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Extrarenal TFE3-Rearranged Renal Cell Carcinoma: Diagnostic Challenges in an Uncommon Scalp Localization

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ABSTRACT

Objective: TFE3-rearranged renal cell carcinoma (RCC) is a rare subtype of MiT family translocation-associated tumors, usually arising in the kidney of young patients. Extrarenal presentations are exceptionally uncommon and represent a major diagnostic challenge. To our knowledge, only two cases of extrarenal TFE3-rearranged RCC have been reported in the literature to date. We report an unusual case arising in the scalp with cranial bone destruction.

Case Report: A 24-year-old man presented with a rapidly enlarging occipital soft tissue mass evolving over five months. Imaging revealed a scalp tumor with lytic destruction of the cranial vault. Histologically, the tumor showed papillary and pseudopapillary architecture composed of cells with clear to eosinophilic cytoplasm and marked nuclear atypia. Immunohistochemistry demonstrated strong positivity for cytokeratins, CD10, PAX8 and TFE3, while CK7, CK20, EMA and GFAP were negative. A metastatic TFE3-rearranged RCC was initially suspected. However, extensive staging including 18F-FDG PET/CT revealed no renal primary tumor or other lesions. Based on the morphological, immunophenotypic and radiological findings, the diagnosis of extrarenal TFE3-rearranged RCC was retained.

Conclusion: This case highlights the diagnostic complexity of extrarenal TFE3-rearranged RCC and expands the anatomical spectrum of this entity to the scalp with bone destruction. Accurate diagnosis relies on the integration of morphology, immunohistochemistry and imaging findings.

Keywords: TFE3, Kidney tumor, Mit family, extrarenal

INTRODUCTION

TFE3-rearranged renal cell carcinoma (RCC) is a rare subtype of MiT family translocation-associated tumors, typically arising in the kidney of young patients (1). Extrarenal occurrences are exceptionally uncommon and pose a major diagnostic challenge, particularly in excluding metastatic disease from an occult renal primary.

We report a rare case of extrarenal TFE3-rearranged RCC arising in the scalp with bone destruction, highlighting the diagnostic difficulties and expanding the clinical spectrum of this entity.

CASE REPORT

A 24-year-old male with no significant past medical history presented to the neurosurgery department with a progressively enlarging occipital mass arising from the soft tissues. The lesion had rapidly increased in size over a period of five months and was not associated with any neurological or systemic symptoms.

Initial ultrasound examination of the soft tissues revealed a well-defined, oval-shaped subcutaneous mass measuring 42 × 23 mm, with regular contours and heterogeneous internal echogenicity. Notably, a scalloping of the outer table of the adjacent skull was observed, without evidence of cortical breach.

Subsequent cranial computed tomography (CT) demonstrated a large, well-circumscribed soft tissue mass of the scalp, extending intracranially. The lesion was associated with lytic destruction of the cranial vault and exerted a mild mass effect on the adjacent brain parenchyma. The tumor measured 55 × 41 × 46 mm (Figure 1). Given these findings, the patient underwent surgical resection.

Histopathological examination using hematoxylin and eosin (H&E) staining revealed a papillary and pseudopapillary tumor proliferation composed of medium-sized cells with clear to eosinophilic cytoplasm. The nuclei were irregular, with finely dispersed chromatin, prominent nucleoli, and moderate to marked nuclear atypia (Figure 2).

