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Review Article

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Sacral Diffuse Large B-Cell Lymphoma presented as Cauda Equina Syndrome: A Case Report and Systemic Review.

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Abstract

Background: Cauda equina syndrome secondary (CES) to primary sacral diffuse large B cell lymphoma (DLBCL) is an uncommon condition, and few cases have been reported in the medical literature. Our three research questions were: What is the current frequency of DLBCL presenting as CES? What is the group of age most affected? What is the most typical modality of therapy reported in the literature? How many patients presenting a primary non-Hodgkin sacral tumour are reported in the medical literature?

Literature Review: We extensively searched the EMBASE, Medline, Scopus online databases, Google Scholar, Science Direct, WHO database, Scielo, LILACS, BIREME, and Cochrane library to identify articles referred to CES, DLBCL, investigations and therapy from January 1, 1995, to April 30, 2021. We found 22 publications related to these topics. The age group most affected was 40-49- years old. The most standard modality of therapy was rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP). A 24-year-old male previously well with two months history of weakness, numbness, and cramps of the lower limbs. Paresthesias more localized to the inner thighs and around the buttocks. There is no radicular pain, but local pain in the sacral region is severely aggravated on lying in the supine position, bending forward, and alleviating in a left lateral position on prone position. MRI and immunohistochemistry studies confirmed atypical large tumour cells positive for common leukocyte antigen (LCA) and CD20 (score 4+), while negative for CD138, CD30, and CD3.With swift response to methotrexate, Adriamycin, 5-fluorouracil, vincristine, and prednisolone regimen.

Discussion and Conclusions: After an extensive literature review related to these topics, we did not find a reported case like our patient. We discussed the association of the *Epstein-Barr virus* and DLBCL tumour and hypothesized about the pathogenesis of the DLBCL.

Keywords: Cauda equina • Sacral B-cell lymphoma • Non-Hodgkin lymphoma • Diffuse large B cell lymphoma • primary sacral tumours• Primary epidural Non-Hodgkin's lymphoma

Abbrivations

CMV: Cytomegalovirus; CSF: Cerebro Spinal Fluid; CT: Computed Tomography; DFS: Disease Free Survival; DLBCL: Diffuse Large B Cell Lymphoma; DWI: Diffusion weighted; EBV: Epstein Barr Virus; FDG-PET: 18F-Fluoro-2-Deoxy-D-Glucose-Positron emission tomography; FLAIR: Fluid Attenuated Inversion Recovery; FT4: Thyroxine; GABA: Gamma Amino Butyric Acid; GM: Grey Matter; HAI: Human Albumin Infusions; Hb: Haemoglobin; HSV: Herpes Simplex Virus; LDL: Low Density Lipoprotein; MCS: Microscopy, Culture, Sensitivity; MRI: Magnetic Resonance Imaging; NMACH: Nelson Mandela Academic Central Hospital; PCR: Polymerase-Chain Reaction; POC: Point-of-care; R-CHOP regimen: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone; RT-PCR or PCR: Reverse Transcriptase Polymerase Chain Reaction; TSH: Thyroid Stimulating Hormone; VDRL: Venereal Disease Research Lab Test; VZV: Varicella-Zoster Virus; WM: White matter; WSU: Walter Sisulu University

Introduction

Paraplegia secondary to compressive myelopathy/cauda equina by primary epidural non-Hodgkin's lymphoma (PENHL) is an uncommon cause of paralysis of the lower limbs; few cases have been reported in the medical literature. Clinically it can be suspected in patients presenting a history of lower back pain (LBP) followed by clinical signs of spinal cord compression (SCC) confirmed by imagenology [1].

PENHL occur in almost 2% of all the lymphomas [2, 3], while other authors reported 6.6 % [4, 5] and 11 % [6], respectively. Plain X-rays of the spine are invariably standard, with no evidence of bone destruction [1]. Primary spinal diffuse large B cell lymphoma (DLBCL) causing paraplegia as the first clinical manifestation has been reported by other authors recently [7,8]. PENHL has usually seen inpatient among 40-50 years old with a male-female ratio of 1.6:1, three-year overall survival (81.1%) and 46.3% disease-free survival [9-12].

Cauda equina syndrome (CES) secondary to compressive myelopathy by PENHL is relatively uncommon as well.

