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CASE REPORT

Sudden Death Due to 5-Fluorouracil-Induced Cardiotoxicity in a Case of Esophageal Carcinoma: A Case Study with Brief Review of Literature

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ABSTRACT

Undifferentiated carcinoma of the esophagus is a rare, aggressive tumor with no specific treatment guidelines and a poor prognosis. 5-Fluorouracil (5-FU), a key drug in the treatment of gastrointestinal cancer, is known for its rare but serious cardiotoxic effects. Here, we report a case of sudden cardiac death of a 47-year-old male with metastatic undifferentiated esophageal carcinoma following his second cycle of chemotherapy (FOLFOX). The patient developed chest pain and breathlessness after being discharged and was later declared dead on arrival at the hospital. Autopsy revealed myocardial infarction, and histopathology confirmed acute ischemic injury without an underlying coronary artery disease. Immunohistochemistry reaffirmed the undifferentiated carcinoma of the esophagus. This case highlights the fatal cardiotoxic effects of 5-FU, emphasizing the need for cardiac monitoring and considering alternate treatment protocols in high-risk individuals. It also underscores the importance of chemotherapy-induced cardiotoxicity as a differential diagnosis while doing postmortem evaluation of sudden deaths following cancer treatment.

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• 5-Fluorouracil • Cardiotoxicity • Chemotherapy • Undifferentiated carcinoma esophagus • Sudden death

INTRODUCTION

The esophagus is a muscular tube connecting the oropharynx with the stomach. It initiates the peristaltic movement, which is vital for the forward movement of food/bolus in the GIT. Esophageal pathology can be broadly classified under congenital disorders, inflammatory disorders, mechanical/neurological disorders, carcinomas, and miscellaneous conditions. Esophageal carcinoma mostly develops from the tissue lining the esophagus. It contributes 5-15% of esophageal pathologies. It is the 11th most common overall type of cancer and 7th most common cause of cancer-related mortality globally, with an estimated 511,000 new cases and 445,000 fatalities in 2022.[1-3]

There are two broad categories of esophageal cancer: Squamous cell carcinoma which constitutes 80-90% of cases globally, mostly in Eastern Asia, Southern Africa, and parts of Eastern Europe, with risk factors including tobacco use and alcohol consumption.[4-5] Adenocarcinoma, which originates from glandular cells in the lower esophagus, constitutes 10-20% of cases and has become increasingly common, particularly in Western countries, because of GERD, Barrett's esophagus, and obesity.[3,6] Other less common forms of esophageal cancer, including small cell carcinoma, sarcomas, undifferentiated carcinoma and esophageal lymphoma, account for less than 1%.[7]

Common symptoms of esophageal carcinoma include progressive dysphagia (difficulty swallowing), unintended weight loss, chest pain, and hoarseness. These symptoms usually appear in later stages of the disease, leading to delayed diagnosis and poor outcomes.

Undifferentiated carcinoma of the esophagus is a rare and aggressive tumor that lacks the typical features of squamous cell carcinoma or adenocarcinoma. Because of its rare and high-grade nature, there are no well-established treatment protocols, and it is treated as advanced esophageal cancer.[7]

Chemotherapy plays an important role in the management of advanced esophageal cancer. For patients with inoperable tumors, definitive chemoradiotherapy, often utilizing cisplatin and 5-fluorouracil (5-FU), serves as the primary curative approach.[8] In metastatic or recurrent disease, palliative chemotherapy, with regimens such as FOLFOX or capecitabine based combinations, are used. Furthermore, targeted therapy (e.g., trastuzumab for HER2-positive tumors) and immunotherapy (e.g., nivolumab/ pembrolizumab for PD-L1 positive tumors) have been used in advanced-stage disease.[8]

5-Fluorouracil (5-FU), a fluoropyrimidine commonly used in esophageal carcinoma, is associated with rare but potentially severe cardiotoxic effects.[9-10] The incidence of fluoropyrimidine-related cardiotoxicity is seen in 1 to 19% and mortality has been reported as 0 % to 13%.[9,11]

In this case report, we describe a case of a middle-aged man with carcinoma esophagus presenting with chest pain and shortness of breath, followed by becoming unconscious post 2nd cycle of chemotherapy, where there is a potential possibility of 5-FU-induced cardiotoxicity, which was explored and confirmed.

