CASE REPORTS

Conventional grade 1 chondrosarcoma: a challenging diagnosis with important implications on therapy and prognosis

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Abstract

Chondrosarcoma (CHS) is a malignant tumor of soft tissue with cartilaginous differentiation that represent one tenth of all malignant proliferations developed from bone tissues. Even if CHS represents the third malignancy with bone localization, after myeloma and osteosarcoma, it is far less diagnosed in the head and neck region. The current paper presented two cases of conventional CHSs, which were diagnosed in Department of Thoracic Surgery and Department of Otorhinolaryngology of Emergency City Hospital, Timișoara, Romania, between February and June 2021. The malignant cases were of peripheral CHSs, one of scapula, and the other one had an extremely rare tracheal location with microscopic features of conventional low-grade tumors (grade 1). In all cases, conservative surgical curative treatment was performed, with a favorable postoperative evolution.

Keywords: chondrosarcoma, immunohistochemistry, tracheal malignancy, atypical chondrocytes.

Introduction

Chondrosarcomas (CHSs) are uncommon diagnosed malignancies characterized by cartilage matrix synthesis. The annual incidence has been reported as one to 200 000 [1]. CHSs can develop in contact with an osseous structure formed by endochondral osteogenesis. The proximal bone of both extremities and the pelvis are by far, the most common affected. The second place of occurrence as incidence is represented by the bones of thorax, skull, and tibia. The tumors arise from the hyaline cartilage that cover the bone's epiphysis. The lesions can appear *de novo* or as a malignant transformation of a benign tumor as chondroma, exostoses, Ollier disease and Maffucci syndrome. The incidence of CHSs in the head and neck region is variable, the sites most affected being the jaws and vertebrae of cervical region. CHSs can also be diagnosed in various extra-osseous sites, in the soft tissue nearby a bone or, rarely, in organs that contain cartilage in their structure as trachea or larynx [2–10]. Tracheal and laryngeal cartilaginous neoplasms occur in hyaline cartilage and only very rare in elastic cartilage, and they are extremely rare [11–13].

There are two main subtypes of CHS: conventional and non-conventional. Conventional CHS accounts for 85–90% of all cases and is subdivided into central, peripheral, and periosteal subgroups. Non-conventional CHSs include three types: mesenchymal, clear-cell and dedifferentiated CHSs [1].

CHSs present in patients between 40 years and 60 years [14].

The symptoms of CHSs developed in a preexisting bone are non-specific and include swelling and local pain for a long period of time, not assigned at anti-inflammatory drugs. Dyspnea, wheeze, cough, hemoptysis, hoarseness is present in tracheal location [15–17]. CHS usually presents as a solitary lesion.

Grossly, CHSs are firm tumors with lobulated appearance, with slippery, glassy, grayish cut surface.

The microscopic exam reveals slightly pleomorphic chondrocytes embedded in a cartilaginous matrix. The myxoid change, calcification or necrosis can sometimes occur. Usually, the atypical chondrocytes present dark, hyperchromatic nuclei. The most important in the treatment of CHS and its prognostic factors is the grading system pronounced on histological criteria [18, 19]. The features

useful for grading are cellularity, pleomorphism, multinucleation, and mitoses. The most common are the grade 1 tumors (low-grade sarcoma), with a favorable prognosis and a slowly progressive growth, although the local recurrence rate is relatively high [20, 21]. In general, immunohistochemical (IHC) reactions play a limited role in the diagnosis of CHSs, which relies on morphological, clinical, and radiological features. The only consistent IHC finding is S100 protein positivity.

CHSs are resistant to chemotherapy and radiation therapy. The large resection of the tumor with free margins increases the 5-year survival rates to 78%. The treatment of choice for tracheal and laryngeal CHSs is conservative surgery, function-preserving surgery, including laser therapy [18–21].

Aim

The aim of the present study was to highlight the importance of the prompt diagnosis of grade 1 CHS in incipient stage, based on clinical features, radiologically aspects, and histopathological (HP) descriptions, bearing in mind that this histological grade has a favorable evolution.

Patients, Materials and Methods

The current paper presented two cases of conventional CHSs with rare localization, one scapular and one tracheal, diagnosed in the Emergency City Hospital of Timișoara, Romania, in February 2021 and the second, in June 2021.

All the data regarding personal and familial medical history, and laboratory test results were noted.

To obtain the diagnosis, the lesions were biopsied and sent to the Service of Pathology of the Hospital in 10% (v/v) neutral buffered formalin, where the harvested specimens were embedded in paraffin. Serial sections, 4 µm-thick, displayed on silanized slides were prepared for the diagnosis using morphological Hematoxylin–Eosin (HE) staining. To complete the diagnosis, histochemical Periodic Acid–Schiff (PAS) reaction for mucin and additional IHC reactions were used. All the data regarding the antibodies used for IHC reactions are centralized in Table 1. All the antibodies and the reagents utilized for immunohistochemistry were acquired from Novocastra™, Leica Biosystems.

