CASE REPORT
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Large neck metastasis with unknown primary tumor – a case report

Velike metastaze u vratu sa nepoznatim primarnim tumorom

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Abstract

Introduction. Metastatic head and neck carcinoma (HNC) from an unknown primary tumor is defined as a metastatic disease in the neck's lymph nodes without evidence of a primary tumor after appropriate investigation. Multiple national guidelines recommend taking essential steps in diagnostic protocols which involve a detailed clinical exam with radiological imaging, fine-needle aspiration (FNA) biopsy of the cervical tumor, esophagogastroduodenoscopy (EGD) with palatine and lingual tonsillectomy, immunohistochemical staining, and human papillomavirus (HPV) detection. Treatment of HNCs of unknown primary origin involves surgery (neck dissection) with radiotherapy (RT), while some authors recommend chemo-radiotherapy in cases of advanced regional disease. **Case report.** A 44-year-old male was referred to the tertiary medical center because of a large ulcero-infiltrative cervical mass on the right side. Examination of the head and neck and flexible nasopharyngolaryngeal endoscopy was conducted, followed by computed tomography (CT) of the head, neck, and thorax with intravenous contrast. The primary localization of the tumor was not confirmed by these diagnostic methods. An open biopsy of the neck mass established a histopathology diagnosis of metastatic squamous cell carcinoma (SCC). Results of EGD with biopsies and bilateral tonsillectomy were negative for malignancy. Treatment included extended radical neck dissection with reconstruction and postoperative ipsilateral RT. The patient presented with an extensive pharyngolaryngeal tumor five years after the first surgery. Biopsy with histopathology examination confirmed the diagnosis of SCC. **Conclusion.** A structured step-by-step diagnostic approach to identifying the primary site of the metastatic HNC is mandatory. Substantial advances in diagnostics and operative techniques have increased the likelihood of primary tumor identification and detection of the disease's regional and systemic spread. The purpose of adherence to guidelines results in higher overall survival and longer regional disease-free survival in these patients.

Key words:
biopsy; diagnosis; endoscopy, digestive system; head and neck neoplasms; neoplasms, unknown primary; tomography, x-ray computed.

Apstrakt

Uvod. Metastaze u glavi i vratu karcinoma (HNC) nepoznatog primarnog tumora definišu se kao metastatska bolest u limfnim čvorovima vrata bez dokaza o postojanju primarnog tumora nakon sprovedene dijagnostike. Više nacionalnih vodiča preporučuje da dijagnostički protokoli obavezno uključe detaljan klinički pregled sa radiološkom dijagnostikom, iglenu aspiracionu biopsiju (FNA) tumorskih promena na vratu, ezofagogastroduodenoskopiju (EGD) sa tonzilektomijom palatinalnih i lingvalnih tonzila, imunohistohemijska bojenja preparata i detekciju humanog papiloma virusa (HPV). Terapija metastaza HNC nepoznatih primarnih tumora podrazumeva hirurško lečenje (disekciju vrata) i primenu radioterapije (RT), dok neki autori preporučuju hemoradioterapiju u slučajevima uznapredovale regionalne bolesti. **Prikaz bolesnika.** Bolesnik star 44 godine je, zbog pojave ulceroinfiltrativne mase na vratu sa desne strane, upućen u tercijarnu medicinsku ustanovu. Učinjen je pregled glave i vrata i fiberoptička nazofaringolaringoskopija, a potom i kompjuterizovana tomografija (CT) glave, vrata i grudnog koša sa intravenskim kontrastom. Primarna lokalizacija tumora nije utvrđena tim dijagnostičkim metodama. Otvorenom biopsijom tumorske promene na vratu postavljena je histopatološka dijagnoza metastaze skvamocelularnog karcinoma (SCC). Bolesniku je potom urađena EGD sa slepim biopsijama, čiji su rezultati bili negativni na malignitet. Lečen je hirurški, proširenom radikalnom disekcijom vrata sa rekonstrukcijom i postoperativnom ipsilateralnom RT. Pet godina nakon operativnog lečenja, bolesnik se javio na pregled sa manifestacijama masivnog faringolaringealnog tumora. Biopsijom i histopatološkim ispitivanjem potvrđena je dijagnoza SCC. **Zaključak.** U slučaju metastaze HNC nepoznatog primarnog tumora, obavezan je dijagnostički postupak „korak po korak" za identifikaciju lokalizacije primarnog tumora. Značajan napredak u dijagnostici i

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operativnim tehnikama uticao je na povećanje verovatnoće utvrđivanja porekla primarnog tumora, kao i detekciju regionalnog i sistemskog širenja bolesti. Krajnji cilj je poboljšanje ukupnog preživljavanja i produženje intervala bez regionalnih recidiva kod tih bolesnika.

Ključne reči:
biopsija; dijagnoza; endoskopija, gastrointestinalna; glava i vrat, neoplazme; neoplazme nepoznatog porekla; tomografija, kompjuterizovana, rendgenska.

