Laryngeal chondrosarcoma associated to cervical lymph node metastasis of papillary thyroid carcinoma. A systematic review.

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Abstract

Objective: Laryngeal chondrosarcomas (LCS) are rare tumors with good prognosis. The coexistence of LCS and cervical metastasis of papillary thyroid carcinoma (PTC) is scarce. The main objective of this research was to review clinical aspects and management of LCS . A secondary objective was to find the coexistence of LCS with cervical Lymph node metastasis of papillary thyroid carcinoma (LNMPTC) in all the cases included in the search. Design: A Systematic Review was performed using PubMed, Web of Science, Scopus and Embase databases. We followed PRISMA guidelines and the PECOS method to characterize different aspects of LCS. Reports of laryngeal chondrosarcoma were included and information about symptoms, imaging technique, treatment modality, histopathological diagnosis, location, tumor size, recurrence, and follow-up data was extracted. Results: Three hundred and eighty one cases of LCS were included. The average age was 61.1 years. The most common symptoms were dyspnea and hoarseness. Cricoid cartilage was the most usual location. Survival was affected by histologic differentiation, tumoral location and surgical technique. We identified the coexistence of LCS and PTC in 2 cases. In none of them the authors reported LNMPTC. Conclusion: The coexistence of LCS and PTC is rare. LCS is a tumor with good prognosis. Different approaches are described in literature.

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Design: A Systematic Review was performed using PubMed, Web of Science, Scopus and Embase databases. We followed PRISMA guidelines and the PECOS method to characterize different aspects of LCS. Reports of laryngeal chondrosarcoma were included and information about symptoms, imaging technique, treatment modality, histopathological diagnosis, location, tumor size, recurrence, and follow-up data was extracted.

Results: Three hundred and eighty one cases of LCS were included. The average age was 61.1 years. The most common symptoms were dyspnea and hoarseness. Cricoid cartilage was the most usual location.

Survival was affected by histologic differentiation, tumoral location and surgical technique. We identified the coexistence of LCS and PTC in 2 cases. In none of them the authors reported LNMPTC.

Conclusion : The coexistence of LCS and PTC is rare. LCS is a tumor with good prognosis. Different approaches are described in literature.

Keywords: Laryngeal; Chondrosarcoma; Papillary Thyroid Carcinoma; Metastasis; Systematic Review.

KEY POINTS

1. Laryngeal chondrosarcomas are rare tumors.
2. The coexistence of laryngeal chondrosarcoma with cervical metastasis of papillary thyroid carcinoma is extraordinary.
3. Dyspnea and hoarseness are the most commonly reported symptoms in laryngeal chondrosarcoma.
4. In Laryngeal chondrosarcomas, survival is affected by histologic differentiation, tumoral location and surgical technique.
5. Different surgical techniques are described for laryngeal chondrosarcoma, being laryngectomy the most commonly used.

1- INTRODUCTION

Chondrosarcomas (CS) are cartilaginous tumors that commonly affect bones like pelvis, ribs or femur [1]. They may also affect the larynx, being the cricoid cartilage the most common site of appearance. Nevertheless CS can also be originated in thyroid or arytenoid cartilages, epiglottis or even from hyoid bone [2].

Laryngeal chondrosarcomas (LCS) are extremely rare tumors, representing less than 1% of all malignancies of the larynx, being the third most common tumor after squamous cell carcinoma and adenocarcinoma[3]. LCS behave as locally aggressive tumors, producing symptoms like dysphonia, dyspnea, dysphagia or hoarseness. In other cases, they may appear as a neck mass. Computed Tomography (CT) scan and Magnetic Resonance Imaging (MRI) are the tests of choice in order to make a presumptive diagnosis [4], although F-18 fluorodeoxyglucose-positron emission tomography (PET) may be used for grading and local recurrence or metastases detection[5]. Final diagnosis is based on histopathological examination. Fine Needle aspiration (FNA) or incisional/excisional biopsies may support initial diagnosis [6] . As surgical treatment may be necessary in most cases, histopathological exam of the tissues will determine the final diagnosis. CS are classified in 3 grades; Grade I, (low-grade, well-differentiated), Grade II (intermediate-grade, moderately-differentiated) and Grade III (high-grade, poorly differentiated). There are different subtypes of CS as clear cell, mesenchymal, extra-skeletal or dedifferentiated (Also considered as Grade IV) CS [7].