Although some cases have been reported, most of them are around the fifth decade of life [13-16]. These authors also agreed most expected location of PENHL in the mid-thoracic spine (69%), followed by the lumbar (27%) and then a cervical segment of the cord (4%) [13-16]. Taylor et al. reported that a 66-year-old man presented a PENHL of the lumbar spine and recommended high-dose methotrexate plus intraventricular rituximab based on their results [17]. In 2016, a 37-year-old man with a three-history of paresthesias and paraplegia due to PENHL mimicking schwannoma of the lumbar spine was reported in the literature [18]. Other authors published more cases of PENHL located at the lumbosacral region [19,20]; this problem remains uncommon.

Recently, Liu et al. [21] published a population-based study of 2558 cases presenting primary lymphoma of bone (PLB) confirmed between 1973 and 2016. These authors reported that the most involved site was spine bone (n=767, 29.98%), the most common histological subtype of lymphoma found was diffuse large B-cell lymphoma (n=1703, 66.58%), and

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in a second place the follicular lymphoma (n=166, 6.49%). Male (51.1%) were more affected than female (48.9%). Age group of 60-80 (39.9%), 40-60 (26.3%), and 20-39 (18.1%). The most frequent type of lymphoma was non-Hodgkin lymphoma (99.1%) compared with Hodgkin lymphoma (0.9%). Most cases did not receive a surgical approach (75.8%), and the rest was treated surgically (24.2%).

Received chemotherapy 75.9%, and 54.4% of the overall group treated with radiotherapy as well. Xiong et al. [22] studied the prognostic factor of PENHL in 36 Chinese patients and concluded that located lesion on the thoracic spine region (HR=4.629, 95% CI=[1.911, 31.667], P=0.042 for OS) had significant poor prognostic factor compared with other locations, and combined modality treatment (HR = 12.697, 95% CI=[2.664, 48.612], P < 0.0001 for DFS) were followed by poor survival. A 72-year-old female anecdotic case with diffuse large cell NHL presenting like acute motor-sensory axonal neuropathy (a variant of Guillain-Barre-Syndrome) has been reported to the literature as a unique publication [23]. PENHL located in the lower part of the spine bone with symptoms and signs of cauda equina compression is an uncommon presentation. In 2014, Dayama et al. [24] published a 66-year-old male patient presenting a follicular NHL causing paraplegia without lymphadenopathy or hepatosplenomegaly. In the following year, Cho et al. [25] reported a 29-year-old male in 2015. His case was characterized by a tingling sensation on both buttocks that was radiating to his calf bilaterally. MRI with IV contrast confirmed a well-defined extradural tumour at the mid L5 to mid S2 level.

The anatomopathological study showed a grade 2 Non-Hodgkin's follicular lymphoma. Although paraplegia is more likely associated with high-grade B cell lymphomas, these authors concluded that attending doctors should consider this exceedingly rare disease in the differential diagnosis of patients with similar clinical manifestations. Recently, Chigurupati et al. reported a 36-year-old man with primary sacral non-Hodgkin lymphoma (PSNHL) and reviewed the medical literature [26].

Our research questions

- What is the current frequency of DLBCL presenting as CES?
- What is the group of age most affected?
- What is the most typical modality of therapy reported in the literature?
- How many patients presenting a primary NHL sacral tumour are reported in the medical literature?

Literature Review

We extensively reviewed the available medical literature looking for publications related to CES like our case, age groups and response to treatment reported in the medical literature.

Literature search strategy

We utilized the PRISMA (Preferred Reporting Items for Systemic review and Meta-Analysis) statement and the PRISMA checklist for the literature review. We searched from January 1, 2010, up to March 30, 2021. We included all studies (case reports, case series, and observational cohort studies) that reported sacral NHL, paraplegia, cauda equina syndrome sacral tumours during the initial search on Google Scholar and then the search was extended to the following databases: EMBASE, Medline, Scopus online databases, Science Direct, WHO database, Scielo, LILACS, BIREME, Web of Science and Cochrane library identify articles using the string: cauda equina syndrome(All fields), flaccid paraplegia(All fields), lymphomas(All fields), sacral tumours(All fields), non-Hodgkin lymphoma(All fields), Hodgkin lymphoma, primary, diffused cell B lymphoma (All fields) and all items about sacrum OR sacralization OR sacral mass OR sacrum (All fields), where is the PubMed wildcard for all word ending or beginning. We did not include other neurological issues beyond the scope of the current work.

