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Rare Metastasis from Oral Cancer: Case Report and Literature Review

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Abstract

Background: Advanced head and neck squamous cell carcinomas frequently develop distant metastases to limited organs, including the lungs, bone, mediastinal lymph nodes, brain, and liver. Peritoneal carcinomatosis as an initial distant metastasis is a very rare presentation for oral cancer. We present the case of a 38-year-old male with a history of locally advanced buccal mucosa squamous cell carcinoma who developed peritoneal carcinomatosis as a distant metastasis immediately after the end of adjuvant therapy. His disease was highly resistant to intensive systemic chemotherapy and progressed rapidly.

Methods: a comprehensive literature review, according to prisma flow diagram was performed to deepen the knowledge of the prognostic factors of metastatic oral cancer. Moreover, immunohistochemistry analysis was conducted to identify any additional risk factors justifying the disease's aggressiveness.

Results: Tissue samples from both the oral cavity and peritoneum revealed heightened expression of αvβ6 integrin, a protein that promotes cancer invasion and p53 mutation which is related to worse prognosis.

Conclusions: we presented the case of a young patient with clinical and immunohistochemical characteristics that that could justify such a rare presentation also according to literature data. Future studies are needed to define if p53 and αvβ6 positivity could justify oral cancer treatment intensification.

Introduction

Oral cancer is a malignant neoplasm that affects the oral cavity and its subsites like mucosal surfaces of the lips, floor of mouth, oral tongue, buccal mucosa, lower and upper gingiva, hard palate and retro molar trigone. It usually occurs after the 5th decade of life, even though cases in people younger than 40 years are increasing [1,2]. Although the incidence is higher in males, the male-female ratio is progressively decreasing, due to a proportional increase in the consumption of tobacco and alcohol in females [2,3]. If it is true that tobacco (including smokeless tobacco) and alcohol are nowadays the main etiological factors [1,4], chronic inflammation and repeated trauma of the mucosa and poor oral hygiene have to be considered important causes of oral cancer [5]. In fact, a review of the literature revealed that persistent irritation of the mucosa caused by dental trauma, as well as introduction of hot foods and beverages, can be regarded risk factors for the development of oral cancer [6,7]. More than 90% of oral cancers are squamous cell carcinomas (OSCCs) [2].

OSCCs begins as a superficial micro-papular lesion, but rapidly tends to ulcerate and infiltrate the adjacent structures (muscles, periosteum, bone). This occurs with variable frequency in relation to the subsite, the dimensions, and some histological characteristics of the primary lesion (thickness, degree of differentiation, perineural invasion). Although early diagnosis is possible with easy self-examination and physical examination, most patients are not symptomatic in the early stages and do not seek medical attention until the onset of pain, bleeding, oral cavity lesions or neck nodules, so that more than 50% of oral cancers are detected at an advanced stage (stage III and IV)[8]. OSCC can have varying degrees of differentiation and frequently presents with nodal involvement. The T stage, as well as the depth of invasion and tumor thickness, are all closely associated to lymphatic spreading into the neck [8,9]. According to staging and risk factors, treatment of OSCC includes single modality surgery, radiotherapy [external beam radiotherapy (EB-RT) and/ or brachytherapy], or various combinations of these modalities with or without systemic therapy (chemotherapy (CH) and/or target agents). Tumor site and size, nearby structures involvement, stage at diagnosis, functional and cosmetic outcomes, patient's comorbidities, and the patient's willingness are the main criteria of treatment decision [10]. Despite the advances in surgery, radiotherapy and chemotherapy have resulted in improved survival statistics over the past three decades, oral cancer still has poor prognosis, since the overall 5-year survival rate after treatment of oral cancer (all the stages included) is reported as 50–63% [2], due to aggressive local invasion and metastasis, leading to recurrence. [11].

