Management of metastatic spinal column neoplasms - an update

Manejo das neoplasias metastáticas da coluna vertebral - uma atualização

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A B S T R A C T

The increased survival of cancer patients due to the improvement and advancement of therapeutic modalities has promoted progressive increase in the prevalence of metastatic tumors of the spine, making it important for healthcare professionals to acquire knowledge in the field. Spinal column metastases are usually secondary to malignant neoplasm of the breast, lung and prostate, male gender being the most often affected and pain being the initial symptom in 90% of patients. It is estimated that 30-90% of terminally ill patients with cancer have metastases at some spinal column segment. Clinical history, physical and neurological assessments are critical to determine the degree and extent of the lesion, and therefore choose the appropriate imaging method to be requested. This study aims to perform a review and didactic description of the main aspects related to the physiopathology, diagnosis and treatment of this disease.

Key words: Patients. Diagnosis. Spine. Neoplasms. Neoplasm metastasis.

INTRODUCTION

The lungs, liver and skeleton are the sites with the highest incidence of metastasis in the human body [1-5]. The spinal column is the most commonly affected site in the skeletal system, and approximately 30-90% of patients with terminal cancer have metastases affecting the spinal column [1-3].

The highest incidence of spinal metastasis is found at the age group of 40-65 years, corresponding to the period of greatest risk of developing malignancies[3]. The male sex is the most commonly affected, probably due to the higher prevalence of pulmonary malignancy in this group, as well as the fact that prostate cancer tends to affect bone [3]. The presence of symptomatic spinal metastasis is the initial presentation in over 10% of all patients with malignancy and pain is the most common symptom, occurring in up to 95% of patients [1,3].

Spinal column metastases are usually secondary to malignant neoplasms of the breast, lung and prostate, reflecting the high prevalence of these tumors and their tendency to result in skeletal metastases [1,3-5]. Brihaye *et al.*[6] reported that 16.5% of symptomatic metastases were secondary to breast carcinoma, 15.6% to lung carcinoma and 9.25% to prostate carcinoma. Other solid tumors that often result in metastases of the skeletal system are renal, gastrointestinal and thyroid carcinomas [5]. Lymphoreticular neoplasms, including lymphoma and myeloma, often affect the spine as well; however, they are considered systemic diseases and do not represent true metastases[7]. In childhood, sarcomas (especially Ewing's tumor) and neuroblastomas are the most common histological types [8].

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PATHOPHYSIOLOGY

Metastases to the spinal column usually occur through hematogenous, lymphatic and cerebrospinal fluid (CSF) spread (the latter being rare) or direct invasion by contiguity. Symptomatic lesions are located in 70% of cases in the thoracic spine, 20% in the lumbosacral region, 10% in the cervical region and are multiple in 17-30% of patients [3,8,9].

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The hematogenous route is the main form of spread of neoplastic cells and usually occurs through the vertebral venous plexus of Batson. This plexus receives the venous drainage of the thoracic, abdominal and pelvic viscera and as a result of increased intracavitary pressure secondary to the presence of neoplasms, retrograde flow occurs to the veins, which are devoid of valves, with consequent neoplastic spread to the spine [3,8,9,10,11]. Breast neoplasms drain through the azygos system and often reach the thoracic spine. Prostate neoplasms drain through the pelvic venous plexus, usually affecting the lumbar spine. Lung neoplasms promote the spread of neoplastic cells through segmental arteries, affecting mainly the thoracic spine [10,11].

Metastases are classified based on the anatomical location into 3 groups: extradural, extramedullary and intradural intramedullary. The vast majority of lesions occur in extradural location, the initial implantation occurring in about 80% of the cases in the vertebral body. Extramedullary and intradural intramedullary lesions (Figure 1) are very rare and usually occur through CSF spread [3].

Classically, metastasis implants are more common in the postero-lateral region of the vertebral body. The explanation is the greater blood supply and bone mass in this region when compared with the posterior vertebral elements and because the vascular supply lies on the posterior and lateral regions of the vertebral body [8,12].

Symptoms are secondary to vertebral periosteum and cortex lesions associated with invasion of paravertebral tissues, compression of nerve elements and bone fragility, with subsequent pathologic fracture and segmental instability [3,4,8,10,13].