Introduction

Head and neck squamous cell carcinoma (SCC) of unknown primary (SCCUP) origin makes up approximately 2–5% of all head and neck cancers (HNC), although advances in imaging and intraoperative visualization of high-risk subsites have increased the likelihood of identifying the primary site [1]. Identification of the primary site allows for planning of targeted treatment and is associated with improved prognosis and survival outcomes [2]. Multiple national guidelines recommending diagnosis and treatment strategies were presented in the last decade [1–5], but the consensus on the diagnostic workup of head and neck SCCUP has not yet been reached. Important steps in diagnostic protocols involve a detailed clinical exam with radiological imaging, fine-needle aspiration (FNA) biopsy of the cervical tumor, and esophagogastroduodenoscopy (EGD) with palatine and lingual tonsillectomy. New research is focused on determining the role of human papillomavirus (HPV) detection, the use of fluorodeoxyglucose [FDG]-positron emission tomography (PET)/computed tomography (CT) – (PET/ CT) combined with EGD in the detection of the primary tumor, or the use of transoral minimally invasive procedures [6–8].

Treatment of head and neck SCCUPs prioritizes locoregional control. Initial recommendations involve surgery (neck dissection) with radiotherapy (RT) [1, 2, 9]. The importance of chemo-RT is stressed for N2, N3, and metastases with extracapsular extension [1, 10]. Treatment remains heterogeneous and still based on retrospective studies, clinical experience, and institutional policies.

We present a case of SCCUP of the neck to illustrate the importance of a structured diagnostic protocol and appropriate treatment choice in achieving better overall and disease-free survival.

Case report

A 44-year-old male patient was referred to our clinic with a painless large ulcerous-infiltrative cervical mass on the right side. The neck mass appeared four months prior to referral. On admission, the patient did not report any other relevant symptoms in the head and neck region or any comorbidities or allergies. He was a heavy smoker (up to 60 cigarettes a day for 20 years) and frequently consumed alcohol (over 500 mL of spirits a day for over 15 years).

We conducted a complete and careful clinical otorhinolaryngology examination, followed by flexible nasopharyngolaryngeal endoscopy. Clinical findings appeared normal. Prior to hospitalization, CT of the head, neck, and thorax with intravenous contrast was done. Imaging findings indicated nodal metastatic disease in the right neck, with central necrosis, infiltration of adjacent muscles, internal jugular vein, and skin. All parts of the pharynx and larynx were without pathological findings (Figure 1).

Biopsy of the neck mass confirmed histopathology diagnosis of metastatic SCC. The patient underwent EGD with biopsies from the nasopharynx, both tonsils, tongue base, and pyriform fossae, but the results were negative.

Intraoperative findings indicated infiltration of the posterior digastric muscle, jugular vein, sternocleidomastoid muscle, parotid, gland, XI and XII cranial nerves, and brachial plexus. The defect was reconstructed with the pectoral's major myocutaneous flap (Figure 2).

Histopathology findings were consistent with grade III metastatic SCC, confirming the neck lymph node metastases from an unknown primary tumor. According to the Oncological Board's decision, the patient underwent postoperative RT of the neck (from the skull base to below the cricoid

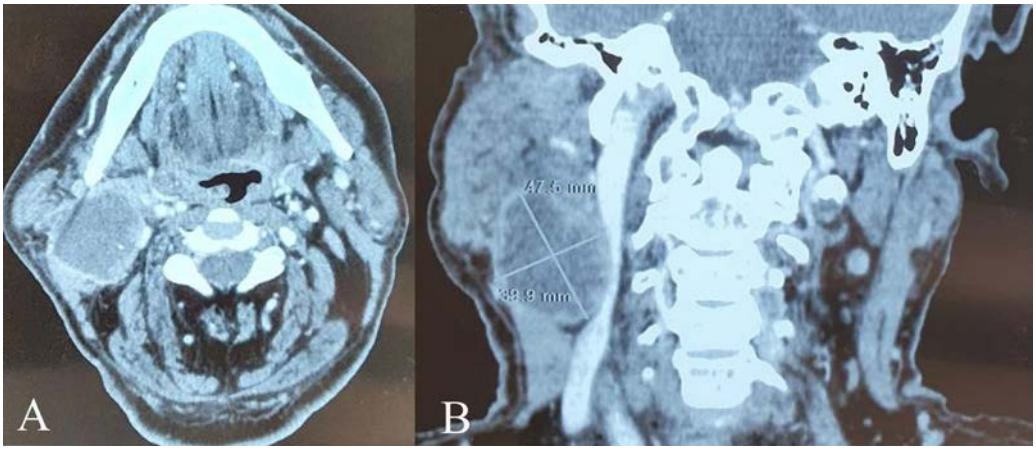


Fig. 1 – Computed tomography (CT) of the patient's neck with nodal metastatic disease in the neck with central necrosis: (A) axial view; (B) coronal view.



