REVIEW ARTICLE

Extranodal marginal zone non-Hodgkin lymphoma mucosa-associated lymphoid tissue type with thoracic vertebral spine involvement: a sistemátic review of the literature and a case report from a university hospital in Brazil

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ABSTRACT

Background: Primary bone lymphomas are rare, accounting for less than 1% of non-Hodgkin's lymphomas (NHL). Extranodal marginal zone non-Hodgkin lymphoma of mucosa-associated lymphoid tissue (MALT) arising in the vertebral spine is extremely rare, with only seven cases reported. **Methodology:** A systematic literature review was conducted on cases from 2012 to 2022 of extranodal marginal zone MALT lymphoma involving the vertebral spine and associated with spinal cord compression. Additionally, a case report from a university hospital in Rio de Janeiro is described. The study was approved by the Research Ethics Committee (approval number: 5.818.416). Searches were performed in SciELO, PubMed, and LILACS databases, using the Health Sciences Descriptors: ("Vertebral Body" OR Spine) AND ("Lymphoma B-Cell Marginal Zone" OR "MALT Lymphoma" OR "Lymphoma of Mucosa Associated Lymphoid Tissue" OR "Mucosa Associated Lymphoid Tissue Lymphoma"). Articles with full texts available in English or Portuguese were selected. **Case Description:** A 56-year-old female presented with right-sided back pain, progressing to right flank irradiation, lower limb weakness (LLLL), and constitutional symptoms. MRI revealed a solid extradural mass occupying two-thirds of the vertebral canal's diameter, displacing and compressing the dorsal cord to the left. A bone marrow biopsy confirmed infiltration. Laminectomy was performed, and histopathology identified stage IVB extranodal marginal zone MALT lymphoma. Adjuvant chemotherapy led to complete remission. **Results and Discussion:** The literature review uncovered two relevant case reports. The thoracic spine was the most commonly affected region, and LLLL weakness was the most frequent symptom, with normal laboratory results. Treatment typically involved surgical tumor removal combined with radiotherapy or chemotherapy. Recurrence occurred in both cases, but follow-up showed no evidence of disease. The clinical presentation and exam findings of the current patient were similar to those in the literature, though with bone marrow infiltration. Treatment was consistent with cases in the review, with no recurrence to date. **Conclusion:** This case represents an uncommon manifestation of primary extranodal marginal zone MALT lymphoma with spinal cord compression, distinguished by bone marrow infiltration—a feature not previously reported in the two cases found in the literature. The case may be considered within the same group of cases reviewed.

Keywords: MALT lymphoma, Spinal cord compression, Lymphoma, B-cell marginal zone.

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INTRODUCTION

Lymphomas are malignant hematological neoplasms originating from cells present in lymphoid tissues[1]. They have a pathophysiology that can be multifactorial and largely associated with genetic abnormalities with neoplastic potential, occurring during the development and maturation of cells in this hematopoietic lineage[1].

They can be classified and divided into two major groups: Hodgkin lymphomas (HL), responsible for about 10% of all lymphomas, and non-Hodgkin lymphomas (NHL), which represent the remainder[2]. HL are neoplasms derived from B cells[3], whereas NHL are neoplasms of B cells in 85-90% of cases, with the remainder derived from T cells or natural killer (NK) cells, usually originating from nodal sites but can occur in virtually any tissue, ranging from indolent to more aggressive forms[2].

The most common subtypes of NHL in developed countries are diffuse large B-cell lymphoma (DLBCL), accounting for about 30%, and follicular lymphoma (FL), accounting for about 20%[1]. All other NHL subtypes have a frequency of less than 10%[1]. Marginal zone lymphomas (MZL) are classified into three subtypes: splenic marginal zone lymphoma, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT), and nodal marginal zone lymphoma[4].

Approximately one-third of NHL originate from sites other than lymphoid tissues, with a predilection for extranodal dissemination[1]. However, some issues remain controversial, such as the definition of primary extranodal lymphoma. Currently, primary extranodal lymphomas are considered those with no or only small nodal involvement with a predominance of extranodal clinical manifestations[5]. As they do not yet have a well-established definition, this hinders statistical data and case classification.

MALT lymphoma is classified as indolent and in the western world accounts for 6% to 8% of all NHL, being the third most common subtype[4]. Its association with chronic inflammation, autoimmune diseases such as Sjögren's syndrome and Hashimoto's thyroiditis, and chronic infections by microorganisms, especially *Helicobacter pylori* in gastric lymphoma[1,5,6], and others, such as *Borrelia burgdorferi* in cutaneous lymphoma, *Chlamydia psittaci* in conjunctival lymphoma, *Campylobacter jejuni* in duodenal, jejunal, and/or ileal lymphoma, is reported, and there is also an increased risk of development associated with chronic infection with hepatitis C virus[6].

