Case Report

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TFE3-rearranged RCC with osseous metaplasia found on bone mass densitometry

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Introduction and importance: Renal cell carcinoma (RCC) is the most common primary renal malignancy in patients between the ages of 50 and 70. A rare described variant of RCC is transcription factor for immunoglobulin heavy-chain enhancer 3 (TFE3) rearranged RCC. Osseous metaplasia, which refers to the occurrence of normal bone tissue in soft tissue, has been observed in all subtypes of renal cell carcinoma (RCC); however, only three previous case reports have documented the occurrence of osseous metaplasia in TFE3-rearranged RCC.

Case presentation: We present a case of a 65-year-old woman presenting with an incidentally discovered calcified Bi-lobed renal mass detected on bone densitometry composed of a calcified thick-walled cyst measuring 7 × 6.5 × 6.5 cm showing intraluminal densities and heterogeneous content, and a lobulated partially exophytic renal mass measuring 4.5 × 5.5 × 4.5 cm. The patient underwent robotic-assisted radical nephrectomy confirming the diagnosis of RCC with osseous metaplasia extending into the pelvic calyces and renal sinus fat implicating a pathological stage of T3a.

Clinical discussion: TFE3-rearranged RCCs represent a rare sub-classification in adult RCCs. It may be associated with unfavorable prognosis and aggressive patterns of disease in the presence of osseous metaplasia.

Conclusion: This is the first case in the literature of TFE3-rearranged RCC with osseous metaplasia on bone mass densitometry scan and the fourth case of TFE3-rearranged RCC with osseous metaplasia. The patient is to be treated as a high-risk patient and to be monitored closely for recurrence of malignancy, as indicated in the EAU guidelines.

Keywords: bone mass densitometry scan, oncology, osseous metaplasia, renal cell carcinoma, TFE3

Introduction

Renal cell carcinoma (RCC) is the most common primary renal malignancy, accounting for 80–85% of all primary renal neoplasms. It develops at the highest rate in patients between 50 and 70 years of age. It accounts for 4.1% of new cancer cases diagnosed in 2022 in the United States[1]. There are three main histologic subtypes of RCC: clear cell (75%), papillary (15–20%), and chromophobe (5%), with clear cell carcinoma being the worst in terms of prognosis[2].

Moreover, a rare described variant of RCC is a transcription factor for immunoglobulin heavy-chain enhancer 3 (TFE3) rearranged RCC or Xp11.2 as defined by the WHO[3], representing 1.6–4% of adult RCC[4]. This variant is mostly found in the pediatric population, accounting for approximately one-third of RCC cases in kids, which are usually indolent and less aggressive compared to their adult counterparts[5,6].

Infrequently, there have been instances where imaging and pathology examinations have revealed the presence of osseous metaplasia, which refers to the occurrence of normal bone tissue in soft tissue, a rare phenomenon in renal masses. This condition has been observed in all three subtypes of renal cell carcinoma (RCC), as well as in kidney allografts. However, only three previous case reports have documented the occurrence of osseous metaplasia in TFE3-rearranged RCC[4,6,7].

In our case report, we present the case of a 65-year-old woman with an incidentally discovered calcified bi-lobed renal mass with

HIGHLIGHTS

- TFE3-rearranged RCC is a distinct subtype of RCC that is more common in pediatrics.
- Osseous metaplasia is rarely described in RCC.
- RCC is usually diagnosed by CT scan, and most cases are found incidentally.
- Treatment of localized RCC is surgical: partial nephrectomy, if possible, for small renal masses or radical nephrectomy.
- This is the first case in the literature of TFE3-rearranged RCC with osseous metaplasia found on a BMD scan.
- This is the fourth case of TFE3-rearranged RCC with osseous metaplasia in the literature.

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a thick calcified wall during a bone mass densitometry scan. Further investigation revealed that the mass was a TFE3-rearranged RCC.

The work has been reported in line with the SCARE criteria[8].