CHARACTERISTICS OF MOST FREQUENT HISTOLOGICAL TYPES

Breast

Breast cancer metastasis is the one with the greatest predilection for the skeleton. Osteolytic lesions are seen in approximately 80% of patients. The cases that initially present with bone metastases have a better prognosis when compared with those with extra-skeletal lesions, since breast neoplasms that cause bone involvement are estrogen-receptor positive and are far more differentiated than those from lung or liver [10,14].

Lung

Lung carcinomas comprise four cell types: squamous cell carcinoma, adenocarcinoma, small-cell carcinoma and large-cell carcinoma. The small-cell carcinoma is the one with the more indolent course, with greater survival period and, therefore, more likely to result in bone metastases. Treatment depends on the histological type, with the small-cell carcinoma being the one with better response to chemotherapy and radiotherapy [10,14].

Prostate

Spinal column metastases are common in prostate carcinoma. The most often affected area is the lumbar spine and the most common lesion type is the osteoblastic one, showing a dense and radiopaque aspect known as "ivory" vertebra sign. Treatment consists of different isolated or associated modalities, such as hormonal treatment, radiotherapy, chemotherapy and surgery [10,14].

CLINICAL MANIFESTATIONS

The most frequent initial symptom in patients with metastatic disease of the spinal column is pain, seen in approximately 90% of cases; thus, pain in cancer patients corresponds to metastasis until proven otherwise [1-4,7,8,10,13]. The pain symptoms can be divided into three categories: local pain, mechanical pain and/or radicular pain. Normally, pain secondary to metastasis is not relieved by rest, persists at night, lasts longer than 6 weeks and may be

Figure 1 - *Phase-contrast MRI of the thoracic spine in the sagittal plane – presence of breast carcinoma metastasis in the topography of the medullary conus.*

accompanied by loss of appetite and fever. Other associated symptoms are decreased muscle strength in the limbs, sensitivity alterations and loss of sphincter control [3,5,8,10].

DIAGNOSIS

History and Physical Examination

Patients with suspected spinal metastases should be thoroughly assessed and a careful physical examination is essential, including detailed history of the symptom onset, presence of systemic involvement, history of smoking, occupational exposure to ionizing agents and family history of neoplasia [3,4,9,13].

Neurological evaluation includes muscle function testing of upper and lower limbs. Sensitivity assessment is essential to define the affected spinal level. Deep tendon reflexes should be tested. The presence of hyperreflexia, abolished or asymmetric reflexes indicates lesions in nervous elements. Pathological reflexes such as Babinski and Hoffman should be investigated [10,15]. Digital rectal examination is mandatory to assess anal sphincter tonus, presence of pre-sacral mass or prostate abnormalities[10]. Neurological assessment is crucial to help define treatment, especially in patients with disease at multiple levels. The American Spinal Injury Association – ASIA – scale (Table 1) is often used to grade neurological deficit [3,8,16].

IMAGING DIAGNOSIS

Plain X-ray

A plain x-ray of the spinal column is the initial examination to be requested for suspected metastasis. Early lesions are difficult to detect, as 30% to 50% of trabecular bone must be destroyed before the x-ray shows any alterations; however, it is useful to evaluate qualitative changes of vertebrae, the affected anatomical site and the structural integrity of the spine [3,8,10]. The first radiological sign of metastatic lesion of the vertebra is the absence of the pedicle, demonstrated in the anteroposterior view [10,13].

The intervertebral disc is usually preserved in neoplastic lesions, unlike infectious conditions, where there is destruction of the adjacent vertebral plateaus and intervertebral disc [3,8,10,13].

Bone Scintigraphy

Scintigraphy evaluates the concentration of bone neoformation and is thus capable of detecting very small lesions, of up to 2 mm in size, in cortical or trabecular bone. Due to its high sensitivity and low specificity, scintigraphy is a useful modality for screening, but it is not appropriate for diagnosis [3].

However when the diagnosis is confirmed, it can help determine the extent of the metastatic process in the skeleton [3,8,10] (Figure 2).

Computed Tomography

Computed tomography (CT) with multiplanar (axial, sagittal and coronal) and 3D reconstructions, allows detailed assessment of bone architecture and therefore the accurate determination of viable residual bone, helping to define the best surgical approach (Figure 3). CT is inferior to MRI in demonstrating the muscular- ligamentous complex, spinal cord and extent of neoplasia [3,10].

