Original Article
Obstructive sleep apnea syndrome caused by uncommon tumors of the upper aerodigestive tract

Shao-Jun Zhu1, Qin-Ying Wang2, Shui-Hong Zhou2, Yang-Yang Bao2, Shen-Qing Wang2

Departments of 1Anesthesiology, 2Otolaryngology, The First Affiliated Hospital, College of Medicine, Zhejiang University, 310003, China

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Abstract: Obstructive sleep apnea syndrome (OSAS) is always caused by anatomic abnormalities, including nasal cavity, pharynx, and neuromuscular dysfunctions, leading to airway narrowing. OSAS associated with a mass in the aerodigestive tract is rare. In the present study, we report OSAS caused by 9 cases of preoperative uncommon tumors in the aerodigestive tract. Two tumors in the parapharyngeal space were pleomorphic adenoma, one oropharyngeal tumor was mucoepidermoid carcinoma, one tumor in the right tonsil was schwannoma, and five tumors were non-Hodgkin’s lymphoma (NHL). Of the five NHL cases, one in the nasopharynx was diffuse large B-cell lymphoma, two were mantle cell lymphoma, one was chronic lymphocytic leukemia/small lymphocytic lymphoma, and one was NHL. Tumors in the aerodigestive tract should be considered in the differential diagnosis of OSAS upon exacerbation of snoring or sudden gasping. Further examinations should be performed, including a routine workup (computed tomography (CT) and magnetic resonance imaging) and positron emission tomography/CT.

Keywords: Obstructive sleep apnea syndrome, upper aerodigestive tract, tumor

Introduction
Obstructive sleep apnea syndrome (OSAS) is always caused by anatomic abnormalities, including nasal cavity, pharynx, and neuromuscular dysfunctions, leading to airway narrowing. OSAS associated with a mass in the aerodigestive tract is rare. In 1981, Moses et al. first reported a patient with OSAS caused by nasopharyngeal carcinoma [1]. Since then, tumors of the upper aerodigestive tract causing secondary OSAS have been reported sporadically. Rada reviewed MEDLINE up to 2005 and found only 30 articles about OSAS caused by head-and-neck tumors (HNTs), including 16 benign neoplasms and 8 malignant neoplasms [2]. Interestingly, a prospective multicenter study had demonstrated that OSAS might, conversely, because the increased incidence of cancer in a large cohort of patients investigated for OSA suspicion, the incidence of which was ~5.3% [3]. However, there is lack of large-sample reports about OSAS caused by preoperative upper aerodigestive tract tumors (ADTTs). To our knowledge, only one such study has been reported by Payne et al. [4], who found that 13 of 17 (76.4%) patients with oral and oropharyngeal cancer had OSAS.

OSAS caused by ADTT or OSAS resulting in cancer is always not diagnosed early and usually results in a series of severe medical conditions, including hypertension, atrial fibrillation, diabetes, and depression [5, 6]. Thus, understanding of the relationship between OSAS and ADTT is important for early diagnosis and management.

In the present study, we reported OSAS caused by 9 cases of preoperative uncommon upper ADTT, not common head-and-neck cancer, including nasopharyngeal squamous cell carcinoma (SCC), oropharyngeal SCC, hypopharyngeal SCC and laryngeal SCC.

Patients and methods

Patients
Nine consecutive patients were enrolled in the present study between January 2005 and August 2014. Their symptoms were snoring and gasping for air at night, or sudden aggravation
Table 1. Characteristics of nine upper aerodigestive tract tumors in OSAS