Case presentation

We herein present a case of a 65-year-old woman known to have type 2 diabetes mellitus who was being followed up regularly by her primary care physician. She underwent a bone mass densitometry (BMD) as part of osteoporosis screening revealing the presence of osteopenia along with the presence of an incidental soft tissue calcification at the level of L3–L4 (Fig. 1). Upon that, a CT of the abdomen and pelvis was done, revealing a calcified thick-walled cyst measuring $7 \times 6.5 \times 6.5$ cm with heterogeneous content showing intraluminal densities and a lobulated partially exophytic renal mass measuring $4.5 \times 5.5 \times 4.5$ cm, predominantly parapelvic in position in the lower pole of the kidney extending into the interpolar region. Collectively, the masses measured 11×6 cm in maximal dimensions (Fig. 2), without renal vein or inferior vena cava involvement. Additionally, there was no loco-regional spread to nearby structures nor evidence of metastasis. The patient denied a history of flank pain, back pain, or hematuria. A decision was made to proceed with a robotic-assisted radical nephrectomy due to the presence of this aforementioned suspicion for RCC.

Postoperative specimen examination revealed a 425 g kidney with a $12 \times 4 \times 2$ cm protruding firm nodule at the anterior aspect of it. Cross-sectioning of the specimen revealed a large tan, brown, friable, cystic mass with a thick fibrous and calcified periphery extending into the perirenal fat measuring $7 \times 6 \times 5$ cm. In addition, the lower pole of the kidney revealed a well-delineated nodule with a yellow heterogenous surface involving hemorrhagic areas measuring $4 \times 4 \times 3$ cm that was connected to the previously described calcified cystic mass. Mass extension into the pelvic calyces and renal sinus fat indicated a pathological stage of T3a.

Histological studies revealed the presence of TFE3-rearranged RCC with solid and cystic features with pseudopapillary structures, eosinophilic cytoplasm, and basophilic inconspicuous nucleoli (Fig. 3B). The fibrotic periphery of the renal cyst contained broad areas of calcification and osseous metaplasia (Fig. 3A). The diagnosis was further confirmed by immunohistochemistry, revealing positive staining for cytokeratin cocktail and carbonic anhydrase, CD10, vimentin, racemase, and TFE3 (Fig. 3C). Additionally, cytokeratin 7 and CD117 staining were negative.

Following the surgery, the patient experienced an uncomplicated recovery and was discharged on the second day after the operation. She is to be followed up using CT scans of the abdomen and pelvis or MR abdomen with gadolinium as a high-risk patient according to the EAU guidelines for follow-up on RCC[9].

Discussion

The incidence of RCC has been on the rise worldwide especially for early-stage tumors detected incidentally by CT scan or other imaging for unrelated causes[10,11]. Factors associated with increased risk of RCC include obesity, hypertension, smoking, and metabolic syndrome[12,13]. Most patients with RCC are asymptomatic; however, if symptoms are to be present, they usually occur in patients with advanced disease, with the classic

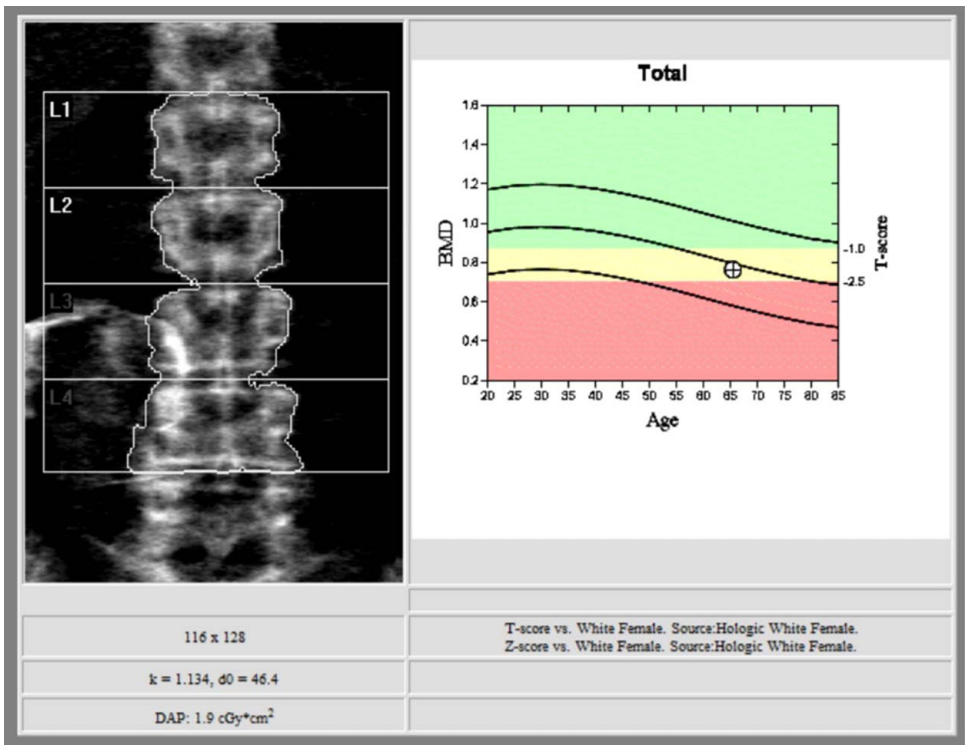

Figure 1. Bone mass densitometry showing an incidental paravertebral calcification on the right.