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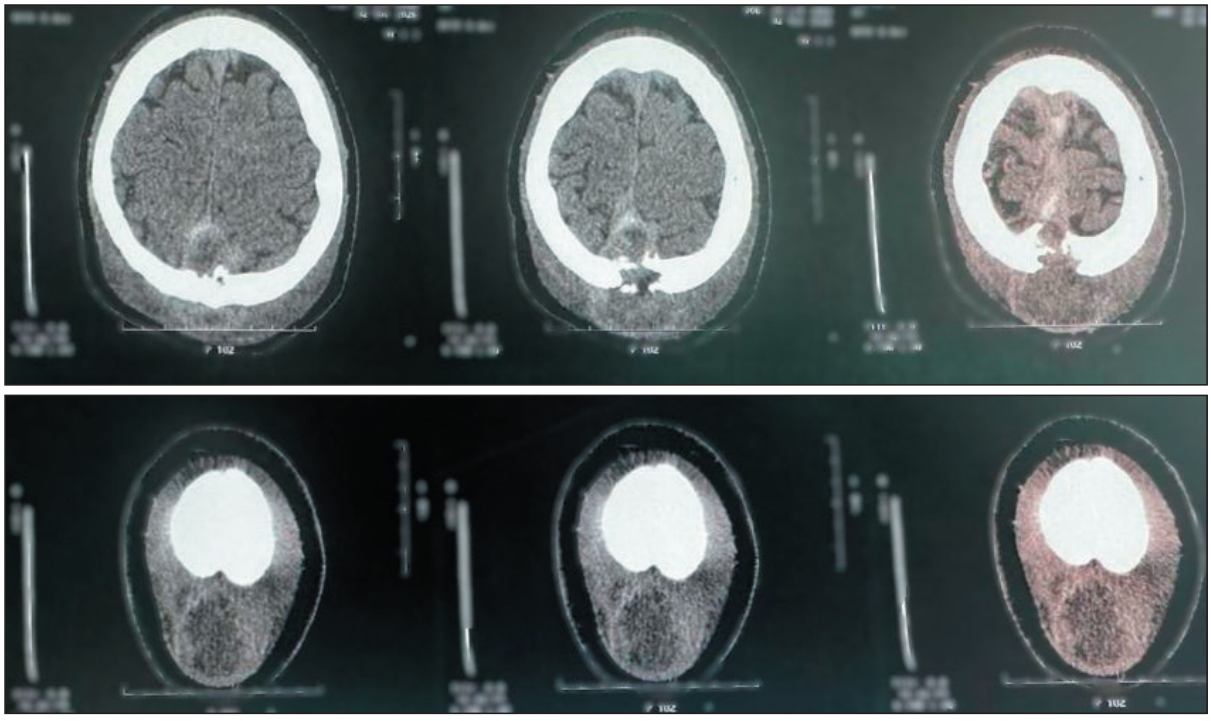


Figure 1: Cranial computed tomography (CT) demonstrated a large, well-circumscribed soft tissue mass of the scalp, extending intracranially. The lesion was associated with lytic destruction of the cranial vault and exerted a mild mass effect on the adjacent brain parenchyma. The tumor measured 55 × 41 × 46 mm.

Immunohistochemical analysis showed strong expression of cytokeratins, CD10, PAX8, and TFE3 (Figure 3). In contrast, tumor cells were negative for CK7, CK20, EMA, and GFAP (Figure 4).

In light of this unusual morphological and immunophenotypic profile, the diagnosis of a metastatic renal cell carcinoma with TFE3 translocation was initially considered. Although molecular confirmation by FISH or RNA sequencing is considered the gold standard for confirming TFE3 rearrangement, these techniques were not available in our institution. Therefore, the diagnosis relied on the characteristic morphologic findings, immunophenotype, and exclusion of a renal primary lesion by imaging.

A comprehensive staging workup was subsequently performed to identify a possible renal primary tumor. Whole-body positron emission tomography using 18F-fluorodeoxyglucose (18F-FDG PET/CT) revealed no hypermetabolic lesions, except for postoperative changes at the surgical site. No renal mass or other primary tumor was identified (Figure 5).

Based on the absence of a detectable renal primary lesion and the characteristic histopathological and immunohistochemical features, a diagnosis of extrarenal TFE3-rearranged renal cell carcinoma was retained.

