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Liver metastasis from a chromophobe renal cell carcinoma 18 years after initial diagnosis: a case report

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Abstract

Background Chromophobe renal cell carcinoma is a rare histological subtype, accounting for only 5–6% of renal cell carcinoma cases. It exhibits low aggressiveness and has an overall favorable prognosis with a very low risk of developing metastatic disease. Genetic syndromes such as Birt–Hogg–Dubbé may be associated with this renal cell carcinoma subtype. Owing to limited clinical data, therapeutic regimens for advanced chromophobe renal cell carcinoma are often extrapolated from treatment protocols for clear cell renal cell carcinoma or studies combining several non-clear cell renal cell carcinoma types.

Case presentation We report a case of a 54-year-old Austrian male patient presenting with metastatic liver disease from chromophobe renal cell carcinoma, confirmed by biopsy, 18 years after the initial diagnosis of a non-metastasized, grade 2, pNO, pT2 tumor with R0 resection. The patient underwent regular follow-up examinations and had no clinical symptoms at the time of recurrent disease diagnosis. Family history for genetic syndromes was negative. The multidisciplinary tumor board decided to treat the patient with a novel first-line palliative therapy using combined immuno-/tyrosine kinase therapy with pembrolizumab/lenvatinib. A multiphasic computed tomography scan performed 3 months after initiation of therapy showed a complete response.

Conclusion Although chromophobe renal cell carcinoma typically has excellent progression-free survival and overall survival rates in localized disease, those patients with larger tumors or those with sarcomatous features, as well as PT53 mutations, seem to have worse outcomes due to metastatic development. This case report affirms that patients with chromophobe renal cell carcinoma exhibiting these risk factors should undergo closer and long-term follow-up after curative surgery.

Keywords Carcinoma, Renal cell, Chromophobe renal cell carcinoma, Neoplasm metastasis, Molecular targeted therapy, Immunotherapy, Rare diseases, Case reports

Introduction

Chromophobe renal cell carcinoma (chRCC) is the third most common type of renal cell carcinoma according to the 2016 World Health Organization (WHO) classification, accounting for 5–7% of all renal cell carcinoma (RCC) cases, with an overall low malignant potential. Nevertheless, the risk of developing metastatic disease is up to 6% [1–4].

They arise from the intercalated cells of the distal tubule and are differentiated into classic and eosinophilic

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types on the basis of their morphological heterogeneity and proportion of cells [2, 5]. This consists of type 1 and type 2 cellular elements, with type 1 showing a small and moderately granular cytoplasm and type 2 containing abundant eosinophilic cytoplasm that is denser at the periphery of the cell. Most chRCC cases are sporadic [6].

Patients with germline mutations in the *PTEN* gene are at increased risk of developing chromophobe-like or oncocytoma-like neoplasms, characterized as Cowden syndrome (CS). Patients with CS exhibit hallmark features, including macrocephaly and distinctive dermatologic manifestations, such as acral keratosis and facial trichilemmomas, alongside the formation of multiple hamartomas. The condition also increases the risk for breast, endometrial, and thyroid cancers. In addition, genitourinary cancers, specifically kidney cancer, are considered one of the diagnostic criteria attributed to CS. While Shuch *et al*. report a low incidence of RCC in patients with CS, these individuals face a > 30-fold increased risk of developing kidney cancer [7]. Other hereditary cancer syndromes linked to RCC include Birt–Hogg–Dubbè syndrome (BHD), characterized by an autosomal dominant predisposition to multiple fibrofolliculomas on the face, lung cysts, and colorectal tumors; and Von Hippel–Lindau disease (VHL), associated with a over 70% lifetime risk of developing retinal and central nervous system hemangioblastomas. The RCC histological subtypes often seen in BHD include chromophobe and oncocytic features, while for VHL-associated RCC, this manifests as the clear cell renal cell carcinoma (ccRCC) subtype [8].