DMs from OSCCs are quite rare, 6% to 9% of cases, and occur predominantly in organs such as the lung (commonest site for distant metastasis for HNSCCs) bone, mediastinal lymph nodes, brain, and liver [18,19,21,22]. Lung is the commonest site of DMs for HNSCCs, followed by bone, mediastinal lymph nodes, brain, and liver [12–14]. Invasion and metastasis of OSCC is favoured by overexpression of integrin αvβ6 in neoplastic cells [15]. This has also been documented in carcinomas arising from different organs (including serous ovarian cancer, colon, stomach, et al.), where it could become a possible target for antibody- and small-molecule-mediated therapies [16,17].

Peritoneal metastasis (PMs) from a primary site in the upper aero digestive tract are extremely rare [18]. PMs are predominantly seen as a manifestation of intra-abdominal malignancy such as gastric, colon, pancreatic and ovarian cancer, and when they occur from an extra-abdominal primary cancer, breast and lung cancers are the most reported [18,19]. Molecularly, PM appear to be mediated by integrin α2 and β1 integrins [20,21]. Only a few cases have been reported in the literature of HNSCCs metastasizing specifically to the peritoneum, further illustrating its rarity [22]. We present the case of a 38-year-old patient with squamous cell carcinoma of the buccal mucosa, without any known preoperative distant metastases, who underwent surgical treatment followed by adjuvant therapy (radiotherapy and chemotherapy) and immediately at the end of the treatments, developed extensive peritoneal carcinosis and multiple bone metastases. Moreover, we performed a systematic review of literature to investigate eventual other similar cases and the molecular causes.

Material and Methods

In order to identify all potentially relevant scientific papers published from June 1954 until September 2023 and reporting original research on the uncommon sites of metastasis of OSCCs, a systematic search of the Medline databases (https://www.pubmed.ncb.nlm.nih.gov/) was carried based on the following criteria:

- Full text papers;
- Available abstracts;
- English text papers;
- Clinical studies, reviews and case reports related to uncommon sites of metastasis compared to the literature data.

Clinical studies were excluded if they met at least one of the following criteria:

- Pediatric or pregnancy patients;
- Interim reports;
- Not about squamous cell carcinoma (other histologies);
- Not uncommon sites of metastasis from OSCC
- Molecular studies;

- Preclinical studies;
- Non-English written language;
- No full text;
- Management of OSCC.

The following search string, sorted by "best match", was used in Medline: oral cancer AND distant metastasis NOT lung NOT liver NOT melanoma. Two authors (AM and FM) independently selected the articles according to the inclusion and exclusion criteria. Any disagreements or differences in selection of the eligible articles were resolved by consultation and discussion with a third assessor (LG). 1954 to 2023 is the period frame that was taken into consideration for the search (the date last searched was 13 September 2023). The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx) (Figure 1) was followed, according to the specific guideline [23]. Consequently, 1896 out of 1944 papers were excluded after a preliminary screening that considered the language (only English texts were included), the accessibility of full texts, and the relevance determined by the title and abstract. Afterwards, out of the 68 full text papers that were evaluated for eligibility, 59 were disqualified, primarily due to their association with the typical sites of metastases from carcinomas of the oral cavity.

Tissue samples were fixed in buffered formalin and routinely processed to paraffin wax. Five-micrometer-thick sections were routinely stained with hematoxylin and eosin. Immunohistochemical (IHC) reactions were performed on additional 3-µm-thick sections using prediluted ready-to-use vials of the antibodies listed in Table 1 with an automated immunostainer (BenchMark Ultra, Ventana Roche Diagnostics) and standardized protocols (Ventana OptiView DAB IHC Detection Kit). Search for somatic variants in the TP53 gene was carried out using next generation sequencing (NGS) on the Illumina MiSeq platform (AmoyDx HANDLE Classic NGS Panel CE-IVD*, Amoy Diagnostics Co., Ltd.)