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age</th>
<th>BMI (kg/m^2)</th>
<th>AHI</th>
<th>Site</th>
<th>Size (cm)</th>
<th>Pathological result</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>22</td>
<td>60</td>
<td>Left parapharyngeal space</td>
<td>3 × 4.5</td>
<td>Pleomorphic adenoma</td>
<td>Excision via tranoral approach</td>
<td>9 yrs later, recurrence</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>21</td>
<td>22</td>
<td>Right tonsil</td>
<td>3 × 4</td>
<td>Schwannoma</td>
<td>Right tonsillectomy</td>
<td>NED, 6 yrs</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>24</td>
<td>80</td>
<td>Nasopharynx</td>
<td>Fdg high uptake</td>
<td>Diffuse large B-cell lymphoma</td>
<td>R-chop-radiotherapy</td>
<td>NED, 68 mo</td>
</tr>
<tr>
<td>4</td>
<td>68</td>
<td>21</td>
<td>67</td>
<td>Bilateral tonsil, nasopharynx, bilateral cervical lymph node</td>
<td>Fdg high uptake</td>
<td>Mantle cell lymphoma</td>
<td>R-chop</td>
<td>NED, 5 mo</td>
</tr>
<tr>
<td>5</td>
<td>59</td>
<td>20</td>
<td>45</td>
<td>Bilateral tonsil</td>
<td>4 × 5</td>
<td>Mantle cell lymphoma</td>
<td>R-chop</td>
<td>DOD, 2 yrs</td>
</tr>
<tr>
<td>6</td>
<td>46</td>
<td>20</td>
<td>27</td>
<td>Bilateral tonsil</td>
<td>4 × 5</td>
<td>Chronic lymphocytic leukemia/small lymphocytic lymphoma</td>
<td>R-chop</td>
<td>under treatment</td>
</tr>
<tr>
<td>7</td>
<td>45</td>
<td>20</td>
<td>31</td>
<td>Left oropharyngeal lateral wall</td>
<td>3 × 4</td>
<td>Mucoepidermoid carcinoma</td>
<td>Excision via thyrohyoid membrane approach</td>
<td>NED, 19 mo</td>
</tr>
<tr>
<td>8</td>
<td>34</td>
<td>19</td>
<td>24</td>
<td>Left parapharyngeal space</td>
<td>4 × 5</td>
<td>Pleomorphic adenoma</td>
<td>Excision via tranoral approach</td>
<td>NED, 2 yrs</td>
</tr>
<tr>
<td>9</td>
<td>74</td>
<td>21</td>
<td>15</td>
<td>Left tonsil</td>
<td>4 × 5</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>R-chop</td>
<td>Under treatment</td>
</tr>
</tbody>
</table>

Note: BMI: Body mass index; AHI: apnea-hypopnea index; NED: no evidence of disease.

of these symptoms. Of the nine upper ADTTs, two were in the parapharyngeal space, two in the bilateral tonsil, two in the unilateral tonsil, one in the unilateral tonsil and nasopharynx, one in the nasopharynx, and one in the oropharynx (only three cases had been reported previously [7-9] (Table 1).

Our study was approved by the Institutional Review Board of The First Affiliated Hospital, College of Medicine, Zhejiang University. Written informed consent was obtained from each patient before inclusion.

Polysomnography (PSG)

Each patient underwent a diagnostic sleep study, either full or standard PSG (Rembrandt), following the American Academy of Sleep Medicine (AASM) guidelines for OSAS diagnosis [2, 11]. PSG included the continuous recording of neurologic variables by electroencephalography, electrooculography, and electromyography; scoring of breathing variables based on flow tracing from an oronasal cannula and thermistor; measurement of thoracoabdominal motion using thoracic and abdominal bands; recording of oxyhemoglobin saturation (SpO₂) using a finger pulse oximeter; and electrocardiography. Apnea was defined as cessation of oronasal flow for more than 10 s. Hypopnea was s as a discernible reduction in the oronasal flow to at least 50% lower than the baseline for more than 10 s, or with an at least 3% decrease in SpO₂ or an arousal for more than 10 s. The apnea-hypopnea index (AHI) was defined as the number of apneas plus hypopneas per hour of sleep and was mapped to disease severity as follows: (1) no disease, AHI < 5; (2) mild disease severity, 5 ≤ AHI < 15; (3) Moderate disease severity, 15 ≤ AHI < 30; and (4) severe disease, 30 ≤ AHI.

Results

Of the 9 upper ADTTs, all were male, and the ages ranged from 33 to 74 years (mean age, 48.1 years). The body mass index ranged from 19% to 24% (average, 21.9%). The AHI was from 15 to 80 (average, 41.2).

Seven patients underwent general anesthesia during surgery according to practice guidelines for the perioperative management of patients with obstructive sleep apnea by the American Society of anesthesiologists [13, 14]. One patient had undergone a previous biopsy of the nasopharynx under local anesthesia [9]. Two patients with parapharyngeal space tumors underwent surgery via a transoral approach (Figure 1), and one patient with an oropharyngeal tumor underwent surgery via a thyrohyoid membrane approach (Figure 2). [18F] 2-Fluoro-2-deoxy-D-glucose ([18F-FDG]) positron emission tomography/computed tomography (PET/CT) imaging demonstrated high FDG uptake in the nasopharynx in one patient [9] and high FDG uptake in the nasopharynx and bilateral palatine tonsils in another patient (Figure 3). The initial biopsy of the nasopharynx in the latter patient demonstrated no malignant findings under local anesthesia, and right tonsillectomy
was performed under general anesthesia. The patients with a tumor in the right tonsil and with an enlarged left tonsil underwent tonsillectomy via a transoral approach under general anesthesia (Figure 4). One patient with an enlarged bilateral tonsil underwent uvulopalatopharyngoplasty (UPPP) under general anesthesia.

