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An Adult Patient With Rare Primary Intracranial Alveolar Rhabdomyosarcoma

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Abstract. *We report a rare case of primary intracranial alveolar rhabdomyosarcoma (ARMS) in the right temporal lobe of a 51-year-old male. ARMS is one of 3 histological subtypes of rhabdomyosarcoma that most commonly presents in older children and younger adults. To our knowledge, there have been no prior published reports of primary intracranial ARMS in adults. Known cases of intracranial ARMS in adults are due to central nervous system (CNS) metastases from the head and neck and extremities. Diagnostic workup did not reveal any primary source outside the CNS. Given that risk factors for ARMS have not been studied in adults, it is difficult to ascertain what aspects of this patient's clinical history may have contributed to his diagnosis. Interestingly, he had prior history of traumatic brain injury requiring evacuation of a right fronto-temporal intraparenchymal hematoma.*

Rhabdomyosarcoma (RMS) is a rare and aggressive malignant soft tissue sarcoma which arises from precursors of skeletal muscle cells (1). RMS is the most common type of soft tissue tumor in the pediatric population and comprises 50% of such cases (2). It is exceedingly rare in adults, comprising <4% of sarcomas and <1% of all malignant solid tumors in this population (3). RMS may present at a variety of anatomic sites, with head and neck being the most common (up to 40%) followed by the genitourinary system (25%), and trunk and extremities (20%) (3). The latter is most common in adult populations. Risk factors associated with RMS in the pediatric population include gender (slightly more common in boys than girls), age<10 [67% of all cases; however, incidence of alveolar RMS is higher in adolescents (4)], certain rare inherited syndromes (1) (*i.e.* Li-Fraumeni, Beckwith-Wiedemann, Neurofibromatosis Type 1, Costello and Noonan) and pre-natal exposure to X-rays (5). Prognosis in pediatric patients has improved markedly [*i.e.* >70% cure rate for localized RMS (6)] as multimodal therapeutic approaches (*i.e.* surgery, radiation, chemotherapy) have become standard of care. However, adults diagnosed with RMS fare much worse, with five-year overall survival (OS) rates of 27% *vs.* 61% in the pediatric population (7).

There are 3 histologic subtypes of RMS: ARMS (alveolar), ERMS (embryonal), and PRMS (pleomorphic) (8). PRMS is found predominantly in adults, while the ARMS and ERMS subtypes are found mostly in children (3). ARMS occurs in ~30% of RMS patients and most commonly presents in older children and younger adults (7). ARMS has a poorer prognosis than the other subtypes, with 5-year OS declining from 86% in Stage 1 and 2 to 34% in Stage 3 with metastases (9). The most common sites of metastatic ARMS include the lung, brain and bone (10). ARMS consists of nests of small round cells arranged in an alveolar architecture with occasional multinucleated giant cells (11). With the increasing use of genomic methods to classify tumor subtypes, the Soft Tissue Sarcoma Committee of the COG has recently defined ARMS as having a predominant (>50%) alveolar component with a FOXO1 gene rearrangement [*i.e.* t(1;13) or t(2;13)] (12). FOXO1 rearrangements t(1;13) and t(2;13) lead to the generation of novel transcription factors PAX7-FOXO1 and PAX3-FOXO1, respectively, and lead to dysregulation of cellular proliferation and angiogenesis (3). FOX01 rearrangements t(1;13) and t(2;13) are found in 60% and 20% of ARMS, respectively, with the former associated with a more favorable 4-year overall survival of 75% *vs.* 8% (p=0.0015) (13, 14). Interestingly, the presence of these two translocations were mutually exclusive in several studies that analyzed ARMS tissue samples and no patients harbored the 2 translocations concurrently (14-16).

Clinical History

The patient was a 51-year-old male who sustained a traumatic brain injury (TBI) following a motor vehicle accident (MVA) in 2010 and underwent emergent evacuation

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of a right fronto-temporal intraparenchymal hematoma causing uncal herniation (Figure 1). Postoperatively he had residual left hemiplegia, left sensory loss, post-traumatic seizures and cognitive impairment. In April 2017, he had a generalized seizure and imaging revealed a right temporal mass measuring 4.7×2.9×4.3 cm with leftward midline shift (Figure 2). The mass was biopsied and showed an ARMS that was described as a poorly differentiated small round cell neoplasm with a prominent lobular and alveolar growth pattern. Mitotic index was very high (up to 20/1 HPF) with large areas of tumor necrosis.

