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Cutaneous Lesion of the Nose as Initial Presentation of Esophageal Adenocarcinoma

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Abstract. *Background/Aim: Cutaneous manifestations of disease are exceedingly rare and commonly overlooked in clinical practice. Allergies or contact dermatitis, autoimmune disease or skin cancer are the most common conditions typically associated with skin lesions. Rarely, cutaneous lesions may be the first sign of internal malignancy, or even resemble recurrent disease in those with history of cancer. Case Report: Herein, we report a case of an otherwise healthy male who presented to his primary care provider (PCP) with a skin lesion misdiagnosed as a furuncle, which eventually led to diagnosis of metastatic esophageal cancer. The patient was a 64-year-old male, presenting with a fungating lesion on the tip of his nose which was biopsied, confirming adenocarcinoma likely from a gastrointestinal source. Staging imaging showed extensive lung, liver, and boney metastatic disease. He was initially treated with chemotherapy and trastuzumab. Conclusion: Cutaneous lesions are a rare presenting sign of malignancy, but rapidly growing lesions should be evaluated for possible metastatic disease.*

Esophageal carcinoma accounts for around 1% of adult malignancies diagnosed in the United States every year. Since there is no uniform screening recommendation for esophageal carcinoma, the delayed discovery and diagnosis usually occur due to symptoms onset. Most presenting symptoms include difficulty in swallowing solid foods that may progress to include liquids in time, indigestion and eventually unexplained weight loss. Metastatic lesions usually represent late manifestations of the disease and confer poorer prognoses.

While the most common location for metastatic lesions from esophageal carcinoma are the liver and lung, there are few case reports about cutaneous metastatic lesions and even fewer with the cutaneous lesions being the initial presenting symptom. Cutaneous lesions from solid tumor disease are overall a rare phenomenon, but new lesions in conjunction with associated symptoms of malignancy like unexplained weight loss and dysphagia should invoke a thorough systemic evaluation. We present here adenocarcinoma of the esophagus that presented initially as a cutaneous lesion of the face.

Case Report

A 68-year-old individual with a past medical history of essential hypertension, hypercholesterolemia and benign prostate hyperplasia presented to his primary care physician office with concerns of a growing mass on the tip of his nose (Figure 1A). The fungating lesion was initially diagnosed as a furuncle and treated with antibiotics but did not regress in size or heal correctly. Additional symptoms at that time included only mild fatigue and decreased appetite. He denied any dysphagia or odynophagia and was experiencing mild weight loss believed to be associated with loss of appetite. The lesion was eventually biopsied and found to be positive for CK7 and CDX-2, negative for CK20, CD56, P63, GATA3, TTF1 and calretinin consistent with malignancy of an upper gastrointestinal origin. He had no past history of smoking or alcohol consumption and had not been on any type of GERD medication in the past.

He was evaluated by oncology for the staging work-up. Imaging for metastatic disease revealed extensive disease in both lungs and the liver with pathologic fractures to L1 and

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L5 of the lumbar spine. An EGD was preformed and showed a distal esophageal mass enveloping 60-70% of the luminal surface. This area was biopsied and found to be positive for MOC-31 and negative for CEA, but stained negative for CK5, CK6, and P63 representing adenocarcinoma, likely the primary site. Within one month of diagnosis, the disease progression was already accelerating as the patient became symptomatic with dysphagia and significant weight loss, and the skin lesion was growing rapidly (Figure 1B). He started to develop abdominal pain and increasing dysphagia that progressed from solids to eventually liquids as well, requiring an esophageal stent to be placed. Due to the rapid progression of his disease, he was given his first dose of FOLFOX (5-florouracil and oxaliplatin) while inpatient. He continued FOLFOX therapy after discharge. A percutaneous endoscopic gastrostomy (PEG) tube was placed as his oral intake status was declining and his nutrition was compromised. Next-generation sequencing testing showed evidence of ERBB2 amplification and mutation in ARID1A. Trastuzumab was added on cycle 4. A repeat CT scan three months after the initial diagnosis and 5 cycles of FOLFOX + trastuzumab showed excellent response in the liver and a significant improvement in the lungs, and stable extensive bony metastatic disease. Before Cycle 9 of this therapy, he did require a PEG tube exchange and esophageal stent replacement. Repeat computed tomography (CT) scans did show interval decrease in the lung and liver metastatic lesions with extensive sclerotic and lytic boney lesions. Unfortunately, the patient continued to decline with continued weight loss and poor nutritional status limiting treatment options. Staging magnetic resonance imaging (MRI) of the head obtained did show new lesions to the right parietal lobe and posterior parietal skull. The patient was admitted at an outside hospital after a fall and seizure like activity shortly after the discovery of new metastatic disease in the head, and was transitioned to hospice care.

