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Case Report

Primary intramedullary extradural Ewing sarcoma ☆

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ABSTRACT

Ewing sarcoma is the second most frequent primary bone tumour of childhood and adolescence. The aim of this report is to describe the imaging, pathology, clinical findings, and treatment of a primary intradural extramedullary Ewing sarcoma with a unique intracranial metastatic component in a pediatric patient. A 14-year-old girl with a history of mood disorders presented to the emergency department with a 3-week history of neck torticollis, cervical pain, paresis, and paresthesia of the upper and lower extremities on the left side. Initially, non-organic causes such as somatization or conversion disorder were suspected. She returned 3 months later when her symptoms worsened. MRI of the head and spine was performed, and demonstrated the presence of a suprasellar, retro-chiasmatic mass lesion. There was also diffuse leptomeningeal enhancement, another well-defined intradural extramedullary lesion the sacral region and several multifocal cauda equina soft tissue nodules. The patient first underwent surgery. The patient was also treated with a combination of chemotherapy (vincristine, doxorubicin and cyclophosphamide alternating with ifosfamide and etoposide (VDC/IE)) and radiation as per the Children's Oncology Group AEWS1221 protocol. Most recent imaging conducted 22 months after the initial mass discovery revealed improvement of the suprasellar mass lesion with residual stable appearance of the prominence and enhancement of the pituitary stalk and tuber cinereum. There was interval improvement of the spinal lesions with no convincing residual. Clinically, at almost three years since initial imaging findings, and 25 months since completing treatment, she is stable from an oncology perspective.

☆ Competing Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Introduction

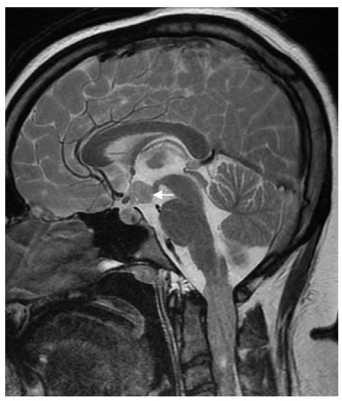
Ewing sarcoma is the second most frequent primary bone tumor of childhood and adolescence [1]. It has an estimated incidence of 2.9 cases per one million children in the United States and accounts for 10%-15% of malignant bone tumors and up to 3% of all pediatric malignancies [2–5]. Histologically, Ewing sarcomas are composed of small round blue cells expressing high levels of membranous CD99, but this is nonspecific [1]. Genetically, they are characterized by chromosomal translocations in which a member of the FET gene family is fused with an Erythroblast Transformation Specific (ETS) transcription factor [1]. The most common fusion is that of EWSR1-FLI1, affecting approximately 85% of cases [6]. The majority of cases of Ewing sarcoma occur in the long bones, pelvis, and ribs [7]. Primary intradural extramedullary Ewing sarcomas (IEES) are extraordinarily rare [7]. The Ewing sarcoma family of tumors are aggressive with high rates of local recurrence [8]. This malignancy can cause severe neurological deficits depending on location. Treatment of Ewing sarcoma often involves a combination of local surgery, radiotherapy, and chemotherapy [1,9].

The aim of this report is to describe the imaging, clinical findings, and treatment of a 14-year-old girl with a primary intradural extramedullary Ewing sarcoma with EWSR-FLI1 fusion and a unique intracranial metastatic component.