Different approaches for the treatment of LCS have been described in the literature [8-11]. Treatment varies depending upon the grade of differentiation of the tumor, and the anatomical involvement, from local resection to total laryngectomy. Radiotherapy (RT) can be considered in some inoperable patients, for recurrences or in case of aggressive tumors [5]. Disease specific survival of LCS is higher compared with other laryngeal tumors [3,12].

Papillary thyroid carcinoma (PTC) is the most frequent thyroid tumor, representing up to 85% of its cancers [13]. It is considered a tumor with good prognosis, with a low risk of recurrence. Nearly 70% of PTC present lymph node metastasis [14]. This fact is associated with local recurrence and a decrement in survival rate [15]. PTC generally appear as a painless mass in the thyroid gland, and in rare cases can produce symptoms like hoarseness or dysphagia. Ultrasound is the imaging test of choice, but also, CT scan, MRI or PET may be useful to detect extrathyroidal extension or recurrences [16]. FNA, ultrasound-guided or not, is often the initial diagnostic method used to detect PTC[17]. Surgical treatment is based on, tumor size, extra-thyroidal extension or lymph node metastasis. The approach can be done through lobectomy, near-total or total thyroidectomy, with or without lymph node removal, depending on the case [18]. Radioiodine is used to ablate remnant normal thyroid tissue[19] and hormone therapy is also used in order to suppress thyrotropin and avoid the growth of remaining papillary cells[20].

We report the case of a patient with LCS and cervical LNMPTC. A systematic review was conducted in order to find similar cases in the literature.

2- CASE REPORT

A 56- year-old man was referred to our department with a 12-month history of dysphonia, and aggravated dyspnea during the last 2 weeks. The patient denied odynophagia or dysphagia. He was a former smoker, and he had a 50-pack-year smoking history. Flexible laryngoscopy revealed a paralysis in his right hemilarynx, with laryngeal rotation and intact mucosa (Figure 1). No lymphadenopathies were evident in the laterocervical region. CT scan and MRI revealed a submucosal expansive lesion at the right posterolateral region of the larynx, arising from cricoid cartilage, compromising the whole circumference of the cartilage, consistent with the suspicion of "*cricoid chondrosarcoma* " (Figure 2). Suspicious, calcified, and oval cervical lymphadenopathies were found at level II in both sides of the neck and level III of the right side. Images did not show evidence of a mass or nodule in the thyroid gland. The patient was evaluated by the Surgical Board, and decided as a first approach, local anesthesia tracheotomy and direct laryngoscopy with biopsy. The histologic analysis showed fragments of well-differentiated hyaline cartilage, with ossification foci, consistent with *"low-grade CS".*

On the basis of the histologic and radiologic findings, the case was discussed by the Oncologic Board. The decision was to perform total laryngectomy, with thyroidectomy and bilateral neck dissection.

A 4 cm chondroid pattern tumor, arising from cricoid cartilage was found, confirming the final diagnosis of a *"moderately-differentiated chondrosarcoma of the cricoid cartilage"* (Figure 3). PTC was detected by metastases in 12/29 lymph nodes isolated in the right neck dissection (Figure 4-5). Surgical margins were free of lesion. Vascular invasion was positive for PTC.

Postoperative course was uneventful, and the patient was discharged from our service 19 days after surgery, with swallowing function preserved. The patient was sent to Endocrinology for evaluation, and ablative treatment with radioactive iodine therapy (I-131) was scheduled. The patient was assessed every 3 months for the first year, planning a CT scan every 6 months. At 19 months follow-up the patient is free of disease and there is no clinical or imaging sign of recurrence.