It is characterized by the presence of lymphoepithelial lesions due to the invasion of mucosal glands and crypts by neoplastic cells[1]. Immunohistochemistry is associated with the expression of antigens CD19, CD20, CD22, and CD79a, and is generally negative for CD5 and CD10[1]. The most common characteristic cytogenetic alteration is the t (11;18) (q21;q21) translocation. In this alteration, part of the *MALT1* gene fuses with part of the inhibitor of apoptosis gene (*API2*) located on 11q21, leading to activation of the nuclear factor κB (NFκB), resulting in dysregulation of this pathway and increased survival of neoplastic cells[2,7-9]. However, the frequency of this translocation varies depending on the tumor's site of origin, being more common in the lung and gastrointestinal tract[9].

This type of lymphoma predominantly affects the intestinal gastrointestinal tract, especially the stomach[5]. However,

other sites, although rare, can be affected, such as salivary glands, lungs, ocular adnexa, breasts, and thyroid[5,9].

Involvement of the bones is a rare event, representing less than 1% of NHL and 4% to 5% of extranodal lymphomas, with indolent lymphomas like MALT accounting for 1% of reported cases[1]. The femur is the most commonly reported site of involvement. However, some Japanese reports have indicated the pelvic bones as the most common site of the disease, suggesting geographic variability may be present[5]. Primary MALT lymphomas involving the vertebral spine are extremely rare, with only 7 similar cases reported in the literature to date[10]. Bone marrow involvement is described in extranodal marginal zone lymphomas (EMZL) in 2% to 20% of cases[11].

This study aims to describe a case observed in a hematology outpatient clinic at a university hospital in Rio de Janeiro, in which there was a rare presentation of extranodal marginal zone lymphoma of MALT type involving the vertebral spine associated with symptoms of spinal cord compression, reporting the clinical presentation, histopathological characteristics, therapeutic management, and case outcome. Additionally, a systematic review of the literature regarding similar cases already reported will be conducted.

METHODOLOGY

This study comprises a case report and a systematic literature review on extranodal marginal zone lymphoma of MALT type, focusing on its atypical presentations involving the vertebral spine with symptoms of spinal cord compression.

For the literature review, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. Searches were conducted in the following databases: Scientific Electronic Library Online (SciELO), PubMed, and Latin American and Caribbean Literature in Health Sciences (LILACS). The search strategy employed the following Health Science Descriptors (DeCS): ("Spinal Cord" OR Spine) AND ("MALT Lymphoma" OR "Lymphoma of Mucosa Associated Lymphoid Tissue" OR "Mucosa Associated Lymphoid Tissue Lymphoma"). Inclusion criteria included articles with full-text availability, published between 2012 and 2022, in English or Portuguese.

The case report was structured following the Case Reports Guidelines checklist (CARE 2020). It details an atypical case of extranodal marginal zone MALT lymphoma involving the vertebral spine, associated with spinal cord compression symptoms, documented at a tertiary university hospital in Rio de Janeiro.

Data collection commenced following approval from the Research Ethics Committee (certificate of ethical appreciation: 65717922.8.0000.5258, approval number: 5.818.416). Informed consent was waived due to the retrospective nature of the chart review, involving a patient who had already been discharged from outpatient follow-up. The collected data were analyzed descriptively, with tables summarizing examinations and serologies. Statistical significance assessments were not applicable, as this was a descriptive study.

CASE REPORT

Patient M.M., a 56-year-old female, first presented in September 2014 with

lower back pain, initially localized to the right side. Over time, the pain became bilateral, increased in intensity, and radiated to the right flank and hypochondrium. She reported partial relief with analgesics, but the pain worsened with movement and weight-bearing. Additionally, she experienced a three-kilogram weight loss over three months and night sweats. The patient denied any fever, flu-like symptoms, or trauma.

During the diagnostic workup, an abdominal ultrasound revealed cholelithiasis, leading to a laparoscopic cholecystectomy in December 2014. One week post-surgery, she returned to the general surgery team, reporting a “shock-like sensation” in her feet, imbalance, and the need for a walker to ambulate. She also developed paresthesia in the lower limbs (LLLL), initially affecting the feet but progressing to the thighs, accompanied by urinary incontinence and constipation. Hospitalization was advised, and intravenous corticosteroid therapy with dexamethasone (4 mg every 6 hours for 4 days) was initiated, resulting in an initial positive response. The dosage was then tapered over the following days to 60 mg, 40 mg, 20 mg, and finally 10 mg per day.

Upon neurological examination at admission, the patient exhibited a steppage gait, grade 4 strength in the LLLL, reduced superficial sensation, absent vibratory sensation, diminished deep sensation, altered proprioception, an exaggerated Babinski reflex, and Achilles hyperreflexia. The remainder of the neurological exam, including assessments of motor coordination, cranial nerves, finger-nose test, and diadochokinesia, was unremarkable. Laboratory tests and cerebrospinal fluid (CSF) analysis were within normal limits.