CASE BACKGROUND

A 47-year-old male with no significant past medical history presented with dysphagia and frequent regurgitation. Medical evaluations, including Contrast-Enhanced Computed Tomography (CECT) scan, revealed a large mass in the distal and mid-thoracic esophagus, extending from the D8 to D12 vertebral levels, and a focal nodule of size 8mm x 6mm is present in segment V of the liver. It was diagnosed as Carcinoma esophagus with liver metastasis and was started on palliative chemotherapy due to metastasis with the FOLFOX regimen, which included oxaliplatin (100 mg), leucovorin (180 mg), and 5-fluorouracil (5-FU). After receiving his second cycle of palliative chemotherapy

(FOLFOX regimen), he was discharged after a few hours of observation, as his vitals were stable.

Upon reaching home, the patient began experiencing symptoms of increasing breathlessness and chest pain following an episode of vomiting. These symptoms progressively worsened, and the patient eventually lost consciousness. He was rushed to a nearby tertiary care hospital, where he was declared dead upon arrival. The postmortem was done within 24 hours of being declared dead. The deceased was of average built and moderately nourished. On external examination, no external injuries were present.

On post-mortem computed tomography (PMCT) examination, a hyperdense mass measuring 12.2 cm x 5.8 cm x 8.2 cm is present at the lower end of the esophagus with a Hounsfield unit (HU) of 40 ± 20, suggestive of an esophageal mass correlating to his medical history of carcinoma esophagus. Bilateral pleural effusion was present. Lungs showed bilateral ground-glass opacities observed in the perihilar regions, along with interlobular septal thickening, indicating pulmonary edema (*Figure 1a*).

