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Review Article

Primary chondrosarcoma of the hyoid bone: a case report and literature review

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Abstract: Chondrosarcoma (CS) located in the hyoid is exceedingly rare, with only a handful cases reported thus far. Because of its rarity, CS is not easily diagnosed by clinicians or pathologists. The present study reports a 42-year-old woman diagnosed with hyoid chondrosarcoma grade 2-3 after a wide local resection. To provide better insight into the disease, this study reviewed and analyzed 21 cases with the same disease, reported between 1990 and 2016. These cases were retrieved by searching PubMed and references. Symptom of hyoid chondrosarcoma are poor in specificity. A slow growing painless mass in the neck is a common sign. CTs and MRIs play important roles in judging whether the neoplasm is benign or malignant. A high false negative rate should be considered before making a diagnosis by fine needle aspiration biopsy. Surgery is the golden standard of treatment. Because of insensitivity, radiotherapy and chemotherapy can be used as accessory treatments in some circumstances. The main factors of prognosis correlate to enough surgical resection and tumor histologic grades.

Keywords: Chondrosarcoma, hyoid bone, surgery

Introduction

Chondrosarcoma (CS) ranks as the second most common malignant primary bone tumor, after osteosarcoma [1, 2]. It can be frequently seen in bones of the pelvis, the proximal femur, proximal humerus, distal femur, and ribs [3]. Approximately 10 percent arises in the head and neck, where it usually involves the nose and paranasal sinuses, mandible, temporal bone, and larynx. However, chondrosarcoma arising from the hyoid is exceedingly rare [4, 5]. Chondrosarcoma carries a good prognosis [6]. The present study reports a woman diagnosed with chondrosarcoma grade 2-3, including symptoms, examinations, diagnosis, treatment, and follow-up. This study also reviewed the current literature and analyzed characteristics of the disease, providing relatively available references. They may be used as guidelines in conducting diagnoses and preparing treatment plans.

Case report

A 42-year-old woman was referred to our institution. She had suffered from a painless palpable mass in the right submandibular region for about 2 months. She was free of upper aerodigestive tract symptoms. Physical examination revealed a 3.0 cm × 4.0 cm, hard, and round like mass. It was not fixed to surrounding structures and mobile with deglutition. There was no evidence of inflammation and no abnormal lymph nodes were palpable. Laryngeal endoscopy revealed that the mucosa was smooth. The right side wall of the hypopharynx pushed inwards and impinged on the right arytenoid. It extended from the horizon of the soft palate to the upper right arytenoid. Cervical ultrasonography demonstrated a hypoechogenic nodular in the right submandibular, with a size of 4.0 cm × 2.9 cm × 2.7 cm. The echo in the mass was not uniform, which showed patchy echo. The boundaries of the echo were unclear. It was dif-

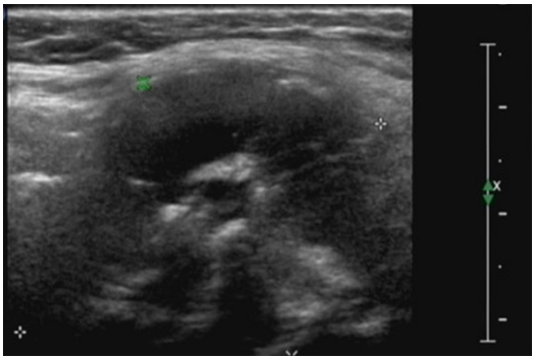

Figure 1. Cervical ultrasonography demonstrated a hypoechogenic area in the right submandibular measuring at 4.0 cm × 2.9 cm × 2.7 cm. The boundaries of the echo were unclear. The echoes in it were not uniform, including speckle echoes. The boundaries of echoes were unclear. Blood-flow signals could be seen inside and around the mass.

