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Metastasis of breast cancer to the bone

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Abstract

Spinal metastases are a complex but common manifestation of primary cancer. The most common use of spinal metastases is breast, lung and prostate cancer. Management of patients suffering from spinal metastases, which take into account the characteristics of cancer and various methods of treatment consisting of surgery, radiotherapy and chemotherapy. Metastatic spine cancer surgery is used with a low risk of complications because it results in significant relief of pain and long-term survival burdens. Pain relief, prevention of bone complications and maintenance of quality of life are included in the recommendations in metastatic bone disease. Knowledge related to the pathophysiology of painful metastases is changing quite quickly. However, for analyzing the pathophysiology of painful bone metastases may be the key to analgesic effects with minimal side effects.

Keywords: breast cancer, spine cancer metastases, pain

Admission

Breast cancer is the most common malignancy in women. Genetic predisposition to developing breast cancer relates to the carrier of BRCA1, BRCA2 genes, which significantly increase the risk of developing the disease. Diagnostic tests for breast cancers should include palpation, mammography, breast ultrasound, chest radiography and scintigraphy. The determination of the expression of ER (estrogen) and PgR (progesterone) receptors, which are responsible for response to hormone therapy, is important in assessing clinical advancement. Determination of HER 2 (epidermal growth factor receptor), which is an adverse prognostic factor, is of great clinical importance. The division of breast cancers concerns non-infiltrating (ductal or lobular) or infiltrating (ductal, lobular, medullary and mucous) cancers. [1]

Pathogenesis of metastases to the spine

Breast cancer is the most common malignancy among patients around the world. Overall survival of breast cancer over time has increased. This is the result of progress achieved in early diagnosis and effective treatment of primary tumors. [2] Bone is a common site for metastasis, and breast cancer, along with prostate and lung cancer, is one of the most common tumors that form bone lesions. [3] These bone changes can cause serious skeletal complications, including compression of the spinal cord or nerve root, bone surgery, tumor hypercalcemia, pathological fractures, and severe bone pain requiring palliative radiotherapy. The bone has a particularly difficult and varied anatomical structure, and its understanding is necessary for a good understanding of the mechanisms occurring in cancer processes within it. It undergoes continuous reconstruction process, which is characterized by its resorption with the participation of osteoclasts and repair with the participation of osteoblasts. The resorption process is activated by osteoblasts that stimulate osteoclasts to destroy bones. After hollowing the resorptive cavity, osteoclasts undergo necrosis, and osteoblasts line it and produce osteoid, which gradually mineralizes. Metastatic cancer is the most common bone tumor. After diagnosis of bone metastases, overall survival of patients with breast cancer significantly decreased and life expectancy was 2-3 years. [3,4] Post-mortem examinations are detected in approximately 30-40% of cancer patients. Over 80% of bone metastases are caused by breast, prostate, lung and kidney cancer. Within the bone affected by metastasis, the following

processes are underway: the formation and enlargement of a metastatic tumor, and bone resorption and reconstruction.

The location of tumor metastasis cells is not accidental and depends on the type of histological lesion, primary location, anatomy as well as the vasculature and receptors present on the tumor cells. [5] The spongy bone is well supplied with blood and has a slowed flow, which is a convenient place for implantation of cancer cells. In metastatic bone, there are always two opposing processes involving bone formation and bone resorption. The healing problem is metastasis causing bone destruction, often leading to pathological fractures. The theory of the formation of distant bone metastases through the circulation of cancer cells in the venous system and the colonization of tissues convenient for development explains about 30% of the metastases formed. It assumes that cancer cells inhabit the first organ or tissue encountered and is closely associated with the anatomy, and especially the vascularization of the body. One of the first researchers to create secondary outbreaks was Stephen Paget, who in 1889 presented his theory called 'grain and soil'. It assumes the interaction of cancer cells and host cells with each other on the soil. Only when the 'seed' and 'soil' match each other does a secondary outbreak occur. [6] For metastasis to occur, not only adequate anatomical structure is needed, but also the specific "affinity" of cancer cells for a specific tissue. The theory explains the formation of bone metastases. Current treatment options for bone metastases rely on surgical resection and stabilization. These methods are effective for individual changes. Patients with multiple metastases or poor general condition are not eligible for surgery. [7]

The ability to form distant metastases is the most typical and most important feature of malignant tumors. Metastasis occurs through the lymphatic and blood vessel system. In about 20% of cases, bone metastasis is the first sign of cancer and forces you to differentiate with primary bone tumors, inflammatory diseases, or endocrine disorders. Symptoms of metastases are revealed in 30 - 60% of patients with bone metastases. The most common and earliest symptom that is manifested is pain. Pain is heterogeneous, especially at night, not related to effort. Three categories of metastatic spine pain are commonly distinguished. Biological pain - occurring at night and in the morning, is constant, disappears after steroids and radiation therapy. It is caused by the secretion of cytokines (serotonin, bradykinin, PGE1, PGE2) by macrophage cells, periosteal irritation, and stimulation of intraosseous nerves. Neurogenic pain associated with neuropathy or myelopathy may be localized within the dermatome, banding the chest or radiating to the limb at the cervical and lumbosacral location. Patients have a symptom of neuropathy associated with instability of the spine resulting in tightening of intervertebral holes during movements. Myelopathy is manifested by the weakening of physiological reflexes

and the appearance of pathological reflexes. Muscle weakness, pain and temperature are impaired.

