Cancer Treatment Reviews 53 (2017) 1–9

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Tumour Review

Neck lymph node metastases from unknown primary

Alberto Daniele Arosio [a], Lorenzo Pignataro [b], Renato Maria Gaini [a], Werner Garavello [a,*]

[a] Department of Otorhinolaryngology, School of Medicine and Surgery, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy
[b] Department of Otorhinolaryngology, Department of Clinical Sciences and Community Health, University of Milan, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

ARTICLE INFO

Article history:
Received 27 September 2016
Received in revised form 23 November 2016
Accepted 29 November 2016

Keywords:
Metastatic cervical carcinoma from unknown primary
Diagnosis
Radiotherapy
Surgery

ABSTRACT

Metastatic cervical carcinoma from unknown primary is a metastatic disease in the lymph nodes of the neck without any evidence of a primary tumour after appropriate investigation. The condition is rare and definite evidence is lacking for both diagnosis and treatment. In this review of the literature, we tried to draw some clinical indications based on the few available studies. We ultimately came to the following conclusions: (1) a thorough and accurate diagnostic work-up should be systematically offered. It includes accurate inspection with fibroscopy, CT or MRI, fine needle aspiration, panendoscopy and positron emission tomography, (2) Patients with low-volume neck disease, N1 and N2a stage and without extracapsular extension on histopathological examination should receive single modality treatment. Radiotherapy and surgery may be similarly effective but, if possible, surgery (excisional biopsy, neck dissection and tonsillectomy) should be favoured because it consents a more precise staging, (3) patients with more advanced conditions require combined treatment in the form of either resection followed by adjuvant radiation (±chemotherapy) or primary chemoradiation (±post-therapy neck dissection).

Introduction

Metastatic cervical carcinoma from unknown primary (MCCUP) is defined as metastatic disease in the lymph nodes of the neck without any evidence of a primary tumour after appropriate investigation [1–3]. The reasons for the failure in the diagnosis of the primary tumour are not fully known, but may include the small size of the primary tumour, the fact that the primary site is difficult to access by diagnostic tests, as well as the slow rate of growth or possible involution of the cancer itself once its cells have migrated into the lymphatic system and/or blood [2,4,5].

MCCUP accounts for 1–4% of all head and neck tumours [6]. In a Danish national study published in 2000, the annual incidence of MCCUP was 0.34 cases per 100,000 population [6], and this rate has remained stable ever since [2,7]. In the same period, the number of new head and neck cancers has increased, suggesting that the proportion of CUP cases has diminished [7]. In the case of a neck lymph node metastasis, squamous cell histology is the most common type, accounting for 75–90% of cases, followed by undifferentiated carcinoma and adenocarcinoma [8,9].

Since 2003 cancers of unknown primary in general have been classified by Pavlidis et al. [10] in two different prognostic categories, favourable and unfavourable subsets. While unfavourable subsets have a poor prognosis in spite of aggressive treatment, with a median survival being around six months [11], MCCUP represents a favourable prognosis subset [8]. This good clinical profile was also highlighted in the last ESMO guidelines on CUP [12] in consideration of recent prognostic algorithms developed by Culine et al. [13] and Petrakis et al. [14]. In addition, the survival of patients with MCCUP has improved if compared to historical controls and this is believed to be related to two important factors: the increasing prevalence of human papilloma virus (HPV)-related cancers, which have demonstrated to have a better prognosis than the alcohol- and tobacco- related head and neck cancers [15] and the substantial improvements in treatment delivery [16].

The purpose of this paper is to realize a review of the published literature to provide up to date information about MCCUPs, as their management is challenging for the clinician as regards both diagnosis and treatment.

Diagnosis

The main goals of the diagnostic evaluation of a patient with MCCUP are to determine the histology of the metastasis and the location of the primary: these two objectives are interdependent,

* Corresponding author at: Department of Otorhinolaryngology, San Gerardo Hospital, University of Milano-Bicocca, Via Pergolesi, 33, 20052 Monza (MI), Italy. Fax: +39 039 324017.
E-mail address: werner.garavello@unimib.it (W. Garavello).

http://dx.doi.org/10.1016/j.ctrv.2016.11.014
0305-7372/

they are pursued in most cases simultaneously and both of them can influence treatment plan.

Clinical presentation

The typical patient with MCCUP has historically been described as male (about 80% of cases), aged between 55 and 65 years, with a smoking and alcohol history [2,6,8,17,18]. This pattern is currently changing due to a rising number of patients suffering from oropharyngeal cancer related to HPV [19].

The symptom that generally leads the patient to the physician is the appearance of a painless cervical mass, not responsive to antibiotic therapy [2,8,17]. This situation applies to 94% of patients of the series reported by Grau et al. [6], while pain and weight loss were reported in only 9% and in 7% of cases respectively.

In the initial diagnostic work-up, attention should be paid to any symptom that may direct to the diagnosis of a possible primary site [2]: nasal obstruction, otitis media or epistaxis can point to a nasopharyngeal tumour, though dysarthria, dysphagia or odynophagia may suggest an oropharyngeal tumour. Moreover, dysphonia might indicate a laryngeal primary, whereas otalgia with normal otoscopic examination may focus the attention towards tonsils, base of the tongue, supraglottic area or hypopharynx as possible primary sites.