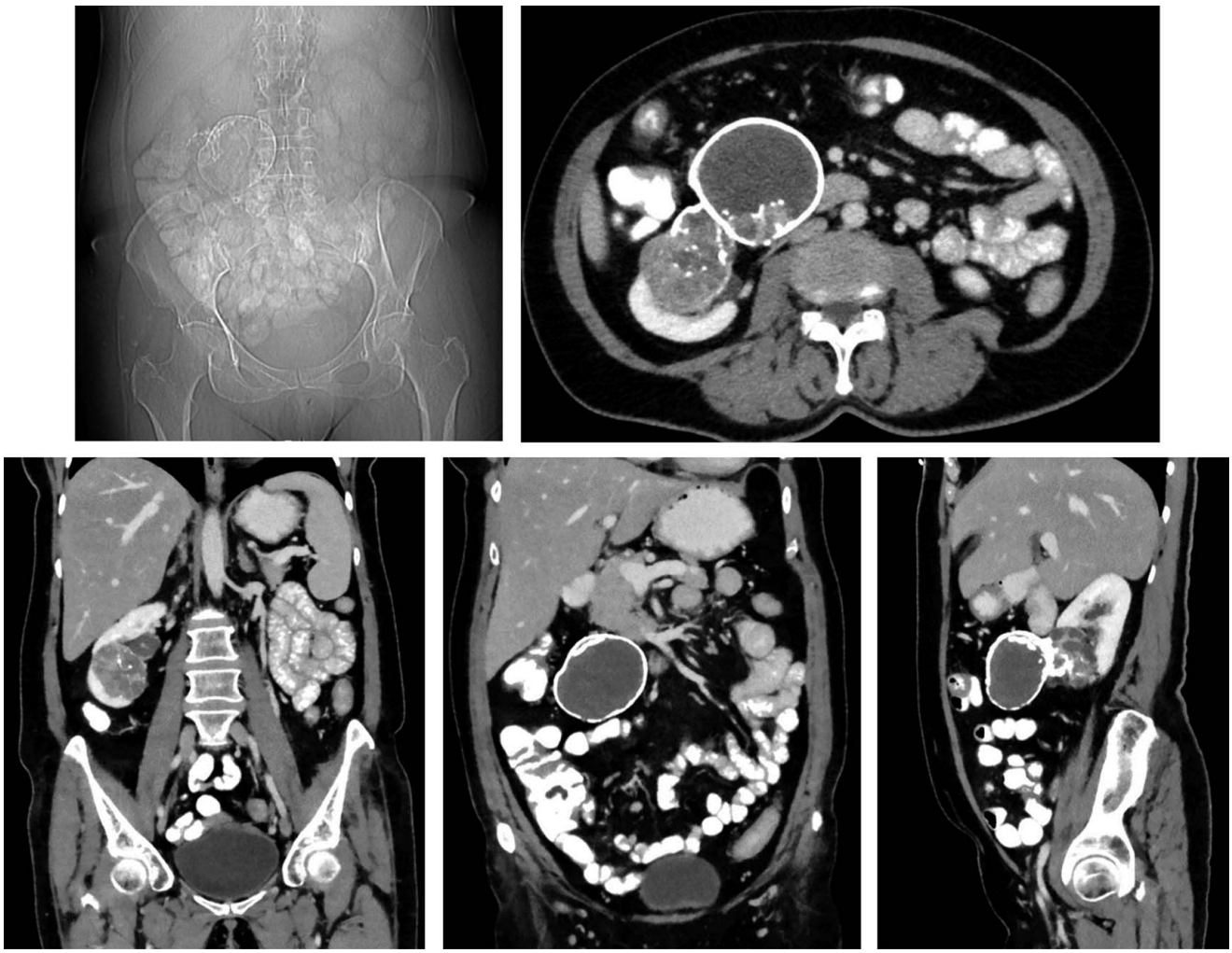

Figure 2. Abdominal X-ray and computed tomography of the abdomen and pelvis showing a large heterogenous mass of the right kidney with cystic, solid, and calcified components with a large calcified cyst wall.

triad of symptoms being flank pain, gross hematuria, and palpable abdominal mass, which in turn correlated with poorer outcomes and higher risk stratification. Bone pain and persistent cough may draw attention to possible occult metastasis to the affected organs[14,15].

