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Case Report

Multiple Synchronous Squamous Cell Cancers of the Skin and Esophagus: Differential Management of Primary Versus Secondary Tumor

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ARTICLE INFO

Article history:

Received: 16 November, 2020

Accepted: 1 December, 2020

Published: 15 December, 2020

Keywords:

Double primary tumor

second primary tumor

multiple primary tumor

esophageal cancer

skin cancer

squamous cell cancer

ABSTRACT

Multiple primary tumors are uncommon in patients with squamous cell esophageal cancer. Conventional imaging methods have limitations in detecting those tumors. Although 18-F-fluoro-deoxyglucose-positron emission tomography scanner increases the detection of multiple synchronous tumors in patients with other malignancies, its contribution in patients with squamous cell esophageal cancer has not been assessed as it is not systematically performed. The detection of synchronous skin squamous cell tumors in patients with squamous cell esophageal cancer presents a challenge for making diagnostic and therapeutic decisions. A metastatic tumor leads to palliative management, whereas the diagnosis of a primary skin tumor requires curative treatment of both squamous cell tumors. Pathological evaluation appears crucial in the decision.

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Introduction

In case of patients unfit for surgery (due to co-morbidities) the Tokio Multiple primary tumors (MPT) are present in 5-10% of patients with squamous cell esophageal cancer (SCEC) [1-3]. This association is attributed to the presence of "cancerization fields", in which the exposure of the regional epithelium to common carcinogenic agents leads to the development of multiple cancers [4]. A significant proportion of these lesions are already present at the time of cancer index diagnosis [2]. The most frequent locations of these second primary cancers are head/neck, lung, and stomach [5]. In the literature, there are few reports of skin involvement in patients with SCEC, with an incidence of < 1% [6]. Conventional imaging methods, such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), have limitations in detecting multiple primary tumors [7]. Nowadays, 18-F-fluoro-deoxyglucose-positron emission tomography scanner (¹⁸F-FDG-PET-SCAN) is a widely used diagnostic method for the evaluation of different types of neoplasms, including esophageal cancer. Although ¹⁸F-

FDG-PET increases the detection of multiple synchronous primary tumors in patients with other malignancies, its possible contribution in patients with SCEC has not been evaluated so far.

In this report, the clinical case of a patient with double primary esophageal and cutaneous squamous cell carcinomas is discussed in order to establish the potential relationship between the carcinomas and define the appropriate diagnostic and therapeutic strategies for both primary tumors.

Case Presentation

In June 2020, a 66-year-old female presented to Strasbourg University Hospital with a month-old mild dysphagia. Esophagogastroduodenoscopy (EGD) revealed one tumor in the middle and lower thirds of the esophagus. The biopsy concluded to a poorly differentiated squamous cell carcinoma (SCC). Endoscopic ultrasound and thoraco-abdominopelvic CT-scan identified a non-stenosing

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usT3N+ tumor of the middle and lower third of the esophagus. The nasolaryngeal-bronchoscopy showed no alterations. The ^{18}F -FDG-PET-SCAN showed, in addition to hypermetabolic signs of the locally advanced primary esophageal tumor, an intensely hypermetabolic subcutaneous occipital nodular thickening suggestive of metastatic disease. Excisional biopsy of this lesion concluded to a moderately differentiated squamous cell carcinoma.

An exhaustive comparative analysis by the next-generation sequencing (NGS) Solid Tumor Panel was not contributory in differentiating primary or metastatic origin of the skin tumor. The differential diagnosis was established using the histological criteria that showed continuity between the carcinomatous proliferation and the epidermal surface lining which, at the edge of the lesion, presented a squamous carcinoma *in situ* component.

A double primary tumor of skin and esophagus was concluded, and resection was indicated with oncological margins of the primary skin lesion and the neoadjuvant radio-chemotherapy with the surgical intention for the esophageal carcinoma.

Discussion

Esophageal cancer is the eighth most common type of cancer worldwide and constitutes the sixth leading cause of cancer deaths [8]. Each year, this disease causes an estimated 570,000 new cases and more than 500,000 deaths worldwide [9]. This disproportionately high mortality rate is due to the diagnosis being usually made late when the disease is already locally advanced or metastatic [10]. Although in recent decades an increase in the incidence of esophageal adenocarcinoma has been observed in Western countries, squamous cell cancer remains the most common histological type with an incidence of around 90% [11].