Fig. 2 – Preoperative (A) and postoperative (B) images of the patient metastatic neck mass on the right; extended radical neck dissection was performed and the defect was reconstructed with the pectoral's major myocutaneous flap.

cartilage, including ipsilateral neck level II, III, IV, and parotid gland) with 65 Gy in 30 fractions during six weeks. After three years of regular oncological controls, the patient was lost to follow-up.

Five years after the first surgery, the patient presented with difficulty swallowing. A pharyngeal tumor of the left lateral oropharyngeal and hypopharyngeal wall, with extension to the pyriform fossa and the right larynx involvement, was visualized with indirect laryngoscopy. Biopsy with histopathology examination confirmed the diagnosis of SCC. CT scan of head, neck, and thorax showed no signs of regional or distant disease spread. The patient underwent total pharyngolaryngectomy, tracheostomy, and left selective neck dissection. The patient received postoperative RT (60 Gy in 30 fractions). Five months after the RT, the patient was without recurrent disease.

Discussion

The failure to detect the primary tumor location in a patient with metastatic HNC poses a clinical challenge that can affect the course of treatment and disease prognosis. New recommendations were made in recent guidelines but were not applied in the case presented above, which further illustrates their importance in the diagnostic protocol, choice of treatment, and better overall and disease-free survival.

After clinical examination and diagnostic imaging, FNA biopsy is crucial in assessing neck nodal mass in SCCUP. The American Joint Committee on Cancer (AJCC) [3] recommended adding HPV staining to the diagnostic workup. HPV-specific marker p16 positive immunohistochemical staining would indicate a potential oropharyngeal primary tumor (palatine tonsil and base of the tongue). Lymph node metastases in SCCUP were positive for HVP in 7.8% to 30% of patients [6, 9]. In Serbia, oropharyngeal carcinoma was positive for p16 HPV in 45% [10, 11]. A positive p16 result should at least be followed by HPV-specific testing (*in situ* hybridization or PCR), especially in cases where no non-keratinizing histology or lymph nodes are not found in II and/or III region.

PET/CT is recommended in all patients where conventional imaging failed to identify the tumor's primary site. PET/CT has high sensitivity (up to 88.3%) and negative predictive value (from 68.9% to 93%), which makes it an excellent complementary diagnostic tool [7, 12, 13]. Diagnostic protocols that use preoperative PET/CT preceding EGD with directed biopsies resulted in the detection of the primary lesion in over 90% of patients [12, 13]. Results of both HPV staining and PET/CT would probably be indicative of the location of the primary tumor in case presentation but were not part of the performed diagnostics in the case presented.

National Comprehensive Cancer Network (NCCN) made recommendations for endoscopy (nasopharyngoscopy, inspection, and palpation of the oral cavity and oropharynx, laryngoscopy, esophagostomy, bronchoscopy) with tonsillectomy and directed biopsies based on the levels of the neck involved under general anesthesia [14]. Oropharyngeal sites, especially the tonsils and tongue's base, are the most common site for primary occult tumors. Tonsillectomy increased the likelihood of identifying a primary by 30%, compared to deep tonsil biopsies, where the identification rate was only 3% [15]. Bilateral tonsillectomy is preferred to unilateral due to a possible bilateral and contralateral tumor location in 15% of the cases with tonsillar malignancies [16]. Recommendation on lingual tonsillectomy is still not firmly established. With advances in operative techniques that include transoral laser microsurgery and transoral robotic surgery, lingual tonsillectomy provided a tumor detection rate of 56% in patients with SCCUP [8]. Bilateral tonsillectomy should always be performed in cases of SSCUP, while in the presented case, only blind biopsies were done in the absence of the evident tumor site. In this case, the pharyngolaryngeal tumor was considered a secondary primary, but we cannot exclude the possibility of the contralateral recurrent disease if the tonsils were positive for occult carcinoma.

Further treatment in patients with unknown primary carcinoma with neck metastases involves neck dissection followed by postoperative RT or consideration of chemo-RT [1, 15]. Multiple retrospective studies had inconsistent results regarding RT field size. Some reports reported that patients who underwent bilateral RT did not have significantly better overall survival and regional recurrence compared to patients treated with unilateral RT to the neck and mucosal surfaces. On the other hand, some studies favor bilateral nodal and mucosal irradiation [17, 18]. The NCCN recommends chemo-RT in N2/N3 disease cases with the extracapsular extension [14], although it should be noted that no randomized trials demonstrate the superiority of this treatment over RT alone. Due to the low incidence of the disease and the lack of high-quality evidence, clear clinical management protocols are not available.

Conclusion

Substantial advances in diagnostics and operative techniques have increased the likelihood of primary tumor identification and regional and systemic spread of the disease. If a CT or magnetic resonance imaging does not identify a primary site, the PET/CT scans should be performed before surgical endoscopy and biopsies. In cases of SCCUP, bilateral tonsillectomy with lingual tonsillectomy is indicated during EGD. Although high-quality evidence of treatment protocols is lacking, patients with more advanced stages of the regional disease require combined treatment in the form of neck dissection followed by concomitant radiation with or without chemotherapy.

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