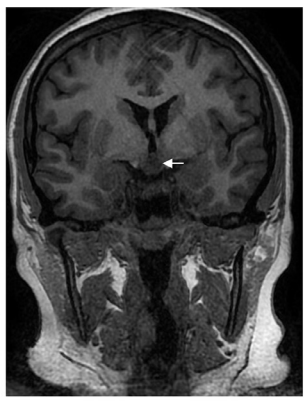
Case report and imaging

A 14-year-old girl with a history of mood disorders presented to the emergency department with a 3-week history of neck torticollis, cervical pain, paresis, and paresthesia of the upper and lower extremities on the left side. Initially, the impression was that of a nonorganic cause such as somatization or conversion disorder. Her symptoms however worsened, and she returned, now with a 3-month history of torticollis, progressively worsening left-sided paresthesia, and paresis now also affecting the right side, difficulty walking, daily headaches, decreased cervical range of motion, and occasional bouts of urinary incontinence. At this time, MRI of the head and spine was performed, and demonstrated the presence of a suprasellar, retro-chiasmatic mass lesion. The mass exhibited predominantly low signal intensity on T1WI, intermediate signal on T2WI, hyperintense signal on FLAIR sequence, and intense enhancement postcontrast administration. The mass showed restricted diffusion on DWI with no blooming in SWI. MRI of the spine demonstrated an intradural extramedullary lesion in the left cervical region extending from C1 to C4 with significant mass effect on the cord, which appeared compressed and displaced to the right side and anteriorly. In addition, there was diffuse leptomeningeal enhancement, another well-defined intradural extramedullary lesion the sacral region at the level of S2, and several multifocal cauda equina soft tissue nodules. The spinal lesions all showed similar signal characteristics to the intracranial lesion. A spinal lesion was biopsied and given the distribution of the lesions and the same imaging characteristics amongst them, drop metastases was assumed. The main differential based on initial imaging was a germ cell tumor with drop metastases. Surgical resection of the cervical spinal mass was pursued for definitive diagnosis and management. Staging workup at diagnosis consisting of bilateral bone marrow biopsies, CT neck, chest, abdomen, and pelvis, and a bone scan, revealed no metastatic disease outside the central nervous system.

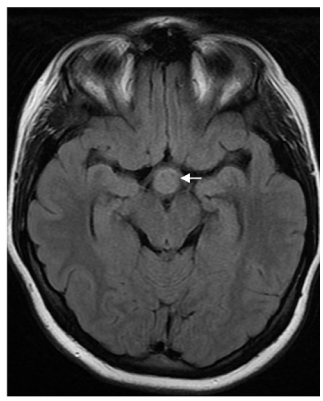
Initial Imaging



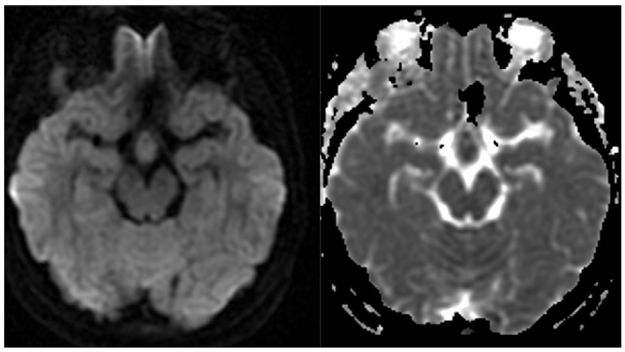
Sagittal T2-weighted imaging displaying well-defined intracranial lesion in the tuber cinerum (white arrowhead).



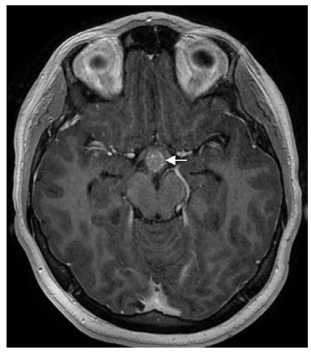
Coronal T1-weighted image of the intracranial mass displaying hypointensity (white arrowhead).



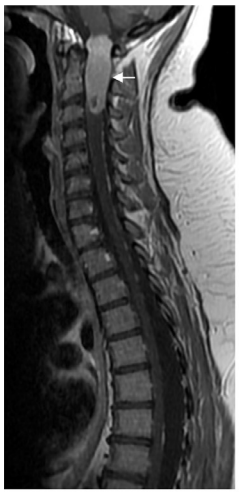
Axial FLAIR imaging of the intracranial mass displaying mild hyperintensity (white arrowhead).



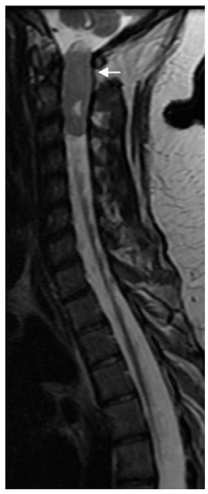
Diffuse-weighted imaging (left) and ADC (right) displaying positive restriction.



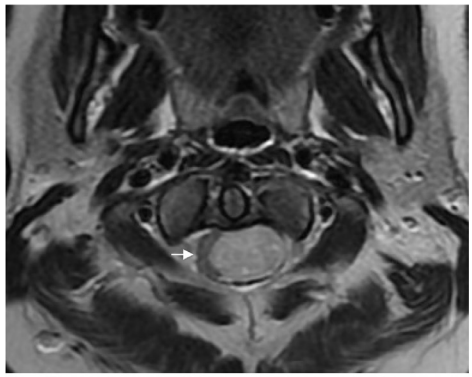
Post-gadolinium imaging of the intracranial mass showed inhomogeneous enhancement (white arrowhead).



