Primary Esophageal Intramural Squamous Cell Carcinoma Masquerading as a Submucosal Tumor: A Rare Presentation of a Common Disease

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ABSTRACT: Esophageal squamous cell carcinoma (ESCC) is the commonest primary malignant esophageal tumor, which typically presents as endoscopically visible surface mucosal ulcerations, irregularities, or polyploidal masses. We here report a rare case of primary ESCC with completely intramural growth under a normal looking intact nondysplastic surface squamous epithelium disguising as a submucosal tumor. Upper gastrointestinal endoscopy-guided mucosal biopsy was negative for malignancy. Endoscopic ultrasound (EUS) revealed a heteroechoic solid mass originating from the muscularis propria of the distal esophagus. Cytological study of EUS-guided fine needle aspiration from the mass was suggestive of squamous cell carcinoma, which was confirmed on immunohistochemistry. There was no evidence of metastatic origin of this tumor or continuous cancer involvement from the surrounding structures, including the head, neck, and lungs on bronchoscopy, computed tomography scan, and positron emission tomography scan. Exclusive intramural squamous cell carcinoma with normal overlying mucosa is an exceedingly rare presentation of primary ESCC with only four cases reported in the literature so far. A high index of suspicion is required by the gastroenterologists and pathologists in diagnosing these cases as these tumors closely mimic the mesenchymal submucosal tumors such as lipoma, leiomyoma, and gastrointestinal stromal tumors. EUS is an indispensable tool in making a preoperative diagnosis and therapeutic decision making.

KEYWORDS: intramural esophageal squamous cell carcinoma, submucosal lesions of esophagus, EUS in esophageal carcinoma

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Introduction

Although it is no longer the most common form of esophageal carcinoma in Western societies, esophageal squamous cell carcinoma (ESCC) continues to be the most prevalent type of esophageal cancer in the East. It represents 90% of all cancers in most Asian, African, and Eastern European countries.[1] Most of the ESCCs are detected in advanced stages when the patient is symptomatic. As they originate from the epithelial layer of the esophagus, a majority of ESCCs present as an endoluminal mucosal abnormality in the form of polypoidal masses or ulcerative growth.[2] In contrast, the submucosal esophageal tumors are a distinct group of tumors originating from the mesenchymal tissues such as leiomyomas, melanomas, and lipomas, which are commonly benign and present typically as submucosal solid masses underneath the intact overlying epithelial mucosa. Completely intramural growth of an advanced primary ESCC is an exceedingly rare presentation, with only four cases reported in the literature so far.[3–6] We herein report a case of endoscopic ultrasound (EUS)-guided diagnosis of a primary ESCC with pelvic bone metastasis masquerading as a submucosal tumor. This case highlights the diagnostic and therapeutic challenges in managing these patients as repetitive mucosal biopsies are negative for malignancy. The correct EUS-fine needle aspiration (FNA)-guided preoperative diagnosis of ESCC was instrumental in avoiding unnecessary surgery in this patient as the patient was subsequently found to have distant metastasis. The patient has given consent for publication of this report.

Case Description

A 45-year-old female presented with complaints of progressively increasing dysphagia mainly to solids for last four months associated with significant loss of weight and appetite. She denied any history of heartburn, regurgitation, caustic ingestion, trauma, fever, cough, hemoptysis, change in voice, difficulty in breathing, hematemesis, or melena. On examination, her vitals were stable, mild pallor was present, and there was no lymphadenopathy. Her respiratory and gastrointestinal