Both patients approved their participation in the study by signing the informed consent of Ethics Committee from both, Hospital and University.

Figure 1 – Binucleated chondrocytes in cartilaginous matrix. HE staining, ×400. HE: Hematoxylin–Eosin.

Table 1 – Data related to the antibodies used for immunohistochemical reactions

Antibody	Substrate	Clone	Dilution
Ki67	Monoclonal mouse	MM1	1:200
S100 protein	Polyclonal rabbit	EP32	1:100
p53	Polyclonal mouse	CM5	1:200
E-cadherin	Monoclonal mouse	36B5	1:25

Case presentations

Case No. 1

A 49-year-old female patient was hospitalized in February 2021 with arthralgia in the left shoulder. Personal medical history was insignificant for present lesion, also the medical treatment. She did not consume alcohol and was non-smoker. At clinical examination, no other abnormalities or palpable lymphadenopathy besides scapular lesion were identified. Paraclinical tests showed: erythrocyte sedimentation rate 70 mm/h, hemoglobin 14 g/dL, hematocrit 41.2%, serum creatinine 0.55 mg/dL. Chest radiography showed normal images. The computed tomography scan revealed peripheral scapular tumor of 4/3.4 cm with muscle and bone invasion.

Under general anesthesia, a suprascapular incision with infrapinuous muscle and *teres major* excision and partial resection of scapular body was performed. The postoperative evolution was favorable.

Macroscopically, on the cut surface, the lesion was characteristically glassy, lobulated, and firm.

The HP examination of HE-stained slides revealed a malignant partially encapsulated proliferation of atypical chondrocytes in cartilaginous matrix, showing a lobulated pattern of growth. The tumor cells presented basophilic or pale cytoplasm, with hyperchromatic nuclei, and minimally pleomorphism. Some of the cells were binucleated (Figure 1). PAS reaction highlighted intracytoplasmic positive inclusion (Figure 2). The chondroid cells were heterogeneously positive for S100 protein, with intense positive areas merged with negative zones and negative for p53 protein and E-cadherin (Figures 3–8). The Ki67 index was high (80%) at tumor invasion front and low in other areas (Figures 9 and 10). Lobules of atypical chondrocytes invaded the striated muscle, adipose and fibrous connective tissues, and osseous structures of scapula. The final diagnosis of peripheral low-grade CHS with bone invasion and negative margins was signed out.

Figure 2 – Atypical chondrocytes with intracytoplasmic inclusions. PAS reaction, ×200. PAS: Periodic Acid–Schiff.

Figure 3 – Most of the tumor chondrocytes were immunohistochemically positive for S100 protein, $\times 200$.

Figure 4 – Atypical chondroblast in mitosis, immunohistochemically positive for S100 protein, $\times 100$.

Figure 5 – Tumor area showing negative immunohistochemical reaction for S100 protein, $\times 100$.

Figure 6 – Lobules of malignant chondrocytes, with negative immunohistochemical reaction for S100 protein, $\times 50$.

Figure 7 – Tumor area showing negative immunohistochemical reaction for E-cadherin, $\times 200$.

Figure 8 – Lobules of malignant chondrocytes, with negative immunohistochemical reaction for p53, $\times 400$.

Figure 9 – Tumor area showing negative immuno-histochemical reaction for Ki67, ×400.

Figure 10 – Lobules of malignant chondrocytes, with positive immunohistochemical reaction for Ki67, ×200.

After the surgical intervention, the patient was discharged without complications and is currently being monitored by her oncologist.

Case No. 2

The patient, a 64-year-old female, presented in June 2021 for dyspnea, cough, and hoarseness for about one month with repeated episodes of wheeze and hemoptysis about one week.

On personal medical background was noted hypertension treated with beta-blockers and family history of cardiac diseases. The patient was non-smoker and did not consume alcohol.

Laryngoscopy documented the existence of a proliferated region at subglottic level, 1/1.5 cm in size, covered by smooth mucosa, with endoluminal occlusion that occupied about 70% of the lumen. Chest radiography reveals a lytic tracheal lesion, with dense spicules of calcification and an eccentric, lobular appearance. Pulmonary normal X-ray image.

Under general anesthesia, emergency tracheostomy and suspended microlaryngoscopy was performed. The surgical treatment was conservative with laser CO₂ therapy and function-preserving surgery. After two days, tracheal decannulation was practiced, with anterior cervical suture after another three days. A new exploratory laryngoscopy

was performed, and the tracheal space was free.

