Case Series

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Xp11.2 translocation renal cell carcinoma with osseous metaplasia

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Abstract

Xp11.2 translocation renal cell carcinoma is an uncommon and distinctive subtype of renal neoplasm. Osseous metaplasia with renal cell carcinoma is extremely rare and only less than 20 cases have been reported in the literature distinctly in clear cell, papillary and chromophobe subtypes. There has only been one report of Xp11.2 translocation renal cell carcinoma with osseous metaplasia in an elderly woman. We present the first case of this unusual renal neoplasm associated with osseous metaplasia in an adolescent male with no history of previous exposure to chemotherapy who presented with symptomatic anemia due to painless haematuria.

Level of evidence: Level 4.

Keywords

Xp11.2 translocation, renal cell carcinoma, osseous metaplasia, haematuria, anaemia

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Background

Microphthalmia family translocation (MiT) renal cell carcinomas (RCCs) are rare renal neoplasms comprising rearrangements of *TFE3* on chromosome 11 (Xp11.2 locus) and *TFEB* loci on chromosome 6.[1] They are more prevalent among children and young adults. Adults usually present with very aggressive, metastatic disease at the time of diagnosis with worse prognosis compared to younger patients. RCCs related to Xp11.2 translocation represent up to 40% of RCCs among pediatric patients and are usually associated with exposure to chemotherapy as the only risk factor, whereas the conventional forms are associated with hypertension, obesity, and smoking.[1] Osseous metaplasia with RCC is extremely rare, and fewer than 20 cases have been reported in the literature, mostly associated with clear cell, papillary, and chromophobe subtypes. After a thorough search of the literature, we could only find one reported case of Xp11.2 translocation RCC with osseous metaplasia in an elderly woman and none in adolescents.[2–4]

Case presentation

A 16-year-old male patient with no known comorbidities presented with a two-week history of painless frank intermittent hematuria complicated by symptomatic anemia associated with lightheadedness, pallor, shortness of breath, and palpitations. He had no previous exposure to chemotherapy. Ultrasound evaluation outlined a complex cyst in the upper pole of the right kidney, which on computed tomography with intravenous pyelography

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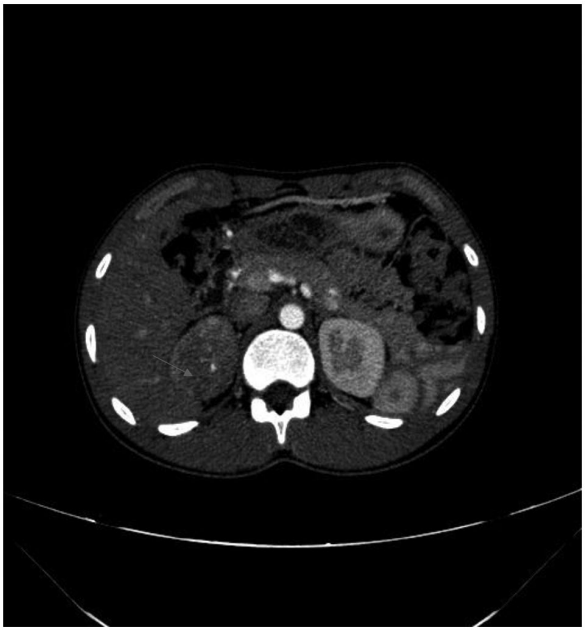

Figure 1. Computed tomography (axial plane) demonstrating the right upper pole mass, which appears to be a hypodense homogenous soft-tissue mass (blue arrow) with early capsular breakthrough posterosuperiorly. There is a focus of dystrophic calcification within the tumor and associated infarction of the surrounding tissue.

(CT-IVP) appeared to be a hypodense homogenous soft-tissue mass measuring 3 cm×4 cm extending into the superior calyx and renal pelvis, with the impression of early capsular breakthrough posterosuperiorly. There was a focus of dystrophic calcification within the tumor and associated infarction of the surrounding tissue (Figure 1). There was no renal vein involvement and no significant lymph nodes detected.

Open right radical nephrectomy was performed, and no lymph nodes were identified. The kidney weighed 165 g with surrounding perinephric fat, and the capsule was intact.

On sectioning, a multinodular, tan-yellow-colored and partly necrotic tumor occupying the entire upper pole was noted, measuring 45 mm×35 mm×35 mm. It appeared confined within the capsule and showed no extension into the renal sinus or perinephric fat.