Antigen	Manufacturer	Clone
p40	Ventana	BC28
p63	Ventana	4A4
p16	Ventana	CINtec ®
p53	Ventana	DO7
CK34bE12	Ventana	CK34bE12
CK8/18	Cell Marque	B22.1 & b23.1
Calretinin	Ventana	SP65
CDX2	GeneTex	EPR2764Y
BerEp4	Cell Marque	BerEp4
αvβ6	Cell Signaling	E4M9P

Table 1: Antibodies adopted for immunohistochemical reactions o formalin-fixed-paraffin-embedded tissue slides.

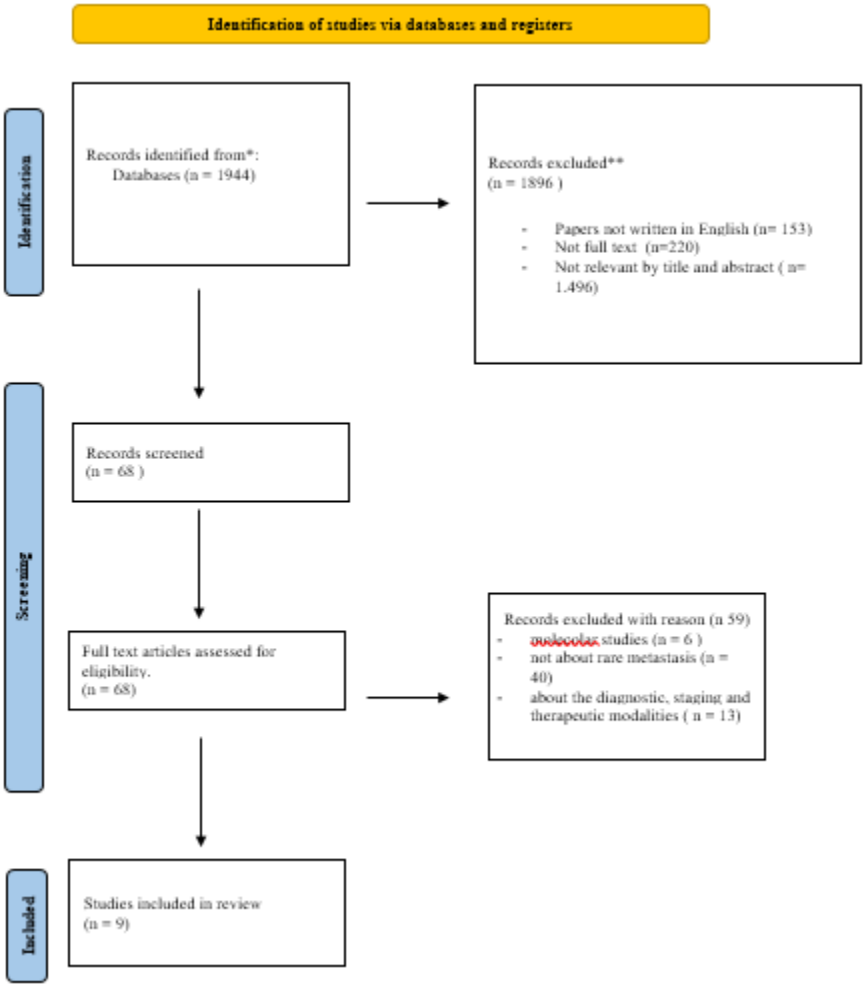

Figure 1: Prisma 2021 flow diagram.