Grossly, the biopsy fragments presented a lobulated, glassy, firm, and white or gray cut surface. The HP examination of HE-stained slides revealed a malignant tumor composed of the hyaline cartilaginous resembling proliferated lobules, that invaded the perichondrium (Figure 11). The tumor was situated in *lamina propria* of a mucosa nearby foci of elastic cartilage and disorganizing the seromucous acini (Figure 12). The lobules of tumor chondrocytes disrupted the respiratory columnar ciliated pseudostratified epithelium or area of mature squamous metaplasia (Figures 13 and 14). The tumor consisted of atypical chondrocytes, with large quantity of basophilic cytoplasm, and enlarged nuclei with big nucleoli, some of them showing highly nuclear pleomorphism and acidophilic inclusions in cytoplasm (Figure 15). An important number of atypical chondrocytes were binucleated (Figure 16). PAS reaction highlighted the presence of cytoplasmic inclusions (Figures 17 and 18). The tumor destroyed the ossified hyaline cartilage and presented foci of osseous metaplasia (Figures 19 and 20). The tumor cells were heterogeneously positive for S100 protein, and negative for p53 protein and E-cadherin (Figures 21–23). The Ki67 index was 10% (Figure 24).

The diagnosis of conventional grade 1 CHS affecting the proximal part of the trachea was pronounced and the patient was referred for oncological treatment.

Figure 11 – Atypical chondrocytes, some of them binucleated. HE staining, ×400.

Figure 12 – The tumor infiltrated the seromucous acini. HE staining, ×100.

Figure 13 – Respiratory mucosa lined by pseudostratified columnar epithelium disorganized by the tumor. HE staining, $\times 50$.

Figure 14 – Area of mature squamous metaplasia disrupted by the tumor. HE staining, $\times 100$.

Figure 15 – Atypical chondrocytes with intracytoplasmic inclusions, in a myxoid stroma. HE staining, $\times 200$.

Figure 16 – Atypical chondrocytes with intracytoplasmic inclusions. HE staining, $\times 400$.

Figure 17 – Atypical chondrocytes with intracytoplasmic inclusions. PAS reaction, $\times 200$.

Figure 18 – Atypical chondrocytes with intracytoplasmic inclusions, invading the lining epithelium. PAS reaction, $\times 200$.

Figure 19 – Atypical chondrocytes invaded ossified cartilage. HE staining, $\times 100$.

Figure 20 – The tumor showed areas of osseous metaplasia. HE staining, $\times 100$.

Figure 21 – Atypical chondrocytes immunohistochemically positive for S100 protein, $\times 50$.

Figure 22 – The negative immunohistochemical reaction for p53, $\times 200$.

Figure 23 – The negative immunohistochemical reaction for E-cadherin, $\times 50$.

Figure 24 – Ki67 index in atypical cells, $\times 200$.

Discussions

The CHSs are malignant mesenchymal bone tumors composed of atypical chondrocytes embedded in chondroid matrix. After osteosarcomas and myelomas, CHSs rank third in the group of primary malignant bone tumors [22, 23].

The etiology of CHSs remains unclear, although several hypotheses have been proposed. Disordered ossification found in hyaline cartilage in older patients, occurs in areas of muscle insertions, and may serve as a nidus for tumor development. Other predisposing factors are radiotherapy, injection of radioactive material, usually after a latent period of many years, or repeated trauma. In our cases, no predisposing or risk factors for CHSs were identified [24].

Histological features include a lobulated growth pattern, with disorganized chondrocytes. Lacuna occupied by double-packed atypical chondrocytes are often seen. Tumor cells present mild pleomorphism, but the presence of nucleoli is a constant encountered feature. In conventional CHS, the histological grading represents the main prognostic factor. The features useful in tumor grading are cellularity, pleomorphism, multinucleation and mitoses. Most CHSs are grade 1 (low grade), with a very good prognosis. They show a pattern of lobular disarray and destructive invasion of native cartilage and bone. Moderately differentiated tumors (grade 2) show a higher degree of cellularity and nuclear pleomorphism than grade 1 tumors and may have few mitoses. Grade 3 tumors have high cellularity, significant multinucleation, nuclear atypia, hyperchromic nuclei, areas of necrosis, and increased mitotic index [1].

