

LETTERS TO THE EDITOR

Revisiting melanoma of unknown primary: do not overlook the uveal tract**To the Editor,**

I read with great interest the article by Küçükdemirci et al. [1] and would like to thank the authors for presenting this intriguing case.

At the end of the case presentation, the authors note that the multiple foci of melanoma in the duodenum may represent either primary lesions or metastases. As is well known, melanocytes are derived from the neural crest and are located in the basal layer of the epidermis, primarily in the skin, but also in the uveal tract of the eye, mucosal epithelia, hair follicles, and the meninges [2].

Contrary to the suggestion in the article, malignant melanoma is among the most common tumors to metastasize to the gastrointestinal (GI) tract. The top three malignancies associated with GI metastases are lung cancer, breast cancer, and melanoma. These cancers have been reported to *disproportionately frequently affect the gastrointestinal tract* [3]. Approximately 50% of melanoma-related GI metastases are multifocal. Due to the hematogenous route of spread and the vascular anatomy of the intestinal wall, the submucosal layer is often involved, with the overlying mucosa appearing intact. The small intestine is the most commonly affected region of the GI tract in such cases [3]. The case under discussion shows many of these typical features, suggesting that the duodenal lesions are more likely metastatic rather than primary.

As mentioned, one of the primary sites of malignant melanoma is the eye - specifically the uvea, which accounts for approximately 85% of ocular melanomas. Among these patients, around 50% will develop metastases during the disease course [4]. Although the most common presenting symptoms include blurry vision, photopsia, visual field defects, ocular pain, and metamorphopsia, up to one-third of patients may remain asymptomatic [5].

A case similar to that presented by Küçükdemirci et al. [1] reported uncountable liver metastases from uveal melanoma

detected incidentally during computed tomography imaging of the head [6].

Indeed, the high metastatic potential of uveal melanoma is well recognized. Notably, a peak in mortality typically occurs two to three years after treatment of the primary tumor (e.g., enucleation). This phenomenon, known as the Zimmerman effect, was first described by the ophthalmic pathologist Lorenz Eugene Zimmerman [7, 8].

In conclusion, when metastatic melanoma is identified based on histology from metastatic sites, an ophthalmological examination - particularly focusing on the uveal tract - should be considered before diagnosing melanoma of unknown primary or in cases where the primary site is uncertain.

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Amiodarone-induced decompensated liver cirrhosis successfully managed with N-acetylcysteine and supportive therapy

To the Editor,

A 64-year-old female presented with loss of appetite, recurrent vomiting, ascites, and hepatomegaly. She was known with paroxysmal atrial fibrillation, hypertension and dyslipidemia for 6 years; she had an ischemic stroke with hemiparesis 4 years prior to admittance in our department. She had therapy with amiodarone 200 mg BID for 4.5 years. She denied alcohol, tobacco or toxin exposure. Laboratory results showed hepatocytolysis 2xULN, mild cholestasis, hypoalbuminemia and INR 1.91. The workup for viral hepatitis, autoimmune hepatitis and other causes was negative. Contrast-enhanced computed tomography (CECT) confirmed the dysmorphic, hyperdense liver (arrow) and ascites (Fig.1). She was diagnosis with decompensated cirrhosis (Child-Pugh B, MELD 23), probably induced by amiodarone (the serum concentration of amiodarone was 4.9 mg/l). A transjugular liver biopsy was obtained. The histopathological examination showed (H&E, Van Gieson – Perls stain): mild portal inflammation including neutrophils, portal and bridging fibrosis, perisinusoidal collagen deposition, Mallory bodies, ballooning degeneration of hepatocytes and microvesicular steatosis (Figs. 1 b, c). Based on the medical history, the radiological appearance of the liver, the histopathological examination, and the measurement of the serum level of amiodarone, the diagnosis of decompensated hepatic cirrhosis induced by amiodarone consumption was confirmed.

The patient was treated with repeated volume paracenteses (10 L every 2 weeks) and albumin (8 g/L) (the ascites was refractory to diuretics), and supportive therapy with branched chain aminoacids. We also started N-acetylcysteine (NAC) 1200 mg/day intravenously for 1 month, then orally. The anticoagulant therapy with acenocumarol was continued. Seven months after stopping amiodarone, the patient showed significant clinical and biochemical improvement, without signs of decompensation (serum levels of amiodarone 0.61 mg/l and of desestilamiodarone 0.73mg/l).

Amiodarone is an extremely effective class III antiarrhythmic agent, but serious organ toxicity, including drug-induced hepatitis and pulmonary fibrosis and were reported [1].

