Depression and anxiety in recurrent giant cell tumor of bone

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Abstract

Giant cell tumor of bone (GCTB) is a benign neoplasia more frequently encountered in young females. The pathogenic and evolutionary dynamics of the disease is strongly influenced by the presence of depression and cellular mechanisms, especially proinflammatory and immune. Although it is not a malignant tumor, it is often recurrent, which determines a high level of depression, anxiety, and fear of the patients. Cytokine mechanisms, especially through increased tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6), as well as the involvement of the receptor activator of nuclear factor-kappa B (RANK)–RANK ligand (RANK-L) system, can be correlated with the risk of malignancy. Unfavorable evolution is associated with persistent pain, difficulties of movement and body dysmorphic symptoms. The diagnosis is based mainly on histopathological (HP) assessment. The patients can be treated with pharmacological agents (Denosumab), surgery with tumor excision, reconstruction or osteosynthesis, and radiotherapy. Patients with GCTB require HP and imaging evaluations, especially of relapses, to detect the risk of metastasis or malignancy, simultaneously with psychological and psychiatric monitoring to detect depression, addictive behaviors, and suicide risk. It is necessary to evaluate in a multidisciplinary team to avoid unfavorable oncological and psychiatric developments. Through its clinical, HP, and therapeutic features, GCTB has multiple connections with the psychological and psychopathological dimension.

Keywords: giant cell tumor of bone, depression, anxiety, pain, cytokine.

Introduction

Giant cell tumor of bone (GCTB) or osteoclastoma is a benign neoplasia which represents approximately 4–10% of all primary tumors located in the bone system [1, 2]. This type of tumor occurs most commonly in young people aged 20–45 years, especially affects the metaphyseal and epiphyseal areas of long bone, such as femur, tibia, radius or humerus. This tumor is more common in women and can be diagnosed in patients over 50 years old [3]. The main symptoms are represented by local chronic pain, swelling, difficulties of movement of the adjacent joint [1, 3, 4]. Acute pain is associated with pathological bone fracture, which can occur in 15–20% of cases due to bone destruction or trauma [5]. Persistent pain that accompanies neoplasms (benign or malignant) is a major risk factor for depression [6] and suicidal behavior [7, 8].

Neurobiochemical support of depression and suicide risk may be correlated with dopaminergic system dysfunction due to chronic pain [9]. Dopamine deficiency predominates in the mesolimbic system, associating affective comorbidities related to the dysconnectivity of the nucleus accumbens with the frontal cortex and amygdala. These comorbidities associated with chronic pain are mainly represented by depression and vulnerability to addictive behavior, depression can have a prevalence of up to 30% [10]. Before the onset of depression, an increase in anxiety and social stress was observed, which often delays the diagnosis of depressive disorder.

Diagnosis and treatment options in GCTB

The diagnosis of GCTB consists in radiological evaluation and bone biopsy. If the tumor is recurrent, computed tomography (CT) scan is needed to exclude lung metastases [11, 12]. Metastases can occur in 1–9% of cases, most commonly found in the lungs and rarely occur in lymph nodes, skin or even other bones. Histopathological (HP) examination of metastatic nodules showed a benign character, similar to that of the primary
tumor [13]. Treatment of the primary tumor consists in surgical resection followed by reconstruction with cement, internal fixing with plate and screws, or bone grafting [14–16]. Relapses can be observed in 2.5% to 45% of the cases, depending on the location of the tumor and the surgical method used in the treatment of the primary tumor [17].

The treatment of relapses consists in surgical resection or, if the resection cannot be performed, radiotherapy and embolization. Pharmacological treatment may use bisphosphonates in neoadjuvant settings for targeting osteoclast-like giant cells inducing apoptosis and limiting the progression of the tumor [18, 19]. Denosumab is the only drug approved by The United States Food and Drug Administration (FDA), for patients with unresectable, recurrent or metastatic GCTB, or in cases where surgery has a high risk of death [20]. Denosumab is a monoclonal antibody [immunoglobulin G2 (IgG2)] of fully human type, which decreases bone resorption by specific binding to the receptor activator of nuclear factor-kappa B ligand (RANK-L), which inhibits the RANK receptor [5, 21].

