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Case Report

A rare cause of esophageal stricture: undifferentiated carcinoma of the lower esophagus

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ABSTRACT

Undifferentiated carcinoma of the esophagus (UEC) is an uncommon esophageal malignancy. Patient with UEC has a notably poor prognosis because of extensive metastasis despite at the early stage. A standard treatment regimen for UEC has not yet been established. We reported a case of undifferentiated carcinoma in a 46 years old male with a common chief complaint of progressive dysphagia accompanied by chest discomfort after meal and significant weight loss. Base on the history of illness, physical examination, imaging, and histopathology we concluded that the patient was diagnosed with UEC at the gastroesophageal junction. The patient the received chemoradiotherapy of CDDP + 5-FU along with radiation, but declined the temporary gastrostomy as nutritional intervention. Esophageal undifferentiated carcinomas are rare neoplasms and often associated with locoregional recurrence and/or distant metastasis. Multidisciplinary involvement for the treatment of this disease is necessary to obtain a better outcome.

Keywords: Undifferentiated carcinoma, Esophageal carcinoma, Esophageal stricture, Dysphagia, Chemoradiotherapy

INTRODUCTION

Esophageal cancer is a pernicious malignancy which can be disclosed at an early stage but is more often diagnosed in its advanced stage. It can affect both male and female, inflicting both the young and the elderly.[1] Esophageal cancer is the seventh most common malignancy globally, with more than 500,000 new cases diagnosed annually. It is the sixth most common cause of death from cancer and is the eighth most common cancer worldwide. [1,2] Patients with esophageal cancer have an overall 5-year survival rate below 20%. Esophageal carcinoma increases in incidence with age, peaking in the seventh and eighth decades of life. [2] There are multiple underlying factors involved in the pathogenesis of this cancer including chronic inflammation.[2,3] There are two main types of cancer of the esophagus according to its cell origin, squamous cell carcinoma and adenocarcinoma. But there are also other uncommon forms of esophageal malignancy include melanomas, sarcomas, lymphomas, undifferentiated carcinoma, and carcinoid tumors.[2,3] Early diagnosis of esophageal carcinoma is associated with a good prognosis, whereas poor outcomes are related to advanced stages of disease and the propensity for metastasis.

Undifferentiated carcinomas of the esophagus (UEC) are rare neoplasms and associated with a poor prognosis. Reports of these neoplasms have been limited. However, the prevalence of undifferentiated carcinoma within the previous varies widely and ranges from 0.15% to 4.5%.[3,4] This difference in prevalence reflected the lack of diagnostic criteria for esophageal undifferentiated carcinomas. Other than the absence of recognizable histologic differentiation beyond an epithelial phenotype. Also, a specification of pathologic features for undifferentiated carcinomas has not been established. Considering that undifferentiated carcinomas are aggressive neoplasms, an accurate diagnosis and

appropriate classification of these neoplasms are clinically relevant.[4]

CASE REPORT

A 46 years old male was admitted to the bronchoesophagology department in the ENT Outpatient Clinic in DR Sardjito Public Hospital with a chief complaint of progressive difficulty in swallowing over the pass 6 months as well as unintentional 30-pound weight loss. At first, the difficulty was only with swallowing solids but this progressed to liquid as well within the last two months. The patient also stated that the main complaint was accompanied with heartburn and discomfort around the lower chest to the upper stomach area. He reported heavy tobacco smoking since he was 10 years old about 2 packs per day and no alcohol consumption. His occupation was a construction worker, no history of cancer in the family, diabetes mellitus, heart disease or hypertension.

A double-contrasted esophagogram using high resolution MSCT was done and revealed circular thickening of esophageal wall at the level of 7th thoracic vertebrae into the gastric antrum with an enhancement of contrast suggesting malignant feature and causing stricture and obstruction of the esophageal lumen, also esophageal dilatation proximal to the obstruction. The MSCT imaging also showed contrast-enhanced lymphadenopathy in the lower carinae with the diameter of 4.6 cm suggesting nodular metastasis to the regional periesophageal lymph node.