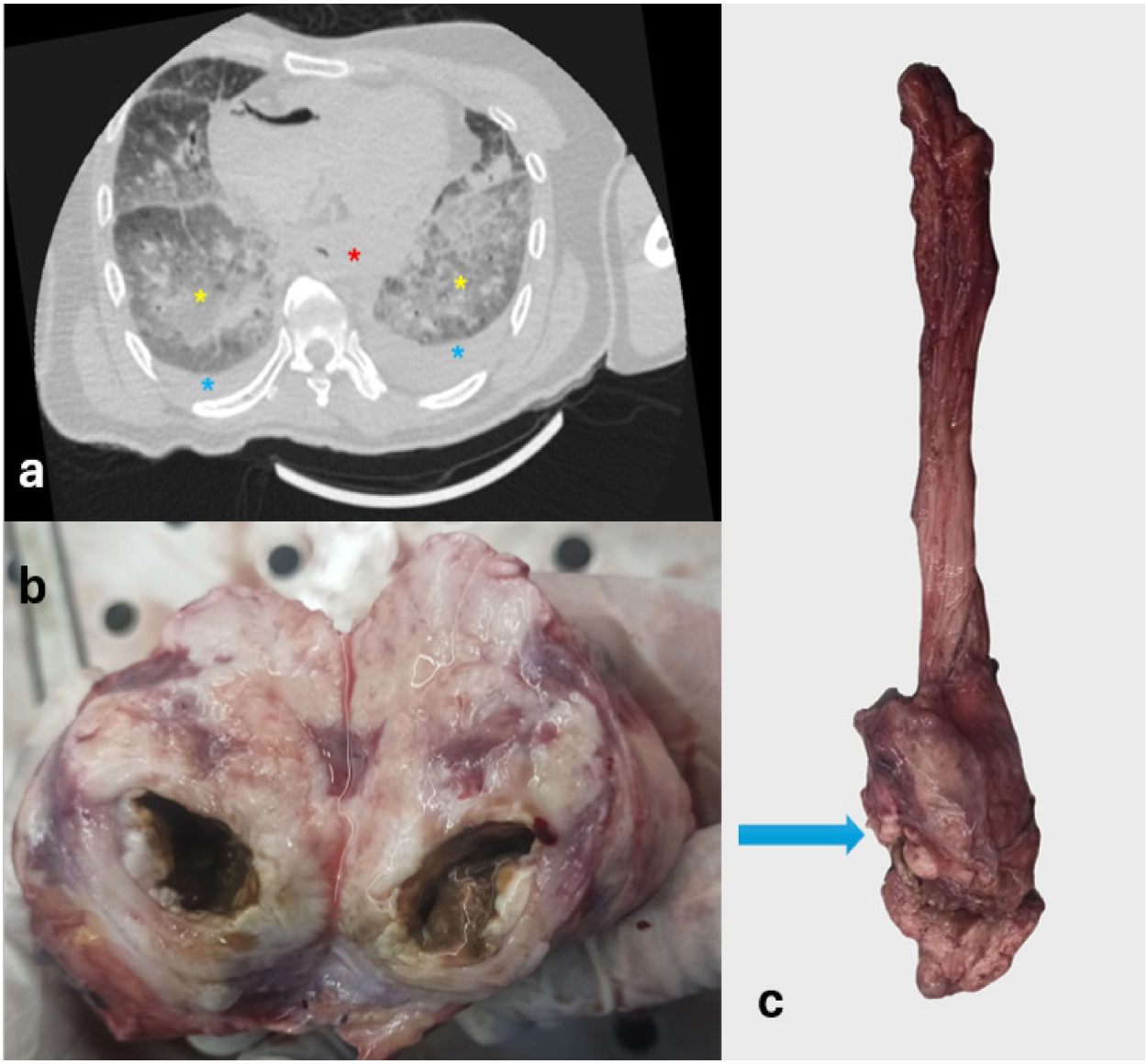

Figure 1: A: Postmortem CT axial section in lung window showing a hyperdense mass at the lower end of the esophagus (Red Asterix), bilateral pleural effusion (Blue Asterix) and bilateral ground-glass opacities along with interlobular septal thickening (Yellow Asterix); **B:** The cut section of esophageal mass showing irregular and uneven margins, and areas of necrosis; **C:** showing a mass located at the lower end of the esophagus (Blue arrow).

Traditional autopsy was done with lettules technique of dissection, which showed a mass of 12 cm x 6 cm x 8 cm located at the lower end of the esophagus. The mass was firm in consistency, with irregular and uneven margins, and areas of necrosis (*Figure 1b,c*). On gross examination of the heart, a 13 cm x 3 cm red hemorrhagic infarct was noted in the left ventricle, extending into the myocardium, and multiple petechial hemorrhages were observed on the posterior aspect of the heart (*Figure* 2a,b). On dissection, all coronary vessels were patent throughout their course with no atherosclerotic plaques. The thickness of the left ventricle was 1.7 cm, the thickness of the interventricular septum was 1.4 cm, and the right ventricle was 0.7 cm. All the valves and chambers were normal. The weight of the heart was 300 grams. About 200 ml of serous fluid was present in the bilateral pleural cavity. Lungs were congested and edematous, weighing 650 and 600 grams. The liver capsule was intact, and the parenchyma appeared pale and softened. No other grossly distinguishable pathology was noted in the liver. All the other organs were grossly unremarkable.