The tumor was strongly and diffusely immunopositive for CD56 and vimentin, consistent with ARMS. Extensive testing did not reveal a primary source outside the CNS including multiple imaging modalities such as CT scan of the chest, abdomen and pelvis and whole-body PET-CT. The patient stopped smoking in 1995 but had no personal or family history of malignancy. He received external beam radiation therapy (60 Gy in 30 fractions) to the right temporal mass without concurrent or adjuvant chemotherapy. The patient was followed with serial brain MRIs with contrast and was clinically and radiologically stable until he enrolled in hospice and eventually passed away in August 2018. The patient's survival from diagnosis to death was 17 months. The patient's tumor was not sequenced to assess the presence of FOXO1 rearrangements due to his passing away.

Discussion

This case presents a rare case of adult primary intracranial ARMS. Several case reports have previously described primary intracranial ARMS in pediatric patients (17-19). In adults however, the reported literature is limited. A case series by Dropcho and Allen described 34 patients ranging from age 9 months to 52 that were diagnosed with primary intracranial RMS (19). Unfortunately, histologic subtypes for each patient were not known, and thus correlating clinical history to the presence of primary intracranial ARMS was not possible. Moreover, the authors did not disclose risk factors for each patient that may have predisposed them to RMS. Out of the 34 patients with primary intracranial RMS, 24 were pediatric patients. Out of the remaining 11 adult patients, location of the intracranial tumor varied: cerebellar hemisphere (3/11), parietal dura (2/11), frontal lobe and/or dura (2/11), occipital lobe (1/11), cerebellopontine angle (1/11), cerebral hemisphere (1/11), and diffuse meningeal (1/11).

The majority of reports of intracranial ARMS described patients with CNS metastases secondary to a primary tumor most often localized to the head & neck or extremities (11, 20-23). In one case series that examined RMS patients with CNS relapse, 16 out of 23 patients were confirmed to have alveolar RMS and 15 were adults (24). Location of primary ARMS tumor included seven patients in the facial sinuses, six in the trunk or extremities and three in other organs. There were two other cases of patients with primary intracranial RMS, but neither had the alveolar subtype. Celli *et al*. reported a 46-year-old male diagnosed with primary fronto-parietal embryonal RMS who underwent surgery and chemotherapy and survived recurrence-free for at least 30 months (25). Palta *et al*. reported a 44-year-old male with a primary meningeal lesion who was initially diagnosed with anaplastic meningioma (26). Upon re-review of his pathology, the authors determined the primary intracranial mass to be RMS that was negative for alveolar translocation t(2;13).

While the risk factors for developing primary intracranial ARMS in the pediatric population have been identified (e.g. age, gender, inherited syndromes, pre-natal exposure to X-rays), they have not been definitively identified in the adult population. An exhaustive review of the literature revealed no studies examining the etiologies of RMS in adults. Our patient does not have any personal or family history of the inherited syndromes mentioned above, and extensive diagnostic workup failed to reveal a primary tumor in any organ except the CNS. Furthermore, our patient's age at diagnosis (51 y.o.) puts him outside the most common range for developing ARMS (10-25 years).

The patient's history of TBI in 2010 followed by the development of the right temporal primary ARMS tumor was an interesting aspect of this case. While there are no reports of post-TBI patients who subsequently develop any subtype of RMS, there are several published reports of post-injury gliomas in adult patients (27-29). Bo and Weiguo (27) reported a 45-year-old male who developed a glioblastoma (GBM) in the right temporal region ten years after experiencing an intracranial hematoma in the same region following a MVA. Henry and Rajshekhar reported a 57-year-old male who was diagnosed with high-grade glioma in the left temporal region after having developed a small acute subdural hematoma following an MVA 2 years ago (28). The authors attributed the pathogenesis of his glioma formation to transformation of proliferating glial cells recruited to the site of the trauma.