Case Presentation

A 38-year-old man came to our attention in June 2021 for the appearance of an ulcerated lesion of the left buccal mucosa (specifically a squamous cell carcinoma on biopsy) with homolateral cervical lymphadenopathy causing reflex otalgia. The patient had no relevant past medical history without any familiarity for cancer. He had been e-cigarette smoker for 2 years till July 2021 (by 2019 he had been smoking 10-12 cigarettes per day for 20 years (10 p / y)). He stated that, over the previous two years, he had visited the dentist multiple times to have the second upper left molar filed since its contact had injured the buccal mucosa. Therefore, he had underestimated the emergence of a papule in the traumatize sites two months earlier. Clinical examination confirmed the presence of an ulcerated lesion of the posterior half of the left buccal mucosa at the level of first and second upper molar tooth, with discomfort and tenderness on palpation in apparent continuity with adenopathy package at levels Ib and IIa. On imaging (Magnetic Resonance Imaging, MRI with contrast), the lesion, which measured 30 x 14 x 26 mm in size (Figure 2a-b), appeared heteroproductive in the context of the adipose tissue of the buccal space and the Bichat's fat pad, reaching close to the outlet of the Stensen duct; it had an extensive posterior contact with the masseter muscle and with the anterior margin of the upper branch of the mandible, occupying the region of the retro molar trigone up to the pterygomandibular raphe, and anteriorly infiltrating the buccinator muscle. Superiorly the tissue was infiltrating the gum and marginally the adjacent superior alveolar process surrounding the 1st molar. There wasn't any sign of evident infiltration of the mandible, nor of the internal pterygoid muscle or of the pterygopalatine fissure. Several partial colliquated and confluent lymph node swellings, with a maximum diameter of 40 mm and inseparable from the submandibular gland and the lower region of the parotid gland, were

observed postero-inferiorly to the mandibular body. An additional 17 mm lymph node nodulation was seen inferiorly contiguous with the anterior portion of the ipsilateral sternocleidomastoid muscle. In the right latero-cervical area, globally small lymph nodes including a more evident lymph node with irregular profiles at level IIa of 16x 8 mm, inhomogeneous after contrast of uncertain inflammatory significance.

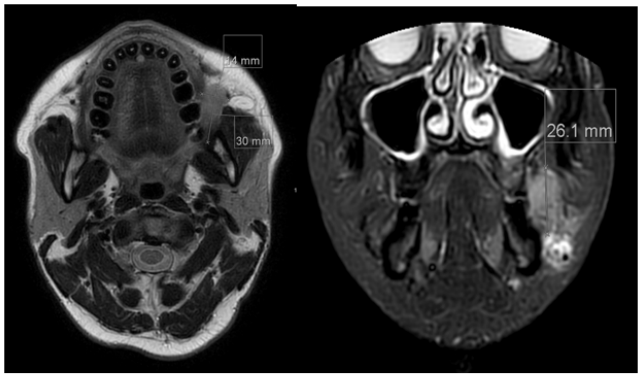

Figure 2a-b: MRI showing the primary lesion (a= axial; b= coronal).

We completed the pre-operative staging with a Positron Emission Tomography (PET) scan, total body Computerized Tomography (CT) scan with contrast and cervical-lumbar spine CT scan with contrast without any evidence of distant metastases. His clinical TNM stage was determined as cT2N3bM0. In July 2021 the patient underwent surgery treatment with exeresis of the left buccal mucosa squamous cell carcinoma, complete left parotidectomy, left modified radical neck dissection (MRND) type III, right laterocervical lymphadenectomy (level IIa), temporary tracheostomy and reconstruction with right radial forearm free flap (RFFF). Histopathology report showed moderately differentiated squamous cell carcinoma (G2) infiltrating the buccinator muscle (DOI: 11 mm), with IHC hyper expression of p53 and integrin αvβ6 as well as negative p16 (Figure 3). The neoplasm reached the anterior resection margin of the operative piece and close (< 5 mm) to the posterior and inferior margin of the operative piece. Moreover, metastases were found in the lymph node of the deep left parotid lobe with extranodal spread and in 20 out of 40 left laterocervical lymph nodes, with extra nodal spread in 3 lymph nodes (ENE+). There was no evidence of lymph vascular invasion but perineural invasion was present. pT3 pN3b, R1, PNI + Stage IVB (AJCC, TNM 8 ^ ed. 2017).