DISCUSSION

Renal cell carcinomas (RCCs) associated with microphthalmia transcription factor (MiT) family rearrangements constitute a distinct molecular entity in the current WHO Classification of Urinary and Male Genital Tumours classification (1). These neoplasms are characterized by chromosomal translocations involving members of the MiT family, most commonly TFE3, leading to oncogenic gene fusions and aberrant transcriptional activation (1,2).

Xp11 translocation RCC (TFE3-rearranged RCC) represents the most frequent subtype within this group and typically arises from renal tubular epithelial cells (2,3). These tumors are defined by specific gene fusions (e.g., PRCC–TFE3), which drive tumorigenesis through dysregulation of cellular proliferation and differentiation pathways (3,4). While classically renal in origin, increasing evidence suggests that tumors with identical molecular and phenotypic features may arise in extrarenal sites, raising important questions regarding their classification and histogenesis (2,5).

Extrarenal TFE3-rearranged RCC remains exceedingly rare, with only a very limited number of cases reported to date. Notably, a recent case report described a metastatic extrarenal TFE3 translocation RCC arising in the adrenal

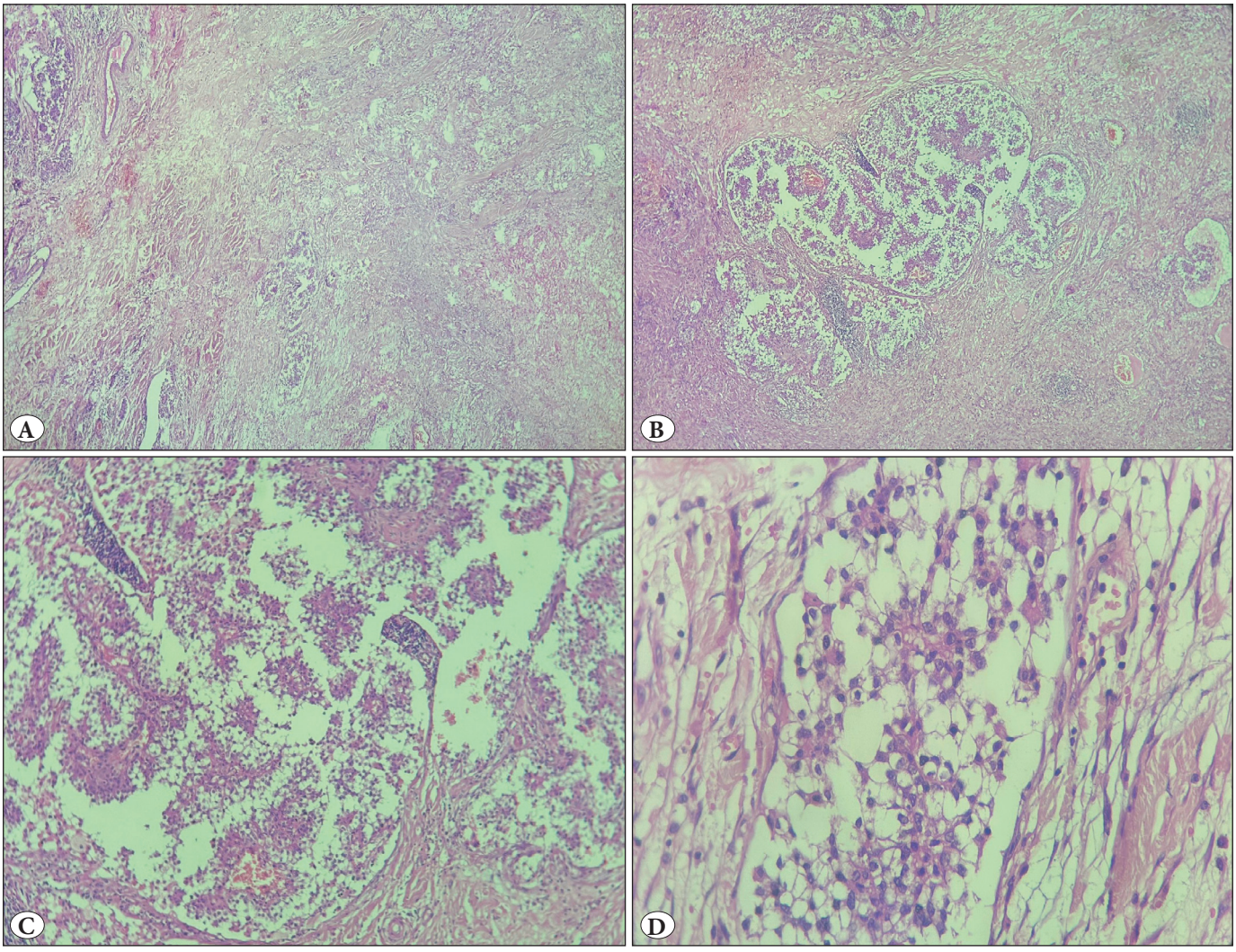


Figure 2: H&E stain (A x10, B x20, C&D x 40). A papillary and pseudopapillary tumor proliferation composed of medium-sized cells with clear to eosinophilic cytoplasm. The nuclei were irregular, with finely dispersed chromatin, prominent nucleoli, and moderate to marked nuclear atypia

