sugest that each one plays a different role during embryogenesis. GATA-3 is involved in the differentiation of T-lymphocytes and expressed in diferent stages of the kidney's development during embryogenesis, being expressed in the Wolffian duct since its emergence, in the colecting ducts of the mesonephros until its involution, in the ureteric bud of the metanephros, and in the glomerular mesangium and adjacent endocapilary cells of both the meta- and mesonephros[4]. GATA-3 has already shown significant promise as a biomarker in the management and prognosis of multiple neoplasms, such as breast and urothelial cancers[5,11].

Recent studies have identified consistent immunoexpression of GATA-3 in LOT[6,7], as well as significant underexpression in clear cell renal carcinoma[8,15]. We sought to investigate whether GATA-3 expression might differ between RO and ChRCC, as well as other emerging oncocytic renal tumour entities, constituting a useful biomarker for discrimination among renal oncocityc tumours. Additionally, we looked for possible associations between GATA-3 expression clinicopathologic parameters.

Materials and Methods

Sample collection

In this retrospective study, a cohort of patients with oncocytic renal cell tumours (in part already reported and validated by us), diagnosed and treated by the same multidisciplinary team at the Portuguese Oncology Institute of Porto, Portugal (IPO Porto), between the years of 2017 and 2022, was enrolled. The diagnoses were reviewed and classified according to the norms established in the 8th Edition of the American Joint Comittee on Cancer (AJCC)[9] and the 2022 World Health Organization Classification of Tumours of the Urinary Tract System and Male Genital Organs (5th Edition)[10]. Follow-up was last updated on March 2024.

Formalin-fixed and parafine-embeded samples were selected. 46 (41,82%) corresponding to radical nephrectomy specimens and 64 (58,18%) to partial nephrectomy specimens. Slides were reviewed according to the 2022 WHO classification and a representative block was selected for immunohistochemistry. Consultation cases and cases with no representative blocks available were excluded from this study.

This study is part of a larger project dedicated to the pathologic and epigenetic characterization of renal cell tumours, which has been approved by the IPO Porto Ethics Committee (Comissão de Ética para a Saúde, CES.518.10).

Immunohistochemistry

GATA-3 immunohistochemistry (IHC) was performed using a specific primary monoclonal antibody (clone L50-823, ready to use, Ventana, Roche). This antibody is used in the routine diagnostic procedures conducted at the Department of Pathology of IPO Porto and subjected to validation and quality control procedures. Appropriate controls (e.g., positive control - breast tissue) were included in each slide. Reaction was performed in automated platforms used in diagnostics routine (BenchMark Ultra, Ventana, Roche). Immunostaining was evaluated by the same dedicated uropathologist, who was blinded to clinicopathological data, prior to reviewing pathological diagnosis.

GATA-3 immunoexpression was evaluated using a digital image analysis system (GenAsis™ Israel), which allows for semi-automated quantification of nuclear immunostaining (intensity, on a scale from 0 to 3, and percentage of positive cells for each staining intensity category). The histo-score (H-score) for each sample was then calculated, corresponding to the sum of the products of each immunostaining score by its proportion. Between 500 and 1000 viable tumour cells were evaluated in each sample, whenever possible. Non-tumour cells, such as stromal and lymphoid cells, were excluded from analysis using operator-dependent tools of the software.

Statistical analysis

Data was tabulated using Microsoft Excel for Office 365 and analyzed using IBM SPSS Statistics version 29. Normality was assessed using the Kolmogorov-Smirno test. Differences in continuous variables between diagnostic subgroups were assessed by the Kruskal-Wallis test. Statistical significance was set at $p<0,05$ and adjusted to multiple testing using Dunn's test.

Results

Cohort characterization

A total of 110 primary tumour components were studied (Table 1), corresponding to a cohort of 109 patients, 50 (45,87%) females and 59 (54,13%) males.

Average age at diagnosis was 63,48 years. There was no significant age difference at diagnosis among patients with the different entities. In 51 (46,79%) of the patients the tumor was located on the right side, and in 58 (53,21%) it was located on the left side. None of the patients presented with metastatic lymph nodes or systemic metastatic disease. Syncronous or metarconous neoplasia in other organs (mostly breast, prostate and colon) was found in 21 (19,27%) patients.