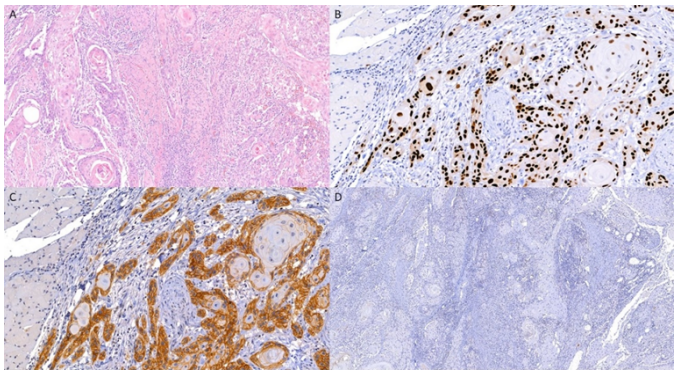

Figure 3: Oral squamous cell carcinoma (OSCC) showing nests and cordons of neoplastic cells with abundant pinkish cytoplasm, round nuclei, intercellular bridges, and squamous pearls formation. Immunohistochemical profile features hyper expression of p53 and αvβ6, while p16 is negative. (A. EE, 5x; B. p53, 20x; C. αvβ6, 20x; D. p16, 5x).

Considering the histological outcome, the patient was given adjuvant radiotherapy for a total radiation dose of 66Gy in 30 fractions and concomitant chemotherapy with a total of 300mg/m2 CDDP (from 30th August 2021 to 11th October 2021). Due to the patient's intense actinic pharyngeal edema and mucositis, which was causing dysphagia and odynophagia, and because of the inadequate buccal opening brought on by the post-operative analgesic trismus, a nasogastric tube was placed during adjuvant therapy (September 23, 2021). So, from this point forward, the patient only received enteral nutrition. Blood tests were performed around one week after the therapy ended (October 20,2021), and the results were within normal ranges.

On 25th October 2021 the patient came to our attention for severe abdominal pain and vomiting. Upon clinical examination, he showed signs of weakness, severe suffering and fever with a flat abdomen, tense, pain, and tenderness in all four quadrants, as well as no peristalsis. In the suspicion of peritonitis, we sent the patient to the emergency room for appropriate management and treatment. Blood tests showed WBCs 10.8 x 10^9/L, RBCs 4,54 x 10^12/L, Hgb 12,9 g/dL, Hct 38.8 %, PLT 324 x 10^9/L, neutrophil 88,4 %, creatinine 0,65 mg/dL, Na+ 131,6 mmol/L, K+ 4.42 mmol/L, Ca2+ 2.41 mmol/L, PCR 148.3 mg/L. An abdominal CT scan was performed with the evidence of diffuse hyper density of the endoabdominal adipose tissue of dubious interpretation (inflammation? carcinosis?); lytic lesions of secondary substitutive significance affecting some of the skeletal segments included in the field of study, the most significant ones to the right hemi some of D10 and to the pelvic bones (Figure 4-5).

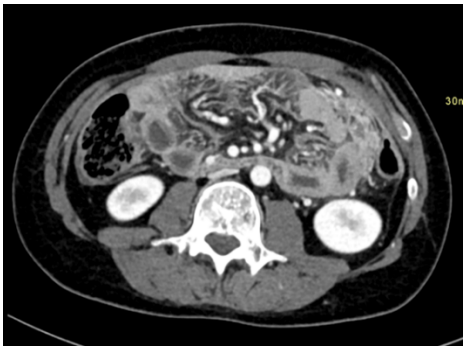

Figure 4: Axial CT scan showing hyper density of the endoabdominal adipose tissue due to peritoneal neoplastic involvement.