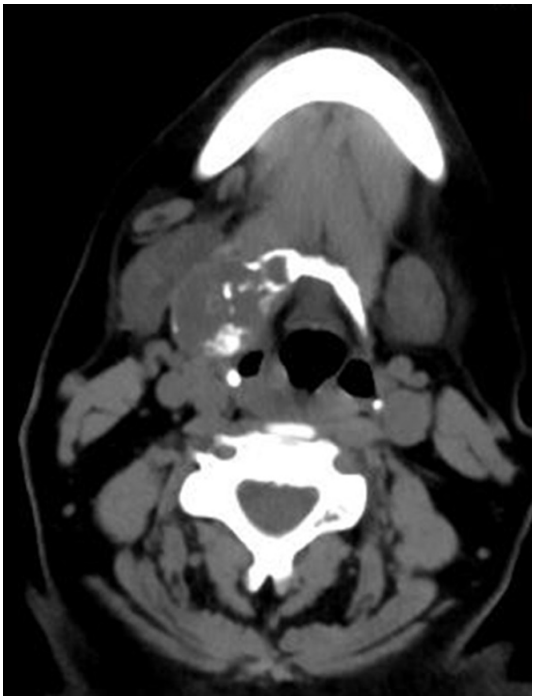

Figure 2. CT showed an expansive, irregular, and mixed mass originating in the right side of the hyoid bone, with bone destruction and speckle calcification. There were no typical pathological cervical lymph nodes.

ficult to differentiate the mass from surrounding tissues. Blood-flow signals could be seen inside and around the mass (**Figure 1**). A cervical CT scan showed an expansile lesion with cortical destruction on the right side of the hyoid bone. The diameter of the lesion measured 2.7 cm. It had a mixed density with nodular calcification. The morphology of the hyoid bone was less structured. Visible bone destruction and soft tissue density could be also seen, with scattered patchy calcifications (**Figure 2**). Low-density hyoid bone destruction and visible 1.9 cm × 2.2 cm soft tissue density was detected with bone scintigraphy by 99mTc-MDP with a dosage of 25 mCi (**Figure 3**). Fine needle aspiration biopsy under ultrasound guidance revealed that S-100 protein was positive. Pleomorphic adenoma and cartilage-derived mesenchymal origin tumors could not be ruled out. The biopsy tissue did not have any typically malignant characteristics.

The patient underwent an excision of the mass and right side of the hyoid bone via a transcervical approach. The capsule of the right submandibular gland was intact. The lesion was located in the right side of the hyoid bone. It presented with a smooth grey-white appearance. Most of the external surface was surrounded by a fibromuscular capsule. At surgery, the tumor was resected together with the right side of the hyoid bone. A total of 1 cm of normal tissue was resected more beyond the lesion. Tumor surgical margins were sent to fast icy cross-sections during the operation with surgical margins. It was suggested that the atypia of the tumor was not obvious. In other words, it was possible that the tumor was benign. The final histopathological diagnosis was grade 2-3 chondrosarcoma of the hyoid bone. Gross examination showed an irregular tumor measuring 4.9 cm × 2.7 × 3.0 cm composed of friable tissue (**Figure 4**). Microscopic examination revealed that chondrocytes invaded the bone cortex. However, the surgical margins were clear. Immunohistochemical testing revealed: Desmin (-), CK (AE1/AE3) (-), S-100 (focal+) (**Figure 5**), CD34 (-), Ki67 (positive rate of 50) (**Figure 6**), SMA (-), EMA (-). The patient showed no evidence of recurrence over a 23-month follow-up period.

Discussion

Chondrosarcoma in the head and neck area is uncommon. The hyoid bone is a very rare site of involvement [3]. A systematic search in PubMed was conducted, with terms “hyoid” and “chondrosarcoma”, resulting in 24 articles published in English, along with another 2 publications