In January 2015, a magnetic resonance imaging (MRI) of the thoracic spine revealed: “A solid extradural expansive lesion with intermediate signal intensity on T1 and T2, showing intense contrast enhancement, located in the vertebral canal posterior to the D9 and D10 vertebral bodies, right-lateralized. The lesion extends through the right neural foramina of D9-D10 and D10-D11, which are widened, with more pronounced involvement at the upper levels, where there is apparent erosion of the posterior arch of D9 on this side. At the D9-D10 level, the lesion occupies two-thirds of the vertebral canal diameter, measuring 5.3 cm (craniocaudal) x 1.5 cm (anteroposterior) x 2.8 cm (latero-lateral), displacing and compressing the dorsal spinal cord to the left.”

Given the findings of imaging studies in January 2015, microsurgery was performed to remove the intradural extramedullary (extradural) spinal tumor, with laminectomy of T7-T9, and the excised tissue was sent for biopsy. Screening tests for investigating a primary tumor at another site were also conducted (Table 1).

Table 1 - Results of primary tumor investigation examinations.

Exam	Date	Result
Gallbladder histopathological report	December 09th, 2014	Chronic cholecystitis with calculi embedded in the walls, in addition to adenomyosis
Cranial computed tomography	January 21th, 2015	No abnormalities
Chest computed tomography	January 21th, 2015	Absence of spinous processes from D7 to D10, no other abnormalities
Abdomen and pelvis computed tomography	January 21th, 2015	Nodular thickening of the right adrenal with fat density, measuring 2.3 x 2.1 cm. Suggestive of adenoma
Mammography	January 21th, 2015	Right breast with benign-appearing calcifications. Axillary lymph nodes are not visualized. Right breast BI-RADS 2 and left breast BI-RADS 1
Breast ultrasound	January 29th, 2015	Echogenic area without nodular expression in the upper lateral quadrant of the right breast, which may correspond to a surgical sequel. No evidence of solid or cystic nodules in the breasts

Source: Compiled by the authors, 2023.

No suspicious malignant lesions were found in the conducted examinations. However, the histopathological report of the thoracic spine, obtained through laminectomy, revealed extranodal marginal zone lymphoma of MALT type. The immunohistochemical study showed positivity for CD20, Bcl-2, and Bcl-6, Ki-67 proliferation antigen detected in approximately 3% of the cells, and negativity for CD10, CD3, MUM-1, CD23, and CD21.

In light of the findings, a referral to the hematology outpatient clinic was made. During the hematology evaluation, the patient reported night sweats for the past 2 years, with worsening since December 2014. No peripheral lymphadenopathy was observed, physical examination was unremarkable, and there was a family history of chronic leukemia. Serological and laboratory tests were requested and collected in March 2015 (Table 2), and a bone marrow biopsy was performed, which showed infiltration by small B lymphocytes (CD20+). With this presentation, the clinical impression became extranodal marginal zone lymphoma of MALT type with bone marrow infiltration and the presence of B symptoms.

Table 2 - Results of laboratory tests and serologies conducted.

Blood count
Red blood cells: 4.390.000/mm^3 Hemoglobin: 13,5 g/dL Hematocrit: 40,7% Mean corpuscular volume (MCV): 92.7 fL Mean corpuscular hemoglobin (MCH): 30.8 pg Mean Corpuscular Hemoglobin Concentration (MCHC): 33.2 g/dL Red cell distribution width (RDW): 12,4 % Total Leukocytes: 6.100/µL Basophils: 0% Eosinophils:1% Myelocytes: 0% Metamyelocytes: 0% Band cells: 3% Segmented: 48% Lymphocytes: 38% Monocytes:10% Platelets: 344.000/mm^3
Coagulogram
Prothrombin time (PT): 11.1 seconds International normalized ratio (INR): 1.02
Biochemistry
Glucose: 94 mg/dL Urea: 30 mg/dL Creatinine: 0.56 mg/dL Lactate dehydrogenase (LDH) enzyme: 419 U/L Serum glutamic-oxaloacetic transaminase (STOG): 42 U/L Serum transaminase glutâmico-pirúvica (STGP): 77 U/L Gamma-glutamyl transferase (GGT): 50 U/L Alkaline phosphatase (ALP): 113 U/L Total bilirubin (TB): 0.3 mg/dL (indirect bilirubin 0.1 mg/dL and direct bilirubin 0.2 mg/dL)
Serologies
Anti HAV total: IgG non-reactive HBsAg: non-reactive Anti-HBc: non-reactive Anti-HBs: < 2.0 IU/mL Anti-HCV: non-reactive Anti-Toxoplasmosis: IgM non-reactive / IgG 624.2 IU/mL Anti-Rubella: IgM non-reactive / IgG > 500 IU/mL Anti-CMV: IgM non-reactive / IgG > 500 IU/mL Anti-HSV 1 and 2: IgM non-reactive / IgG 30 IU/mL Anti-EBV: IgM non-reactive / IgG 430 U/mL Anti-HIV 1 and 2: non-reactive Anti-HTLV 1 and 2: non-reactive

Source: Compiled by the authors, 2023.

