Original Article

Giant-cell tumor: analysis on the importance of early diagnosis and the epidemiological profile

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ABSTRACT

Objective: This study aimed to ascertain the relationship between early diagnosis of giant-cell tumors (GCT) and their prognosis, by correlating the time of symptom onset with the staging of the injury (through the Campanacci classification at the time of diagnosis), and with the type of treatment. The secondary objective of the study was to outline the epidemiological profile of patients with GCT in the region where the data were gathered, and to compare them with data in the literature.

Methods: The authors present an evaluation on 61 patients diagnosed with bone GCT, with regard to the site of involvement, age, initial symptoms, time of symptom onset, classification and type of treatment, among patients attended between May 1994 and August 2009.

Results: The threshold indicated as the limit for Campanacci stage I tumors to be the commonest diagnosis, with a 98.2% chance that the treatment would be non-aggressive, was 2 months after symptom onset. This finding was statistically significant (p = 0.017). Every additional month increased the chance that a patient would be diagnosed with an advanced-stage tumor by 10.94%, in relation to the chances of having the other two stages of the tumor.

Conclusion: The study result not only suggests that the alternative hypothesis that the earlier the diagnosis of GCT is, the less severe the lesion will be, has been confirmed; but also especially predicts the relationship between the time of symptom appearance and the severity of the tumor.

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Introduction

Bone giant-cell tumors (GCTs) are benign mesenchymal neoplasms with aggressive characteristics. Histologically, it is known that GCTs were first described by Cooper apud McCarthy and were considered to be "fungal medullary exostoses". In 1845, Lebert et al. apud McCarthy described a group of bone tumors with giant multinucleated cells that presented a tendency to recur, but which could be cured through amputation. Histopathological evaluations on GCTs reveal that they are formed by vascularized tissue consisting of stroma of fusiform or ovoid cells and by the presence of numerous multinucleated giant cells that resemble osteoclasts. They present characteristics common to many different tumor and pseudotumoral lesions, and analysis together with the clinical and imaging characteristics is needed in order to confirm the diagnosis.

According to a series at the Mayo Clinic, these tumors account for 5% of bone neoplasms and are slightly more prevalent in females. The age group most affected is between the second and fourth decades of life. GCTs generally affect a single bone. The commonest sites affected are the distal femur, proximal tibia and distal radius.

The clinical condition consists of progressive pain and increased joint volume, which may be associated with joint symptoms such as mechanical blocking and synovitis. These symptoms are often initially related to physical activity and the pain only rarely becomes incapacitating. A diagnosis of GCT is suspected when, in addition to the abovementioned clinical condition, radiographic evaluation reveals a tumor of osteolytic appearance that destroys the entire epiphysis and may reach as far as the joint cartilage (characteristics of aggressiveness in the radiological evaluation). The diagnosis is confirmed through histopathological analysis.

In 1990, Campanacci et al. presented a radiographic classification for GCTs that describes three different grades: stage 1 – small, quiescent and intraosseous lesions; stage 2 – active or aggressive tumors, with compromised bone cortex, but presenting intact periosteum; stage 3 – aggressive, with invasion of adjacent soft issues.

Historically, the treatment consisted of simple curettage, but this method was shown to give rise to a high recurrence rate. Currently, the techniques most used are curettage with adjuvant therapy, resection of the affected segment with fusion-like reconstruction or auto/homograft replacement or use of endoprostheses.

Non-specific initial symptoms, lack of medical training directed toward primary care and difficulty in accessing referral hospitals makes it harder to achieve early diagnosis and adequate treatment for GCTs. The present study had the aim of evaluating the relationship between early diagnosis of GCT and its prognosis and correlating the length of time since symptoms appeared with the staging of the lesion, by means of the Campanacci classification at the time of diagnosis, and with the type of treatment. This study also had the aim of establishing time markers for early diagnosis of GCT that would be capable of allowing the assumption of low severity of the lesion, with the need for less aggressive types of treatment, and serving as a guide for public policies for diagnosing and providing early treatment for GCT.
Material and method

In September 2014, a cross-sectional descriptive study was conducted among patients at the Cancer Hospital of Pernambuco. All the medical files of patients who had been diagnosed with GCT between May 1994 and August 2009 were reviewed. Patients with soft-tissue GCT; patients hospitalized due to tumor recurrence; cases in which the time that had elapsed between the onset of symptoms and the diagnosis records was not mentioned; and records with conflicting or incomplete data, i.e. absence of histopathological confirmation, illegible information, incomplete admission forms and non-explanatory surgical descriptions, were excluded from the data-gathering.

