REVIEW AND CASE SERIES

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Primary gallbladder melanoma – a rare entity or a diagnostic pitfall?

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Abstract

Primary gastrointestinal (GI) melanoma is an exceptionally rare and controversial diagnostic entity. Because the mucosa of the gallbladder, stomach, small bowel, and large bowel is not considered a common site of melanocytic proliferation, most GI melanomas are regarded as metastatic lesions originating from a primary cutaneous melanoma. Whether some of these tumors may truly arise primarily in GI sites remains a matter of debate. The diagnosis is further complicated by the possibility of occult, clinically subtle, or amelanotic cutaneous melanomas that may remain unrecognized until advanced metastatic disease becomes symptomatic. In addition, spontaneous regression of the primary cutaneous lesion may lead to complete or partial disappearance of the original tumor, creating further diagnostic uncertainty. We performed a literature review focused on GI and gallbladder melanoma, with emphasis on the distinction between primary and metastatic lesions and the role of spontaneous regression. In addition, we analyzed all cases of GI and gallbladder melanoma diagnosed in our department during the last five years. Three cases were identified: one gallbladder melanoma and two small bowel melanomas. These cases illustrated distinct clinical scenarios, including GI bleeding associated with gallbladder involvement, amelanotic ileal melanoma, and intussusception caused by metastatic melanoma from a known cutaneous primary lesion. Our findings support the need for cautious interpretation when diagnosing primary GI melanoma. Metastatic disease from occult, regressed, or previously undiagnosed cutaneous melanoma should always be carefully excluded through multidisciplinary clinicopathological evaluation.

Keywords: primary gallbladder melanoma, spontaneous regression, gastrointestinal melanoma, metastatic melanoma.

Introduction

Cutaneous melanoma is an aggressive malignant neoplasm arising from melanocytes, specialized dendritic pigment-producing cells [1, 2]. The principal histopathological (HP) forms of cutaneous melanoma are superficial spreading, nodular, and acral lentiginous melanoma [3]. Melanocytes are predominantly located in the skin and uveal tract, which represent the most common sites of melanoma development. Beyond the skin and uveal tract, melanoma may rarely develop in atypical locations involving neural tissues and mucosal epithelia, including structures of the upper aerodigestive tract, gastrointestinal (GI) system, and female reproductive tract [4].

Cutaneous melanoma most frequently metastasizes to regional lymph nodes and distant organs such as the liver, lungs, and brain, whereas GI involvement has been reported in approximately 2–4% of patients with advanced disease diagnosed during life [5–7]. In contrast, primary GI melanoma is considered exceptionally rare. Several hypotheses have been proposed to explain its occurrence, including the presence of ectopic melanocytes within the GI mucosa or aberrant migration of neural crest-derived melanocytic precursors during embryogenesis [5].

One of the main challenges in establishing a diagnosis of primary GI melanoma is the exclusion of an occult cutaneous primary lesion. In some patients, the absence of identifiable skin primary may be related to spontaneous regression of the original melanoma, a phenomenon well documented in the literature. Melanoma regression is considered to be mediated by an enhanced host immune response, particularly through the activity of cluster of differentiation (CD)8-positive cytotoxic T-lymphocytes, increased CD4-positive T-cell infiltration, and circulating antibodies directed against tumor-specific antigens [8,9]. In advanced disease, a heightened systemic immune response triggered by metastatic burden has also been proposed as a possible mechanism contributing to regression of the primary lesion [9].

Given these considerations, the diagnosis of primary GI melanoma remains controversial in selected cases. Some lesions classified as primary tumors may instead represent metastatic disease originating from an undetected, regressed, or clinically inapparent cutaneous melanoma. The present study explores this diagnostic dilemma through an analysis of the available literature together with cases from our institution, with particular emphasis on gallbladder melanoma

and the potential role of spontaneous regression in obscuring the true primary site.

Materials and Methods

A literature review was conducted using several electronic databases, including *PubMed*, *Google Scholar*, and *Springer Link*, to identify publications addressing GI and gallbladder melanoma, with particular emphasis on primary melanoma and spontaneous regression. Only articles published in peer-reviewed journals were considered. Relevant data were selected and organized into thematic sections concerning gallbladder and GI melanoma.

