Primary giant cell tumor of soft tissue on mandibular region: a case report and literature review*

Mandibuler bölgesinde yumuşak doku primer dev hücreli tümör: olgu sunumu ve literatür derlemesi

Ömer Fahrettin Göze1,2, Ahmet Muslehiddinoğlu2

1Department of Pathology, Cumhuriyet University School of Medicine, Sivas; 2Department of Pathology, Dr. Cevdet Aykan State Hospital, Tokat

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Abstract

Primary giant cell tumor of the soft tissue was first defined by Salm and Sissons as a tumoral lesion histologically identical to the giant cell tumor of the bone and clinically benign even though having some local recurrences. However, subsequent studies have demonstrated that besides benign forms, tumor also had potentially malignant and malignant forms. In this case, we evaluated a tumor seen on a woman at 27 years old and rare in location (mandibular region) and diagnosed as 'primary giant cell tumor of the soft tissue' (PGCT-ST). We also impressed on the differential diagnosis of the case by evaluating the morphological and immunohistochemical properties of the tumor. Moreover, since potentially malignant and malignant forms of the tumor were also defined, we reviewed the criteria of differential diagnosis and the literature again and tried to make the clinical behavior of the tumor clear.

Keywords: Low grade giant cell tumor, soft tissue, mandibular region

Özet

Yumuşak dokuların primer dev hücreli tümörü ilk olarak Salm ve Sissons tarafından histolojik olarak kemiğin dev hücreli tümörüne benzer ve klinik olarak bazı lokal rekürensleri olsa da benign bir lezyon olarak tanımlanmış; ama daha sonraki çalışmalar benign formların yanında tümörün potansiyel olarak malign veya malign formlarının olduğunu göstermiştir. Bu olguda 27 yaşında bir kadında ve mandibuler bölge gibi nadir bir yerde saptanan yumuşak dokunun primer dev hücreli tümörü olarak tanımlanan bir...
Introduction

Primary giant cell tumor of the soft tissue (PGCT-ST) was first defined by Salm and Sissons as a tumoral lesion histologically identical to the giant cell tumor of bone [1]. The authors have noticed on that even though having some local recurrences on two patients, these tumors was clinically benign without metastases. Since then, tumor has been evaluated in some other studies from different aspects, different study groups from different countries have worked on the tumor internationally and other features of the tumor have been revealed and especially malignant and potentially malignant types of the tumor has been defined [2, 3].

In this work, PGCT-ST seen on a women at the age of 27 which causes difficulty on diagnosis due to morphological features and seldom localization (mandibular area) is presented which has never been defined up to now. Literatures were reviewed.

Case Report

The patient was admitted to the Otorhinolaryngology Inpatient Service of our hospital, in August 2000 with the complaint of awareness of a mass on the right side of the mandible and a sudden enlargement of the mass in the last month. The patient didn’t suffer from any other complaint. On physical examination there was a mass on the right angulus mandibula extending to mentum which was 8x6 cm. in size, semi-mobile, hard and painless. On CT analysis there was a mass having a size of 5x4x3 cm. pushing skin and subcutaneous tissues outward on right submandibular region and on contrast sections the mass was seen as a contrasting, well circumscribed, clearly heterogenic structure and there was no cortical irregularity and destructions on neighboring bony structures (Fig. 1-2). The mass was widely excised. Excised surgical material examined in our Pathology Laboratory. Macroscopically, the mass was 6x3x1.5 cm. in size, having nodular appearance, well circumscribed and red-brown in color and on cross sections it was mostly composed of solid structures. Also there were some small cystic areas and in surrounding areas harder in consistency there were some structures having sandy appearance. In microscopic examination we saw the tumoral tissue between the local architectural elements, which having an appearance of osteoid tissue and oblique bone trabecules in the connective tissue containing striated muscle fibers. This tumor was composed of heterogeneously scattered giant cells between spindle and polygonal mononucleated stromal cells (Fig. 3). In this main architecture there were large fibromyxoid stromal areas, congestion of the vessels having thickened walls, irregular components similar to aneurysmal bone cyst (ABC), reactive bone formation and areas with hemorrhage (Fig. 4 a and b). We made immunohistochemical analysis including a standard avidin-biotin-peroxidase complex method using antibodies directed against CD68, vimentin, smooth muscle actin, desmin, S100 and Factor VIII. Osteoclastic giant cells stained strongly positive and some
fibrohistiocytic cells in tumor stained weakly positive with CD68 (Fig. 5) and vimentin cytoplasmically. Small vessel walls and fusiform histiocytic cells in tumor stained strongly positive with smooth muscle actin. There were no staining properties with desmin and Factor VIII.

