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ZNAČAJ PANENDOSKOPIJE U OTKRIVANJU NEPOZNATOG PRIMARNOG KARCINOMA VRATA – PRIKAZ SLUČAJA

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SAŽETAK: UVOD:Cistične mase vrata kod odraslih pacijenata predstavljaju značajan dijagnostički izazov, jer mogu prikriti metastatsku bolest. Iako se cistične cervikalne metastaze najčešće povezuju sa HPV-pozitivnim planocelularnim karcinomima orofarinksa, cistična prezentacija ne isključuje HPV-negativnu etiologiju. Cilj rada je da se ukaže na značaj sistematskog dijagnostičkog pristupa, uključujući panendoskopiju sa bilateralnom tonzilektomijom, u obradi cervikalnih metastaza nepoznatog primarnog porekla. **PRIKAZ SLUČAJA:**Prikazana je pacijentkinja starosti 47 godina sa bezbolnom cističnom promenom u levoj parotidnoj regiji, inicijalno radiološki tumačenom kao benigna lezija. Histopatološka analiza nakon hirurške ekstirpacije pokazala je cističnu metastazu planocelularnog karcinoma sa ekstrakapsularnom ekstenzijom, uz p16 negativnost. Daljom dijagnostičkom obradom, uključujući panendoskopiju i obostranu tonzilektomiju, identifikovan je sinhroni bilateralni HPV-negativni planocelularni karcinom tonzila. Nakon obostrane selektivne disekcije vrata sprovedena je adjuvantna radioterapija uz hemioterapijskupotencijaciju. Na kontrolnom pregledu nije bilo znakova recidiva bolesti. **ZAKLJUČAK:** Cistična masa vrata kod odraslih mora se smatrati malignom dok se ne dokaže suprotno. Negativan radiološki nalaz ne isključuje postojanje primarnog tumora u orofarinksu. Prikazani slučaj potvrđuje dijagnostičku vrednost panendoskopije sa bilateralnom tonzilektomijom u identifikaciji okultnog primarnog tumora, naročito u kontekstu HPV-negativne bolesti.

Ključne reči: cistična masa vrata; cervikalna metastaza; panendoskopija; planocelularni karcinom tonzila; HPV-negativan

UVOD

Izraštaji na vratu kod odraslih pacijenata predstavljaju čest klinički problem i značajan dijagnostički izazov u svakodnevnoj otorinolaringološkoj praksi. Za razliku od pedijatrijske populacije, kod koje su cistične promene vrata najčešće kongenitalne i benigne, kod odraslih pacijenata svaka novonastala masa zahteva temeljnu i sistematsku dijagnostičku obradu zbog realne mogućnosti malignog porekla [1]. Upravo u ovoj populaciji inicijalno benigno tumačenje lezije može dovesti do kašnjenja u postavljanju dijagnoze i odlaganja adekvatnog onkološkog lečenja.

Posebnu dijagnostičku dilemu predstavljaju cistične lezije vrata, koje se u odsustvu lokalnih simptoma, inflamacije ili infiltrativnog rasta često percipiraju kao benigne promene. Međutim, kod odraslih pacijenata cistična morfologija ne isključuje malignitet, već naprotiv može predstavljati manifestaciju metastatske bolesti.

Cistične cervikalne metastaze najčešće se dovode u vezu sa HPV-pozitivnim planocelularnim karcinomima orofarinksa, naročito tonzila i baze jezika [2]. Ova povezanost je tokom poslednjih godina dovela do raširenog kliničkog uverenja da cistična struktura metastaze implicira HPV-pozitivnu etiologiju i potencijalno povoljniju biološku karakteristiku tumora. Međutim, HPV-negativni orofaringealni karcinomi predstavljaju biološki i klinički različit entitet, sa drugačijim faktorima rizika, agresivnijim tokom bolesti i nepovoljnijom prognozom [3]. Prikazi cističnih metastaza poreklom iz HPV-negativnih tumora su retki i uglavnom potiču iz starije literature, zbog čega i dalje predstavljaju dijagnostičku zamku u savremenoj kliničkoj praksi.