The liver appearance on CECT was also described in the literature in several cases of amiodarone-induced cirrhosis. It is due to the liver loading with iodine (accumulated in the liver following the hepatic degradation of amiodarone) [1]. There are no defining histological features for amiodarone-

induced liver injury. Liver biopsy in amiodarone-induced liver injury closely resembles the appearance seen in alcoholic liver disease; in the early phase of liver damage, there is micro- and macrovesicular fat, ballooning degeneration, and mild inflammation, whereas later there is moderate inflammation (sometimes granulomatous) and variable amounts of fibrosis and Mallory bodies, but little steatosis [1]. In non-alcoholic steatohepatitis (or metabolic steatohepatitis - NASH/MASH) steatosis is mainly macrovesicular, inflammation could be mononuclear or polymorphic, in the portal spaces and predominantly lobular. However, the final diagnosis should be based on the clinical and biological context of the patient [2].

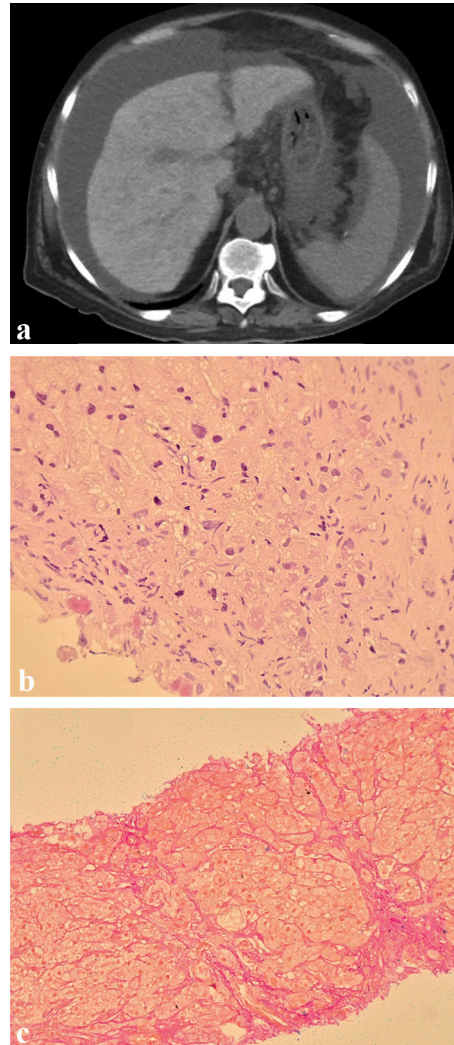


Fig. 1. a). Abdominal CT (non-contrast): dysmorphic, hyperdense liver with perihepatic and perisplenic ascites; b-c) Histological assessment: b) H&E stain: microvesicular steatosis, Mallory bodies, mild portal inflammation, 200x; c) Van Gieson-Perls stain: bridging fibrosis with perisinusoidal collagen deposition, 100x.

Previous reports showed that a daily dose of 1200 mg NAC could rapidly improve liver enzyme levels [3, 4]. NAC replenishes glutathione stores, reduces oxidative stress, and promotes hepatocyte regeneration [5].

To our knowledge, our case highlights for the first time in literature that a sustained prolonged daily therapy with NAC and supportive therapy could recompensate a severe decompensated amiodarone-induced cirrhosis.

For patients undergoing treatment with amiodarone, it is recommended to assess liver function at treatment initiation and then every 6 months [6].

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Esophageal hematoma in a patient with prior chest radiation therapy and aspirin use

To the Editor,

Spontaneous intramural esophageal hematoma (EH) is an uncommon condition characterized by bleeding into the esophageal wall. It typically presents with acute chest pain,

odynophagia, and dysphagia, often mimicking life-threatening conditions such as aortic dissection. Most cases are associated with trauma, vigorous retching, coagulopathy, or anticoagulant therapy [1, 2].

We report the case of a 73-year-old woman with a remote history of Hodgkin's lymphoma treated with chemotherapy and extensive chest radiotherapy, which subsequently led to aortic valve degeneration requiring TAVI. She was chronically treated with aspirin 100 mg daily for secondary prevention. She presented with acute chest pain and severe dysphagia. On admission, blood pressure was 160/110 mmHg and heart rate 97 bpm. ECG revealed sinus tachycardia. Given the suspicion of acute aortic syndrome, CT angiography was performed, excluding dissection but demonstrating marked esophageal wall thickening from the oropharyngeal junction to the gastroesophageal junction (Fig 1B). Esophagogastroduodenoscopy revealed a long, submucosal hematoma extending along the right wall of the esophagus, with luminal narrowing and a small active bleeding point treated successfully with hemostatic spray (Fig 1A). The patient was managed conservatively with nil per os for 48 hours and then gradual refeeding. She was discharged after four days, symptom free. One-month follow-up endoscopy showed complete resolution of the hematoma but revealed severe reflux esophagitis (LA grade D) (Fig 1C). She was treated with high-dose proton pump inhibitors, with subsequent follow-up at two months demonstrating complete mucosal healing (Fig 1D).

