CASE REPORT

RJME Romanian Journal of Morphology & Embryology http://www.rjme.ro/

Melanoma of unknown primary presenting as intestinal obstruction: a diagnostic challenge

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Abstract

Background: Metastatic melanoma concerning the gastrointestinal (GI) tract is a well-documented yet often clinically silent phenomenon, with the most common site of involvement being the small intestine. Intussusception in adults is rare and usually secondary to an underlying tumor. Melanoma of unknown primary (MUP), a diagnosis made in the absence of identifiable cutaneous, mucosal, or ocular lesions, adds further diagnostic complexity. *Case presentation*: We present the case of a 64-year-old female who was referred to the Emergency Department with subacute symptoms of intestinal obstruction. Imaging revealed ileal intussusception with a suspected tumoral cause. Surgical exploration confirmed an ulcerated intraluminal mass acting as the lead point. A segmental enterectomy with primary anastomosis was accomplished. Histopathological (HP) and immunohistochemical results confirmed the diagnosis of malignant melanoma, with positive staining for S100, Melan-A, preferentially expressed antigen in melanoma (PRAME), and cluster of differentiation 117 (CD117). No primary lesion was identified on full-body dermatological and mucosal examination. The patient had a favorable postoperative outcome and was discharged with a favorable clinical status. *Discussions*: This particular case illustrates an uncommon initial manifestation of metastatic melanoma in the form of small bowel occlusion. MUP remains an infrequent disease with a paradoxically similar or even more favorable prognosis compared to melanomas with known primaries. Literature review supports surgical resection as the primary therapeutic strategy in isolated GI metastasis, particularly in symptomatic patients. Immunohistochemistry plays a critical role in establishing diagnosis, although it cannot reliably distinguish primary from metastatic lesions in the small bowel. *Conclusions*: Melanoma should be taken into consideration in the differential diagnosis of adult intussusception and small bowel tumors, even without a known primary lesion. This particular case highlights the importance of HP evaluation and multidisciplinary assessment in reaching an accurate diagnosis.

Keywords: metastatic melanoma, melanoma of unknown primary, small bowel obstruction, ileal intussusception.

Introduction

Malignant melanoma is an aggressive neoplasm derived from melanocytes, most commonly of cutaneous origin, but with potential to arise in mucosal or ocular locations. It accounts for approximately 1.7% of all cancers worldwide, yet is responsible for a disproportionately high number of cancer-related deaths due to its metastatic potential [1]. The five-year survival for metastatic melanoma has improved significantly with immunotherapy and targeted agents, but prognosis remains poor in late-stage disease, with five-year survival rate of 34.6% for stage IV [2, 3].

The gastrointestinal (GI) tract is a frequent site of distant melanoma metastasis, especially the small intestine, which is involved in up to 50–60% of cases at autopsy, yet clinically diagnosed in only 2–4% of patients during life. The discrepancy is attributed to the non-specific nature of symptoms (*e.g.*, vague abdominal pain or discomfort, weight loss, anemia) and low index of suspicion, especially when no primary melanoma is known [4, 5].

Among GI presentations, mechanical obstruction from intussusception is rare but well-documented. Adult intussusception accounts for only 1–5% of all bowel obstructions and approximately 5% of all intussusception cases, in contrast to its pediatric counterpart where it is common and usually idiopathic [6, 7]. In adults, up to 90% of intussusceptions have a pathological lead point, with malignancy responsible for 30–50% of small bowel cases, often metastatic lesions, including melanoma, lymphoma, or gastrointestinal stromal tumors (GISTs) [8–10].

Aim

The purpose of this report was to highlight a rare and diagnostically challenging case of small bowel obstruction caused by ileal intussusception, ultimately diagnosed as

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metastatic melanoma of unknown primary (MUP) origin. By presenting this case, we aimed to raise awareness of the possibility of melanoma as an etiology for adult intussusception, even in the absence of a known primary lesion, and to underscore the critical role of histopathological (HP) and immunohistochemical (IHC) evaluation in establishing the diagnosis. Furthermore, the report contributes to the limited body of literature addressing MUP presenting with acute surgical abdomen, emphasizing the need for a multidisciplinary approach in such atypical scenarios.

