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High-grade urothelial carcinoma with squamous differentiation metastasizing to the tongue

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Tumors metastasizing to the head and neck region are uncommon. Metastasis of urothelial carcinoma to the maxillofacial region is exceedingly rare and mostly involves the jaw. We present a case of urothelial carcinoma metastasizing to the tongue. Immunohistochemistry in conjunction with fluorescent in situ hybridization was used to confirm the relation between the primary and metastatic lesions, making it the first such reported case employing the UroVysion (Catalogue number 02 J27-025, Abbott Molecular Inc., Des Plaines, IL, USA) fluorescent in situ hybridization probe in a metastatic lesion in the head and neck region. (Oral Surg Oral Med Oral Pathol Oral Radiol 2015; ■ e1-e5)

CASE REPORT

A 90-year-old male was referred by his general practitioner to the local oral and maxillofacial surgery clinic with a 3-week history of pain involving the left lower jaw. The patient complained of severe pain involving his left lower face and difficulty swallowing and eating. As a result, he had suffered significant weight loss and was restricted to a soft mashed diet. The patient had a previous history of chronic stage 3 kidney disease and heart failure and was on a range of related medications. The patient was a nonsmoker and only occasionally consumed alcohol. He also had a history of high-grade UC with invasion of the muscularis propria, which had been diagnosed a year earlier and for which he had declined treatment.

The patient had been referred to the Urology department with hematuria 12 months before the oral symptoms manifested. Endoscopic examination showed a solid lesion involving the right side of the bladder wall, and the patient underwent computed tomographic urography, blood investigations, and a transurethral biopsy. Hematologic investigations showed low mean cell hemoglobin concentration at 315 g/L (normal 335-370) and raised eosinophils at 0.58 × 10^9/L (normal 0.04-0.5). Urea and electrolytes showed raised urea 9.9 mmol/L (normal 2.5-7.8) and raised total bilirubin at 25 μmol/L (normal 0-21). Histologic examination of the bladder biopsies confirmed a focally plasmacytoid UC (grade 3 WHO 1973; high-grade WHO 2004/ISUP) with invasion of the muscularis propria but without vascular invasion. The patient was deemed unfit for surgery following a multidisciplinary team discussion. Radical radiotherapy was considered because the tumor appeared treatable; however, this was declined by the patient, who decided against any treatment interventions and wished to be treated expectantly.

Approximately a year later, the patient presented with oral symptoms and was found to have a large (6-cm), palpable, erythematous lesion involving the left side of the tongue (Figure 1A). The tongue appeared fixed, with reduced mobility, and there was a suggestion of mandibular bone involvement. There was no obvious infiltration into the pharynx, and occasional small cervical lymph nodes were palpable in level I on the left. The clinical impression was that of an oral squamous cell carcinoma, and metastatic UC was included in the provisional diagnosis because of the clinical history.

An orthopantomogram was obtained and did not reveal any significant findings. Magnetic resonance imaging showed a large mass measuring 6.5 cm anteroposteriorly, involving the entire left tongue and extending across the midline (Figure 1B). Involvement of the extrinsic tongue muscles and the floor of mouth and mandibular bone invasion were evident. There was no extension into the lateral wall of the pharynx or the parapharyngeal fat. The level I lymph nodes on the left appeared reactive.

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e1
An incisional biopsy of the tongue mass was performed. Histologic examination of hematoxylin and eosin sections showed mucosal fragments widely infiltrated by islands of malignant cells with focal squamous differentiation. Tumor islands showed nuclear and cellular pleomorphism, prominent nucleoli, focal areas of keratinization, and a high mitotic rate. The overlying surface epithelium did not exhibit dysplasia, and the origin was not evident from the overlying epithelium in the biopsy (Figure 2). The surrounding stroma had a poor host response.

Immunohistochemistry was performed for CK5/6, CK7, CK20, thrombomodulin, Kif67, GATA3, and uroplakin III to establish the origin of the infiltrative tumor cells. Tumor islands showed strong expression of CK5 and CK6 and thrombomodulin, with no expression of CK7, CK20, GATA3, or uroplakin III (Figure 3). Ki67 showed a proliferation index greater than 30% (not shown).

Due to the lack of CK7 and CK20 expression, FISH analysis was performed on the bladder and tongue specimens by using the UroVysion Bladder Cancer Kit (Abbott Molecular Inc.) to determine the association between the two. The UroVysion multiprobe FISH kit (Abbott Molecular Inc.) was developed to overcome the diagnostic limitations of urinary cytology. Probes for chromosomes 3, 7, and 17 are included because polysomies of these are quite frequent in bladder cancer. The 9p21 region is the site of the tumor suppressor gene \( p16 \), with its deletion being a frequent and early event in UC development. Recent studies have shown that it can be used with similar accuracy between fresh and formalin-fixed paraffin-embedded (FFPE) tissue.