In addition, we retrospectively reviewed all cases of GI and gallbladder melanoma diagnosed in our department over the last five years. Three cases were identified during this period: one case of gallbladder melanoma and two cases of small bowel melanoma.

Tissue specimens were fixed in formalin, embedded in paraffin, and stained with Hematoxylin–Eosin (HE). Immunohistochemical (IHC) analysis was performed in all cases using antibodies against S100 protein, Melan-A, human melanoma black 45 (HMB45), vimentin, cytokeratins (CK AE1/AE3, CK7, CK20), caudal type homeobox 2 (CDX2), carcinoembryonic antigen (CEA), CD99, synaptophysin, and inhibin. Molecular testing for B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) mutations was also performed where appropriate.

Case presentations

We reviewed all cases of GI and gallbladder melanoma diagnosed in our department during the last five years and identified one patient with gallbladder melanoma and two patients with small bowel melanoma.

A 75-year-old man was admitted to the Emergency Department for hematochezia that had begun 48 hours earlier, associated with pain in the right hypochondriac and epigastric regions, nausea, and vomiting. The patient was known to have arterial hypertension under treatment. His medical history revealed that, one year prior to admission, he had developed epigastric discomfort associated with loss of appetite. Despite previous gastroenterological consultations, no GI pathology had been identified.

Clinical examination revealed abdominal tenderness on palpation, predominantly in the epigastric and right hypochondrial areas, without guarding. Laboratory investigations revealed severe post-hemorrhagic anemia [hemoglobin (Hb) 6.3 g/dL; normal range: 12–13.5 g/dL]. A computed tomography (CT) scan performed in the Emergency Department did not identify the source of GI hemorrhage but demonstrated a distended gallbladder containing multiple irregular intraluminal masses, as well as a probable tumoral lesion measuring 5×3 cm located in the infundibulum. The patient was initially admitted to the Gastroenterology Department, where upper GI endoscopy was performed. Endoscopy revealed several pigmented lesions of the duodenal mucosa, considered the source of bleeding.

After remission of the hemorrhagic episode, the patient was referred to the General Surgery Department following the development of clinical signs of acute cholecystitis. During surgery, the gallbladder appeared enlarged, filled with hemorrhagic bile, and contained multiple bleeding pigmented exophytic tumoral lesions (Figure 1).

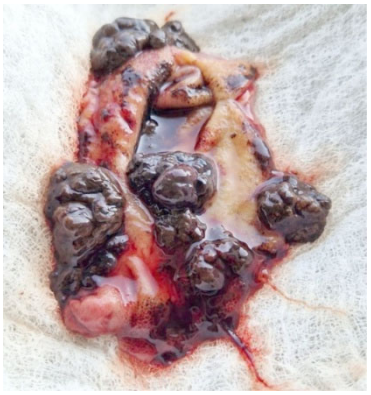

Figure 1 – ***Cholecystic melanoma lesions.***

HP analysis of the gallbladder specimen confirmed the presence of melanoma. Microscopic examination showed malignant tumor proliferation arranged in nests of medium-to-large polygonal/epithelioid cells displaying marked nuclear pleomorphism and enlarged nucleoli with eosinophilic features (Figure 2, A and B). The cytoplasm of the tumor cells contained a moderate amount of brown melanin pigment. IHC staining demonstrated positivity for S100 protein, HMB45, and Melan-A in the tumor cells, whereas CK 8/18 expression was absent.

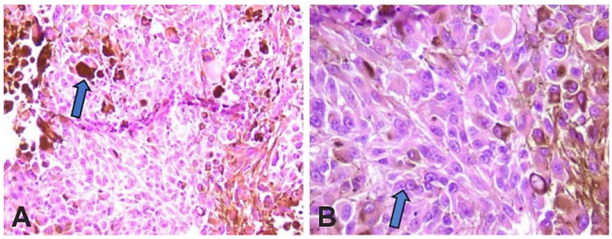

Figure 2 – ***Microscopic appearance in Hematoxylin–Eosin (HE) staining: (A) Tumor cells with nuclear pleomorphism and brown melanin pigment (arrow), ×200; (B) Tumor cells with pleomorphic nuclei and eosinophilic nucleoli (arrow), ×400.***

Subsequently, the patient underwent dermatological evaluation, which identified two suspicious cutaneous lesions located on the posterior thoracic region. Dermoscopic examination followed by biopsy demonstrated metastatic melanoma in both lesions: one partially pigmented metastasis and one amelanotic metastasis. The pigmented cutaneous lesion showed two pigmented areas separated by scar tissue and surrounded by a depigmented halo, findings suggestive of regression of a possible primary cutaneous melanoma.