Anselmi *et al*. reported two patients who developed GBMs in scar tissue remaining after TBI (29). One patient was a 40-year-old male who was found to have a GBM in the right parietal region, the same site as an intracranial hematoma he suffered following an MVA 20 years prior. The second patient was a 60-year-old male who was found to have GBM in the same location as scar tissue that formed following an MVA 15 years ago. Our patient had several similarities to the cases described above. He was an older male with no prior history of malignancy that was involved in an MVA several years prior and was later diagnosed with a CNS tumor at the same site as the injury. Whereas prior

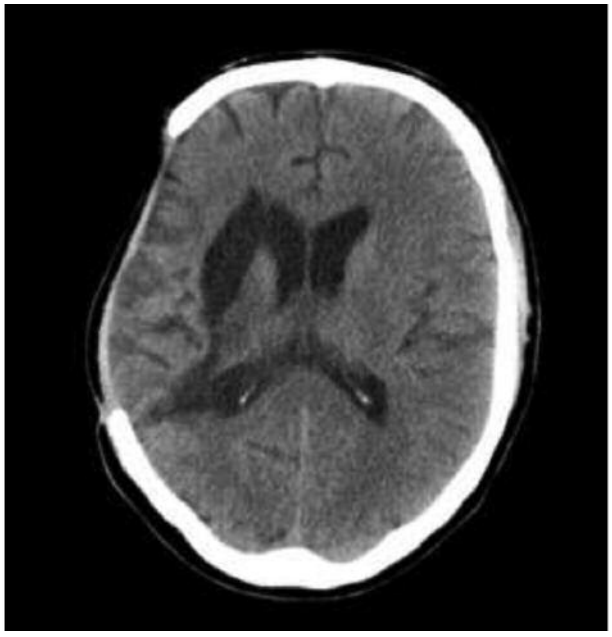

Figure 1. *Non-contrast head CT status post right decompressive hemicraniectomy (August 2010).*

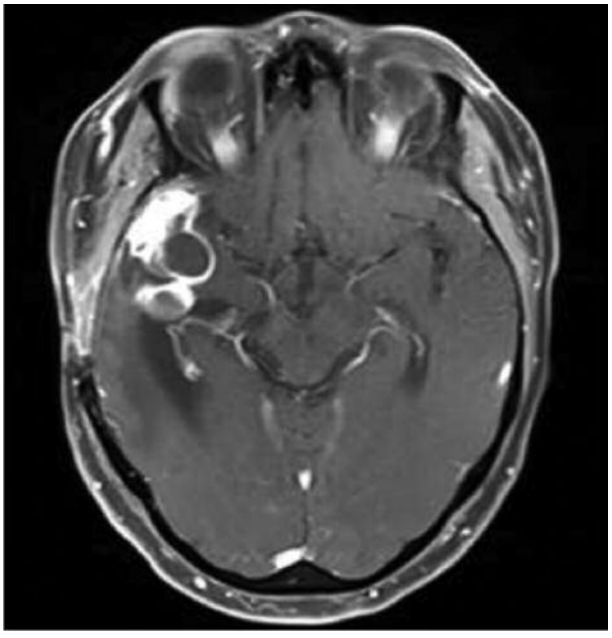

Figure 2. *Contrast-enhanced axial brain MRI showing nodular enhancement of the right temporal lobe mass with cystic components (April 2017).*

case studies have reported incidence of gliomas following TBI, our case is the first known incidence of post-injury ARMS. However, definitive epidemiological evidence of a causal link between the two is lacking.

Conclusion

To our knowledge, this is the first reported case of a primary intracranial ARMS in an adult patient. Interestingly, his CNS tumor developed in the same location as his prior TBI. Whether there is a causal connection between TBI and the development of CNS tumors remains to be determined.

Conflicts of Interest

Dr. Kunal Desai declares that he has no conflicts of interest that might be relevant to the contents of this manuscript. Dr. Divya Mella's fellowship was partially funded by educational grants from AbbVie Pharmaceuticals and Leadiant Biosciences. Dr. Edward Pan declares that he has no conflicts of interest that might be relevant to the contents of this manuscript.

Authors' Contributions

EP conceived and designed the analysis, collected the data, edited the manuscript and supervised the data analysis of the manuscript. KBD wrote the manuscript with support from DM and EP. DM provided clinical information regarding the patient and edited the manuscript.

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