FISH was performed on FFPE tissue sections, as described previously. Analysis of 100 interphase nuclei in FFPE sections from both specimens showed evidence of aneuploidy for chromosomes 3, 7, and 17, in addition to loss of p16 on chromosome 9. The FISH findings for the tongue deposit were identical to those of the original bladder lesion. Given that specific FISH probes were chosen

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**Fig. 1.** A, Clinical examination showed a nodular, firm, and erythematous swelling involving the left tongue. The smaller nodular lesion seen on the buccal aspect of the edentulous mandibular alveolar ridge was consistent with denture-related fibrous hyperplasia. B, Magnetic resonance imaging (coronal view, T2 weighted) showing a large, ill-defined lesion involving the left tongue and crossing the midline.

**Fig. 2.** A, Hematoxylin and eosin section of oral specimen with infiltrative tumor showing focal squamous differentiation. No obvious origin from the overlying epithelium was evident. A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM00743. B, Infiltrative primary urothelial carcinoma (UC) from the same patient (×10 original magnification).
Furthermore, some aggressive tumors, such as pancreatic cancer, usually present in the sixth or seventh decade of life, rarely metastasize to the oral cavity, but rarely to the head and neck region or the oral cavity deposit using the UroVysion Bladder Cancer Kit (Catalogue number 02 J27-025, Abbott Molecular Inc., Des Plaines, IL, USA). Tumor nuclei showed an increased copy number (polysomy) of the chromosomes 3 (aqua, 4 signals), 7 (spectrum-red, 4-5 signals), but a normal copy number of chromosome 17 (spectrum-green, 2 signals) and loss (deletion) of 9p21 (spectrum-gold, 0-1 signals) (×10 original magnification). FISH was also performed on the primary urothelial carcinoma, which exhibited an identical pattern to that of the tongue mass (not shown).

Fig. 3. Immunohistochemistry for the metastatic deposit. 

A. Cytokeratin (CK) 5/6. A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM00739. B. Thrombomodulin. A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM00745. Strong staining for CK 5/6 and thrombomodulin was seen in the infiltrating tumor islands (×10 original magnification). Staining for CK7, CK20, Uroplakin III, and GATA3 was negative (not shown). CK7. A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM00740. CK20. A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM00741. Uroplakin III. A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM00742. GATA3. A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM00746. Ki-67 showed a high proliferation index. A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM00744.

Fig. 4. Fluorescent in situ hybridization (FISH) analysis of the tongue deposit using the UroVysion Bladder Cancer Kit (Catalogue number 02 J27-025, Abbott Molecular Inc., Des Plaines, IL, USA). Tumor nuclei showed an increased copy number (polysomy) of the chromosomes 3 (aqua, 4 signals), 7 (spectrum-red, 4-5 signals), but a normal copy number of chromosome 17 (spectrum-green, 2 signals) and loss (deletion) of 9p21 (spectrum-gold, 0-1 signals) (×100 original magnification). FISH was also performed on the primary urothelial carcinoma, which exhibited an identical pattern to that of the tongue mass (not shown).

DISCUSSION

Malignant tumors metastasizing to the oral cavity or maxillofacial region are rare and are most commonly those with a tendency for bone metastases (such as breast, lung, kidney, thyroid, and prostate carcinomas). However, there are numerous reported cases of these being presentations of undiscovered malignancies.3

Trends of metastasis to the oral cavity also do not reflect the incidence, biologic behavior, and aggressiveness of the primary tumor. For example, lung carcinoma is one of the most common cancers with oral metastasis in males and is followed by carcinomas of the kidney, liver, and prostate, which show a much lower incidence. In contrast, prostate carcinoma is the most common malignancy in males, followed by lung, colorectal, and bladder cancers.6,7 Furthermore, some highly aggressive tumors, such as pancreatic cancer, rarely metastasize to the oral cavity.

UC represents 90% of bladder malignancies and usually presents in the sixth or seventh decade of life, with a male predilection (3:1 to 4:1).8 It is an aggressive neoplasm, which can metastasize frequently and early, but rarely to the head and neck region or the oral cavity. Direct invasion and spread into structures adjacent to the bladder is commonly seen, and metastases usually involve the regional lymph nodes, lung, liver, and lumbar and thoracic vertebrae.9-11
Table 1. Studies reported in the English language literature, to date, on urothelial carcinoma metastasizing to the maxillofacial/oral region