Case presentation

A 64-year-old female patient, with a known medical history of type 2 diabetes mellitus under oral hypoglycemic medication, arterial hypertension, and mild mitral valve insufficiency, and with no prior history of abdominal surgery, presented to the Emergency Department of the University Emergency Hospital Bucharest, Romania, in May 2024, with subacute symptoms suggestive of partial intestinal obstruction. The clinical picture had insidiously evolved over approximately 30 days, with progressive worsening. The patient reported alternating episodes of diarrhea and constipation, nausea, and diffuse abdominal discomfort, without significant weight loss.

Previous to admission, the patient had undergone imaging evaluations in another medical center. A contrast-enhanced computed tomography (CT) scan of the abdominal and pelvic regions, followed by a pelvic and abdominal magnetic resonance imaging (MRI), detected an ileal intussusception with a suspected intraluminal tumoral lead point.

On general clinical examination, the patient was alert, cooperative, and hemodynamically and respiratory stable. Her body mass index (BMI) was 24 kg/m^2. The integumentary examination revealed pale and mildly dehydrated skin and mucosae, with no suspicious lesions identified. Hair and nails appeared normal, and no superficial lymphadenopathy was noted. Musculoskeletal and locomotor systems were within normal limits. Respiratory examination showed a normally shaped thorax with bilateral vesicular breath sounds and no adventitious sounds. Cardiovascular evaluation revealed rhythmic heart sounds and a normal apical impulse located in the fifth left intercostal space. Urinary output was normal. Giordano's sign was negative bilaterally. Neurological examination revealed the presence of bilateral osteotendinous reflexes.

The abdomen was moderately distended, tender on palpation, with no signs of peritoneal irritation. Digital rectal examination indicates a normotonic anal sphincter, uncomplicated internal hemorrhoids, without any presence of fecal matter or bleeding.

During the first day of hospitalization, the patient developed recurrent episodes of bilious vomiting, prompting the placement of a nasogastric tube. Approximately 1500 mL of bilious and partially digested alimentary material was evacuated. An abdominal X-ray showed multiple air-fluid levels predominantly in the right flank and upper abdominal quadrants, consistent with small bowel obstruction.

Laboratory evaluation detected a normal complete blood count, mild hyperglycemia (145 mg/dL), and hypokalemia (serum potassium 3.0 mmol/L), with no other significant biochemical abnormalities. A diagnosis of small bowel obstruction was made in light of the clinical presentation and corroborated by radiological and laboratory findings.

An emergency exploratory laparotomy under general anesthesia was carried out after informed consent was obtained. Intraoperatively, a moderate volume of clear serous peritoneal fluid was aspirated. The small bowel loops were markedly distended and dilated up to approximately 2 m from the duodenojejunal flexure, with edematous walls. Manual reduction of an ileal intussusception was achieved, revealing the underlying lead point: a 4 cm ulcerated, vegetating, and stenosing intraluminal tumor mass (Figure 1).

A segmental enterectomy was performed with oncologically safe margins, followed by a termino-terminal ileo-ileal anastomosis. The resected specimen was submitted for HP examination (Figure 2).

Postoperative evolution was favorable. The patient showed progressive clinical improvement, with restoration of bowel transit, good oral intake tolerance, preserved diuresis, and remained afebrile and hemodynamically stable. She was discharged in good general condition, with normal respiratory and cardiovascular parameters.

Histopathological findings

Macroscopic examination

The surgical specimen consisted of a segment of small intestine measuring approximately 15 cm in length. Located at about 6 cm from one resection margin, a sessile, polypoid tumor measuring 4×2.5 cm was identified. The lesion was brown-gray in color, with a lobulated appearance on sectioning, and displayed areas of hemorrhage and necrosis. The tumor appeared to infiltrate the intestinal wall up to the *muscularis propria*. The remaining mucosa was largely preserved, with focal atrophic changes (Figure 3).

Microscopic examination

Histological analysis revealed an ulcerated neoplastic proliferation involving both the mucosal and serosal surfaces of the intestinal wall. The tumor exhibited an infiltrative growth pattern with solid architecture, consisting of nests of large epithelioid cells with round to oval vesicular pleomorphic nuclei, prominent nucleoli, abundant eosinophilic cytoplasm, and intracytoplasmic coarse brown pigment consistent with melanin. Numerous atypical mitotic figures were observed. Tumoral invasion of the muscular and connective tissue layers was evident, along with perineural and lymphovascular involvement. The surgical resection limits were free of tumor infiltration (Figures 4 and 5; Figure 6, A and B).