Discussion

Esophageal cancer is currently the 7th most lethal cancer for men in the United States and 6th most deadly in the world, likely secondary to its aggressive nature and late detection (1). It can further be broken down into squamous cell and adenocarcinoma variants, although both subtypes represent equally poor outcomes and survival rates. A study of relative 5-year survival from 2002-2008 revealed median overall survival of about 16.9% with black men being the lowest at 10.2% (2). Squamous cell carcinoma has its peak incidence in the 7th decade of life with prevalence in the upper third of the esophagus and in African Americans. Adenocarcinomas are more prevalent in the more distal esophagus and appear to be more common in white men (2). Barrett's esophagus – metaplasia of the distal epithelium of the esophagus – can be directly related to the development of adenocarcinoma and must be closely monitored once the initial diagnosis is made.

Several reasons exist for the lack of overall survival in these patients. One major reason is that up to 30% of the population with EC already has metastatic disease on presentation (2). In a study of 838 patients with EC, 147 (18%) presented with metastatic disease most commonly to the lymph nodes, liver, and lung; with skin representing 2 patients or 1% of the sample (3). Late presentation combined with the lack of an adequate screening regimens (outside of screening those with known Barrett's esophagus) contribute to the commonly poor outcomes (2). The esophagus' unique anatomy is currently believed to help explain the unusual metastatic distribution. Its venous drainage to both the inferior vena cava and portal system help explain the metastatic disease to both liver lungs. The complex lymphatic system surrounding the esophagus also explains how retrograde and bidirectional spread of metastatic esophageal cancer. Finally, arterial spread has been proposed as well to support its more unusually metastatic spread to distant regions (4).

Metastatic disease to the skin is a rare manifestation of internal neoplastic disease, with the presenting symptom of a dermatologic growth being extraordinarily rare representing only 0.6-10.4% of patients with cancer (5-6). With metastatic disease to the skin usually being considered a later manifestation often signaling advanced disease already involving the lungs and liver, much like the individual referenced in our case, the overall prognosis of the patient is considered poor. The most common internal malignancies to metastasize to the skin are breast in women and lung in men, with esophageal falling lower on the list (7). There are several proposed pathways of how metastatic disease can spread to these distal sites. Depending on the type of cancer, hematologic or lymphatic spread could be the method of distal travel. There is some evidence to suggest that lymphatic congestion causing shunting of lymph flow from deep routes to more superficial cutaneous pathways could lead to cutaneous spread. There is also some evidence of endothelial damage secondary to radiation treatment leading to tumor cell trapping that can lead to cutaneous metastatic disease (7).

With the increasing incidence of cancers on the national scale, it will become important to recognize all signs of possible malignancies. Most metastatic lesions to the skin can mimic otherwise benign dermatologic conditions, therefore it is important to complete a proper work up of skin lesions of an unknown cause even in the absence of other clinical symptoms of disease. Lesions can be classified morphologically as nodular, infiltrative, diffuse or intravascular, and top heavy or bottom heavy; with the later classification defining superficial or deep dermal involvement (8). They are also mostly asymptomatic with only five case reports of painful metastatic lesions being