Study and cohort selection

We select all publications (case reports, case series, clinical trials, and observational cohort studies) reporting cauda equina syndrome, flaccid paraplegia due to sacral tumours, sacral lymphomas, age group, modality of therapy and response to treatment written in English, Spanish, and Portuguese were extracted, and selected data were tabulated.

Between January 1, 1995, and April 30, 2021, our literature search yielded 658 publications.

After removing articles by title and abstract contains without reporting PNHL, DLPNHL, sacral lymphoma or CES, we retained 152 unique records from Medline and Scopus plus other17 publications from other databases. Removing duplicate reports, we kept 169 items; then, after screening full text, we removed 139 publications, plus other 12 no well-investigated/confirmed cases. After all, four publications were removed because the manuscript was written in other languages. Therefore, only 22 matches all the selected parameters (Figure 1).

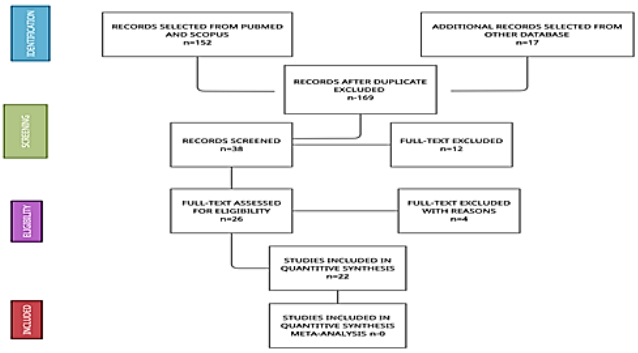

Figure 1. PRISMA. Flow diagram of the included publications.

From this group of publications, most article reported one or two patients while only one reported 35 cases but unfortunately, these authors did not inform about their immunohistochemical findings, the modality of treatment used and follow. Total reported cases presenting NHL were 54, and among them, 63.15% had DLBCL, two B cell NHL without CES, three cases presented Hodgkin's disease, and two cases had an associated EBV without CES. The rest of the publications communicated one case each, but from this group, none one presented with cauda equina syndrome, completed the destruction of the sacral bone by PSNHL, remarkable good response to cytostatic medicine without rituximab and meta-analysis.

From 54 patients presenting primary sacral lymphoma published in literature till April 30, 2021, most of them were allocated in the group of 40-49 years old (n-37), followed by the group of 20-29 (n=4), and 50-59 (n=4). In 36 cases, the outcome was not communicated, and 88.88% of patient had an excellent response to R-CHOP treatment (Table 1).

Table 1. Group of age with references, type of tumour and outcome found in the Systematic review.

Age group(Yrs) & References	Type of tumour	Treatment	Outcome
1-9-n=1 [32]	NOS-n=1	Surgery	Good
10-19-n=1 [33]	HD-n=1	R-CHOP-n=1	Good
20-29-n=4 [34,35]	HD-n=2, DLBCL-n=1, NR-n=1	R-CHOP-n=1	Good
30 -39-n=3 [26, 36-38]	LCL-nl, DLBCL-n=2	NR-n=1 SURGERY-n=2	Good
40-49-n=37 [39-41]	NOS-n=35, DBLCL-n=2	NR-n=35	NR-n-35
50-59- n=4 [29, 42-45]	NOS-n=1, DBLCL-n=3	NR-n=1 R-CHOP-n=2	NR-n=2
60-69-n=4 [46]	DBLCL-n=2	R-CHOP-n=2	Good

70-79-n=1 [47]	DBLCL-n=1	R-CHOP-n=1	Good
80-89-n=2 [31,48]	DBLCL-n=1	R-CHOP-n=1	Good
Total n= 54/100%	DBLCL-63.15%	R-CHOP-19.04%	Good-88.88%

Note: NR: no reported; DLBCL- Diffuse large B cell lymphoma; HD: Hodgkin's disease; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

Case

A 24-year-old immunocompetent male previously well presented to NMAH Neurology MOPD with two months history of weakness, numbness, and cramps of the lower limbs. Paresthesias more localized to the "saddle" area (inner thighs and around buttocks). No radicular pain, but local pain in the sacral region severely aggravated on lying in the supine position, bending forward and was relieved in a left lateral position on prone position. He gradually worsened and started losing the sensation of the lower limbs, inability to control bladder and bowel movement. Nil comorbidities, nil previous hospitalizations. Pt of sober habits. Pt completed his nursing degree and was supposed to start working in Feb 2021.

