Unusual relationship between skin lesions and esophageal cancer: a case report and review of literature

Ungewöhnliche Beziehung zwischen Hautläsionen und Ösophaguskarzinom: ein Fallbericht und eine Literaturübersicht

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Schlüsselwörter
- Ösophagus
- Krebs
- Barrett-Ösophagus
- Hautmetastasen
- oberen Magen-Darm-Tumoren
- Fallbericht und Literatur

Key words
- esophagus
- cancer
- Barrett's esophagus
- skin metastases
- uper GI tract
- case report and literature review

Zusammenfassung

Ösophaguskarzinome stellen eine seltene Tumorentität dar. In Spanien ist das Ösophaguskarzinom der dritthäufigste Tumor des Magen-Darm-Traktes nach Kolon- und Magenkarzinomen. Adenokarzinome der Speisenröhre metastasieren mit einer Wahrscheinlichkeit von 1 % in die Haut (v. a. Nacken, Hals und Abdomen). Meistens treten die Hautmetastasen in der Nähe des Primärtumors auf. Manifestationen in entfernteren Bereichen sind ebenfalls beschrieben, wobei die Kopfhaut am häufigsten betroffen ist. Die Pathogenese des Ösophaguskarzinoms ist bis dato nicht gut verstanden. Genetische Veränderungen in Tumor-Suppressor-Genen bzw. die Beteiligung von Onkogen (z. B. c-erbB-2) sind nachgewiesen. Adenokarzinome des Ösophgus exprimieren Cytokeratin 20 und 7. Hautmetastasen solider Tumoren manifestieren sich typischerweise als symptomlose Knoten in der Nähe des Primärtumors, die spontan auch schmerzhaft sein können. Die Gastroskopie mit Biopsie stellt das Verfahren der Wahl zur Sicherung eines Ösophaguskarzinoms dar. Die Weiterentwicklung chirurgischer Techniken und die Entdeckung neuer zytotoxischer Medikamente hat zu einer deutlichen Senkung der lokoregionären Rezidivrate geführt, sodass heutzutage ein Rezidiv des fortgeschrittenen Adenokarzinoms durch eine hämatogene Streuung bedingt ist. Die Exzision der Hautläsionen führt zur Schmerzlinderung. Patienten mit Ösophaguskarzinomen mit gutem Ansprechen nach Chemotherapie, Bestrahlung und Operation haben eine lange Remissionszeit. Aus diesem Grund sollten Hautärzte bei der amulanten Untersuchung von Patienten mit neu aufgetretenen Hautläsionen differenzialdiagnostisch an die Möglichkeit von Hautmetastasen denken.

Abstract

Esophageal cancer is a rare disease. In Spain, this tumor is the third most common gastrointestinal malignancy after colorectal and gastric cancer. Esophageal adenocarcinoma metastasizes to the skin with an incidence of 1 %, generally located in the neck, head and abdomen. It usually occurs in the overlying skin of the primary tumor, but may also appear in a distant site, the scalp being the most common place. Although the pathogenesis of esophageal adenocarcinoma is not well known, the existence of genetic alterations, such as the suppressor gene, has been proved and the involvement of oncogene c-erbB-2 amplified. Cytokeratin 20 and 7 are expressed in esophageal adenocarcinoma. Typically, cutaneous metastases from internal malignancy present as firm asymptomatic nodules. These nodules usually occur in multiple arrays on the skin adjacent to the primary tumor; however, they can occasionally become painful spontaneously. The main diagnostic test of esophageal cancer is the upper endoscopy, along with histopathology for confirmation of the tumor. The developments in surgery and the discovery of new cytotoxic agents have considerably decreased the locoregional recurrence. To date, the combination of these treatment modalities for advanced adenocarcinoma revealed that the recurrences mainly occur from hematic spread. Excision of the skin lesions produces pain palliation. In patients diagnosed with esophageal cancer who have responded satisfactorily to treatment with chemotherapy, radiation and surgery while having a long history of remission, and dermatology outpatient visits by the appearance of skin lesions, should make us think among the different differential diagnoses, the possibility of cutaneous metastases.

received 15.6.2014
accepted 14.12.2014

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DOI http://dx.doi.org/10.1055/s-0034-1398791
Z Gastroenterol 2015; 53: 115–119 © Georg Thieme Verlag KG Stuttgart · New York · ISSN 0044-2771

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Clinical Case Report

A 57-year-old male patient with a history of hiatal hernia treated with omeprazole, cigarette smoking (50 cigarettes/day) and habitual drinking presented to the Emergency Department with weight loss (15 kg), dysphagia for solids, anorexia, asthenia, arthralgia and non-tender erythematous indurated nodules on the head, thorax and back (**Fig. 1**). Blood tests showed a hemoglobin level of 12.3 g/dL, WBC = 10.13 × 10^3/µL, Ca 19.9 = 75 U/mL and Ca 125 = 209 U/mL.