In the present study, there were performed IHC markers (S100 protein, Ki67 index, p53, E-cadherin), and histochemical stainings both for diagnostic and outcome purposes. According to the published data, the Ki67 index can be used in the diagnosis and prognosis of cartilaginous tumors, malignant cartilaginous tumors having a greater Ki67 index in comparison to the benign counterparts [25, 26]. The scapular tumor presented a high Ki67 index (80%), helping us to rule out an enchondroma. A study on cartilaginous tumors shows that the Ki67 index has a higher immunoreactivity ($p=0.0044$) in comparison to enchondromas, recommending using it as a marker in the diagnosis of cartilaginous tumors [25]. Another study on CHSs indicates the value of Ki67 index as a prognostic factor for this type of tumors, suggesting that patients with a high Ki67 index might benefit from adjuvant therapy, immunotherapy, or biological modulation [26]. Taking into consideration that the scapular tumor has a higher Ki67 index (80%) than the tracheal tumor (10%), we conclude that the scapular tumor could benefit from adjuvant or immunomodulatory therapy. The same prior mentioned study shows the existence of PAS-positive intracytoplasmic globules, suggesting that hyaline intracytoplasmic globules were more frequently found in malignant than in benign cartilaginous neoplasms ($p=0.042$) [25]. Relying on this finding, we performed a PAS staining, which highlighted the presence of these intracytoplasmic granules, thus helping in the differential diagnosis between malignant and benign.

There are few studies in the literature regarding p53 and E-cadherin immunoreactivity in high-grade CHSs. Nevertheless, a study performed on 39 CHSs shows that

17 of them are immunoreactive for p53 and concludes that a direct correlation between this expression and the outcome in CHSs could not be established, which is also our fact that we also sustain [26].

Microscopically, our cases were conventional low-grade CHSs, which coincides with the data in the literature. Based on histological and imagistic aspects, CHS of the scapula was considered peripheral, with bone invasion.

Tracheal CHSs are rarely reported. With age, hyaline cartilage from different parts of the body undergoes ossification. It is presumed that during this process pluripotential mesenchymal cells reach the cartilage and could be the source of malignant cartilaginous tumors. The ossification of hyaline cartilage is intensified with age, the frequency of the tumor is higher between fifth and eighth decades of life corresponding to the high rates of bone formation.

Tracheal CHSs have been a diagnostic challenge for both clinicians and pathologists. The differential diagnosis includes chondroma, fracture callus and *tracheopathia chondroplastica*. The last is a condition restricted to trachea, with unidentified etiology. Laryngoscopy reveal gritty small submucosal nodules. The tumor interests the part of trachea that includes hyaline cartilage, the posterior wall not being involved. Microscopically, the connective tissue of *lamina propria* presents foci of microcalcification and area of newly formed bone. Clinical and imagistic correlation can aid in this distinction. The fractures can interest the ossified hyaline cartilage of trachea. The resulting callus may represent an important differential for CHSs, but the callus is not lobulated and do not show pushing margins as malignant tumor does, even if the osseous trabeculae are lined by osteoblasts. Usually, the clinicians can point out a previous trauma. For tracheal tumors, the differential diagnosis, before surgery, between a benign cartilaginous tumor and its malignant counterpart cannot be done. For the CHSs arisen in the long bones, the differential diagnosis with a benign tumor imposes the surgical procedure. The decision is a teamwork between clinicians and radiologists. On X-ray exam, benign cartilaginous tumors of long bones are encapsulated and do not destroy bone cortex. Because of the architectural particularities of tracheal ossified cartilage with restricted medullary space, even a benign tumor can destroy the bone cortex. For that, the preoperative distinction between chondromas and CHSs is moot. On histological grounds, even if, similar to malignant cartilaginous tumor, chondromas present hypercellular areas and an intensification of matrix eosinophilia, the tumor cells show no atypia and the nuclear cytoplasmatic ratio is unchanged.

Grade 1 conventional-type CHS is a slow-growing neoplasm and is resistant to chemotherapy and radiation therapy [16, 27]. Alternative therapeutical methods can be tested to enhance the treatments benefits and to improve the patient's life quality [28]. The tumorectomy of bones CHSs with free margins increase the life expectancy at five years from 54% to 78% [29].

The prognosis for tracheal CHS is favorable although the local recurrence rate is relatively high (18–50%), usually due to incomplete resection [30]. Distant metastases are very rare. The treatment of choice is conservative surgery, function-preserving surgery, including laser therapy [31–33].

✉ Conclusions

CHSs are very rare mesenchymal tumors, and their diagnosis is a challenge for pathologists. Low-grade CHS requires a differential diagnosis with enchondroma and reactive changes. This was done by correlating the histological aspects in the usual staining, with the result of IHC and histochemical reactions, as well as with clinical and imaging data. The article presented two interesting cases of conventional grade 1 CHS with different location, one of them with a very rare presentation.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Gabriel Veniamin Cozma and Laurențiu Vasile Sima equally contributed to the manuscript.

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