On examination. Vitals: BP 109/66. HR 108 bpm, SATS>97% on RA. General exam: Grossly NAD CNS: Level of Consciousness: Awake, Alert, Cognition and Orientation: Oriented x 4, MMSE 30/30 Meningism: Nil. Cranial Nerves: Nil palsies. Motor Exam Right upper limb Left upper limb Right lower limb Left lower limb Inspection No tics, fasciculations, tremors. Signs of atrophy were visible in the upper thighs bilaterally. However, a sizeable sacral mass was noted in the midline, smooth surface, immobile, firm, and tender.

The patient could not lie in the supine position and complain of severe pain over the sacral area. Motor power in the lower limb varied across muscle groups: hip flexors (2/5 bilaterally), knee extensors (1/5 bilaterally), ankle dorsiflexion (1/5 bilaterally), long toe extensors (1/5 bilaterally), and ankle plantar flexors (1/5 bilaterally). The sensation for light touch and pinprick of lower limbs was decreased bilaterally, but bowel and bladder habits were regular. Areflexia in the lower limbs was present. Cutaneous-plantar reflexes were normal bilaterally. The straight leg raising test was standard on both legs. Laboratory test results can be seen in Table 2.

Table 2. Laboratory test results.

White cell count	6.3 x 109/L	3.9-12,6 x 109/L
Hb	12.4 g/dL	12-15g/dl
Platelets	289 x 109/L	186-454/L
Sodium	143 mmol/L	136 – 145mmol/L
Potassium	4.8 mmol/L	3.5-5.1mmol/L
Chloride	102mmol/L	98-105mmol/L
Urea	5.7 mmol/L	2.1-7.1mmol/L
Creatinine	74 µmol/L	48-90µmol/L
Calcium	2.4 mmol/L,	2.15 - 2.5mmol/L
Magnesium	0.91 mmol/L,	0.63-1.05mmol/L
Phosphate	0.86 mmol/L	0.78-1.42mmol/L
C-reactive protein	6 mg/L	<10mg/L
Erythrocyte sedimentation rate	9.8 mm/hr	0-10mm/hr
Total protein	70 g/L	60 – 78g/L
Total Bilirubin	6 umol/L	5-21umol/L
Alkaline phosphatase	88 U/L	42-98U/L
Aspartate transaminase	42 U/L	13-35U/L
Alanine transaminase	24 U/L	7-35U/L
Total cholesterol	3,9 mmol/L	<4,5mmol/L
HbA1C	4.90%	<7%
INR	1	1
D-dimer	0.12 mg/L	0.00-0.25mg/L
Rheumatoid factor	17 IU/L	<20 IU/L
Vitamin B12	130 pmol/L	145-569 pmol/L
Folate acid	30,5 nmol/L	
Thyroid stimulating hormone	1.07 Miu/L	0.27-4.2Miu/l
Anticardiolipin antibody	negative	
Protein S	79 IU/dL	55-123IU/dl
Protein C	111 IU/dl	70-130IU/dL
Angiotensin-converting enzyme	226 IU/L	8-53IU/L
Anticardiolipin antibody	negative	
Anti-streptolysin O titre	103 IU/ml	<200IU/L
Toxoplasmosis Gondi IgG antibody	Negative	
Cytomegalovirus IgG antibody	Negative	
Rubella IgG antibody	Negative	
Rubella IgM antibody	Negative	
Cytomegalovirus IgM antibody	Negative	
PCR	Negative	
Ferritin	403 ng/mL	12 to 300 ng/mL
D-dimer	0.97ug/ml	<0.50mg/l (ug/ml=mg/l)
C3	1.0 g/L	0.9 -1.8g/L
C4	0.3 g/L	0.1-0.4g/L
Anti-nuclear antibody	Negative	
Anti-double strand DNA antibody	Negative	
CD4	1069 cells/uL	
Viral load	<21 copies.ml	
Anti-RNP antibody	Negative	
POC COVID-19 antibody tests	Positive	
CSF (herpes simplex virus, cytomegalovirus, ADA, cryptococcal, toxoplasmosis).	Negative	
CSF (Epstein Barr virus)	Positive	
Alpha fetoprotein	2.1 ng/mL	
Ca 125	110 U/mL (high)	
Ca 15-3	27.7 U/mL	
Ca 19-9	22.2 U/mL	
Ca 27-29	27.7 U/mL	
Carcinoembryonic antigen	1.8 ng/mL	
LDH	268 U/L (high)	
Calcium	9.2 mg/dL	

Additionally, urine and stool analysis looking for schistosomiasis as a cause of paraplegia came back negative.