Figure 1. A representative picture of computerized tomography imaging. The appearance of the right submandibular region which was taken on the cranioaxial level. This mass was well circumscribed, clearly heterogenic structured and showed no destructive effects on bone.

Figure 2. A detailed picture of the same mass on the cranioaxial level in computerized tomography imaging.
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Figure 3. A panoramic view of the mass tumoral lesion are seen which was formed giant cells heterogeniously scattered in the periphery and between vessel-like large channels in the fibrocellular stroma (HE X 100).
Figure 4. a. A detailed picture from the tumoral lesion. Reactive bone formation on the left-up corner (arrow) and hemorrhage on the right-up corner (HE X 250). b. An another detail from the adjacent area. Aneurysmal bone cyst-like cleft (HE X 125).
Discussion

Soon after the first definition of the tumor by Salm and Sissons in 1972, Guccion and Enzinger have described the malignant type of the tumor in the analysis of another series composed of 32 cases [4]. Later Soule and Enriquez has reported the benign and malignant forms of histiocytic lesions in 65 cases including 5 tumors which were histologically similar to the tumors defined by Guccion and Enzinger [5]. Even though defined as a 'clinically benign' tumor at first, with the increases in the knowledge about clinical and morphological features and histogenesis of the PGCT-ST, directly the malignant forms of this tumor has been defined apart from potentially malignant on low malignant potential forms of the tumor [6-12]. Lastly, in the study of another series composed of 22 cases done by Oliveira et al. [2], 16 cases has been followed for 51 months and only one of them have shown recurrence and lung metastases and patient has died. In a different study done by O’Connell et al. [3], 18 cases were reported as 11 benign and 7 malignant cases separately. In their study, benign cases no recurrences or metastases has occurred but among four patients with malignant forms of tumor, one patient has died because of widespread lung metastases after 13 months and also one patient has had local recurrence after 84 months. At last according to the common opinion this entity has been discussed under the topic of fibrohistiocytic tumors of intermediate malignancy and defined as 'soft tissue giant cell tumor of low malignant potential [6].

In our case the tumor mass was a painless mass on submandibular area which first detected one year ago as having a size of chickpea and later on enlarged very fast in 20 months. Our patient is still living since that date without recurrence or similar condition.
Morphological criteria of this tumor have been started to be classified after the malignant forms of the tumor have appeared together with the benign forms. According to O’Connell et al. [3], these criteria should be available to identify the tumor as PGCT-ST:

- The tumor should be a primary soft tissue tumor which never invades the skeletal structures beneath.
- There should not be a history of osseous giant cell tumor previously.
- Histological appearance of the tumor should be fusiform or ‘histiocytic-epithelioid characterized by equal mixture of mononuclear cells and osteoclastic giant cells.
- These mononuclear cells should comprise at least 75% of the tumor and should not be differentiated to a specific type (osteoblastic or smooth muscle differentiation etc.).

Our case was suitable to these criteria. But the suspicion about the bone invasion eliminated when evaluated together with radiological findings.

Macroscopically while the benign tumors vary between 0.8-9.0 cm. in size, malignant ones takes place between 1.8-9.0 cm. Mean diameter is 3.1 cm. in benign tumors and 4.2 cm. in malignant counterparts [3]. Oliveira et al. [2], has given these measures between 1.0-10.0 cm. for benign tumors. So there are no prominent size difference between malignant and benign tumors. Similarly the growth patterns of these tumors are nearly the same, both malignant and benign tumors form well defined, multinodular, dark brown or red masses. Although the dominant pattern is solid in nearly all of the tumors, some small cystic areas or mineralized bones in sandy appearance in periphery of the mass have been noticed. There is no gross finding for differentiation of benign and malignant tumors [2, 3]. In microscopic architecture, in addition to the main cell composition, there is a growth pattern paralleling with multinodularity seen in macroscopic structure. The main architecture is formed frequently with cellular nodules including lots of hemosiderin loaded macrophages which are separated by collagenous tissue bundles. Septae are relatively hypocellular and devoid of osteoclastic giant cells. Tumor nodules are composed of mononuclear and osteoclastic giant cells arranged in equal distribution. These mononuclear cells show a large spectrum from oval histiocytic or epithelioid cells to blunt fusiform cells. Both have eosinophilic cytoplasm and central nuclei similar to neighboring osteoclastic cell nuclei. Histiocytic cells frequently have convoluted or cleaved nuclei. Mitotic figures are found only in mononuclear cells and the number of them are 1-5/10 HPF (mean 3 mitoses per 10 HPF) [3]. But in some extreme cases the number of the mitoses increases 2 to 3 fold and reaches to 9-10/10 HPF [2]. In most of the cases the areas rich tumor combines with the areas poor in giant cells. In the latter areas fusiform mononuclear cells are distributed in a storiform pattern and together with collagen synthesis. Also there may be lots of foamy histiocytes in these areas. These areas are typically identical to the fibrohistiocytic changes seen in the periphery of the giant cell tumor of the bone [3].