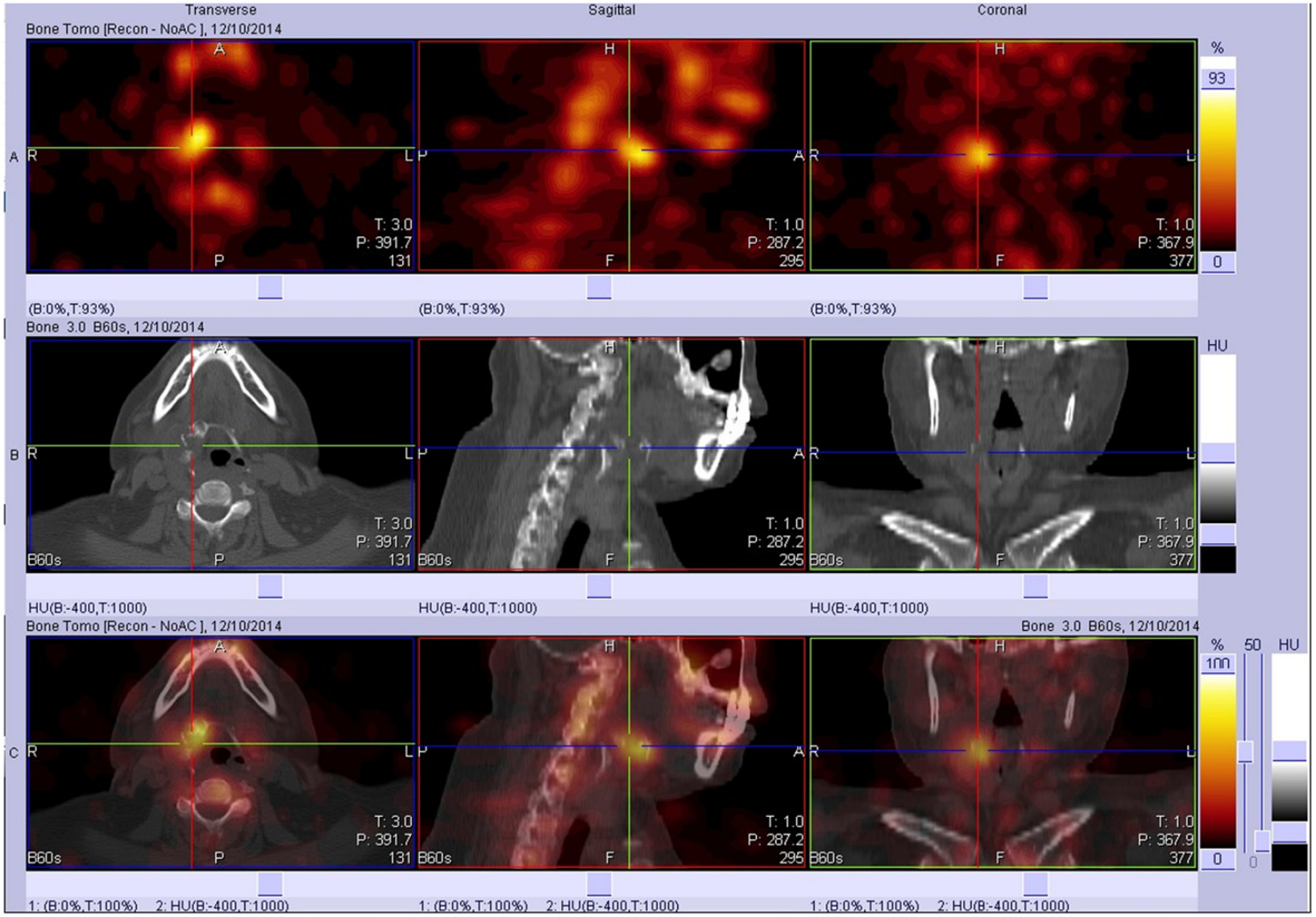

Figure 3. CT showed an expansive, irregular, and mixed mass originating in the right side of the hyoid bone, with bone destruction and speckle calcification. There were no typical pathological cervical lymph nodes.