The psycho-pathological dimension in GCTB

Even though GCTBs are benign, they bring an important psychology response associated with the fear of relapse, metastasis or malignant and the presence of pain and difficulties of movement. This fear of recurrence is probably similar to the fear of cancer recurrence, associated with young age, severity of physical symptoms (especially pain) and functional impairments and the presence of stress-inducing factors [22]. In addition to the possibility of recurrence or metastasis of GCTB, the ability of malignancy was highlighted, with a variable rate of 1–11%, an aspect that positions it in a real challenge for the clinician. Aggressive tumor growth and local recurrences are risk factors for metastasis [23], while depressive-anxiety disorders may be considered risk factors for GCTB recurrence.

The association with depression and multiple recurrences seem to favor malignancy, which is why the correct strategies to approach this pathology must be interdisciplinary [24–26]. Regardless of the prognosis of GCTB, persistent chronic pain favors the risk of developing suicidal ideation and behavior, but also of depression frequently accompanied by addictive tendencies, especially by dopaminergic deficiency [27, 28]. On the other hand, body dysmorphic symptoms and social isolation may occur in GCTB, which can be interpreted by the “interpersonal psychological theory of suicide” as risk factors for suicide [29].

In the treatment of malignant tumors, the approach is interdisciplinary and psychopathological manifestations, especially depressive-anxiety disorders, and stress, are recognized as evolutionary and prognostic risk factors. In the case of benign tumors, this translational strategy is less considered. GCTB highlights, through its clinical, HP and therapeutic particularities, the multiple connections with the psychological and psychopathological dimension. This relationship is amplified by multiple recurrences and surgical bone reconstruction therapies, which can cause body dysmorphic symptoms, but also by persistent pain. These symptoms are risk factors for the development of depressive disorder with suicidal potential. In this context, must be understood the multidisciplinary aspects and the multifactorial mechanisms involved in the therapeutic and recovery process that suggest the imperative need for an interdisciplinary approach. Even if GCTB is benign, it cannot be overlooked that persistent pain, body dysmorphic symptoms, and decreased adaptive coping capacity are evolutionary and prognostic risk factors, which are common to those with malignancies. This similarity raises the suspicion that malignancy could be favored precisely by the multisystemic inflammatory, angiogenetic, and cellular mechanisms favored by depressive disorder.

Histopathological assessment

From a clinical point of view, the diagnosis of GCTB goes through several stages, the initial one being dominated by pain, motor dysfunction, depression, anxiety, and fear of a possible oncological diagnosis. After surgery for tumor resection, patients experience a false impression of healing, not being psychologically prepared for possible recurrences or risks of metastasis, especially in the lung, or even malignancy. Usually, the initial therapy is based on pharmacological treatment with analgesics, anti-inflammatory drugs and sometimes anxiolytics, without obtaining good quality results. Patients with suspected GCTB are referred to surgery for HP diagnostic evaluation to confirm the diagnosis. The evolution of GCTB is often associated with a favorable prognosis, but may be accompanied by local recurrences, persistent pain that exacerbates depressive disorders, with the occurrence of a possible risk of malignancy.

HP examination can most frequently highlight the following disease-specific variants: numerous giant multinucleated cells with osteoclastic aspect, uniformly distributed in a proliferation of mononucleated cells, round-oval and fusiform, with mitotic rate of 7 mitoses/10 high-power fields (HPFs) (×40 objective fields). Nuclear characteristics of the multinucleate cells were similar with the mononucleated ones. No tumor necrosis, but tumor proliferation consists of polygonal or ovoid mononucleated cells, with vesicular nuclei, fusiform cells with long vesicular nuclei, arranged in interlaced beams. Frequent giant multinucleate cells with osteoclastic aspect, variate size, density and position, multiple vesicular nuclei in resemblance with stromal cell’s nuclei. Frequent mitoses, over 10 mitoses/10 HPFs. Hemorrhagic areas, no necrosis, small areas of fibrosis. Tumor proliferation is osteolytic, relatively rare bone lashes, sub periosteal with the invasion of periosteum (Figures 1–4; Figure 5, A and B).