Plain lumbosacral spinal bone X-ray showed completed destruction of the sacral bone and remanent of coccygeal bones. Graphic representation of the tumour in the anteroposterior view is shown in Figure 2a and 2b.

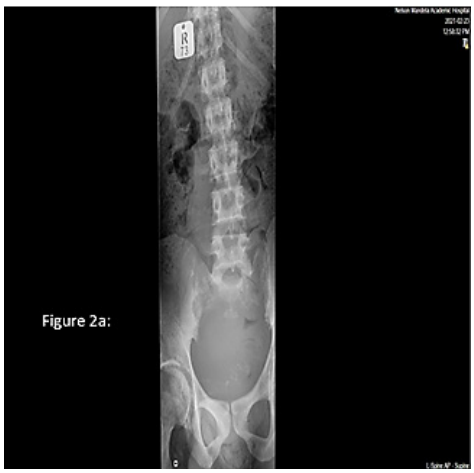

Figure 2a. Lumbo-sacral plain X-ray shows the destruction of the sacral bone.

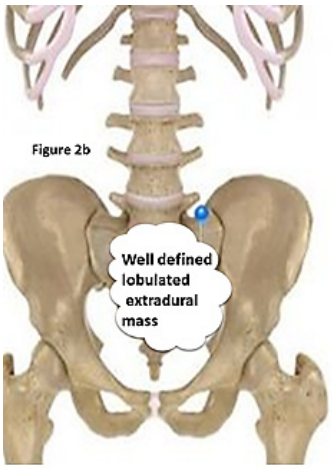

Figure 2b. Graphical representation of the tumour.

The patient underwent MRI scan, which was performed using a 3-Tesla MR imaging system (Magnetom Vision, Siemens Medical Systems, Erlangen, Germany), included T1- and T2- weighted, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted (DWI) with apparent diffusion coefficient (ADC), susceptibility-weighted imaging (SWI) sequences.

MRI brain: Axial: FLAIR, SWAN, DW/ADC, and T1WI pre-and post-contrast. Coronal T2WI. Axial SWI. DWI/ADC Sagittal T1W1 pre-and post-contrast, showing a well-defined lobulated extradural mass lesion of size 4.2 × 4.0 × 4.0 cm L5-S1 to mid S4 level (Figure 3).

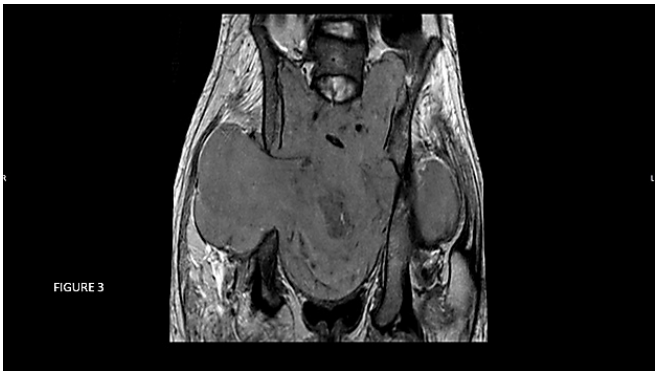

Figure 3. MRI axial view showing a mass lesion in the presacral region with underlying destruction of the bone tissue.

This lesion was iso- to hypo-intense on T1 and T2 weighted images, hyper-intense on short T-1 inversion recovery and showed homogenous enhancement on post-contrast images (Figure 4).

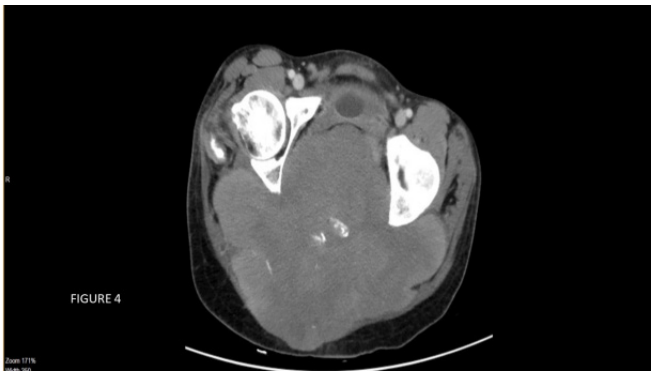

Figure 4. MRI sagittal view showing a well-defined lobulated extradural mass with bone destruction.