3- MATERIAL AND METHODS

Systematic review. Protocol and registration

The systematic review was carried out by OACI and is registered in PROSPERO (Ref. CRD42021224412). The review was designed following PRISMA guidelines and the PECOS method: patients with LCS and lymph node metastasis of thyroid papillary carcinoma (P= patient); histopathologic analysis (E=exposure); non laryngeal location (C=comparator); clinical-pathological aspects (O=outcome); case reports (S=type of study). Eligibility criteria were studies describing cases of LCS written in Spanish or English language. Exclusion criteria were letters to the editor, meetings proceedings and articles with no abstract or full text available (Figure 6).

We performed a comprehensive literature search using the PubMed, Web of Science, Scopus and Embase databases for studies published until December 2020.

The search included the terms *"Larynx [MeSH terms] OR Laryngeal [MeSH terms] OR Larynx [Title/Absctract] OR Laryngeal [Title/Absctract] AND Chondrosarcoma [MeSH terms] OR Chondrosarcoma [Title/Absctract]".* This process was supplemented by hand searching in different peer-reviewed journals and databases. Reference lists of retrieved articles were also checked.

The main objective of the research was to found all the cases of LCS published to date. A secondary objective was to find the coexistence of LCS with cervical LNMPTC in all the cases included in the search.

Study selection

Two independent researchers (OACI and MPS) analyzed the articles. First, they read the abstracts and exclude those not fulfilling inclusion criteria. After that, both authors analyzed the full-text and, again, decided whether they should be included or excluded. A third investigator (ALP) acted as a mediator in case of dispute. Agreement was calculated using Cohen's kappa coefficient, with a k value of 0.92.

Data collection process

Data retrieved from all articles were collected by both researchers (in duplicate) independently and corroborated by the third party, who acted as a mediator as was mentioned before.

Data items

Different information was extracted from each study: first author, year of publication, journal, sex and age of the patient, symptoms, imaging technique, treatment modality, histopathological diagnosis, location, tumor size, recurrence, and follow-up data.

Risk of bias in individual studies

The methodological quality of the included studies and the possibility of bias were assessed using the modified Newcastle–Ottawa, Pierson and Bradford Hill scales for case and case series reports[21]. The authors of this scale recommend assessing the quality of the studies according to four categories, selection, ascertainment, causality and reporting, with eight specific questions to answer giving low (1–3 questions), medium (4–6 questions) and high (7–8 questions) quality values. This analysis was carried out independently by each of the two investigators, and in cases of disagreement, the third acted as a mediator.

This study was sent to the Ethics Committee of Clinical Research of Galicia (Spain), stating that ethical approval was not required for this type of study. Written consent of the patient was obtained.

4- RESULTS

Systematic review

The systematic review included 148 articles (mostly case and case series reports), with a total of 381 cases of LCS (Figure 7). In 2 of them (0.5%) the authors described the coexistence of LCS associated to a PTC. None of them had cervical metastasis. In terms of quality, the articles were classified within medium quality values.

The sample consisted of 254 men (74.3%) and 88 women (25.7%) with a mean age of 61.1 ± 12.1. Diverse symptoms were described in 325 patients (85.3%). A different grade of dyspnea was the most commonly reported symptom (42.8%) followed by hoarseness (35.7%) and neck mass sensation (10.8%). Most of the patients reported more than one symptom. Impairment of at least one vocal cord mobility was reported in 66 patients (17.3%). Imaging studies were described in 213 patients (55,9%). CT scan was the most commonly used, in 209 patients, followed by MRI in 46. Other techniques as ultrasound or X-ray were also described. In Figure 8, more information regarding demographics, symptomatology, location, and imaging is provided.