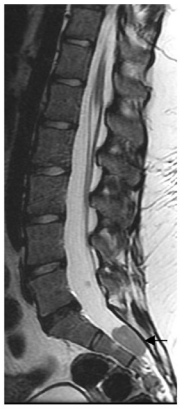
Gadolinium-enhanced sagittal T1-weighted imaging showed well-defined intradural lesion extending from C1-C4 (white arrowhead). The mass demonstrated restricted diffusion on the DWI and ADC map (not included).



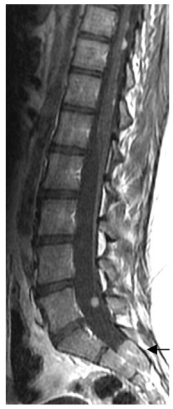
T2-weighted sagittal imaging of the intradural lesion extending from C1-C4 exhibits intermediate signal intensity with small cystic components at C3 (white arrowhead).



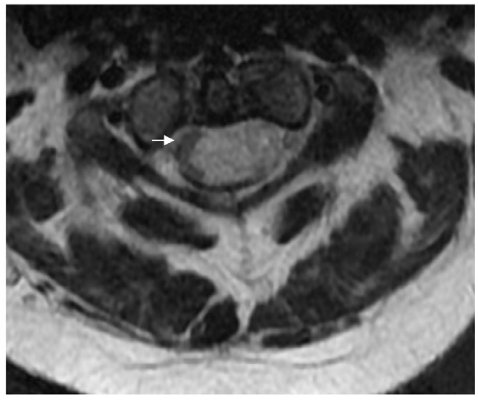
T2-weighted axial imaging of the cervical spinal lesion demonstrates intermediate intensity. It appears to exert severe mass effect compressing and flattening the cord towards the right side (white arrowhead).



Sagittal T2-weighted imaging of the lumbar spinal lesion (black arrowhead).

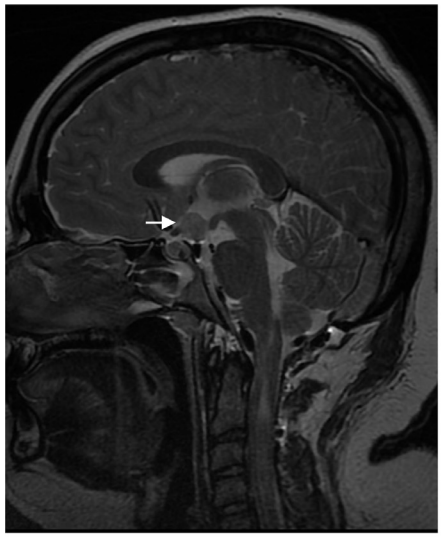


Sagittal post-gadolinium enhancement T1-weighted imaging of the lumbar spinal lesion (black arrowhead).

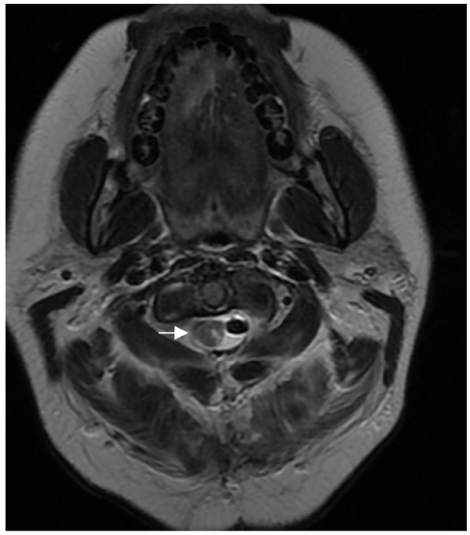


T1-weighted axial imaging of the cervical spinal lesion showing mild post-gadolinium enhancement (white arrowhead).

Postsurgical

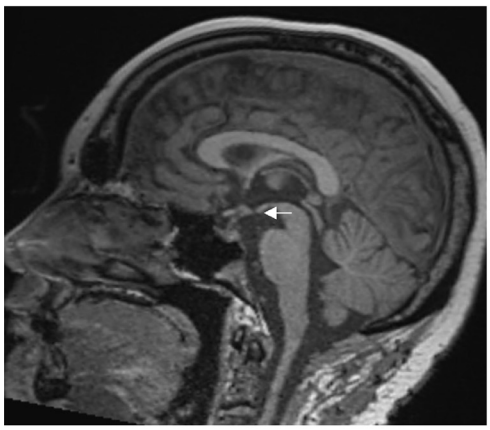


Post-surgical sagittal T2-weighted image demonstrates stability in size of the mass in the tuber cinerum (white arrowhead).