The diagnosis of esophageal cancer is based on an endoscopic biopsy and classifying its histology according to the World Health Organization (WHO) criteria [12]. The stage is identified according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM staging system [13]. Staging should include a complete clinical examination and a computed tomography (CT) scan of the neck, chest, and abdomen. In candidates for surgical resection, endoscopic ultrasound (EUS) should be carried out to evaluate the T and N tumor categories. In order to exclude a synchronous second cancer in the aerodigestive tract, a tracheo-bronchoscopy should be carried out as well as a meticulous assessment of the oral cavity, oropharynx, and hypopharynx [14]. Decisions on treatment approach should be taken based on clinical staging, and multidisciplinary treatment planning is mandatory.

As mentioned above, the incidence of synchronous MPT in patients with SCEC is around 5%-10% [1-3]. Head and neck, and lung cancers are the most common locations (40.9%), followed by gastric cancer (18.2%), pancreatic cancer (13.6%), colon cancer (9%), and hepatocellular cancer (4.5%) [15]. Although very uncommon, the association of MPT affecting the skin and esophagus has already been described and could be the reflection of shared etiological factors or the result of increased surveillance due to the cancer index [16, 17].

MPT is defined according to the Warren and Gates criteria:

- i. The tumors must be clearly malignant on histological examination,
- ii. The tumors must be separated by normal mucosa, and
- iii. The possibility that the second tumor represents a metastasis must be excluded [18].

Because the immunohistochemical profile of SCEC is similar to that of its skin counterpart (CK7-, CD20, CK5/6+, CK10+ and CK14+), the distinction between primary and metastatic cutaneous lesions of squamous cell carcinoma is at present still mainly based on histological architecture [19]. In cutaneous metastases, atypical cells are observed histologically within the dermis and subcutaneous fat without attachment to the overlying squamous epithelium, whereas in primary lesions, the continuity between the tumor and the normal epithelium is preserved [20].

Up to 20% of MPT in SCEC patients are undetectable through conventional imaging methods [15]. In this context, ^{18}F -FDG-PET has proven to be helpful to identify otherwise undetected MPT [21]. Currently, ^{18}F -FDG-PET is not only a standard method for staging and planning multimodal therapy for esophageal cancer, but also useful for detecting MPT with a sensitivity of 91% and a positive predictive value of 69% [22]. Therefore, ^{18}F -FDG-PET should be carried out in patients with SCEC who are candidates for surgery in order to rule out any operative contraindications, avoid missing an indication for neoadjuvant treatment, and/or clarify doubts about a secondary lesion on the CT scan [23]. This test should also be performed in patients with planned radiation therapy to assist in radiation target volume delineation [24].

The detection of MPT in patients with SCEC presents a challenge for making therapeutic decisions. Treatment plans for both the index cancer and the second primary tumor may require to be adapted or modified. Previously, based on the consideration that second tumors are directly related to the first one and influenced by its prognosis, it was accepted that patients with SCEC and MPT were candidates only for palliative therapy [25]. Nevertheless, since the opportunities for survival for each MPT appear to be independent and have increased considerably due to recent advances in multimodal therapies, this approach may not be the most appropriate. As a result of advances in the treatment of esophageal and skin cancers, it is now possible to make decisions with curative intent for each separately. A better understanding of the behaviour and interactions between SCEC and MPT may result in earlier detection of second primary cancers and improve therapeutic outcomes.

Conclusion

Although multiple primary tumors are still very uncommon, recent diagnostic advances along with the increased survival of oncological patients have made their presentation increasingly frequent. The distinction between second tumors and eventual metastatic disease can be challenging. Similarly, making therapeutic decisions can be difficult. However, due to the increasing number of curative therapeutic options available, it is recommended that all diagnostic efforts be made to offer patients treatments tailored to their particular conditions. An individualized therapeutic plan decided after a multidisciplinary analysis can positively influence the quality of life and prognosis of patients with synchronous multiple primary tumors.

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