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Case report

Primary Ewing sarcoma of the axis-C2: A case report and the review of the literature

Kyriakos Paraskeva [a], *Dimitrios Giakoumettis* [b], *Ioannis Nikas* [d], *George Georgoulis* [c], *George Sfakianos* [c], *Marios S. Themistocleous* [c,*]

[a] *Neurosurgical Clinic, Nicosia General Hospital, Cyprus*
[b] *Department of Neurosurgery, University of Athens Medical School, "Evangelismos" General Hospital, Athens, Greece*
[c] *Department of Neurosurgery, Children's Hospital "Aghia Sophia", Athens, Greece*
[d] *Imaging Department, Children's Hospital "Aghia Sophia", Athens, Greece*

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ABSTRACT

Introduction: Neck pain and torticollis are common symptoms in the pediatric population that rarely requires further investigation. However, in case symptoms persist, then a more meticulously approach should be considered. Underlying conditions such as infections, neck injury, autoimmune disorders or even cervical spine cancer should be excluded from diagnosis. Cervical spine cancer is a rare neurosurgical entity in the pediatric population and even rarer is atlantoaxial Ewing's sarcoma. In this report, we present a rare case of primary Ewing's sarcoma of the axis.

Case report: A 3.5-year-old female with progressive neck pain and intermittent episodes of torticollis was referred to our outpatient clinic. Imaging studies revealed a malignant tumor located on C2 vertebra. Diagnosis of Ewing's Sarcoma was confirmed via open biopsy and the patient was treated with Euro-EWING 99 chemotherapy.

Conclusion: Pediatric neck pain and/or torticollis should raise high suspicion for malignancy of cervical spine. Modern diagnostic means and techniques can assist in the screening and diagnosis of these tumors.

* *Corresponding author.*
E-mail address: mthemistocleous@gmail.com (M.S. Themistocleous).

Abbreviations: BSAP, B-cell-specific activator protein; CD, cluster of differentiationv; CT, computed tomography; EWS/FLI, oncogenic transcription factor; FLi-1, friend leukemia integration 1 transcription factor; INI-1, integrase interactor 1; MRI, magnetic resonance imaging; NCAM, neural cell adhesion molecule; PAX-5, paired box protein; PNET, primitive neuroectodermal tumor; RT-PCR, reverse transcription polymerase chain reaction; TdT, terminal deoxynucleotidyl transferase.

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1. Introduction

Asymmetrical head and/or neck position with or without neck pain constitutes torticollis. It can be divided in many categories depending on the cause such as traumatic, congenital, infectious, cancerous, spasmodic, drug induced, psychogenic, ocular, osseous, vascular, toxic or metabolic [1]. However, neck pain without accompanying symptoms in a pediatric patient rarely requires further investigation. In the occasion where the symptoms persist, underlying conditions such as meningitis, serious neck injury, autoimmune disorders or even cervical spine cancer may have to be considered and excluded from diagnosis [2]. In this report, we present a rare case of torticollis with neck pain due to primary Ewing's sarcoma of the axis.

Ewing's sarcoma belongs in a tumor category known as the Ewing's Family tumors. It is primitive neuroectodermal tumor and constitutes 3% of all pediatric malignancies with a male to female ratio of 1.6:1. Peak incidence is during the second decade of life and most common presenting sites include the pelvis, femur, humerus, ribs and clavicle [3]. Ewing's sarcoma can also be found in the spine, where the most common location is the sacrococcygeal region in contrast to cervical spine localization.