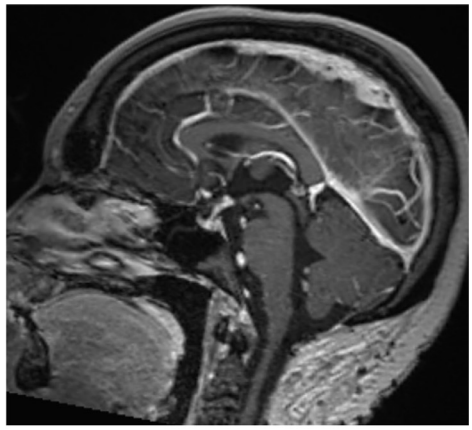


Axial T2-weighted imaging after interval resection of the intradural cervical lesion shows significant improvement of the mass effect on cord with a tiny focus of T2 hyperintensity within the left side of the cord (white arrowhead).

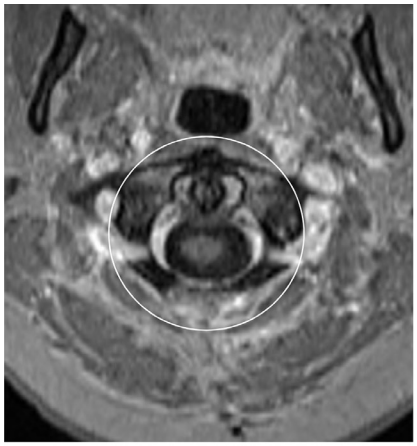
Last imaging follow-up (22 months after initial imaging)



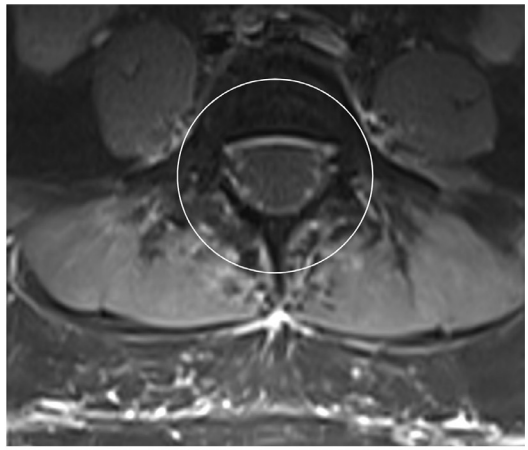
Sagittal T1-weighted imaging at last follow-(22 months after initial imaging) shows interval decrease in size of the mass in the tuber cinerum (white arrowhead).



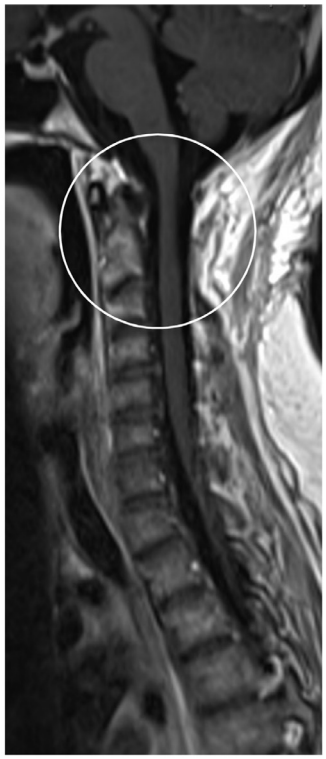
Post gadolinium enhanced sagittal T1-weighted imaging at last follow-up (22 months post-initial imaging) demonstrates no new intra-axial or extra-axial areas of enhancement.



