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Case Report

Neck Node Squamous Cell Metastasis from Unknown Primary and Mutagen Sensitivity: A Case Series

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Neck node metastasis · Unknown primary carcinoma · Mutagen sensitivity · HPV+ or cystic squamous cell cancer

Abstract
Most of the neck node metastases from cancer of unknown primary (CUP) are squamous cell carcinomas (SCCs). The majority of which are human papillomavirus (HPV)-related, frequently show cystic morphology referring to Waldeyer's ring origin. Here, we report four cases of neck node SCCs metastases from CUP. In our institute, 432 patients with head and neck (HN) SCC underwent pretreatment mutagen sensitivity (MS) assay between 1996 and 2006. Among them, 4 patients ≤50 years of age had metastatic cervical nodes from CUP. The primary treatment was cervical node dissection ± radiotherapy. All patients had elevated (>1.0 chromatid break/cell) MS. One male patient died of progressive neck metastasis within 3 years and the 3 female patients are still alive more than 15 years after initial treatment of HPV+ (two) or cystic (one) SCC. Two female patients developed second and third distant site metachronous primary cancers. HPV+ or cystic HNSCC from CUP with elevated MS indicates good outcome. Distant site metachronous cancers of different histologic origins cannot be explained by field cancerization. The clinical significance of elevated MS in neck node SCC metastasis from CUP requires further investigation.

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Introduction

Cancer of unknown primary (CUP) is a metastatic disease defined by the absence of a clinically identified primary malignancy at the time of diagnosis, despite appropriate diagnostic work-up. CUP is a relatively frequent cancer type causing incomparable difficulties in pathological diagnosis as compared to other tumor types [1]. The primary may even remain unknown at autopsy due to microscopic size or previous regression. Confirmed CUP accounts for 2–5% of all cancers. Most of the neck node metastases from CUP are squamous cell carcinomas (SCCs). The rate of head and neck (HN) cancers with unknown primary can be reduced to less than 3% after appropriate investigation [pan-endoscopy, computer tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)/CT examination [2]. The majority of neck lymph node SCC metastases in CUP originate from the HN site. A substantial number of primary tumors identified in squamous cell CUP (SCCUP) patients are found in the oropharynx and are human papillomavirus (HPV)-related, with HPV16 being the predominant high-risk subtype. The incidence of oropharyngeal SCC is increasing, due to the epidemic emergence of HPV-mediated oropharyngeal SCC. Besides tobacco and alcohol consumption, HPV is an accepted risk and prognostic factor for oropharyngeal SCC. In addition, patients with HPV-positive oropharyngeal SCC have a much better clinical response to therapy than patients with HPV-negative oropharyngeal SCC and other HN cancers, but site, stage, and smoking are also significant prognostic factors [3–5]. The predominant pathology in HPV-related SCCUP is the non-keratinizing SCC [6]. A non-keratinizing morphology of neck node metastasis of CUP suggests a tonsillar or base of the tongue localization. HPV-related metastatic carcinoma may correlate with the following morphologic characteristics: large size, cystic nature, and limited extracapsular extension [6]. Cystic neck node metastasis also predicts better outcomes [7].

It is well-known that only a fraction of all individuals exposed to environmental carcinogens (tobacco and alcohol) will develop HN cancer. Deficiencies in DNA (deoxyribonucleic acid) repair capacity are thought to be associated with the risk HN cancer in smoking and drinking patients [8]. SCC of the upper aerodigestive tract has a high propensity to develop second primary malignancy [9]. An explanation for this phenomenon was proposed by Slaughter, who gave the concept of “condemned mucosa” developing after chronic carcinogenic exposure [10]. It is an unresolved issue whether mutagen sensitivity (MS) has a causative role in the development of squamous cell neck node metastases from CUP with or without multiple distant site primary cancer.