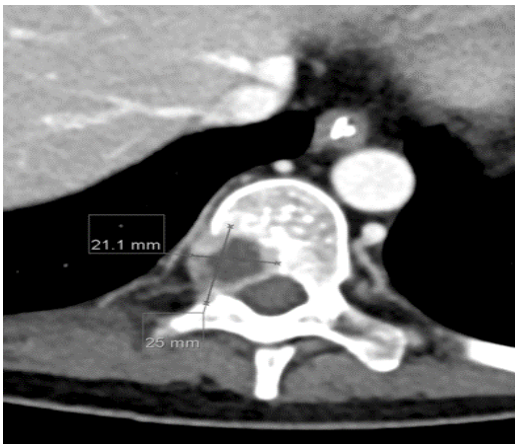

Figure 5: axial CT scan showing D10 hemisome' lytic lesion.

The patient immediately underwent to an exploratory laparoscopic surgery, peritoneal washing and omental biopsy with macroscopic evidence of diffuse fibrinous peritonitis. Histopathology report showed squamous cell carcinoma metastasis with the same immunohistochemistry as the primary tumor in the buccal mucosa (p63+, p40+, CK34betaE12+, focal CK8-18+, calretinin-, CDX2-, BerEp4-) (Figure 6).

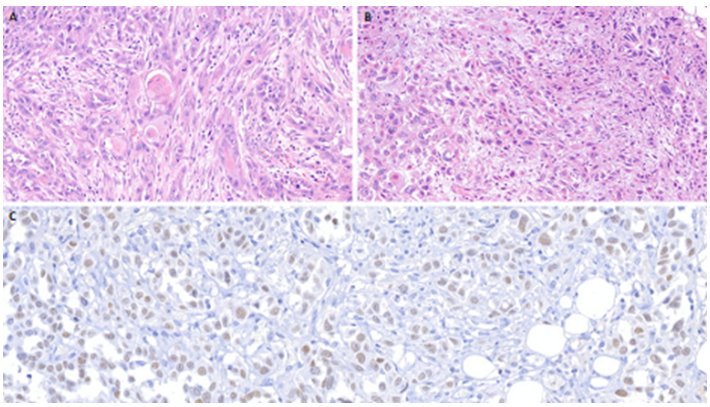

Figure 6: Peritoneal localization of a squamous cell carcinoma, which is immunophenotypically compatible with OSCC (A. and B. EE, 20x; C. IHC p40, 20x).

In the meantime, he was hospitalized in the general surgery department until November 5th, 2022, with a clinical course characterized by a slow recovery both of gastric emptying (frequent vomiting attacks) and intestinal canalization (digestive tube x-ray performed), which required prolonged maintenance of the nasogastric tube, and in general by a slow recovery of the general clinical picture. As a further investigation during hospitalization, a brain CT was performed which excluded the presence of intracranial metastases. Blood tests revealed an electrolyte imbalance including hyponatremia and hypercalcaemia (WBCs 13,2 10^9/L, RBCs 3.67 10^12/L, Hgb 10.1 g/dL, PLT 512 10^9/L, Na+ 132,8 mmol/L, K+ 3,64 mmol/L, Ca2+ 3,26 mmol/L, PCR 153.0 mg/L).

The hospitalization was then organized in the medical oncology department for the case's investigation and treatment. Given the rarity of abdominal metastases from squamous cell carcinoma of the head and neck region, total body CT with contrast was performed on November 15th, which excluded the presence of other primary lesions (as well as dermatological examination and esophagogastroduodenoscopy). Moreover, it showed further rapid progression of the abdominal disease, a renal vein thrombosis and

a minor peripheral pulmonary embolism. According to the tumor platin resistance, firstly, the patient underwent to immunotherapy with anti PDL1 (Nivolumab), but after the first two cycles, considering the rapid deterioration of patient's general conditions (intestinal sub occlusion, paraneoplastic hypercalcemia, peripheral pulmonary embolism), was chosen best supportive care and the patient died 1.5 months later, due to disease progression.

Results

Of the sixty-eight full-text articles screened for uncommon sites of metastasis, fifty-nine were excluded due to the following reasons: (1) molecular studies about metastatic process (n = 6; 8,8 %); (2) not about uncommon metastasis (n = 40; 58,8%); (3) about the diagnostic and staging modalities (n = 13; 19,11%). In turn, nine papers about uncommon metastatization met the inclusion criteria and are listed in Table 2.