Subsequently, the patient was worked up for systemic disease with MR images of the brain, CT scan of abdomen and pelvis, and CT thorax, which were normal. Bone marrow and cerebrospinal fluid examinations were normal. Cardiac ultrasound and ECG showed no abnormalities.

Lumbar punction: opening pressure: 15.1 cm of H20. CSF: Poly: 0, Lymph: 2, Glucose: 4.9. Protein: 0.34, and normal lactate level. On immunohistochemistry, the atypical large tumour cells were positive for common leukocyte antigen (LCA) and CD20 (score 4+), while negative for CD138, CD30, and CD3. The final diagnosis was high-grade non-Hodgkin's lymphoma, diffuse large B cell lymphoma (DLBCL) immunophenotype.

For proper subtyping of the tumour, apart from immunohistochemistry, immunocytochemistry was done as well, then the patient was staged as - IA-E and received the following treatment: Vitamin B12 supplementation (1000 µg IM daily), Pyridoxine (50 mg daily), Thiamine (100 mg daily), Ibuprofen 400mg BD/day, acetaminophen 1 gr/TID/day. Chemotherapy using a methotrexate, Adriamycin, 5-fluorouracil, vincristine, prednisolone regime; six cycles over six months was recommended.

Discussion

The overall percentage of primary bone lymphoma (PBL) among all primary bone malignancy is 0.4% [27], and only 53 cases of DLBCL have been published in the medical literature. Eleven cases located in the sacrum, plus one case reported by Chigurupati [26] complaining of lower back pain and radicular syndrome, and our patient was presenting local pain and CES. Almost all reported cases complained of back pain with or without the radicular syndrome. PBL is usually seen in patients between 40 to 60 years and males [28]. Our case is the youngest one, and the other four patients allocated into his group did not present CES. Therefore, answering the first, second, and third research question, we respond 1. CES as presentation of CES is extremely rare, and we did not find a case with that presentation on the systematic review. 2. Most patients reported in the literature were in the group of 40-49- years old (n=37) and 3. The most used modality of therapy was R-CHOP.

After searching the literature, as a general observation, the prognosis of PNHL in the bone tissue is good and compared with those with bone involvement due to systemic disease is even better [29]. Despite an excellent response to chemotherapy, we consider it necessary to study a large population to establish an accurate prognosis.

Some author concluded that plain X-rays of the spine is usually standard [1], while other investigators found osteolytic bony destruction in 70% of patients [26]. Our patient had broad destruction of the sacrum.

The first MRI findings suggested the diagnosis of chordoma and requested to differentiate it from NHL, giant cell tumours, solitary plasmacytoma, other primary bone tumours. It is quite common to observe low signal intensity on T1 weighted images and T2 weighted images high signal intensity, although these signs are not specific to a lymphoma of the bone tissue [30]. On the other hand, calcification specks are seen in sacral chordoma and chondrosarcoma.

If osteolytic bone destruction is absent, the investigation of choice is 18F-fluoro-2-deoxy-d-glucose-positron emission tomography (FDG-PET) [26], mainly to differentiate lymphoma from multiple myeloma, which presents similar MRI characteristic. FDG-PET is particularly useful in disease staging and response to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) [31]. Confirmation of the final diagnosis is reached by histological studies (atypical lymphoid cell proliferation) and immunochemistry (positive CD20 and common leukocyte antigen (LCA)), as was observed in our case. LCA is also helpful to differentiate metastasis from small cell carcinoma from the lung (cytokeratin positive).

From our review, the R-CHOP chemotherapy regimen may be the treatment of choice, but a clinical trial should be done before arriving at conclusions. We did not use rituximab, and our combination of cytostatic medication was different with a similar good response. Some authors recommend a surgical approach for decompression first, followed by radiotherapy [29]. Following our hospital oncology team, we started chemotherapy first. Seems to be, DLBCL has an excellent response to chemotherapy.