Rigid esophagoscope was performed and biopsies were taken from the lesion. Located at the gastroesophageal junction was a fungating mass measuring up to 4.5 cm in greatest dimension. The mass was so fragile that the whole protrusion of this was evacuated leaving a small hole of the remaining esophageal lumen. The specimen of the lesion was then sent to the pathology anatomy department for the histopathology feature.

Histological study from biopsy samples revealed the tumor was undifferentiated carcinoma, however, this was not the initial result. At first, the histological study showed solid and infiltrative atypical polymorphic tumor cell with a few cytoplasm, round nuclei, hyperchromatic, and abundant mitosis with tumor infiltrating leucocytes (TIL)±5%. The first conclusion was non-Hodgkin's lymphoma large cell type with differential diagnosis of Undifferentiated carcinoma.

Immunohistochemistry staining of LCA and CK were needed to confirm the diagnosis so we did the staining and found out that the CK staining was positive with moderate to strong intensity in the membrane and cytoplasm in all tumor cells, whereas the LCA staining was negative. Therefore, we decided that the final histopathology result was undifferentiated carcinoma.

The patient was diagnosed with undifferentiated carcinoma of esophagus T2N1M0 stage IIB.

The lesion was diagnosed as stage IIIA according to IASLC Cancer Staging: Esophagus and Esophagogastric Junction and was determined to be a severe case because surgical control of undifferentiated carcinoma of esophagus is almost impossible even at the early stages. Chemoradiotherapy consist of cisplatin (CDDP)+5-fluorouracil (5-FU) with radiotherapy was selected as the first treatment for this case. We also proposed surgical temporary gastrostomy to fulfil the appropriate nutritional intake for this patient but the patient had declined the procedure.

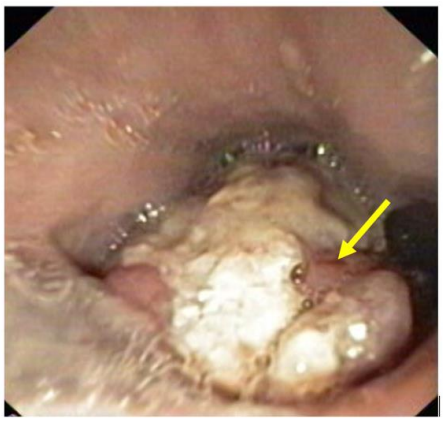

Figure 1: Protruding mass from flexible esophagoscopy with debris of food residues and saliva (yellow arrow) inside the esophageal lumen.

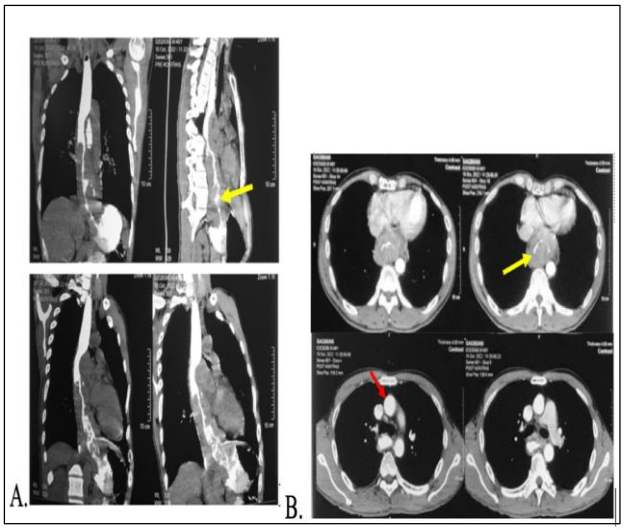

Figure 2: Doubled-contrast MSCT of esophagus (A) coronal and sagittal view of thickening esophageal wall causing filling defect of the esophagus (yellow arrow); and (B) axial view showed thickening of the esophageal wall (yellow arrow) and lymphadenopathy periesophageal at the lower carina (red arrow).