The patient was admitted to the Internal Medicine Service for further evaluation. Esophagogastroscopy revealed the presence of a Barrett's esophagus located in the lower third of the esophagus with a mammilated surface and a large ulceration affecting the cardia and appearing to extend into the subcardial area (**Fig. 2**). Biopsy results revealed undifferentiated adenocarcinoma of the esophagus. Another lesion was detected in the antrum measuring 0.7 cm with a central depression, which was shown to contain undifferentiated cells with a high mitotic index by biopsy. The results of punch biopsy of the nodular lesions showed cutaneous metastasis from undifferentiated adenocarcinoma of the esophagus. A thoraco-abdominal computed axial tomography (CAT) scan identified an irregular thickening of the esophageal wall located predominantly in the lower half and invading the stomach, including the gastric fundus; preaortic and subcarinal mediastinal adenopathy; multiple pulmonary nodules; small hypodense regions in the hepatic parenchyma indicating possible hepatic metastases; 4 cm diameter masses in both suprarenal glands and a solid 1.5 cm nodule in the middle third of the right kidney.

On the basis of clinical examination and laboratory test results, chemotherapy with docetaxel, cisplatin and 5-fluorouracil (TPF) was started. After three chemotherapy cycles, a control thoraco-abdominal CAT scan showed a partial radiological response to treatment. The patient died 6 months after the start of chemotherapy.

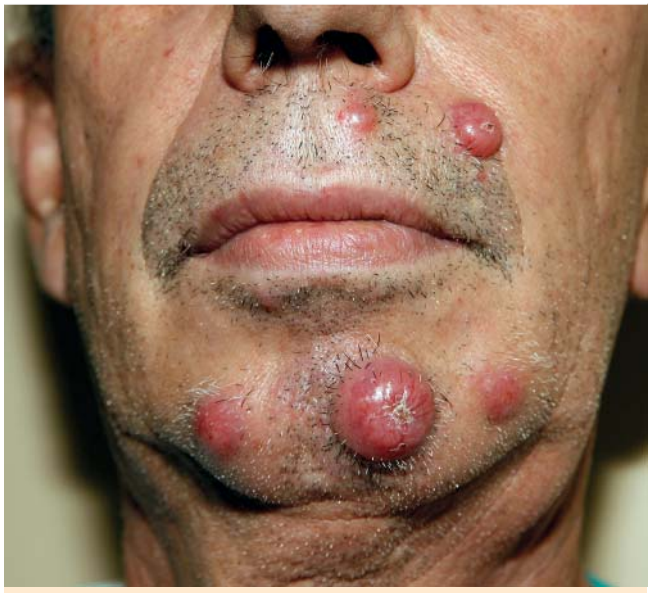

Fig. 1 Erythematous, indurated, and painless nodules in upper and lower jaw. Skin biopsy reported cutaneous metastasis of non-differentiated esophageal adenocarcinoma origin.

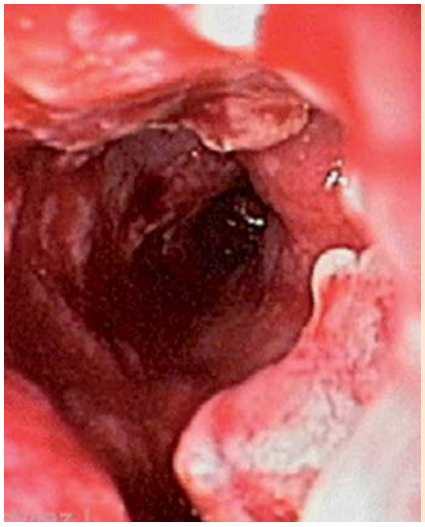

Fig. 2 Esophagogastroscopy shows the presence of a Barrett's esophagus located in the lower third of the esophagus with a mammilated surface and a large ulceration affecting the cardia and appearing to extend into the subcardial area. Biopsy results revealed undifferentiated adenocarcinoma of the esophagus.