Here, we report 4 cases of younger (≤50 years) adults with HN node-positive SCC from CUP who were involved in the MS assay before initial treatment. In our institute, 432 HN cancer patients with HNSCC underwent pretreatment MS assay between 1996 and 2006. The aim of MS assay measured by bleomycin test was among others to determine the MS of HNSCC patients, alcoholic patients, healthy nonsmokers and nondrinkers, and nondrinking smokers. MS was significantly elevated in HNSCC patients as compared with the healthy controls [11]. Among 432 patients with HNSCC four younger (≤50 years) patients were found with SCC of neck lymph nodes from CUP and 124 patients had primary HPV-negative HNSCC. MS was measured by determining the mean number of chromatid-breaks per peripheral lymphocyte after in vitro bleomycin exposure. The long-term results of patients with known primary cancers have been published recently [12]. The Eighth Edition of TNM system [13] was used to classify metastases of neck nodes of CUP patients. We review the literature based on our cases and discuss the challenging diagnostic and treatment aspects. The CARE Checklist has been completed by the authors for this case report and is included as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533708).

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Case Series

Patient 1

A 44-year-old female smoker patient presented with cystic mass measuring 5 cm on the right side of neck in 1999. The patient had a history of treatment for TisN0M0 urothelial cancer of urinary bladder. In 1997, she underwent transurethral excision and BCG installation at another hospital, but the details are unknown. She was subjected to ipsilateral upper node dissection. The largest size of SCC metastasis was 25 mm in the metastatic node. Hematoxylin and eosin stain described well differentiated squamous cell cancer without extracapsular tumor extension. Ten nodes were negative (T0pN1M0). MRI and panendoscopy examination did not find primary tumor. Pretreatment value of MS assay by bleomycin test was 1.17 b/c (break/cell). Observation was recommended. Five years later (2004), the neck node metastasis recurred. Four lymph nodes were dissected, and two of them had SCC metastasis. The size of the largest deposit was 20 mm with capsular invasion, but no extracapsular tumor extension was observed. Histopathologic examination showed SCC. Biopsies from the tonsils were negative. The patient underwent unilateral epi- and oropharyngeal and regional (upper neck nodes) radiotherapy (to 50 Gy, 25 fractions). In 2011, she underwent sigmoid polypectomy (pTisN0M0 adenocarcinoma). In 2021, molecular pathology examination of neck node metastasis (from a regional relapse in 2004) showed HPV16-genotype and p16 over expression by immunohistochemistry. She had distant site metachronous in situ cancers: urothelial cancer and sigmoid colon adenocarcinoma. In situ cancer does not give metastasis and her neck node metastasis was SCC both in 1999 and 2004. The patients are alive without relapse. The overall survival is 274 months.

Patient 2

A 43-year-old female smoker presented with enlarged (55 mm) right submandibular lymph node of the neck in 2000. An ipsilateral upper node dissection was performed and 1 out of 19 lymph nodes showed poorly differentiated non-keratinizing-cystic SCC (Fig. 1) metastasis without extracapsular extension (T0pN1M0), which may indicate tonsillar cancer, but histologic findings of tonsils biopsies were negative. Postoperative positron emission tomography/computer tomography (PET/CT) and panendoscopy did not show primary cancer. Postoperative radiotherapy was given (epi- and oropharynx and ipsilateral upper neck nodes to 50 Gy, 2 Gy fraction). The pretreatment value of the bleomycin test for MS was 1.04 b/c. She was subjected to right-side colon cancer surgery at another hospital on April 9, 2014: adenocarcinoma, pT3pN0M0. On September 3, 2014, she underwent left-side nephrectomy: clear cell cancer, pT1apN0M0. She developed abdominal lymph node metastasis from colon cancer in 2015 and was treated with chemotherapy. In 2019, hepatic and pulmonary metastases were diagnosed. In 2022, the retrospective molecular pathology of neck node metastasis showed no HPV16 DNA infection or p16 over expression. She is living with a progressive disease. The histology of her distant site metachronous invasive cancers was adenocarcinoma and clear cell kidney cancer but the neck node metastasis was SCC. The overall survival is 243 months.