gland, with no identifiable renal primary lesion (6). In that case, the tumor presented with both adrenal and pulmonary involvement, highlighting its potential for aggressive behavior despite the absence of a renal origin (6).

Similarly, another report documented a retroperitoneal PRCC–TFE3 fusion-related RCC occurring outside the kidney, representing only the second reported case of this subtype in an extrarenal location (7). In this study, the tumor showed typical morphological and immunophenotypic features of TFE3-rearranged RCC, with molecular confirmation of the fusion transcript, further supporting the concept of primary extrarenal occurrence (7).

Beyond TFE3-associated tumors, a few additional cases of extrarenal RCC of other histological subtypes (clear cell, papillary) have been described, most frequently arising in the retroperitoneum or adrenal region (6,8). However, these remain anecdotal, and the true incidence of extrarenal RCC is unknown.

Compared to previously reported cases, our observation is particularly unusual due to its cranial soft tissue location with bone destruction, a presentation not previously emphasized in the literature, thereby expanding the anatomical spectrum of extrarenal MiT family tumors.

TFE3-rearranged RCCs predominantly affect children, adolescents, and young adults, with a slight female predominance (3,4,7). Clinically, conventional renal cases often present with hematuria, abdominal mass, or nonspecific systemic symptoms (7). However, extrarenal tumors may present solely based on their anatomical location, often mimicking primary tumors of the involved site.