Cilj ovog rada je da se kroz prikaz slučaja ukaže na značaj panendoskopije u dijagnostici cervikalnih metastaza nepoznatog primarnog porekla, kao i da se naglasi potreba za strukturiranim i sistematskim pristupom

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THE IMPORTANCE OF PANENDOSCOPY IN DETECTING AN UNKNOWN PRIMARY HEAD AND NECK CARCINOMA – A CASE REPORT

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ABSTRACT: Introduction: Cystic neck masses in adult patients represent a significant diagnostic challenge, as they may conceal metastatic disease. Although cystic cervical metastases are most commonly associated with HPV-positive oropharyngeal squamous cell carcinomas, a cystic presentation does not exclude an HPV-negative etiology. The aim of this study is to highlight the importance of a systematic diagnostic approach, including panendoscopy with bilateral tonsillectomy, in the evaluation of cervical metastases of unknown primary origin. Case Report: We present a 47-year-old female patient with a painless cystic lesion in the left parotid region, initially interpreted radiologically as a benign lesion. Histopathological analysis following surgical excision revealed a cystic metastasis of squamous cell carcinoma with extracapsular extension and p16 negativity. Further diagnostic workup, including panendoscopy and bilateral tonsillectomy, identified synchronous bilateral HPV-negative tonsillar squamous cell carcinoma. Following bilateral selective neck dissection, adjuvant radiotherapy with concomitant chemotherapy was administered. At follow-up, there were no signs of disease recurrence. Conclusion: A cystic neck mass in adults should be considered malignant until proven otherwise. A negative radiological finding does not exclude the presence of a primary tumor in the oropharynx. This case highlights the diagnostic value of panendoscopy with bilateral tonsillectomy in identifying occult primary tumors, particularly in the context of HPV-negative disease.

Keywords: cystic neck mass; cervical metastasis; panendoscopy; tonsillar squamous cell carcinoma; HPV-negative

INTRODUCTION

Neck masses in adult patients represent a common clinical problem and a significant diagnostic challenge in everyday otorhinolaryngology practice. Unlike the pediatric population, in which cystic neck lesions are most often congenital and benign, in adults any newly developed mass requires thorough and systematic diagnostic evaluation due to the real possibility of malignancy [1]. In this population, an initially benign interpretation of a lesion may lead to delayed diagnosis and postponement of appropriate oncological treatment.

Cystic lesions of the neck pose a particular diagnostic dilemma, as in the absence of local symptoms, inflammation, or infiltrative growth, they are often perceived as benign. However, in adult patients, a cystic morphology does not

exclude malignancy; on the contrary, it may represent a manifestation of metastatic disease.

Cystic cervical metastases are most commonly associated with HPV-positive oropharyngeal squamous cell carcinomas, particularly those of the tonsils and the base of the tongue [2]. This association has led in recent years to a widespread clinical assumption that a cystic metastatic structure implies HPV-positive etiology and potentially more favorable tumor biology. However, HPV-negative oropharyngeal carcinomas represent a biologically and clinically distinct entity, characterized by different risk factors, a more aggressive disease course, and a poorer prognosis [3]. Reports of cystic metastases originating from HPV-negative tumors are rare and largely derive from older literature, which continues to make them a diagnostic pitfall in contemporary clinical practice.

cističnim promenama vrata kod odraslih pacijenata.

PRIKAZ SLUČAJA

Pacijentkinja starosti 47 godina javila se na otorinolaringološki pregled zbog bezbolne promene u levoj parotidnoj regiji, koju je primetila nekoliko meseci ranije i koja je postepeno rasla, bez znakova inflamacije ili drugih lokalnih simptoma. Negirala je otorinolaringološke tegobe. Aktivni pušač duže od 20 godina, dok alkohol ne konzumira. U ličnoj anamnezi navodi depresiju, zbog koje je na terapiji antidepressivima. Nije bilo podataka o ranijem malignitetu. U porodičnoj anamnezi zabeležen je karcinom orofarinksa kod sestre pacijentkinje.

Kliničkim pregledom uočena je jasno ograničena, elastična, pokretna i bezbolna tumorska promena prečnika oko 3 cm u levoj parotidnoj regiji. Koža iznad promene bila je urednog izgleda. Ostali otorinolaringološki nalaz bio je uredan.