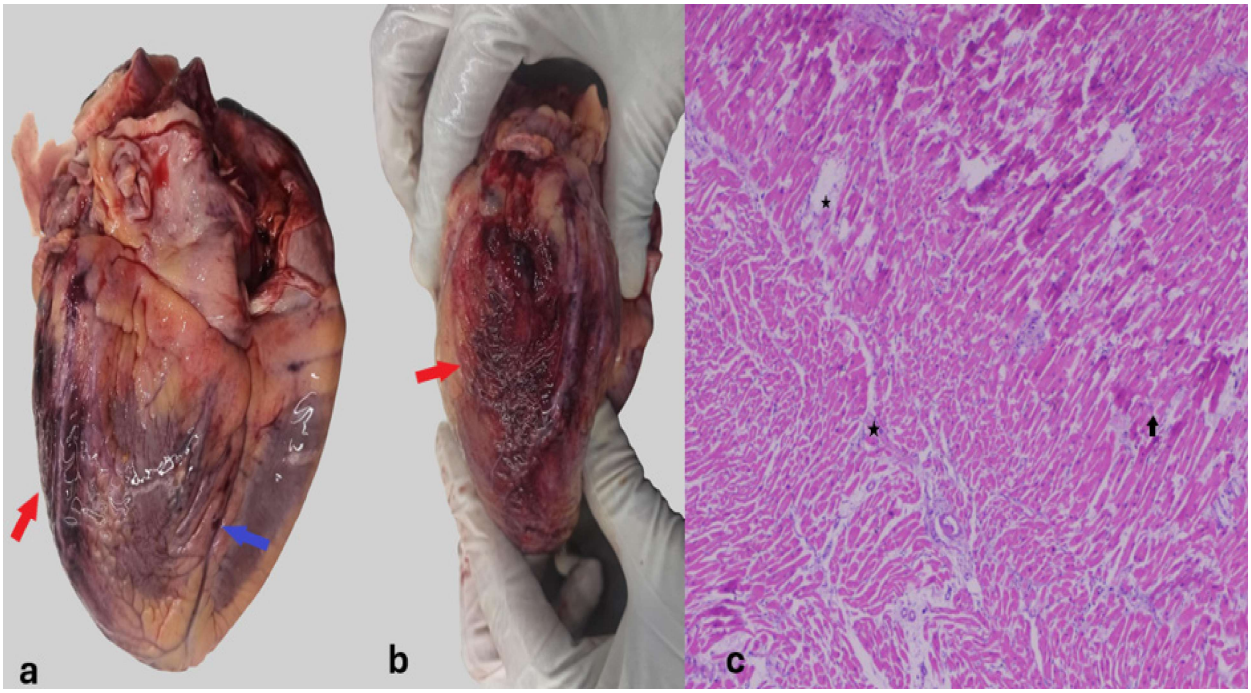

Figure 2: A: Gross examination of the posterior surface of heart showing a red hemorrhagic infarct over the left ventricle (red arrow), and multiple petechial hemorrhages over the posterior surface of the heart (blue arrow); **B:** Lateral view of the heart showing a red hemorrhagic infarct over the free wall of the left ventricle (red arrow); **C:** Histopathological examination of the heart showing patchy ischemic changes (black arrow), with loss of striations in the affected tissue, along with prominent interstitial edema (black stars).

Histopathological examination of the heart revealed patchy ischemic changes, with loss of striations in the affected tissue, along with prominent interstitial edema. The vessels were congested and were associated with surrounding infiltration by inflammatory cells. These findings confirmed a localized ischemic event, resulting in cellular damage and tissue dysfunction (Figure 2c). Lungs showed marked vascular congestion and pulmonary edema, characterized by fluid-filled alveolar spaces and engorged capillaries. Liver parenchyma showed a loss of architecture with ballooning of hepatocytes with areas of necrosis, and inflammatory cells.

The esophageal mass showed large areas of necrosis and was composed of round to oval cells having scant cytoplasm, increased nuclear to cytoplasmic ratio, granular to clear chromatin and conspicuous nucleoli in some of the cells. Focal osteoid formations were also seen (Figure 3a & b). The tumor cells were focally immunopositive for Pancytokeratin and are immunonegative for p40, chromogranin and synaptophysin, confirming the diagnosis of undifferentiated Carcinoma of the Esophagus (Figure 3c & d).