Further molecular testing identified a $BRAF^{V600E}$ mutation, and combined therapy was subsequently initiated with Vemurafenib/Cobimetinib.

In addition to the gallbladder melanoma, we identified an interesting case of amelanotic small bowel melanoma. A 70-year-old male patient was admitted to the Emergency Department with pain involving the left hypochondriac and left lumbar areas. However, clinical examination demonstrated tenderness localized to the right iliac fossa. The patient was known to have arterial hypertension under treatment.

Abdominopelvic CT revealed an ill-defined intra-peritoneal mass in the right iliac fossa measuring

approximately 3.7×5.9 cm, associated with inflammatory changes in the surrounding tissues and adjacent adherent ileal loops. Another well-defined tissue mass, with an estimated diameter of 3 cm, was identified adjacent to the first lesion and nearby ileal loops. The terminal ileum showed thickened edematous walls adherent to the previously described formation.

During surgery, a conglomerate mass formed by the terminal ileum, greater omentum, and abdominal wall was identified in the right iliac fossa. During dissection, purulent discharge was observed. An ileal tumoral mass located 20 cm from the ileocecal valve, measuring 7 cm in diameter, extending beyond the serosa and adherent to the anterior abdominal wall, was also identified. Considering the tumor location, a right hemicolectomy was performed, followed by a hand-sewn side-to-side ileocolic anastomosis.

HP examination revealed amelanotic melanoma with extensive areas of suppurative tumor necrosis. IHC staining showed expression of vimentin and Melan-A in the tumor cells, whereas S100 protein, HMB45, and *BRAF* mutation testing yielded negative results.

After discharge, the patient underwent further dermatological evaluation in order to identify a possible primary cutaneous lesion. No suspicious cutaneous lesion was found.

As the tumor tested negative for *BRAF* mutation, the patient received combined immunotherapy with Nivolumab/Ipilimumab, although no additional suspicious cutaneous or metastatic lesions were identified. Follow-up CT performed after six months demonstrated no signs of persistent disease.

In contrast with the previous case, we also identified a patient with documented primary melanoma and secondary small bowel metastasis. A 46-year-old woman was admitted to the Emergency Department with epigastric pain associated with region, nausea, vomiting, and bowel transit disturbances. Clinical examination revealed abdominal distension and tenderness on palpation predominantly in the epigastric region.

Abdominopelvic CT demonstrated entero-enteric intussusception accompanied by small bowel obstruction. Several osteolytic lesions involving the thoracolumbar spine, suggestive of metastatic disease, were also observed. The patient was transferred to the General Surgery Department, where surgical intervention was performed.

Intraoperatively, an intussusception measuring approximately 20 cm in length was identified. After reduction of the jejunal loop, a pigmented circumferential tumor mass causing bowel obstruction was observed. Numerous adjacent pigmented lymph nodes measuring up to 1 cm in diameter were also present (Figure 3, A and B). The affected jejunal segment was resected and an entero-enteral hand-sewn anastomosis was performed.

HP examination confirmed that ileal and lymph nodal metastatic melanoma consisting of epithelioid cells exhibiting nuclear pleomorphism. IHC analysis revealed expression of S100 protein, HMB45, and Melan-A in the tumor cells, and molecular testing was positive for $BRAF^{V600E}$ mutation.

The patient had been diagnosed with primary cutaneous melanoma four years before the episode of intussusception caused by metastasis. The primary lesion had been excised but the disease subsequently progressed with intestinal and osseous metastases.