Ultrazvučnim pregledom vrata opisana je ovalna, dobro ograničena cistična promena bez suspektne vaskularizacije na kolor-dopler pregledu. MSCT vrata i sva tri sprata ždrele sa kontrastom pokazao je cističnu leziju lokalizovanu ispod donjeg pola leve parotidne žlezde, bez znakova infiltracije okolnih struktura i bez uvećanih cervikalnih limfnih čvorova. Na osnovu radioloških nalaza promena je inicijalno tumačena kao benigna.

S obzirom na nejasnu etiologiju i lokalizaciju lezije, maksilofacijalni hirurrg je indikovao hiruršku ekstirpaciju promene. Histopatološkom analizom utvrđeno je da se radi o limfnom čvoru sa cističnom metastazom planocelularnog karcinoma. Imunohistohemijski nalaz pokazao je pozitivnost na CK i p40, uz negativan p16 i CK7, kao i negativan EBER-ISH nalaz. Uočena je ekstrakapsularna ekstenzija metastaze.

Nakon dobijanja histopatološkog nalaza sprovedena je dalja dijagnostička obrada u cilju identifikacije primarnog tumora. Učinjena je panendoskopija gornjeg aerodigestivnog trakta sa ciljanim biopsijama, kao i obostrana tonzilektomija. Histopatološkom analizom oba tonzilarna preparata potvrđen je infiltrativni planocelularni karcinom, HPV-negativan (p16-), uz prisutnu limfovaskularnu invaziju i bez perineuralne invazije.

U daljem toku lečenja pacijentkinja je podvrgnuta obostranoj selektivnoj disekciji

vrata, pri čemu u odstranjenim limfnim čvorovima nije utvrđena rezidualnaneoplastična proliferacija. Slučaj je prikazan multidisciplinarnom konzilijumu za karcinome glave i vrata, nakon čega je indikovana postoperativna radioterapija uz hemioterapijskupotencijaciju. Sprovedena je radioterapija ukupne doze 64 Gy u 32 frakcije, uz dva ciklusa cisplatina (CDDP) u dozi od 100 mg/m².

Na kontrolnom pregledu nakon završenog lečenja lokalni i regionalni nalaz bio je bez znakova recidiva bolesti. Kao terapijsku komplikaciju pacijentkinja je razvila postterapijsku kserostomiju II gradusa. Indikovano je intenzivno onkološko praćenje u kraćim vremenskim intervalima.

DISKUSIJA

Prikazani slučaj ilustruje tipičan scenario u kome cistična morfologija i odsustvo simptoma dovode do benignog tumačenja nalaza. Poznato je da cistične mase vrata kod odraslih predstavljaju dijagnostičku zamku. Savremene smernice naglašavaju da se svaka perzistentna cervikalna masa kod odraslih mora smatrati malignom dok se ne dokaže suprotno, te da dijagnostički algoritam treba da bude sistematski i jasno sekvenciran, sa preferencijom aspiracione biopsije tankom iglom kao inicijalne metode, uz izbegavanje primarne otvorene biopsije limfnog čvora [1]. Iako je kod naše pacijentkinje otvorena biopsija predstavljala prvi dijagnostički korak, dalja obrada je sprovedena u skladu sa savremenim preporukama.

U kontekstu planocelularnog karcinoma nepoznatog primarnog porekla, orofarinks, a naročito palatinalnetonzile, predstavlja najčešće mesto okultnog primarnog tumora. Savremene serije pokazuju da se primarna lezija identifikuje u tonzili kod približno jedne četvrtine pacijenata nakon dijagnostičke tonzilektomije. Takođe, sistematske analize ukazuju da prevalenca sinhronog bilateralnog ili kontralateralnog tonzilarnog karcinoma može dostići oko 10% kod bolesnika sa karcinomom glave i vrata nepoznatog primarnog porekla, što dodatno opravdava rutinsku obostranu tonzilektomiju u dijagnostičkom algoritmu [4].

Značajno je istaći da unilateralna tonzilektomija može dovesti do propuštanja kontralateralnog ili sinhronog tumora. Literatura navodi da se kod određenog procenta pacijenata sa planocelularnim karcinomom nepoznatog

The aim of this paper is to highlight, through a case report, the importance of panendoscopy in the diagnosis of cervical metastases of unknown primary origin, as well as to emphasize the need for a structured and systematic approach to cystic neck lesions in adult patients.