Introduction

Esophageal cancer is a relatively uncommon but highly lethal malignancy with one of the highest mortality rates of all cancers [1, 2]. Fewer than 50 % of esophageal cancer patients survive one year after diagnosis, and the 5-year survival rate is less than 10 % [2]. In 2008, an estimated 16 470 patients were diagnosed with esophageal cancer and 14 280 died from the disease [3].

There is a close relationship between Barrett's esophagus and esophageal adenocarcinoma, and in the United States, approximately 80 % to 90 % of esophageal tumors are attributed to excessive alcohol consumption, long-term tobacco use or both risk factors [4 – 6].

Esophageal cancer metastasizes to different locations and the most common metastatic sites are the tracheobronchial tree, the aorta, pericardium and recurrent nerve nodes, whereas metastasis to the skin is rare [5].

The most common cancers to metastasize to the skin are breast, colon and lung cancers [5, 7]. On the other hand, cutaneous metastasis from esophageal adenocarcinoma is detected in 1 % of patients and is predominantly localized to the neck, head and abdomen [1, 7 – 9]. Cutaneous metastases are asymptomatic in a high percentage of cases, although they can occasionally be painful [4 – 7].

Discussion

Epidemiology

Esophageal cancer is a rare malignancy with a variable incidence rate, which has been reported to be 5 – 7 cases per 100 000 inhabitants per year in Europe and the United States, where esophageal cancer is responsible for 4 % of all cancer-related deaths. These rates differ from those reported in France, Southeast Africa, India, Iran and China, where the incidence increases to 20 – 30 cases per 100 000 inhabitants per year [10].

Esophageal cancer is one of the deadliest malignancies, and is the sixth most common cause of cancer-related death worldwide, although the incidence of this disease shows considerable geographic variation [1, 2, 6]. In the United States, it is the seventh most common cause of death from cancer, and its incidence is particularly high in the African American population

(13 cases/100 000 inhabitants/year) compared to other ethnic groups [1].

Esophageal cancer is more common among men than women (2 – 5:1), although in high risk populations, the incidence rate is the same in both sexes [3, 6]. The incidence of esophageal carcinoma is higher among Caucasians than African Americans (4:1) whereas esophageal squamous cell carcinoma is more common among African Americans, and both types of tumor occur predominantly in middle-aged individuals (50 – 70 years old) [2, 3, 6].

Currently, adenocarcinoma of the gastroesophageal junction is more frequent than squamous cell carcinoma, accounting for 60 – 70 % of all esophageal malignancies in some series and approximately 30 % in others [1, 3, 5, 7].

Pathogeny

Although the etiology of esophageal cancer is unknown, extensive epidemiological evidence suggests a close relationship between the development of this malignancy and several factors including alcohol [11 – 13], tobacco [2, 11 – 13], the ingestion of certain carcinogens such as nitrites and nitrosamines [11, 14], smoked opiates [11, 12], and certain mycotoxins [11, 15] (**Table 1**).

Other risk factors include those that cause physical damage to the mucosal lining of the esophagus, such as extremely hot foods resulting in thermal damage [11, 13], caustic ingestion, which can result in a 1000- to 10 000-fold increase in the risk of injury [13, 16], radiation-induced stenosis [13] and chronic achalasia [11, 13]. In addition, individual susceptibility is associated with Plummer-Vinson syndrome [17], tilosis [13], and certain nutritional deficiencies (selenium, zinc, β-carotene) [11] (**Table 1**).

Most cases of esophageal adenocarcinoma are related to Barrett's esophagus, and of these, approximately 90 % arise in the distal third of the esophagus [4, 5]. This alteration is observed in approximately 10 % of patients presenting with symptoms of GERD who undergo endoscopy [2]. The incidence of esophageal adenocarcinoma in patients with Barrett's esophagus is estimated at 0.2 – 2.1 % per year [2].

