The case of mistaken identity: Extraskeletal Ewing sarcoma of the prostate masquerading as small cell neuroendocrine carcinoma

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INTRODUCTION

Ewing sarcoma (ES) is a rare, small round blue cell tumour that is characterized by specific chromosomal translocations. Most ES arise in bone but 20-30% are extraskeletal (EES).[1] EES occur in soft tissue and viscera and is generally diagnosed in adults over the age of 35.[1] Most ES arise from a gene translocation/fusion between a gene of the FET family (e.g. FUS, EWSR1, TAF15) and a gene of the ETS transcription factor family (e.g. ERG, FLI1, FEV).[2-4] Histologically, ES appears similar to other small round blue cell tumours like small cell neuroendocrine carcinoma (SCNC), neuroblastoma, and lymphomas making the histologic diagnosis of ES challenging. In this case report, we present the diagnostic and treatment challenges associated with EES of the prostate which was initially diagnosed as SCNC.

CASE REPORT

A 33-year-old male mechanic presented with progressive obstructive lower urinary tract symptoms, rectal pain, and decreased stool calibre. On digital rectal exam, he had a firm irregular mass involving the right prostate lobe. His PSA was 0.73 with a free-to-total ratio of 0.18. Computed tomography (CT) scan revealed an enlarged, diffusely heterogeneous prostate with a focal mass in the right posterolateral gland with extracapsular extension. There was no evidence of metastatic disease, confirmed by a bone scan. Pelvic magnetic resonance imaging

(MRI) showed diffuse signal intensity throughout the central and peripheral zones of the prostate with suspected extraprostatic extension from mid gland to apex abutting the right anterior rectal wall. Measured prostate volume was 92 mL (Figure 1). A transrectal ultrasound (TRUS)-guided biopsy was done, demonstrating small round blue cells that stained positive for CKPAN, synaptophysin and Ki-67 on immunohistochemistry, with weak focal staining of chromogranin. They stained negative for NKX3.1, GATA 3, CK7, S100, Melan-A, CD45, TTF-1, Rb, P40, CD56, and desmin (Figure 2). Given the positive staining for neuroendocrine markers, a preliminary diagnosis of high-grade neuroendocrine carcinoma of the prostate was made. An outside second opinion was sought. Meanwhile, the case was reviewed at a local tumour board, and as the patient was very symptomatic, curative-intent chemotherapy and radiation was recommended based on a provisional diagnosis of limited-stage prostatic SCNC.

The patient was prescribed cisplatin and etoposide, and radiation to the prostate, 60 Gy in 20 fractions, was delivered concurrent with the fourth cycle of chemotherapy. A subsequent pelvic MRI demonstrated a dramatic reduction in prostate volume to 34 mL. After six cycles of chemotherapy and all planned radiation, the external pathology report was issued and indicated diffuse CD99 expression with variable positivity in synaptophysin and chromogranin, but negative staining for NKX3.1, PSA, PSAP, INSM1, WT1, and MYF4. The working diagnosis was revised more broadly to a malignant small round blue cell tumour, recognizing the possibility of a fusion-associated sarcoma. To clarify this, further genetic testing via the Trusight RNA Pan-Cancer sequencing panel was requested.

The RNA panel identified the presence of an oncogenic EWSR1:FEV fusion, resulting in a final diagnosis of EES of the prostate, and the strong diffuse cytokeratin staining was interpreted as aberrant. The patient's case was discussed at a sarcoma multidisciplinary conference with experts from Canada and the United States, and an ES regimen was recommended. As the patient had already completed six cycles of cisplatin and etoposide, a further eight cycles of alternating vincristine, doxorubicin and cyclophosphamide (VAC) with ifosfamide and etoposide (IE) chemotherapy was advised. One member of the team (E.W.) met with the patient and his partner. The change in cancer diagnosis and treatment plan was discussed with complete transparency and an apology. The patient acknowledged a good understanding of the rarity of his diagnosis, the extra time required to confirm this, as well as the rationale for additional chemotherapy. Greatly improved lower urinary tract symptoms and evidence of tumor response on imaging helped with the delivery of this difficult news. The patient completed the additional chemotherapy despite experiencing much fatigue over the last few months of treatment. Repeat TRUS-guided biopsy was negative for residual malignancy. The patient currently remains well with restaging scans up to 16 months post-treatment confirming no local or distant recurrence (Figures 3 and 4).