The sections examined revealed a neoplastic infiltrate showing a distinct papillary growth pattern (Figure 2(a)). There were occasional areas of a solid alveolar growth pattern observed (Figure 2(b)). The neoplastic cells showed a voluminous granular eosinophilic cytoplasm (Figure 2(e)). The nuclear grade was high. Mitotic activity and necrosis were apparent. Psammomatous calcification was also a feature (Figure 2(f)). Interestingly, there was frank osseous metaplasia admixed with the tumor (Figure 2(c) and (d))

Immunohistochemical stains showed nucleus staining for transcription factor E3 (TFE3) (Figure 3(a)). CD10 was positive in the cytoplasm and the cell membrane (Figure 3(b)). A positive racemase was noted (Figure 3(c)). Vimentin was also positive (Figure 3(d)). There was scanty focal CK7 staining in the cytoplasm (Figure 3(e)). EMA was also positive.

The following immunohistochemical stains were negative: CD34, HMB45 (Figure 3(f)), and melan-A (Figure 3(g)). The pathological stage was stage I: pT1bN0M0.

A follow-up Chest X-ray, abdominal ultrasound at one year, and CT scan at two years have not shown any recurrence.

Discussion

MiT Xp11.2 RCC is an uncommon renal malignancy that comprises up to 40% of pediatric and up to 4% of adult RCC, with a better prognosis in children than in adults.[1,5] The most commonly observed Xp translocations are t(X;1)(p11.2;q21), t(X;17)(p11.2;q25), and t(X;1)(p11.2;p34) fusing respectively the *PRCC* and *TFE3* genes, the *ASPL* and *TFE3* genes, and the *SFPQ* (PSF) and *TFE3* genes.[5]

About 400 genetically confirmed Xp11 translocation RCCs have been reported in the literature, with a slight female predominance (F:M=1.6:1) and a variable clinical presentation, with one third being asymptomatic.[1,5] Renal tumors are frequently incidentally diagnosed or usually suspected on ultrasound then confirmed on CT-IVP or magnetic resonance imaging.[6] Unlike conventional RCCs, which are associated with smoking, hypertension, family history, and obesity, the Xp11.2 translocation is associated with prior exposure to cytotoxic chemotherapy.[1,5] Our patient was an adolescent male who had had no previous exposure to cytotoxic chemotherapy and who presented with symptomatic anemia as a result of painless hematuria.

The gross features of Xp11.2 translocation RCC resemble conventional clear cell RCCs, as they usually present as tan-yellow solitary cortical masses with foci of hemorrhage, necrosis, and occasionally focal cystic degeneration on the cut surface.[1,5] Microscopically, these tumors are characterized by a combination of nested and papillary structures with clear-to-granular eosinophilic cytoplasm. These cells present with large nuclei with prominent nucleoli. These tumors can often contain calcific deposit as a form of dystrophic calcification called psammomatous bodies.[1,5] *TFE3* immunostaining is commonly used for detection of Xp11.2 translocation, with high sensitivity (97.5%) and specificity (99.6%). Fluorescence *in situ* hybridization as a confirmatory test may be useful in order to overcome issues related to staining technique or non-reliable immunostaining assays.[1] Our patient's macroscopic, microscopic, and immunostaining findings as well as his age were in favor of an Xp11.2 translocation RCC. Moreover, osseous metaplasia was noted within the section