Chromosomal abnormalities, such as losing chromosomes 1, 2, 6, 10, 13, 17, and 21, are also associated with chRCC [8]. The chromosome abnormalities in chromosomes 1, 2, 6, 10, 13, and 17 are more common in the classical type of chromophobe RCC than in the eosinophilic type, indicating that this type has more chromosome instability [9]. Gaining copies of chromosomes 4, 7, 11, 12, 14q, and 18q may also be observed in chromophobe RCC [10]. In addition, a mutation in the short arm of chromosome 7 is associated with loss of the *mTOR* gene, a tumor suppressor and activator of C-KIT. Although germline mutations of the *PTEN* gene are the most common gene alteration in chromophobe RCC, a low incidence of somatic mutations of TP53 has been observed in this type of renal cancer. Other genes that are frequently mutated in chromophobe RCC include *FAAH2*, *PDHB*, *PDXD1*, *ZNF765*, *PRKAG2*, *ARID1A*, and *ABHD3* [11]. In immunohistochemistry, tumor cells in chRCC are diffusely positive for CD117 (C-KIT) and CK7 [2].

The gold-standard treatment for localized chRCC (stages I–III) is surgery without the need for adjuvant therapy, while advanced stage IV disease requires cytoreductive nephrectomy with additional systemic therapy [2]. Compared with clear cell renal cell carcinoma (ccRCC), chRCC has an overall better recurrence-free survival (RFS) and overall survival (OS) owing to its distinct biological characteristics, including chromosomal aneuploidy. TP53 mutations in chRCC seem to be associated with a more aggressive chromophobe phenotype [2, 5]. Advanced stage (T3 or T4), larger tumor size, and sarcomatous differentiation negatively affect RFS and OS [12].

Owing to the low incidence of the chromophobe subtype of RCC, first-line systemic treatments for chRCC are derived from ccRCC protocols or subgroup analysis, as noted by Garje *et al*., and outlined in the ESMO clinical Practice Guidelines by Escudier *et al*. [2, 13]. Recently, the use of non-chemotherapy regimens in the CLEAR trial have shown efficacy as first-line treatments in ccRCC [14, 15].

Case presentation

We report the case of a 54-year-old Austrian male with liver metastasis 18 years after radical nephrectomy and adrenalectomy for non-metastasized chRCC, without any associated genetic syndrome. In 2005, our patient presented with left upper quadrant pain. An ultrasound revealed a large mass on the left kidney, suspicious of renal cell carcinoma. A multiphasic computed tomography (CT) of the kidneys, and a staging CT of the chest, confirmed a 15 cm left renal parenchymal tumor without renal vein involvement or evidence of extracapsular or metastatic disease. Following the diagnosis, the patient underwent radical left-sided nephrectomy and adrenalectomy. Histopathology confirmed a compact chromophobe renal cell carcinoma G2, infiltrating the renal pelvis but sparing the ureter and left renal vein, staged as pT2 R0. No sarcomatous changes were noted, and no referral to the epithelial–mesenchymal transition.

The patient received annual outpatient follow-up. In 2023, suspicious liver lesions were reported on abdominal CT, which were further evaluated by dedicated magnetic resonance imaging (MRI) of the liver. Contrast-enhanced MRI, using a liver specific agent (10 ml gadoxetate disodium), depicted multiple liver lesions up to 2 cm, predominantly in the right liver lobe. For example, T2 weighted half-Fourier acquisition single-shot turbo spin-echo fat-suppressed (HASTE FS) imaging showed a 2 cm hyperintense lesion in liver segment VII (Fig. 1A), with signal loss on T1-VIBE Dixon Opp-phase images (Fig. 1B), and a high signal on diffusion-weighted images with the corresponding apparent diffusion coefficient map (ADC-map) (Fig. 1C, D). Unfortunately, due to signal artifacts, the