Legend: Anti HAV total (antibodies against hepatitis A virus); HBsAg (hepatitis B surface antigen); Anti-HBc (antibodies against the viral core antigen of hepatitis B virus); Anti-HBs (antibodies against hepatitis B surface antigen); Anti-HCV (antibodies against hepatitis C virus); Anti-Toxoplasma (antibodies against the Toxoplasma Gondii protozoan); anti-Rubella (antibodies against rubella virus); Anti-CMV (antibodies against cytomegalovirus); Anti-HSV 1 and 2 (antibodies against herpes simplex virus types 1 and 2); Anti-EBV (antibodies against Epstein-Barr virus); Anti-HIV (antibodies against human immunodeficiency virus); Anti-HTLV (antibodies to human T-cell lymphotropic virus); IgG (immunoglobulin G); IgM (immunoglobulin M).

The patient received a final diagnosis of extranodal marginal zone lymphoma of MALT type - Stage IVB involving the thoracic spine. The treatment consisted of 8 cycles of R-CHOP protocol chemotherapy (Rituximab 600mg / Cyclophosphamide 1g / Doxorubicin 80mg / Vincristine 2mg / Prednisone 100mg) in March 2015, followed by monthly Rituximab maintenance therapy until February 2017.

During treatment, the patient experienced motor improvement after 3 cycles of chemotherapy and received physiotherapy support. However, throughout the cycles, she reported mouth ulcers and paresthesias in the hands, as well as joint stiffness in the knees and ankles. Neurosurgery outpatient follow-up was initiated, and she was prescribed gabapentin 300 mg, 1 tablet every 8 hours, and amitriptyline 25 mg, 1 tablet at night, but the symptoms persisted.

In November 2020, she presented with suspected pheochromocytoma due to suggestive findings on abdominal computed tomography (CT), associated with hypertensive episodes and hot flashes. She started being monitored by the general surgery team for further evaluation and treatment. The patient remained in remission, and she was discharged from hematology care in April 2021.

RESULTS AND DISCUSSION

A total of 14 articles were found in the used databases. No articles were found in the searches in the SciELO and LILACS databases, and 8 articles were found in PubMed. Six articles were excluded for not being within the mentioned period, and all the remaining articles had full text available and were in the selected languages. Of these, 6 were excluded due to titles or abstracts not corresponding to the theme, leaving 2 articles for full reading, all of which were case report studies. Two reviewers discussed and consensually resolved disagreements regarding the evaluation of the articles and read the selected articles in full (Figure 1).