DISCUSSION

In this case report, EES of the prostate was initially diagnosed and treated as SCNC given the limited information available. Diagnosing ES in adults can be difficult due to its rarity, which has been reflected in other case reports including EES of the kidney initially diagnosed as renal cell carcinoma and intracranial Ewing sarcoma initially diagnosed as a glioblastoma.[5,6] EES involving the prostate is exceedingly rare, with only nine other cases described in the literature.[7] Our patient presented with non-specific symptoms, and his low PSA could not differentiate between EES or SCNC as neither malignancy secretes PSA. Furthermore, ES and SCNC both appear as small round blue cells tumours with scant cytoplasm, and both can stain positive for cytokeratin, synaptophysin, and other neuroendocrine markers.[5,8-10] What established the diagnosis of EES in our patient was the identification of a pathognomonic EWSR1:FEV fusion via the TruSight RNA Pan-Cancer panel. This panel uses next-generation RNA sequencing to identify 1385 genes linked to oncogenesis and is superior to detecting fusion genes compared to DNA sequencing.[11] Given its high sensitivity, specificity, and short assay time, RNA sequencing is a valuable diagnostic tool that should be used earlier and more widely in diagnostic pathways; however, availability and cost may be barriers to implementation.

In North America, ES treatment consists of induction chemotherapy with nine alternating cycles of VAC and IE chemotherapy, followed by local treatment with surgery or radiation.[1] After local treatment, consolidative chemotherapy with five alternating cycles of VAC and IE is given. Our patient initially received six cycles of dual-agent chemotherapy as opposed to a longer course of multiagent induction chemotherapy. Additionally, the patient received cisplatin, which is not commonly used in ES, and radiation was initiated concurrent with chemotherapy. Furthermore, the biologically equivalent dose of radiation that was delivered to the patient exceeded the standard doses used for ES. There is evidence to suggest that dose escalation improves local control in ES, and this may have contributed to the excellent disease response.[12] Radiation was delivered in a hypofractionated manner at 3 Gy per fraction versus the standard 1.8-2 Gy per fraction regimens, though the latter were designed to minimize the late effects of radiation in the pediatric population and may be less relevant in adults. Regarding local treatment options, previous evidence has suggested that surgery offers superior local control compared to radiation, but most of these studies were retrospective in nature and subject to selection bias. In our patient, radiation was given because of the initial concern for SCNC, which is a radiosensitive disease where surgery has a limited role. However, a delayed cystoprostatectomy – possibly with en bloc proctocolectomy – was considered but ultimately not undertaken given the negative post-treatment biopsies and the long-term morbidity of the procedure.

While the patient's treatment did deviate from the typical ES paradigm, there is no established standard of care for prostatic EES given its rarity. For example, a 33-year-old patient with prostatic EES underwent a prostatovesiculectomy, regional lymph node dissection, and pelvic floor resection followed by post-operative chemotherapy in one case report.[7] In contrast, a 29-year-old patient with prostatic EES was treated with neoadjuvant chemotherapy followed by a

total pelvic exenteration in another case report.[13] The variations in practice in managing prostatic EES are likely influenced by both local physician expertise and the rarity of the disease. Despite deviations from the classic ES paradigm, the treatment our patient received has been effective thus far, with a marked reduction in prostate volume and a complete pathologic response on post-treatment biopsy. Further follow-up imaging and prostate biopsies are planned.

CONCLUSIONS

This case report of EES of the prostate highlights the challenges associated with diagnosing and treating rare prostatic malignancies, especially when establishing the definitive diagnosis is delayed and impacts treatment.

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FIGURES AND TABLES

Figure 1. Pre-treatment pelvic magnetic resonance imaging with T2-weighted images of the prostate in the (A) sagittal, (B) axial, and (C) coronal planes showing an enlarged prostate gland with extracapsular extension in the right posterolateral peripheral zone. (D) T1-weighted image of the prostate in the axial plane with evidence of extracapsular extension abutting the rectum.