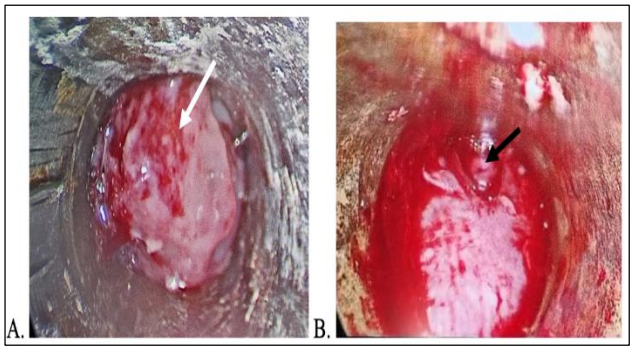

Figure 3: (A) Fungating and fragile mass of the esophageal lumen view from rigid esophagoscope (white arrow); and (B) stenosis of the esophageal lumen after the mass was evacuated (black arrow).

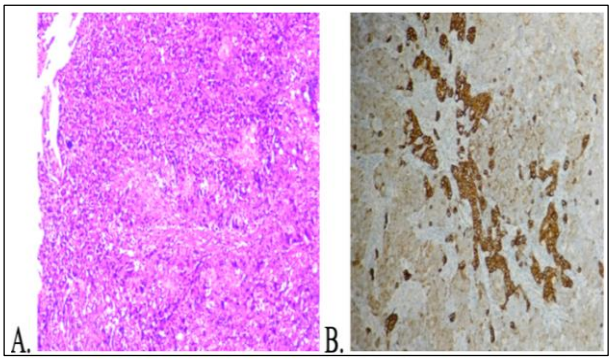

Figure 4: Histologic feature of the biopsy tissue (A) hematoxylin eosin staining of the tissue; and (B) IHC CK positive staining.

DISCUSSION

Undifferentiated carcinoma of the esophagus (UEC) is not common among esophageal malignancies. UCE is rare among esophageal malignancies, with a reported incidence of approximately 1%. [5] The prognosis is poor because of extensive lymphatic and hematogenous metastasis in its early stages. Unfortunately, the most favorable treatment approach for this malignancy has not been established.[5,6]

The etiology of this type of esophageal cancer is still unclear but it is believed to be multifactorial due to the genetic predisposition, food, occupational, and environmental factor. The join effect of smoking and alcohol consumption on mortality of UEC had never been observed because its low incidence number. Excessive use of alcohol, tobacco, low intake of fruits and vegetables, and low socioeconomic status increased the risk of esophageal squamous cell carcinoma, whereas gastroesophageal acid reflux, obesity, smoking, and absence of H. Pylori are important risk factor of adenocarcinoma. However, there's no previous source that specifically mentioned the risk factor for undifferentiated carcinoma.[7] When UEC was compared with other types of esophageal carcinoma, clinically there was no significant difference in tumor location, length, depth of invasion, macroscopic feature, lymph node and distal metastasis. Most patient with esophageal cancer presents in their 5th and 6th decade of life. The most common presenting symptoms of patients with esophageal cancer are dysphagia and weight loss, occurring in nearly 90% of patients.[7,8] The dysphagia is typically progressive from solid initially to liquids due to the tumor obstructive process, other symptoms may include odynophagia, hoarseness, cough, chest pain, melena, and also sequel of locally advanced disease or metastasis if it appears such as neck masses or shortness of breath if there's pulmonal spread. Over 75% will have lymph node involvement at the time of presentation but not always detected in every case.[7-9]

After a complete history taking of the duration and severity of the symptoms, it would be necessary to determine the nutritional status for the patient. It must be decided whether the patient will need nutritional intervention through feeding tube or even gastrostomy. In this case, the use of nasogastric tube was no longer possible due to the stricture and obstruction caused by the tumor. Therefore, we offered a temporary gastrostomy as a nutritional intervention for the patient but he declined since he felt that he could still be able to eat orally even if it's only bit by bit.

Previous study has shown that cytokeratin (CK) and epithelial membrane antigen (EMA) are useful as immunohistochemical markers of epithelial differentiation.[10,11] These antibodies have been used to examine the histogenesis of the undifferentiated carcinoma. CK is an intermediate filament protein in epithelial tissues. EMA is also expressed by most epithelial tumor, including esophageal cancer.[12,13] Expression of these markers indicates that the tumor was originated from epithelial cells. The p53 gene product can act as a transcription factor with an important role in controlling cell proliferation and differentiation. The origin of this tumor is undifferentiated cell with potential to differentiate in multiple ways.[12,13]

This case also showed positive moderate to strong staining of the CK, therefore, could confirm our histopathologic feature and establish the diagnosis. We only able to stain the specimen with CK due to the unavailability of the EMA, but we also did LCA staining to the specimen that yielded negative result which means the differential diagnosis of lymphoma could be excluded.

