Chondrosarcoma of the hyoid bone: a case report

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Abstract
Chondrosarcoma is a malignancy of the mesenchymal tissue derived from transformed cells that produce the cartilage matrix. In the neck area, it represents less than 0.5% of malignant tumor pathology. Chondrosarcoma of the hyoid bone is extremely rare, only 20 cases having been published so far (PubMed 2014). We present the case of a 30-year-old patient from the urban area, admitted in the ENT (Ear, Nose & Throat) Emergency Service with inspiratory dyspnea, dysphagia, stomatolalia, with evolutive and progressive clinical history of 2–3 months. Endoscopic examination revealed a pharyngolaryngeal tumor process located in the right vallecula, who by mass effect displaces the above-hyoid epiglottis. CT (computerized tomography) scan described a cervical polycystic tumor aspect, with multiple septae and inside calcifications with a diameter of 3–4 mm. Surgery consisted in removal of the tumor process together with the hyoid bone. Histopathological and especially immunohistochemical examination established the diagnosis of low-grade chondrosarcoma of the hyoid bone. For assessment of the phenotype of the tumor cells, the following immunohistochemical markers were used: p53, Ki67. The patient followed radiochemotherapy playing an adjuvant role. Regular tracking of the patient is mandatory.

Keywords: chondrosarcoma, hyoid bone, immunohistochemistry, tumors.

Introduction
Solid primary tumors of the hyoid bone are exceedingly rare. Reported cases have included chondrosarcoma, plasmacytoma, osteosarcoma, giant cell tumor, aneurysmal bone cyst, and benign osteoma. Patients with hyoid bone tumors usually present with dysphagia and may have a palpable neck mass. The goal of imaging is to distinguish benign from malignant causes and to assist in surgical planning [1].

Chondrosarcoma, mesenchymal tissue neoplasm derived from transformed cells that produce cartilage matrix, is a member of a class of bone and soft tissue tumors known as sarcomas. Most chondrosarcomas have a slow growth rate and the histopathological and immunohistochemical findings. Here, we describe a case of low-grade chondrosarcoma of hyoid origin, that was diagnosed and treated at our institution, and we reviewed the current literature on management options. We also discuss its symptomatology, preoperative imaging features, treatment, its recurrence rate and the histopathological and immunohistochemical findings.

Case report
We present the case of a 30-year-old patient admitted in our ENT (Ear, Nose & Throat) Emergency Service in January 2013, with inspiratory dyspnea, dysphagia, stomatolalia, with evolutive-progressive clinical history of 2–3 months.

From patient’s history, we note only that six months ago he underwent surgery, which consisted of an excision of a “cystic” tumor from the lingual face of the epiglottis, through suspended microlaryngoscopy (in another hospital service).

On clinical examination, the patient displayed the presence of a discrete tumefaction in the anterior neck region. Endoscopic examination revealed a pharyngolaryngeal tumor process located in the right vallecula, which by mass effect displaces the above-hyoid epiglottis, which it then dislocates and directs with the concavity towards the left lateral wall of the hypopharynx, leaving a respiratory slot resembling an equilateral triangle with the side of 5 mm.

Laboratory tests were normal. ECG (electrocardiography): sinus rhythm, QRS axis normal. Chest X-ray: no active pleuro-pulmonary lesions.

Cervical CT (computerized tomography) scan revealed cervical tumor formation of polycystic appearance, inside having multiple septae and calcifications with a diameter of 3–4 mm; the formation interests the right vallecula and is well shaped, aspect that suggests a possible chondroma (Figures 1–3).

Tracheotomy was performed under local anesthesia, followed by endotracheal intubation and excision of the
tumor together with the hyoid bone by transvallecular approach (Figures 4 and 5).

Afterwards, we performed epiglottopexy, pharyngeal suture, mounting of nasal feeding tube and installation of Portex-type tracheal cannula.