In 1991, Tomlinson *et al.*[16], described the first case of TFE3-rearranged Renal Cell Carcinoma, also known as Xp11.2 Renal Cell Carcinoma, in a 17-month-old baby. In 2004, the World Health Organization (WHO) identified it as a distinct subtype of Renal Cell Carcinoma. More recently, in the 2022 revision, this subtype has been further classified within the category of Molecularly Defined Renal Cell Carcinoma[3]. TFE3-rearranged RCCs are responsible for approximately one-third of renal cell carcinoma cases in the pediatric population, but they represent only 0.9% of diagnosed Renal Cell Carcinomas across all age groups[4]. In terms of microscopic features, our specimen showed a predominance of eosinophilic cells with a pseudopapillary pattern, which is consistent with findings from multiple studies[4,6,17]. However, other studies have reported tumor cells with abundant clear cytoplasm, displaying a clear cell pattern[18]. This variation in morphologic features, coupled with the absence of distinct pathological characteristics and a lack of standardized genetic testing techniques in the past, may have led to the misdiagnosis of TFE3-rearranged RCC subtypes as clear cell or papillary RCC. Furthermore, the tumor presented exhibited a significant amount of calcification around its periphery, which was clearly visible on radiological imaging. This calcification played a crucial role in the diagnosis of the hidden tumor during the bone mass densitometry (BMD) scan, prompting further imaging investigations.

Osseous metaplasia is a rare phenomenon observed in RCCs, with reported cases occurring in Clear cell, Papillary, and Chromophobe RCC subtypes[6]. However, there have been only three documented cases of osseous metaplasia in TFE3-rearranged RCCs found in the existing literature[6,7,19]. The available literature remains limited in providing comprehensive prognostic implications for TFE3-rearranged RCC, with conflicting reports on its behavior. Some cases have reported an indolent course[6], while other studies argue that the prognosis is poor with an aggressive progression[4,5,20]. A study conducted by Sukov *et al.* compared TFE3-rearranged RCC with Clear Cell and Papillary RCC, revealing no significant difference in survival rates.