In cellular areas hemorrhages (diffuse interstitial or focal) may be found in half of the cases. Sometimes there may be some non-endothelial cystic spaces filled with blood which reminds ABC. This change that may cause some difficulties in diagnosis according to the site of the lesion, was reported 6/22 (27.2%) in one series and 4/11 (36.4%) in another one. This change which also takes place in our case and makes the diagnosis difficult is not more than a focal change and all of the tumors show a solid growth pattern predominantly. Also
the coagulation necrosis is not seen every time. Coagulation necrosis has been reported in a wide margin of 4% to 36% in two series [2, 3]. There were no necrosis in our case. Also the vascular invasion was 1/11(9%) in the series of O’Connell et al. [3], it has been increased to 7/22 (31.8%) in the series of Oliveira et al. There was no vascular invasion in our case. In these tumors another important structural element which causes difficulty in diagnosis is the reactive-metaplastic bone formation. In the studies of Oliveira et al. [2], the incidence of metaplastic bone formation has been found 40.1%. In the studies of O’Connell et al. [3], it has been seen that in 8 of 18 cases benign bone formation was extending to the center of the mass especially in a form of sheet at the periphery and also it has been seen that this bone was in the form of both woven and lamellar bone in most of the specimens. Furthermore, it has been concluded that the matrix in tumors had much more immature osteochondral morphology. In our case we saw bone formation in immature osteochondral morphology in central area and mature calcified bone in periphery which is in the form of a sheet giving a suspicion of cortical bone. While the bone has an appearance giving the thought of osteogenic tumors, no suspicion of osteosarcoma has been thought in those tumors. In our case also no ossification in amount and structure giving the idea of osteogenic tumor in these forms was present.

Malignant forms generally show a similar morphologic features to benign forms so that multinodular growth pattern (5/7), diffuse interstitial hemorrhage (6/7), focal cystic changes (4/7), necrosis (4/7), partial benign ‘woven’ bone shell (1/7) are seen while the distribution of osteoclastic giant cells are similar especially to the benign tumors. These tumors are classified as malignant or benign according to the nuclear atypia outcoming in mononuclear cells [3]. O’Connell et al. [3] also reported that following features had been taken attention in their cases:

- Mononuclear cells in malignant tumors show evident nuclear pleomorphism and hyperchromasia.
- Giant mononuclear cells with hypersegmented nuclei are frequent.
- Atypical mononuclear cells are scattered diffusely in the lesion.
- There has never been detected that there was histologically transitional areas between malignant and benign areas.
- Mitotic figures has been found much more in malignant tumors and 7 to 53 (mean 25) mitotic figures has been detected per 10HPF. Also atypical mitoses additionally were found in malignant tumors.

Because of these rich morphological features, PGCT-ST is a tumor that should be differentiated from lots of lesions such as giant cell tumor of bone (GCTB), non-skeletal osteosarcoma, giant cell variant of malignant histiocytic tümör (GCVMHT), aneurysmal bone cyst (ABC), plexiform fibrohistiocytic tumors (PFT), pleomorphic sarcoma rich in giant cells (PSRGC), giant cell tumors of tendon sheet (GCTTS).

PGCT-ST is identical to GCTB histologically and in gross appearance. The tumor characteristically has a meaty appearance and brown in color. Necrosis, mitotic activity, metaplastic bone formation, are as similar to ABC, regression and regeneration signs (such as foamy histiocytes and hemorrhages) and reactive fibrosis have all been reported frequently in GCTB. Also PGCT-ST is devoid of pleomorphism and atypical mitoses.
similarly. Furthermore in some cases, the strangely appeared bone formation around the tumor that is in shape of a shell is identical to GCTB when recurs in soft tissues.2 Besides GCTB generally grows in secondary ossification areas that means at the epiphysis-metaphysis line of the long tubular bones [2, 3, 13], they are generally solid and involves frequent cystic changes. Microscopically GCTB is composed of multinuclear giant cells scattered between oval or fusiform mononuclear cell bundles. Despite the tumor cells do not produce bone directly, frequently there are ‘woven’ bone spicules at the margins of tumor. Many of conventional giant cell tumors show areas with the absence of osteoclastic cells at the periphery and these areas begins to be composed of only the mixed storiform aggregates of fusiform fibroblastic cells with foamy histiocytes (fibrohistiocytic change).