Patient 3

A 34-year-old nonsmoking female patient presented with cervical lymph node enlargement in 2006. Both MRI and PET/CT showed bilateral suspect neck nodes and increased glucose metabolism was found in the base of the tongue by PET/CT. She underwent pretreatment MS examination. The bleomycin test value was 1.60 b/c. She underwent bilateral cervical lymph node dissection and excisional biopsy from base of the tongue. Fifty-two cervical lymph nodes were dissected and the histopathological examination revealed poorly

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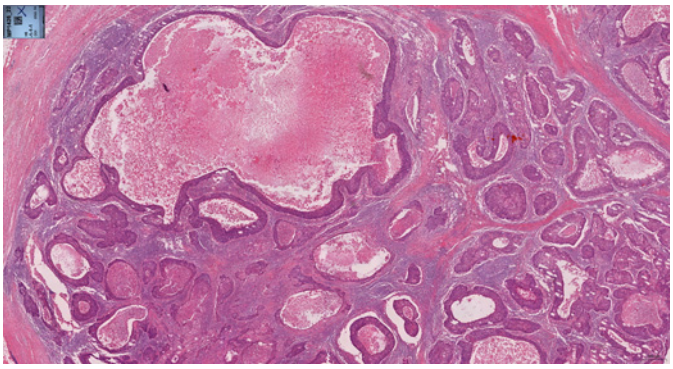

Fig. 1. Extensive cystic changes can be seen in tumor cell nests. Stained with hematoxylin and eosin.

differentiated SCC metastasis in five nodes (three on the right side and two on the left side) (Fig. 2a). The largest node size was 55 mm, and the largest metastasis was 30 mm. No extracapsular tumor extension was detected (T0pN2 M0). The biopsy specimen from the base of the tongue was free of cancer. The panendoscopic examination was also negative. No primary tumor was found. After surgery, radio-chemotherapy was given (Cisplatin 6 × 152 mg; 1.8 Gy/fraction, neck lymph nodes (bilateral) and hypopharynx to 55.8 Gy; epi- and oropharynx to 66.6 Gy). Molecular pathology was performed in 2020. Tumor cells were p16 positive and the presence of HPV16 was confirmed from tumor DNA (Fig. 2b). The patient was followed up as an outpatient and after 198 months, there was no evidence of recurrence.

Patient 4:

In 2001, a 50-year-old male smoker and alcoholic presented with bilateral fixed metastatic neck nodes (T0N3M0). Biopsy of a fixed node showed non-keratinized SCC. Panendoscopy examination did not find primary cancer. The pretreatment value of MS was 2.06 b/c. Radio-chemotherapy resulted in a partial response. He died of a progressive disease in 2003. Overall survival was 30 months. Molecular pathology was performed in 2022: no HPV DNA was detected and no p16 stain was seen in the squamous epithelium.

Discussion

Various methods are used to identify the primary cancer in neck node SCC metastasis of CUP. Aro et al. [14] emphasize the use of panendoscopy including tonsillectomy. Standardized diagnostic workup including PET/CT imaging, bilateral tonsillectomy followed by neck node dissection, and risk-factor adapted therapy improves survival of patients with neck node HPV-positive SCC metastasis from unknown primary malignancy [15]. The appropriate treatment for HNSCC patients with CUP has not been determined. Primary-specific therapy has to be consistent with that of an equivalent known primary tumor. Primary treatment generally consisted of neck node dissection and radio- or radio-chemotherapy. In operable cases, the 5-year overall survival is around 70% with neck nodes dissection followed by radiotherapy with or without chemotherapy. The majority (80%) of patients have HPV-positive cancer [16, 17]. Patients with HPV-positive tumors, particularly in CUP in the HN region, tend to have better clinical outcomes than those with HPV-negative tumors [18, 19]. In the Danish study [19] 60 cases were analyzed. Thirteen of them were HPV-positive and ten of this group had cystic morphology. It is noteworthy that only 1 patient was female but our 3 patients with HPV-positive or cystic histology were women. In the Danish study [19] HPV positivity was an