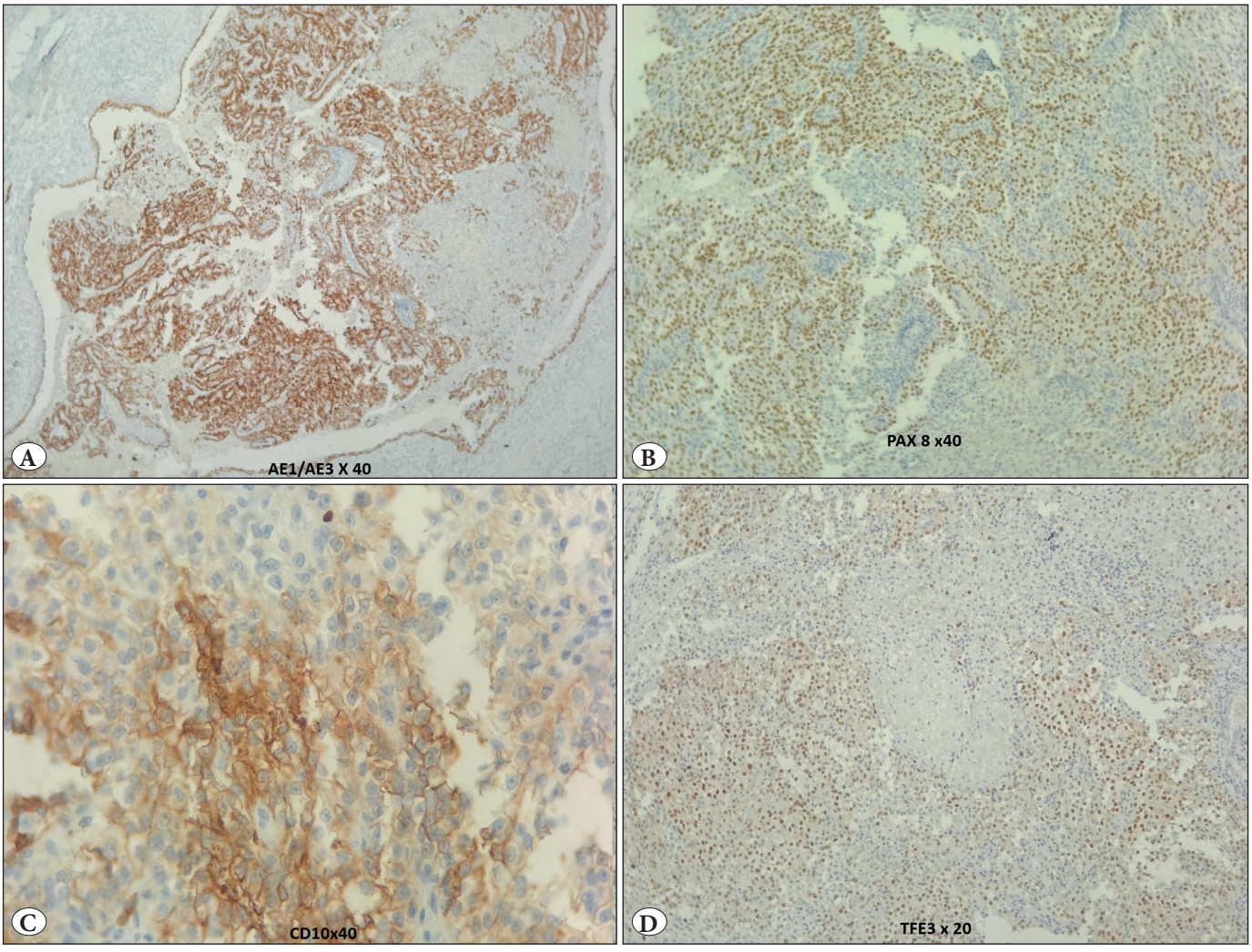


Figure 3: Positive IHC stains: (x40). Strong positivity for cytokeratins, Pax8, CD10 and TFE3.

Radiologically, these tumors are typically described as heterogeneous masses with variable enhancement and frequent necrosis or calcifications (4,7). In our case, imaging revealed a destructive scalp mass with lytic cranial involvement and intracranial extension, illustrating the locally aggressive nature of these tumors even in unusual locations.

The pathogenesis of extrarenal TFE3-rearranged tumors remains controversial. Several hypotheses have been proposed, including ectopic renal tissue origin: tumors may arise from remnants of metanephric blastema that failed to properly migrate or differentiate during embryogenesis (7,9). Mesonephric duct remnants: particularly for tumors arising in the retroperitoneum or genital tract (7). Pluripotent embryonic cells: capable of divergent differentiation in extrarenal sites (7). Occult or regressed renal primary tumor: a hypothesis that must always be excluded (6,10).

In the present case, extensive imaging, including PET/CT, failed to identify any renal lesion, favoring a true extrarenal origin rather than metastatic disease.

