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CORRESPONDENCE

Pediatric soft tissue neoplasms with *BRAF* activating mutations

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Penning et al. have recently reported [1] an intriguing series of five soft tissue neoplasms with histologic overlap between infantile fibrosarcoma and cellular congenital mesoblastic nephroma, harboring point mutations in *BRAF* (one of which also harbored a *BRAF-ADCK2* fusion). These novel tumors were described alongside a larger cohort of nine cases harboring *BRAF* fusions. The *BRAF* point mutation cases were diagnosed from gestation through up to 18 months, in three males and two females, and showed no evidence of disease at 6 and 24 months in the two cases with available follow up. Their findings are, in our assessment, strikingly similar to two cases we have studied and had presented at the 2018 European Congress of Pathology [2] in the hope of identifying additional examples encountered by colleagues. Both of our cases arose in male infants, showed histologic features in the morphologic spectrum described by Penning et al., and harbored *BRAF* V600E mutations.

Case 1 was a male who presented at 11 months for ventriculoperitoneal shunt placement for hydrocephalus seen on workup for developmental delay. The patient, who was transferred from abroad for surgical management, on arrival showed a bulging, ulcerated 10 cm soft tissue mass, apparently present since birth, over the cervical and thoracic vertebrae (Fig. 1). MRI showed a spinal cord mass (8.9 cm) with extensive involvement of C5 through T9 and extension into adjacent paraspinal soft tissues. Staged subtotal excision of the soft tissue and spinal mass was performed. Resection specimens showed an infiltrative proliferation of monomorphic small ovoid to spindle cells reminiscent of diffuse-type neurofibroma, deeply infiltrative of subcutaneous fat and skeletal muscle, with areas of variably ectatic, thin-walled vessels, and in other areas with perivascular whorling. Lipomatous differentiation was present in several foci. Mitoses were very infrequent (1 per 50 HPF) outside of areas adjacent to ulceration. Given the cutaneous base and diffuse CD34 positivity, *PDGFB* break apart FISH was performed and was negative for rearrangement. Pancytokeratin AE1/AE3, EMA, SMA, Desmin, MyoD1, Myogenin, SOX10, (nuclear) β-catenin, MUC4, STAT6, and ERG were all also negative. Our institutional targeted ampliseq-based NGS of 50 cancer-related genes revealed mutations of *BRAF* (V600E), and also *TP53* (R290H). During the patient's complicated inpatient course, retroperitoneal exploration and nephrectomy were performed, which upon histologic review identified that the lesion either extended inferior to the diaphragm or exhibited a second focus in perinephric/periadrenal soft tissue (interesting in light of Case 5 of Penning et al.). Nonetheless, the patient recovered and was discharged, albeit with paraplegia related to surgical resection. At 18 months after presentation, no further progression was noted, though paraplegia persisted.

Over a decade ago, in Case 2 first presented as a 3-month-old male with a 2.7-cm cutaneous polypoid lesion in the lumbar area of the lower back; incidentally a tethered cord was noted on MRI at the time. Excision of

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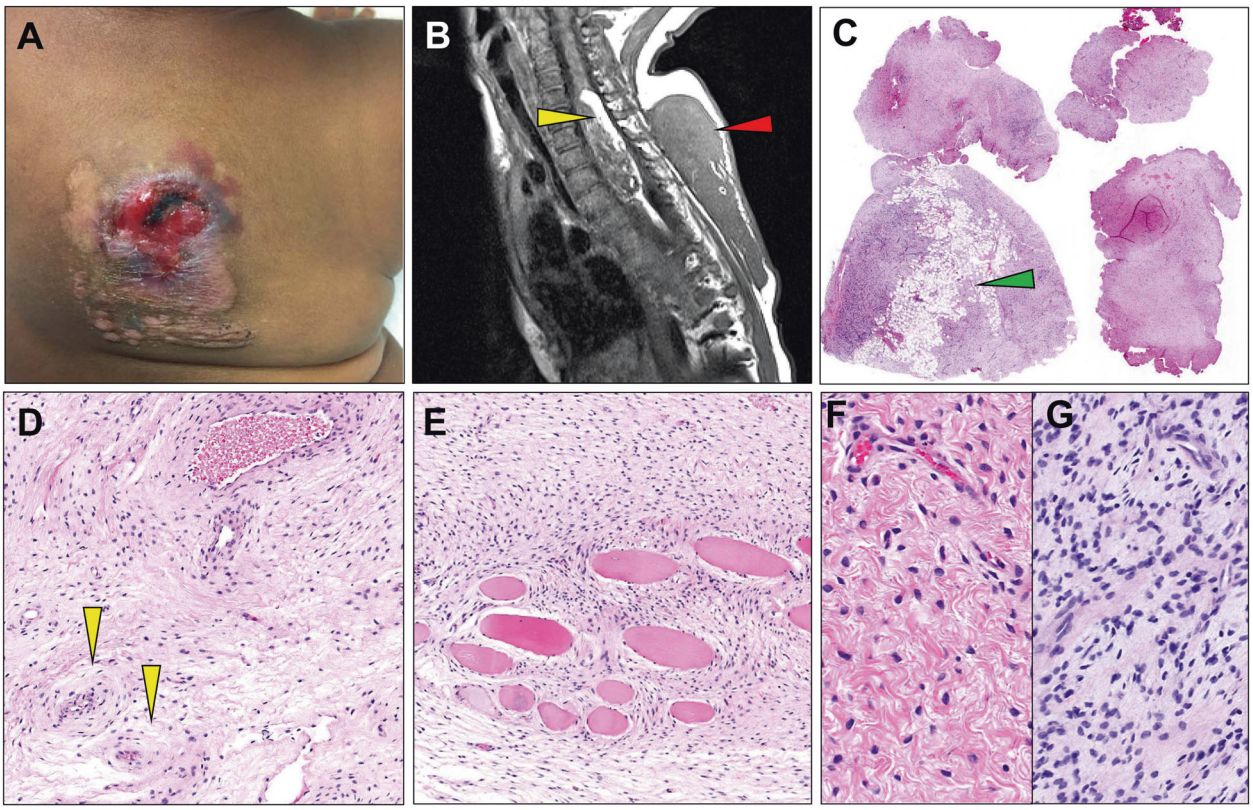