Diagnosis

The HP features were suggestive of metastatic melanoma. IHC analysis was recommended to confirm the diagnosis and to exclude other differential diagnoses.

Immunohistochemical findings

IHC analysis was performed to confirm the melanocytic origin of the tumor and to support the differential diagnosis. The neoplastic cells manifested:

- S100 protein (clone 4C4.9) diffusely positive in the nuclei and cytoplasm;
- Diffuse cytoplasmic positivity for Melan-A/melanoma antigen recognized by T-cells 1 (MART-1) (clone A103);

▪ Nuclear positivity for preferentially expressed antigen in melanoma (PRAME; clone RBT-PRAME) in approximately 50–60% of tumor cells, with moderate intensity;

▪ Membranous positivity for cluster of differentiation 117 (CD117)/c-KIT (clone RM359) in approximately 80% of tumor cells;

▪ No reactivity for pan-cytokeratin (CK) AE1/AE3, excluding epithelial origin.

The immunophenotype, together with the histological features – presence of brown granular melanin pigment, high mitotic activity (26 mitoses/mm^2), and ulcerated epithelioid growth pattern – were consistent with a diagnosis of malignant melanoma with epithelial ulceration. However, the IHC profile did not allow for definitive distinction between a primary intestinal melanoma and a metastatic lesion.

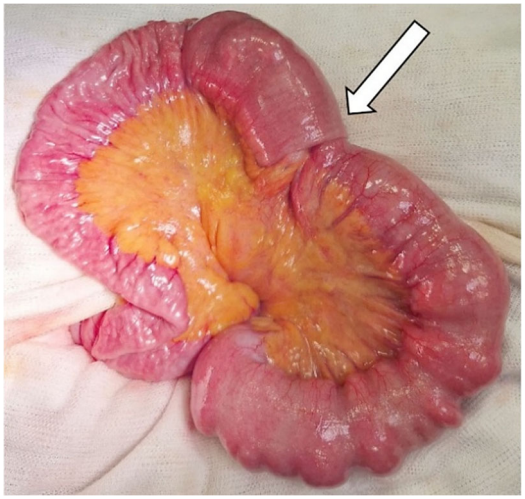

Figure 1 – *The intraoperative aspect of the ileal intussusception (arrow).*

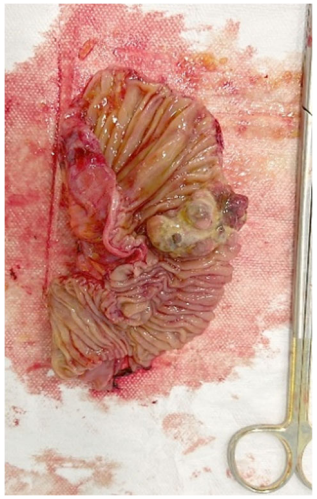

Figure 2 – *The enterectomy specimen showing a polypoid tumor.*

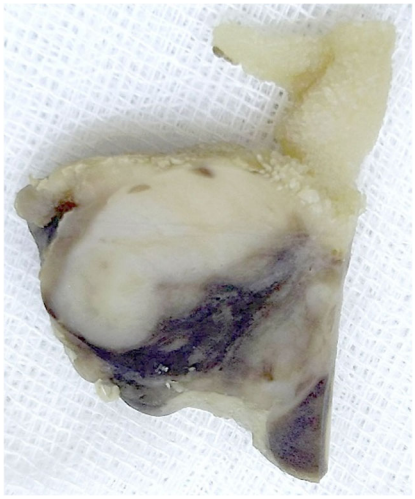

Figure 3 – *Macroscopic examination, following fixation, revealed a residual tumor consisting of a whitish mass with interspersed brown to black areas.*