Prior chest radiotherapy represents a plausible predisposing factor. Ionizing radiation is known to induce long-term vascular injury through endothelial apoptosis, senescence, and disruption of vascular remodeling [3, 4]. These chronic alterations can weaken the esophageal wall and create susceptibility to spontaneous hemorrhage even decades later. In addition, long-term aspirin therapy increases the risk of bleeding events, with previous reports suggesting a potential association with EH [5]. In our patient, the combination of prior radiotherapy and aspirin may have acted synergistically to predispose the esophageal wall to hematoma formation.

Typical triggers for EH include vomiting, retching, coughing, or ingestion of large food boluses or foreign bodies [6, 7]. Careful anamnesis, including food intake history, did not identify such triggers in our case. Importantly, the absence of an acute precipitating event strengthens the argument for underlying tissue fragility as the dominant mechanism. Viral infections such as herpes simplex have also been implicated as triggers [8, 9]. Although serological or histopathological testing was not performed, there were no clinical signs of viral esophagitis, and infection was not suspected.

It should also be noted that aspirin therapy has been described in a few reports as a possible contributor to EH [5], although this remains uncommon. In our case, the chronic background of prior chest irradiation may have further increased the vulnerability of the esophageal wall, making aspirin exposure a more relevant factor than in previously reported cases.

This case highlights the importance of distinguishing predisposing factors (radiotherapy, aspirin, anticoagulants, tissue fragility) from triggering factors (increases in intraluminal pressure or acute insults). Awareness of this distinction may facilitate early recognition and appropriate management. As the

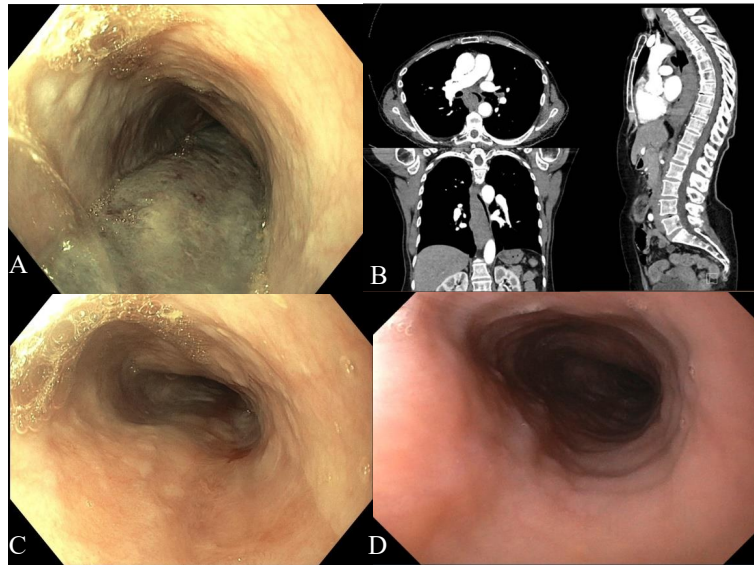


Fig. 1. A) Esophagogastroduodenoscopy: long, submucosal hematoma extending along the right wall of the esophagus, with luminal narrowing and a small active bleeding point. B) Computed tomography (angiography): marked esophageal wall thickening from the oropharyngeal junction to the gastroesophageal junction C) One-month follow-up endoscopy showed complete resolution of the hematoma but revealed severe reflux esophagitis. D) Two-months follow-up endoscopy: complete mucosal healing.

number of cancer survivors treated with thoracic radiotherapy continues to rise, late esophageal complications, though rare, are likely to be encountered more frequently in clinical practice.

In conclusion, we report a unique case of EH in a patient with a history of chest radiotherapy and chronic aspirin therapy, without identifiable acute triggers. This observation raises awareness of the potential long-term vulnerability of the irradiated esophagus. Clinicians should maintain a high index of suspicion for EH in patients presenting with acute chest pain and dysphagia, particularly when predisposing factors such as prior irradiation or antiplatelet therapy are present.