Median follow-up time was 61,05 (IQR: 48,56). Overall, 106 (97,25%) patients had no evidence of disease (NED) on their most recent clinical evaluation, 1 (0,92%) remained alive with disease (AWD) and 2 (1,83%) have died of causes other than renal cell tumour (DFOC)- one of difuse B cell lymphoma, and one of endometrial serous adenocarcinoma.

Concerning the individual tumor components, 38 (34,55%) were identified as RO, 64 (58,18%) as ChRCC, 1 (0,91%) as LOT, 2 (1,82%) as oncocytic renal cell carcinoma not otherwise specified (oRCC-NOS), and 5 (4,55%) as ORNLMP. Of the malignant tumours, 22 (30,56%) were classified as pT1a, 19 (26,39%) as pT1b, 9 (12,50%) as pT2a, 19 (26,39%) as pT3a, and 3 (4,17%) could not be evaluated. Only 3 (2,73%) of the surgical specimens had identifiable lymph nodes, and, all were classified as N0. Because RO are benign tumours, TNM does not apply.

GATA-3 immunoexpression

An average of 666,14 cells were evaluated per tumour component. Overall, 68 (61,82%) of the tumor components had no GATA-3 immunoexpression, whereas in the remaining 42 (38,18%) of cases, some degree of expression was depicted. Hence, the median H-score was 0 (IQR= 1,25), and average H-score was 6,76 (SD= 20,19). Among the different tumour types, the average H-score was 6,94 (SD=19,97) in ChRCC, 5,16 (SD= 19,24) in RO, 16,6 (SD= 34,56) in ORNLMP, and 0 (SD=0) in oRCC-NOS. The H-score for the single case identified as LOT was 19,6. The analyzed diagnoses' corresponding mean and median H-scores are organized in Table II.

No statistically significant difference in GATA-3 H-score among the diverse tumour types was disclosed, as depicted by Table III. Furthermore, no significant associations were disclosed bewteen GATA-3 H-score and clinicopathologic parameters.

Discussion

Differential diagnosis amongst entities included in the group of renal cell neoplasms with oncocytic features has been described as challenging[16]. In this setting, both morphological characteristics and immunoprofile are determinant for discriminating among these entities. The number of immunohistochemical markers which might prove useful for this analysis of these tumours is relatively small, however, with CD117, CK7, and vimentin constituting the most widely used[3,17].

The number of studies that have investigated differences in GATA-3 expression between different types of oncocytic tumours is relatively limited. Nonetheless, there are overlapping features which have been emphasized[18]. In this regard, GATA-3 has also been implicated as an essential and useful marker in the evaluation of oncocytic renal cell tumours, showing strong and diffuse positivity in LOT[6,7,11,12,13,17]. This consistent finding has led some authors to sugest that this specific type of tumour originates from the distal nephron[13]. Given that our cohort only included a single case of LOT, which showed only positive, weak nuclear staining in approximately 20% of analyzed cells, it is impossible to withdraw any significant conclusion regarding a significant difference of GATA-3 expression in this entity, as compared, for example, with ChRCC and RO.

Interestingly, and contrarily to our expectations, no significant difference in GATA-3 immunoexpression between ChRCC and RO was disclosed in this study. Immunostaining seemed to be more pronounced and frequent in ChRCC in comparison with RO, although this subjective impression was not confirmed by statistical analysis. Despite this lack of significance, this difference in staining seems to be in acordance with published literature, in which RO are more frequently described as less frequently positive for GATA-3 comparatively to ChRCC[11]. In the experience of some authors (e.g. Hes O and Trpkov K), RO have been found to be generally negative for GATA-3 immunoexpression[12], sugesting that GATA-3 staining, even when only considering a singular type of tumour, in this case, RO, may exhibit significant intra- and inter-tumour variablility.