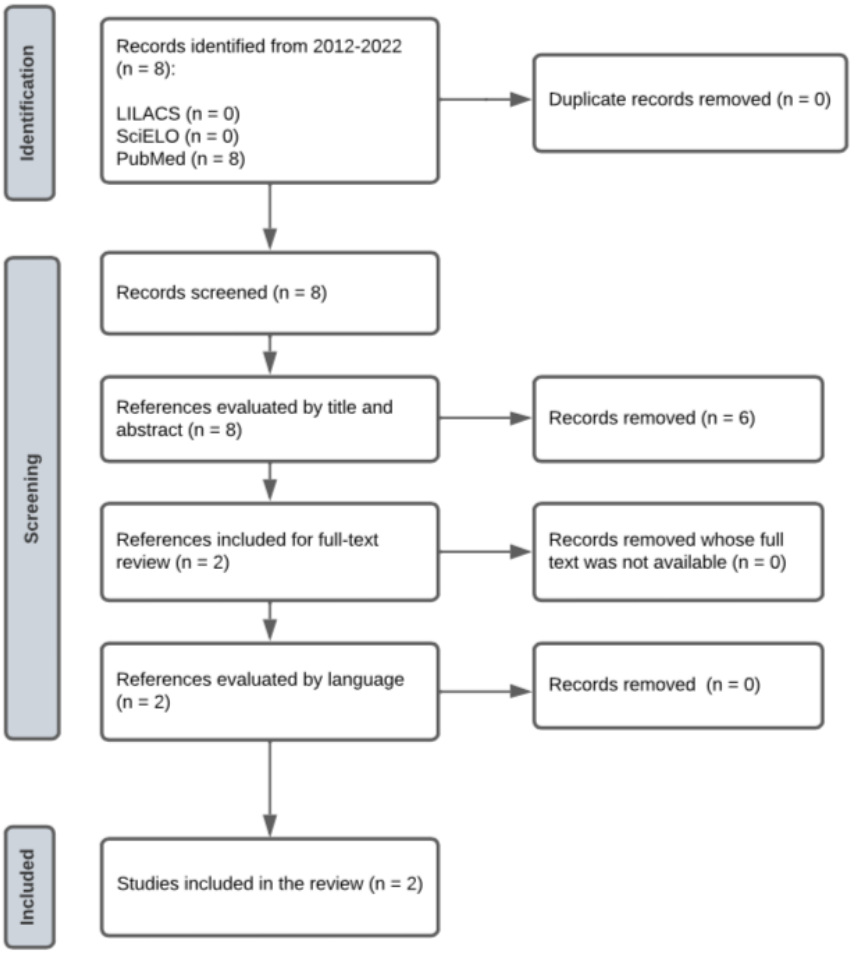

Figure 1: Flowchart of the article selection process based on the PRISMA[12] model.

The case reports found in the literature included one male and one female case, with an age of 58 and 68 years, respectively (Table 3). Regarding the location, the literature mentions that the thoracic region is the most affected[10]. In this review, all cases involved the thoracic spine. The most common symptom described was weakness in the lower limbs, but other reported symptoms included dorsal pain, intestinal and vesical dysfunction, pain in the anterior thigh region, foot drop, sensory alterations in the LLLL and perianal area, and gait disturbance[10,14]. Reported physical examination findings included pain in the thoracic spine region, hypoalgesia, motor weakness in the lower limbs, bilateral spasticity of the lower limbs, pathological reflexes in the LLLL, and positive pathological reflexes[10,14].

As for complementary exams, in the described cases, laboratory tests such as CSF and tumor markers did not show any alterations[10,14]. Bone marrow aspiration and biopsy also did not show any alterations[10,14]. Imaging exams, including spinal MRI and positron emission computed tomography (PET/CT), were performed in all cases[10,14]. Spinal MRI showed a spinal mass with medullary compression in both cases[10,14]. PET/CT indicated only hypercaptation in

the thoracic spine in one case[10] and abnormal uptake in the thoracic spine, right iliac, and right liver in the other case[14].

In immunohistochemistry, all reported cases were positive for CD20[14,15]. Ki-67 proliferation antigen research was performed only in the case described by Dong R. *et al.*[10], with a Ki-67 labeling index of 15%. Both cases were negative for CD3 and CD5[10,14], and one case was negative for CD10[14]. The research and expression of the remaining requested markers varied in each case.

Disease recurrence occurred in both reported cases[10,14]. In one case, recurrence occurred in the same location as the first lesion, but with signs of metastasis to the iliac crest and liver four months after the initial diagnosis[14]. In the other case, recurrence occurred again after 3 years, in the spinal column but in a different location from the first lesion, leading the author to question whether the second lesion was the growth of residual tumor from the first lesion or the growth of other tumor foci[10].

The therapeutic management of extranodal marginal zone lymphomas of MALT type is extremely heterogeneous, and there are still no universally accepted therapeutic guidelines[10]. Previous studies cited in the cases suggest that radiotherapy is an effective treatment for controlling MALT lymphoma in the cranial dura mater and spinal column, and surgical resection of the epidural tumor as the main role in determining its pathological diagnosis[14]. However, in patients with progressive neurological deficits due to intracranial or spinal MALT lymphomas, neural decompression by surgical resection of the main tumor mass should be performed in combination with radiotherapy[14].

Treatment should take into consideration the location, stage, and clinical characteristics of each patient. When systemic treatment is necessary, chemotherapy (and/or immunotherapy with anti-CD20 monoclonal antibodies) can be considered[10]. But there are reports of cases in the literature where only chemotherapy was administered as adjuvant treatment, and also reports showing long-term survival with methotrexate, but the scientific evidence of chemotherapy's efficacy for extranodal marginal zone lymphomas of MALT type has not yet been established[14].

In one of the cases in this review, hemilaminectomy was performed on the first lesion, but complete tumor resection was not possible, and radiotherapy was associated. Recurrence occurred, and laminectomy and adjuvant radiotherapy were performed[14]. In another described case, partial laminectomy of the lesion was performed, and as there was metastatic recurrence, systemic treatment with rituximab, methotrexate, cyclophosphamide, vincristine, and prednisone was administered[10].

Regarding the prognosis, despite both cases experiencing recurrence[10,14], with one being metastatic[10], there was remission of the disease in all cases up to the time of follow-up[10,14]. These tumors progress slowly and tend to remain localized in their sites of origin for many years before dissemination[10]. However, the authors emphasize the possibility of histological transformation into more aggressive forms of lymphoma, requiring monitoring to detect possible transformation into high-grade lymphoma[10,14].

Table 3 - Selected study reports of extranodal marginal zone lymphoma MALT type, with primary and secondary involvement of the vertebral spine with symptoms of spinal cord compression.