Positron-Emission Tomography

Positron-emission Computed tomography (PET) with [18F] fluorodeoxyglucose (FDG) is superior to scintigraphy when determining skeletal metastases [3]. The great usefulness of this examination modality lies in cancer patient staging and the differentiation between degenerative bone disease and fracture caused by the neoplastic lesion, which is often difficult to achieve with other imaging techniques [17]. Quantification of FDG is used to monitor the neoplasia in relation to adjuvant therapy response [17]. The use of this modality is currently restricted in our country due to its high cost [3,17]

Magnetic Resonance Imaging

Magnetic resonance imaging is currently considered the modality of choice in the evaluation of

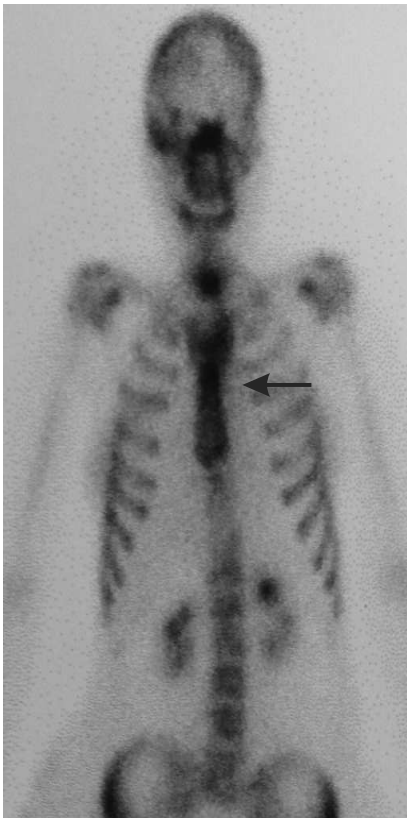

Figure 2 - *Scintigraphy showing involvement of multiple vertebrae in the high thoracic spine segment of the spinal column.*

metastases of the spine, allowing proper assessment of the morphology and extent of the neoplasm [3,4,8,10,13,18]. The specificity is 97% and sensitivity is 93% for the diagnosis of medullary compressions [8]. The high sensitivity of this method is due to the superior resolution, when compared with other modalities, to define vertebral soft tissue structures, including the intervertebral discs, roots, meninges, spinal cord, muscular and ligamentous complex and paravertebral muscles [3,4,10,13,18].

The evaluation of the patient with suspected spinal metastasis should include all segments of the spine in images in the sagittal view, with and without contrast, reserving the images in the axial and sagittal planes with the contrast agent for regions with abnormalities or evidence of metastasis [8,18].(Figure 4A and 4B)

TREATMENT

Therapeutic modalities are aimed at symptom control, neurological function preservation and improved quality of life.

The Karnofsky scale is classically used to stratify patients regarding functional performance [8,19] (Table 2). The scale by Tokuhashi *et al.* [20] (Table 3) is the most commonly used system in neurosurgical practice to estimate survival in months of patients with spinal metastases and help to decide on the type of treatment. A score of 0-8 represents a life expectancy of less than 6 months and involves conservative treatment; a score of 9-11 represents a life expectancy between 6 and 11 months and palliative surgical treatment is appropriate, and a score of 12-15 implies a survival higher than 12 months and the patient can benefit from radical surgical treatment [20]. We will perform a review of the main clinical and surgical treatment methods.

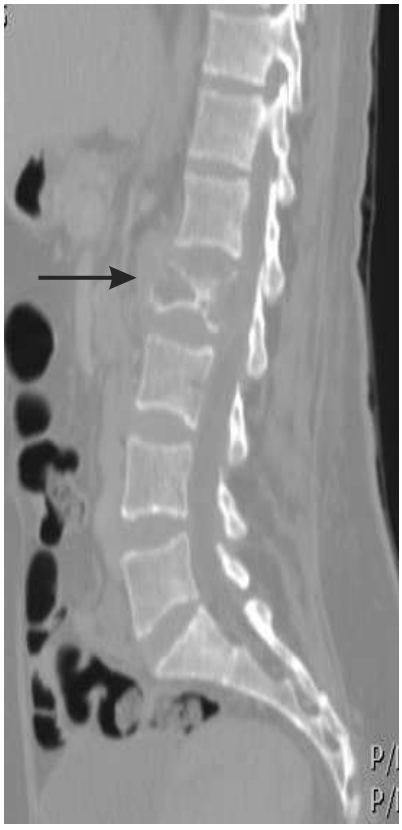

Figure 3 – *Lumbosacral spine CT in the sagittal plane (bone window) - presence of L2 body fracture secondary to lytic metastases of pancreatic carcinoma.*