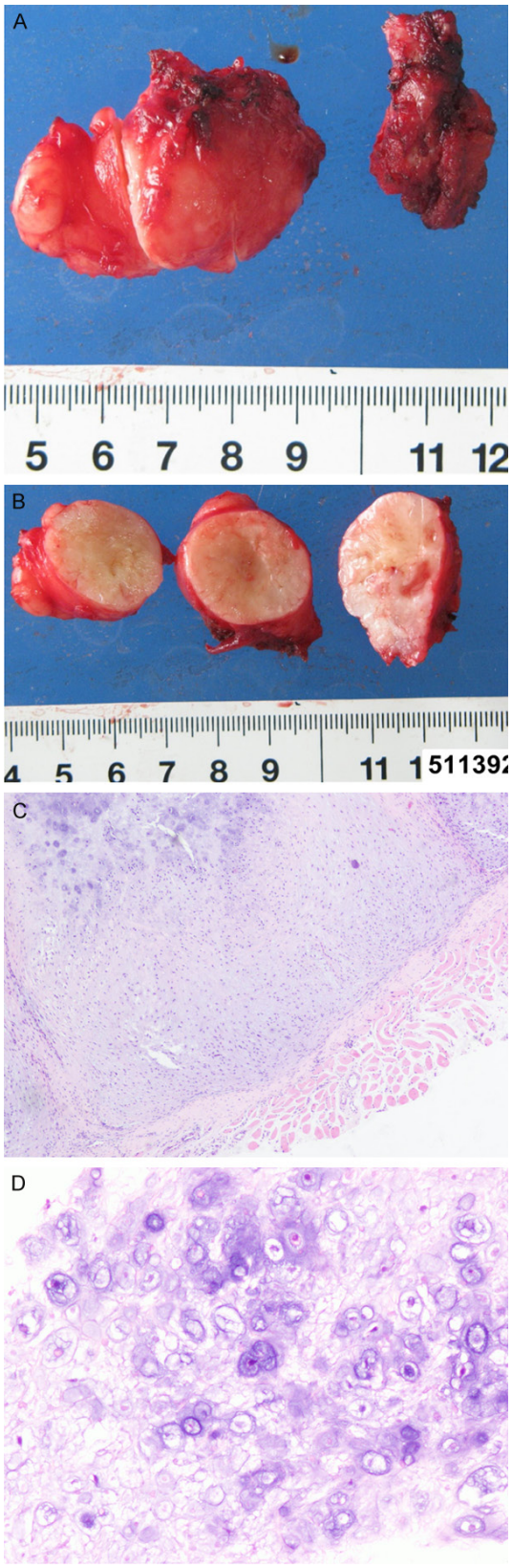

Figure 4. A. The tumor was irregular, crisp, and with a size of 4.9 cm × 2.7 cm × 3.0 cm. B. The tumor was gray-white. We can see the liquidation within it. C. HE staining (× 100). Chondrosarcoma cells infiltrate the cortex of the bone and surrounding striated muscle HE staining (× 100). D. HE staining (× 400). Hypercellularity, pleomorphism, and heteromorphism of tumor chondrocytes can be seen in microscopic images. Less chondroid matrix and rich cytoplasm spread over the field. Binucleated and multinucleated chondrocytes are common. The chondrocytes nuclei are enlarged and hyperchromatic or vesicular.

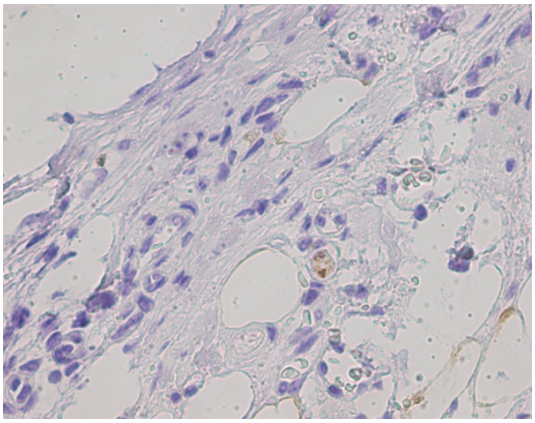

Figure 5. Immunoblotting with anti-S100 (focal) (× 400). Positive nuclear and cytoplasmic staining is seen in a handful of cells.

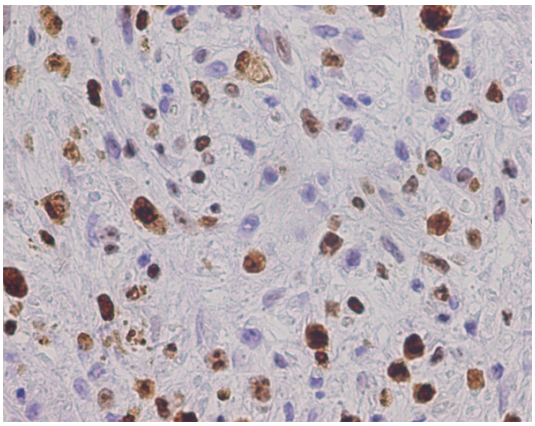

Figure 6. Immunostaining with anti-ki67 (× 40). The positive rate was about 50%.

from references. A total of 21 full-text cases were retrieved, including the present case. A systematic literature review of these 21 cases was performed. This study analyzed these cases in terms of symptoms, imaging tests, pathological diagnosis preoperative and postoperative, surgical margins, additional therapy, and prognosis. Extracted data are listed in **Table 1**.