In literature there are many of the soft tissue tumors have been reported which are similar to ABC [14-16]. These lesions show correspondence to benign edge of the spectrum of PGCT-ST [3]. Salm and Sisson [1] had impressed at the base of the relatively absence or minimality of solid component and uniformly cystic nature of the tumor. Also O'Connell et al. [3] thinks the same with Salm and Sisson about this issue. In our case irregular areas similar to ABC. This tumor is predominantly cystic in structure, but may have small solid component.

PFT's are the intermediate (potentially malignant) soft tissue neoplasms which are characteristically the tumors of upper extremities and appearing in deep dermis and superficial subcutaneous tissue neighboring to deep dermis. Microscopically multinodular architecture is typical. Tumor nodules are different in appearance and composed of histiocytic cells mixed with osteoclastic giant cells [17-21]. These nodules similar to PGCT-ST are big ones but the nodules are much more small in PFT's and typically together with abundant collagen bundles rich in fusiform cells similar to fibromatosis and as the most important feature each nodule are separated from each another by normal adipose tissue [17-20]. Transition to the areas composed of fusiform cells is not a feature of the PFT's. Because of clinical and morphological similarity between these entities, correct diagnosis can be reached if the biopsy specimen is big enough [3]. In our case no areas similar to PFT was present.

Another lesion that including differential diagnosis is fibrous histiocytomas [22, 23]. According to O'Connell et al. [3], perhaps the classification of these tumors as fibrous histiocytoma nosologically is correct but the terminology is not specific enough.

Lastly, these tumors can be confused with GCTTS of localized or diffuse type [3]. The differential diagnosis can be made by these three criteria:

- Opposite to PGCT-ST's, GCTTS's have osteoclastic giant cells separated as clusters and have more uniform histiocytic mononuclear cell population showing prominent cell membranes.
- GCTTS's typically comprise much more homogeneously separated extracellular collagen that surrounds the separate cells or cell clusters. On the contrary PGCT-ST's have large collagen bundles that leads to multinodular development.
- In PGCT-ST's cystic changes and reactive bone formation is frequent whereas it is very seldom in GCTTS's [24].
In spite of the differential diagnosis, also the relationship between the giant cell tumors of soft tissue and the bone is not clearly understood. As most of the authors pointed out, the term GCT is used frequently to define a sarcoma which develops in the place of conventional osseous giant cell tumor at the same time or priorly [14-27]. But O'Connell et al. [3] has made clear that the term of malignant GCT of ST could be used for the cases which never show a differentiation in one direction (especially osteoblastic or smooth muscle) but cytologically composed of malignant mononuclear cells and at least 75% of the tumor is composed of conventional osteoclastic giant cells. When all those criteria are used, it may be seen that most of the lesions called malignant giant cell tumors of the bone are osteosarcoma, fibrosarcoma or malignant fibrous histiocytoma without giant cells in fact [3]. PGCT-ST biologically behaves more moderately and has a much lower incidence of local recurrences compared with the ones of bone [9, 11]. According to O’Connell et al. [3], difference in biological behavior appearing between osseous and soft tissue variants of giant cell tumors is due to complete excision of osseous forms of tumors without articular surface sacrifice of the joint, rather than the biological behavior of the tumor. Osseous giant cell tumors if excised completely local recurrence rate is reported to be so low that more similar to the histologically benign tumors in soft tissues [25, 26].

In recent years, methods of immunohistochemistry is applied by using CD68, smooth muscle actin, desmin, Ham56, vimentin stains for these tumors [3]. We applied these stains and Factor VIII additionally except Ham56. By CD68 and vimentin osteoclastic giant cells stained strongly, some of the fibrohistiocytic cells stained weakly cytoplasmically, with smooth muscle actin small vessel walls and some of the fusiform histiocytic cells stained strongly positive. There was no staining with desmin and Factor VIII. In this case it is supposed that the vessel walls should be stained with vimentin and desmin, but since negative staining was seen and it can be said that this helps to differentiate these tumors from ABC.

In summary, in this article we report on a PGCT-ST on the mandibular region that is similar to the classic GCT of bone and generally treated by wide local excision. Our case was treated with widely local excision and is currently well with no recurrence or metastases about twelve years after the operation.

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References

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