2. Case report

A 3.5-year-old girl presented in our outpatient clinic complaining of progressive neck pain and intermittent episodes of torticollis with relapses and remissions. The symptoms had initiated the past year. Since then the child had visited several times the emergency department of pediatric institutions and was usually referred to the Orthopedic Department with the diagnosis of spasmodic torticollis only to receive analgesics without proceeding to any further diagnostic tests. A detailed history was obtained from the parents, who reported mood changes, loss of appetite and mild to moderate pain induced during head rotation. Family history was unremarkable for congenital and hereditary diseases. Clinical examination revealed only torticollis without any neurological signs. Nevertheless, persistency of the symptomatology raised the suspicion of neck injury or infection and therefore blood work and imaging studies were performed. Eye exam was also performed in order to rule out diplopia induced pseudotorticollis. Cervical X-rays revealed C2 bone structural abnormalities. Routine laboratory results were within normal limits and ultrasonography of the neck revealed no abnormal enlargement of lymph nodes. An MRI scan of the cervical spine was performed revealing a space occupying solid lesion on C2 vertebral body with infiltration of lamina, pedicles, facet joints, transverse processes and with intramedullary extension (Fig. 1). Contrast enhanced Computed Tomography showed enlargement of C2 vertebra, destruction of its architecture with focal lytic and sclerotic areas surrounded by soft tissue mass compressing the spinal cord (Figs. 2 and 3).

Radionuclide bone scan with Technitium-99m and full-body CT scan were performed to detect any other foci. The CT scan displayed increased activity at the level of C2 only during the 3rd phase of infusion while CT staging excluded foci of primary disease, other than C2. Hematological malignancies were ruled out by bone marrow biopsy. After setting the diagnosis of cervical spine tumor a surgical biopsy was performed with standard posterior approach. Since there were no neurological deficits a conservative approach of surgical biopsy was chosen in contrast to reconstructive surgery and instrumentation. The rationale behind this decision lies in the location of the sarcoma, the necessity to preserve vital anatomical structures and mostly in the need to gather more information of the nature of the tumor before deciding to perform a major surgical operation to such a young patient.

Pathology revealed focal infiltration by malignant small round cellular neoplastic cells as well as increased cellularity

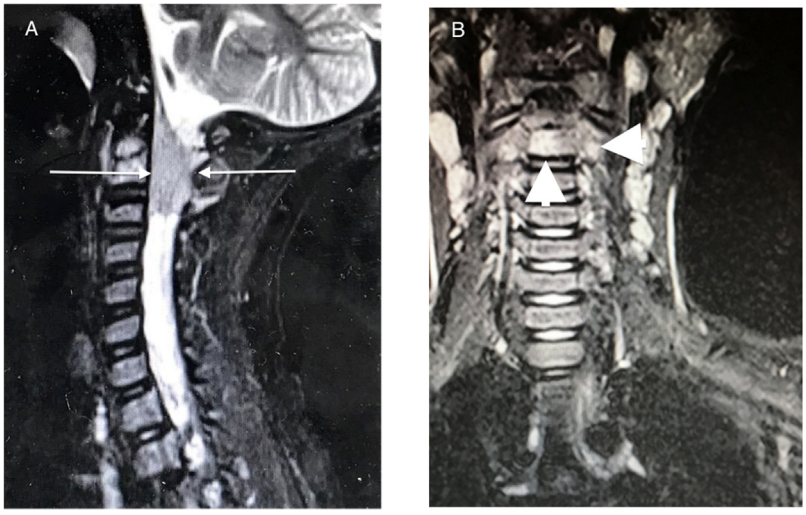

Fig. 1 – MRI T2 weighted images with *fat suppression*. (a) Sagittal and (b) coronal images of the cervical region demonstrated the intramedullary extension of the lesion (white arrows), and the infiltration of the vertebral body of axis and transverse process spanning (arrowheads).