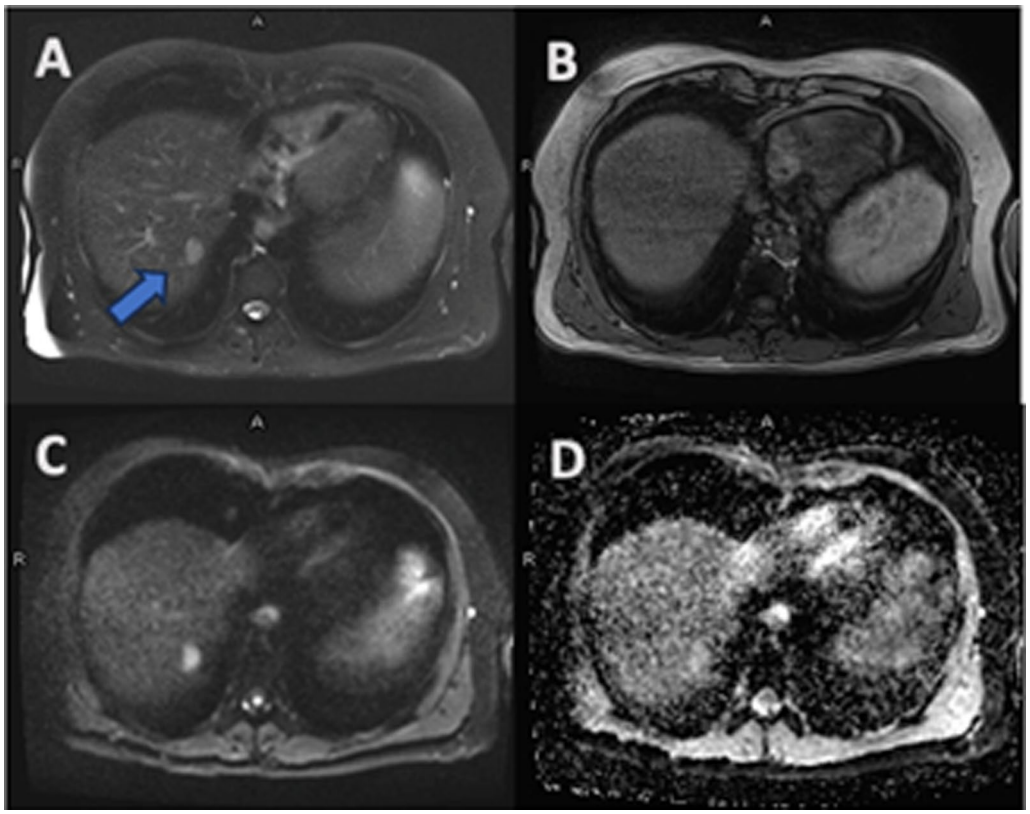

Fig. 1 Axial T2 half-Fourier acquisition single-shot turbo spin-echo fat-suppressed image (blue arrow shows a hyperintense lesion in the right liver lobe) (**A**), T1-VIBE Dixon Opp-phase image (**B**), diffusion-weighted image B800 (**C**), and apparent diffusion coefficient (**D**)

diffusion coefficient maps could not be adequately correlated, but it was possible to outline a corresponding signal without diffusion restriction. After intravenous contrast injection the lesion showed a slight enhancement with wash-out on the delayed phase (Fig. 2A–D; blue arrow on D corresponding with A–C). Besides the liver, there were no other organs involved. The patient underwent CT-guided liver biopsy, confirming metastases from a renal cell carcinoma of the chromophobe subtype with an epithelial–mesenchymal transition index Ki-67 of 5–10%.

Immunohistochemical analysis showed positive reactions with CK7, C-KIT, PAX8, and CD10; and negative reactions with vimentin and racemase. Germline mutations in PTEN and TP53, along with other gene mutations, were not investigated.

The case was discussed in an interdisciplinary team meeting, and the patient received first-line palliative therapy with pembrolizumab and lenvatinib [14], which was initiated in October 2023. In January 2024, follow-up abdominal CT showed no liver lesions, indicating complete remission (Fig. 3). On chest and abdomen CT there was no evidence of other distant metastases.

Discussion

Chromophobe renal cell carcinomas (chRCC) is a rare histological subtype, accounting for only 5–6% of RCC cases. It exhibits low aggressiveness and has an overall favorable prognosis with a very low risk of developing metastatic disease [3, 4]. A small percentage of chRCC exhibit sarcomatous growth, with the epithelial–mesenchymal transition estimated at 2–8%, reaching 26% in metastatic disease [16]. Identifying those patients with an increased risk of disease progression can be done using the two-tiered tumor grading system proposed by Ohashi *et al.*, based on the presence of sarcomatoid differentiation and tumor necrosis [17].