CASE REPORT

A 47-year-old female patient presented for an otorhinolaryngology examination due to a painless mass in the left parotid region, which she had noticed several months earlier and which had gradually increased in size, without signs of inflammation or other local symptoms. She denied any ENT-related complaints. She had been an active smoker for more than 20 years, while she did not consume alcohol. Her past medical history was notable for depression, for which she was receiving antidepressant therapy. There was no history of prior malignancy. Family history revealed oropharyngeal carcinoma in the patient's sister.

Clinical examination revealed a well-defined, elastic, mobile, and painless tumor mass measuring approximately 3 cm in diameter in the left parotid region. The overlying skin appeared normal. The remainder of the otorhinolaryngological examination was unremarkable.

Ultrasound examination of the neck demonstrated an oval, well-circumscribed cystic lesion without suspicious vascularization on color Doppler imaging. Contrast-enhanced MSCT of the neck and all three levels of the pharynx showed a cystic lesion located below the lower pole of the left parotid gland, without signs of infiltration into surrounding structures and without enlarged cervical lymph nodes. Based on radiological findings, the lesion was initially interpreted as benign.

Given the unclear etiology and location of the lesion, a maxillofacial surgeon indicated surgical excision. Histopathological analysis revealed a lymph node with cystic metastasis of squamous cell carcinoma. Immunohistochemical findings showed positivity for CK and p40, with negative p16 and CK7, as well as a negative EBER-ISH result. Extracapsular extension of the metastasis was observed.

Following histopathological diagnosis, further diagnostic workup was performed to identify the primary tumor. Panendoscopy of the upper aerodigestive tract with targeted biopsies was carried out, along with bilateral tonsillectomy. Histopathological analysis of both tonsillar specimens confirmed infiltrative squamous cell carcinoma, HPV-negative (p16-), with lymphovascular invasion and no evidence of perineural invasion.

In the subsequent course of treatment, the patient underwent bilateral selective neck dissection, with no residual neoplastic proliferation identified in the removed lymph nodes. The case was presented at a multidisciplinary tumor board for head and neck cancers, after which postoperative radiotherapy with concurrent chemotherapy was indicated. Radiotherapy was administered to a total dose of 64 Gy in 32 fractions, along with two cycles of cisplatin (CDDP) at a dose of 100 mg/m².

At follow-up after completion of treatment, local and regional findings showed no evidence of disease recurrence. As a treatment-related complication, the patient developed grade II post-therapeutic xerostomia. Intensive oncological follow-up at shorter intervals was recommended.

DISCUSSION

The presented case illustrates a typical scenario in which cystic morphology and the absence of symptoms lead to an initial benign interpretation. It is well established that cystic neck masses in adults represent a diagnostic pitfall. Contemporary guidelines emphasize that any persistent cervical mass in an adult should be considered malignant until proven otherwise, and that the diagnostic algorithm must be systematic and clearly sequenced, with fine-needle aspiration biopsy as the preferred initial method, while avoiding primary open lymph node biopsy [1]. Although in our patient an open biopsy was the first diagnostic step, further evaluation was conducted in accordance with current recommendations.

In the context of squamous cell carcinoma of unknown primary origin, the oropharynx—particularly the palatine tonsils—represents the most common site of occult primary tumors.

primarnog porekla primarni tumor identifikuje isključivo nakon bilateralne tonzilektomije, dok se bilateralni tonzilarni karcinom, iako retka pojava, smatra klinički značajnim entitetom. U našem slučaju, sistematski pristup sa obostranom tonzilektomijom omogućio je detekciju sinhronog bilateralnog HPV-negativnog karcinoma tonzila, čime je potvrđena dijagnostička vrednost ovakvog algoritma. Ovi nalazi imaju neposredne kliničke implikacije i dodatno opravdavaju rutinsku bilateralnu tonzilektomiju u okviru panendoskopske obrade, čak i u situacijama kada slikovne metode ne ukazuju na jasno suspektu leziju [4,5].