Autonomic disorders may occur with urinary and stool retention. Isolated disorders of voiding and defecation in the absence of paresis and sensory disorders indicate damage to the spinal cord end cone or tumor in the sacrum. Mechanical pain increases after exercise, walking, and decreases after rest and immobilization of the spine. Mechanical and root pain (associated with spinal instability, axis disorder and pathological fractures) do not respond to inoperable treatment (steroids and radiation therapy). Opioid analgesics and immobilization give relief. Mechanical pain is usually greater if the pathology concerns the segment of the spine with greater mobility, i.e. the cervical and lumbar. The spine is the most common metastasis in breast cancer and can cause severe pain that worsens patients' quality of life and is difficult to treat. Pain from spinal metastases also appears when there are no fractures or nerve compression. [8] Bone metastases can lead to pain by stimulating nociceptors. The involvement or invasion, stretching or squeezing of pain-sensitive structures, such as nerves, blood vessels and periosteum, and microcracks in various joint structures can also lead to pain. Pain due to bone lesions may also be due to the mechanical instability of "weakened bone" or high intraosseous pressure. [9]

It is estimated that 70-80% of patients with metastases have varying degrees of sensory disturbances. Paresis is observed in about 60%, while voiding and defecation disorders in 14 - 77% of patients. A change in the shape of your spine or a noticeable tumor are less common symptoms. Palpable lumps and deformations in the bone area should be alarming signals, because a broken bone is already a symptom of advanced stage of the disease. Not often metastatic tumors are large enough to cause pressure on neighboring structures, thereby causing ischemia or organ dysfunction.

A characteristic symptom is disturbed body posture. Tenderness of the spinous processes, spinal axis disorder, are often found. Paralysis and paresis appear late. Neurological symptoms occur in the form of sensory disturbances, muscle weakness, root syndromes, voiding disorders or defecation.

Bone metastasis to the bone marrow, mainly consisting of hematopoietic stem cells (HSCs) located in two different biological structures, is required for bone metastasis. Communication between tumor cells and hematopoietic bone marrow stem cells is important for the development of bone metastases. Bone metastases consist of consecutive stages including: tumor growth (detachment of cancer cells and invasion of the tissue stroma), neoangiogenesis, extravasation of the tissue, survival in circulation, chemotraction (retention of the bone marrow

endothelial vessel wall, establishing a microenvironment with metastasis through interaction between cancer and bone cells [10].

Discussion

Metastatic spine disease (MSD) is a serious event in cancer patients. Experimental data indicate that bone metastases are mediated mainly by blood flow-dependent, passive arrest of circulating cancer cells into a niche with bone metastases (BMN). In research Onken JS et al. experimental observations in clinical conditions were tested. Retrospective examination of 507 patients treated for spinal metastases in our facility in the years 2005–2015. Data analysis included bone metastasis locations, underlying malignancies, and time to MSD development. The pattern of bone metastasis prevalence was correlated with the content of red bone marrow (RBM) in the corresponding bone as a measure of blood flow. Spinal metastases were most common in lung cancer (21%), prostate cancer (19%) and breast cancer (12%). When MSD is diagnosed, most patients have multiple bone metastases outside the spine (2/3). The distribution of bone metastases outside the spine and the spine is mainly proportional to the content of RBM in the affected bone. According to the high RBM content, the thoracic spine, pelvic bones and ribs are the privileged site for bone metastases. Regarding bone metastases, all primary cells show a uniform distribution pattern, confirming the hypothesis that cancer cells depend mainly on blood flow and passive BMN retention, and not on spine-specific guiding mechanism. prostate cancer (19%) and breast cancer (12%). [11]

The results of metastatic changes of the spine depending on their location were presented in the considerations of Chang SY et al. Metastatic changes concerned the cervical spine in 21 cases, the thoracic in 60 people, the lumbar in 34 and the sacrum in 2. The research of Chang SY et al. Shows that in the studied group of patients lung cancer was the most common site of primary malignant tumor (n = 29.3%), followed by breast, liver, kidney and prostate cancer. [12]

Coleman et al., Presenting individual individual experiments, found among those patients with breast cancer whose disease first metastases to the bone, a subset of purely bone patients. These patients were elderly and mostly had lobular cancer and minimal axillary lymph node involvement at the time of diagnosis. The median survival of these patients with pure bone disease was 2.1 years. Coleman et al. Studies provide information that breast cancer with bone metastases is characterized by a good response to hormone therapy as well as systemic therapy. [13]