Table 1. Case material

Year	Sex/ age	Size (cm)	Exami-nation	DBO	DIO	Tumor grade	Treatment	Surgery option	Surgical margin	Status	Follow-up Time (months)
1992	F/30	5.0*5.0	②⑤	/	/	1	S+RT	TB	Negative	NR	29
1992	F/45	3.0*3.0	⑤	O	/	2	S+RT	SB+TS	Negative	NR	19
1993	M/66	5.0	②③	O	/	1	S	TB	/	NR	15
1997	F/82	6.0*4.0*2.0	②	/	/	1	S*3+RT	SB	Positive	R (36 m)	60
1998	M/66	5.2	②	/	/	1	S*2	SB	Close	R (48 m)	72
1998	F/39	2.2*2.0*2.0	②	O	/	1-2	S	SB	Positive	NR	4
2000	M/57	2.2	②③	/	/	1	S	SB	Negative	NR	6
2004	F/68	10.0*12.0	②③	O	/	1	S	SB	Negative	NR	12
2005	M/36	7.0*6.2*4.5	①②	O	/	1	S	SB	/	NR	18
2006	F/30	7.0	①②	/	/	1	S	TB	Negative	NR	/
2008	M/28	5.0	②	/	/	1	S	SB	/	NR	21
2008	F/37	3.0*1.5*1.5	①③	/	/	1	S	SB	/	NR	24
2009	M/74	3.4*2.4	①②	C	/	1	PDT*2	/	/	shrinking	19
2012	M/42	3.0*2.8	②③④	/	/	1	S	TB	Negative	NR	12
2014	M/53	6.0*4.0*3.5		/	/	2	S	SB	Negative	NR	1
2015	M/73	5.5*4.3*3.7	②	O	/	2	S+RT	TB	/	NR	12
2015	M/30	7.5*5.5*6.5	②	/	/	2	S+RT+CT	TB+TS	/	NR	24
2015	M/73	5.0*4.0*3.0	②	O	/	2	S+RT	SB	close	NR	12
2015	F/42	8.0*6.0*4.0	②	/	/	1	S*2	SB	Negative	R (5 m)	8
2016	M/33	5.5*4.9*4.7	②③	C	/	2	S	SB+TS	Negative	NR	29
2016	F/42	4.9*2.7*3.0	①②④	O	O	2-3	S	SB	Negative	NR	23

Year: The time of the paper published. Sex/age: F-Female; M-male. Size (cm): accurate to one decimal place. Examination: ① Ultrasonography/② Computer tomography (CT)/③ Magnetic resonance imaging (MRI)/④ Isotope scan/⑤ cervical X-ray. DBO: the diagnosis before the operation (/: not done; B: benign; C: chondrosarcoma). FNAB: fine-needle aspiration biopsy; CNB: core needle biopsy. Grade: the grade of the tumor ("low grade" equals to "grade 1"). DIO: the diagnosis of fast icy cross-section during operation (/: not done; O: other diseases except for chondrosarcoma; C: chondrosarcoma). Treatment: S-surgery; RT-radiotherapy; CR-chemotherapy, PDT-photodynamic therapy. Surgical option: TB-total excision of the hyoid bone; SB-subtotal excision of the hyoid; TS-tracheostomy. Surgical margin: Negative-there was no tumor cell in surgical margins; Positive-tumor cells was found in surgical margins; Close-the extension of the surgery is close to the tumor; /- there was not given if the surgical margins were clean or not. Status: NR-not recurrence; R-recurrence.

Table 2. Age analysis of patients

Age (years)	20-29	30-39	40-49	50-59	60-69	70-79	80-89
Number	1	7	4	2	3	3	1
Percent	4.76	33.33	19.05	9.52	14.29	14.29	4.76

From the review cohort of 21 cases, including the present case, patient ages ranged from 28 to 82 years, with a mean age of 49.8 years. This was similar to other chondrosarcomas throughout the body [7]. In this investigation, peak age was between the third and fourth decades of life (**Table 2**). The ratio of men to women was 1.3:1, which was close to 1.9:1 reported by Isabella Zhang et al. in 2014 [2], revealing little gender bias. In contrast, there was a 3:1 male to female ratio in laryngeal chondrosarcoma [8], while other head and neck chondrosarcomas reported 10 times as much in men [9]. The discrepancy among them is attributed to the number of reported CS cases. The high incidence of head and neck cancers in men is closely connected with environmental factors (tobacco and alcohol). However, these risk factors have no evidence linking them to chondrosarcomas [2]. In the present review, only two patients reported smoking histories [9, 10], one male and one female. Their pathology after surgery was grade 1.