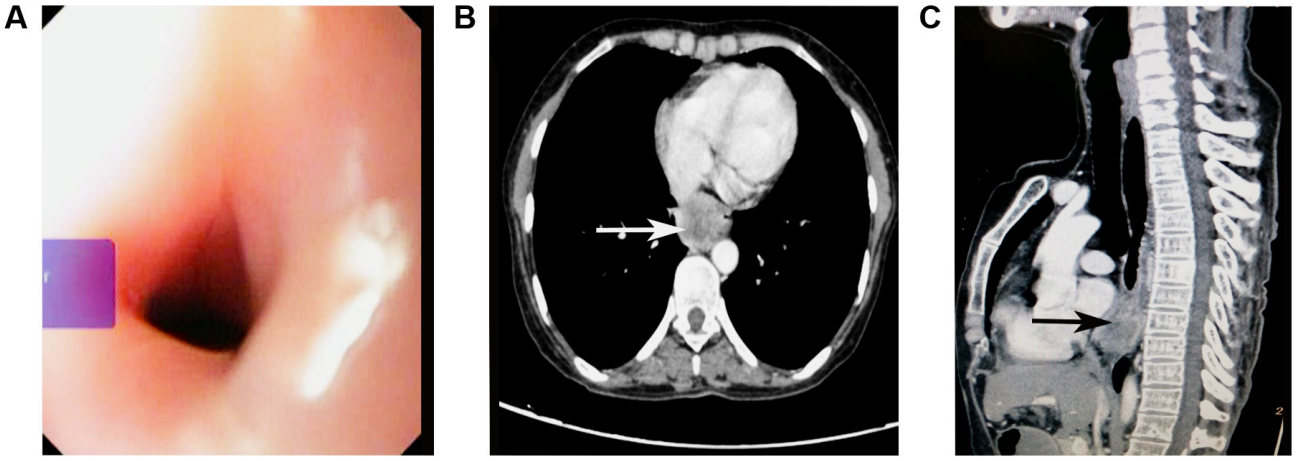

Figure 1. Upper gastrointestinal endoscopy reveals a smooth stricture with normal overlying mucosa in the lower esophagus starting at 28 cm from central incisor (**A**). A heterogeneously enhancing soft tissue lesion of size approximately 3.2 cm × 2.5 cm involving the distal thoracic esophagus with near complete lumen occlusion can be seen on the cross-section (white arrow in **B**) and sagittal section (black arrow in **C**) contrast-enhanced computed tomography images.

examination was within normal limits. On routine investigation, the hemoglobin level was 9.1 gm%, the total cell count was 8800/cumm, the platelet count was 180,000/cumm, the serum creatinine level was 1 mg/dL, the aspartate transaminase level was 40 IU/mL, and the alanine transaminase level was 38 IU/mL. Her barium swallow showed a smooth indentation of distal esophagus along the right lateral aspect with significant luminal compromise. Upper gastrointestinal endoscopy was suggestive of a smooth stricture with normal overlying mucosa seen in the lower esophagus starting at 28 cm from the central incisor (Fig. 1A). The scope could not be negotiated beyond. Subsequently, a contrast-enhanced computed tomography (CT) of thorax revealed a heterogeneously enhancing mass lesion at the lower one-third of the esophagus causing near-complete lumen occlusion (Fig. 1B and C). In order to characterize the lesion and enable biopsy, esophageal dilatation was done using the Savory-Gillard dilator. Subsequently, the visualized esophageal mucosa at the stricture site was normal, and a repeat mucosal biopsy was negative for malignancy. Then, an EUS was done revealing a 3.3 cm × 2.5 cm heteroechoic mass lesion in the submucosal region of the distal thoracic esophagus, which was in close proximity to the left atrium (Fig. 2A). EUS-guided FNA of the mass showed a cellular smear with clusters of atypical cells with nuclear polymorphism, scant cytoplasm, coarse chromatin, and small nucleoli suggestive of squamous cell carcinoma (SCC) (Fig. 2B and C). This was confirmed on immunohistochemistry, which was positive for cytokeratin 5/6 and p53. The serum carcinoembryonic antigen level was 18 ng/mL. To rule out a metastatic disease, a whole body 18-flourodeoxy glucose–positron emission tomography (PET) scan was done, which showed an avid uptake in the esophagus in the region of the mass and in the pelvis, suggestive of bone metastasis (Fig. 3A and B). ENT examination and bronchoscopy were normal. A final diagnosis of primary esophageal intramural SCC with bone metastasis was made. The patient is currently on palliative chemoradiotherapy. She was given capecitabine and oxaloplatin-based chemotherapy together with external