Macroscopic examination of the piece of excision revealed a tumor formation with diameters of 7.5/5.5/6.5 cm, polylobed, polycyclic, with relatively smooth capsule, of firm consistency. Through the transparency of the capsule, there is a brindle aspect, with red-purple areas, alternating with light-colored areas. On the section there is a brindle, hard aspect of the white zones, having the size of a grain of rice, non-confluent, separated by areas of purplish tint, fleshy, firm (Figure 6).

The excision sample was fixed in 10% diluted formalin for 48 hours and then was sent to the pathology laboratory for histopathological examination.

The biological material has been included in paraffin and then cut with microtome, obtaining sections with a 3 μm thickness. For the classic histopathological study, three stainings were used: Hematoxylin–Eosin (HE), Goldner–Szekely (GC) trichromic, and Periodic Acid–Schiff (PAS)–Hematoxylin.

For the immunohistochemical study, out of the material included in paraffin, histological serial sections were realized which were collected onto slides coated with poly-L-Lysine and then kept in a thermostat at 37°C for 24 hours to increase the adhesion of biological material to the histological blade. Following dewaxing and hydration of histological sections, the biological material was incubated for 30 minutes in a solution of 1% hydrogen peroxide. Then, the sections were washed in tap water before being cooked in citrate pH 6 solution for 20 minutes in the microwave for antigen unmasking. After boiling, the sections were cooled and then washed in phosphate buffered saline (PBS), followed by blocking of endogenous peroxidase phase in 2% skim milk for 30 minutes. Then, the sections were incubated with primary antibody overnight (16 hours) at 4°C, and the next day, the signal was amplified for 30 minutes using the secondary antibody with peroxidase on polymer substrate, the detection system (EnVision, Dako). The signal was detected with 3,3’-diaminobenzidine (DAB) (Dako). For immunohistochemical study, we used the following antibodies (Table 1).
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Table 1 - The antibodies used in this study

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Producer</th>
<th>Clone</th>
<th>Clonality</th>
<th>Unmasking</th>
<th>Dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Ki67</td>
<td>Dako</td>
<td>MIB-1</td>
<td>Ms/Hu/Monoclonal</td>
<td>EDTA, pH 9</td>
<td>1:50</td>
</tr>
<tr>
<td>Anti-p53</td>
<td>Dako</td>
<td>DO-7</td>
<td>Ms/Hu/Monoclonal</td>
<td>Sodium citrate, pH 6</td>
<td>1:50</td>
</tr>
<tr>
<td>Anti-S100</td>
<td>Abcam</td>
<td>EP1576Y</td>
<td>Rb/Hu/Monoclonal</td>
<td>Sodium citrate, pH 6</td>
<td>1:500</td>
</tr>
<tr>
<td>Anti-EMA</td>
<td>Dako</td>
<td>E29</td>
<td>Ms/Hu/Monoclonal</td>
<td>Sodium citrate, pH 6</td>
<td>1:100</td>
</tr>
</tbody>
</table>

Microscopic examination revealed a nodular myxochondroid proliferation, bounded by collagen fibrosis, which shows reduced xanthomatous inflammation and is represented by chondrocytes (Figure 7). Cartilage is composed of chondrocytes with irregular hyperchromic nuclei, low mitotic activity and areas of bone metaplasia (Figure 8).

 Conjunctive septae between the islands of cartilaginous tissue appeared as formed of fibrillar collagen, organized in bunches with numerous fibroblasts, some with tendency to transform in chondroblasts. In these septa, it was highlighted the presence of abundant vascularizations (Figure 9) and sometimes the presence of chronic inflammatory infiltrates mostly made of round mononuclear cell of lymphoma type (Figure 10). PAS–Hematoxylin staining allowed us to highlight the presence of chondrocytes of various shapes and sizes containing PAS-positive material in the cytoplasm. In the intercellular connective matrix were found small amounts of PAS-positive material (Figure 11). In the periphery of the myxochondroid areas stands striated muscle tissue. The described aspect suggests hamartoma tumor type (choristoma).

For positive and differential diagnosis, we felt the need to make immunohistochemical reactions. Immunohistochemical exams showed that some chondrocytes were positive (focal) to the marker p53, weak positive to Ki67 (<5%) (Figure 12), weak positive to EMA (Figure 13) and intensely positive to S100 (Figure 14).