Symptoms for hyoid CS patients are unitary. They are described as unilateral painless swelling masses in the neck [9]. Comparatively, CSs in the larynx tend to cause various symptoms,

Table 3. Characteristics of tumors

Year	Tumor site	Dimension (cm)	FNAB presentation	Grade
1992	Left submandibular region	3.0*3.0	A salivary gland tumor with myxoid and calcific material	1
1993	Submental area	5	No evidence of malignancy	1
1998	Right submandibular region	2.2*2.0*2.0	(CT-guided) suggestive of hemangiopericytoma	1-2
2004	Right-sided neck	10.0*12.0	Not diagnostic	1
2005	Left-sided neck	7.0*6.2*4.5	Mature chondroid cells	1
2015	Right submandibular region	5.5*4.3*3.7	Pleomorphic adenoma	2
2016	Left-sided neck	4.0*5.0	Hyaline cartilage matrix and sparse proliferation of mildly atypical cells, immunostaining was positive for S100 protein—diagnosed low-grade CS	2
2016	Right submandibular region	4.9*2.7*3.0	Pleomorphic adenoma or cartilage-derived mesenchymal origin tumors	2-3

such as hoarseness, dysphagia, or respiratory distress [11]. However, there were three patients in the present statistical group presenting other symptoms. Kazunor Itoh et al. reported that a 66-year-old man had been experiencing dysarthria, along with asymptomatic swelling, in the submental area for a month in 1993. He underwent a tracheostomy and hyoid excision, with surgery pathology showing grade 1. He continued to do well over a 15-month follow-up period [12]. The next one was a 68-year-old female that presented with swelling in right-sided neck and dysphagia for 6 months. The tumor (grade 1) with the right greater horn of the hyoid bone was totally resected. The patient was free of recurrence for 1 year [6]. Farai Nhembe et al. described a 74-year-old man complaining with a painless mass in the cervical region in 2009. He accepted examinations, including incisional biopsy (grade 1), which showed tumor invasion into thyro-hyoid muscle and superior larynx. He developed symptoms of dysphagia before deciding on therapeutic methods. Rejecting sacrificing the function of the larynx via operation, he was referred for photodynamic therapy (PDT) to prevent the growth of the tumor. Two rounds of PDT were performed, while 19 months of close follow-up revealed the smaller tumor [13]. Differences of symptoms are closely relative to the size and location of tumors. No affiliation with tumor grades is apparent [11]. Duration of symptoms ranges from 1 month [12] to 84 months [14]. The mean time was 12.63 months and the median time was 11 months (an ambiguous datum was removed) [2].

This study also compared the dimensions (longest diameter) of tumors. The mean size was 5.3 cm (range 2.2 cm-12.0 cm). Relatively, sizes of laryngeal CSs are usually less than 3-4 cm [15]. Laryngoscopical images of hyoid CS patients usually show normal for extralaryngeal growing characteristics of hyoid CS [9]. For suspect laryngeal CS patients, submucosal bulging must be searched for and vocal cord mobility must be checked via endoscopic examinations [15]. Laryngeal mucosa covered by a mass and mucosal ulcerations can be seen in advanced tumors [11].

Ultrasonography (US) is a widely used initial imaging tool to evaluate soft tissue masses in the head and neck. There were only five patients taking this examination in the investigational group. Three of them, including the present case, revealed hypoechogenic solid nodular lesions [9, 13], while the others did not describe the details [10, 16]. US may play an important role in guidance toward an accurate fine needle aspiration biopsy. To the best of our knowledge, no reported cases used US as a guidance in FNAB, except the present one (**Table 3**). In addition, the superiority of US mainly lies in that it is non-invasive, relatively low-priced, widely available, performing quickly, and with good repetition [17].