Recent studies highlight additional morphological heterogeneity, including pigmented/adenomatoid, multicystic, neuroendocrine, and papillary features [16]. Nevertheless, chRCC has a favorable outcome, with reported 10-year survival rates between 80% and 90% [16, 18], and a mean age at diagnosis around 58–60 years, with slight female predilection [3, 12]. The main prognostic factors for metastatic development include tumor size and the presence of a sarcomatous morphology, with the liver, lungs, and retroperitoneal lymph nodes being the most common metastatic sites [3, 12, 16]. ChRCC can also be

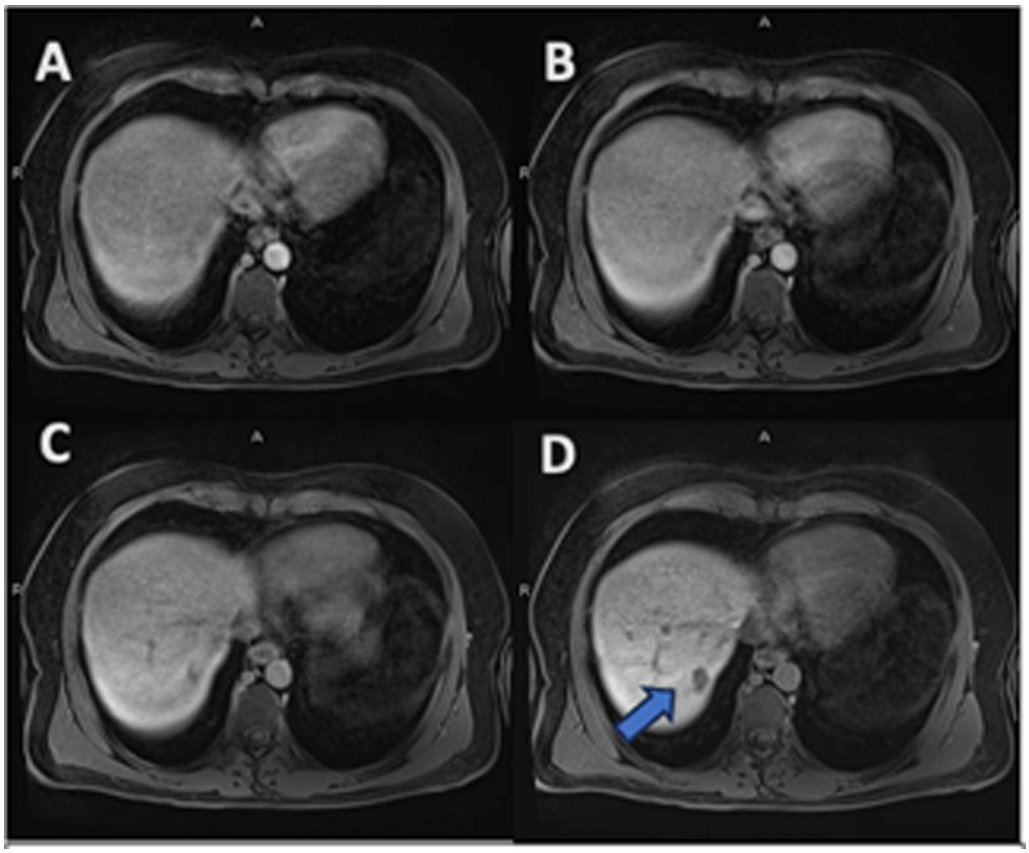

Fig. 2 Axial contrast-enhanced T1-VIBE Dixon: 28 seconds (**A**), 60 seconds (**B**), 3 minutes (**C**), and 20 minutes (**D**). Blue arrow on D shows a liver lesion with contrast washout in the delayed phase, corresponding with **A**–**C**