Conclusion of the histopathological exam: low-grade chondrosarcoma.

Figure 7 – Microscopic aspect of the tumor. It is observed the presence of islands of cartilaginous tissue with irregular contour, delimited by conjunctive septa rich in collagen and fibroblasts. HE staining, ×100.

Figure 8 – Cartilaginous matrix with small areas of bone metaplasia (detail inset). GS trichromic staining, ×100.

Figure 9 – Tumor stroma with a rich network of blood vessels. GS trichromic staining, ×200.

Figure 10 – Area of tumor stroma heavily infiltrated by lymphocytes. GS trichromic staining, ×200.
Figure 11 – Fragment of tumor with accentuated cell pleomorphism because of extremely varied forms of chondrocytes. Their cytoplasm is intensely PAS-positive. In the cartilaginous stroma it is noted the presence of a small amount of PAS-positive material, which gives these abnormal aspect of these tissue structures. PAS–Hematoxylin staining, ×400.

Figure 12 – Very weak immunohistochemical reaction to Ki67 antibody (2–3 cells per field). Immunostaining with anti-Ki67, ×200.

Figure 13 – Moderate reaction of tumor cells to epithelial membrane antigen (EMA). Immunostaining with anti-EMA, ×400.

Figure 14 – Intense reaction of tumoral chondrocytes to the S100 protein. Immunoblotting with anti-S100 antibody, ×400.

Patient’s postoperative evolution was favorable. Postoperative chemoradiation therapy followed. The patient returned for regular ENT checkups at three months interval. He also had a chest X-ray at six months and a cervical CT after one year. At 24 months postoperatively, evolution remains favorable, with no signs of loco-regional recurrence or metastasis away.

**Discussion**

Chondrosarcomas, tumors of mesenchymal origin, developed mainly from cartilage matrix forming cells, are divided by origin in ‘de novo’ chondrosarcomas and secondary chondrosarcomas [7]. Primary chondrosarcomas are highly unusual, showing in the central area of the bones, especially in children. Secondary chondrosarcomas develop on preexisting, benign lesions, like osteochondromas or enchondromas. They are frequent in the age segment of 30–60 years [2], with a peak incidence around 40 years. The male/female ratio is 1.5 to 1. Some authors found no significant gender differences in the incidence of chondrosarcomas [2].

Chondrosarcomas develop predominantly at the axial skeleton level: bones of the pelvis, femur, proximal humerus or ribs [8]. In the region of the head and neck is a rare disease and represents approximately 0.1% of all malignancies developed in these regions [9].

Chondrosarcomas developed at the level of the hyoid bone are very rare, only 20 cases being cited in literature [6, 4, 8–13].

Most chondrosarcomas are painless tumors that slowly grow. When painful symptoms appear, it is already the case of a large tumor. In our case, the tumor was large and it caused dyspnea, dysphagia and stomatolalia.

CT scan is the imaging method of choice, better classifying the extension and tumoral origin in the case of chondrosarcomas. It can pinpoint bone destruction or irregularities. Location under the mylohyoid muscles of a tumor formation coming from the hyoid bone with chondroidal calcification suggests the diagnosis of chondro-
Chondrosarcoma of the hyoid bone. Approximately 75% of chondrosarcomas show intrinsic tumor calcification [14]. In our case, the CT scan did not reveal bony destruction.

Histopathological and immunohistochemical examination establish the diagnosis, showing the grade of cellular differentiation [15]. There are three histological degrees aiming at cell differentiation, abnormality and pleomorphism [16]: Grade 1 – Low – similar smear to enchondroma – high cellularity, round nuclei and open chromatin structure; Grade 2 – Intermediate – increased cellularity – nucleoli present in most cells – signs of myxoid transformation; Grade 3 – High – increased cellularity, nuclear atypia and mitotic presence. The higher the degree, the higher the probability of metastasis.