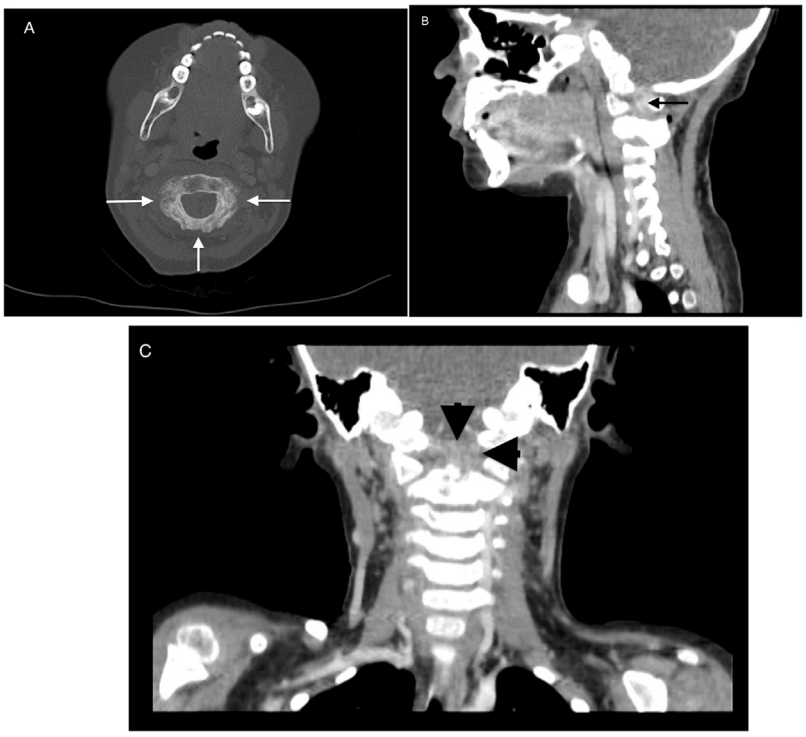

Fig. 2 – Contrast enhanced Computed Tomography. (a) Axial, (b) sagittal and (c) coronal images of the cervical spine reveal focal lytic and sclerotic areas (white arrows), destruction of Atlas posterior arch (black arrow) and odontoid process erosion, by soft tissue mass (black arrowheads).

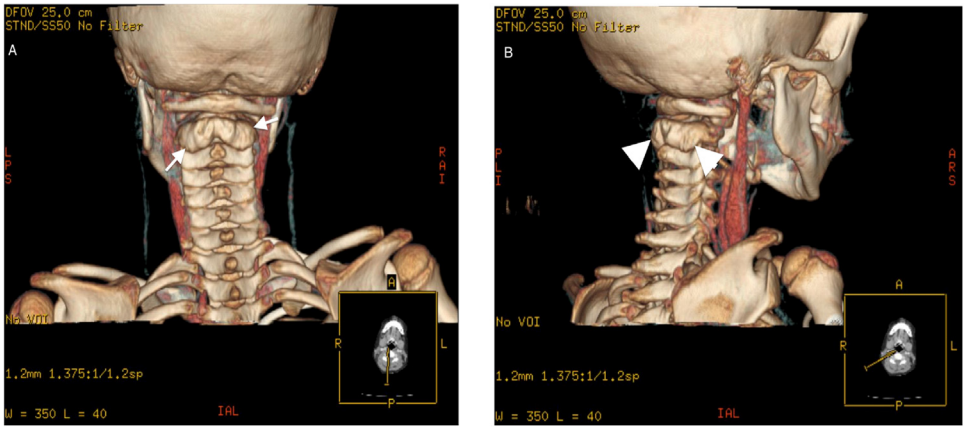

Fig. 3 – 3D reconstruction computed tomography. (a) Posterior and (b) posterolateral view of C2 vertebra discloses enlargement and destruction of C2 architecture (white arrows), rotation and instability (arrowheads).

with absence of Homer – Right type rosette. Immunohistochemical evaluation revealed cytoplasmic positivity for CD99/MIC-2, diffuse protein expression of FLi-1, focal expression of CD56/NCAM < 5% and retained INI-1 protein expression > 99% of neoplasmatic cell core. Synaptophysin, Desmin, GFAP, Ceratin, TdT, CD34, PAX-5/BSAP, CD3, CD1a expression was not detected. Genetic analysis (RT-PCR) detected hybrid gene EWS/FLI from chromosomal translocation t (11;22) (q24;q12). The presence of EWS gene exon 7 and gene FLI exon 6 translocation, confirmed the diagnosis of Ewing's sarcoma of the axis.