Through excluding the groups cited above from the data-gathering, 61 patients were selected. These cases had medical files that had been filled out legibly, with the abovementioned information complete and non-conflicting. The following information was sought in these medical files: time elapsed between the onset of symptoms and the tumor diagnosis at the referral oncological hospital; site of tumor involvement; patient’s age; patient’s place of origin; type of treatment implemented; Campanacci classification on admission; and symptoms presented during the attendance. The process of clinical investigation, lesion classification and treatment was implemented by qualified professionals who were members of the Brazilian Society of Oncological Orthopedics.

The sample was classified in accordance with the Campanacci system and was divided into two groups relating to the treatment required. The patients with GCTs that could be resected through curettage with adjuvant therapy were grouped as “non-advanced” cases, while those who required interventions that were more “aggressive” were considered to be “advanced” cases.

This study was submitted to the ethics committee of the healthcare institution indicated through the Brazil platform, for authorization.

Statistical analysis

The results from the quantitative variables were expressed as means and standard deviations, while the results from the qualitative variables were expressed as absolute and relative frequencies. The Kruskal–Wallis test was used to ascertain possible differences in mean time taken for treatment and in patient age, in relation to tumor stage. A logistic regression model was used to correlate the time taken for treatment and the tumor stage.

Results

The mean age among the patients with a tumor in Campanacci stage I was 38.3 ± 13.7 years, while those in stage II presented a mean of 29.5 ± 10.6 years. Patients with a stage III tumor presented a mean of 34.1 ± 13.9 years. It was seen that there was no statistically significant difference in mean age in relation to tumor stage ($p = 0.311$) (Table 1).

The patients with stage I tumors presented a mean time taken until the diagnosis of 1.5 ± 0.5 months. Those with stage II tumors presented a mean of 6.4 ± 0.8 months and those with stage III tumors, 10.4 ± 2.1 months. It was observed that there were significant differences in the time taken until the diagnosis, in relation to the tumor stage ($p = 0.017$), i.e. patients at the initial stage presented shorter times taken to make the diagnosis than those at advanced stages of the tumor (Table 1).

It was seen that patients in stage I presented shorter times to make the diagnosis than those in stages II and III: $p < 0.0001$ and <0.0001, respectively (Fig. 1).

It was seen that the time taken to make the diagnosis for patients with stage III tumors was longer than the time for patients with stage II: $p = 0.013$ (Fig. 1).

Through logistic regression analysis (Eq. (1)), it was observed that for every 1-month increase, the chance that a patient would be diagnosed with a tumor at the advanced stage was 10.94% greater than at the other two tumor stages.

\[ \log(-\log(1 - P(x))) = -1.64 + 0.1 \text{ tempo} \]  

where $P(x)$ is the probability that a patient would be classified as having an advanced stage of the tumor.

It was seen from Table 2 that patients with a time of 1 month taken to make the diagnosis presented a probability of 0.5% of being classified as having an advance stage of the tumor, while if this same patient were to be diagnosed only in the fifth month, this probability would be 13.7%. If this same patient were to be diagnosed only after 12 months, this probability would be 81.5%.

![Fig. 1 - Boxplot of the time taken to make a diagnosis for the patients, in relation to tumor stage.](image-url)
Table 2 – Probability of tumor stage classification, in relation to the length of follow-up.

| Probability of classification | Length of follow-up (months) |
|------------------------------|-----------------------------|
|                              | 1  | 2  | 5  | 8  | 10 | 12 |
| Advanced                     | 0.5| 1.8|13.7|48.2|63.3|81.5|
| Non-advanced                 | 99.5| 98.2|86.3|51.8|36.7|18.5|

Fig. 2 – Probability of tumor classification in an advanced stage, in relation to the time taken to make the diagnosis.

It was seen in Fig. 2 that approximately 20% of the patients were classified as presenting an advanced stage of the tumor in the sixth month. In the eighth month of the follow-up, approximately 50% of the patients presented tumors at an advance stage, while 80% of the patients were classified as presenting an advanced stage of the disease around the 11th month.

Table 3 presents the prevalences of symptoms among the patients studied. It shows that pain alone was the commonest symptom and tumor formation was the commonest clinical sign.