The staging of the disease is of paramount importance and every treatment decision should routinely be based on multidisciplinary discussion in the tumor board. The clinical staging of esophageal cancer is assessed with the widely accepted TNM system developed by the American Joint Committee on Cancer (AJCC). Pretreatment staging of esophageal cancer will directly affect overall treatment options available to each patient and their prognosis, so accurate staging is essential. T staging of esophageal cancer focuses on identifying the depth of invasion of the

primary tumor. A critical aspect of T staging focuses on establishing if the primary tumor has invaded the surrounding mediastinal structures, given that these patients would no longer be considered surgical candidates. When assessing the esophagus by CT, a basic starting point to consider is the esophageal wall thickness. A wall thickness greater than 5 mm is considered abnormally thick, given that the distended wall of the esophagus is usually less than 3 mm.[12-14]

Asymmetry is a classic but nonspecific CT finding of esophageal cancer and esophageal wall thickness symmetry should always be considered when evaluating the esophagus by CT.[12] The most useful aspect of CT imaging in determination of T status is evaluating if the primary tumor invades into adjacent structures. Obliteration of the fat planes between the primary tumor and the adjacent structures on CT would establish the primary tumor as a T4 stage cancer. The sensitivity and specificity of CT to detect mediastinal invasion ranges between 85%-100%. esophageal ultrasound (EUS) is now considered the most accurate imagining modality available to establish T staging of esophageal cancer. In comparison to CT, EUS is more accurate to differentiate between T1, T2 and T3 tumors. [12-14]

In esophageal cancer, N Staging can be defined by the involvement (N1) or absence of involvement (N0) of peri-esophageal lymph nodes. Sensitivity and specificity of CT scans to detect periesophageal lymph node involvement depends on the size of the lymph nodes. This case also showed a regional lymph node metastasis in periesophageal lymph node at the level of carina with the diameter of 4,6 cm.[12-14] Most studies used common size criteria of 1 cm to define lymph node as enlarged. The CT imaging was used to detect this lymph node metastasis for its accuracy to detect a metastatic enlargement in UEC is around 72-80%. Esophageal cancer is notoriously aggressive and invasive in nature. Esophageal cancer is notoriously aggressive and invasive in nature. In fact, 20%-30% of patients with esophageal cancer will have distant metastasis at time of initial diagnosis. Common sites of distant metastasis include liver, lung, and bones. [12-14] Base on these references, we decided to diagnosed this patient as UEC stage IIIA with T2N1M0 from the CT imaging and histopathology results using IASLC cancer staging: esophagus and esophagogastric junction.

Management of esophageal cancer has evolved since the two last decades.[12,13] Esophagectomy remains the primary treatment for early stage esophageal cancer although its specific role in superficial cancers is still under debate since the development of endoscopic mucosal treatment. [14] Although combined treatment including surgery, chemotherapy, and radiotherapy has been attempted, the prognosis for UEC remains poor. Radiotherapy has been used concurrently with multidrug chemotherapy to enhance local control in UEC. The role of surgery for patients with limited UEC is controversial.[14] Previous studies reported success in treatment for advanced UEC using nedaplatin, 5-FU, and radiotherapy. Induction chemotherapy followed by concurrent CRT was believed to yield successful results in the treatment for undifferentiated carcinoma.[14,15] However, there is no clear evidence that any anticancer agent or irradiation can increase the survival time of patients with UEC at this time. Further studies to clarify the response rate and survival effect of CRT in patients with UEC are expected.[15]

CONCLUSION

UEC is a very rare case that has a highly malignant potential due to rapid progression of the primary tumor or metastasis. Even though clinically similar to any other tumor in esophagus, immediate and adequate multidisciplinary treatment for this disease is necessary in order to obtain a better outcome. It is also important to establish a basic standard therapy for UEC.

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