Case Report

Pathologically Complete Response after Triple Therapy in Locally Advanced Esophageal Cancer in a Hereditary Hemorrhagic Telangiectasia Patient

Robin Park[a]   Alisdair Philp[b]   Alykhan S. Nagji[c]   Anup Kasi[b]

[a]Department of Medicine, MetroWest Medical Center, Framingham, MA, USA; [b]Department of Medicine, Division of Medical Oncology, Kansas University Medical Center, Kansas City, KS, USA; [c]Department of Cardiovascular and Thoracic Surgery, Kansas University Medical Center, Kansas City, KS, USA

Abstract

Hereditary hemorrhagic telangiectasia (HHT) is a disorder characterized by vascular manifestations including mucocutaneous and visceral telangiectasias and arteriovenous malformations. Herein we present the case of a relatively young patient with HHT with an incidentally discovered locally advanced esophageal cancer on endoscopic screening and pathologically complete response after neoadjuvant chemoradiation. This case highlights an unusual tumor response to chemoradiation in locally advanced esophageal cancer, and the surveillance care of HHT patients.

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Introduction

Hereditary hemorrhagic telangiectasia (HHT) is a genetic disorder with an autosomal dominant inheritance and variable penetrance characterized by structural abnormalities of the vasculature, resulting in mucocutaneous telangiectasias and arteriovenous malformations (AVMs) that may involve various organs including the brain, lungs, and the gastrointestinal (GI) tract [1–4]. Prevalence of HHT as suggested by epidemiological studies ranges from

Anup Kasi
Department of Medicine
Division of Medical Oncology, Kansas University Medical Center
2650 Shawnee Mission Pkwy, Westwood, KS 66205 (USA)
akasi@kumc.edu

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1:5,000 to 1:8,000 [5–10]. The Curaçao Criteria have been developed to guide the diagnosis of HHT. The diagnosis is based on the following clinical findings: spontaneous and recurrent epistaxis; multiple mucocutaneous telangiectasia at characteristic sites; visceral manifestations including GI telangiectasia or pulmonary, cerebral, or hepatic AVMs; and a first-degree relative with HHT. Three out of four criteria define "definite," two out of four "suspected," and one out of four "unlikely." Although not necessary, genetic testing may confirm the diagnosis by identifying pathogenic sequence variants in the genes linked to HHT, namely *ENG, ACVRL1,* or *SMAD4* [10, 11].

Locally advanced esophageal cancer patients have the option of undergoing triple therapy which includes concurrent neoadjuvant chemoradiation followed by esophageal resection [12]. A minority subset of patients undergoing triple therapy may achieve pathologically complete response (pCR) with studies indicating a range of 19–30% with a lower rate in adenocarcinoma [13–20]. Such patients enjoy favorable prognoses compared to their non-pCR achieving counterparts in terms of recurrence-free survival and overall survival [14, 21–23]. Therefore, achieving pCR is an important prognostic measure of locally advanced esophageal cancer patients who have undergone therapy. Herein, we present a patient with underlying HHT who achieves pCR following triple therapy for locally advanced esophageal cancer.

Case Report

This is a 40-year-old male patient with a recently diagnosed HHT who had undergone screening endoscopy for surveillance of vascular complications. He notes occasional epistaxis and buccal macules but denies nausea, vomiting, dysphagia, and weight loss. His past medical and surgical history is unremarkable. He is a 15-pack-year smoker and drinks 588 g of alcohol weekly but does not use illicit drugs. Family history is significant for cancer in multiple relatives. His mother suffered from head and neck cancer, his maternal grandmother from colon cancer, his maternal grandfather from prostate cancer, and his paternal grandmother from leukemia. His physical examination is remarkable for buccal telangiectasias and he has a BMI of 32.23. Laboratory studies are remarkable for polycythemia. Upper GI endoscopy shows a friable mucosa with contact bleeding of the esophagus and normal stomach. Several duodenal ectasias are found and treated with plasma coagulation. Capsule endoscopy is done, which is unremarkable. Endoscopic ultrasound shows two periesophageal lymph nodes, 11.6 and 7.2 mm in diameter (Fig. 1). PET-CT confirmed hypermetabolic primary esophageal tumor but the periesophageal lymph nodes were non-hypermetabolic due to small size. No metastatic lesions are discovered (Fig. 2). Endoscopic biopsy of the ulcerated mucosa of the esophagus confirms moderately differentiated adenocarcinoma in a background of high-grade dysplasia. The patient is diagnosed with stage IIB, cT1bN1 esophageal adenocarcinoma and undergoes neoadjuvant chemoradiation with carboplatin/Taxol then surgical resection with the IVOR-Lewis approach. Postoperative pathology confirms pCR. His 1-month, 1-year and 2-year post-operative surveillance upper GI endoscopies reveal no recurrence.

