Sri Lanka Journal of Medicine **SLJM**

Case Report

Citation Lazar MV, Zacharia GS, Varghese AS et al. 2026 An Esophageal Neoplasm Sans Lineage: Undifferentiated Carcinoma. Sri Lanka Journal of Medicine, pp. 59-63.
DOI: https://doi.org/10.4038/sljm.v35i1.620

An Esophageal Neoplasm Sans Lineage: Undifferentiated Carcinoma

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ABSTRACT

Undifferentiated esophageal carcinoma is an infrequently encountered but highly aggressive variant of esophageal cancer, recently recognized by the World Health Organization as a distinct pathological entity. It lacks definitive lineage-specific differentiation and represents <4% of all esophageal malignancies. We here report a middle-aged male with progressive dysphagia and weight loss, diagnosed with metastatic undifferentiated esophageal carcinoma and initiated on palliative chemotherapy and immunotherapy. Despite its rarity, undifferentiated neoplasia poses significant diagnostic and therapeutic challenges due to its aggressive nature and the absence of established treatment protocols. This case underscores the importance of comprehensive histopathologic and immunophenotypic evaluation in modern-day oncology. Further research is essential to elucidate the molecular mechanisms underpinning dedifferentiation, explore targeted therapies, and improve outcomes in this highly malignant tumor subset.

Keywords: Esophagus, Undifferentiated cancer, Dysphagia, Barret's

INTRODUCTION

Esophageal carcinomas are relatively frequent: the seventh most common cancer worldwide and the sixth frequent offender in cancer-related mortality; they are closely linked to Barret's esophagus, smoking, and ethanol use. Squamous cell carcinoma and adenocarcinoma are the most common histological variants; trends show a decline in the incidence of the former and an increasing incidence of the latter over the past decades.[1] Less frequent esophageal neoplasia include adenosquamous, mucoepidermoid, verrucous, carcinosarcoma, adenoid cystic, cuniculate, neuroendocrine, melanomas, stromal tumors and undifferentiated carcinomas. [2] A neoplasm devoid of differentiating markers, or undifferentiated carcinoma, is an exceedingly rare finding in the esophagus, with a prevalence of 0.15% to 4%. [3] It was only in 2020 that the World Health Organization (WHO) recognized 'Undifferentiated Esophageal Cancer" (UEC) as a separate entity. The variant is typically very aggressive and carries a poor prognosis., with a mere 25% one-year survival rate. [4] The diagnostic criteria for this rare tumor variant have yet to be clearly defined. Still, they primarily rely on excluding differentiated neoplasia through a battery of immunohistochemical staining methods. There are no specific treatment

Received: 2025-05-24 **Accepted revised version: 2026-04-10** **Published: 2026-04-22**

strategies for UEC; the same approach is employed for other esophageal neoplasia.

CASE REPORT

This 44-year-old gentleman presented with progressive dysphagia and pain in the lower chest and epigastrium of three weeks' duration. He reported anorexia and unexplained weight loss of fifteen kilograms over the past three months. He had no vomiting, overt gastrointestinal bleeding, yellowish discoloration of eyes or body, altered bowel habits, fever, or altered mental status. He was diagnosed with diabetes mellitus and dyslipidemia six years ago, and ever since then, he has been on regular medications for the same. The physical examination was unremarkable, except for a scaphoid abdomen; no palpable organomegaly, abdominal mass, or free fluid was noted during the abdominal examination. The routine hematological and biochemical parameters were generally normal, except for anemia and hyperglycemia, as summarized in Table 1.

Table 1: Summary of hematological and biochemical results at presentation

Parameter	Results	Reference range
Hemoglobin (gm/dL)	11.3	14 – 17.5
Leukocyte count (cells/µL)	7800	4400 - 11300
Platelet count (x 103 cells/ µL)	278	150 - 450
Bilirubin Total/Direct (µmol/L)	7.7/3.8	0 – 21 / 0 -5
AST/ALT (IU/L)	26/21	5 – 40
ALP (IU/L)	150	40 – 129
Sodium (mmol/L)	139	135 – 148
Potassium (mmol/L)	4.2	3.5 – 5.5
Albumin (g/L)	40	39.7 – 49.4
Prothrombin time (scc)	11.1	9.1 – 12.1
CRP (mg/L)	55	0 – 5
BUN (mmol/L)	4.34	2.14 – 7.14
Creatinine (µmol/L)	87	62 – 106
HbA1c (%)	9.2	<5.7%

The esophagogastroduodenoscopy (EGD) revealed an eccentric, esophageal ulceroproliferative lesion extending 25 to 37 centimeters from the incisors (Figure 1). A computed tomography (CT) of the abdomen and thorax imaged an abnormal long-segment asymmetrical circumferential wall thickening involving the mid and lower third of the esophagus (Figure 1), with multiple enlarged subcarinal, mediastinal, gastrohepatic, and retroperitoneal lymph nodes, as well as hepatic metastatic lesions. The esophageal lesions were sampled using endoscopic biopsy forceps.