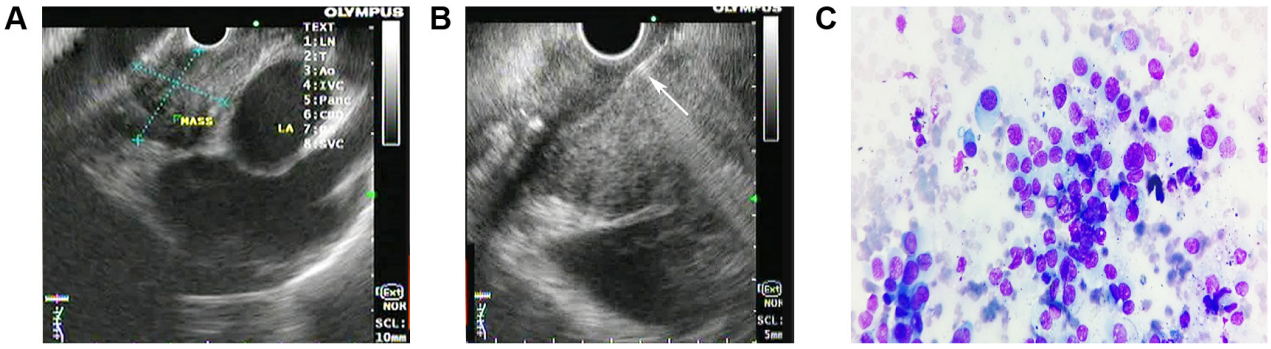

Figure 2. Endoscopic ultrasound image shows a 3.3 cm × 2.5 cm mixed hypoechoic–isoechoic mass lesion in the submucosal region of distal thoracic esophagus, which was in close proximity to the left atrium (**A**). Fine needle aspiration of the mass (white arrow) (**B**). FNA smear showed a cellular smear with clusters of atypical cells with nuclear polymorphism, scant cytoplasm, coarse chromatin, and small nucleoli suggestive of squamous cell carcinoma (**C**).

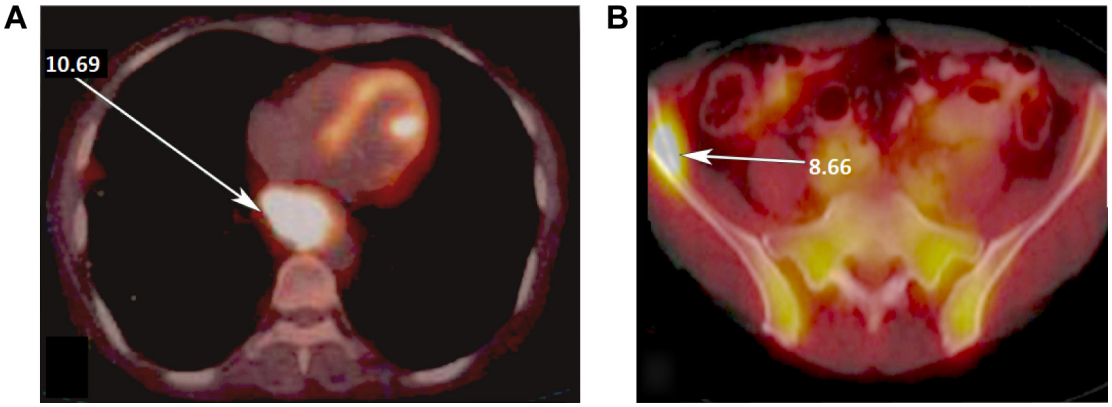

Figure 3. (**A**) PET scan images showing FDG avid well-defined soft tissue mass seen in the esophagus extending from the subcarinal region till the lower esophagus with the SUVmax value of 10.69 (white arrow) suggestive of malignant lesion. (**B**) Hypermetabolic lesion in the right iliac crest with the SUVmax value of 8.66 suggestive of skeletal metastatic involvement (white arrow) is seen.

beam radiotherapy to achieve a durable response to relieve the malignant dysphagia as repeated settings of endoscopic dilatation had only short-lived response. The patient was nonaffording for self-expandable metal stenting, and brachytherapy was technically difficult. At present, on two months of follow-up, her dysphagia has partially relieved. Bone pain is controlled with opioids. There is no change in the size of the original tumor on imaging.