Immunostaining highlights giant multinucleate cells positive for cluster of differentiation 68 (CD68), fusiform cells positive for alpha-smooth muscle actin (α-SMA), cytokeratin (CK) AE1/AE3 negative (no epithelial cells), p53 protein positive in 30% of the fusiform cellular nuclei, Ki67 index positive 10% in fusiform component (Figures 6 and 7, A and B; Figure 8, A–C; Figures 9 and 10, A and B).
Figure 1 – Proliferation of mononuclear cells with sporadic typical mitotic figures, including frequent large-cell nuclei with multiple nuclei (over 20/cell), sporadic intratumoral lymphocytes. Hematoxylin–Eosin (HE) staining, ×100.

Figure 2 – Remnants of bone lashes, marginal to tumor proliferation. HE staining, ×200.

Figure 3 – Tumor proliferation with multiple nucleated cells with more than 50 nuclei. HE staining, ×400.

Figure 4 – Bone tumor detail with mononuclear cells and multinucleated cells. HE staining, ×100.

Figure 5 – (A) Bone tumor detail with typical mitosis in mononuclear cells. (B) Bone tumor detail with sporadic mitosis in mononuclear cells. HE staining: (A and B) ×400.
Figure 6 – (A and B) Bone tumor with positive immunoreaction to α-SMA in mononucleate cells. Anti-α-SMA antibody immunomarking: (A) ×100; (B) ×200. α-SMA: Alpha-smooth muscle actin.

Figure 7 – (A and B) Bone tumor with negative immunoreaction to desmin. Anti-desmin antibody immunomarking: (A) ×100; (B) ×200.

Figure 8 – (A–C) Bone tumor with positive CD68 immunomarker in multicellular cells and dispersed mononuclear cells. Anti-CD68 antibody immunomarking: (A) ×50; (B) ×100; (C) ×200. CD68: Cluster of differentiation 68.
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Multifactorial model of psychiatric disorders in GCTB

GCTB tumor, due to the constant presence of pain generated by the disease but also by resection and reconstruction surgery, frequently associates severe depression, which can be present even in 85% of patients with chronic pain [30]. Reconstructive surgeries are associated with increased distress due to excessive pain and alteration of body image perception. This rises the anxiety levels and the risk of suicidal behavior [8, 31]. In psychiatric disorders of bone tumors, it is important to choose a proper antidepressant therapy, that would not increase prolactin levels, these being involved in bone loss [32, 33], but it would be efficient in obtaining a stable remission of depression and anxiety, incomplete remission favoring immune system dysfunction [34] (Figure 11).

The association of psychological factors of stress, especially of depression, favors the increase of cytokine-type proinflammatory factors, such as tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6) and IL-1β [35]. Thus, IL-6 can become a marker for predicting the severe evolution of depression, especially in the context of a particular physical symptomatology (body dysmorphic symptoms). This symptomatology is more common in young women, being an important factor in decreasing compliance with therapy and psychometric assessments, but also a factor in increasing the therapeutic resistance of depression, which may favor oncogenesis processes. On the other hand, the relationship between the presence of adipose tissue of CD68, IL-6 and TNFα with obesity and resistance to insulin treatment was highlighted [36].
Simultaneous increase in these factors may be a risk of predicting the occurrence of psychotic disorders, persistent pain, and cognitive impairment. The use of antipsychotics may lower the level of CD68, involved in inflammatory processes. The use in GCTB of antipsychotics for the control of chronic pain, treatment-resistant depression, and psychotic symptoms, may bring predominantly symptomatic benefits [37].