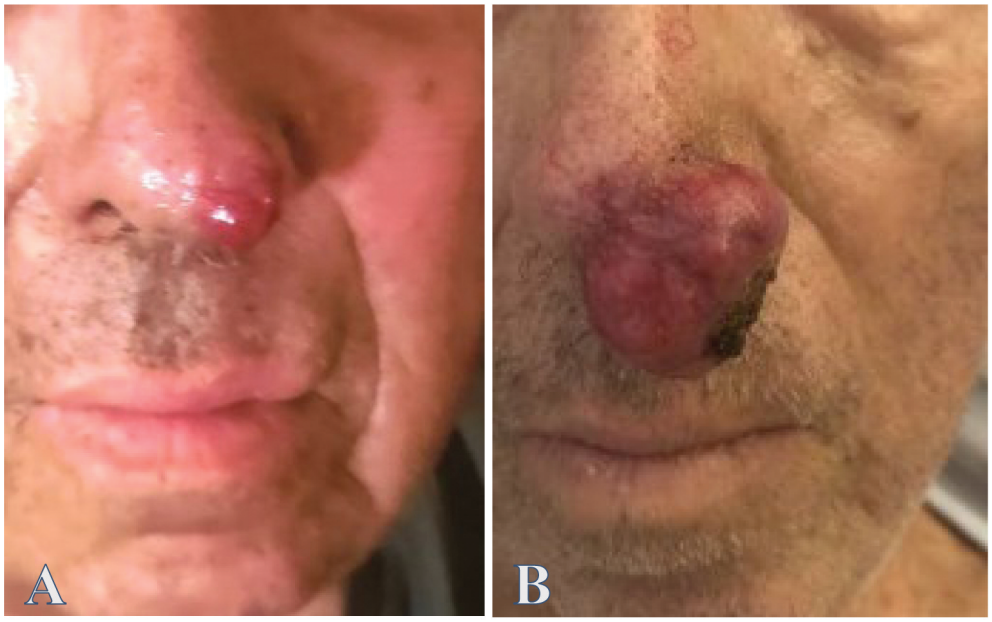

Figure 1. *Initial presentation of lesion at the primary care office (A) and presentation four weeks later (B) showing a rapid increase in lesion's size.*

found (9). Furthermore, there is no formal algorithm for the proper diagnosis of cutaneous metastatic disease of unknown origin (10). When there is evidence directing towards a primary, more focused staining can be completed for specificity in confirmation. Immunohistochemical analysis containing p63, B72.3, calretinin, CK5/6 can be used to differentiate metastatic carcinoma from primary skin adnexal tumors (11).

A case study examining 750 patients in a tertiary referral center in Southern India discovered that of 52 patients had cutaneous lesions, 14 of these lesions were non-contiguous with the primary site (12). This study was of note because it monitored the overall different types of carcinoma, and the overall survival of the patients. This population showed a different primary with Hodgkin's lymphoma being the most common cause of cutaneous manifestations. After the detection of cutaneous disease, the overall survival of these patients was about 3 months, reflective of the often-advanced state of the primary malignancy.

In reviewing case reports about cutaneous metastatic EC, several distinct themes can be followed. The overall prognosis after developing cutaneous metastatic disease is poor, with life expectancy ranging from several weeks to six years. In several cases, multiple cutaneous lesions spread throughout the body were found (13, 14). Most of these lesions are asymptomatic, but one case of painful metastatic disease to the scalp was believed to be caused by entrapment of the nerve in the subdermal tissue (9). In the majority of cases, these lesions represented recurrent metastatic disease ranging several months to several years after treatment (15, 16). In only one case report, the patient was asymptomatic with no history of previous disease with the initial diagnosis being made off a cutaneous biopsy (17).

Even after surgical resection with negative lymph nodes, a positive history of EC is important to note so that it is not confused with a new neoplastic disease. In one case a diagnosis of apocrine cancer was made, and treatment was initiated before being appropriately diagnosed as recurrent metastatic disease (18). When lesions did appear, they progressed rapidly over the course of weeks to months and appeared resistant to treatment with chemotherapy, with one case of more nodules developing even after the initiation of chemotherapy (14, 19). Oddly enough, in many cases in which single nodules were the identifying lesion, there was a predilection of metastatic disease to the head and scalp (16-18).

Clinicians must also hold a high suspicion for new cutaneous lesions that do not respond to conventional therapy or that are rapidly growing in patients with a history of malignant disease. Thorough investigation into medical and social history could provide key details into other possible cutaneous lesions. Cutaneous metastatic disease can be recurrent in some disease up to ten years after the initial diagnosis of malignancy (7). Even after pursuing curative treatment and chemotherapy, distant metastatic disease is still possible that can drastically change the management and goals of care of your patients. This case study showed that

EC can present in unique ways, both as initial and recurrent manifestation of disease, and will likely have a poor overall outcome.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Study concept and design: AH, YS. Drafting the manuscript: All Authors. Critical revision of the manuscript for important intellectual content: All Authors. Administrative, technical, or material support: YS, LG.

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