Iako kontrastni MSCT vrata predstavlja standardnu inicijalnu dijagnostičku metodu u obradi cervikalnih metastaza, njegova senzitivnost za detekciju malih, submukoznih ili kriптиčnih HPV-vezanih orofaringealnih tumora ostaje ograničena. Umerena senzitivnost (oko 60–70%) uz relativno visoku specifičnost (80–90%) ukazuje da negativan radiološki nalaz ne isključuje postojanje primarnog tumora u orofarinksu [6]. Zbog toga savremeni dijagnostički algoritmi preporučuju multimodalni pristup koji obuhvata kombinaciju imidžing metoda, endoskopski pregled u opštoj anesteziji i selektivne hirurške procedure, uključujući bilateralnu tonzilektomiju i, po potrebi, lingvalnutonzilektomiju.

HPV-negativni orofaringealni karcinomi predstavljaju biološki različit entitet u odnosu na HPV-pozitivne tumore. Češće su povezani sa klasičnim faktorima rizika, pre svega dugotrajnom izloženošću duvanu i alkoholu, pokazuju izraženiju keratinizaciju, veću genetsku nestabilnost i u pravilu agresivniji klinički tok. Za razliku od HPV-pozitivnih tumora, kod kojih p16 imunohistohemija ima značajnu prognostičku i terapijsku vrednost, HPV-negativni karcinomi povezani su sa lošijom ukupnom i specifičnom stopom preživljavanja. U tom kontekstu, prikazani slučaj dobija dodatnu kliničku težinu, jer ukazuje da cistična metastaza može predstavljati prvu i jedinu manifestaciju biološki agresivnijeg, p16-negativnog tumora [7].

Prisustvo ekstrakapsularne ekstenzije u metastatskom limfnom čvoru predstavlja nepovoljan prognostički faktor i snažan argument za intenzivniji terapijski pristup. Zbog toga je pravovremena identifikacija primarnog tumora od presudnog značaja, jer omogućava adekvatno planiranje multimodalne terapije i precizno definisanje polja zračenja [6].

Zanimljiv nalaz u prikazanom slučaju predstavlja i podatak da sestra pacijentkinje boluje od istog tipa tumora, što potencijalno može ukazivati na postojanje genetske predispozicije. Iako se porodično javljanje karcinoma orofarinksa retko opisuje u literaturi, epidemiološki podaci ukazuju na izvestan porast rizika kod osoba sa pozitivnom porodičnom anamnezom. U multicentričnoj studiji *Garavello* i saradnika, porodična anamneza oralnog ili faringealnog karcinoma kod prvog stepena srodnika bila je povezana sa približno 2,6 puta većim rizikom za nastanak ovih tumora (OR 2,6; 95% CI 1,5–4,5) [8].

Nakon završenog lečenja, pacijenti sa orofaringealnim karcinomom zahtevaju intenzivan nadzor, naročito tokom prvih godina, kada je rizik od recidiva najveći. U kliničkoj praksi u našoj sredini kontrole se sprovode na 1–2 meseca tokom prve godine, na 2–3 meseca tokom druge godine, zatim na 4–6 meseci do pete godine, a nakon toga jednom godišnje. Ovakav režim praćenja omogućava pravovremeno otkrivanje lokalnog ili regionalnog recidiva, kao i kasnih komplikacija sprovedene terapije [9].

U tom kontekstu, prikazani slučaj objedinjuje više dijagnostičkih izazova – cističnu prezentaciju, HPV-negativnu biologiju i bilateralnost primarnog tumora – čime dodatno potvrđuje potrebu za sistematskim pristupom.

ZAKLJUČAK

Cistična masa vrata kod odrasle osobe mora se smatrati malignom dok se ne dokaže suprotno. Negativan radiološki nalaz ne isključuje postojanje primarnog tumora u orofarinksu, naročito utonzili.

Prikazani slučaj potvrđuje da cistična cervikalna metastaza može biti prva manifestacija HPV-negativnog planocelularnog karcinoma, uključujući i sinhroni bilateralni tonzilarni tumor.

Panendoskopija sa bilateralnom tonzilektomijom predstavlja ključni dijagnostički korak u sistematskoj obradi metastatskog planocelularnog karcinoma vrata nepoznatog primarnog porekla.

SAGLASNOST PACIJENTA

Dobijena je pisana saglasnost pacijentkinje za objavljivanje ovog prikaza slučaja.