Drug control of pain

Vertebral metastases result in pain that has either neuropathic or nociceptive origin, or both. The inadequate management of pain in cancer patients contributes to depression, anxiety, fatigue and consequently to unsatisfactory response to treatment [3]. Initially the pain of nociceptive origin should be managed with conventional painkillers; in our country, paracetamol, ibuprofen and dipyrone can be used. It is often necessary to introduce opioid therapy, which is initially administered orally; the dose must be increased with the goal of completing pain control without the addition of side effects. The neuropathic pain secondary to the involvement of nerve roots or plexuses is more effectively controlled with anticonvulsants, tricyclic antidepressants and neuroleptic agents [3,5].

Corticosteroids

Corticosteroids reduce the inflammatory process, thus decreasing pain in the metastatic pictures, as well as reducing vasogenic edema of the nerve structures, with improved neurological status. They show oncolytic activity, mainly on lymphoma, multiple myeloma and breast carcinoma. Dexamethasone is often used and there is no consensus on the optimal dose – higher doses of up to 96 mg/day and lower doses of 16 mg/day can be used [1,3,5,8]. In neurosurgical practice the dose should be individualized and an adequate initial dose is 16 mg/day.

Bisphosphonates

The main action of bisphosphonates is to inhibit osteoclastic activity, with suppression of bone resorption related to bone metastases. There is evidence of reduced pathological fractures, pain control and reduction of malignancy-induced hypercalcemia. Pamidronate disodium is used at a dose of 90 mg every 4 weeks [3,5,21].

Chemotherapy and hormonal therapy

The use and choice of the chemotherapeutic agent is directly related to the tumor histological type and biology. The neoplasms that usually respond to chemotherapy agents are lymphomas, breast carcinomas and germ-cell tumors [3,8].

The spinal column metastases that respond to hormonal therapy are those originating from breast and prostate cancer. The response to this modality is related to

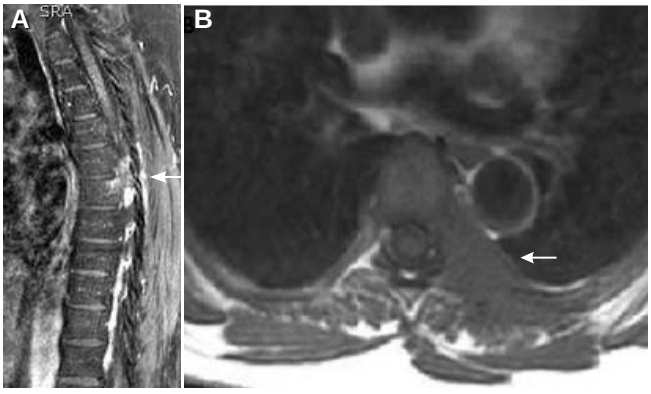

Figure 4A – *Phase-contrast MRI of the thoracic spine in the sagittal plane – presence of metastasis of cervical cancer in the body of T6.* ***4B*** *- Axial view showing no metastatic invasion of the costal arch, pedicle and left postero-lateral region of the body of that vertebra.*

the presence of receptors. Some drugs that selectively block estrogen receptors such as tamoxifen and aromatase inhibitors such as letrozole, anastrozole and exemestane have shown to be effective against breast carcinoma [3,22]. In prostate carcinoma, GnRH agonists and antiandrogens such as flutamide and bicalutamide are effective drugs in the control of neoplastic growth, by drastically reducing serum testosterone levels [23].

Radiotherapy and Radiosurgery

The indications for radiotherapy in spinal metastases include high tumor radiosensitivity and in cases of myeloma, lymphoma, testicular seminoma and small-cell lung carcinoma. Patients that have minimal or no neurological deficit, unable to tolerate the surgical procedure, with involvement of multiple vertebral levels (> 2), with pain resistant to other treatment modalities, KPS < 70 and those with life expectancy less than 3 months are candidates for radiotherapy [1,8]. The irradiated site usually involves the affected vertebra and a 5-cm margin, with subsequent irradiation of surrounding tissues including the spinal cord. The irradiation of adjacent tissues can cause radiation-induced myelopathy, with consequent impact on neurological function [8]. Radiotherapy is usually carried out in 8 to 10 fractions, with a total dose of 25 to 40 Gy [1].