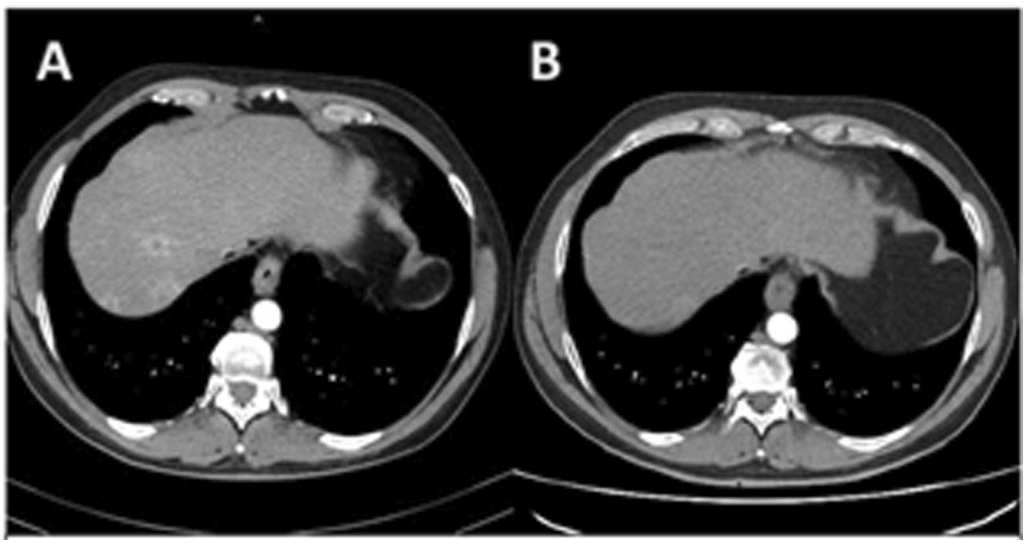

Fig. 3 Axial computed tomography image post-intravenous contrast, arterial phase; at time of diagnosis (**A**) and after immune therapy (**B**)

associated with genetic syndromes, such as BAP1 tumor predisposition syndrome, hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome, Cowden syndrome, tuberous sclerosis, and Birt–Hogg–Dubbé (BHD) syndrome; an autosomal dominant syndrome with mutations of the tumor suppressor folliculin gene (*FLCN*) that regulates angiogenesis and tumor growth [2, 3].

In our case, the patient was diagnosed at age 36 years with a pT2 staged tumor and no known genetic predispositions. The early stage diagnosis, and subsequent radical nephrectomy with an R0 resection, offered a favorable prognosis for developing metastatic disease; nevertheless, the large tumor size should be taken into consideration, adding a considerable risk factor for further planning and follow-up. Although there is missing evidence for influencing the outcomes of early and advanced RCC for any follow-up scheme, long-term follow-up is common [13]. The recommended time interval for CT follow-up, depending on risk factors, is 3–6 months in high-risk patients for the first 2 years, while a yearly interval is sufficient in low-risk patients [13]. For metastatic disease, 2- to 4-month follow-ups during systemic therapy is suggested [13]. In a retrospective cohort study conducted by Dabestani *et al*. on long-term follow-up for initially localized ccRCC (RECUR database, 2019), the data suggested an age- and risk score-dependent follow-up [19]. According to a single-centered cohort study by Casuscelli *et al*. [12], involving 496 patients diagnosed with chRCC and follow-up times up to 25.2 years, the 10-year RFS was 91.7% and the 10-year OS was 82.1% [12]. When correlating our case with the estimates for OS in the study by Casuscelli *et al*., the percentage of surviving subjects at 18-year follow-up was 3.6%.

Treatment options for metastatic chRCC are limited by insufficient clinical data. Current treatment strategies rely on small prospective studies and subgroup analyses, primarily focusing on testing tyrosine kinase inhibitors (TKI) or mTOR inhibitors, where Armstrong *et al*. demonstrated an improvement of progression-free survival in patients with metastatic non-ccRCC treated with sunitinib compared with everolimus; however, there was a better PFS for the chRCC cohort with everolimus [2, 20]. The benefit from mTOR inhibitors is linked to mutations on chromosome 7, which lead to a loss of the folliculin gene and upregulation of mTOR [21]. The recommended first-line systemic treatments for non-ccRCC are sunitinib and everolimus, alongside pazopanib, which is an oral multi-targeted receptor kinase inhibitor [13]. Pazopanib showed efficacy in treating metastatic non-ccRCC in two separate studies [22, 23]. Some data suggest sensitivity to immune checkpoint inhibitors for sarcomatoid tumors with poor-risk features [13]. In a more recent study, the CLEAR trial demonstrated the efficacy of combining a tyrosine kinase inhibitor, affecting multiple receptors (lenvatinib), with an immune checkpoint inhibitor acting against PD-L1 (pembrolizumab) showed significantly longer survival compared with sunitinib alone; nevertheless, the study focused on patients with ccRCC [14, 15].