Title	Primary spinal mucosa-associated lymphoid tissue lymphoma: A case report	Primary spinal marginal zone lymphoma relapse at a different spinal level after remission of the primary lesion
Authors, year	Dong, R. *et al*., 2018[10]	Hojo, Y. *et al*, 2013[14]
Age (years) / Gender	68/F	58/M
Location	In September/2016: Vertebral bodies of T6-T8 extending through the right intervertebral foramen of T6-T7 Four months later: Thoracic spine from level T6-T8, right iliac crest, and right liver	First lesion: Abnormal mass in the epidural space of the thoracolumbar spine from T11-L1, compressing the spinal cord Three years later: Abnormal lesion in the peridural space of T8-T10, compressing the spinal cord
Clinical symptoms	In September 2016: Back pain and progressive bilateral lower limb weakness for the past 2 months Four months later: Progressive asymmetric weakness in both lower limbs and increased back pain with bowel and bladder dysfunction	First lesion: Bilateral pain in the anterior thigh region. After 6 months, experienced worsened pain, bilateral foot drop, urinary dysfunction, and sensory changes in the lower extremities and perianal area Three years later: Gait disturbance and numbness in both legs and perineal area
Physical examination	In September 2016: Pain in the thoracic spine region. Bilateral spasticity of the lower limbs with an asymmetric pyramidal pattern of weakness Four months later: No report	First lesion: Spastic gait, accelerated tendon reflexes in knees and ankles, and positive pathological reflexes in both lower limbs. Motor weakness in both legs below the hip joints. Hipoalgesia in lower limbs Three years later: No report
Laboratory tests	In September 2016: Laboratory investigations, including tumor markers, showed no abnormal findings Four months later: Cerebrospinal fluid analysis did not reveal infiltration	First lesion: Blood tests and tumor markers showed no abnormal findings Three years later: No report

Imaging studies	In September 2016: MRI showed an epidural mass at the T6-T8 vertebral bodies with spinal cord compression Four months later: PET/CT showed abnormal uptake in the thoracic spine at T6-T8, right iliac crest, and the liver	First lesion: MRI showed an abnormal mass in the thoracolumbar epidural space compressing the spinal cord. PET/CT showed increased uptake in the thoracic spine Three years later: MRI showed an abnormal lesion in the peridural space at T8-T10, compressing the spinal cord
Diagnosis	In September 2016: Primary MALT lymphoma of the vertebral spine Four months later: Stage IVB primary MALT lymphoma of the vertebral spine	First lesion: MALT lymphoma of the vertebral spine Three years later: MALT lymphoma of the vertebral spine
Bone marrow biopsy	In September 2016: No report Four months later: No signs of infiltration	First lesion: Bone marrow aspirate showed normal hematopoiesis Three years later: No report
Histopathology and immunohistochemistry	In September 2016: The majority of tumor cells were small monomorphic B cells with small to medium-sized nuclei and abundant pale cytoplasm surrounding germinal centers. Immunohistochemically, most tumor cells were positive for CD20, CD21, CD45, CD79a, CD43, Bcl-2, with a Ki-67 labeling index of 15%, but negative for CD3, CD5, cyclin D1, Bcl-6, and CD23. CD3 and CD5 expression was restricted to reactive T lymphocytes Four months later: Distant lesions were not biopsied or surgically resected	First lesion: Lymphocytic infiltrate, mainly composed of small lymphocytes. Immunohistochemical study showed that most tumor cells were positive for CD20 and CD79a and negative for CD3, CD5, CD10, and CD138. Light chain expression was restricted to lambda chain Three years later: Histopathological and immunohistochemical features of the lesion at T9 were consistent with those observed at T12 three years earlier

Treatment	In September 2016: Laminectomy from T3-T8, the dorsal mass was almost entirely resected with partial removal of the ventral and lateral tumor. Complete resection was impossible due to significant adherence of the tumor to the dural sheath Four months later: Systemic therapy with rituximab, methotrexate, cyclophosphamide, vincristine, and prednisolone (R-MAX-COP protocol) every 3 weeks, and central nervous system prophylaxis (intrathecal cytarabine and dexamethasone)	First lesion: Hemilaminectomy at T12 and removal of the mass over the dural sac. Complete tumor resection was not possible due to its expansion into the neural foramen and ribcage. Radiation therapy of 40 Gy/16 fractions at T10–L3 after surgery Three years later: Laminectomy at T9 and resection of the epidural tumor over the dural sac. Radiation therapy consisting of 40 Gy/20 fractions was initiated 10 days after surgery
Prognosis	In September 2016: Recurrence in the vertebral column at another site, with metastasis to the right iliac crest and liver Four months later: After the first cycle of chemotherapy, there was an improvement in back pain, motor weakness, and urinary dysfunction. After 4 cycles, the spinal MRI confirmed continuous clinical remission of the primary lesion and the right iliac crest. No development of new disease manifestations up to the recent follow-up	First lesion: After surgery, her urinary dysfunction and motor weakness showed remarkable improvement Three years later: After the second surgery, the patient's neurological functions returned to normal. In the MRI, there was no evidence of residual lesion or tumor recurrence in the peridural space at 2 years post-operation

Source: Compiled by the authors, 2023.