Among the eight patients, the postoperative pathological results showed that two tumors in the parapharyngeal space were pleomorphic adenoma (cases 1 and 8) [1], the oropharyngeal tumor was mucoepidermoid carcinoma (case 7), one tumor in the right tonsil was schwannoma (case 2) [8], and five tumors were non-Hodgkin’s lymphoma (NHL). Of the five NHLs, one in the nasopharynx was diffuse large B-cell lymphoma (DLBCL; case 3), two were mantle cell lymphoma (cases 4 and 5), one was chronic lymphocytic leukemia/small lymphocytic lymphoma (case 6), and one was NHL (case 9).

One patient with oropharyngeal mucoepidermal carcinoma received postoperative radiotherapy (50 Gy). Five patients with NHL received chemotherapy: case 3 received the R-CHOP regimen (rituximab, cyclophosphamide, epirubicin, vincristine, and prednisone) and radiotherapy (50 Gy), and cases 4, 5, 6, 8, and 9 received the R-CHOP regimen.

OSAS-related symptoms in all of the patients were absent after treatment. One patient with pleomorphic adenoma in the left parapharyngeal...
Figure 2. CT of case 7 showed a mass in the left oropharyngeal wall. (A) Noncontrast axial CT showed an irregular soft tissue mass in the left oropharyngeal cavity, and the CT value was 46 HU. (B) Contrast-enhanced CT showed that the lesion was heterogeneously enhanced, and the CT value was 68 HU. (C) Transoral finding of the tumor. (D) The tumor was excised completely via a thyrohyoid membrane approach, and (E) the tumor sample measured approximately 3 × 4 cm.

Figure 3. PET/CT of case 4 demonstrated increased18F-FDG uptake in the bilateral palatine tonsils (maximum standardized uptake value (SUVmax = 13.47) (A), nasopharynx (SUVmax = 8.54) (B), and no distant metastasis (C).

Figure 4. MRI of case 9 showed an enlarged left tonsil. The T1-weighted signals were hypointense (A), the T2-weighted signals were hyperintense (B), DWI suggested that hyperintense lesions were in the left tonsil (b = 1000 s/mm²) (C), and the contrast-enhanced T1-weighted MRI images showed strong enhancement (D). The tumor was found to measure approximately 3 × 6 cm (E).
geal space (case 1) presented with sudden breath apnea 9 years after surgery. CT and MRI showed a lobular mass in the left parapharyngeal space (Figure 5). The tumor was excised via a transoral approach again, and the pathologic results demonstrated pleomorphic adenoma. There was no evidence of disease during the 5-month follow up. There was no evidence of disease in cases 2, 3, 4, 7 and 8 during the follow-ups at 6 years, 68 months, 5 months, 19 months, and 2 years, respectively. PET/CT was performed postoperatively for case 6, and no FDG uptake was seen at other sites, with the exception of the bilateral tonsillar region and cervical lymph nodes. Cases 6 and 9 underwent treatment.

Figure 5. CT and MRI of Case 1 showed a lobular mass in the left parapharyngeal space 9 years after initial surgery. A: CT; B: $T_1$ W of MRI; C: $T_2$ W of MRI; D: Sample of tumor.
Discussion