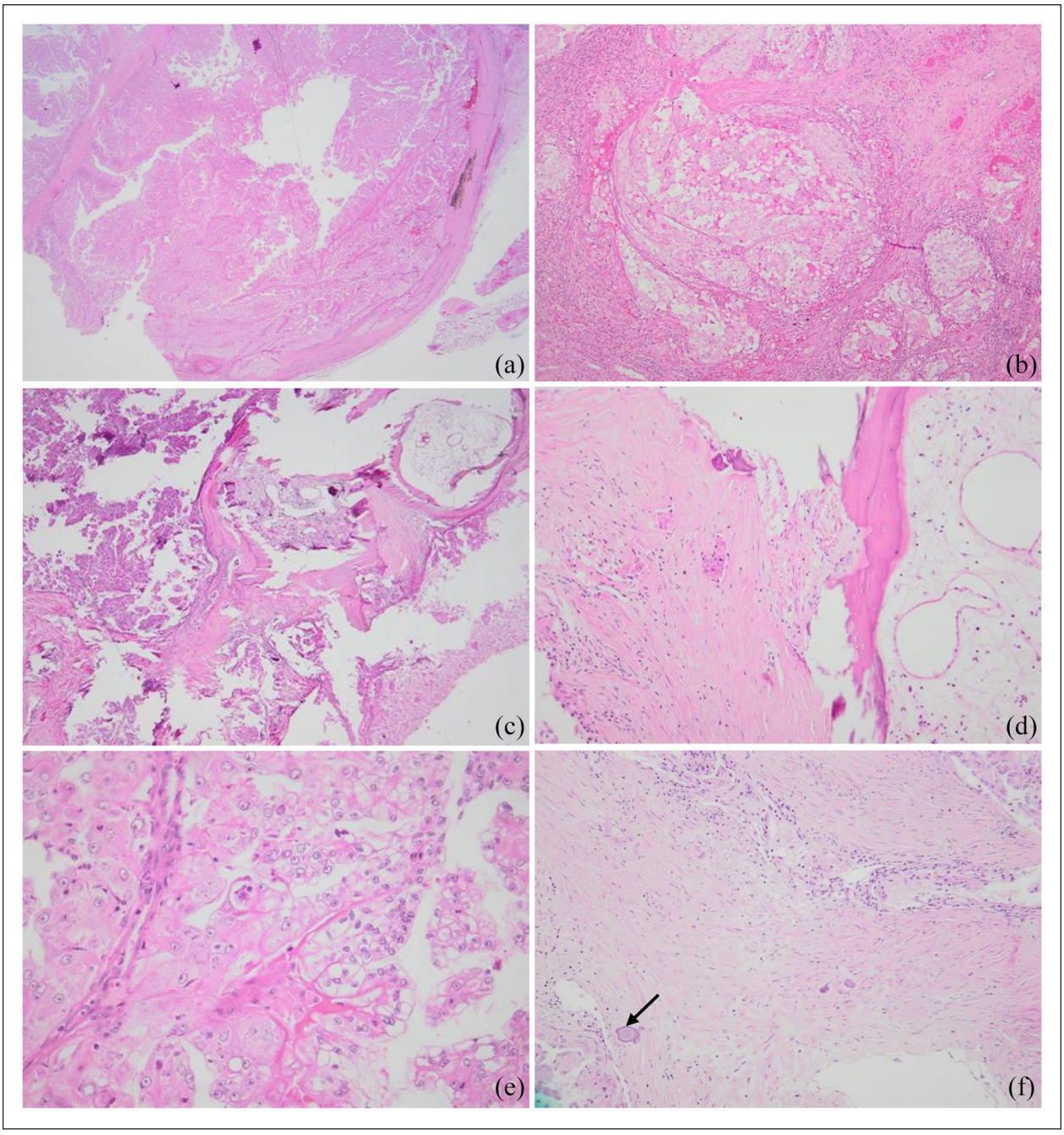

Figure 2. All images are of hematoxylin and eosin–stained tissues. (a) A neoplasm with a distinct papillary architecture. (b) Areas of the tumor with a solid alveolar growth pattern observed. (c) Striking osseous metaplasia within the tumor. (d) Adjacent lamellar bone forming a trabecula. (e) Neoplastic cells with abundant eosinophilic to clear cytoplasm. (f) Psammomatous calcification noted (arrow).

examined. Osseous metaplasia with RCC is extremely rare, and fewer than 20 cases have been reported in the literature, mostly associated with clear cell, papillary, and chromophobe subtypes, with only one associated with Xp11.2 in an elderly woman.[2–4]

The pathogenesis of osseous metaplasia in tumors is still not clear. Several hypotheses have been suggested, including bone morphogenetic protein 2 (BMP2) that induces bone formation and inhibits RCC tumor growth; ischemia-induced production of bone by tumor cells; reparative responses in the tumor or surrounding tissues or calcification of preexisting mucin; and necrosis or inflammation in the tumor or surrounding tissue.[7,8]

The prognostic significance or implications of osseous metaplasia in RCC is debatable and has not been clearly established. Some reports have suggested its presence to