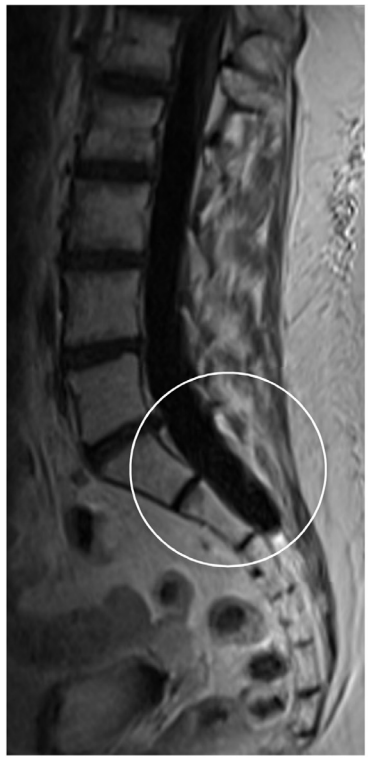
Axial gadolinium-enhanced imaging at the C1/C2 level at last follow-up (22 months post-initial imaging) demonstrates interval improvement of the mass effect caused by cervical lesion (white circle).



Axial T1-weighted fat suppressed gadolinium enhanced imaging at the L5 level at last follow-up (22 months post-initial imaging) demonstrates interval resolution of the sacral lesion (white circle).



Sagittal T1-weighted imaging at last follow up (22 months post-initial imaging) demonstrates no recurrence of the cervical lesion (white circle).



Sagittal T1-weighted imaging of the lumbar spine at last follow-up (22 months post-initial imaging) demonstrates no recurrence of the lumbar lesion (white circle).

Pathology

Histopathological analysis of the cervical intradural extramedullary mass showed malignant round blue cells arranged in sheets and lobules with occasional Homer-Wright rosettes with central neuropil, multifocal areas of necrosis, and frequent mitotic figures and apoptotic bodies with a ki67 proliferative index of 30%-40% (see Fig. 1 A, B, and F). By immunohistochemistry, there was evidence of neuronal differentiation with significant positivity for synaptophysin (Fig. 1 C), chromogranin, and Neu-N. There was diffuse immunopositivity for CD99, which focally appeared membranous in keeping with Ewing sarcoma (Fig. 1 D). The immunophenotype was however noted to be somewhat unusual for Ewing sarcoma as the tumor cells were diffusely strongly positive for cytokeratins (CK8/18, AE1:AE3) and negative for vimentin. Epithelial membrane antigen (EMA) also showed scattered foci of dot-like positivity. S100, GFAP, CD45, and markers for other types of sarcoma were negative. Molecular analysis using a pediatric sarcoma fusion gene panel by NanoString was positive for a EWSR1-FLI1 fusion, confirming the diagnosis of Ewing sarcoma.

Treatment

Resection of the spinal tumor, cervical laminectomy at C1-C2 and craniocervical decompression was performed which improved the mass effect on the cord. Given the metastatic nature of the disease, the patient was treated with a combination of chemotherapy (vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (VDC/IE)) and radiation as per the Children's Oncology Group AEWS1221 protocol. She underwent 6 cycles of induction chemotherapy and 8 cycles of consolidation chemotherapy. This was followed by 6 weeks of craniospinal radiotherapy with a boost to areas of disease. She received 54 Gy to the pituitary stalk, pineal gland, cervical spine, thoracic spine, and caudal nerve roots. Total dose to the tumor was 50.4 Gy in 28 fractions to the spine and 54 Gy in 30 fractions to the brain.

Most recent imaging as of this report was conducted 22 months after the initial mass discovery and revealed improvement of the suprasellar mass lesion with residual stable appearance of the prominence and enhancement of the pituitary stalk and tuber cinereum. There was interval improvement of the spinal lesions with no convincing residual. Clinically, at