In patients with GCTB and chronic pain, complex mechanisms and stress-favored cardiovascular effects may exacerbate the risk of severe cardiovascular effects following prolonged QT interval. The QT interval may be increased by hypocalcemia induced by denosumab treatment [38]. In this context, antipsychotic treatment has a major contraindication in patients with hypocalcemia and requires specific cardiological monitoring, because it increases the risk of sudden death by multiple cellular mechanisms. The vulnerability of patients with GCTB and distress favors the activation of the hypothalamic–pituitary–adrenal (HPA) axis, with the symmetrical disturbance of the functionality of the autonomous system. This dysautonomia is dominated by sympathomimetic hyperactivity, which increases the risk of cardiovascular and cerebrovascular events [39]. In addition to prolonging the QT interval, hypocalcemia may also be a risk factor for exacerbation of depressive-anxiety disorder, cognitive impairment, extrapyramidal symptoms, dysautonomia, seizures [40, 41].

The risk of suicide in cancer is frequently associated with body dysmorphic syndrome, which determines a permanent stigma and a decrease in adaptive coping capacity by aberrant perception of social exclusion and loss of self-esteem (colostomy, amputation of a limb, breast resection, colon resection). The same situation was observed in solid brain tumors (glioblastoma or astrocytoma), in which chronic hyperalgesia is a vulnerability factor for suicidal behavior due to reduced therapeutic response to chemotherapy and significant neurological, psychiatric, and cognitive sequelae, following radical surgical techniques. Suicide risk is estimated at 62% in glioblastoma [42], and 15% in astrocytoma [43].

In these circumstances, as well as in conditions of GCTB malignancy, which can cause limb amputation [44], the use of alternative therapeutic strategies could improve the prognosis by reducing suicidal risk behaviors. These alternative therapies are based on pain control by stopping the action of hyperglutamatergy, following astroglia activations, while for brain tumor cells the use of compounds with specific pro-apoptotic action is discussed [45-47].

The risk of malignancy can also occur in the case of another benign tumor, giant condylopa Buschke–Löwenstein tumor, being associated with depression, social isolation, and a negative psychiatric prognosis [48]. The risk of malignancy also occurs in meningiomas, which are 92.8% benign on HP examination [49]. Long-term survival of patients with meningioma raises complex therapeutic management problems due to depression [50] and cognitive deficit [51]. On the other hand, these psychiatric disorders can occur even before the diagnosis of brain tumor.

Psychopharmacological precautions in GCTB

The pharmacological perspective of the standardized treatment in oncological pathology requires a personalization according to the complex characteristics of each case, from a HP, immunohistochemical (IHC), psychological and psychopharmacological point of view. The use of antipsychotics as an adjuvant medication may be useful in limiting the evolution of glioblastomas, and those that act by inhibiting N-methyl-D-aspartate (NMDA) receptors simultaneously have antidepressant effects [52, 53].

The psychological perspective requires careful monitoring and early psychiatric therapeutic intervention, from the early stages of GCTB, to correct depression and reduce suicidal potential, caused by diagnostic uncertainty, but also in advanced stages, with multiple recurrences that induce body dysmorphic symptoms. The high levels of depression, anxiety and stress can be correlated with the risk of recurrence, surgical reintervention and the possibility of metastasis or malignancy.

If for the attending physician, patients with GCTB are considered with a favorable evolution since the tumor is benign, the prognosis of the disease, viewed from the perspective of biological psychiatry and psychopharmacology, highlights multiple conditions of evolutionary risk. Chronic pain, difficulties in movement, functional and structural change of self-image (body dysmorphic symptoms) increase anxiety, social stress, and depression. These factors may favor through the multisystemic mechanisms of depression the increase of the risk of malignancy, but especially of the number of recurrences that require reconstruction techniques through new surgeries.