The treatment of primary cancers continues to improve, and patients diagnosed with cancer live statistically longer. Therefore, it is suggested that the number of patients with spinal metastases will increase. Spine tumors can have a devastating effect on quality of life and cause complex neurological sequelae as a result of e.g. compression of the spinal cord. The management of spinal metastases does not have one scheme, but the importance of surgical treatment of these patients is very important. Patchell et al. Demonstrated increased post-operative survival in a groundbreaking randomized controlled study comparing surgical decompression and radiotherapy versus radiotherapy alone for compression spinal metastases. The operation of metastatic spine disease is at all risk of non-oncological spine surgery, with additional complicating factors of radiation, chemotherapy, coagulopathy and medical fragility of cancer patients. Potential benefits are required to make informed decisions about whether to continue surgery. [14]

Conclusions

Bone metastases can be a paralyzing complication of various cancers. Patients often remain bedridden or wheelchair-bound, and suffer from pain. Pain relief, prevention of bone complications and maintenance of quality of life are the main goals in the treatment of patients with metastatic bone disease. Knowledge related to the pathophysiology of painful metastases is changing quite quickly. However, it is the analysis of the pathophysiology of painful bone metastases that may be the key to improving the analgesic effect with minimal side effects. It is expected that potential future therapeutic agents used in this type of disease entity may change the current pharmacological approach and lead to better results in the treatment of patients and improvement of their quality of life. Strategies for treating pain in patients with bone metastases include a range of non-pharmacological approaches. These can be: physical medicine methods, tai chi, yoga, muscle stretching and stretching methods, thermotherapy, cold medicine. Galvanic ultrasound is recommended for physical treatment. In the area of therapeutic techniques, methods of behavioral medicine, cognitive-behavioral therapy, mediation, hypnosis, relaxation techniques are listed. A better understanding of the pathophysiology of painful bone metastases can lead to an improvement in pain relief with minimal side effects by using targeted therapy. Potential future therapeutic agents for the treatment of painful bone metastases are expected to revolutionize current pharmacological approaches and lead to better patient outcomes by improving their quality of life.

Reference:

1. Carey L.A, Ahmed A.A et al.; Molecular classification and molecular forecasting of breast cancer: Ready for clinical application? *J.Clin. Oncol.* 2005, 23, 7350 - 360.
2. Siegel RL, Miller KD, Jemal. Cancer statistics, 2018. *CA Cancer J Clin.* 2018 Jan;68(1):7-30.
3. Li S, Peng Y, Weinhandl ED, I in. Estimated number of prevalent cases of metastatic bone disease in the US adult population. *Clin Epidemiol.* 2019; 4:87-93.
4. Zhang H, Zhu W, Biskup E, Yang W, Yang Z Incidence, risk factors and prognostic characteristics of bone metastases and skeletal-related events (SREs) in breast cancer patients: A systematic review of the real world data. *J Bone Oncol.* 2018 Feb 3;11:38-50.
5. Guzik G. Przerzuty do kręgosłupa – diagnostyka i leczenie. Alfa- medica press. 2015. 39-51.
6. T Fidler IJ (2003) The pathogenesis of cancer metastasis: the “seed “ and “soil” hypothesis revised. *Nature Cancer Rev* 3: 453 - 458.
7. Suva LJ, Washam C, Nicholas RW Bone metastasis: mechanisms and therapeutic opportunities *Nat Rev Endocrinol.* 2011 Apr;7(4): 208-18.
8. Larid BJ, Walley J, Murray GD Characterization of cancer-induced bone pain: an exploratory study. 2011; 19 (9): 1393-401.
9. Christie JM et al (1998) Dose-titration, multicenter study of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients using transdermal fentanyl for persistent pain. *J Clin Oncol* 16(10):3238–3245.
10. Hwang SS, Chang VT, Kasimis B (2003) Cancer breakthrough pain characteristics and responses to treatment at a VA medical center. *Pain* 101(1–2):55–64.
11. Onken JS, Fekonja LS, Wehowsky R, Hubertus V, Vajkoczy P. Metastatic dissemination patterns of different primary tumors to the spine and other bones. *Clin Exp Metastasis.* 2019.
12. Chang SY, Chang BS, Lee CK, Kim H. Remaining Systemic Treatment Options: A Valuable Predictor of Survival and Functional Outcomes after Surgical Treatment for Spinal Metastasis. *Orthop Surg.* 2019 Aug;11(4):552-559.
13. Coleman RE, Smith P, Rubens RD. Clinical course and prognostic factors following bone recurrence from breast cancer. *BR J Cancer* 1998;77:336-340.
14. Patchell RA, Tibbs PA, Regine WF i in. Bezpośrednia dekompresyjna resekcja chirurgiczna w leczeniu ucisku rdzenia kręgowego spowodowanego rakiem z przerzutami: Badanie randomizowane. *Lancet* 2005; 366: 643-8.