Articles	Age	Site of primary tumor	Stage	Treatment	Evidence	Uncommon site of DM	Onset time of DM from therapy	Risk Factors	Survival
Wurm (2015)[24]	52	floor of the mouth	pT3 pN1 (1/46) cM0	Surgery + RT	Case report	upper arm	About 12 months later	L0 V2 Pn1 G3, local R0)	-
Yao-Te Tsai (2010)[25]	62	retromolar trigone	T4N1M0	Surgery + RT	Case report	cardiac tamponade	About 12 months later	-	-
Frolich (2013) [26]	36	floor of the mouth	pT2 pN2b cM0	Surgery	Case report	Bone marrow carcinosis	3 days later	G3, LVI +, ENE+	6 weeks after surgery
Vahtsevanos (2007)[27]	80 53 39 39	Lip Lip Lip Lip	pT3N2bM0 T4N2cM0 pT2NxM0 pT2N1M0	surgery + RT surgery + RT surgery + RT surgery	Case series	Axillary nodes + T6-T7+ T12-L1+ scapula 5th rib multiple vertebral foci multiple vertebral foci	7 m 6 m 9 m 12 m	G2, R0 G2, R1 G2, R0 G3, R0	13 m 17 m 23 m 35 m
Deshpande (2019)[28]	45	Buccal mucosa	T2 N2b M0	Surgery	Case report	Small intestine	Before adjuvant treatment	G2, PNI +, R0	-
Aoyagi (2011) [29]	40	Tongue	cT4cN3bM0	CT + surgery + RT	Case report	Mediastinum Abdominal wall	17 m	G2	-
Mathew (1997)[30]	35	Buccal mucosa	-	RT + surgery	Case report	Bone marrow carcinosis	24 m	-	-
Lee (2007)[31]	52 60	Tongue Tongue	/ ./	CTRT Surgery + CTRT	Case series	spinal cord impingement spinal cord impingement	15 d 13 m	./ /	/ /
Fan (2019) [32]	53	Buccal mucosa	M+ at the diagnosis	CT	Case report	Peritoneum	/	/	< two months

Table 2: Selection of articles regarding uncommon sites of OSCC metastasis.

Discussion

DMs from OSCCs are extremely rare. According to the literature data, the following are the main risk factors that increase the probability of having DMs in OSCCs: advanced T staging, cervical lymph node involvement even more if contralateral and with extracapsular extension, tumor thickness, angiolymphatic invasion, perineural invasion and loco regional recurrence (one of the most important risk factors for the development of DMs) differently from gender, age, smoking, alcohol consumption, histological differentiation, and positive surgical margins that do not seem to influence the incidence of distant metastases [18,30,33,34].

In our clinical case, the patient had an advanced stage tumor (stage IVb, pT3N3b) with many risk factors (perineural invasion and lymph nodes with extra nodal extension) which is the reason why he received adjuvant concomitant radiotherapy and chemotherapy with the aim to improve overall, specific disease, disease-free, and metastasis-free survival [31-33]. The peculiarity of our clinical case is that he developed early isolated distant metastases, in a completely improbable site, i.e. the peritoneum, without loco-regional recurrence or other site of metastasis, despite a comprehensive therapy strategy. In general, abdominal metastasis from a primary HNSCC are uncommon, and especially peritoneal metastasis are particularly rare.

We have conducted a literature search to identify cases of oral cavity carcinomas with development of unusual distant metastasis and fourteen cases were found, two of which originated from the floor of the mouth, one from the retro molar trigone, three from the genial mucosa, and three from the tongue. The bone skeleton (upper arm, scapula, ribs, vertebrae), spinal cord, heart, and abdomen (small intestine and peritoneum) have been identified as atypical areas impacted by distant metastases (Table 1), almost all related to a worse and rapid prognosis. Only four of them [24,26,28,29] indicate the presence of the aforementioned risk factors associated with a higher probability of distant metastases and perineural infiltrate, angiolymphatic infiltration and extra nodal extension appear to be the only risk factors outlined, like our clinical case.