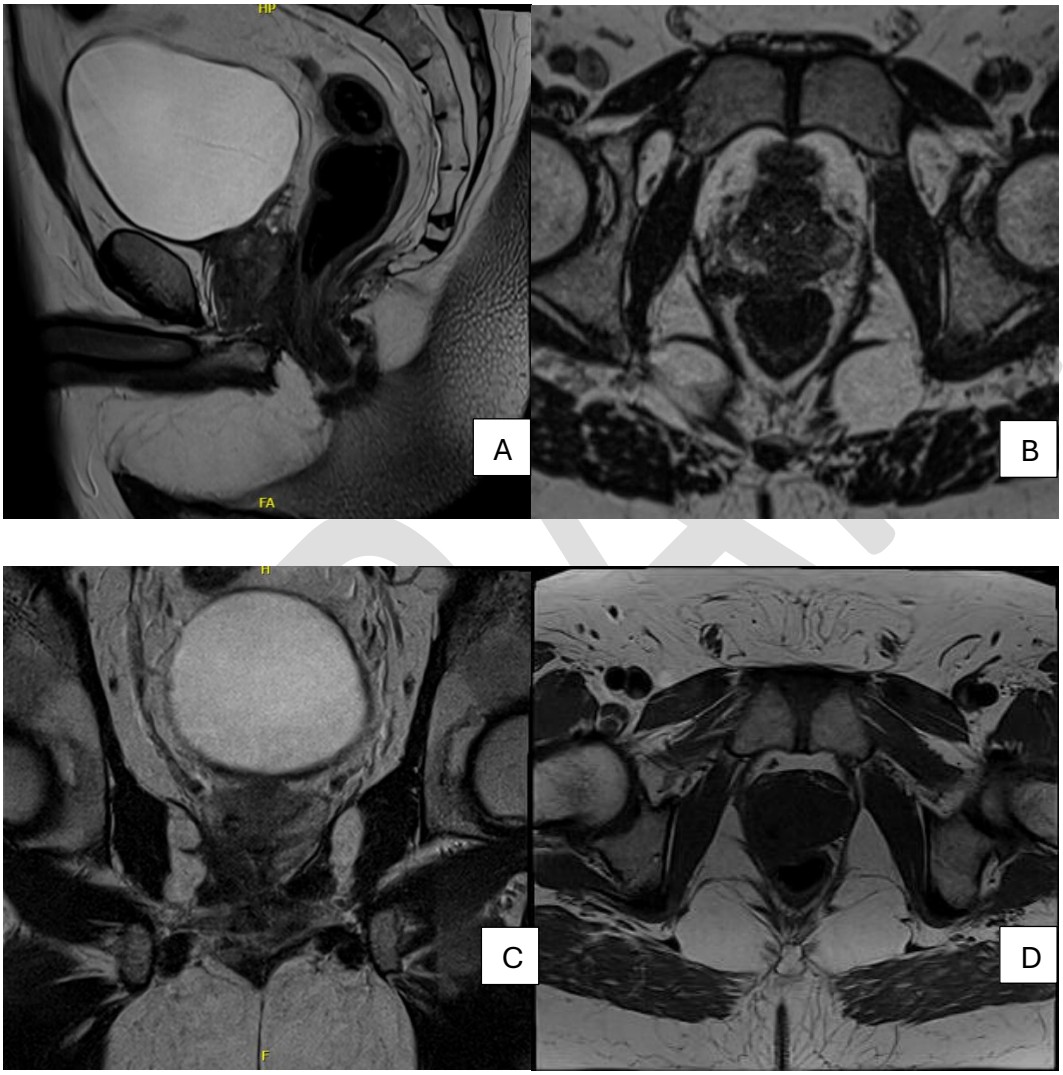

Figure 2. Histological images from initial prostate biopsy with (A) hematoxylin and eosin staining as well as immunohistochemistry with (B) negative staining for NKX3.1, (C) positive staining for synaptophysin and (D) weak focal staining for chromogranin.