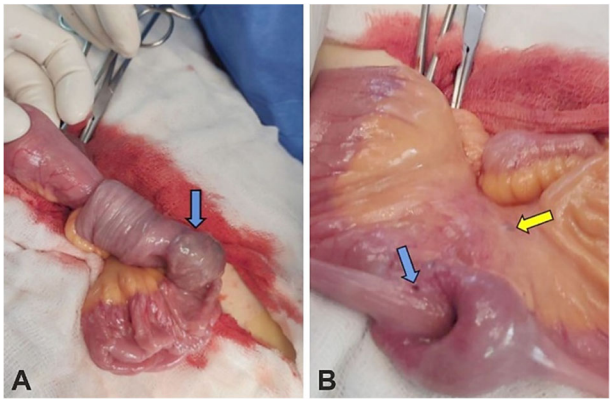

Figure 3 – ***Intussusception caused by metastatic melanoma: (A) Melanoma metastasis (arrow); (B) Pigmented lymph node (yellow arrow) and a small melanoma metastasis (blue arrow).***

Despite further oncological treatment, the patient died four months later due to advanced disease.

All identified cases of GI or gallbladder melanoma from our department did not have a known cutaneous primary lesion at admission, except for the patient with documented melanoma history. Due to the unusual location for primary melanoma, metastatic disease was initially considered in all cases. After thorough investigations, only the case presenting with small bowel intussusception had a previously confirmed cutaneous primary melanoma, while in the remaining two cases no primary cutaneous lesion was identified despite additional evaluation.

Discussions

Cholecystic primary melanoma and other gastrointestinal melanoma

GI melanoma is a rare condition and most frequently represents metastatic disease originating from a primary cutaneous lesion. The small bowel, colon, and stomach represent the most frequent sites of GI metastatic involvement, while gallbladder involvement is distinctly uncommon [10, 11]. Primary GI melanoma is considerably rarer, with approximately 39 cases of primary gallbladder melanoma reported in the literature [12, 13].

Among mucosal melanomas, the anorectal and oropharyngeal regions are the most commonly involved sites, accounting for 31.4% of cases in the anal canal, 22.2% in the rectum, and 32.8% in the oropharyngeal region. By comparison, primary melanomas originating in the esophagus (5.9%), stomach (2.7%), small bowel (2.3%), gallbladder (1.4%), and large bowel (0.9%) are exceedingly rare [14].

Distinguishing primary from metastatic melanoma on histological grounds alone is often challenging, as both entities may show substantial morphological overlap [15]. Several clinical and pathological criteria have therefore been proposed to support a diagnosis of primary gallbladder melanoma. These include exclusion of another primary site, a solitary lesion arising from the gallbladder mucosa, and the presence of junctional activity [16, 17]. Junctional activity, defined as intraepithelial extension of atypical melanocytic cells in the mucosa adjacent to the tumor, has traditionally been considered an important finding. However, the presence of atypical melanocytes in the overlying epithelium does not definitively establish a primary lesion [18, 19].

Melanocytes are generally considered absent from normal gallbladder mucosa, although some authors have reported rare melanocytic cells within otherwise normal mucosa [20, 21]. Several hypotheses have been proposed to explain the possible presence of ectopic melanocytes in the GI tract. One theory suggests migration of melanocytes from the anal transitional zone toward the rectal mucosa, although this concept is mainly applicable to anorectal melanoma. Other hypotheses include differentiation of pluripotent stem cells into melanocytes or aberrant migration of neural crest-derived melanocytic precursors to endodermal tissues during embryogenesis [6, 22].

Recent evidence also suggests biological differences between cutaneous and non-cutaneous melanocytes, and melanomas arising from cutaneous and extracutaneous sites may demonstrate distinct clinicopathological and molecular characteristics [14, 23]. In addition, ultraviolet radiation, a major risk factor for cutaneous melanoma, is not relevant for GI sites because of the absence of sun exposure [14].

Taken together, these observations indicate that primary GI melanoma remains a rare and controversial diagnostic entity. Although some reported cases may indeed represent true primary tumors, metastatic disease from an occult or regressed cutaneous melanoma should always be carefully excluded before establishing this diagnosis.

Spontaneous regression of primary cutaneous melanoma

Spontaneous regression involving the primary cutaneous lesion has been reported in association with metastatic melanoma. Although regression may occur in several malignant tumors, it appears to be particularly relevant in cutaneous melanoma, where partial regression has been reported in up to 50% of primary lesions [24]. One study demonstrated that regressing cutaneous melanomas metastasized in 45.5% of cases, compared with 12% of non-regressing melanomas [25]. In addition, 5–10% of patients with metastatic melanoma present with an unidentified primary lesion or with complete disappearance of the original lesion [26]. These observations support a possible association between complete regression of the original melanoma and progressive metastatic disease [27].