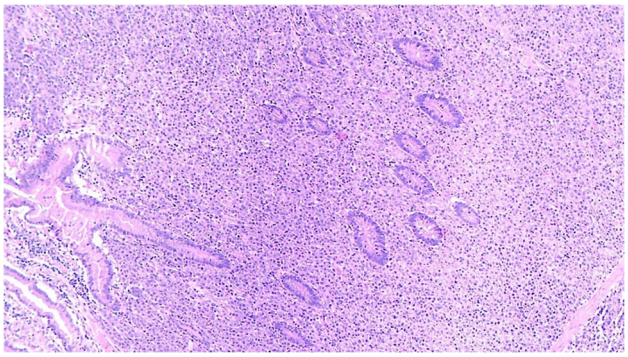

Figure 4 – *Diffuse tumoral proliferation with an infiltrative growth pattern and solid architecture, without glandular structure formation. Residual intestinal glands and crypts are observed. Hematoxylin–Eosin (HE) staining, 100×.*

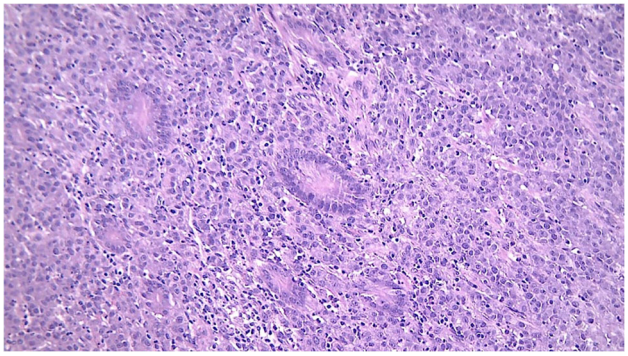

Figure 5 – *Diffuse, infiltrative tumoral proliferation with solid architecture infiltrating the intestinal mucosa, with Paneth cells present. Tumor cells show marked pleomorphism, vesicular nuclei, prominent nucleoli, occasional eosinophilic nucleoli, and atypical mitoses, with numerous interspersed eosinophilic inflammatory cells. HE staining, 200×.*

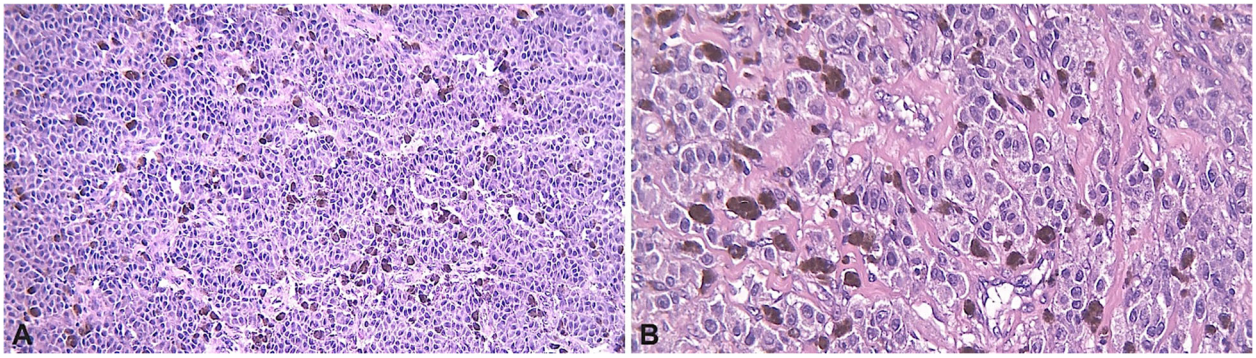

Figure 6 – *(A and B) Area of solid tumoral proliferation composed of pleomorphic cells arranged in nests, with hyperchromatic and vesicular nuclei, prominent nucleoli (occasionally eosinophilic), atypical mitoses, and intracytoplasmic brown granular pigment consistent with melanin. HE staining: (A) 200×; (B) 400×.*

Dermatological evaluation

A thorough dermatological examination was performed by a specialist, including full-body skin assessment, scalp, nail beds, and mucosal surfaces. No suspicious pigmented or amelanotic lesions were identified, and no history of excised skin tumors was reported. Positron emission tomography (PET)–CT examination did not identify any other oncological lesions. Based on clinical, histological, and IHC findings, and in the absence of any perceptible primary cutaneous, mucosal, or ocular lesion, the final diagnosis was consistent with intestinal metastasis of MUP.