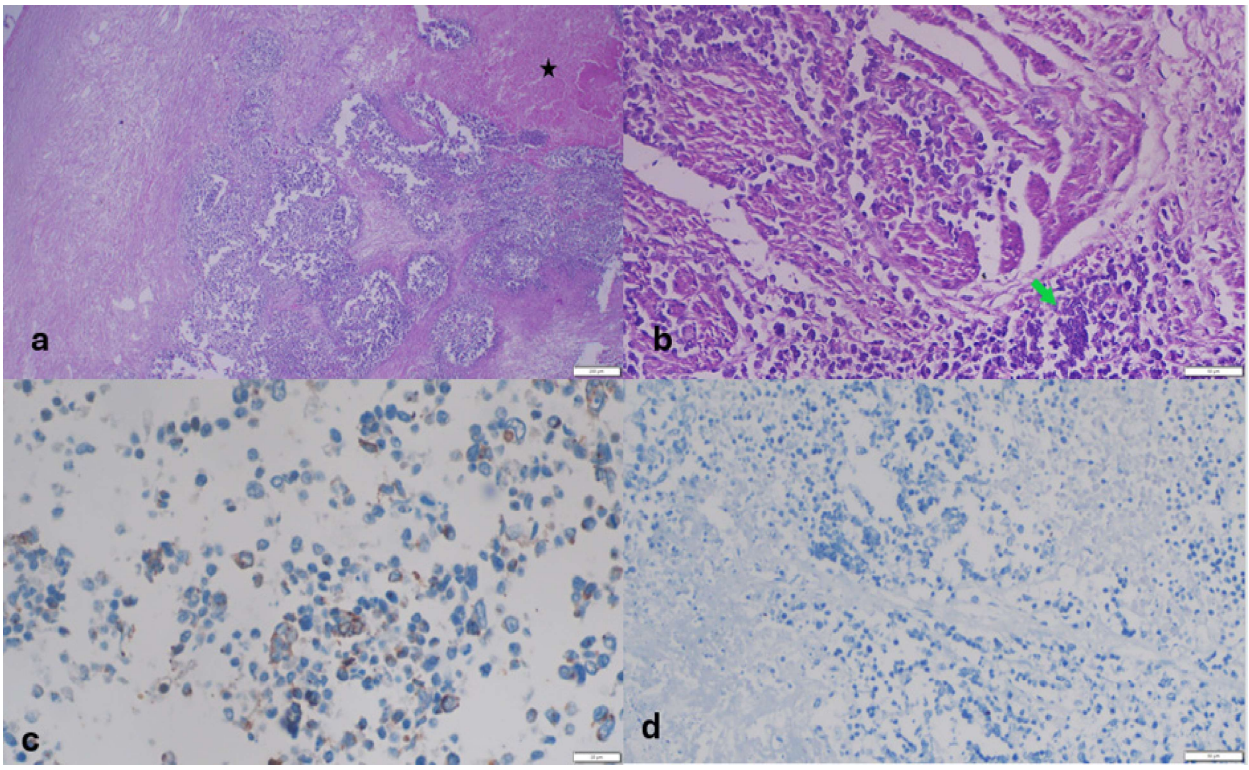

Figure 3A: Esophageal mass histopathological examination in hematoxylin and eosin stain at 10x magnification showing large areas of necrosis (black star); **B:** Hematoxylin and eosin stain at 40x magnification showing round to oval cells having scant cytoplasm, increased nuclear to cytoplasmic ratio, granular to clear chromatin and conspicuous nucleoli in some of the cells (green arrow); **C:** The tumor cells were focally immunopositive for Pancytokeratin; **D**: The tumor cells were immunonegative for p. 40**.**

The cause of death was opined as Acute Myocardial Infarction due to 5-Fluorouracil-induced Cardiotoxicity.

DISCUSSION

Undifferentiated carcinoma of the esophagus is an uncommon, extremely aggressive histological type in which has no characteristic features of squamous differentiation or glandular differentiation are present. This represents less than 1% of all the esophageal malignancies and is related to a rapid clinical course and poor prognosis.[7] Histologically, these tumors have marked atypia, necrosis and disorganized cellular patterns. Immunohistochemical examination is usually pancytokeratin positive, but p40 (indicative of squamous differentiation), chromogranin, and synaptophysin (indicative of neuroendocrine) are negative features in line with diagnostic considerations in their cases. The undifferentiated character of the neoplasm may have promoted the aggressive nature of the disease and limited the effectiveness of treatments, thus worsening the impact of chemotherapy-induced toxicity.[7]

It usually precipitates as an angina, but myocardial infarction, arrhythmias, heart failure, acute pulmonary edema, pericarditis and asymptomatic ECG changes can also be seen.[9-10] The incidence of cardiotoxicity of 5-FU is less common compared to anthracyclines.[12-13] If left untreated, cardiotoxicity of 5-FU shows an increased risk of morbidity and mortality.[12]

5-Fluorouracil, a fluoropyrimidine antimetabolite, is a cornerstone drug in the chemotherapeutic treatment of gastrointestinal cancers, including esophageal cancer. Its application extends to curative, adjuvant and palliative therapy.[9] 5-FU has an association with unusual yet potentially lethal cardiotoxicity, which can manifest as angina, arrhythmias, myocardial infarction, congestive cardiac failure and in severe cases, sudden cardiac death.[10,14] Even though the incidence of 5-FU cardiotoxicity varies from 1% to 19%, sudden cardiac death is exceptional but well-documented.[10] In 5-FU-induced cardiotoxicity,

acute cardiac events such as ventricular arrhythmias, myocardial infarction, and cardiac arrest can occur suddenly, which results in sudden cardiac death.[10,14]