CES as presentation of sacral DLBCL is exceedingly rare based on our systematic review. Due to the scanty report found, some of them after noticeably short follow-up, incomplete investigations, lack of information about treatment and therapy response, we cannot arrive at accurate conclusions. Therefore, incidence, prevalence, and prognosis will remain unclear until new studies clarify it. All patients found in the systematic review were included in Table 1.

The most relevant differences between cases reported in the literature [26, 29, 31-48] and our patient care: 1. Age group, 2. CES as a presentation of the DLBCL. 3. Destruction of the sacrum. 4. Faster response to chemotherapy. 5. Exclusion of Rituximab as part of the therapy. The last case reported in the literature was not included in this group because the confirmed diagnosis is a Sacral Giant Cell tumour [49].

The pathogenesis of DLBCL is not clearly understood, and some authors have been considering that these malignant cells arise from the paraspinal soft tissue like epidural lymphoid tissue and paravertebral ganglion. Most probable, this tissue goes to epidural space through lumbar vertebral foramen leading to bony destruction [50], as happened in our case. This mechanism of invasion is only seen in spinal lymphomas, while other tumours affecting the cord is achieved by the destruction of the vertebral spine [51]. Other investigators concluded that the source of epidural lymphomas is the epidural lymphoid rests responding to antigenic stimulation with transformation cascade [52]. From our review, we could not get a general agreement about the origin of PENHL, although some investigators suggest that the source of DLBCL can be retroperitoneal tissues, vertebral bodies, or paraspinal tissues [13-15,52].

Based on the literature review's findings and own observation, we highlight the importance of core biopsy and immunohistochemistry studies to confirm the diagnosis of DLBCL over other procedures like needle aspiration cytology despites clinical manifestations and results of imagenology even when 18F-fluorodeoxyglucose (18F-FDG)-positron emission tomography is unavailable as happened to us.

Apart from DLBCL, other malignancies can cause CES apart from stenosis of the spinal canal, local infections, inflammation, haemorrhage, a severe rupture in the lumbar intervertebral disk (the most typical cause). These conditions are graphically shown in Figure 5. Another common aetiology is the fracture of the sacral bone [53].

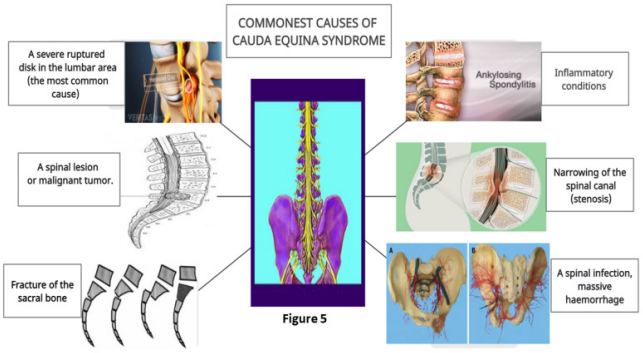

Figure 5. Graphical representation of the most typical cause of CES.

Epstein-Barr virus and DLBCL

The *Epstein-Barr virus* (EBV) is an enormously B lymphotropic member of the Gammaherpesvirinae subfamily, an aetiology of infectious mononucleosis and neoplastic process (human cancers) [54-62]. Some author confirmed and other isolated EBV in patients with carcinoma of the nasopharynges [55,58,61]. Also, in pulmonary lymphoepithelioma-like carcinoma [62] plus other malignancies such as NK/T cell lymphoma, Non-Hodgkin's disease, gastric cancer, cervical cancer, head, and neck squamous cell carcinoma. All these pathologies are strongly related to EBV, and currently, some of these tumours have been treated with pembrolizumab with promising results [58].

EBV invade epithelial cells supporting lytic replication and primary B cell, initiating unlimited cell growth. This oncogenic γherpesvirus (EBV) is associated with 2% of all cancers in human being [63]; other investigators consider that 9.9 % of all cancer are attributable to virus infection, while the World Health Organization establish that 15.4 % of all malignancies are linked to infections [64,65]. Although many neoplasms are initiated by viral oncogeneses like hepatitis C virus, hepatitis B virus and papillomavirus, without doubt, EBV play a relevant role in the pathogenesis of B cell malignancies, and our case serves as a contribution to this postulate. It is classically known that EBV induces (infected cells) a viral latency leading to cell proliferation and production of virus progeny [54], which has been confirmed by other researchers [66,67].