Histologically, TFE3-rearranged RCCs display a broad morphological spectrum, including papillary, nested, and alveolar patterns, often composed of epithelioid cells with clear to eosinophilic cytoplasm and prominent nucleoli (3,4). In our case, the presence of papillary and pseudopapillary architecture with moderate to marked nuclear atypia is fully consistent with this spectrum.

Immunohistochemically, these tumors typically express epithelial markers, CD10, and renal lineage markers such as PAX8, along with strong nuclear TFE3 expression (1,3). The immunoprofile observed in our case (PAX8+, CD10+, TFE3+, CK7–) strongly supports this diagnosis and aligns with previously reported findings.

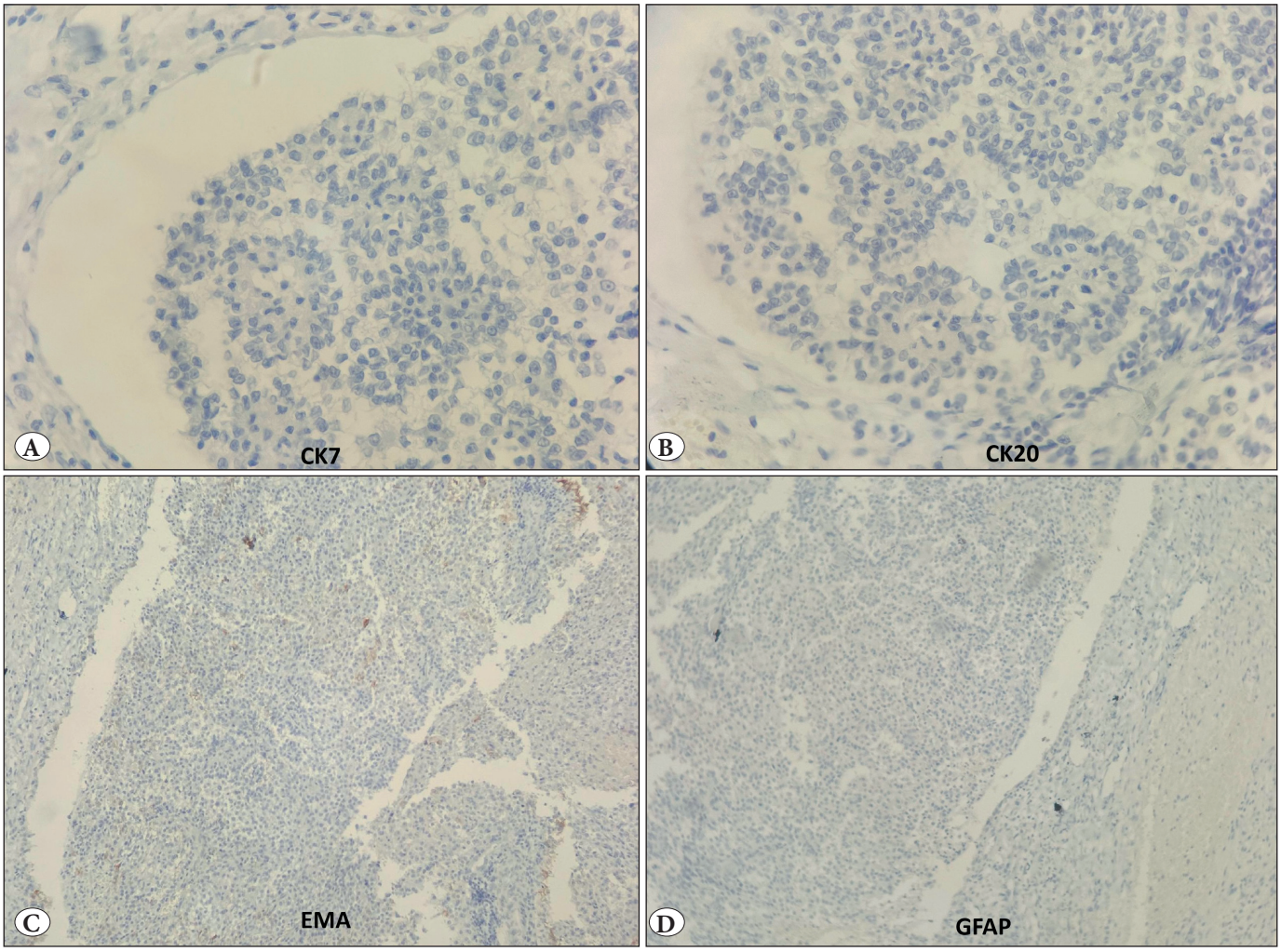


Figure 4: Negative IHC stains: (x40). Negativity for CK7 CK20 EMA and GFAP.

The main differential diagnoses include alveolar soft part sarcoma (ASPS), PEComa, and other RCC subtypes. ASPS may show TFE3 positivity but lacks epithelial markers and PAX8 expression, while PEComas express melanocytic markers such as HMB45 and Melan-A (2,3). Clear cell RCC typically expresses CAIX, whereas papillary RCC is usually CK7-positive (4). Therefore, integration of morphology and immunohistochemistry is essential for accurate diagnosis.The combined use of morphology and immunohistochemistry is therefore essential to establish the correct diagnosis (6,7).

In our case, no other immunostains were performed in this case. The diagnosis was supported by the characteristic morphology together with diffuse PAX8, CD10, EMA, and TFE3 expression, while clinicoradiological investigations excluded a renal primary lesion. The combined morphologic, immunophenotypic, and radiologic findings were considered sufficient to establish the diagnosis and exclude the principal differential diagnoses, including PEComa.

Management of TFE3-rearranged RCC is similar to other RCC subtypes and primarily relies on complete surgical resection for localized disease (5,11). In advanced or metastatic settings, targeted therapies and immune checkpoint inhibitors have shown promising results (6,7).

These tumors are generally considered aggressive in adults, with a higher risk of recurrence and metastasis compared to conventional RCC (4,12). Adverse prognostic factors include advanced stage, presence of metastasis, and high proliferative activity (11,12).

In our case, the tumor exhibited locally aggressive behavior with bone destruction and intracranial extension, underscoring the need for close postoperative surveillance despite complete resection. As this is a recent case, the patient