Radiological tools include cervical X-rays and computer tomography (CT). Diagnosis of chondrosarcoma is mainly dependent on bony destruction and tumor matrix mineralization [14]. There were only 2 patients taking the former type, which revealed a soft tissue swelling in the submandibular area in 1992 [14]. This examination has not been seen since then (**Table 1**). In contrast, CT is more often used for assessment of the origin and extension of tumors (19/21). Pathologically, chondrocytes produce peripheral endochondral ossification and interior hyaline cartilage matrix rich in water. Consequently, CT scans show geographic lytic lesions and “ring-and-arc” calcification (reflect mineralized matrix), which demonstrate

a cartilaginous tumor. CS is the most conventional. Other than what has been referred to above, the involved cortical bone shows various figures from CT, such as scalloping destruction and surrounding tissue invasion [18]. However, there was an exception. Hediger R et al. reported a recurrent case. CT scans showed a mixed-attenuate lobulated mass without calcification. The patient underwent three subtotal surgeries and was treated with radiotherapy after the last surgery. The surgery margins kept positive and the tumor was proven to be grade 1 [19]. CT images of tumors originating from bones depend on imaging equipment, imaging techniques, and the experience of technicians. Even though CT scans do not show bone destruction and characteristic calcification, diagnosis of chondrosarcoma cannot be ruled out. The present case clearly confirms the characteristics of hyoid CSs in CT (**Figure 2**).

Magnetic resonance imaging (MRI) is ideally non-invasive in evaluating the grade of tumors, the extension of the surrounding soft tissue, and differentiating high-grade from low-grade of the CS, regardless of its high-cost. MRI features (bone expansion, active periostitis, presence of a soft tissue mass, intraosseous extent of a tumor) to differentiate high-grade from low-grade tumors are statistically significant [20]. It has been reported that an inhomogeneous area of low signal intensity was seen in a T1-weighted image of CS. A considerable inhomogeneous area with mixed high and low signal intensity was presented in T2-weighted image [12]. In the present investigation, only 6 patients performed this check-up. Moreover, 4 of 6 cases described the presentation in detail. Three of these presented the essential factors referred to before [12, 21, 22]. The other one showed a high-signal intensity in a T2-weighted image [10]. Because of a lack of high-grade hyoid CS cases published, identification points could not be summarized.

Bone scintigraphy is rarely used in hyoid CSs. FDG-PET is helpful in grading tumors and forecasting local recurrence and distant metastasis. Poor intake in the CS itself and morbid intake in the destroyed area of involved bone are mainly revealed. An intake value more than 1.3 is considered to be a sign of malignance [21]. In the present case, the inspection instrument was set as non-quantitative, thus there was no way to retrieve the intake value. However, it revealed a tissue mass invading the adjacent bones, osteolytic bone destruction, and characteristic intake (**Figure 3**).

Diagnosis is approximate based on imaging, however, there are some other rare tumors originating from the hyoid bone. A definitive diagnosis can only be established by histopathology and immunohistochemistry. On basis of cell differentiation, heteromorphism, and pleomorphism, CS has three degrees: Grade 1 (Low)-similar to normal chondrocytes with few atypical cells; Grade 2 (Intermediate)-increased cellularity, cells have 2 or more nucleus, myxoid intercellular space; and Grade 3 (High)-increasing overall cellular density, nuclear size and polymorphism, a lot of mitoses. The lower the degree, the lower the probability of metastasis [2]. For CSs, the metastasis rates of Grades 1 to 3, respectively, are 0%, 10%, 66%, and 5-year survival rates are 90%, 81%, and 29% [23]. As noted above, differences between Grade 1 and Grade 2 are small, while they are huge between Grade 2 to 3. Incidence of CSs Grade 1 and 2 accounts for about 95%, similar to “more than 90%” in another study [23].

Fine-needle aspiration biopsy (FNAB) is known as a safe, reliable, and inexpensive procedure, establishing the diagnosis of manifold solid tissue neoplasms. However, it is worth evaluating the role of FNAB in diagnosing primary CSs. In this investigation, 9 of 21 patients were performed the process, with only one diagnosed as CS (1/9), combining FNAB and radiographic findings. Microscopic analysis showed mild nuclear atypia and increased cellularity on hematoxylin. Immunostaining positive for S100 protein and no mitotic figures prove it to be Grade 1. Its final diagnosis was CS Grade 2 [4]. In the present case, immunohistochemical tests also showed focal positive for S100 protein. However, histopathologic findings held no brief for malignant tumors. In a retrospective study employed by Dodd LG, the diagnostic accuracy for primary CS and recurrent or metastatic lesions, respectively, were 67% (18/27) and 86% [24]. There are three reasons to analyze these mistakes. First, the diagnostic criteria of each sample changes with pathologists having varying levels experience and backgrounds. Second, it lacks clear boundaries among benign tumors, low and intermediate tumors microscopically, for two different grades areas can appear simultaneously. Third, there was

inadequate sampling of the lesion via fine-needle aspiration.