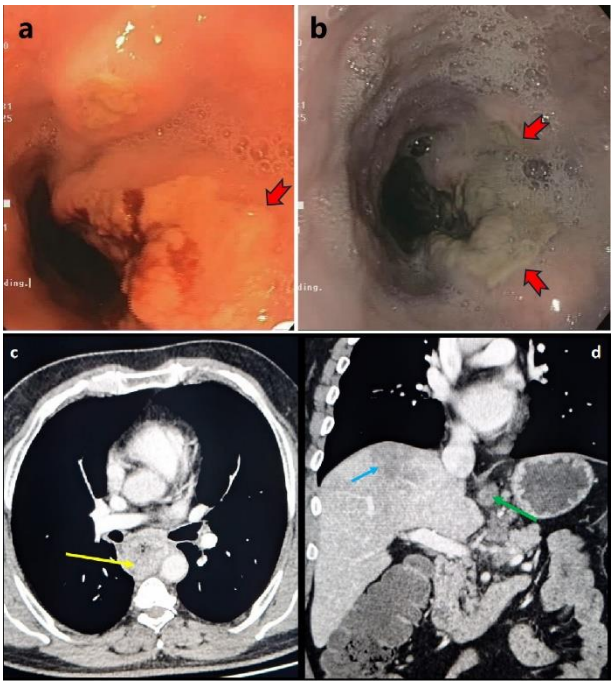

Figure 1: (a, b) Endoscopic images demonstrating the eccentric, esophageal ulceroproliferative lesion (red arrows). (c) The axial CT image reveals asymmetrical circumferential wall thickening involving the mid and lower third of the esophagus (yellow arrow). (d) The coronal CT images reveal an irregular hypodense peripherally enhancing lesion in the right lobe of the liver (blue arrow) and enhancing gastrohepatic lymph nodes (green arrow).

Histopathology revealed extensive neoplastic infiltration composed of sheets of medium to large

cells with poorly defined amphophilic cytoplasm and moderately pleomorphic, vesicular nuclei, accompanied by conspicuous nucleoli, prominent apoptosis, necrosis, and scattered mitotic figures. Upon extensive immunohistochemical work-up, these neoplastic cells showed patchy moderate staining for epithelial membrane antigen (EMA) and were negative for other epithelial lineage markers, including pan-cytokeratin (CK), CK7, and CK20. The immunomarkers for squamous (p63, p40), glandular (Ber-EP4, MOC31), and neuroendocrine (synaptophysin, chromogranin) differentiation were also negative.

The wide panel of immunomarkers including CD 117, DOG-1, SOX-10, CD45, CD20, CD3, PAX 5, MPO, CD15, SMA, Desmin, CD138, CD30, ALK-1, bcl2, CD99, TLE-1, and ERG, performed to evaluate for epithelioid GIST, mucosal melanoma, germ cell tumors, hematolymphoid and mesenchymal neoplasms were noncontributory. INI-1 was retained, while Spalt-like transcription factor 4 (SALL4) expression was noted. The overall immune-pathological picture was consistent with undifferentiated esophageal cancer. The neoplastic cells were negative for HER-2 (score 0), and the combined proportion score (CPS) for PD-L1 (Ventana 22C3) was 15. Among the biopsy fragments, columnar-lined mucosa with intestinal metaplasia was present, favoring the probable pathogenesis of this undifferentiated carcinoma from Barrett's metaplasia to adenocarcinoma and its dedifferentiation. Figure 2 depicts the microphotographs, including immunochemical profiling of the neoplasm.

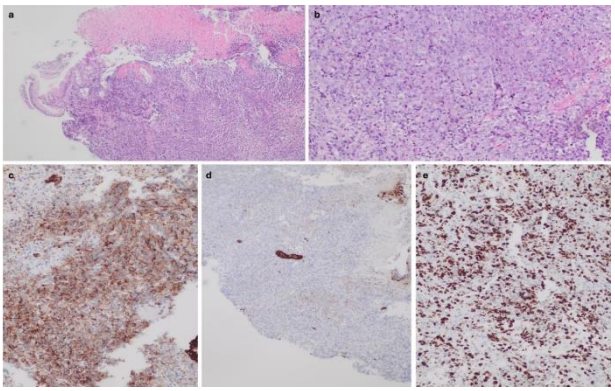

Figure 2: (a) Hematoxylin & Eosin, 4x: Gastroesophageal mucosa with ulceration and extensive infiltration by malignant neoplasm. (b) Hematoxylin & Eosin, 10x: Malignant neoplasm composed of sheets of medium to large cells with poorly defined amphophilic cytoplasm and moderately pleomorphic vesicular nuclei, featuring conspicuous nucleoli and exhibiting prominent apoptosis and scattered mitotic figures. (c) Granular cytoplasmic immunohistochemical staining for EMA (Epithelial Membrane Antigen) in neoplastic cells. (d) Negative staining for pancytokeratin immunohistochemistry in the neoplastic cells. (e) Neoplastic cells with a high Ki67 index of 80%.