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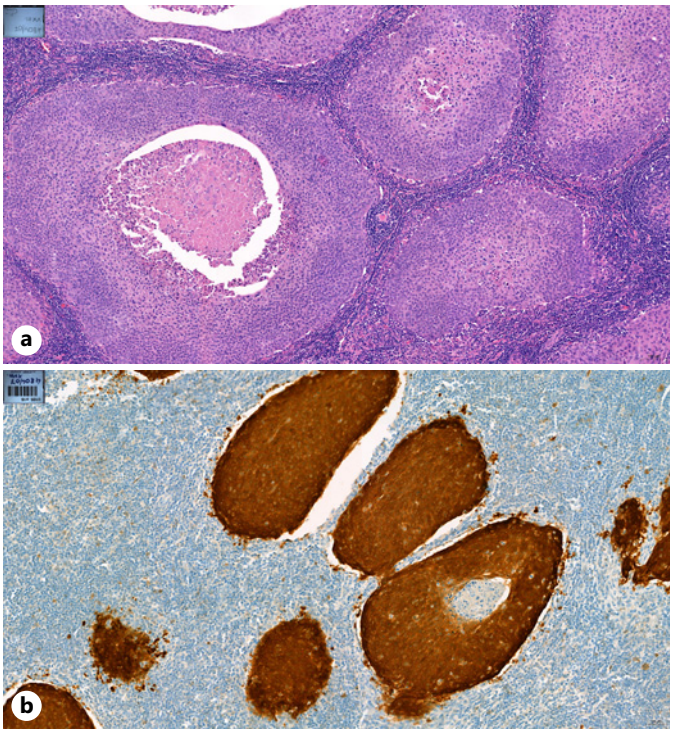

Fig. 2. a Lymph node metastasis of squamous cell carcinoma. Tumor cells show mainly basaloid morphology. Tumor cell nests show extensive central necrosis. Stained with hematoxylin and eosin. **b** Diffuse intensive p16 expression suggests HPV association. Immunohistochemistry for p16.

independent predictor of better overall and disease-free survival. The favorable outcome was related to the fact that the HPV-positive cancers responded better to treatment. It was suggested in the Danish study that the presence or absence of HPV/p16 should be determined early in the diagnostic work-up of CUP patients, as their status may influence treatment decisions. Two of our patients had HPV-positive SCC, but HPV infection was diagnosed more than 15 years after initial presentation. Rassy et al. [6] from the Institute Gustave Roussy emphasized that if a cervical metastasis is considered HPV-positive, the primary lesion is likely to be in the oropharynx, and further diagnostic interventions such as tonsillectomy seem to be mandatory. It remains a matter of debate whether the optimal treatment for extra-nodal extension or advanced lymph node stages is neck node dissection followed by adjuvant radiotherapy or concomitant radio-chemotherapy, or definitive radio-chemotherapy followed by neck node dissection (in the case of positive fluorodeoxyglucose F 18-PET/CT). The clinical significance of gen-expression profiling-based site-specific treatment for CUP patients is also under debate [20]. On the basis of our experience, we believe that neck node HPV-positive or cystic metastases from CUP can be effectively treated with standard multimodality treatment: neck node dissection + radiotherapy + platinum-based chemotherapy. In our patient with bilateral neck node metastasis, the PET/CT showed a suspect area in the base of the tongue but the biopsy did not find cancer. She was treated with bilateral radical neck node dissection followed by radio-chemotherapy and alive without relapse. Her primary cancer site has not been confirmed to date.

Investigation of MS would provide more detailed information on HPV-related cancer risks. The activation of DNA damage repair factors in HPV-positive oropharyngeal cancers has been studied recently. In the cervix, the activation of DNA damage repair pathways is critical for viral replication, but little is known about their role in oropharyngeal (OP) SCC.

HPV-related OPSCC exhibits increased activation of the ataxia telangiectasia mutated-dependent DNA-related pathway as compared to HPV-negative lesions or normal epithelia in marginal regions. The results suggest that members of these pathways may be important in HPV-induced disease in the oropharynx [21].