A complete and careful ear nose and throat examination is warranted. This includes the accurate inspection and palpation of the oral cavity, including tonsils and tongue base. In submucosal cancers, a useful tip for clinical detection of the primary site is to re-examine the patient looking for bleeding after the initial palpation of the tonsil and tongue base, and retraction of the tonsillar pillars [17]. It is also important to perform a thorough cutaneous examination of the head and neck region for both undiagnosed tumours and scars associated with previous treatment of cutaneous lesions. Flexible endoscopy should be performed to inspect the nasopharynx, oropharynx, hypopharynx and larynx [2]. The characteristics of the neck metastases are crucial in the evaluation of these patients. The special features of the lymphatic drainage of the head and neck region in the cervical area make the location of the neck mass suggestive for a potential primary tumour site (Table 1). Typically the neck mass appears in level II, followed by level III, with bilateral involvement reported in less than 10–20% of the cases [17,20–22].

Bilateral metastases should focus attention on the nasopharynx, base of tongue, hypopharynx and midline structures. The involvement of both the upper and the lower nodes should prompt the physician to assess the patient for distant metastases which are far more frequent in these patients compared to the patients with involvement of just the upper nodes [2,17].

Table 1
Most likely primitive sites in relation to the neck levels involved by the metastatic disease.

Level	Anatomic Site	Draining Source
IA	Submental triangle	Lips, chin, nasal tip, incisors/canines
IB	Submandibular triangle	Cheek, premolar and molar teeth, anterior tongue
IIA	Base of skull to upper border of hyoid bone: anterior to SAN	Oropharynx, anterior and posterior tongue
IIB	Base of skull to upper border of hyoid bone: posterior to SAN	Oropharynx, parotid
III	Upper border of hyoid bone to upper border of cricoids	Oropharynx, larynx
IV	Upper border of cricoids to upper border of clavicle	Oropharynx, larynx, upper thorax
VA	Posterior triangle: anterior to SAN	Occiput and scalp
VB	Posterior triangle: distal to SAN	Occiput and scalp
VI	Lower borer of hyoid to suprasternal notch. Lateral border is common carotid artery	Thyroid gland, larynx, piriform sinus, esophagus

Abbreviation: SAN, spinal accessory nerve.
Adapted from Robbins, Shaha AR, Medina JE, et al. Consensus statement on the classification and terminology of neck dissection. Arch Otolaryngol Head Neck Surg 2008; 134(5):536–8.

Imaging

Diagnostic imaging is performed to identify primary cancer and to assess the extent of cervical lymph node metastases. Imaging should be performed before any invasive procedure in order to avoid false-positive results or other misinterpretation due to trauma of the tissues, and to guide tissue biopsies [17].

Classic imaging studies in the workup of MCCUP are *Computed Tomography (CT)* and *Magnetic Resonance Imaging (MRI)*, whereas other examinations can be obtained when the primary tumour is suspected to be located outside the head and neck region. CT from skull base to the clavicle can assess the extent and location of cervical disease, its relationship to other cervical structures, the presence of extracapsular extension (ECE), the status of the retropharyngeal nodes and contralateral neck. MRI instead has a superior soft tissue resolution, particularly for the evaluation of nasopharynx and oropharynx [9,17]. Performances of these two diagnostic tests in identifying a primary tumour range between 9 and 23% [23–25], rising to 60% when suspicious radiologic findings lead to subsequent endoscopic biopsies [5]. When reviewing a radiologic image of the cervical region in a patient with MCCUP it is also important to evaluate the nature of the neck mass, because a cystic appearance has been strongly associated with HPV as etiologic factor and with oropharynx as probable primary site [26,27].

Positron emission tomography (PET) and the PET/CT fusion-imaging technique can help identify small primaries not appreciated by anatomic imaging or physical examination [28]. Several studies evaluated the utility of PET/TC in the detection of the occult primary tumour [23,24,29,30]. Kwee and Kwee [31] realized a meta-analysis of studies published between 2005 and 2007 and reported a detection rate of the primary tumour by combined PET/CT ranging from 27% to 57%, with sensitivity and specificity of 84% and a false-positive rate for oropharyngeal and lung primaries of 15%. By analyzing other 8 studies from 2000 to 2009 with a total of 180 patients, Al-Ibraheem et al. [32] reported a 28% detection rate of primary tumours with a 37% false-positive scans. Other studies report a detection rate ranging from 27 to 68% [33–35]. As regards the comparison between PET and PET/CT, there is evidence about the superiority of the latter [25,33], but this aspect remains controversial [34]. However, when attempting to assess the added value of PET (with or without CT), one must be aware of several limitations of the available studies [36]. Moreover, PET scanning is known to have high rate of false-positive and false-negative cases, limited availability, costs, exposure to radiation and burden to the patient [36]. Despite these limitations, MCCUP is considered one of the most solid indication for the execution of PET(/CT): it may help guiding the biopsy, determine the extent of disease, facilitate the planning of radiation therapy and help with surveillance [37]. Current Guidelines from the National Comprehensive Cancer Network (NCCN) recommend the execution of PET in patients suspected for an unknown primary cancer [3].

Pathology

Fine-needle aspiration (FNA) of the presenting lymph node is the preferred method for obtaining a tissue diagnosis [2,17,38]. It