HOCT are a relatively less understood entity, and analysis of the available literature, regarding its immunohistochemical profile, may be misleading, because a significant proportion of publications on this matter were released before the recognition of LOT and other eosinophilic renal cell tumours, and subsequent changes in classification that affected the HOCT group[13]. These have been described as variably GATA-3 positive by Miettinen et al[11]. Given that our cohort has no such cases, it is impossible to extrapolate any conclusion.

Nonetheless, our cohort included several unclassifiable cases, some with predominantly high-grade features (warranting their classification as oRCC-NOS), and some lower-grade (classified as ORNLMP). ORNLMP showed average GATA-3 immunoexpression, similar to the one seen in the singular case of LOT studied, reinforcing a similar origin and behaviour, as demonstrated by their inclusion in the same category of tumours by the 2022 WHO classification[10].

Among the patients enrolled in this study, none of them had metastatic disease at diagnosis. This might result from the relatively small dimension of the cohort and/or because of early diagnosis. Indeed, a significant portion of the patients were under clinical and imagiological monitoring for cancers affecting other organs, previously diagnosed, and treated. In these cases, renal tumour diagnosis was mostly incidental.

This study has several limitations, the most important of which is the retrospective design and the limited sample size, especially for the categories other than RO and ChRCC. Furthermore, because all patients have been treated at IPO Porto, the geographical catchment area corresponds mostly to the northern region of Portugal, which may undermine demographic and genetic variability among cases. Finally, the only diagnoses analyzed in this study were ChRCC, RO, ORNLMP, LOT and oRCC-NOS, leaving out other entities such as EVT and HOCT, which are relevant differential diagnoses in this context. Nonetheless, the use of an image analysis system to assess and quantify GATA-3 immunoexpression provides a less biased estimation and, eventually, a more reproducible one, addressing a key issue in current diagnostic Pathology scenarios.

In future studies, a larger number of cases should be included, and to guarantee a better representativity of the general population, these patients should be selected from multiple diferent institutions belonging to different geographical regions. Simultaneously, a larger variety of cases, namely a more diverse group of diagnoses, would be advantageous to more thoroughly evaluating differences in GATA-3 immunoexpression among oncocytic renal cell tumour subtypes.

Conclusion

Despite the higher proportion of GATA-3 staining in ChRCC in comparison to RO and other entities, the lack of statistical significance precludes its use in a routine diagnostic setting, which could prove very usefull for pre-surgery diagnosis, using needle-core biopsy. In future studies, a larger cohort size and greater variety of diagnoses is requires to better evaluate differences in GATA-3 immunostaining among oncocytic renal cell tumour entities.

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Diagnosis		**ChRCC**	**RO**	**ORNLMP**	**oRCC-NOS**	**LOT**
Age (yrs, Average [STD])		63,06 (11,61)	63,95 (11,90)	67,60 (8,01)	55,50 (17,68)	70 (N/A)
Sex (n [%])	M	37 (57,81%)	20 (52,63%)	1 (20%)	1 (50%)	0 (0%)
	F	27 (42,19%)	18 (47,37%)	4 (80%)	1 (50%)	1 (100%)

Table I- Average age at diagnosis per diagnostic group and sample distribution according to patient sex.

Diagnosis	**ChRCC**	**RO**	**ORNLMP**	**oRCC-NOS**	**LOT**
H-score (Average [STD])	6,94 (19,97)	5,16 (19,24)	16,60 (34,56)	0 (0)	19,6 (N/A)
H-score (Median [IQR])	0 (1,50)	0 (1,13)	0 (41,50)	0 (0)	19,6 (N/A)

Table II- Mean and median H-score per diagnosis. As the median H-scores were identical across all the diferent groups except for LOT, we decided to also include the mean H-score in order to more accurately characterize the immunohistochemical study.

Sample 1	**Sample 2**	**p-value**
oRCC-NOS	ChRCC	0,301
oRCC-NOS	RO	0,302
oRCC-NOS	ORNLMP	0,269
oRCC-NOS	LOT	0,059
ChRCC	RO	0,977
ChRCC	ORNLMP	0,693
ChRCC	LOT	0,119
RO	ORNLMP	0,709
RO	LOT	0,122
ORNLMP	LOT	0,205

Table III- Comparison between the mean H-score of diferent diagnostic groups.