Discussion

A potential molecular relationship may exist between a genetic variant underlying a specific subtype of HHT and esophageal cancer pathogenesis. Namely, HHT subtype 1 is associated with pathological variants of *ENG* which encodes a transformation growth factor beta (TGF-β) super-family auxiliary receptor [24]. Previous studies have demonstrated downregulation of *ENG* in esophageal squamous cell cancer cell lines and patient tumor specimens [25]. Furthermore,

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Fig. 1. Endoscopic ultrasound showing 2 periesophageal/perigastric lymph nodes (11.6 mm, 7.2 mm).
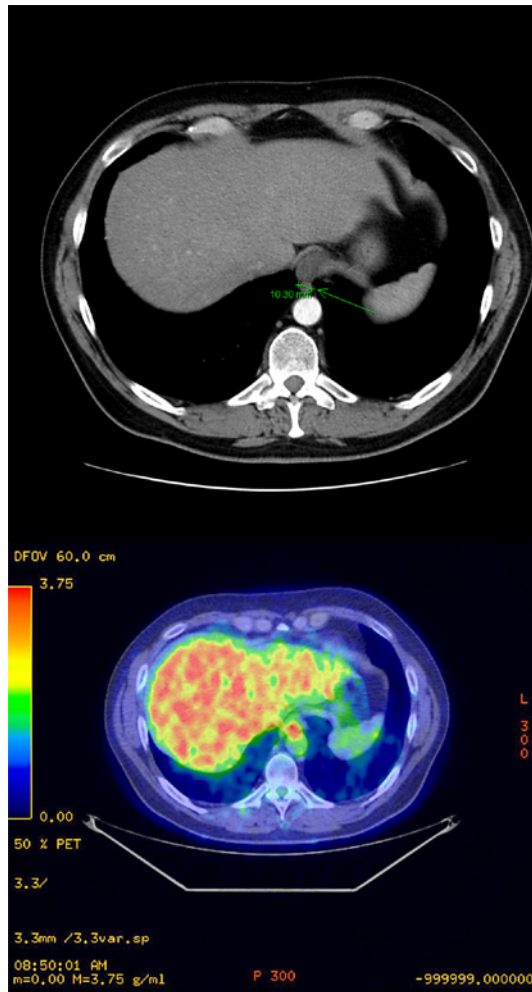

Fig. 2. Staging CT scan of the abdomen showing thickening of the gastroesophageal junction corresponding to the primary lesion. Arrow indicates the neoplastic lesion at the gastroesophageal junction with a diameter of 10.30 mm (upper panel). Staging PET scan of the abdomen showing hypermetabolism in the corresponding primary lesion. The neoplastic lesion at the gastroesophageal junction demonstrates hypermetabolism (lower panel).

functional in vitro and in vivo studies demonstrate the suppressive effects of *ENG* on tumor invasion and tumorigenicity [26]. Other studies suggest the involvement of TGF-β mediated tumor suppression in the pathogenesis of esophageal adenocarcinoma as well [27, 28]. Our patient, as part of his previous diagnostic evaluation of HHT, underwent genetic testing, which

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revealed a genetic variant in *ENG*. It is difficult to ascertain if and whether the underlying genetic variant was associated with the onset of esophageal cancer in this relatively young patient, given that he did have risk factors including male sex, obesity, and cigarette smoking [29–32]. However, several epidemiological studies show that HHT1 patients have different specific cancer rates and specific cancer mortality outcomes that differ from the non-HHT1 population [7, 33, 34]. So far, esophageal cancer has not been named as having a different specific cancer rate compared to the healthy population but further studies to evaluate the epidemiological relationship between HHT and esophageal cancer may be warranted.

The management of HHT patients involves timely and judicious screening for clinically significant AVMs. Although international guidelines have been established to facilitate appropriate screening, consensus is still lacking and indications for screening remain unclear in several areas. The major visceral vascular abnormalities that are the subject of screening include cerebral, pulmonary, GI, and hepatic vascular malformations. Evidence for screening for pulmonary AVMs in all patients with possible or confirmed HHT is strong. On the other hand, the evidence is weak for cerebral vascular malformations. Screening for GI AVMs is recommended in patients who are suspected of GI bleeding, namely if anemia appears out of proportion to blood loss by epistaxis. Similarly, screening for liver AVMs is recommended when the liver function test is abnormal or clinical complications arising from liver involvement are suspected [35]. Upon HHT diagnosis, our patient underwent pulmonary screening and GI screening when laboratory studies discovered iron deficiency anemia out of proportion to epistaxis.

As aforementioned, pCR is a positive prognostic indicator and is achieved in approximately 19–30% of patients who undergo trimodal therapy with neoadjuvant chemoradiation and surgery. Certain clinical factors are associated with lower or higher probability of pCR. Among clinical factors associated with lower pCR are older age (>60), poorly differentiated histology, presence of signet ring cells, higher T stage, and adenocarcinoma subtype [13]. Based on the findings of this study, other than the histological subtype, the patient had none of these oncologic factors, which in retrospect indicated a relatively high pretreatment probability of pCR. Furthermore, the pCR suggests a favorable prognosis for this patient. In fact, the patient is without evidence of recurrence at his 2-year follow-up.

The lessons of this case are the following: (1) screening guidelines and indications for complications in HHT patients are established but many aspects are controversial; (2) certain genetic variants associated with HHT may also be involved in esophageal cancer pathogenesis; and (3) despite its reputation as an aggressive cancer with poor treatment response, locally advanced esophageal cancer can have pCR with surprising frequency.

Conclusion

This case describes the diagnosis of a locally advanced esophageal cancer in a relatively young patient with a variant gene suspected to be involved in esophageal cancer pathogenesis.

Statement of Ethics

The authors are accountable for all aspects of the work ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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