Fig. 1 Case 1. A Upon transfer for shunt placement for hydrocephalus, a 10 cm ulcerated soft tissue mass was seen over the thoracic vertebrae. **B** T1 weighted MRI-imaging characterized a subcutaneous tumor (red arrow) extending into the spinal canal, where a significant adipocytic component was apparent (yellow arrow). **C** Histologic review of the spinal tumor specimen confirmed adipocytic differentiation (green arrow). **D** The lesion was composed predominantly of bland spindle cells with variably gaping thin-walled vessels (upper right) and smaller vessels with perivascular whorling or cuffing (yellow arrows). **E** Deep infiltration of soft tissue was seen in the subcutaneous resection specimen. **F**, **G** Cytologically the cells showed small ovoid to spindled nuclei with varying cellularity in a collagenous to myxocollagenous stroma.

the cutaneous mass was performed, and extramural consultation at the time rendered diagnosis of a "giant cell fibroblastoma/dermatofibrosarcoma protuberans" based on CD34 positivity, though RT-PCR-based testing for *COL1A1- PDGFB* rearrangements performed by the consultant were negative. No clinical recurrence occurred. The patient again presented 14 years later, after a sports injury, revealing an incidental but worrisome enhancing intradural "mass" (Fig. 2) involving the lumbar spinal cord, located deep to scars from the prior resection at infancy. L1–L3 laminectomy was performed, and comparison of the new spinal mass and original subcutaneous one revealed identical bland cells with spindled to ovoid nuclei in a delicate fibrous stroma. The proliferation infiltrated structures including dermal adnexal, neurovascular, and adipose tissue in the cutaneous excision, and large vessels and nerves in the spinal resection, though mitoses were sparse (3 per 50 HPF). CD34 was diffusely positive in both, with focal S100 (all other negative stains described in Case 1 were also negative). Based on the similarity of the morphology to Case 1, the same NGS assay was performed, revealing *BRAF* (V600E) and *APC* (Q1291*) mutations. At 40 months further follow-up, the patient remained well with no recurrence.

In summary, our experience further supports the existence of rare pediatric soft tissue neoplasms with *BRAF* activating mutations, as described by Penning et al., while adding longer term follow-up without apparent progression. Comparing the morphology of our *BRAF*-mutated to the *BRAF*-rearranged cases of Penning et al. and other series [3, 4], our cases show a similar spectrum of histologic features, albeit with somewhat less cellularity and lower mitotic rate. We also have noted reported cases in the literature showing similar clinical and histologic features, albeit without any sequencing data, including tumors characterized as fibrous hamartoma of infancy arising at dorsal/ paraspinal sites [5–8], or even tumors diagnosed as connective tissue nevus [9] arising in soft tissues. Given the perinephric involvement seen in one of our and one of the Penning et al. series, we would be remiss not to note the similar features shared between our neoplasms and