Tumoral location was reported in 340 patients (89.2%). The cricoid cartilage was the most commonly affected with 271 cases (79.9%), followed by the thyroid cartilage in 67 cases (19.7%). In 41 patients (10.8%) the tumor involved more than one anatomical site. Different treatment modalities were used. Total laryngectomy was reported in 131 patients (34.4%), local excision in 104 cases (27.3%), partial laryngectomy in 92 (24.1%), and laser surgery in 34 patients (8.9%). Uni or bilateral neck dissection was reported in 18 cases (4.7%). First choice radiotherapy was used in 7 patients (1.8%). Adjuvant therapy with RT was described in 28 patients (7.34%) and chemotherapy in 2 patients (0.52%). The size of the tumor was reported in 135 patients (35.4%), being the mean size 3.8 ± 1.7 cm. Histological information was found in 323 patients (84.7%). Pathological grading was reported as Grade I (well-differentiated) in 210 cases (67.1%), Grade II (moderately-differentiated) in 62 cases (19.8%), Grade III (poorly differentiated) in 8 cases (2.6%) and Grade IV (dedifferentiated) in 18 cases (5.8%). Other cases were reported as clear cell CS, or myxoid CS. Distant metastases were unfrequent, and appeared in 21 patients (5.5%) in different locations like lungs, soft tissue,

bone or peritoneum. Lung metastasis was the most frequent location, being present in 15 cases (71.4 %). The mean follow-up time was 57.7 ± 53.4 months. In this period, tumoral recurrence was reported in 62 cases (16.3%). Total Laryngectomy was the treatment of choice in 25 of the recurrences (6,6%). Local excision and laser were used in 18 patients (4.7%) while partial laryngectomy was described in 8 patients (2.1%). Death was reported in 47 patients (12.3%), mostly as *"not related or other cause"* (74%), or *"distant metastasis"* (17,4%). Only 8.7% were reported as *"dead of disease"* . Death was found to be more frequent in those patients with tumoral recurrence who were treated with total laryngectomy (55.3%, p = 0.001). In Figure 9 additional information about treatment, tumoral characteristics, and follow-up period is provided.

Using Kaplan-Meier curves, a mean survival of 207.5 months (95% CI 176.4-238.7 months) is estimated (Figure 10). Regarding survival in relation with tumoral location, the estimate is lower for those cases with combined location, with 98.5 months (95% CI 73-124 months) compared to those affecting only one location, with a mean of 191.6 months (95% CI 163.1-220 months) (log-rank = 6.6, p = 0.01) (Figure 11). Survival is also affected by histological differentiation, being the lowest for grade IV (dedifferentiated) with 118.7 months (95% CI 64.8-172.6 months) and the longest for grade I (well-differentiated) with 253.8 months (95% CI 215-292.5 months) (log-rank = 18.3; p = 0.003) (Figure 12).

Taking into account treatment modality, the estimate for survival is lower for those who underwent total laryngectomy with 156.6 months (95% CI 127.5-185.6 months) compared with those who were treated with laser excision with 276.1 months (95% CI 229.4-322.9) (log-rank = 11.7; p=0.008) (Figure 13).

5- DISCUSSION

We presented an extremely rare case of a LCS with cervical LNMPTC. To our best knowledge, this is the first case reported in literature, where these two malignancies coexist. In 2012 Buda et al [22], reported one case of a LCS arising from cricoid cartilage associated to a PTC. Vahidi et al [23] reported a case of a LCS arising from thyroid cartilage with an incidental PTC. Lymph node metastasis was absent in both reports.

As mentioned before, LCS are rare tumors, which often require surgical treatment. The key in order to choose the appropriate treatment is to balance the oncological with the functional outcomes. The goal in these patients should be to remove the tumor with adequate margins avoiding local recurrences or distant metastasis, trying to preserve the voice and normal swallow. For this reason, surgeons have described different surgical techniques, including minimally invasive local resections, laser procedures, hemicricoidectomy, partial laryngectomies with reconstruction or not, and more aggressive techniques like total laryngectomy. Theoretically, less aggressive techniques are indicated for low-grade and not extensive tumors, and total laryngectomy is the choice for high-grade, extensive tumors and recurrences. In our case we decided to perform total laryngectomy, given the extension of the lesion[24,25]. In our systematic review, laryngectomy (total or partial) was the treatment of choice in most of the patients, followed by local excision or laser removal of the tumor. Survival appeared to be lower in those patients treated with total laryngectomy, and this may have an explanation, probably because those candidates to this surgical technique might have more advanced tumors.