Several studies [22–24] have discussed the association between oropharyngeal HNSCC and cystic neck node metastasis. Most cases of cystic SCC metastasis in the upper neck nodes are associated with HPV-positive oropharyngeal primary cancer [23]. In the majority of CUP patients with cystic SCC lymph node metastasis of the HN region, occult primary cancers are localized in the oropharynx [24]. In our female patients, the biopsy of tonsils or base of the tongue did not show cancer. At the Pennsylvania State Medical Center, 20 cases of cystic neck node metastases were studied. Seventeen of these patients had primary tumors arising in the palatine or lingual tonsil. Three were "unknown primary" [23]. Lateral solitary cystic masses in adults often represent occult primary cancers arising from the epithelium within Waldeyer's ring. The poor histological differentiation and the absence of transitions from benign epithelium to malignant carcinoma in lymph node metastases are indicators for metastases of SCC of Waldeyer's ring origin rather than a primary branchiogenic carcinoma. The survival is good with cystic lymph node metastasis [7, 22]. Our patient with cystic morphology is alive more than 15 years after the initial presentation but has progressive distant metastases from a second primary (colon) cancer. The other 2 female patients with HPV-related cancer are still cancer-free.

SCC of the upper aerodigestive tract has high propensity to develop multiple primary malignancies. An explanation for this phenomenon was proposed by Slaughter, who gave the concept of a "condemned mucosa" developing after chronic carcinogenic exposure [10]. However, metachronous three primary malignancies of different histology and distant site origin (as in our 2 cases) cannot be explained by field cancerization. There may be a possible association with genetic and/or immunologic alterations. Vikesa et al. [25] from the University of Copenhagen found that CUP was characterized by chromosomal instability leading to DNA double-strand breaks. Tobacco use is an exogenous risk factor to develop HN cancer and urinary bladder or colon malignancy too. Due to variations in individual susceptibility, only a fraction of all individuals exposed to environmental carcinogens will develop cancer. Endogenous risk factors are also involved in the multifactorial genesis of HNSCC. Individual MS and DNA repair capacity are likely to be candidates affecting an individual's susceptibility to cancer [26, 27]. MS (intrinsic risk factor) plays a role in developing urothelial and colorectal cancers [28, 29]. In our patients with known primary cancer, the majority (19 of 20, 95%) of the metachronous SPC was located in the upper aerodigestive tract [12]. Two of our patients with CUP developed distant site primary cancers: bladder and colon or kidney and colon cancer. Our patient with in situ bladder and in situ colon cancer is living without relapse. The other patient is living with a progressive disease. Patients with HNSCC are at high risk of developing multiple cancers in the upper aerodigestive region, but distant site new primary cancer is a rare event [30, 31]. In our above-mentioned study [12] the number of hypersensitive or not hypersensitive patients was 65 (52.4%) and 59 (47.6%), respectively. In the present study, all patients had elevated MS (b/c > 1.0). The association between MS and CUP has not been previously studied.

Conclusion

We conclude that neck node SCC from CUP is characterized by elevated MS which indicates decreased DNA repair capacity. The clinical significance of MS in CUP requires further examination. HPV positivity or cystic morphology of neck node metastasis from CUP signifies good outcome and can be treated effectively with conventional site-specific therapy. HPV examination should be performed before treatment of CUP.

Statement of Ethics

This study protocol was reviewed and approved by ETT TUKEB (Medical Research Council), approval code: 19098/2016/EKU (0556/16), approval date: March 30, 2016. Ethics statement (study approval statement and a consent to publish statement): the patients has provided written informed consent to the publication of this case report and accompanying images. Written informed consent was obtained from the next of kin of the patients for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Bukovszky B. participated in the study design, analysis of clinical events, and drafting the manuscript. Fodor J. conceived the study, participated in its design and coordination, and helped draft the manuscript. Székely G. participated in the bleomycin assay. Tóth E. carried out the immunoassays and histology. Major T. contributed to drafting the manuscript. Oberna F. participated in the study design. Takácsi-Nagy Z. participated in the study design. Polgár C. participated in the study design and helped draft the manuscript. All authors contributed to the article and approved the submitted version.

Data Availability Statement

Clinical and treatment characteristics and ethics statements of the patients can be found in the database of the National Institute of Oncology Budapest, Hungary. The data that support the findings of this study are available through Dr. Botond Bukovszky or Dr. János Fodor.

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