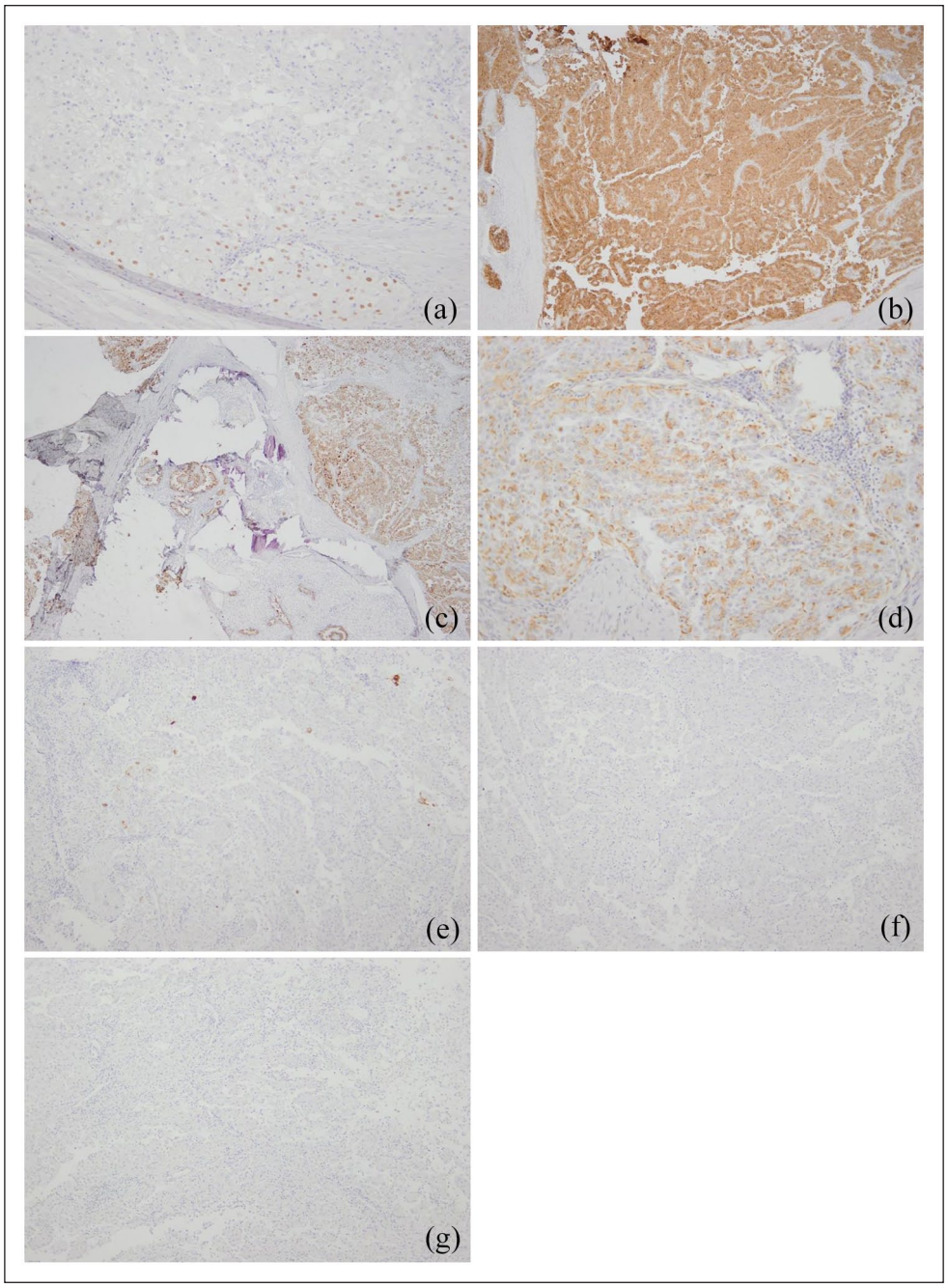

Figure 3. Immunohistochemical features in Xp11.2 translocation renal cell carcinoma (RCC). (a) The nucleus shows staining for transcription factor E3 (TFE3). (b) CD10 positive staining in the cytoplasm and the cell membrane. (c) Positive staining P504S. (d) Vimentin positive staining. (e) Scanty focal CK7 staining in the cytoplasm. (f) Negative staining for HMB45. (g) Negative staining for melan-A.

be a marker for a favorable prognosis, as it is mostly associated with early-stage disease or the absence of metastatic disease at presentation. However, when associated with high-grade tumors, the prognosis is poor.[3,7,8] Our patient had non-metastatic disease at presentation, and there was no sign of recurrence at the 24-month follow-up scan, which implies a good prognosis.

The optimal therapy for MiT RCC remains to be determined. Radical nephrectomy for patients with or without positive regional lymph nodes is recommended for Xp11.2 translocation RCCs. Partial nephrectomy is an alternative, with favorable outcomes for small RCCs.[5,9] For metastatic disease, therapies targeting vascular endothelial growth factor receptor have demonstrated some efficacy. Moreover, other therapeutic options have also been used, including mTOR inhibitors, immunotherapy, and target therapies for the MET signaling pathway.[5,9] However, radiotherapy and chemotherapy have not proven to be

effective for treatment of MiT tumors therefore must be reserved for palliative care of patients not eligible for surgical treatment.[1]

Conclusion

Xp11.2 translocation RCC is a rare subset of RCC with good prognosis in children, even with locally advanced disease. The presence of osseous metaplasia seems not to affect the prognosis of the disease and therefore may be considered as a prognosticator implying favorable outcome. This was the first reported case of Xp11.2 translocation RCC with osseous metaplasia in an adolescent.

Conflicting interests

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Ethical approval

The Wits Human Research Ethics committee approved this study (study approval number M191098).

Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

Guarantor

A.M.M.

Contributorship

M.Z. wrote the manuscript, and revised it for critical content. A.M.M. obtained ethical approval, designed the study, wrote and revised manuscript for critical content, and prepared the manuscript for submission. F.D. revised the manuscript for critical content. N.M. provided histopathological content and slides. P.M. provided histopathological content and slides. All authors approved the final version of the manuscript.

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