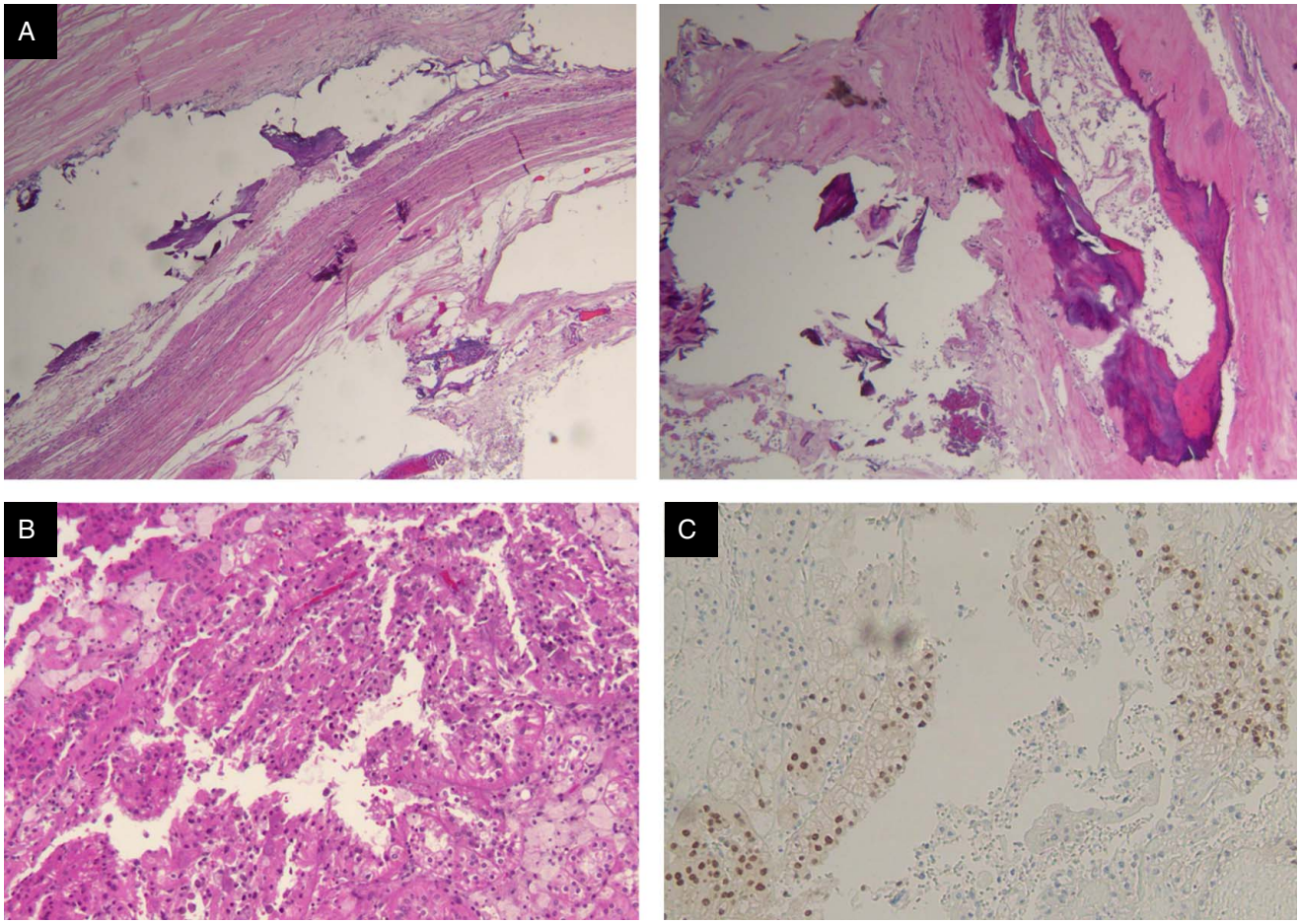

Figure 3. (A) Fibrotic periphery of the renal cyst showing areas of calcification and osseous metaplasia. (B) Pseudopapillary architecture with eosinophilic cytoplasm. (C) Immunohistochemistry showing diffuse nuclear labeling for TFE3.

However, this evidence is constrained by a small sample size of only four patients[4]. Other studies suggest that the disease tends to exhibit an indolent course in children and adolescents but follows a more aggressive path in adults[20,21]. Overall, there is a notable scarcity of current data regarding the morphology, behavior, and prognosis of TFE3-rearranged RCC. Additionally, there is no single study providing management recommendations for this specific subtype, highlighting the absence of a clear framework for follow-up and indications for preoperative and postoperative treatment.

Conclusion

In conclusion, TFE3-rearranged RCCs represent a rare subclassification in adult RCCs. It may be associated with unfavorable prognosis and aggressive patterns of disease. While osseous metaplasia is a frequently observed occurrence in RCC, it has been only reported three times in TFE3-rearranged RCCs. In this study, we present a case of osseous metaplasia in TFE3-rearranged RCC, which was incidentally diagnosed through bone mass densitometry. Vigilant patient follow-up with imaging is required to identify any recurrence of the disease due to the potentially high-risk nature of the TFE3-rearranged RCC diagnosis. This is the first case in the literature that identified a calcified renal mass on bone mass densitometry scan, which turned out to be the fourth case of TFE3-rearranged RCC with osseous metaplasia.

Ethical approval

As this publication is a case report that contains no identifiable content about the patient, this publication was exempt from ethical approval by the Human Research Protection Program (HRPP) and its Institutional Review Board (IRB) at the American University of Beirut Medical Center, Beirut, Lebanon.

Consent

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

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None.

Author contribution

A.E.H.: conceptualization, review and editing, and supervision; O.G.N.: resources, writing – original draft, and supervision – review and editing; B.A.J.: resources, writing – original draft, review, and editing; A.E.K.: writing – original draft; J.E.A.: resources, writing – original draft, review, and editing.

Conflicts of interest disclosure

The authors declares no conflicts of interest.

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The article is a case report and does not need to be registered.

Guarantor

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Data availability statement

The images provided and the chart reported in the article are available upon request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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