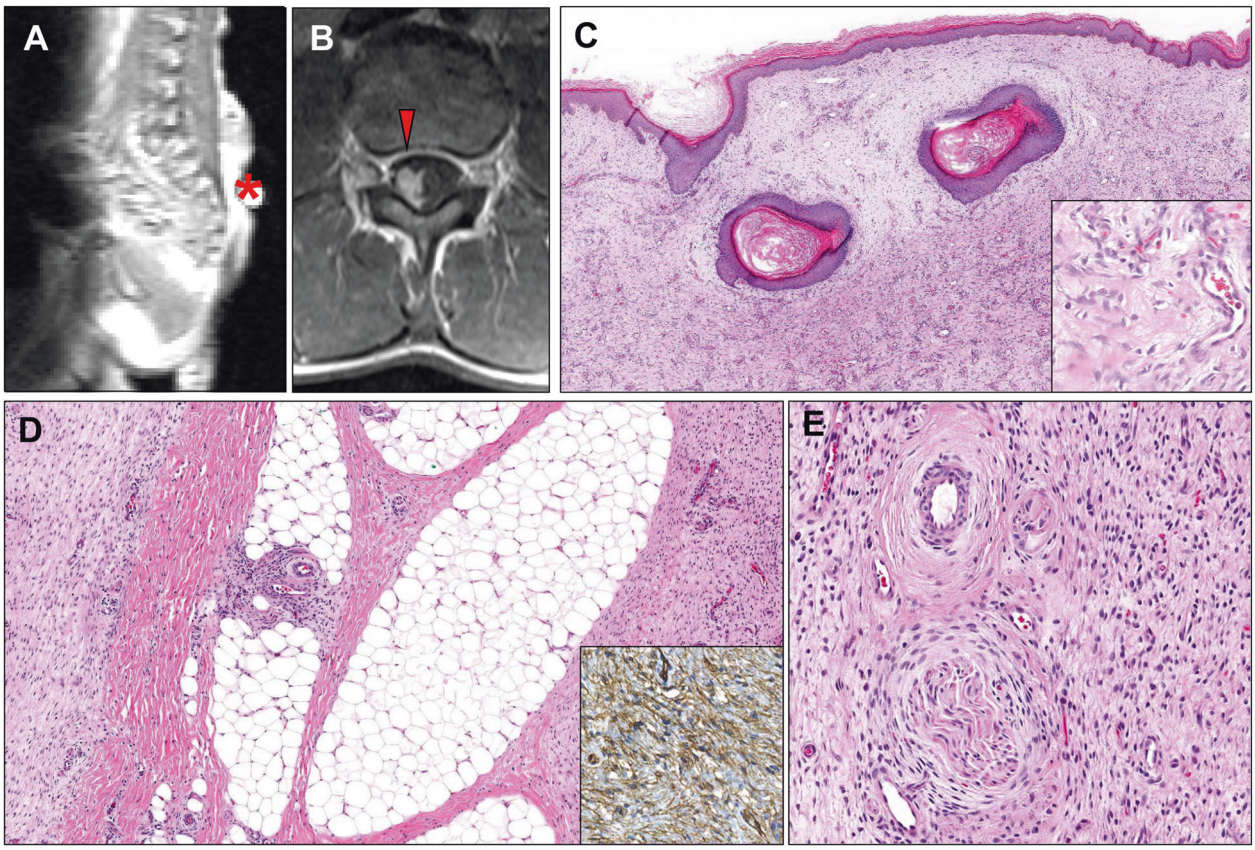

Fig. 2 Case 2. **A** T1 weighted MRI from the age of 3 months demonstrates lipogenic lumbar soft tissue tumor. **B** At re-presentation 14 years later, MRI demonstrates an enhancing subdural tumor involving and displacing the cord. **C** Re-review of the subcutaneous specimen showed a bland tumor with spindled-to-ovoid cells and prominent vasculature (inset). **D** After this tumor had been diagnosed as giant cell fibroblastoma, re-resection of the tumor bed showed deep invasion across soft tissue and fascial planes; no recurrence was noted in the subsequent 14 years (inset, diffuse CD34 positivity). **E** The spinal tumor showed identical bland spindle cell morphology and perivascular and perineural whorling to that seen in Case #1.

metanephric stromal tumors [10, 11]. These neoplasms share a generally infantile age range, prevalent *BRAF* mutations [12], bland spindle cell cytology, propensity for concentric growth around native structures, and CD34 positivity with our tumors, raising the possibility of a relationship between these entities.

Overall, considering the congenital/infantile presentation and apparent lack of progression in the small number of these *BRAF*-mutated soft tissue neoplasms, definitive assessment of the biologic potential of these tumors awaits larger cohorts with follow up. For that matter, the additional *TP53* and *APC* mutations seen in our two cases are of uncertain significance. We hope that the observations of Penning *et al*. and those herein spur recognition and study of these most unusual neoplasms.

Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest with regards to this manuscript. Disclosures of relationships that do not represent conflicts of interest include that JW is an employee and shareholder of Bristol Myers Squibb. SCS discloses that he is a consultant/author for Elsevier Publishing.

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