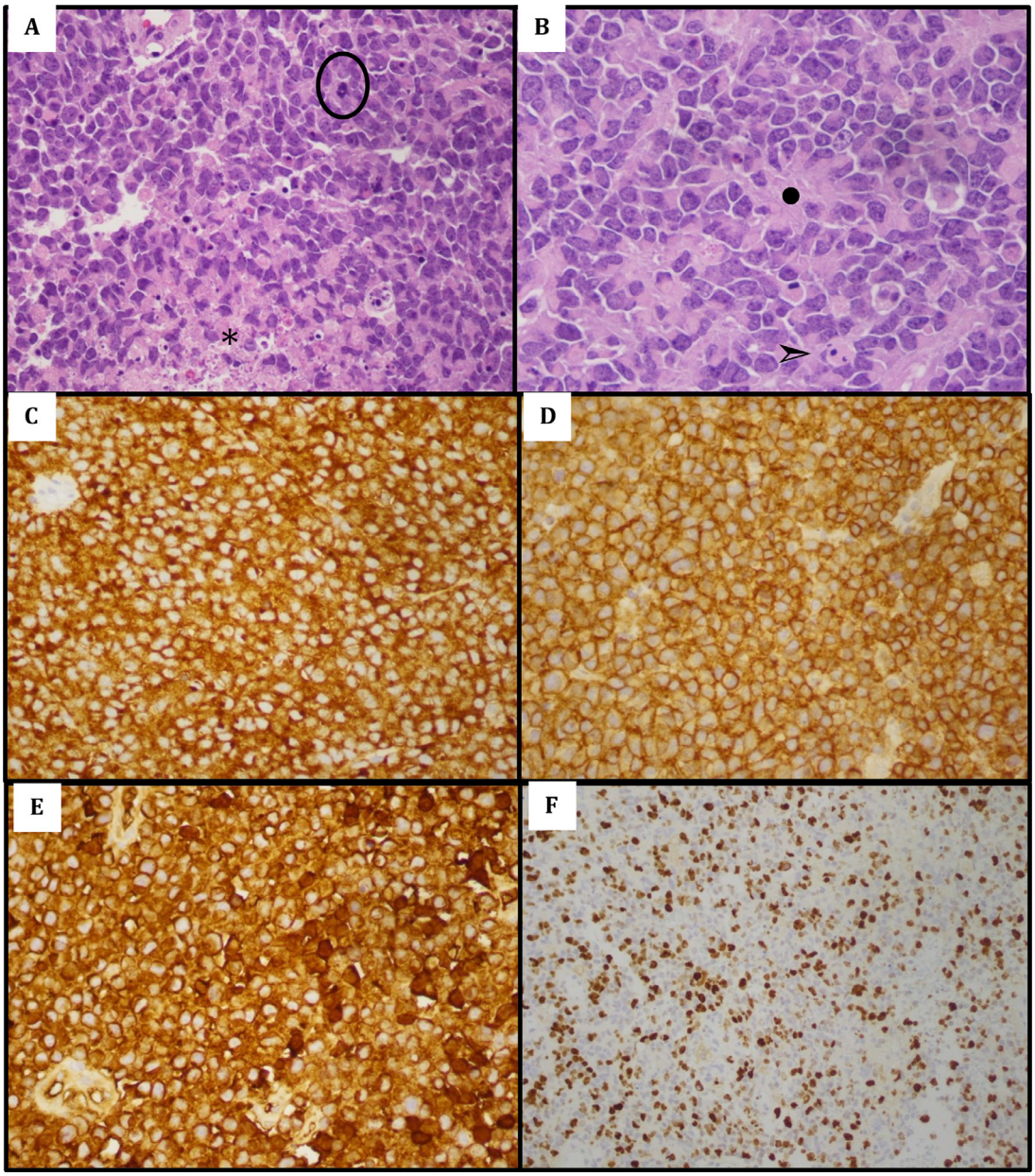


Fig. 1 – (A and B) H&E slides (A, 40x; B, 60x): Histopathology showed a densely cellular malignant small round blue cell tumor arranged in sheets and lobules with necrosis (*), Homer-Wright rosettes (•), and frequent mitotic figures (°) and apoptotic bodies (➢). In keeping with Ewing Sarcoma, immunohistochemistry showed diffuse strong positivity of the tumor cells for synaptophysin (C, 40x) and membranous positivity for CD99 (D, 40x). Interestingly, there was also diffuse strong positivity for pan-cytokeratin (D, 40x). Ki67 (F, 20x) showed a proliferative index of 30%-40%.

almost 3 years since initial imaging findings, and 25 months since completing treatment, she is stable from an oncology perspective. She continues to have limited mobility, but this is improving with intensive rehabilitation therapy.

Discussion

Ewing sarcomas are aggressive tumors that are relatively frequent in the childhood and adolescent population. However, IEES is exceedingly rare and consequently little evidence exists regarding appropriate treatment for this condition [10–12]. Existing literature in pediatric cases outline a combination of surgery, systemic chemotherapy and localized radiation as treatment [10,13]. Similarly in this case, the patient was treated with a combination of surgical resection, chemotherapy, and radiation therapy. Only six case reports exist on primary IEES in the pediatric population [10,13]. However, our case is unique in the unusual intracranial component of the tumor, which to our knowledge, has not been

previously described in a case of IEES. All previous cases described in the literature are limited to intraspinal lesions. Interestingly, in this case a mass in the brain at the level of the optic chiasm was seen on initial imaging. This well-defined mass was centered in the tuber cinereum measuring 1.3 × 1.5 × 1.2 cm. There were no other intracranial masses seen. Post treatment there is no signs of progression, and the residual lesion has remained stable as of the most recent head MRI.