To our knowledge, this is the first case of peritoneal metastasis from OSCCs cancer that has been documented in the scientific literature suddenly occurred at the end of adjuvant therapy. Our research has revealed only one other case of peritoneal metastasis from oral cancer but the DMs were synchronous [32]. Specifically, in the latter case since ascites and a heterogeneous fat filament of the peritoneum were found on the abdominal CT, the patient underwent an exploratory laparotomy with biopsies positive for epithelioid carcinoma. Therefore, the patient underwent a series of diagnostic investigations but only PET / CT identified the primary tumor located in the right buccal mucosa and compatible with the histology of peritoneal carcinomatosis. In addition, an immunohistochemistry analysis was carried out to determine whether the tumor had exhibited any traits linked to the emergence of peritoneal metastases as ovarian cancer: tumor cells from both the primary site and the peritoneum turned out to be negative for tumor necrosis factor alpha (TNFα) and CD24, but positive for CD44 and CD36.However, this report lacked information about the IHC clones adopted, making the experiment not fully reproducible.

We instead opted to identify any additional risk factors to justify the aggressiveness of the disease, we made molecular research founding the overexpression of αvβ6 in neoplastic cells. While PMs are associated to the presence of integrin α2 and β1 [20,21], αvβ6 has been reported to regulate extracellular matrix degradation in serous ovarian cancer, a disease with high rates of PMs [17]. Moreover, searching for characteristics which could explain this aggressiveness we detected pathogenic variant in the TP53 gene ((NM_000546.5): c.742C>T, p.(Arg248Trp), allele frequency 15%, coverage 1512X), known to be a poor predictor of OCSS outcome [35,36].

A recent review published by Bellala Ravishankar et al. emphasized the expression of P53 is related to the severity of the disease. In fact, there was a significant association between P53 expression and advanced T stage, histopathological grade, increased depth of invasion, involved margin, positive nodes, and extra nodal extension which mean a worse prognosis [37]. With this regard, many works have highlighted the importance of TP53 mutations in head and neck cancer development and response to treatment, using both pre-clinical models and retrospective patient cohorts [38]. Biologically, TP53 in OCSCC tumor cells seems to be associated with adrenergic neurogenesis leading to higher peritumoral neural density and correlating with worse OS [38].

In fact, in our case, histopathology report underlined the presence of extra nodal spread and prineural invasion as major and minor risk factors of relapse and metastatization. These findings encourage to study the efficacy of personalized treatment intensification such as suggested by Perrone et al. in 2010 publishing a correlation between TP53 status and a pCR induced by cisplatin-based neoadjuvant chemotherapy in squamocellular carcinoma of oral cavity, identifying the most effective treatment [39] also since TP53 mutations provide resistance to various chemotherapeutic agents, including cisplatin [40].

Conclusion

In conclusion, we presented the case of a 38-year-old patient with a p53-positive p16-negative OSCC which gave rise to extensive peritoneal carcinosis. Neoplastic cells showed an expression of αvβ6, an integrin which favors neoplastic invasion, development

of metastases and also extracellular matrix degradation in serous ovarian cancer. This evidence not only shed light on the pathogenesis of PMs in OSCC, but it also identifies a potential therapy target. Even if PMs specifically derived from OSCCs are quite rare, future research on PMs could reveal more details about the interplay among the different integrins and the other markers involved in the development of PMs. Considering the poor prognosis associated with PMs, it would be important both to deepen our knowledge about their pathogenesis, to identify new therapy targets and to define if p53 and αvβ6 positivity could justify oral cancer treatment intensification.

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Ethical Guidelines: the patient signed a consensus form to clinical study

Conflict of Interest: The authors declare no conflict of interest.

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