Research on the tumor microenvironment (TME) of RCC has focused on uncovering the mechanisms of its pathogenesis. Despite some success with immune checkpoint inhibitors in treating RCC, our understanding of immune response and dysregulation in RCC remains incomplete [24]. Different histologic subtypes of RCC exhibit distinct immune microenvironments, for example, ccRCC shows the highest degree of immune infiltration, while chRCC is linked with increased T_H17 gene signatures [25]. As stated by the National Cancer Institute, results from genome testing indicate that structural rearrangements of the *TERT* gene promoter, which regulates telomerase (the chromosome elongation enzyme), may drive this cancer. In addition, the host microbiome could influence immune response to RCC. A phase 1 randomized trial by Dizman *et al*. found that adding CBM588, a bifidogenic bacterial product, to nivolumab and ipilimumab in patients with metastatic RCC significantly improved PFS (12.7 months versus 2.5 months) without adding toxicity [26]. Considering the aspects of the tumor microenvironment, underlying genetic alterations, and possible influence of the host microbiome, it is plausible that some of these factors, although not specifically investigated in this case, may have contributed to the delayed onset of the metastatic progression observed.

Effective therapy regimens for metastatic chRCC are crucial, particularly given its rarity. We would like to emphasize the importance of enrolling this particular group of patients in transnational databases and standardized clinical trials, with focus on immunohistochemical and molecular pathology features, as well as genome sequencing and TME.

Conclusion

Despite the low malignant potential of chRCC, patients can develop late metastatic disease; in our case, even with localized tumor stage at diagnosis followed by surgery. More importance should be given to their histological appearance, with focus on sarcomatoid differentiation and necrosis, as well as chromosomal alterations and molecular pathways. Therefore, identifying individual molecular markers can be considered the main goal for characterizing the heterogeneous phenotype of chRCC to ensure the correct treatment approach, as a stepping-stone for personalized medicine. It is highly recommended to consider risk factors when establishing follow-up schemes and to maintain

regular CT or MRI follow-up for early detection and treatment, especially in low-risk patients with chRCC, even after a long disease-free interval, thereby potentially increasing overall survival.

Abbreviations

RCC	Renal cell carcinoma
chRCC	Chromophobe renal cell carcinoma
ccRCC	Clear cell renal cell carcinoma
non-ccRCC	Non-clear cell renal cell carcinoma
BHD	Birt–Hogg–Dubbè
CS	Cowden syndrome
PGL/PCC	Paraganglioma/pheochromocytoma
MDTB	Multidisciplinary tumor board
CT	Computed tomography
MRI	Magnetic resonance imaging
CE-MRI	Contrast-enhanced MRI
TKI	Tyrosine kinase inhibitor
PFS	Progression-free survival
OS	Overall survival
RFS	Recurrence-free survival
TME	Tumor microenvironment

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Author contributions
Alexandra Ökrosi (first author): data acquisition and preparation of the manuscript. Lothar Ponhold: performed liver biopsy and scientific review. Simon Turba: current case manager of the patient and scientific review. Melitta Kitzwögerer: reporting histology and evaluating histological history of the patient. Gertraud Heinz (last author): scientific review and approval of the final version of the manuscript.

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Availability of data and materials
All supporting data of this case report are available for review by the authors of this case report on request.

Declarations

Ethical approval and consent to participate
The authors certify that this case report was performed in accordance with ethical standards as laid down in the Declaration of Helsinki and its later amendments, or comparable ethical standards for research involving human participants and/or animals.

Consent for publication
A written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors have no conflicts of interest to declare.

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