Leucovorin itself is not cardiotoxic but may potentiate 5-FU-induced cardiotoxicity by enhancing thymidylate synthase inhibition.[15-16] On the other hand, oxaliplatin-associated cardiotoxicity is extremely rare (<0.5%), making it at least 10-30 times less common than 5-FU.[9]

The patient had onset of chest discomfort and dyspnea after his second dose of FOLFOX chemotherapy and died shortly thereafter. The postmortem changes consisting of a hemorrhagic infarct in the myocardium, histopathology confirmed ischemic myocardial damage and pulmonary edema, supporting an acute cardiac event as the cause of sudden death clearly explaining the lethal cardiotoxic effects of 5-FU.

The pathophysiology of 5-FU cardiotoxicity is not completely understood, but a lot of mechanisms have been proposed based on experimental findings:

1. **Coronary Vasospasm:** Thyss et al. provided evidence of elevated plasma endothelin-1 levels in patients who developed cardiotoxicity with 5-FU. Endothelin-1 is an extremely potent vasoconstrictor that reduces myocardial perfusion causing ischemic events.[10]
2. **Direct Myocardial Injury:** 5-FU is metabolized within the liver to α-fluoro-β-alanine (FBAL), which is further metabolized to fluoroacetate and fluorocitrate. These metabolites disrupt the Krebs cycle through inhibition of citrate metabolism, leading to mitochondrial dysfunction in cardiomyocytes and vascular smooth muscle. Thus, it may result in ischemia, arrhythmia and heart failure. Elevated FBAL has been reported in a patient by Muneoka et al. after 5-FU induced myocardial infarction, affirming its toxicity.[17]
3. **Vascular Endothelial Dysfunction:** Another theory is endothelial injury resulting in the development of microthrombi, which might not be apparent on gross or radiological examination but can decrease myocardial perfusion. Reactive oxygen species (ROS) accumulation, as explained by Focaccetti *et al*., results in endothelial dysfunction and a pro-thrombotic state, resulting in silent ischemic damage.[9]
4. **Impaired Oxygen Delivery:** 5-FU also changes the erythrocyte shape from biconcave to an echinocyte or spiky shape. This change impairs the oxygen-carrying capacity of erythrocytes and therefore, oxygen delivery to cardiac tissues, increasing ischemic injury. This hypoxia may result in arrhythmias and myocardial damage.[9]

The short interval between the administration of 5-Fluorouracil and the sudden cardiac death, along with gross and histopathological evidence of an acute cardiac injury even in the absence of any structural heart defects or atherosclerotic pathology, confirmed the fatal cardiotoxic effects of 5-Fluorouracil.

Discrepancies in the incidence of 5-fluorouracil induced cardiotoxicity reported may be due to varied routes of administration (bolus vs. continuous infusion), comorbidities, and genetic susceptibilities mainly dihydropyrimidine dehydrogenase (DPD) deficiency, which compromises 5-FU metabolism and enhances systemic toxicity.[9,18] Though DPD genotyping was not done in this case, its addition to pre-chemotherapy screening is highly recommended to identify high-risk patients and possibly avoid life-threatening complications.[9]

CONCLUSION

This case highlights the need for enhanced clinical awareness, particularly during the initial cycles of chemotherapy. Cardiac surveillance, such as baseline ECG, echocardiogram, and immediate assessment of new cardiac symptoms should be considered, especially in high-risk patients. In addition, the selection of chemotherapy regimen would need to be reevaluated cautiously in those with early signs of toxicity. Replacement of 5-FU with less cardiotoxic agents like capecitabine could be considered. In acute situations, administration of uridine triacetate, a 5-FU antidote, within 96 hours of overdose or onset of severe toxicity may help in reversing life-threatening effects.

This case report is novel in highlighting

sudden cardiac death due to 5–fluorouracil–induced cardiotoxicity in a patient with undifferentiated carcinoma of the esophagus, a rare and aggressive histological type with limited literature. To the best of our knowledge, this is among the very few autopsy confirmed cases of acute myocardial infarction secondary to 5-FU toxicity in a rare tumor, underscoring the importance of postmortem examination and the need for monitoring in chemotherapy-related cardiotoxicity. This case further adds to the increasing body of evidence regarding the paramount importance of awareness, early recognition, and timely intervention for fluoropyrimidine-related toxicity.

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