<table>
<thead>
<tr>
<th>Serial no.</th>
<th>Paper</th>
<th>Site of metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Koper et al., 1975</td>
<td>Tongue</td>
</tr>
<tr>
<td>2</td>
<td>Treggiden, 1976</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>Dannick and Anderson, 1979</td>
<td>Mandible</td>
</tr>
<tr>
<td>4</td>
<td>Edwah et al., 1981</td>
<td>Submandibular gland</td>
</tr>
<tr>
<td>5</td>
<td>Polastry, Giugiaro, and Gerbino, 1986</td>
<td>Mandible</td>
</tr>
<tr>
<td>6</td>
<td>Weithmann, Morrison, and Hurt, 1988</td>
<td>Mandible</td>
</tr>
<tr>
<td>7</td>
<td>Cohen et al., 1989</td>
<td>Right maxilla</td>
</tr>
<tr>
<td>8</td>
<td>Hirshberg et al., 1993</td>
<td>Mandible</td>
</tr>
<tr>
<td>9</td>
<td>Doval et al., 1994</td>
<td>Maxilla</td>
</tr>
<tr>
<td>10</td>
<td>Doval et al., 1994</td>
<td>Mandible</td>
</tr>
<tr>
<td>11</td>
<td>Cardona, Bagon, and Perez, 2000</td>
<td>Mandibular gingiva</td>
</tr>
<tr>
<td>12</td>
<td>De Courten et al., 2001</td>
<td>Right maxilla</td>
</tr>
<tr>
<td>13</td>
<td>Siriwardena et al., 2005</td>
<td>Mandible</td>
</tr>
<tr>
<td>14</td>
<td>Pouloupolou, Vahsseyanos, and Kiziridu, 2007</td>
<td>Submental soft tissue</td>
</tr>
<tr>
<td>15</td>
<td>Lee et al., 2002</td>
<td>Right buccal vestibule</td>
</tr>
<tr>
<td>16</td>
<td>Qiu et al., 2013</td>
<td>Left mandible condyle</td>
</tr>
<tr>
<td>17</td>
<td>Kumar Goyal et al., 2013</td>
<td>Right cheek</td>
</tr>
<tr>
<td>18</td>
<td>Kaleva et al., 2015</td>
<td>Right tongue</td>
</tr>
</tbody>
</table>

ND, Not described.

Both hematogenous involvement and lymphatic involvement can result in wider tumor dissemination. Metastases may also arise from tumor cells being shunted into alternate vascular compartments in the presence of occluded local lymph nodes through intercommunication of the perivascular lymphatic and vascular systems. Hematogenous spread of bladder cancer can result from tumor infiltration into the vesical or prostatic venous plexuses and bypass the major caval system to cause distant metastasis through the vertebral venous system.

Metastasis of bladder carcinomas to the maxillofacial region is quite rare, with only 18 published cases reported in the literature, most of which involve the maxilla or the mandible. There are three reports involving the cheek, submental soft tissue, and the submandibular gland (Table 1). Metastasis of UC to the tongue is exceedingly rare, with only two cases reported in the literature to date. Within the jaws, the posterior mandible and maxilla distal to the canines are usually involved. In most cases, the available treatment options are palliative rather than curative, with associated mortality within several months to 2 years.

The immunophenotype was not typical, but UCs with squamoid features are known to show positive reactivity for CK5 and CK6. The absence of CK7 staining by the metastatic tumor in the current case was somewhat unusual, but CK7 expression in UC with squamous differentiation has been reported to be variable. These can exhibit strong CK5 and CK6 staining, absence of CK20, thrombomodulin and uroplakin III staining, and at times only focal CK7 positivity. Staining patterns in metastatic bladder lesions can also vary from the primary lesion. A recent study compared expression of these markers in metastatic UC and suggested that uroplakin expression is lost but that CK7 staining and thrombomodulin staining are seen in 92% and 80% of metastatic UCs, respectively. However, Only 28% of metastatic UCs showed CK20 staining in this study.

GATA3 expression has been shown as a promising marker for primary UC and regional metastases. Expression of GATA3 has been reported in greater than 70% of primary UCs and matched regional metastases. This pattern is similar among conventional, micropapillary, and plasmacytoid UCs, with weak staining in sarcomatoid and small-cell variants. However, it is not known whether GATA3 expression is maintained in distant metastases.

FISH has been shown to be a reliable technique for the detection of increased chromosome copy number (polysomies), amplifications and deletions of DNA loci, and translocations. It is now a standard method to identify chromosomal aberrations in urine cytology specimens with prognostic, screening, and predictive utility. The Urovysion kit (Abbott Molecular Inc.) comprises a mixture of four different DNA probes, each with a different fluorophore (three centromere probes for chromosomes 3, 7, 17, and 17 and a probe for the 9p21 locus). This, therefore, is designed to detect aneuploidy for chromosomes 3, 7, 17, and loss of the 9p21 which are consistently expressed in UC. The tumors in our study showed changes identical to the changes reported in high-grade UC.

The Urovysion FISH probes (Abbott Molecular Inc.) have been shown to be highly specific in diagnosing UC with a higher sensitivity (86%) compared with cytology (61%). However, FISH has significant implications in relation to the cost of reagents, availability of infrastructure, and expertise of analysis. We recommend the use of FISH in metastatic bladder cancers only in selected cases showing absence of CK7, CK20, and GATA3 expression.

To our knowledge, the current case is the third reported case of UC metastasizing to the tongue and the first to employ FISH testing to establish the correlation between the primary and metastatic tumors. The rarity of these lesions can make diagnosis challenging, especially in cases with prominent squamous differentiation and limited CK7 expression. Multimodality pathologic testing helps refine the diagnosis, and our experience suggests that the UroVysion probe kit (Abbott Molecular Inc.) provides a useful method to establish the diagnosis of metastatic UC.
Molecular Inc.) offers a reliable method for identifying such lesions and in establishing the urothelial origin. Metastatic UC should be included in the differential diagnosis of poorly differentiated lesions in the head and neck region without obvious origin from the surface epithelium and with limited or absent CK7 expression.

REFERENCES