The incidence of GCTs according to their location in the skeleton is presented in Table 4, which shows that they affect the epiphyses of long bones, most commonly at the knee. In addition to these regions, GCTs have also been found in the calcaneus, proximal humerus, ulna, hop and proximal radius.

Table 4 – Incidence of GCT according to location in skeleton.

| Site of involvement | No. of patients | Percentage |
|---------------------|-----------------|------------|
| Distal femur        | 20              | 32.78%     |
| Proximal            | 7               | 11.47%     |
| Distal tibia        | 6               | 9.83%      |
| Distal radius       | 6               | 9.83%      |
| Phalanges           | 5               | 8.19%      |
| Others              | 17              | 27.86%     |

Discussion

The results from this study suggest not only that it has provided confirmation of the optional hypothesis that the earlier the diagnosis of GCT is made, the lower the severity of the lesion will be, but also especially, that this predicts the relationship between the time of symptom onset and the severity of the tumor. For example, in patients who are diagnosed 1 month after symptoms first appear, their chance of presenting a lesion that can be treated through curettage plus adjuvant treatment 99.5%, which has benefits both for the patient and for the public healthcare system, in comparison with surgical procedures that are more aggressive.

GCTs were found in our series of 61 patients mostly between their third and fourth decades of life, and this finding is in line with the data in the literature. Unlike a study in which 31% of the patients were diagnosed with pathological fractures, we found in our series that only 3.3% of our patients had such lesions.

The observation that only one patient in our study presented metastasis (1.6%) is concordant with the worldwide literature, in which it has been estimated that the risk of metastasis from GCT is between 1 and 3%. According to Renard et al., the explanation for the metastatic foci lies in the fact that tumor cells may be found in peripheral vessels of the bone site affected.

Comparing the incidence of GCTs regarding their location in the skeleton with what was demonstrated by Jesus-Garcia et al., we obtained similar data, as can be seen in Table 4. The knee is the location of highest incidence and accounts for 44% of the cases.

With the aim of establishing time markers for early diagnosis in cases of GCT, the objective that was taken on was to identify lesions classified as Campanacci stage I or II that it would be possible to treat through curettage plus adjuvant therapy, which were grouped as non-advanced cases in the statistical analysis of this study. The results showed that a time marker of 2 months after the onset of symptoms was the time limit for the period in which the commonest diagnosis would be a Campanacci stage I tumor, with a 98.2% chance of being capable of non-aggressive treatment. This finding was statistically significant (p = 0.017).

In order to reach the time marker demonstrated in this study, improvements in public healthcare policies will be needed. Investment in human and structural resources within primary care, capacitation of healthcare professionals and

Table 3 – Prevalence of symptoms.

| Symptoms                  | N   | %   |
|---------------------------|-----|-----|
| Pain                      | 28  | 46.7|
| Tumor formation           | 17  | 28.3|
| Pain and tumor formation  | 4   | 6.7 |
| Increased volume          | 4   | 6.7 |
| Pain and increased volume | 2   | 3.3 |
| Pathological fracture     | 2   | 3.3 |
| Pain and pathological fracture | 2 | 3.3 |
| Edema and pain            | 1   | 1.7 |
regularization of rapid passage between primary care and specialist units for oncological treatment are ways of making the public healthcare system capable of timely diagnosis for GCT cases.

The present study found that there was high prevalence of generic signs and symptoms, which caused difficulty regarding clinical suspicion and early diagnosis. The presence of joint pain and/or tumor formation was shown to be a sign of suspicion for investigating possible GCTs.

From analysis on the result obtained regarding mean age in relation to lesion severity at the time of diagnosis, it was concluded that there was no statistical significance. Thus, symptoms that are highly prevalent among older patients, such as joint pain, need to be better investigated. Likewise, in attending younger patients, tumor etiology needs to be noted, given that the data obtained in several studies have demonstrated its importance for early diagnosis.

**Conclusion**

This study demonstrated that the mark of 2 months after symptom onset was the time limit for the period in which a diagnosis of Campanacci stage I tumors would be more common, with a 98.2% chance of only needing non-aggressive treatment. This finding was statistically significant (p = 0.017). With every 1-month increase, the chance that a patient would be diagnosed with a tumor at an advanced stage is 10.94% greater than in relation to the other two tumor stages. The epidemiological profile of patients with GCT in this region is concordant with the data in the worldwide literature, with regard to age, risk of metastasis and site affected.

**Conflicts of interest**

The authors declare no conflicts of interest.

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