Cervical metastases of CS are rare, and neck dissection should be performed only if radiological or clinical evidence of disease is present. In our case, neck imaging revealed pathological nodes, so bilateral neck dissection was performed. Besides, due to tumor size and location, total thyroidectomy was performed. Treatment of PTC is debatable. Some authors advocate for active surveillance in cases of thyroid microcarcinoma or occult PTC [26]**.** In other cases, based upon different risk factors, a thyroid lobectomy or total thyroidectomy can be the option [18]. Different authors described the appearance of incidental metastatic PTC in neck dissections of non-thyroidal surgery, with a prevalence up to near 2%[27]. Thyroid carcinoma in cervical lymph nodes can have two possible origins. First, the possibility of malignant transformation of ectopic or heterotopic thyroid tissue. This fact can be explained due to anomalies in the migration of the thyroglossal during embryologic development. Also, alterations in development of the pharyngeal pouch endoderm can explain the presence of ectopic tissue in cervical lymph nodes [28]. Although ectopic thyroid malignancies commonly appear together with tumoral native tissue, in some cases a benign thyroid gland was found with ectopic PTC in different

upper body locations including the neck [29]. Second, the appearance of PTC lymph node metastasis from thyroid is not unfrequent in patients with thyroidal cancers as reported by So et al. in up to 90% of the cases [30]. This fact is associated with locoregional recurrence and a poor prognosis. In our systematic review, few cases reported cervical metastasis of CS [31-33]. In none of them PTC lymph node metastasis was found.

Comparing our systematic review with the biggest series previously published [3,12], in general, our results are in agreement, regarding tumor grading, anatomical site, tumor size, treatment modality, symptomatology and follow-up with them.

Thus, LCS are more common in men, affect people in their sixties, the main symptoms are dyspnea and hoarseness, CT scan is the most common imaging technique for diagnosis, cricoid cartilage is the most frequent location, total laryngectomy is the most commonly used surgical technique, well-differentiated CS is the most frequent histopathologic finding, distant metastases are rare and survival is related to histologic differentiation, anatomical involvement, surgical technique and recurrence.

The main limitation for this systematic review was the heterogeneity in data reporting, primary and secondary outcomes and follow-up. The search included articles from 1968 to 2020, and clinical information in different series were unavailable or inaccurate. This fact made that some series, had to be excluded from our systematic review[34-40] despite the high number of cases reported.

In conclusion, with this systematic review we provide a reliable general view of different aspects of LCS. These tumors are rare, and generally with a better prognosis than other laryngeal tumors. We also presented an extremely rare case of coexistence of LCS and cervical LNPTC. This is the first case reported in literature where this 2 entities appear simultaneously in a patient.

Conflict of interest

The authors declare that they have no conflict of interest.

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FIGURE LEGENDS:

Figure 1: Flexible Laryngoscopy with intact mucosa.

Figure 2: MRI with cricoid CS and lymph node involvement.

Figure 3: HE 40x. Neoplastic proliferation with increased cellularity, nuclear pleomorphism, hyperchromasia and invasion of the cricoid cartilage. There are more than one cell per lacunae.

Figure 4: HE 20 x. A Metastasis from a conventional PTC with papillary pattern and a Psammoma body is present in this cervical lymph node.

Figure 5: TTF-1 20x. PTC cells are immunoreactive for TTF-1.

Figure 6: Flow Chart. Systematic Review.

Figure 7: Articles included in the systematic review.

Figure 8: Demographics, symptoms, location, imaging.

Figure 9: Treatment, tumor characteristics, and follow-up period.

Figure 10: Overall Survival.

Figure 11: Survival according to location.

Figure 12: Survival according to histological differentiation.

Figure 13: Survival according to surgical treatment.

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