Patients presenting post-transplant lymphoproliferative disorder (PTLD), DLBCL account in most cases and the presence of aggressive EBV/DLCBL have been associated with lytic and latent viral cycles [68,69]. On the other hand, this subtype (EBV/DLBCL) is monomorphic B cell positive for EBV-encode small RNAs typically expressing pan-B-cell markers like CD19, CD20 and sometimes CD30 and the EBV latency pattern is type III [68,70].

Between 30 to 40% of DLBCL cases have primary resistance to the treatment of early relapse after standard treatment, and there is no treatment of choice for aggressive EBV/DLBCL [70]. However, with our regimen, we got an excellent swift response. Frequently, a biomarker for these processes can be a high detectable expression of PD-L1(known as B7-H1 or CD274) in EBV/PTLD and DLBCL [71-73]. It is essential to highlight that PD-L1 induction in EBV cancers happens via AP-1 and JAK/STAT pathways [71] and through the assistance of EBV-LMP-1 and IFN-γ signalling [74] and in cases of EBV/DLBCL, the PD-L1 positive malignancy express elevated levels of indoleamine 2,3-dioxygenase, suggesting a tolerogenic tumour microenvironment (TME) [72].

Patients with EBV/DLBCL has a different TME compare with those with DLBCL no related EBV, and they present high expression of immune checkpoints (lymphocyte activation gene 3, PD-L1, PD-L2, and mucin domain-containing protein 3 and T cell immunoglobulin) plus an increased level of immunosuppressive M2-type macrophages [73]. In cases with PTLD/DLBCL, the standard care should reduce immunosuppression first according to the clinical situation plus rituximab as a monoclonal antibody that targets the CD20/malignant cells, providing an excellent response rate is around 65% of patients [75].

Based on information obtained from our systematic review, we assume that different EBV strains are responsible for the further development of lymphoid tumours, with a noticeable difference in the efficacy of therapy in immunocompromised cases. There is probably a parallel between the lineage of the tumours they induce and the cell tropism of the viral strains. Ming-Han et al. reported three EBV strains (YCCEL1, GP202, and SNU719) isolated from carcinomas of the stomach.

They also isolated a different virus (M81) from nasopharyngeal carcinoma and some type-A strains apart from B95-8. They confirmed that Akata and GP202 leads a cell growth with more efficacy than SNU719, M81 and YCCEL1, and better correlation with the expression levels of the BHRF1 miRNAs. Finally, these authors concluded that all strains except Akata and B95-8 produce lytic replication in invaded B cells, which is a risk factor for developing malignant tumours, although with minor accuracy than M81.[76] This novel information may support the hypotheses that an overly aggressive EBV can induce an extremely invasive DLBCL causing rapid and complete destruction of the sacrum and secondary CES. Answering the first question we can conclude that only 13 cases presenting a primary sacral NHL have been published in the medical literature [19,26,29,30,34,37,39,40,42,43(2 cases),46-48] up to date.

Conclusion

Our current report is the 14th patient. As far as we know, non-patient

with primary sacral DLBCL an associated Epstein Bar virus infection presenting as CES and responding well to medical treatment (without rituximab) has been published up to date. This novel information may support the hypotheses that an overly aggressive EBV can induce an extremely invasive DLBCL causing rapid and complete destruction of the sacrum and secondary CES.

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Key Clinical Message

We report a young patient presenting with CES by compression of a DLBCL confirmed by histopathology and immunohistochemistry. We did a systemic review and found thirteen reported cases but none one like our patient. We about the associated *Epstein-Barr virus* infection and proposed one hypothesis

Declaration

Ethical issue and consent to publish

Ethical approval is not required as the patient consented in writing for publication Patient agreed to include all medical information for publication purposes. We certify that we did not disclose any identity issues of this patient in this publication, and we guarantee the patient's anonymity.

Availability of data

Data used in this study are available on reasonable request from the corresponding author.

Competing interest

All authors: reported no conflicts of interest.

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We did not receive funds or any contribution to this publication.

Author's contribution

Both authors made equal contribution to the elaboration of this manuscript. HFS searched Medline by PubMed, Google Scholar, Science Direct, Scopus, and LdeFIV searched Embase, Scielo, LILACS, BIREME, Cochrane library and WHO database. Both authors collected all patient's information and planning this report; LdeFIV wrote the first draft. HFS wrote the final draft. All authors reviewed the final manuscript, made changes, and agreed to publications.

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