The phenomenon of spontaneous regression involves partial or complete tumor disappearance occurring without any form of specific antitumor therapy [28]. Clinically, the process may begin with hyperpigmentation followed by partial or complete depigmentation, resulting in residual areas with heterogeneous discoloration, ranging from pale and whitish to grayish or bluish hues. These changes reflect substitution of melanoma cells by reactive host tissue changes, including mononuclear inflammatory infiltrates, melanophages, dermal fibrosis, and increased local vascularity [29, 30]. As tumor cells are progressively eliminated, the inflammatory infiltrate may regress, ultimately leading to the formation of a fibrovascular scar with variable residual pigmentation, which may or may not contain persistent melanoma cells. To varying degrees, regression may also involve the adjacent intraepidermal component and extend to surrounding benign melanocytes located within the basal layer of the epidermis, producing a depigmented halo [31].

The clinical manifestations of regression are variable and may include inflammatory nodules, scarring of the primary lesion, pigmented scars containing residual tumor cells, pigmented foci surrounded by depigmented halos, or lesions composed of several separate pigmented areas. Such lesions may mimic multicentric melanoma; however, histological examination of the tissue between pigmented foci may demonstrate scarring changes consistent with regression, while residual superficial spreading melanoma may still be present [31].

Several features suggestive of regression were identified in our 75-year-old patient with gallbladder melanoma. The pigmented cutaneous metastatic lesion showed a depigmented halo and intervening scar tissue, findings comparable to those described in regressing melanoma. A second unusual lesion was represented by an amelanotic cutaneous metastasis (Figure 4, A and B). Although both lesions showed atypical clinical features, HP examination confirmed metastatic melanoma. These findings raise the possibility that regression-related changes may also occur in metastatic lesions, although this hypothesis requires further investigation.

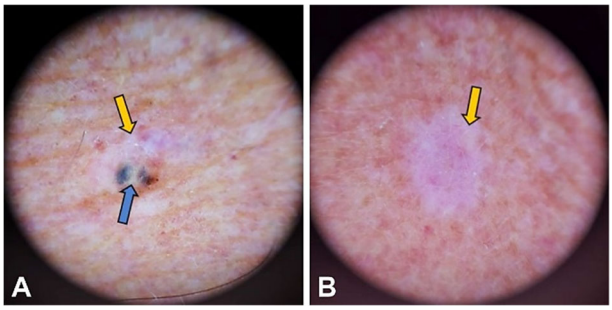

Figure 4 – ***Metastatic cutaneous melanomas: (A) Melanoma metastasis with aspects of regressing cutaneous melanoma – depigmented halo (yellow arrow) and scarring tissue (blue arrow); (B) Amelanotic melanoma metastasis.***

Although the mechanisms underlying spontaneous regression have not been completely elucidated, the host immune system is considered to play a central role, as suggested by early immune activation against primary cutaneous melanoma [32]. This process is particularly associated with the activity of CD8-positive cytotoxic T-lymphocytes, increased infiltration by CD4-positive T-lymphocytes and T helper 1 (Th1) cytokines within tumor tissue, as well as elevated circulating levels of tumor-specific antibodies and cytotoxic T-lymphocytes [8, 9]. Regression may also result from inflammatory responses targeting melanocyte-associated antigens, including Melan-A [33]. Another proposed mechanism is an enhanced systemic immune response stimulated by the presence of multiple metastatic deposits [9].

T-lymphocytes contribute substantially to antitumor immune responses through the recognition of tumor-rejection antigens presented by major histocompatibility complex molecules. These antigens can be classified into several categories, including mutated tumor-specific oncogenes, products of tumor suppressor genes, germ cell antigens, and differentiation antigens [34, 35].

Tumor-specific mutated oncogenes encode neoantigens generated through point mutations during tumorigenesis

and may contribute to spontaneous regression [8]. Germ cell antigens are proteins aberrantly expressed during oncogenesis and may function as tumor-associated antigens, such as melanoma antigen family proteins [36, 37]. Differentiation antigens include proteins involved in melanogenesis, such as glycoprotein 100 (gp100), a melanocytic lineage antigen recognized by HMB45, and tyrosinase. The presence of CD8-positive T-lymphocytes recognizing tyrosinase may mediate the lysis of melanoma cells by overcoming immune tolerance and promoting anti-melanoma responses [38].