The tumor was classified as stage cT3 cN3 cM1 (IVB), and he was initiated on palliative systemic chemotherapy and immunotherapy: oxaliplatin 160 mg, 5-fluorouracil 5,600 mg, leucovorin 800 mg, and nivolumab 240 mg, administered every two weeks for a total of six cycles. As per the institutional tumor board consensus, he is planned for reassessment and radiotherapy subsequently

DISCUSSION

Esophageal undifferentiated carcinomas are infrequent by aggressive neoplasia with an overall poor prognosis. The exact incidence or prevalence of UEC is unclear, but the reported prevalence ranges from 0.15% to 4%. [3] The published literature suggests an association with Barrett's esophagus, a link that still needs to be confirmed. [3] The current WHO classification recognizes UEC as a distinct entity, with an International Classification of Diseases Oncology, Third Edition (ICD-O-3) code 8020/3. [5] Case studies report that the UEC is more frequent in men, with a mean age of diagnosis of 65 years, frequently involving the distal esophagus, with a high incidence of lymphovascular involvement and distant metastasis. [3] In line with all esophageal neoplasia, EUC typically presents with dysphagia; other manifestations include weight loss, chest pain, or upper gastrointestinal bleeding. The diagnosis largely relies on esophagogastroduodenoscopy and histopathological analysis. The classical appearance is of an exophytic ulceroproliferative lesion, often involving the distal esophagus. Pathology reveals nests or sheets of medium to large-sized cells with amphophilic to eosinophilic cytoplasm and oval vesicular nuclei with multiple mitotic figures. Interspersed multinucleated osteoclast-like giant cells may also be identifiable.

[3] Small areas, less than 5%, of peripheral adenocarcinomatous tissue have been reported histologically, which, together with the distal esophageal location and association with Barrett's esophagus, support the hypothesis that undifferentiated carcinomas arise from the dedifferentiation of adenocarcinoma. [3,4] Mutations involving the tumor suppressor gene SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin subfamily A member 4/2 (SMARCA4/2) is associated with UEC. [6]

The diagnostic criteria for UEC are poorly defined beyond the lack of evident squamous, adenomatous, neuroendocrine, or other specific differentiation. Tumor staging utilizes the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) system. The AJCC recommends histological grading of esophageal tumors to grade not assessed (Gx), well-differentiated (G1), moderately differentiated (G2), and poorly or undifferentiated (G3). If an undifferentiated neoplasm, after further analysis, reveals a glandular component, it is graded as undifferentiated adenocarcinoma. Conversely, if it has a squamous component or if no definite origin can be ascertained, it should be graded as undifferentiated squamous carcinoma. [7] Immunohistochemical analysis with markers for mucins (adenocarcinomas), p63 and p40 (squamous cell carcinomas), chromogranin A and synaptophysin (neuroendocrine tumors), and cytokeratins and epithelial membrane antigen (epithelial tumors) aids in the diagnosis of EUC. [3,8] SALL4 expression is described in 67% of UEC, associated with an unfavorable prognosis and overexpression of proliferative and metastasis-related genes. [3] Computed tomography and endoscopic ultrasound enable accurate loco-regional staging, while positron emission tomography is considered the gold standard for detecting distant metastases. [9]

The treatment of esophageal cancers depends on the stage and grade of the disease. In early disease, T1N0M0, endoscopic resection techniques are recommended. In locally advanced resectable disease (T1-T4, N0-N3, M0), surgery, with or without perioperative chemotherapy or radiotherapy, is the gold standard. Owing to its excellent response to chemoradiotherapy, it alone can be utilized as curative therapy in selected patients with squamous cell cancer in combination with close surveillance. The treatment of advanced esophageal neoplasia includes immune checkpoint inhibitors like pembrolizumab, nivolumab, or palliative intent chemotherapy. In advanced cancers, esophageal stenting or stoma feeding might have to be resorted to ensure enteral nutrition. [10].

CONCLUSION

Undifferentiated esophageal carcinoma is a recently recognized, rare, but aggressive malignancy with an overall poor prognosis. Due to its lack of morphologic differentiation, the diagnosis relies upon comprehensive immunohistochemical profiling, largely to exclude differentiated neoplasia. Emerging evidence suggests an association with Barrett's esophagus and possible origin from a dedifferentiated adenocarcinoma.

Author declaration

Acknowledgement
None.

Authors' contributions:
MVL: Methodology design, data curation; GSZ: Conceptualization, manuscript preparation, manuscript revision; ASV: Methodology design, data curation; MA: Methodology design, data curation. HP: Methodology design, data curation.

Conflicts of interest:
The authors declare that there is no financial or non-financial conflict of interest.

Funding statement:
Self-funded.

Ethics statement:
Written informed consent was obtained from the patient before they participated in the case, ensuring their understanding of the purpose, procedures, and potential implications involved.

Statement on data availability:
All data are available upon request.

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