Contemporary series show that the primary lesion is identified in the tonsil in approximately one quarter of patients following diagnostic tonsillectomy. Additionally, systematic analyses indicate that the prevalence of synchronous bilateral or contralateral tonsillar carcinoma may reach around 10% in patients with head and neck carcinoma of unknown primary origin, further justifying routine bilateral tonsillectomy within the diagnostic algorithm [4].

It is important to emphasize that unilateral tonsillectomy may result in missing a contralateral or synchronous tumor. The literature reports that in a subset of patients with squamous cell carcinoma of unknown primary origin, the primary tumor is identified exclusively after bilateral tonsillectomy. Although bilateral tonsillar carcinoma is rare, it represents a clinically significant entity. In our case, a systematic approach including bilateral tonsillectomy enabled the detection of synchronous bilateral HPV-negative tonsillar carcinoma, confirming the diagnostic value of such an approach. These findings have direct clinical implications and further support routine bilateral tonsillectomy as part of panendoscopic evaluation, even when imaging studies do not indicate a clearly suspicious lesion [4,5].

Although contrast-enhanced MSCT of the neck is a standard initial diagnostic modality in the evaluation of cervical metastases, its sensitivity for detecting small, submucosal, or cryptic HPV-related oropharyngeal tumors remains limited. Moderate sensitivity (approximately 60–70%) with relatively high specificity (80–90%) indicates that a negative radiological finding does not exclude the presence of a primary tumor in the oropharynx [6]. Therefore, modern diagnostic algorithms recommend a multimodal approach, including a combination of imaging techniques, endoscopic examination under general anesthesia, and selective surgical procedures such as bilateral tonsillectomy and, when indicated, lingual tonsillectomy.

HPV-negative oropharyngeal carcinomas represent a biologically distinct entity compared to HPV-positive tumors. They are more frequently associated with traditional risk factors, particularly long-term tobacco and alcohol exposure, exhibit more pronounced keratinization, greater genetic instability, and

generally a more aggressive clinical course. Unlike HPV-positive tumors, in which p16 immunohistochemistry has significant prognostic and therapeutic value, HPV-negative carcinomas are associated with poorer overall and disease-specific survival. In this context, the presented case gains additional clinical importance, as it demonstrates that a cystic metastasis may represent the first and only manifestation of a biologically more aggressive, p16-negative tumor [7].

The presence of extracapsular extension in a metastatic lymph node is an unfavorable prognostic factor and a strong indication for a more aggressive therapeutic approach. Therefore, timely identification of the primary tumor is crucial, as it allows for appropriate planning of multimodal therapy and precise delineation of radiation fields [6].

An interesting finding in this case is the fact that the patient's sister had the same type of tumor, which may suggest a potential genetic predisposition. Although familial occurrence of oropharyngeal carcinoma is rarely described in the literature, epidemiological data indicate an increased risk among individuals with a positive family history. In a multicenter study by Garavello et al., a family history of oral or pharyngeal carcinoma in first-degree relatives was associated with approximately a 2.6-fold increased risk of developing these tumors (OR 2.6; 95% CI 1.5–4.5) [8].

After completion of treatment, patients with oropharyngeal carcinoma require intensive follow-up, particularly during the first years when the risk of recurrence is highest. In clinical practice in our setting, follow-up examinations are performed every 1–2 months during the first year, every 2–3 months during the second year, then every 4–6 months up to the fifth year, and annually thereafter. This follow-up regimen allows for timely detection of local or regional recurrence, as well as late complications of treatment [9].

In this context, the presented case integrates several diagnostic challenges—cystic presentation, HPV-negative biology, and bilateral primary tumors—thereby further emphasizing the need for a structured and systematic diagnostic approach..

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CONCLUSION

A cystic neck mass in an adult should be considered malignant until proven otherwise. A negative radiological finding does not exclude the presence of a primary tumor in the oropharynx, particularly in the tonsil.

The presented case confirms that a cystic cervical metastasis may be the first manifestation of an HPV-negative squamous cell carcinoma, including a synchronous bilateral tonsillar tumor.

Panendoscopy with bilateral tonsillectomy represents a key diagnostic step in the systematic evaluation of metastatic squamous cell carcinoma of the neck with an unknown primary origin.

PATIENT CONSENT

Written informed consent was obtained from the patient for publication of this case report..

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