Although the pathogenesis of esophageal adenocarcinoma is not as well understood as that of other tumors, different genetic alterations have been associated with this cancer, including alterations in the p53 tumor suppressor gene, which occur in more than 50 % of esophageal adenocarcinomas, and the amplification of the c-erbB2 oncogene, which is present in 20 % of cases [2]. Ren et al. [18] showed a correlation between the level of c-myb mRNA expression and the development of Barrett's esophagus and esophageal adenocarcinoma, and proposed its use as a marker for the early detection of these pathologies because tissue c-myb mRNA levels are higher in patients with these diseases than in healthy patients and those with GERD. Recent studies have shown the involvement of cytokines and their receptors in tumorigenesis and metastasis. The cytokeratins CK20 and CK7 are expressed in esophageal adenocarcinoma, and CK20 has been detected in gastrointestinal tumors and CK7 in Barrett's esophagus [2]. These two cytokeratins are also used to differentiate between Barrett's esophagus and intestinal metaplasia of the gastric cardia [7]. Hu et al. [19] showed that the expression of the chemokine receptors CCR10 and CXCR4 in tumor cells did not correlate well with their capacity to metastasize to the skin, which indicates that these cytokines are unnecessary and insufficient for the development of cutaneous metastases. Therefore, other factors associated with the development of cutaneous metastases from esophageal cancer must exist.

Clinic

In the early stages, esophageal adenocarcinoma is asymptomatic or presents with gastroesophageal reflux as the only symptom. When the tumor reaches an advanced stage, it can be accompanied by progressive dysphagia for solids, retrosternal pain, and ferropenic anemia caused by chronic gastrointestinal hemorrhage [6]. Another possible complication is the formation of tracheobronchial fistulas [2, 6].

This type of tumor metastasizes mainly by proximity to the tracheobronchial tree, pericardium and recurrent nerves; via lymphatic spread to mediastinal and cervical lymph nodes; and during the later stages, via the blood to the liver and lungs [5].

Malignancies that have the highest propensity to produce cutaneous metastasis are colon, lung and breast cancers [5, 7, 19], which can spread by direct invasion, via lymphatics, hematogenously, and by iatrogenic implantation [5, 19]. They are extremely rare in esophageal carcinoma, with an estimated incidence of 1 – 3 % [2, 4, 8]. In fact, only 1 % of esophageal cancers metastasize to the skin [1, 5, 7, 9], and the most common locations are the neck, head, thorax and abdomen [7, 8] (**Table 2**). Metastases to the fingertips rarely affect the bone and are usually limited to the skin, resembling inflammatory lesions that are often misdiagnosed [8].

In 1990, a study by Lookingbill analyzed 7316 patients with cutaneous metastasis, and an esophageal origin of the primary tumor was not detected in any of them [1, 4, 20]. In another study conducted in 1993 that included 4020 cancers with cutaneous metastases, esophageal cancer was detected in only three patients, and squamous cell carcinoma was the common histological type in all three [1, 4, 21]. In a study by Hu et al. [19] of 12 146 patients with malignant tumors, 124 (1.02 %) had cutaneous metastases,

Table 1 Several risk factors involved in the genesis of esophageal tumors.

risk factors associated with esophageal cancer
alcohol
tobacco
nitrites and nitrosamines
smoked opiates
mycotoxins
hot foods
caustic ingestion
radiation
chronic achalasia
Plummer-Vinson syndrome
nutritional deficiencies (selenium, zinc, β-carotene)
tilosis

Table 2 Esophageal cancer and skin metastasis.

cutaneous metastasis	
incidence	1 %
location	neck, head, thorax and abdomen
histological types of esophageal cancer	squamous cell carcinoma
clinic	nodules hard and painless, with a red or blue color
diagnosis	biopsy
treatment	excision
differential diagnosis	blue nevus, dermatofibromas, leiomyomas, neuromas, eccrine poromas, angiomyolipomas, endometriomas, neurilemmomas, glomus

of which only three had an esophageal origin and one of these showed a histological subtype of adenocarcinoma. These studies show the low incidence of cutaneous metastasis from esophageal cancer.

The clinical presentation of cutaneous metastasis is nodules that are frequently firm and not painful, with a red or blue color, and often showing as a change in the coloration of the skin [7] (**Table 2**, **Fig. 1**). They usually arise in the skin adjacent to the primary tumor but can also appear at distant sites, in which cases the most common location is the scalp [4]. These metastases are not included among the majority of painful tumors of the skin because under normal conditions, they are not painful; however, they can occasionally become painful spontaneously, in which case a differential diagnosis must be performed to rule out other cutaneous lesions such as blue nevus, dermatofibromas, leiomyomas, neuromas, eccrine poromas, angiomyolipomas, endometriomas, neurilemmomas, glomus tumors and granular cell tumors [4] (**Table 2**).