Radiosurgery uses stereotactic location to define the irradiation site, which grants great precision to the method. With radiosurgery, only the chosen target is irradiated, so it is possible to use high doses of radiation in a single session without the risk of injury to adjacent tissues [1,3]. The main indications of radiosurgery are absence of biomechanical instability of the spine, absence or minimal neurological deficit, involvement of a maximum of 2 adjacent vertebral levels, KPS > 70% and life expectancy > 3 months [24]. The total dose used is around 8 to 18 Gy [24].

Surgical Treatment

The choice of the neurosurgical access depends on several factors, such as patient life expectancy (Scale of Tokuhashi et al. [20]), clinical status (KPS) of the affected vertebral segment, degree of spinal instability, degree of neurological impairment, available resources at the hospital and the neurosurgeon's experience.

Kyphoplasty and vertebroplasty are minimally invasive procedures performed in the lumbar and/or thoracic column, indicated in patients with axial pain secondary to vertebral body collapse and no evidence of nerve structure compression. Vertebroplasty consists in the percutaneous injection, usually through the vertebral pedicle, of methyl methacrylate (bone cement) into the vertebral body[8,10].

In kyphoplasty, differently from vertebroplasty, previous dilatation of the collapsed vertebral body is performed with an appropriate balloon, forming a cavity that allows injection of the aforesaid substance with gradual pressure. Both procedures are performed under the guidance of radioscopy or computed tomography and aim to fill the anterior two thirds of the body with methyl methacrylate and consequent correction of deformity [1,3,4,8,10]. The major complications of these methods are inadvertent methyl methacrylate leakage into the spinal canal, with consequent damage to nerve structures and substance absorption by the epidural plexus vessels, causing pulmonary embolism [8]. Pain control is possible in 50-80% of cases [4].

In patients with significant compression of nerve elements, associated to significant instability of the spine, it is necessary to perform decompression of the spinal cord, vertebral body reconstruction and spinal stabilization in order to maintain the anatomical and biomechanical properties of the spine and preserve neurological function [1,4,8,10,13].

Surgical access to the spine may be performed by the anterior route, the posterior one, or a combination of both. The anterior approach aims to provide access to the vertebral body, which can be achieved through anterior cervicotomy, thoracotomy or thoracoscopy, retroperitoneal laparoscopy or laparotomy, depending on the affected vertebral segment. These routes are used in cases with indication for anterior decompression via corpectomy or vertebrectomy. After decompression, it is crucial to reconstruct the body with titanium implants (cage, plates and screws). The posterior approach is most often used in neurosurgical practice and is based on laminectomy followed by fixation of the adjacent vertebrae with transpedicular titanium screws. The extent of fixation depends on bone quality, the vertebral segment, the type of implant and the presence of metastases in other vertebrae [1,4,10].

In brief, the rationale for the surgical treatment of vertebral metastases is the possible improvement in neurological deficit, pain control, histopathological diagnosis, vertebral body reconstruction and stabilization of the affected segment.

CONCLUSION

The treatment of spinal column metastases should be individualized and multidisciplinary, involving neurosurgeons, oncologists, cancer surgeons, radiation therapists, physiatrists, pain specialists, psychologists and others. The rational choice of treatment modality should be based on the patient's clinical and neurological condition, life expectancy, degree of spinal involvement, histological tumor type and the expectations of patients and their families, aiming at neurological function preservation and improved quality of life.

R E S U M O

O aumento da sobrevivência do paciente oncológico decorrente da melhoria e do avanço das modalidades terapêuticas promove progressivo aumento da prevalência das neoplasias metastáticas da coluna vertebral, tornando o seu conhecimento condição sine qua non *para os profissionais da área de saúde. As metástases na coluna vertebral são usualmente procedentes de neoplasia maligna da mama, pulmão e próstata, o gênero masculino é o mais acometido e a dor é o sintoma inicial em mais de 90% dos pacientes. Estima-se que 30-90% dos pacientes com câncer em estágio terminal apresentem metástase em algum segmento da coluna vertebral. A alta prevalência das neoplasias malignas e a significativa experiência dos autores no tratamento das metástases na coluna vertebral motivaram uma atualização do tema. Acreditamos que a padronização da conduta e o conhecimento pormenorizado dos principais aspectos da doença, podem promover a melhor opção terapêutica. O presente estudo visa à revisão e descrição didática dos principais aspectos relacionados à fisiopatologia, diagnóstico e tratamento desta entidade.*

Descritores: *Pacientes. Diagnóstico. Coluna vertebral. Neoplasias. Metástase neoplásica.*

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