Discussions

Melanoma of unknown primary

Melanoma metastasis in the absence of a detectable primary lesion, termed MUP, is an uncommon but recognized clinical entity, comprising 3–4% of all melanoma cases [11]. Several mechanisms are proposed:

- Spontaneous regression of a cutaneous primary (supported by histological evidence of regression in up to 30% of known cutaneous melanomas);
- Unrecognized mucosal or ocular primaries;
- Primary nodal or visceral melanomas, arising *de novo* from aberrant melanocytes in ectopic locations (controversial and rare);
- Previously excised lesions without proper HP assessment [12].

Some studies suggest that MUP patients may have comparable or even better survival than those with known primary melanomas, possibly due to enhanced immune-mediated tumor regression [13]. A pooled analysis of over 1200 MUP cases reported a 5-year overall survival of 58% in stage III MUP, compared to 40–50% in stage III with known primary [13, 14].

Diagnostic approach in suspected small bowel melanoma metastasis

The diagnosis of small bowel involvement by melanoma, especially when presenting as acute obstruction, is challenging and often made intraoperatively. However, when the clinical context allows, a stepwise approach is recommended. For initial evaluation, it is necessary to find the history of previous melanoma or suspicious skin/mucosal lesions. Patients typically present with vague symptoms, including abdominal pain, anemia, GI bleeding, obstruction. Routine bloodwork could find anemia or elevated lactate dehydrogenase (LDH).

The imaging holds an essential role in differential diagnosis. Contrast CT scan of the abdominal region is the "gold standard" in acute settings; may reveal target sign (intussusception), soft tissue mass, or obstruction. ^{18}F–Fluorodeoxyglucose (FDG) PET–CT is highly sensitive in identifying metabolically active melanoma metastases (both GI and extra-GI); also useful in detecting primary lesions in MUP. MRI can be useful as an adjunct tool for small bowel lesion detection. Endoscopy is limited to proximal small bowel unless assisted by capsule which is not indicated in patients with subocclusive symptoms [15].

The definitive diagnosis is made by surgical exploration often required, especially in acute obstruction or bleeding. Histopathology and immunohistochemistry are the keys for confirmation. Melanoma cells are commonly positive for Melan-A/MART-1, human melanoma black-45 (HMB-45), and S100 [16].

The next step for a final diagnosis in case of metastasis is the search for the primary lesion. A full body dermatological exam, including scalp, nail beds, genital and perianal regions is needed, followed by an ophthalmological examination (to rule out uveal melanoma). Ear, nose and throat (ENT)/ mucosal exam for sinonasal, oral, or anorectal melanomas for ruling out a primary lesion in the areas. If no primary is found, diagnosis of MUP is made [17].

Overview of small bowel melanoma

GI tract melanoma metastasis is not uncommon upon autopsy (50–60% in advanced cases), but clinical detection occurs in only 2–5% of patients [18]. Within the digestive system, the small bowel is most frequently incriminated (50–60%), the stomach being the second most affected organ (27%), colon (22%), and esophagus (5%). As a primary tumor in the digestive tract, they arise from the linings of the oral cavity and nasopharynx mucosa 35%, mucosal epithelium of the anus 31%, rectum 22%, esophagus 6%, stomach 3%, small intestine 2% and large intestine 1%, respectively [19].

Primary vs. secondary melanoma in small bowel

Melanoma involving the small bowel can be:

- Secondary (metastatic): far more common, representing the majority of cases;
- Primary intestinal melanoma: extremely rare.

Criteria for true primary small bowel melanoma include solitary lesion, no history of excised melanoma, histological *in situ* changes in adjacent mucosa, and survival beyond 12 months post-resection [20, 21].

Melanoma of unknown primary

MUP is responsible for 3–4% of melanoma diagnosed cases [11]. Possible mechanisms include spontaneous regression of a primary lesion, missed or misdiagnosed cutaneous/mucosal melanomas, or true primary visceral origin (rare/debated). Intriguingly, MUP may confer equal or even superior prognosis compared to known primary melanoma in similar stages [13, 22].

This report underscores a scarce and diagnostically challenging clinical manifestation of metastatic MUP, manifesting as small bowel occlusion due to ileal intussusception on a tumor lead point. Melanoma is well known for its capacity to metastasize widely, with the small intestine representing the most common GI site involved in disseminated disease [19]. However, clinical diagnosis of small bowel metastasis remains rare, and presentation with intussusception is even more unusual, accounting for a small fraction of adult bowel obstructions [23].