Legend: M (male); F (female); RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone); PET/CT (positron emission computed tomography); MRI (magnetic resonance imaging); MALT (mucosa-associated lymphoid tissue); Gy (gray - the international system unit of absorbed dose); EBV (Epstein-Barr virus); RNA (ribonucleic acid); Ara-C (cytarabine).

In terms of the epidemiology of primary bone lymphomas (PBL), the reported median age at the time of diagnosis varies from 45 to 60 years, with a slight male predominance[5]. In the case reported in this study, the patient falls within the age range described in the literature and among the patients in the cases found. Regarding gender, one of the described cases was male[14], and the other was female[10], as the patient in the reported case.

As for clinical presentation, the literature typically mentions bone pain (80-95%)[5]. Symptoms related to spinal cord compression are present in only 14% of patients[5]. The patient initially presented with lower back pain alone, which evolved over about 3 months with weakness in both LLLL, accompanied by urinary incontinence and constipation. Such symptoms are frequently associated with spinal cord compression, consistent with the symptoms reported in the literature[10,14]. The patient also reported night sweats for 2 years, which are compatible with B symptoms, raising suspicion of lymphoma. However, these symptoms were not mentioned in the cases found in the literature[10,14].

On neurological examination, the patient exhibited a high-stepping gait, weakness in both LLLL, altered superficial, vibratory, and deep sensation, as well as impaired proprioception, exaggerated plantar cutaneous reflex, and hyperreflexia of the Achilles tendon. These findings are consistent with the cases described[10,14]. Laboratory tests were within the normal range, and a lumbar puncture was performed to investigate central nervous system (CNS) infiltration during the management of spinal cord compression, but it did not show abnormalities or signs of lymphoma infiltration, consistent with cases found in the literature.

According to the literature, immunohistochemistry is associated with the expression of antigens CD19, CD20, CD22, and CD79a, generally negative for CD5 and CD10[1]. The immunohistochemical study in the reported case showed positivity for CD20, as in all the reported cases. Bcl-2 expression was positive in the case by Dong R. *et al*.[10], as well as in the patient, but the patient also tested positive for Bcl-6, which was negative in this literature case[10]. The second case did not describe the immunohistochemical study for Bcl-2 and Bcl-6[14]. The Ki-67 proliferation antigen research in this case was about 3% of the cells, and the only study that reported this had a Ki-67 labeling index of 15%[10]. Both CD10[14] and CD3[10,14] markers were negative, as in the literature cases. CD23 was negative in the case described by Dong R. *et al*., as in this patient's case, but it was not requested in the second case. The CD21 marker was negative in the patient, different from the case reported by Dong R. *et al*.[10], and there is no record in the second case. MUM-1 expression was negative in the patient's case, but it was not recorded in either of the two cases studied.

While CT is the primary method for staging, restaging, and monitoring primary bone lymphomas (PBL), as well as nodal lymphomas, MRI better detects the local extent of the disease and cortical alterations[11]. PET-CT has become the standard imaging technique for staging PBL, despite data being derived from small retrospective series[11]. Bone marrow aspiration (with morphology and flow cytometry) and biopsy are indicated in extranodal MALT lymphomas, especially in non-gastric lymphoma and when only local treatment is planned[11]. The patient was screened for investigation of a primary tumor in other sites through CT scans, but no suspicious malignant lesions were found, as in the reported cases. PET/CT was not performed due to its unavailability. In this case, thoracic spine MRI detected a solid extradural expansile formation, displacing and compressing the dorsal spinal cord to the left. Surgical laminectomy was performed to define the histological type of the lesion, as indicated by the literature[10], confirming histopathological analysis of extranodal marginal zone lymphoma of MALT type.

During the laminectomy surgery, a mass was removed from the extradural intrathecal canal, which corresponds to a tumor within the spinal canal, but outside the CNS, between the vertebrae and the dura mater. The absence of a CNS biopsy prevents confirmation of a neurological origin of the lymphoma in question. Therefore, it is unlikely that the case presented primarily arose from the CNS.

Despite controversies regarding the definition of primary extranodal lymphomas, which could question the diagnosis of the case in question, primary extranodal lymphomas can be considered those lymphomas with no or minimal nodal involvement,

associated with predominant extranodal symptoms[5]. This definition is appropriate for the patient, given the absence of findings proving nodal involvement at other sites and manifestations and symptoms primarily related to spinal cord compression.

