CASE REPORT

Cervical Carcinoma of Unknown Primary Site

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Abstract

Cervical carcinoma of unknown primary site is a condition characterized by the presence of a metastatic lymph node neck mass in the absence of the primary tumor, despite extensive diagnostic procedures. This condition affects more often male patients with a history of tobacco and alcohol abuse or human papilloma virus (HPV) or Epstein-Barr virus (EBV) chronic infection. The detection of the primary tumor and identification of the histopathological type have a key role in the management of patients with unknown primary tumors. Treatment is multimodal, including surgery, radiotherapy and chemotherapy.

Keywords: *cervical carcinoma, head and neck cancer, unknown primary site, cervical metastasis*.

Introduction

Carcinoma of unknown primary site (CUP) is a type of cancer where the primary tumor cannot be detected despite extensive diagnostic procedures and follow-up [1]. Head and neck cancer of unknown primary site (HNCCUP) represents approximately 5-10% of all the cases with carcinoma from occult primary site and 2-5% of all head and neck malignancies [2]. The most frequent histological type is squamous cell carcinoma (SCC) followed by adenocarcinoma, undifferentiated carcinoma and melanoma [2,3]. HNCCUP affects more often male patients with a history of addiction to tobacco and alcohol, although a proportion of the cases may include non-smokers with high-risk types of human papilloma virus (HPV) chronic infection of the oropharynx [4,5]. The diagnostic procedures should be aimed at establishing the histopathological type of the cervical tumoral mass and detecting the primary site [1].

The pathogenesis of CUP is a multi-step process that involves molecular pathways like oncogene over-expression, angiogenesis activation, evasion of apoptosis and immune destruction, gene mutations, tissue invasion and widespread dissemination through circulation, which are not yet fully understood [5,6]. The most common genetic mutation involves the TP53 tumor suppressor gene [5]. The diagnostic approaches aim at establishing the histopathological type of the cervical tumoral mass and detecting the primary site [7]. The diagnostic protocol must include a pan endoscopy of the upper aerodigestive tract, with directed biopsies and bilateral tonsillectomy and PET-CT examination [7-10].

Information regarding the consumption of alcohol and tobacco, history of previous radiation, occupational hazards, facial or

cervical skin lesion that had disappeared and symptoms related to the aero-digestive upper tract can guide the diagnosis [7,8].

Usually, the typical clinical presentation is a painless unilateral cervical mass which has been present for weeks to months [8]. The location of the cervical lymphadenopathy can suggest the possible primary tumor site [9]. Usually, the involvement of the I-II levels indicates the primary tumor to be in the oral cavity, a mass at the levels II-III suggests that the primary tumor is in the oropharynx and the supraglottic region, whereas affliction of the IV-V levels indicates a lower neck tumor [1,9]. The examination of the node should determine its site, size, mobility, fixation and relationship with other relevant structures of the neck [7]. Both flexible or rigid pan endoscopy of the upper aero-digestive tract must be conducted in order to thoroughly inspect the nasal cavities, nasopharynx, oropharynx, hypopharynx and the glottis [8]. Endoscopy can also allow biopsies to be performed from clinically or imaging suspicious areas, as well as blind biopsies from high-risk anatomical sites such as the base of the tongue, nasopharynx, pyriform sinuses and postcricoid area [8-11]. Bilateral tonsillectomy is recommended because it is estimated that 18-40% of the patients with HNCCUP have the origin of the primary tumor in the tonsils, also there is a 10% rate of contralateral spread from tonsil lesions [7,12].

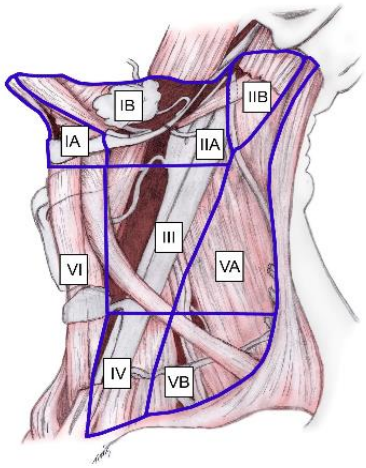

Figure 1. Lymph nodes of the neck [13].

The imaging techniques include ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT) [1]. It is recommended that imaging should be performed before any decision regarding the treatment [9]. Ultrasonography of the neck can identify the particularities of the neck tumor and can also guide a fine-needle aspiration biopsy (FNAB) [3]. CT, MRI and contrast-enhanced CT of the neck are examinations that can determine the location of the adenopathy and its connection to the adjacent structures, the presence of contralateral ganglia and the detection of the primary site [1,9]. For lymph nodes situated in levels IV or V, a thoracic, abdominal and pelvic CT is required [1]. The MRI is recommended for a greater precision in the evaluation of the soft tissue extension, especially in the involvement of oropharynx and nasopharynx [9]. PET-CT is recommended when standard radiological techniques did not achieve a conclusive result [1] and it should be performed before any invasive procedure, to reduce the false positive results and to achieve a guided biopsy from the suspected sites [7]. It has a sensitivity ranging from 63% to 100% and a specificity of 90-94% [7].