In some cases, the removal of skin lesions by excision may provide relief from pain [5]. Several theories have attempted to explain this phenomenon: sensitive dermal nerves may be invaded by the metastases, or small nerves may be trapped by the metastatic lesions. Furthermore, inflammatory reactions or responses to tumor antigens in these lesions may increase the sensitivity to pain or induce the synthesis of substances such as cytokines that may generate a painful sensation [4].

Diagnosis

In the diagnosis of esophageal cancer, in addition to clinical and physical findings, a contrast esophagogram is often performed as an initial test and may provide typical images showing stenosis or esophageal ulcers [22]. However, the most important test for the detection of esophageal cancer is upper gastrointestinal endoscopy in combination with histopathological confirmation of malignancy (**Fig. 2**). Echoendoscopy of the upper gastrointestinal tract plays a critical role in defining tumor depth of invasion (T-stage) and is more sensitive than the CT scan for the detection of lymph node involvement ("N"). In addition, it is a useful method for predicting the stage of the tumor and the extent of metastatic lymph node involvement in 70 – 80 % of patients [22]. Thoraco-abdomino-pelvic CT scan has a sensitivity of 90 % for the detection of metastasis, 85 % for abdominal adenopathy and 90 % sensitivity for the diagnosis of paraesophageal adenopathy, and it is therefore the method of choice for estimating the extent of tumor involvement [6]. The detection of regional lymph node invasion has improved with the use of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) [23].

Treatment

The development of multimodal treatment protocols has significantly decreased the locoregional recurrence rates [1, 2]. Surgical resection is the treatment of choice for carcinoma of the thoracic and/or abdominal esophagus and should be considered as the standard treatment for the early stages of the disease independently of investigative multimodal therapy protocols because it is associated with the highest survival rates [24, 25]. Esophagectomy is associated with a high mortality rate (approximately 8 %), which is mostly due to postoperative complications such as anastomotic fistulas, subphrenic abscesses and respiratory complications [24].

In cases of unresectable disease, the use of palliative surgical (exclusion, gastrostomy) or endoscopic (laser, photodynamic therapy, brachytherapy, expandable prostheses) methods is recommended [24].

Despite the wide use of definitive chemoradiotherapy for the treatment of locally advanced adenocarcinoma of the esophagus, there is little evidence that this therapy improves the survival of patients in comparison to radiotherapy alone [26].

In the past, patients with esophageal adenocarcinoma died from locoregional recurrence and tumor progression. However, advances in neoadjuvant chemotherapy, surgical techniques and the discovery of novel cytotoxic agents as well as the combination of different treatments have significantly decreased locoregional recurrence rates [1, 2].

When cutaneous lesions appear in patients with esophageal adenocarcinoma who responded successfully to chemotherapy, radiotherapy and surgery and who present with a long history of disease remission, the possibility of cutaneous metastasis must be considered after performing differential diagnosis to rule out other cutaneous lesions because local recurrence from esophageal carcinoma is rare [2].

Hedeshian et al. [1] showed that a subpopulation of slow-growing esophageal tumor cells are refractory to chemotherapy and remain viable despite treatment; these malignant cells, which localize to dermal lymphatic vessels, remain quiescent for a prolonged period of time until their clinical presentation as cutaneous nodules. Therefore, in their study, these authors predicted an increased incidence of recurrent metastatic disease after esophagectomy in patients with locally advanced disease.

Excision of a solitary cutaneous lesion from esophageal cancer must be considered in cases in which the disease was absent for a long time and in the absence of other metastases [5].

The prognosis of esophageal cancer is poor, with a 5-year survival rate of approximately 8 % and a median survival of 9 months [5]. Two of the most important prognostic factors determining the survival of esophageal cancer patients are the degree of invasion of the primary tumor (T), the presence or absence of nodal metastasis (N) [5] and the relationship between the number of affected lymph nodes and that of resected lymph nodes [27, 28]. Other prognostic factors are early diagnosis, the R factor, and the degree of experience of the surgical team [29, 30].

Conclusions

The detection of cutaneous lesions in patients with esophageal cancer may indicate the presence of metastasis, and differential diagnosis should be performed to rule out other skin lesions despite the prolonged absence of disease in patients treated with surgical resection and chemoradiotherapy.

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