Because of resistance to radiotherapy and insensitivity to chemotherapy, surgery resection is the preferred choice of treatment for CS. The aims of treatment are reducing the rate of local and metastatic recurrence, while retaining organs and function to the greatest extent [18]. In the choice of surgery, scrape or the tumor segment resection has been advised to perform in tumors in Grade 1 and 2, while tumors in Grade 3 need a wide resection, including the entire tumor with a cuff of surrounding normal tissue [23]. In this study, there were 6 patients accepting total hyoid bone excision, 14 subtotal excisions and 1 photodynamic therapy. In these surgical cases, 3 people underwent tracheotomies at the same time (**Table 1**). Respiratory and swallowing functions remained intact postoperatively in all surgical patients. This provides experience for clinical surgeons in choosing whether to perform tracheotomies.

If safe widening surgical margins are controversial, especially when the tumor is in the head and neck, close follow-ups should be carried out. In this situation, recurrence and metastasis appear frequently [25]. In the present study, 14 of 21 surgical margins were examined, with 2 cases revealing that tumor cells invaded the margins. One of the two (50%) underwent 3 recurrences and surgeries. Rejecting the operation, she was treated with radiotherapy after the third recurrence [19]. The other one had no evidence of recurrence after 4-months of follow-up. This patient rejected any additional therapies. The follow-up time was too short to evaluate the prognosis [26]. There were 2 cases reporting close-margins. One of the two (50%) was recurrent after 48 months follow-up [27]. One of ten (10%) negative-margins cases reported recurrence [28]. All three recurrent cases were diagnosed as CS Grade 1. Because of differences of surgical margins, they had different recurrence rates.

Currently, radiotherapy (RT) is used in patients that refuse surgery, lose the opportunity of surgery, and want relief from symptoms by shrinking the tumor. Chemotherapy is considered an ineffective treatment, except that it plays a potential role in dedifferentiated and mesenchymal CSs. The survival rate of adding chemotherapy is higher than that of resection alone. Chemotherapy is also a controversial treatment [18]. Brenton B. Koch et al. analyzed 400 cases of chondrosarcoma of the head and neck in the American College of Surgeons National Cancer Data Base (NCDB), between 1985 and 1995. They suggested chemotherapy to be used in high-grade tumors to prevent distant metastasis, although the statistical evidence was still deficient [29]. From **Table 1**, four patients were given radiotherapy after the surgery and one underwent radiotherapy after three relapses and surgeries. There was one patient graded 2 that underwent radiotherapy and chemotherapy, besides surgery. None reported recurrences after radiotherapy, no matter whether the surgical margins were clear or close. However, follow-up times were too short to ensure the effectiveness of radiotherapy. In the present case, the tumor was shown to be Grade 2-3, which has never been reported before. The surgical margin was negative and she refused radiotherapy and chemotherapy. After 23-months of follow-up, the patient has no evidence of recurrence.

The mean follow-up time was 21.0 months, except for one that was not referred. The mean recurrent time was 29.7 months in three cases. In NCDB data, 29 of 72 were defined with recurrence. Median follow-up times in local recurrent cases for patients that were alive and dead, respectively, were 73.0 months and 28.5 months. In contrast, present investigative cases need longer follow-up data to evaluate the effectiveness of various treatments.

Conclusion

Hyoid chondrosarcoma is a rare disorder with unknown etiology and slow growth clinical features. A painless welling mass in the unilateral submandibular region is the most common symptom. In generally, people between the ages of 30-50 are predisposed to it and there is no gender bias. CTs and MRIs assist in making a diagnosis and evaluating prognosis to some extent before the operation. However, an accurate diagnosis can be only established by histopathological and immunohistochemical examinations. The necessity of FNAB is still a controversy because of the high false negative rate. The “gold-standard” treatment for localized chondrosarcoma remains surgical excision. In

primary unresectable tumors, incompletely excised lesions, and un-tolerant cases, radiotherapy does play a role. Chemotherapy is considered less effective, except for mesenchymal and dedifferentiated subtypes. The prognosis of a patient is related to histological grade and surgical margins. Close follow-ups are mandatory.

Disclosure of conflict of interest

None.

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