The young patient was referred to the oncology department in order to receive euro EWING 99 chemotherapy. The child was eligible for this type of treatment, according to the criteria of histologically confirmed Ewing Tumor (Ewing's sarcoma or peripheral PNET) of bone or soft tissue. The eligibility criteria comprise of i) age less than 50 years, ii) completed pre-treatment investigations allowing prognostic group definition, iii) no previous chemotherapy, iv) informed consent according to national guidelines prior to study entry and finally, v) appropriate ethical committee approval (EURO – E.W.I.N.G 99 trial, 2006).

Table 1 – Clinical characteristics and treatment approach of previously reported cases of Ewing's Sarcoma including the present case.

Author	Year	Period of evaluation	Number of patients	Mean age	Clinical presentation	Protocol of treatment applied by each Institution
Present case	2017	2017	1	3.5	• Neck pain • Torticollis • Mood changes • Loss of appetite • Pain induced during head rotation	1) Surgical Biopsy 2) Euro – EWING 99 Chemotherapy
Hao et al. [4]	2010	–	1	15	• Neck pain and tenderness • Shoulder pain • Right upper extremity numbness • Right hand weak grasp force • Limitation of motion in the cervical vertebra	1) Surgical excision and spine stabilization 2) Postoperative Multiagent Chemotherapy 3) Radiotherapy
Gradoni et al. [5]	2010	1996–2009	3	9.33	• Tender facial swelling • Recurrent otalgia and facial nerve palsy • Frontal swelling	1) Surgical biopsy and CT/Resection R0 after CT 2) Surgical biopsy and CT/additional RT ts 3) Surgical biopsy and CT/Resection R0 after CT
Chhabra et al. [6]	2014	–	1	24	• Swelling over the left mastoid region • Sensory and motor weakness in the Left upper limb	1) Partial resection 2) CT & Local RT
Aydin et al. [7]	2013	–	1	7	• Neck pain • Intermittent low grade fever • Skin pallor • Restricted neck movement • Diffuse tenderness in the upper cervical spine • Left-sided torticollis • Bilateral positive Babisnki sign	Local RT
Allam et al. [8]	1999	1975–1996	24	16.5	• Painful swelling of the maxilla • Pain and tenderness • Visual problems • Anemia/Fever	• Biopsy & systemic CT plus local RT (58%) • Complete or incomplete surgical excision & postoperative CT (21%) • Systemic CT (92%) • RT (83%) • Biopsy (67%) • Incomplete excision (25%) • Complete excision (8%)
Dini et al. [9]	2006	–	1	18	• Progressively worsening back pain • Lower extremity weakness (frankel B) • Bladder dysfunction • Bilateral paraspinal tenderness • Decreased sensation below the level L1	1) Combined subtotal vertebrectomy and laminectomy with anterior reconstruction and posterior instrumentation 2) Postoperative CT/ Additional RT
Gopalakrishnan et al. [10]	2012	–	1	16	• History of mild intermittent low back pain • Bilateral spastic paraplegia with only a flicker of movement at the right ankle joint • Positive Beevor's sign • Hypoesthesia below the level of D10 dermatome • Exaggerate muscle stretch reflexes • Bilateral extensor Babinski response	1) Radical excision 2) Adjuvant systemic CT and Local RT

Table 1 (*Continued*)