Adult intussusception differs fundamentally from its pediatric counterpart in both etiology and clinical course. While idiopathic causes are common in children, over 90% of adult cases are attributable to an underlying pathological lesion, with approximately 30–50% of small bowel intussusceptions being secondary to malignancy [7]. Although not a frequent cause, melanoma has been well documented in literature as a lead point for enteric

intussusception, particularly in cases with widely disseminated disease or in long-term melanoma survivors [24, 25].

In the present case, the patient had no previous history of melanoma, and no suspicious lesions were identified on dermatological examination. HP analysis confirmed the diagnosis of malignant melanoma based on morphological features and IHC profile: diffuse positivity for S100, Melan-A, and PRAME, and absence of pan-CK expression. The expression of CD117 (c-KIT), although not specific, has been observed in a subset of melanomas and may reflect oncogenic pathway activation rather than diagnostic subtype [26, 27].

The lack of an identifiable primary site places this case within the spectrum of MUP, a distinct clinical entity representing 3–4% of all melanoma cases [11]. Theories proposed to explain MUP include complete regression of a cutaneous primary lesion, misdiagnosis or excision without histological confirmation, or less commonly, *de novo* development from ectopic melanocytes in visceral sites [28]. Although the existence of true primary intestinal melanoma remains controversial and rare, the existence of a single enteric lesion, neither metastases nor primary lesion identified might raise the question. Nonetheless, in the absence of *in situ* changes in adjacent mucosa and due to the tumor's invasive nature, a metastatic origin remains the most plausible interpretation [15].

A striking aspect of this case is the absence of any systemic symptoms typically associated with advanced melanoma (*e.g.*, weight loss, cachexia, anemia, or multi-organ involvement), which underscores the importance of considering melanoma even in isolated GI tumors with atypical presentation. Furthermore, MUP has been paradoxically associated in several studies with survival rates equal to or slightly better than those of known primary metastatic melanoma, potentially owing to heightened immune surveillance and spontaneous regression mechanisms [11, 29, 30].

In patients with symptomatic GI melanoma metastasis, surgical resection represents the primary therapeutic approach, especially in settings of obstruction or bleeding. In our case, a segmental enterectomy with clear oncological margins and primary anastomosis was successfully performed, with favorable postoperative evolution. While systemic therapy (*e.g.*, immune checkpoint inhibitors or targeted therapy) is generally considered metastatic disease, the absence of other detectable lesions may delay initiation until further progression is documented.

Clinical implications

This case emphasizes several important clinical and diagnostic points:

- Adult intussusception, though rare, should prompt consideration of an underlying neoplasm, including melanoma;
- Metastatic melanoma can be the first clinical manifestation of disease, even in cases where a primary lesion remains unidentifiable;
- A thorough dermatological and mucosal examination is mandatory, but its normal findings do not exclude melanoma;
- IHC profiling is essential for diagnosis but cannot definitively distinguish between primary and metastatic lesions;
- MUP, although rare, should be recognized as a valid diagnosis, with implications for staging, prognosis, and management.

Conclusions

Our case illustrates an uncommon clinical manifestation of small bowel obstruction due to ileal intussusception due to a metastatic melanoma tumor, in a patient with no identifiable primary tumor site. It underlines the need for heightened awareness for melanoma in cases of adult intussusception, especially when imaging suggests a mass lesion. The diagnosis of MUP remains a clinically challenging, but should be considered when no cutaneous, mucosal, or ocular lesions are identified, even after thorough evaluation.

Surgical intervention – enterectomy – continues to be the cornerstone of management for symptomatic small bowel melanoma metastases, offering both diagnostic and therapeutic benefits. Immunohistochemistry plays a critical role in confirming the prognosis of the disease and the predictive markers, although it cannot definitively distinguish primary from metastatic disease.

This presentation contributes to the ongoing process of better understanding this pathology, emphasizing the impact of melanoma metastasis and supports the inclusion of melanoma in the diagnostic workup of GI tract tumors in adults, particularly in acute surgical settings.

Conflict of interests

The authors declare no conflict of interests.

Informed Consent

The patient provided written informed consent for both the surgical procedure and the publication of this case. All ethical standards and requirements for publication were fully respected, in accordance with institutional and international guidelines.

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Received: July 31, 2025 *Accepted: February 23, 2026*