In relation to PBL, they are classified into three forms: PBL consisting of a single bone lesion with or without regional lymphadenopathy, polyostotic lymphoma characterized by multifocal disease involving only the skeleton, and disseminated lymphoma with secondary bone involvement[5]. In the case of the patient in question, she could be categorized as having the first type, with only a single bone lesion found, without evidence of lymphoma or other disseminated neoplasia in other parts of the body[5]. It is important to note that in this case, it can be discussed whether it is indeed a primary bone lymphoma. However, no other involvement that could represent an initial lymphoma in another site was found. Furthermore, bone marrow biopsy showed lymphocytic infiltration of small B cells (CD20+), paratrabecular location, suggesting bone involvement, as described in extranodal MALT lymphomas in 2% to 20% of cases[11].

There is a question of whether the case presented in this work could be a presentation of primary extranodal marginal zone lymphoma of MALT type in the CNS with contiguous bone involvement. It is also worth noting the presence of immunoglobulin G, with a value of 430 U/mL for the Epstein-Barr virus found in the patient's serological test. This virus is associated with the development of primary CNS lymphoma, although the relationship is more consistent in immunocompromised patients[2]. However, the normal CSF collected and lymphoma infiltration in the bone marrow argue against this hypothesis.

Given its rarity (5%), there is limited data on the management of indolent bone lymphomas. Globally, patients with localized disease are candidates only for radiotherapy, while patients with disseminated disease can be treated similarly to patients with other disseminated indolent lymphomas[5]. The patient received the final diagnosis of extranodal marginal zone lymphoma of MALT type - Stage IVB of the thoracic spine, and she underwent chemotherapy with 8 cycles of the R-CHOP protocol (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) due to the staging of the disease, followed by rituximab maintenance. During treatment, the patient showed improvement in motor response after 3 cycles of chemotherapy and received physiotherapy follow-up.

However, outside the CNS but within the vertebral canal, there are cases of extradural space lymphomas. One of the first reviews on the subject, conducted in 1976[15], gathered 94 patients with lymphomas involving the extradural space and evolving with spinal cord compression. This review highlights that the majority of patients had NHL (72 patients), and a minority had HL (22 patients). The most common initial symptom was pain, and 49 cases were considered primary or localized extradural lymphomas. In this study, all patients underwent laminectomy, and para-spinal involvement was detected in 28 patients, while direct involvement of vertebral bone was seen in 27 patients. This review may have been one of the first to describe lymphomas similar to the one reported in this study, involving extradural spaces causing spinal cord compression, with some cases also involving bone, as in this case. However, it should be noted that this pioneering

review did not describe immunohistochemical markers to determine the subtypes of these lymphomas[15].

It is worth noting that the cases found in the literature represent tumors that manifested with spinal cord compression and, in their histopathology and immunohistochemistry, proved to be extranodal marginal zone lymphomas of MALT type, with involvement of the spinal column, extradural and anatomically outside the CNS and dura mater. Thus, it is possible that these cases presented in the literature[10,14] share significant similarities, have similar pathophysiology mechanisms and origins as the one presented in this work, despite not reporting bone involvement. Therefore, the case in this report would represent a group different from the majority of others previously found, where there is an origin in the CNS, such as MALT lymphomas of the extranodal marginal zone originating in the dura mater or brain parenchyma. Because the reported case is a lymphoma formed in the intrathecal canal, in the vertebral canal but outside the spinal cord.

One limitation of this study is that a PET/CT scan was not performed on the patient in the case, as would be ideal for screening for lesions in other organs. Although the case has been followed for 8 years, in 2 cases in the review, the described follow-up was only 2 years, requiring a longer follow-up period, as recurrences or transformation into a high-grade lymphoma may still occur.

CONCLUSION

The presented case highlights an exceptionally rare occurrence of extranodal marginal zone lymphoma of MALT type, with primary involvement of the vertebral spine within the intrathecal canal, manifesting as spinal cord compression. A review of the literature revealed only two similar cases within the study period, neither of which involved bone marrow infiltration. The optimal treatment approach for such cases remains uncertain, with various strategies, including surgical resection combined with radiotherapy, being reported. Treatment decisions should be individualized, considering the tumor's location, stage, and the patient's clinical profile. Further research is warranted to investigate the potential of novel targeted therapies. Although the prognosis in the reported cases has generally been favorable, vigilant follow-up is essential to monitor for recurrence or progression to high-grade lymphoma.

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Moraes GLV: proposed the theme developed, carried out the bibliographic survey, participated in the collection, analysis, interpretation of data, writing of the work.
Frigotto KG: participated in the analysis and writing of the work and its final version.
Ferreira MN: interpreted the data, wrote the paper and revised the text.
Avila MGF: participated in the analysis, interpretation of data, and writing of the work.
Valviesse VRGA and Magalhães MC: participated in the theoretical discussion, writing of the work, revision of the text and elaboration of the final version of the work.
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