The common clinical symptoms at presentation of IESS are pain, motor disturbances in upper or lower extremities, and bladder or rectal disturbances [7,14]. Pain in the extremities is a common complaint in the pediatric population and is overwhelmingly attributed to nonmalicious etiologies [15,16]. However, back and neck pain as well as nonresolving pain complaints, especially in association with neurological complaints such as paresthesia and paresis should raise concern for more malicious pathogenesis, and although rare, intraspinal malignancies should be considered. In our case, the patient's initial presentation of cervical pain and paresthesia was attributed to a nonorganic etiology. Only after worsening of the symptoms was imaging requested, but given the nonspecific findings associated with such detrimental disease processes, a clinician's threshold for imaging, especially in the context of no identifiable organic cause, should be low.

The pathological features of IEES are similar to Ewing sarcoma at other sites. In this case, there was initial diagnostic uncertainty due to the presence of only focal membranous CD99 positivity, diffuse expression of cytokeratins and negativity for vimentin. Ewing sarcoma tumors are known to express epithelial markers, but usually in a patchy or focal fashion. However, strong diffuse expression of cytokeratins has been reported to occur in some cases and this does not negate the diagnosis [17,18]. Most Ewing sarcomas of the nervous system require molecular confirmation of a FET:ETS fusion, which can be demonstrated by EWSR1 break-apart FISH assays or next generation sequencing [19].

This is the only case report of metastatic IEES in a pediatric patient [10]. Metastatic disease is a significant predictor of worse overall survival in Ewing sarcoma, and survival drops to 20%-40% in cases with metastasis compared to 60%-70% with localized disease [8,20]. This is 1 of 3 documented cases in the pediatric realm utilizing a VDC/IE chemotherapy regimen and 1 of 2 that utilized craniospinal radiation, as opposed to focal radiation [7,10,11]. Scantland et al. document a case of a 14 year old female with nonmetastatic IESS treated with surgical resection, focal radiotherapy and VDC/IE chemotherapy [10]. Similarly, Klimo et al. report a case of a 10-year-old boy with a non-metastatic intraspinal Ewing sarcoma treated with the same regimen [21]. Both patients had stable disease at 14 months and 12 months post-therapy, respectively. Kunwald et al. report the only other case of craniospinal radiation in addition to surgical resection and chemotherapy in an adolescent female. At 17 months post-treatment, they report no sequelae of disease aside from hypogonadism and no evidence of recurrent disease on imaging at 36 months [13]. In our case, despite the metastatic nature which is unlike the other cases, there is no evidence of disease recurrence at 25 months post-treatment completion.

Conclusion

Given the scarcity of information regarding this disease process and management, the aim of this case report is to contribute to our growing knowledge of the condition. Clinicians should consider aggressive treatment with curative intent using chemotherapy and radiation for cases of IEES. Moreover, a clinician's threshold for investigative imaging in the context of concerning findings with no identifiable organic causes should be low as early identification of neoplastic processes can limit the disability they induce and improve overall outcomes. Metastatic intradural extramedullary Ewing sarcoma is a very rare disease in the pediatric population. This report adds to our limited understanding, and hopefully, can improve our approach in future patients.

Patient consent

On behalf of my co-authors and I, this statement is to confirm that written and informed consent was obtained from the patient and/or their legal guardian for the presentation of their case in this case report, entitled "Case Report: Primary Intramedullary Extradural Ewing Sarcoma".

REFERENCES

[1] Grünewald TGP, Cidre-Aranaz F, Surdez D, Tomazou EM, de Álava E, Kovar H, et al. Ewing sarcoma. Nat Rev Dis Primers 2018;4(1):5.

[2] Esiashvili N, Goodman M, Marcus RB. Changes in incidence and survival of Ewing sarcoma patients over the past 3 decades: surveillance epidemiology and end results data. J Pediatr Hematol/Oncol [Internet] 2008;30(6):425–8. Available from https://journals.lww.com/jpho-online/Fulltext/2008/06000/Changes_in_Incidence_and_Survival_of_Ewing_Sarcoma.3.aspx .

[3] Franchi A. Epidemiology and classification of bone tumors. Clin Cases Miner Bone Metab 2012;9(2):5–92.