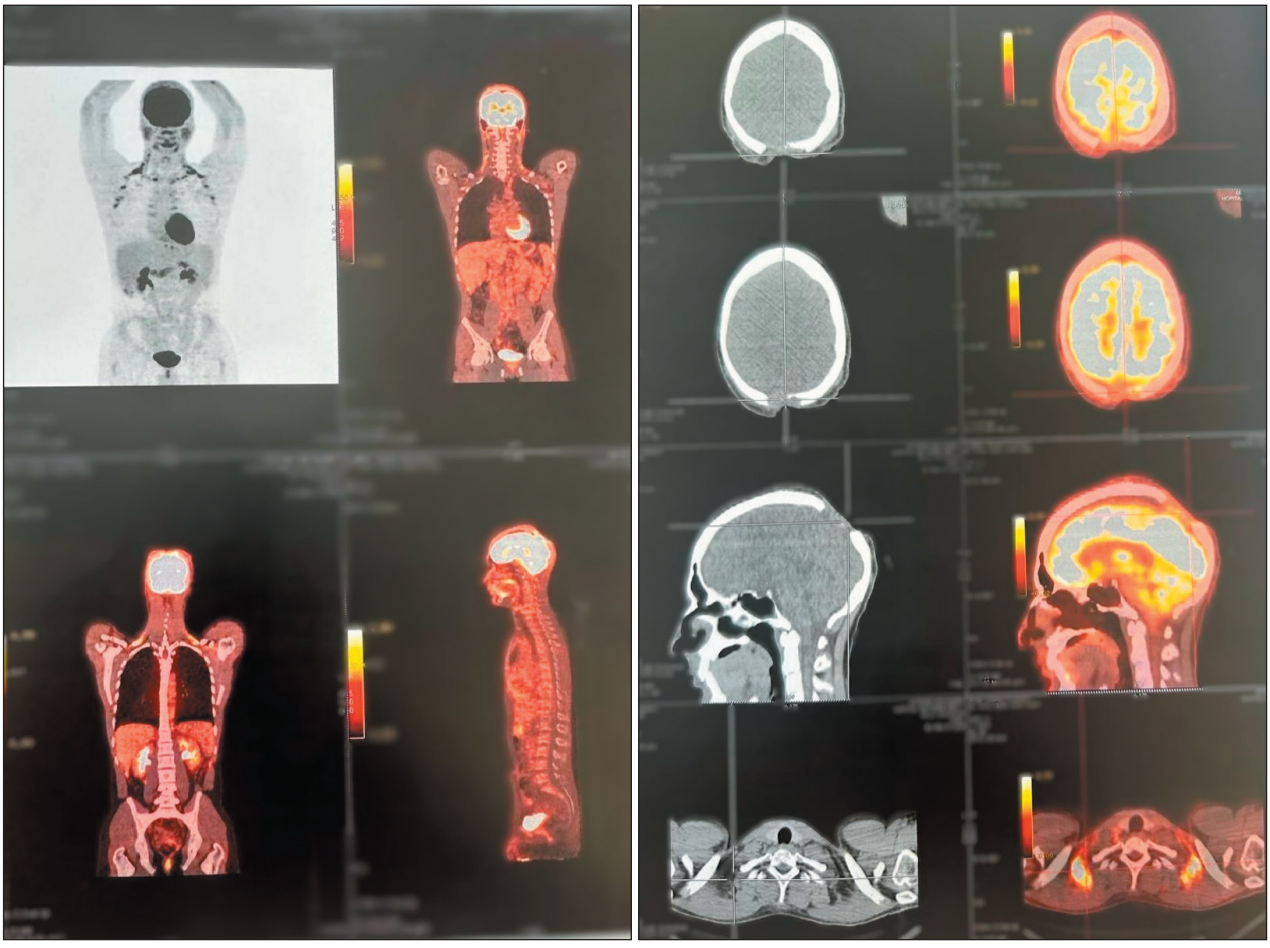


Figure 5: Whole-body positron emission tomography using 18F-fluorodeoxyglucose (18F-FDG PET/CT). No hypermetabolic lesions, except for postoperative changes at the surgical site. No renal mass or other primary tumor was identified

continues to be reviewed in multidisciplinary team meetings to ensure appropriate management and to discuss the indication for potential adjuvant chemotherapy.

At the time of writing, the case is recent, with a postoperative follow-up of less than three months. The patient is under close surveillance by the multidisciplinary oncology team and remains in good general condition, with no clinical or radiological evidence of local recurrence or distant metastatic disease.

To our knowledge, this is the first reported case of extrarenal TFE3-rearranged RCC presenting as a scalp mass with associated bone destruction and intracranial extension, thereby expanding the known anatomical and clinical spectrum of this entity.

CONCLUSION

This case highlights the diagnostic complexity of extrarenal TFE3-rearranged renal cell carcinoma, particularly in the absence of a detectable renal primary. Beyond its rarity, the locally aggressive presentation with bone destruction and intracranial extension raises important considerations regarding its potential behavior and management. To our knowledge, this is the first reported case presenting as a scalp mass with these features, further expanding the anatomical and clinical spectrum of this entity. Given the current uncertainties, careful postoperative follow-up and multidisciplinary discussion remain essential to guide therapeutic decisions.

Authorship Contributions

Concept: **IT,** Design: **IT, AmE, AM, AD,** Data collection and/or processing: **IT, HC, MA,** Analysis and/or interpretation: **HC, MA, MREO,** Literature search: **AbE,** Writing: **IT,** Approval: **HC.**

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