From our point of view, chronic pain is the major point of interest because it determines the reduction and dysfunction of the dopamine system, being considered that the persistent painful syndrome is accompanied by a “hypodopaminergic state” [54, 55]. The involvement of low dopamine levels in central pain has been reported in Parkinson’s disease (PD), associated with altered nigrostriatal system and non-motor structures, which may precede by years the onset of motor symptoms in PD. Hyperalgesia is accompanied by depression and autonomic nervous system dysfunction especially by orthostatic intolerance syndrome [56].

Dopamine deficiency-induced depressive disorder is generally underestimated in psychopharmacology, and therapy with pro-serotonergic antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants causes worsening dopaminergic deficiency and a lack of therapeutic response. This type of depression is a common psychopharmacological form, responsible for the therapeutic resistance to nondopaminergic antidepressants, especially in women [57].

Dopamine-dependent depression is associated with altered dopaminergic circuits involved in the brain reward system [58]. Biological psychiatry can define depression as the chronic inability of the individual to obtain a satisfactory reward. This hypothesis is objectified by involving the dysconnectivity of the nucleus accumbens and the caudate nucleus [59]. Dopamine deficiency in the
diminishing the mechanisms of reward and adaptive dopamine-lowering mechanisms at the mesolimbic level, dysmorphic symptoms amplify depression through complex mechanisms. Chronic pain and body massaging to assess depression, addictive behaviors, and suicide risk of relapses, to detect the risk of metastasis or malignancy, a multidisciplinary team.

The decrease of the adaptive coping capacities can be favored by the alteration of the microglial system, especially from the nucleus accumbens, which releases massive glutamate. Hyperglutamatergy amplifies suicidal ideation and catastrophic anticipation of disease progression in 30% of patients with chronic pain [28]. The psychological problems associated with recurrent tumors, such as depression, anxiety, fear, and stress, should not be neglected, as they could lead to a poor prognosis and low quality of life [63].

Early diagnosis and treatment of psychiatric symptoms associated with bone tumors could reduce the risk of suicide and significantly prolong the patient’s life. Psychotropic therapy should avoid the use of pro-serotonergic antidepressants, which decrease dopamine levels and increase the phenomenon of angiogenesis by increasing vascular endothelial growth factor (VEGF), with the risk of metastasis. Serotonin is an angiogenesis factor that amplifies tumor vascularity more than VEGF [64, 65]. On the other hand, the excess of serotonin and antipsychotic medication lowers the level of dopamine with increased prolactin levels. Hyperprolactinemia is a factor involved in the risk of developing breast cancer in women [66] and prostate cancer in men [67].

Interestingly, in conditions of depression and stress, there is an amplification of TNFα, and the RANK–RANK-L–osteoprotegerin cytokine system, considered TNF-related proteins, is involved in bone tumors as well as breast and prostate cancer [68, 69]. HP and IHC assessment must be correlated with a preventive attitude towards psychiatric risks. Based on these arguments, we recommend the therapeutic approach of these patients in a multidisciplinary team.

Conclusions

Patients with GCTB need a HP evaluation, especially of relapses, to detect the risk of metastasis or malignancy, simultaneously with psychological and psychiatric monitoring to assess depression, addictive behaviors, and suicide risk. This type of benign tumor has a risk of malignancy that can be increased by depression, anxiety, and stress through complex mechanisms. Chronic pain and body dysmorphic symptoms amplify depression through dopamine-lowering mechanisms at the mesolimbic level, diminishing the mechanisms of reward and adaptive coping, thus increasing the risk of addictive and suicidal behavior. A personalized pharmacological management is required associated with an adequate psychological training of the patient regarding the chronic pain. GCTB, after HP diagnosis, require an interdisciplinary therapeutic approach, including psychiatric, to improve treatment adherence and compliance, evolution and prognosis, and the patient’s quality of life.

Conflict of interests

The authors declare that they have no conflict of interests.

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