Discussion

Intramural growth with sparing of the overlying mucosa is an exceedingly rare presentation of primary esophageal SCC, with only four cases reported in the literature so far.[3–6] McGregor et al reported a case of an ESCC presenting as a cystic submucosal mass that required surgical exploration for diagnosis.[3] Von Rahden et al reported a case of an intramural ESCC of the proximal esophagus presenting as an esophageal wall thickening without any obvious mass, which also required surgical exploration as EUS also did not clinch the diagnosis.[4] In their case, Kishino et al reported a submucosal esophageal mass with submucosal intragastric metastasis.[5] Preoperative endoscopy-guided biopsy was positive in this case. In another case, Schmitz et al found intramural SCC of gastroesophageal junction on postoperative surgical specimen as preoperative diagnosis was not possible.[6] Our case differs from those reported earlier from the fact that the ESCC presented as a solid submucosal mass mimicking mesenchymal tumors and EUS-FNA was able to make a preoperative diagnosis. After the tissue diagnosis of ESCC, PET scan confirmed pelvic bone metastasis, and thus operative intervention was not done. EUS prevented unnecessary surgical exploration of the mass, which would have been noncurative as patient had distant metastasis.

Repeated mucosal biopsies had revealed a normal nondysplastic esophageal squamous epithelium. Immunohistochemistry of the cell block prepared from the EUS-FNA-guided cytology specimen of the mass showed positivity for cytokeratin 5/6 and p53, which confirmed SCC. There was no expression of S100, vimentin, chromogranin, and melan-A, ruling out mesenchymal or melanocytic differentiation of the tumor.

Endoscopy and radiological investigations can mislead to a diagnosis of a submucosal tumor rather than an SCC due to nonsuspicious appearance of the overlying mucosa. Differential diagnosis considered in our case after endoscopy, CT scan, and EUS included leiomyoma, gastrointestinal stromal cell tumor, lipoma, or a carcinoid tumor. EUS-FNA leads to the diagnosis of SCC. There was no evidence of metastatic origin of this tumor or continuous cancer involvement from the surrounding structures including the head, neck, and lungs on bronchoscopy, CT scan, and PET scan in our case.

Although intramural growth and spread of a visible exophytic esophageal SCC presenting as metastasis to stomach has been reported in a large series as well as in few case reports, primary intramural esophageal SCC has rarely been encountered.[7,8] Exact pathogenesis of intramural origin of SCCs is not known. It has been hypothesized that they may originate from squamous cells of the esophageal duplication cyst, submucosal glands, or a small diverticulum. Esophageal submucosal glands that open into the lumen are located more commonly in the upper and lower esophagus and are lined by cuboidal epithelium in deeper portions, becoming stratified squamous epithelium at the surface. SCC may originate from the superficial portion of these glands. Squamous metaplasia of the deeper cuboidal epithelium has also been observed, which may give rise to SCC. Another theory hypothesized in previously reported cases was that surface squamous intraepithelial neoplasia may have reached the submucosal layers by intraductal spread along the ducts of the submucosal glands.

There are certain limitations in EUS-guided Fine Needle Aspiration Cytology (FNAC) for diagnosis of submucosal tumors as the average diagnostic accuracy rate of EUS-FNA is 60%–80%.[9] Sampling error during sample processing is important as it can affect the diagnostic yield. Combination of

cytology and immunohistochemical staining using cell blocks as done in our case is very useful to increase the diagnostic yield.

Esophageal SCC with exclusive intramural growth poses a diagnostic and therapeutic challenge as it is an exceedingly rare presentation, and repeat endoscopic mucosal biopsies will be negative. EUS is an indispensable tool in managing these patients and should be used before surgical exploration.

Author Contributions

Designed and wrote the article: PMR, NS, VBP, and SU. Evaluated the patient and did the literature search and recorded clinical findings: SJ, NS, and PMR. Conceptualized the article, gave the intellectual input, and did critical review of the article: NS, RS, PMR. All authors contributed substantially to the manuscript.

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