Histopathological diagnosis of chondrosarcomas degree is sometimes quite difficult because there is a relative variability of the criteria and the modalities of interpretation of injuries between histopathologists, taking into consideration the experience and training of each of them [17]. This aspect is worrying because the therapy of first-degree chondrosarcomas and second-degree chondrosarcomas is different. It is therefore essential to develop new methods of histopathological diagnosis (of molecular medicine, immunohistochemistry, cytogenetics) to increase diagnostic accuracy [18].

In our study, histopathological and immunohistochemical interpretation was made independently by two histopathologists in different laboratories. Although initially the histopathological diagnosis was hamartoma, the immunohistochemical exams and the histopathological reevaluation concluded that the lesion is a low-grade chondrosarcoma. However, some histopathological aspects such as the myxochondroid appearance of tumor areas, nuclear and cellular pleomorphism, the presence of an intense stromal vasculature, of inflammatory infiltrates in stroma and the positivity of the p53 protein would suggest that tumor lesions were classified in Grade II. However, a very little Ki67 proliferation index has made us to believe that the correct diagnosis is a low-grade chondrosarcoma.

Changes in p53 reveal modification of the nuclear material, and in particular the TP53 gene. Some authors found that p53 mutations are present in about half of chondrosarcomas [19]. Strongly positive P53 protein reactions were identified in high degree chondrosarcomas, suggesting that changes in TP53 gene play an important role in the progression of chondrosarcomas [20–22]. TP53 gene is a tumor suppressor gene because it is involved in cell cycle regulation, in genomic stability, induces apoptosis and inhibits abnormal angiogenesis [23].

We too, like other authors [24–26], found that tumor cells of chondrosarcomas are weakly positive at EMA and moderately or strongly positive at S100. All these immunohistochemical aspects show molecular and genetic changes of the tumor cells, some poorly explained until now, others still unknown.

It should be emphasized that the genetic changes underlying the initiation and progression of chondrosarcomas are little known mainly due to the limitations of current research techniques for studying these neoplasms. We believe that further researches of molecular biology, cytogenetics and immunopathology are required to enable a better understanding of the disease and to help develop specific methods of treatment.

Conform to staging of the chondrosarcomas [27, 28], our patient was diagnosed with stage 1A chondrosarcoma with low degree of differentiation, sizes up to 8 cm.

Chondrosarcoma treatment is surgical, with large excision of the tumor array, within oncological safe limits. Operator success depends on tumoral extension, low-grade lesions offering the best prognosis. Neither radiotherapy, nor chemotherapy does not play a significant role in the primary treatment. Chondrosarcoma is considered to be radioresistant, although radiotherapy can be considered as aiding treatment or for patients that refuse or cannot undergo surgery [2, 29].

In our case, the treatment was surgical with tumor removal together with the hyoid bone, followed by adjuvant chemo- and radiotherapy.

Larger tumors behave more aggressively than the smaller ones. Dissemination occurs primarily through blood and lymph vessels.

The likelihood of metastasis is correlated with the increase in the degree of malignancy, resulting in a bad prognosis [30]. Five-year survival rate for all cases of chondrosarcoma is 90% for first grade, 81% for the second grade, 43% for the third grade [31].

Therefore, periodic monitoring is necessary. Loco-regional recurrences will be pursued as well as emergence of possible metastasis. Because pulmonary metastasis is the most common, lung radiography is recommended every six months.

**Conclusions**

The hyoid bone chondrosarcoma, extremely rare malignant tumor (20 cases cited in the literature so far), manifest symptoms the moment the tumoral extension reaches large sizes, like our case. In our study, CT exam suggested the diagnosis of chondrosarcoma, but correct diagnosis and tumor grade were established after surgery based on histopathological and immunohistochemical examinations. Surgery is the only effective therapeutic method. The prognosis of our patient, influenced by result of the surgery, histological grade and tumor extension, is good. Regular follow-up of the patient diagnosed with chondrosarcoma is mandatory.

**Conflict of interests**
The authors declare that they have no conflict of interests.

**Consent**
Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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