Author	Year	Period of evaluation	Number of patients	Mean age	Clinical presentation	Protocol of treatment applied by each Institution
Burnet et al. [11]	1997	1967–1986	96	16	• Metastatic disease (22.9%) • Fever or malaise (4.16%) • Central nervous system involvement (0%)	1) Diagnostic biopsy (100%) 2) Definitive surgical resection (19.8%) 3) Amputation (5.2%) 4) CT (84.3%) 5) RT (86.5%)
Kaspers et al. [12]	1991	–	1	7	• Low back pain • Loss of anal sphincter function • Urinary retention • Flaccid paresis of the legs • Absent patellar and Achilles tendon reflexes • Extensor plantar reflex on the left	• CT according to CESS-86 protocol • 4 cycles of CT for 9 months
Shimada et al. [13]	1988	1972–1978	15	18.13	• Left leg pain (26.66%) • Right leg pain (6.66%) • Back pain (60%) • Incomplete spinal cord compression syndrome plus neuralgia (6.66%) • Left thigh pain (6.66%) • Left hip pain (6.66%) • Sciatica (6.66%) • Left intercostal pain (6.66%) • Generalized pain (6.66%) • Dropfoot (20%) • Unilateral leg paresis (26.66%) • Bilateral leg paresis (33.33%) • Dysbasia (13.33%) • Paresthesia (26.66%) • Hypesthesia (20%) • Numbness (13.33%) • Urinary retention (13.33%) • Dysuria (6.66%) • Fecal incontinence (6.66%)	• Diagnostic biopsy only (6.66%) • Biopsy plus CT & RT (20%) • Biopsy plus CT & RT and Autologous Bone Marrow Transplantation (6.66%) • Complete surgical resection plus RT (6.66%) • Complete surgical resection plus CT & RT (20%) • Complete surgical resection as definitive treatment (6.66%) • Partial surgical resection plus CT & RT (40%) • Partial surgical resection plus CT (6.66%)
Venkateswaran et al. [3]	2001	1962–1999	33 of 344	13.3	• Pain (97%) • Localized pain (72.7%) • Radiating pain (66.7%) • Neurologic deficit (93.9%) • Motor deficit (81.8%) • Sensory deficit (57.6%) • Bladder dysfunction (42.4%) • Bowel dysfunction (27.3%)	• Only diagnostic biopsy (39.39%) • Laminectomy plus partial or subtotal tumor resection (54.54%) • Tumor surgical resection without laminectomy (6.06%) • Combination CT (100%) RT (100%)
Paterakis et al. [14]	2017	–	1	31	• Back pain • Right leg progressive paresis (muscle strength 3/5) and causalgia • Right leg decreased sensation • Cauda equina syndrome	1) L1 & L3 Laminectomy plus gross total surgical resection of the tumor 2) Postoperative Multiagent CT 3) Revision surgery with subtotal resection regarding local recurrence after 2 years 4) Postoperative CT
Kara et al. [15]	2004	–	1	18	• Fever • Headache • Back pain	• The patient underwent surgery and diagnostic biopsy was performed
Coulibaly et al. [16]	2015	–	1	16	• Progressive weakness of both lower extremities • Inability to walk • Progressive low back pain • Bilateral leg pain and paresthesia • Urinary retention • Bilateral positive Babinski reflex • Motor power 2/5 • Sensory level at T12 for all the modalities of sensation	1) Open biopsy and partial surgical excision 2) Postoperative CT & local RT

Table 1 (*Continued*)