The cervical lymph node biopsy can be acquired through fine needle aspiration biopsy (FNAB), incisional or excisional biopsy or neck dissection [2]. FNAB is the most minimally invasive and cost-effective method [9] and has a very low risk of spreading the tumoral cells along the needle's pathway [1]. It is used to obtain a cytologic diagnosis and repetitive non-diagnostic histology require an open surgery biopsy and possible neck dissection [7,9].

Immunohistochemistry can identify the origin of the tissue using epithelial, melanocytic and lymphoid markers, opening the way for new means of therapy [1].

Regarding the neoplasms of the head and neck, Epstein-Barr virus (EBV) is associated with nasopharyngeal carcinoma [9] while

HPV-positive HNCCUP patients have an oropharyngeal origin [14]. Thus, the detection through polymerase-chain reaction (PCR) of HPV and EBV DNA in a metastatic cervical lymph node in HNCCUP patients should be performed, as it can guide further diagnostic procedures and treatment options [1].

The therapeutic options include surgery, radiotherapy and chemotherapy, depending on the patient's age, performance status, local extension, the site of the lymph node metastases and its histology [1, 12]. Surgery consists of unilateral or bilateral selective neck dissection or modified radical neck dissection and it is recommended in cases of N1 disease whereas in patients with N2-N3 disease surgery should be followed by radiotherapy [2,7]. Regarding the irradiation volume and area, studies had shown that bilateral neck postoperative radiation had significantly increased the loco-regional control in HNCCUP patients [8,15]. Also, a modern strategy when treating HNCCUP could be irradiation of selected sites such as the base of the tongue in HPV-positive non-smokers patients [1].

Chemotherapy is reserved for patients with advanced stages of the disease (e.g., extracapsular extension) to improve loco-regional control and reduce the risk of distant spreading [1,2].

Case report

We report the case of a 35-year-old female who presented to our ENT Clinic complaining of a left neck mass reportedly in evolution for five months. The patient's medical history and family history were unremarkable, with no evidence of malignant diseases. Clinical and ultrasonography examination revealed a painless cystic mass with a diameter of 4 cm in the left superior one third of the neck, covered by normal tegument and surrounded by multiple smaller satellite adenopathies. Fibroscopy of the upper aero-digestive tract did not reveal anything suspicious. Routine blood tests were normal. The neck CT scan was unspecific regarding the primary site of the cervical mass. Left selective neck dissection was performed and both the histopathological examination and immunohistochemistry determined the diagnosis of squamous cell carcinoma metastasis with unknown primary site. The patient refused both the blind biopsies from high-risk anatomical sites and the radiotherapy treatment. After one year, the patients returned to our clinic presenting a right cervical mass in evolution for four months.

The PET-CT examination showed a hypermetabolic area of the bilateral nasolabial folds, bilateral tonsils and a right cervical mass. Right selective neck dissection, bilateral tonsillectomy and biopsies from the base of the tongue, nasopharynx and pyriform sinuses were performed. The patient underwent radiation therapy and after one year is disease-free.

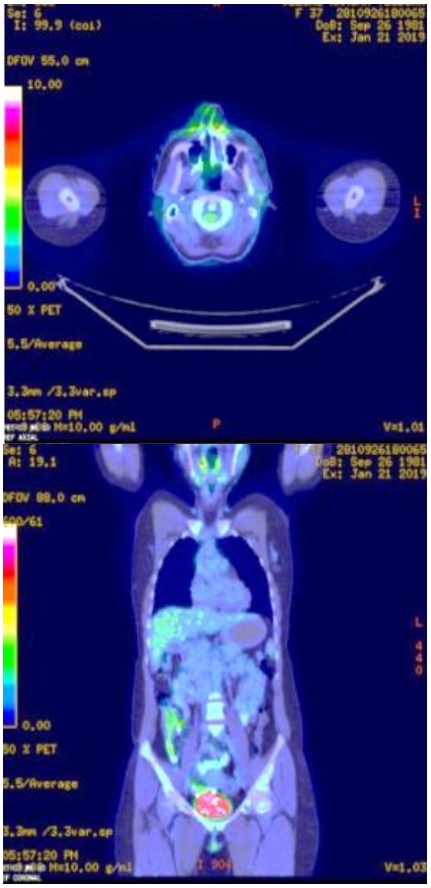

Figure 2. PET-CT scan of the patient showing hypermetabolic area of the bilateral nasolabial folds and bilateral tonsils

Discussion

The diagnosis is based on clinical examination, endoscopic assessment, imaging based on CT or MRI and PET-CT, FNAB or excisional biopsy. Both the diagnostic protocol and treatment modalities of HNCCUP should be standardized to provide clear recommendations regarding the effectiveness of the procedures and therapy [12].

Conclusions

The management of patients with HNCCUP requires a multidisciplinary approach [9]. The treatment of cervical cancer of unknown primary site is still a challenge and the optimal diagnostic and therapeutic approach has not yet been established [1].

Author Contributions:

AM.I-L. conceived the original draft preparation. A.M. and A.A. were responsible for conception and design of the review. AM.I-L., G.G., and VA.I. were responsible for the data acquisition. A.M., and A.A. were responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. AM.I-L., A.M., and A.A. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

Compliance with Ethics Requirements: "*The authors declare no conflict of interest regarding this article".*

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