Melanoma cells may express strongly immunogenic proteins such as Melan-A and gp100. These molecules represent important targets for cytotoxic T-lymphocytes, and melanomas expressing such antigens may therefore be more likely to undergo spontaneous regression [39–41].

Clinical aspects

Melanoma involving the GI tract is frequently asymptomatic; however, symptomatic patients may present with nonspecific manifestations such as abdominal pain, nausea, vomiting, weight loss, bowel obstruction, perforation, or acute GI bleeding [42]. Because these manifestations overlap with those of many more common GI disorders, diagnosis may be delayed until complications occur or the disease reaches an advanced stage. A rare manifestation of small bowel melanoma is intussusception, which may result in bowel obstruction and require urgent surgical management [43]. Another unusual presentation is jaundice when melanoma involves the duodenum or adjacent biliary structures [44].

In cases of gallbladder involvement, melanoma may clinically mimic acute cholecystitis, with manifestations ranging from upper abdominal pain and digestive symptoms to occasional obstructive jaundice, frequently occurring in the absence of gallstones. Several of these manifestations were observed in our patients, ranging from GI hemorrhage associated with signs of cholecystitis to intussusception and extensive suppurative tumor necrosis. These findings illustrate the broad clinical spectrum of GI melanoma and underline the fact that its presentation is often dominated by complications rather than by tumor-specific signs.

From a clinical perspective, it is often difficult to determine whether such signs and symptoms are caused by a primary GI melanoma or by metastatic disease, particularly in the setting of a possible regressed or previously unrecognized cutaneous primary lesion. In many cases, these manifestations may reflect advanced tumor burden rather than the true site of origin. Therefore, clinical presentation alone is generally insufficient to distinguish primary from metastatic melanoma of the GI tract.

For this reason, a thorough dermatological examination should be taken into consideration in every patient diagnosed with GI melanoma. Such evaluation requires awareness of the wide spectrum of melanoma appearances, including atypical and amelanotic lesions, which may be overlooked because of their non-characteristic clinical appearance. Close clinicopathological correlation remains essential for accurate diagnosis.

Taken together, the available literature and the cases presented herein emphasize that GI melanoma remains both a rare clinical entity and a significant diagnostic challenge. Although true primary GI melanomas may occur in exceptional circumstances, metastatic disease from an occult, regressed or previously unrecognized cutaneous primary lesion must always be carefully considered. In this context, HP findings, IHC profile, clinical history, dermatological evaluation, and imaging studies should be interpreted in an integrated manner rather than individually.

Our institutional experience illustrates several possible scenarios, including metastatic bowel disease from a known cutaneous melanoma, melanoma without an identifiable cutaneous primary lesion, and gallbladder involvement associated with lesions suggestive of regression. These observations support the concept that GI melanoma is a heterogeneous condition in which the true site of origin may remain uncertain in selected patients.

Consequently, a multidisciplinary approach involving surgeons, pathologists, dermatologists, gastroenterologists, and oncologists is essential for accurate diagnosis and optimal therapeutic planning. Further clinicopathological studies and molecular investigations are needed to better define the biological behavior of these tumors and to refine the criteria used to distinguish primary from metastatic GI melanoma.

Conclusions

GI melanoma is a rare and diagnostically challenging entity, most commonly representing metastatic disease from a primary cutaneous melanoma. Although primary GI melanoma has been reported, its true incidence remains uncertain, and the diagnosis should be established with caution after exclusion of a cutaneous primary lesion.

The cases presented in our series illustrate the heterogeneous clinical manifestations of GI melanoma, ranging from acute GI bleeding and cholecystitis-like presentation to intussusception and necrotic tumoral masses. They also highlight the possibility of occult, regressed, or clinically atypical cutaneous primary lesions, which may complicate the distinction between primary and metastatic disease.

Accurate diagnosis requires close correlation between clinical findings, imaging studies, HP examination, immunohistochemistry, and thorough dermatological assessment. A multidisciplinary approach is essential for appropriate management. Further clinicopathological and molecular studies are necessary to improve current diagnostic criteria and to clarify the biological nature of presumed primary GI melanomas.

Conflict of interests

The authors declare no conflict of interests.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Emergency Municipal Hospital, Timişoara, Romania (Approval No. E-1319/21.03.2025).

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