Author	Year	Period of evaluation	Number of patients	Mean age	Clinical presentation	Protocol of treatment applied by each Institution
Menezes et al. [17]	2014	1996 – 2010	1 of 23	11	• Neck pain • Headache • Fever • Lump left neck	1) Selective angiography & coil embolization 2) CT – guided biopsy 3) CT & RT 4) Bone Marrow Transplantation
Electricwala et al. [18]	2016	–	1	2	• Progressive weakness of both lower extremities • Difficulty in standing and walking • Progressive loss of bowel and bladder function • Paraspinal fullness • Complete loss of power below the level of knee joint in both lower extremities • Reduced muscle tone • Decreased sensations below the level of L3 dermatone in both lower limps • Reduced perianal sensation • Bilateral absence of Babinski response	1) Urgent laminectomy and diagnostic biopsy 2) Postoperative Multiagent CT & RT
Nair et al. [19]	2015	2009–2013	6	9.9	1) - Back pain and leg weakness - Paraspinal tenderness at D2–D6 levels - Paraparesis (power grade 2/5) 2) - Progressively worsening back pain with acute paraplegia and urinary retention - D4 level sensory loss - Paraparesis (power grade 1/5) 3) - Inability to walk - Urinary retention - Shoulder and back pain - Bilatteral paraparesis (power grade 3/5) 4) - Leg pain and paresthesia - Difficulty in walking - Acute paraplegia (power grade 0/5) - Urinary retention - Sensory loss below D2 level 5) - Difficulty in walking - Back pain - Acute paraplegia (power grade 0/5) 6)- Difficulty in walking - Back & leg pain / muscle weakness - Severe painful immobility of legs - Motor power 3–4	1. a) U/S-guided biopsy plus 12 weeks of CT b) Debulking surgery c) Local RT & neo-adjuvant CT 2. a) CT-guided biopsy b) Local RT & neo-adjuvant CT 3. Surgical slides review: a) Thoracotomy and surgical excision b) Local RT & neo–adjuvant CT 4. a) CT-guided FNA b) Local RT & neo-adjuvant CT 5. Sugical slides review: a) Laminectomy and tumor surgical excision b) Local RT & neo-adjuvant CT 6. a) Open biopsy b) Local RT & neo-adjuvant CT
Iacoangeli et al. [20]	2012	–	1	58	• Progressive worsening, nocturnal bilateral buttock cramping • Left predominant back pain • Left leg paresthesias with tingling • Diffuse tenderness in the lower back • Restriction of the active flexion-extension motion • Positive passive straight leg-raising test more than 45° • Low grade fever	1) Gross total surgical excision via Lateral Retroperitoneal approach and reconstruction plus lateral fixation 2) RT & Concominant CT 3 weeks after surgery

Table 1 (*Continued*)

Author	Year	Period of evaluation	Number of patients	Mean age	Clinical presentation	Protocol of treatment applied by each Institution
Holland et al. [21]	2015	–	1	53	• Intermittent left upper extremity pain radiating down the posterior side to the left proximal wrist • Muscle loss profoundly in the left biceps & deltoid • Weight loss (10 pounds) • Generalized fatigue • Right and Left upper limb decreased muscle strength	1) C6-C7 laminotomy with decompression of the left C7 nerve root and diagnostic biopsy 2) Postoperative CT & RT
Garcia - Perez et al. [22]	2013	–	1	5	• Increased volume of the left mastoid bone • Torticollis • Balance disorders • Discoordinated movements • Positive Romperg sign • Left horizontal nystagmus • Head deviation toward the right side	1) Partial excision of the lesion 2) 2nd operation one month later (the patient died regarding severe postoperative respiratory complications)
Gulati et al. [23]	2011	–	1	11	• Low intensity non radiating pain • Low grade fever • Head deviation toward the right side • Diffuse tenderness in the upper cervical spine • Restriction of active neck motion • Torticollis toward the right side • Painful passive neck movements • Babinski sign present bilaterally • 3 weeks after discharge the patient presented with severe neck pain, upper limps paresthesias, occasional urine incontinence, tenderness, neck rigidity, quadriparesis and upper motor neuron signs	1) Bed rest with Grutchfield long traction and antitubercular therapy 2) 3 weeks later the patient readmitted and underwent an urgent partial anterior decompression and posterior occipitocervical fusion plus surgical biopsy from the lamina of C2 vertebra 3) Postoperative Multiagent CT & RT had to stopped because of wound dehiscence and infection. Patient succumbed to respiratory complications
Marco et al. [24]	2005	1971–2000	13	19	• Local or radicular pain (100%) • Local back or neck pain (69.23%) • Local back or neck pain plus radicular pain (30.77%) • Monoparesis (23%) • Paraparesis with cauda equina syndrome (30.77%) • Bladder dysfunction (15.38%)	• VAC (Vincristine, Adriamycin, Cyclofosfamide)-based CT (100%) • Actinomycin supplementation (30.77%) • RT (100%) • Multilevel laminectomy (61.5%) • Single – level laminectomy (15.38%) • Partial tumor surgical resection (76.92%)
Ilaslan et al. [25]	2004	1936–2001	53 of 1277	–	• Local pain (100%) • Neurologic deficits (40%)	• Local RT (100%) • CT (70%) • Surgery (47.16%) • Bone marrow Transplantation (3.77%)

CT = chemotherapy; RT = radiotherapy; ts = radiation delivered to the tumor site; R0 = resection with histologically clear margins.