[4] Durer S, Shaikh H. Ewing sarcoma [Internet]. StatPearls Publishing, Treasure Island (FL); 2021. Available from: http://europepmc.org/abstract/MED/32644609

[5] Ludwig JA. Ewing sarcoma: historical perspectives, current state-of-the-art, and opportunities for targeted therapy in the future. Curr Opin Oncol [Internet] 2008;20(4):412–13. Available from https://journals.lww.com/co-oncology/Fulltext/2008/07000/Ewing_sarcoma__historical_perspectives,_current.12.aspx .

[6] Delattre O, Zucman J, Plougastel B, Desmaze C, Melot T, Peter M, et al. Gene fusion with an ETS DNA-binding domain caused by chromosome translocation in human tumours. Nature 1992;359(6391):162–5.

[7] Izubuchi Y, Nakajima H, Honjoh K, Imamura Y, Nojima T, Matsumine A. Primary intradural extramedullary Ewing sarcoma: a case report and literature review. Oncol Lett 2020;20(3):2347–55 2020/06/26 ed.

[8] Arpaci E, Yetisyigit T, Seker M, Uncu D, Uyeturk U, Oksuzoglu B, et al. Prognostic factors and clinical outcome of patients with Ewing's sarcoma family of tumors in adults: multicentric study of the Anatolian Society of Medical Oncology. Med Oncol 2013;30(1):469.

[9] Pappo AS, Rhabdomyosarcoma Dirksen U. Ewing sarcoma, and other round cell sarcomas. JCO 2018;36(2):79–168.
[10] Scantland JT, Gondim MJ, Koivuniemi AS, Fulkerson DH, Shih CS. Primary spinal intradural extraosseous ewing sarcoma in a pediatric patient: case report and review of the literature. Pediatr Neurosurg 2018;53(4):222–8.
[11] Yan Y, Xu T, Chen J, Hu G, Lu Y. Intraspinal Ewing's sarcoma/primitive neuroectodermal tumors. J Clin Neurosci 2011;18(5):6–601.
[12] Paterakis K, Brotis A, Tasiou A, Kotoula V, Kapsalaki E, Vlychou M. Intradural extramedullary Ewing's sarcoma: a case report and review of the literature. Neurol Neurochir Pol 2017;51(1):106–10.
[13] Kunwald M, Straszek CL, Bjarkam CR, Ettrup MS, Skajaa T, Thomsen JL, et al. Intradural extramedullary Ewing sarcoma in an adolescent female. Adolesc Health Med Ther 2022;13:39–43.
[14] Kartal A, Akatlı A. Primary intradural extraosseous Ewing's sarcoma in a young child. Child's Nervous System 2016;32(3):409–10.
[15] Tan A, Strauss VY, Protheroe J, Dunn KM. Epidemiology of paediatric presentations with musculoskeletal problems in primary care. BMC Musculoskelet Disord 2018;19(1):40.
[16] King S, Chambers CT, Huguet A, MacNevin RC, McGrath PJ, Parker L, et al. The epidemiology of chronic pain in children and adolescents revisited: a systematic review. Pain 2011;152(12):2729–38.
[17] Gu M, Antonescu CR, Guiter G, Huvos AG, Ladanyi M, Zakowski MF. Cytokeratin immunoreactivity in Ewing's sarcoma: prevalence in 50 cases confirmed by molecular diagnostic studies. Am J Surg Pathol [Internet] 2000;24(3):410–16. Available from https://journals.lww.com/ajsp/Fulltext/2000/03000/Cytokeratin_Immunoreactivity_in_Ewing_s_Sarcoma_.10.aspx .
[18] Woestenborghs H, Debiec-Rychter M, Renard M, Demaerel P, Van Calenbergh F, Van Gool S, et al. Cytokeratin-positive meningeal peripheral PNET/Ewing's sarcoma of the cervical spinal cord: diagnostic value of genetic analysis. Int J Surg Pathol Jan 2005;13(1):93–7.
[19] Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro-oncol 2021;23(8):1231–51.
[20] Cash T, Krailo MD, Buxton A, Pawel B, Healey JH, Binitie O, et al. Long-term outcomes in patients with localized Ewing sarcoma treated with interval-compressed chemotherapy: a long-term follow-up report from Children's Oncology Group study AEWS0031. JCO. 2022;40(16_suppl):11505.
[21] Klimo P, Codd PJ, Grier H, Goumnerova LC. Primary pediatric intraspinal sarcomas: report of 3 cases. J Neurosurg 2009;4(3):222–9.