OSAS caused by upper aerodigestive tract tumors (ADTTs) has been rarely reported in large series; they have been documented mostly in case reports. Payne et al. reported that OSAS was presented in 13 of 17 patients (76%) with malignancies of the oral cavity and oropharynx. In our series, we found that, in nine consecutive patients, upper ADTTs were associated with OSAS lasting over 10 years, except common head-and-neck squamous cell carcinoma, including carcinomas of the nasopharynx, oropharynx, hypopharynx and larynx. Additionally, all of the patients were male. AHI was from 15 to 80 (average, 41.2). The most common symptom was sudden aggravation of snoring or gasping (cases 1, 3, 4, 6, and 7). Thus, we suggested that OSAS caused by head-and-neck tumors should be considered, and further examinations should be performed, including routine workup (CT and MRI) and PET/CT. In our series, case 1 was initially diagnosed with OSAS lasting over 10 years in January 2005 and underwent UPPP surgery. After surgery, the snoring symptom was suddenly aggravated. CT of the head and neck showed a mass in the left parapharyngeal space. Nine years later, his symptoms also included sudden breath apnea. CT and MRI revealed recurrence of a pleomorphic adenoma in the left parapharyngeal space. Case 3 had been diagnosed with OSAS lasting over 20 years, and snoring became suddenly aggravated 2 months prior. PET/CT showed high FDG uptake in the nasopharynx and bilateral cervical lymph node, which suggested malignancy. A biopsy of the nasopharynx demonstrated DLBCL. Case 4 also presented with sudden snoring and apnea for 1 month. Nasendoscopy and CT showed mucosal thickening in the nasopharynx. However, the nasopharynx biopsy showed no evidence of malignancy. PET/CT revealed high FDG uptake in the nasopharynx, bilateral palatine tonsil, and multiple cervical lymph nodes. These findings also suggested malignancy at these sites. Right tonsillectomy was performed, and the pathological results demonstrated mantle cell lymphoma. Case 6 was diagnosed with OSAS lasting over 1 year. UPPP surgery was suggested, but the patient refused it. He was admitted to our department due to symptoms of sudden snoring and apnea lasting for over half a year. He underwent UPPP surgery; however, the postoperative pathological results revealed chronic lymphocytic leukemia/small lymphocytic lymphoma. Case 7 also presented with apnea and dysphagia lasting for over half a year. Strobolaryngoscopy and CT revealed a 4.5-cm × 5-cm mass in the left lateral wall of the oropharynx, and the pathological results revealed oropharyngeal mucoepidermal carcinoma. Thus, upper ADTT should be considered in the differential diagnosis of OSAS upon exacerbation of snoring or sudden gasping. However, our study was inconclusive due to it involving only a small series. A prospective study of the prevalence of OSAS in these common head-and-neck SCCs is warranted.

Among our rare upper ADTTs, the most common malignant tumor causing OSAS was NHL (55.6%). Among the NHLs, two were mantle cell lymphoma, one was DLBCL, one was chronic lymphocytic leukemia/small lymphocytic lymphoma, and one was an undetermined subtype of NHL. As early as 1987, Kong et al. reported a case of tonsillar lymphoma leading to OSAS [14]. To our knowledge, approximately 10 cases of lymphoma-caused OSAS have been reported in the English-language literature [14-18]. Some researchers have suggested that asymmetric tonsillar hypertrophy leading to OSAS should be considered suspected lymphoma; in such a case, tonsillectomy should be recommended and pathological examination should be mandatory [16, 18]. These findings suggested the importance of mandatory pathological examinations. Our experiences were that tonsillectomy should be recommended from this small series for either bilateral symmetric tonsillar enlargement or unilateral asymmetric tonsillar hypertrophy. Williams et al. found three cases of lymphoma among 4,070 patients after tonsillectomy [17].

In the present report, two pleomorphic adenomas in the parapharyngeal space were found to cause OSAS. In the English-language literature, we found nine pleomorphic adenomas causing OSAS [19-26]. Of these, five cases of deep-lobed parotid tumors extending into the parapharyngeal space were found, as in our report. Four cases arose from the minor salivary gland in the oral cavity and pharynx. One tumor in our series recurred 9 years after surgery. However, cases reported in the English-language literature showed a very short follow-up time. Tumors in the parapharyngeal space other than pleomorphic adenoma also include lipoma and angiolipoma [27-29].
Schwannoma in the head and neck causing OSAS is extremely rare; only three cases have been reported (including our previous report) [8]. Other schwannoma cases have been located in the tongue and superior laryngeal nerve [30, 31]. To our knowledge, ours was the first report that mucoepidermoid carcinoma of the oropharynx can cause OSAS.

In conclusion, we reported uncommon tumors in the upper aerodigestive tract. Upper ADTT should be considered in the differential diagnosis of OSAS upon exacerbation of snoring or sudden gasping. Further examinations should be performed, including a routine workup (CT and MRI) and PET/CT.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Shui-Hong Zhou, Department of Otolaryngology, the First Affiliated Hospital, College of Medicine, Zhejiang University, 310003, China. Tel: 86-571-87236894; Fax: 86-571-87236895; E-mail: zhouyunzhoush@163.com

References

Rare upper aerodigestive tract tumors in OSAS