3. Literature review

We reviewed 23 reported cases of musculoskeletal Ewing's sarcoma including more than 250 patients that were published since 1936. The total number of patients was 1816. Their and our patient's clinical presentation and applied treatment protocol from each institution are summarized in Table 1.

4. Discussion

Persistence of neck pain and torticollis in a young patient raise suspicion of a more serious underlying cause. The triad of local cervical pain with point tenderness, limitation of motions and/or neurological deficit in a pediatric patient who is unable to present a precise history of symptoms, prompts for further

evaluation. Cervical pain and torticollis in these ages mainly attribute to infection, muscle spasm and local trauma. However, in rare occasions they can be a result of congenital deformities or even malignancies.

In the aforementioned case, neck pain and torticollis could be attributed to regional anatomy disruption due to focal tumor pressure and infiltration. First of all, atlantoaxial rotatory subluxation developed from osseous or ligamentous abnormalities may have resulted in chronic elongation and contraction of sternocleidomastoid muscles thus promoting the abnormal neck posturing. Furthermore, erosion of the atlantoaxial joint as a result of bony destruction may cause cervical pain and tenderness which may progress to cervical instability requiring instrumentation. Last but not least, tumor infiltration might affect C1 nerve roots adding a neuropathic component to the pain.

Differential diagnosis of cervical spine lesions included Giant cell tumor, Aneurysmal bone cyst, Langerhans cell Histiocytosis, Vertebral Hemangioma, Ewing's sarcoma, Chordoma, Eosinophilic granuloma, Malignant Lymphoma, Metastatic Embryonal Rhabdomyosarcoma, Neuroblastoma and Bacterial infection [17,26–28]. From a histopathological point of view most Lymphomas and Rhabdomyosarcomas are usually challenging in differential diagnosis, where positive leukocyte common antigen and positive actin, desmin and myoglobin respectively are needed to set the diagnosis [6,29,30]. The rest entities from the list are usually diagnosed by their distinctive histopathological pattern and by series of immunohistochemical markers, which most of the times include several antigens and monoclonal antibodies [31–34]. Last but not least, the possibility of metastatic disease was ruled out by CT imaging study.

Ewing's sarcoma of the cervical vertebra is a rare neurosurgical entity that draws attention usually when neurologic signs are present [10]. There are several case reports and case series of intraosseous [4,8,9,24,35] and extraosseous Ewing's sarcoma of the spine [12,14], but very few refer to its presence on C2 vertebra [7]. Ewing's sarcoma can be managed medically with systemic therapy, which consists a multiagent chemotherapy including doxorubicin, vincristine, etoposide and cyclophosphamide and/or ifosfamide [3]. With the addition of systemic therapy during the last 3 decades, prognosis has been significantly improved [36–38]. Nevertheless, undoubtedly the presence of metastatic lesions at the time of diagnosis is a poor prognostic factor in terms of survival. Radiation therapy plays also a great role in the therapeutic strategy of Ewing's sarcoma typically concerning sites that are difficult to approach with surgical resection [11]. The role of surgery is limited to controlling the disease locally, preventing any neurological deterioration and stabilizing, if needed, the spine [5,39]. Due to the fact that Ewing family of tumors is a group of highly aggressive tumors, a multidisciplinary approach is needed [40]. Therefore, chemotherapy and radiation therapy, combined with vertebral resective and reconstructive surgery when needed are currently the most promising treatment strategy.

5. Conclusion

Young patients often are unable to report an accurate medical background; therefore, this might be misleading to the examining physician. In order to extract important information in this range of age, besides high clinical suspicion, routinely performed diagnostic tests should be considered in daily clinical practice. Pediatric diseases are frequently devious, but early diagnosis may be vital for a better prognosis considering life expectancy.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

Conflict of interest

None declared.

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