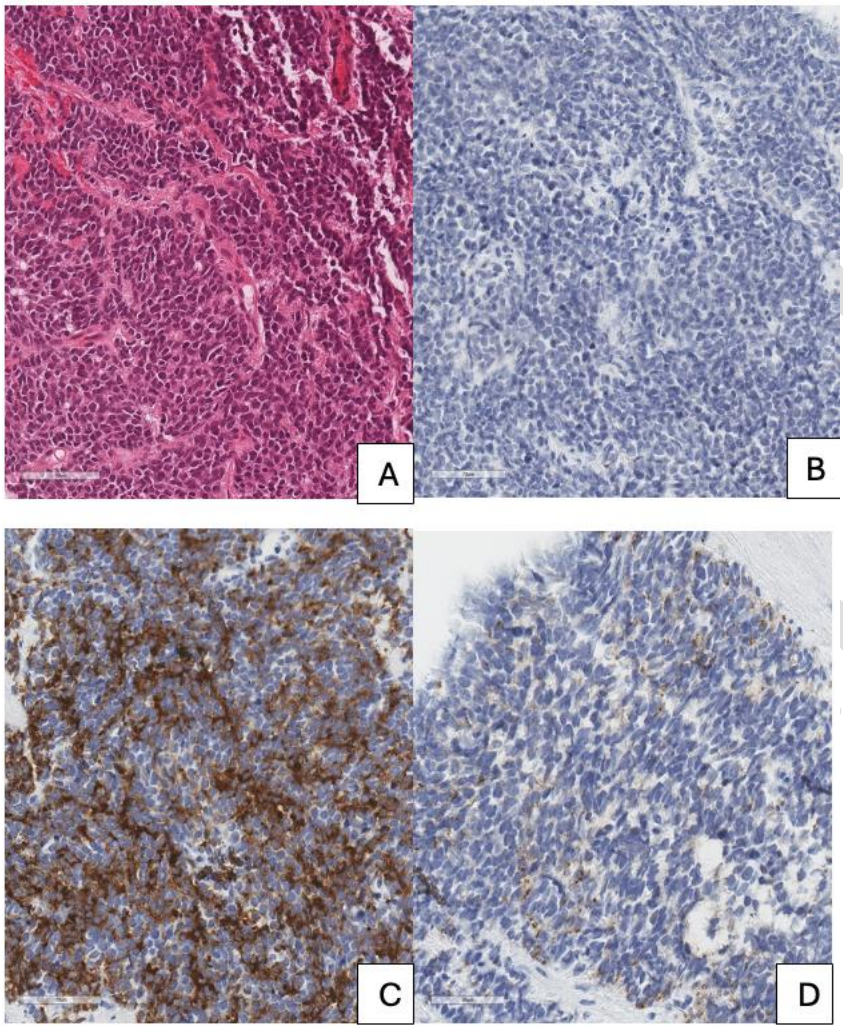

Figure 3. Post-treatment pelvic magnetic resonance imaging with T2-weighted images of the prostate in the (A) sagittal, (B) axial, and (C) coronal planes show response to treatment with a reduction in prostate size and no further evidence of extracapsular disease. (D) T1-weighted image of the prostate in the axial plane illustrates no evidence of extracapsular extension.

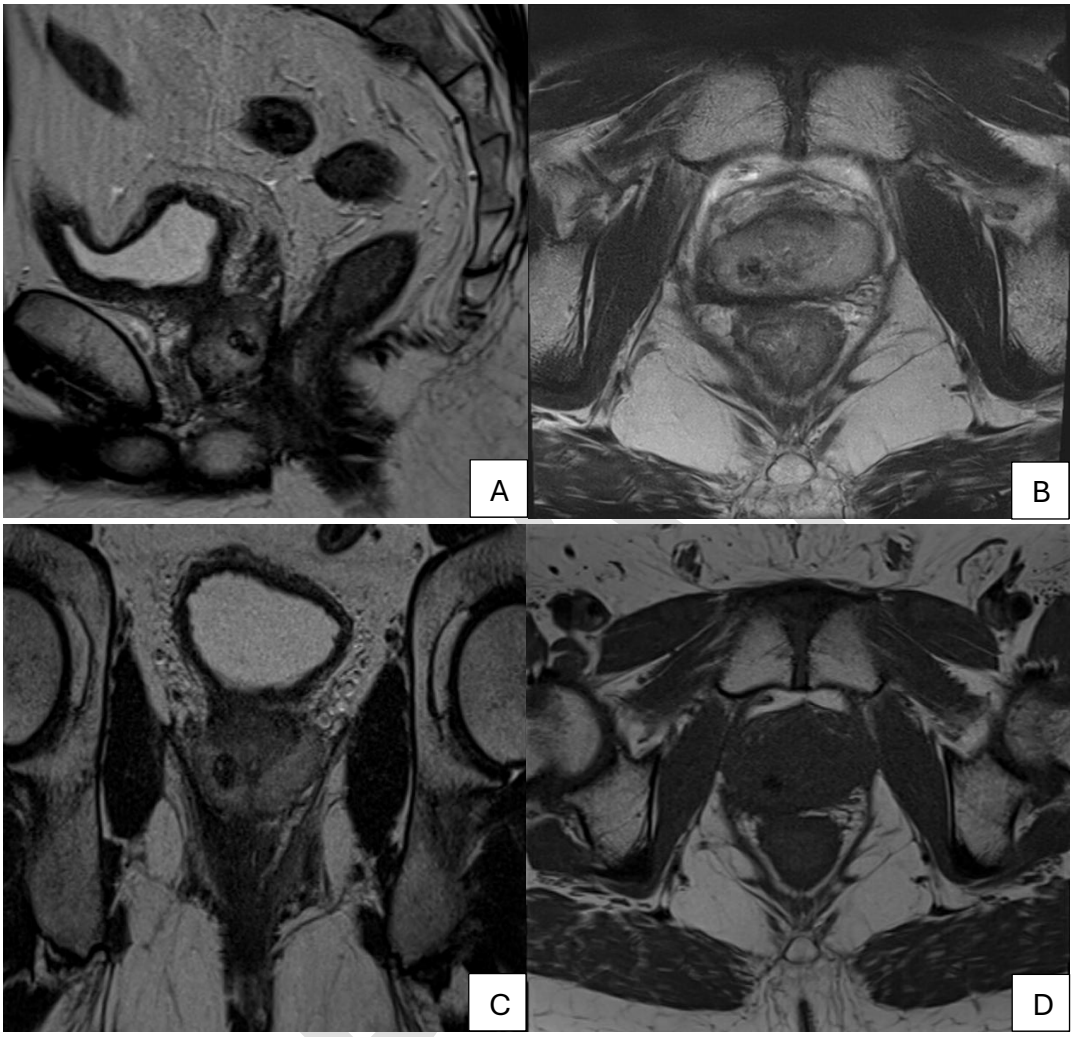

Figure 4. Timeline of events.