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Paraneoplastic hypoglycemia caused by hepatocarcinoma in a patient with acute intermittent porphyria

To the Editor,

Hypoglycemia is a common medical emergency, especially in diabetic patients on insulin or hypoglycemic agents [1]. However, approximately 42% of cases occur in non-diabetic

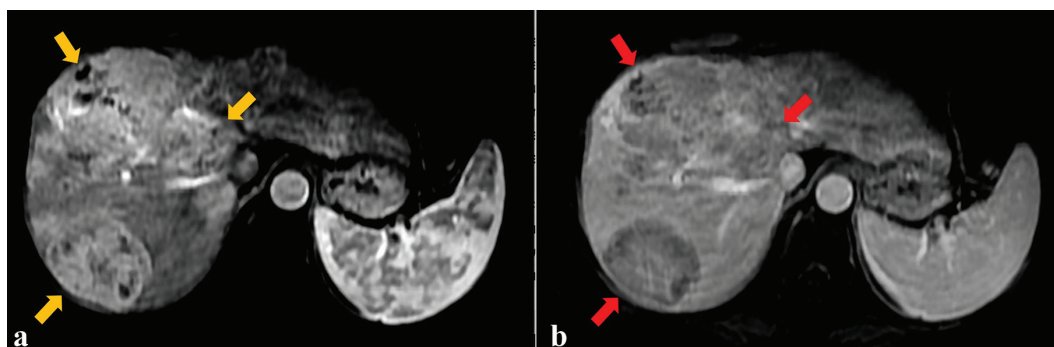


Fig. 1. Abdominal MRI images: (a) axial T1-weighted arterial phase image; (b) axial T1-weighted portal venous phase image. Hepatomegaly with cirrhotic changes related to multiple hypointense focal lesions, in pre contrast image with hyperenhancement in the arterial phase (yellow arrows) and washout on the portal venous phase with capsular enhancement (red arrows).

individuals, posing a diagnostic challenge that requires thorough clinical evaluation and selective testing. Possible etiologies for these patients include sepsis, organ dysfunction, hormonal deficiencies, endogenous hyperinsulinism, and non-islet cell tumor hypoglycemia (NICTH), a rare paraneoplastic syndrome often associated with hepatocellular carcinoma (HCC) [2].

We present the case of a 68-year-old female with a history of acute intermittent porphyria (AIP) and long-term methotrexate user for rheumatoid arthritis, admitted to emergency department with neuroglycopenic symptoms and a confirmed blood glucose of 36 mg/dL (level 3 hypoglycemia). Initial work-up excluded common causes including sepsis, hepatic or renal failure, adrenal insufficiency, and insulinoma. A monitored fasting test verified hypoglycemia without hyperinsulinemia. Further malignancy work-up through endoscopy, colonoscopy, and thoracic imaging was negative. However, abdominal MRI showed a cirrhotic liver with multiple hypervascular nodules (Fig. 1). A biopsy confirmed moderately differentiated HCC with a trabecular pattern. Serum insulin-like growth factor (IGF) assay demonstrated suppressed IGF-1, elevated IGF-2, and increased IGF-2/IGF-1 ratio leading to a diagnosis of NICTH.

NICTH is a rare cause of hypoglycemia in non-diabetic individuals [2]. The pathophysiology involves tumor production of incompletely processed IGF-2 (Big-IGF-2), which then mimics insulin by activating insulin receptors, promoting glucose uptake, and suppressing hepatic glucose output. It also reduces counter-regulatory hormones such as glucagon and growth hormone. The diagnosis is confirmed by an elevated IGF-2/IGF-1 ratio, with values >10 strongly suggestive of NICTH [3].

Treatment approaches focus on decreasing the size of the tumor, which is primarily achieved through surgical resection, embolization, or systemic therapy. In cases where these options are not feasible, pharmacologic therapy involving glucocorticoids and diazoxide may be employed to achieve stability in glycemia. In our patient, who was not a candidate for curative treatment, oral prednisolone and diazoxide successfully controlled hypoglycemia. Multidisciplinary consensus led to initiation of sorafenib as systemic therapy for stage C HCC in a Child-Pugh A liver.

Interestingly, this case highlights a rare form of HCC in an individual lacking the usual risk elements like viral hepatitis, alcohol dependence, or metabolic liver disease. Instead, chronic methotrexate exposure and AIP were implicated. It is noted that hepatotoxic effects from methotrexate can lead to fibrosis or cirrhosis in a small percentage, about 5%, of those who use it chronically [5]. AIP, a less common metabolic disorder, raises the likelihood of HCC, even in non-cirrhotic livers. Research shows that the annual incidence of HCC can reach 0.8% in patients over 55 years with porphyria, which, while lower than the rates associated to viral hepatitis, is still significant. Notably, numerous HCC cases related to AIP arise without the presence of cirrhosis, potentially delaying diagnosis.

This case emphasizes the necessity of considering NICTH when facing unexplained hypoglycemia, especially in patients with known risk factors for malignancy. It also reinforces existing guidelines that recommend regular HCC monitoring in patients with porphyric disorders aged 50 years or older, through biannual liver imaging. Detecting HCC early in this group may enhance outcomes by facilitating prompt treatment options.

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