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Intestinal Perforated Malignant Melanoma: Diagnostic and Therapeutic Difficulties

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Rezumat

Melanom malign intestinal perforat: probleme de diagnostic şi tratament

Melanomul malign intestinal, rar întâlnit în practica medicală curentă, pune delicate probleme de diagnostic şi atitudine terapeutică. Majoritatea cazurilor de melanom malign intestinal reprezintă metastaze ale unei leziuni cutanate dar sunt situaţii în care leziunea iniţială nu poate fi diagnosticată, putând fi considerate melanoame intestinale primitive. Lucrarea prezintă cazul unui bărbat de 50 de ani, diagnosticat şi operat în urgenţă pentru peritonită acută difuză determinată de perforaţia unei tumori jejunale; în cursul laparotomiei exploratorii au fost descoperite şase tumori jejuno-ileale, care au impus practicarea a trei enterectomii segmentare urmate de anastomoze entero-enterale. Evoluţia postoperatorie iniţială fără incidente, a fost marcată, la distanţă, de apariţia de multiple metastaze subcutanate şi o metastază masivă mediastinală care a condus la decesul pacientului la 18 luni de la diagnosticul iniţial. În lucrare sunt discutate problemele de diagnostic şi tratament, în special legate de originea primitivă sau secundară a leziunii intestinale, din moment ce după examinări repetate nu a putut fi diagnosticat un melanom malign cutanat sau într-o zonă cunoscută cu predispoziţie pentru dezvoltarea melanomului malign.

Cuvinte cheie: melanom malign, melanom intestinal, melanom intestinal perforat

Abstract

The intestinal malignant melanoma is a rare occurrence in the daily surgical practice, with difficult diagnosis (even on usual pathologic examination) and therapeutic attitude. Most of the lesions are secondary to a cutaneous primary melanoma, but there are cases in which the original site may not be discovered, and are considered as primitive intestinal melanomas. This paper presents the case of a 50 year old male patient, diagnosed and operated as emergency with acute abdomen caused by a tumoral perforation of the small bowel; several tumors, in different stages of local evolution, were discovered during laparotomy. A triple enterectomy with end-to-end entero-enteral anastomosis was performed, with uneventful postoperative recovery. The later postoperative evolution was marked by the occurrence of multiple subcutaneous recurrences and a bulky metastasis in the mediastinum; 18 month after the initial surgery, the patient died due to the melanoma recurrence. Diagnostic and therapeutic difficulties are discussed in this paper, related especially to the differential diagnosis of the origin of the intestinal lesion (a metastatic melanoma with unknown primary site or a primary malignant melanoma of the small bowel), since no other sites of origin were discovered after a thorough examination.

Key words: malignant melanoma, intestinal melanoma, perforated intestinal melanoma

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Introduction

The existence of a gastrointestinal primary melanoma represents a controversy, most of the intestinal lesions being metastatic; still, Cheung et al, based on the SEER data have found 659 cases of primary gastrointestinal melanomas, representing the largest known database related to primary digestive melanomas (1,2,3).

In the absence of a history of a previously diagnosed malignant melanoma, the preoperative positive diagnosis of intestinal melanoma is virtually impossible; even pathology, using standard examination, may encounter interpretation problems.

On the other hand, regardless of its origin, the digestive melanoma represents an aggressive tumor, often diagnosed as an emergency presentation, due to intestinal obstruction and/or bleeding (2,4,5); tumoral perforation represents a rare onset of the small bowel melanoma but carries a high risk of postoperative mortality (6).

The only treatment that offers the patient a chance for cure is surgical resection of the affected bowel, followed by an accurate pathological assessment and oncologic treatment but the results are usually poor, with a short survival after the initial diagnosis.

Case presentation

Patient O.P.H, male, 50 years old, with no significant medical history, is admitted in our emergency department (14178/03.17.2006) for diffuse abdominal pain, more intense in the lower abdominal quadrants, accompanied by nausea and vomiting; the symptoms onset is for 5 hours, but a 5-6 kg weight loss was recorded in the last month.

Clinical examination reveals a pale, tachycardic patient (98/min.); the abdomen is distended, with diminished respiratory mobility and abdominal diffuse defense, more intense in the lower abdomen, with intense positive Blumberg sign and painful percussion (positive Mandel sign). Rectal tact examination reveals a very painful Douglas pouch.

Usual blood and urine tests were normal, excepting a slight increased of the leucocytes level (9200/mm^3).

The EKG and thoracic X-ray were normal; on plain abdominal X-ray were diagnosed air-fluid levels on the small bowel loops, with a distended transverse colon, without pneumoperitoneum (Fig. 1). Abdominal ultrasound reveals fluid disseminated in the peritoneal cavity, without any other pathologic modifications.

The operative indication is established with acute diffuse peritonitis diagnosis. The laparotomy reveals approximately 400-500 ml of intestinal fluid in the peritoneum; 30 cm below the Treitz angle two jejunal tumors with hard consistency and serosal involvement are discovered; continuing the bowel exploration, it is discovered a group of distended, wall-thickened loops, covered with false membranes, and approximately one meter below the Treitz angle there are discovered two jejunal tumors, similar with previously described, but out of this group one of the tumors is perforated. An enlarged mesentery lymph node is discovered at the level of these loops. Continuing the exploration, on the ileum there are discovered two other similar tumors, without serosal involvement, 0.5, respectively 1 cm in diameter. (Fig. 2)

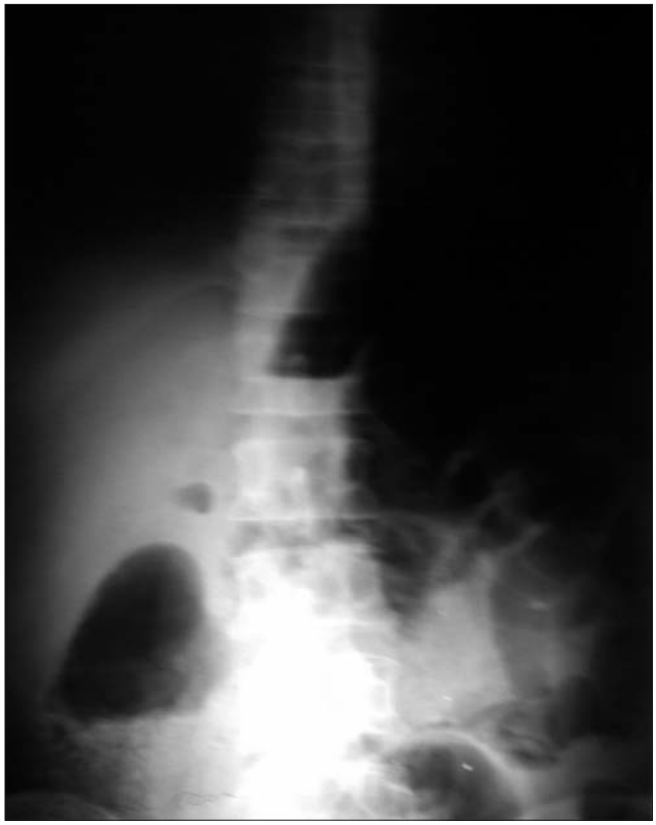

Figure 1. *Plain abdominal X-ray: air-fluid levels, without pneumoperitoneum.*

Considering the distance between the tumors, an en-block resection of all tumors is impossible and three segmental enterectomies were practiced, including the adjacent mesentery with the enlarged mesentery lymph node, followed by hand-sewn end-to-end entero-enteral anastomoses. The operation is ended with an abundant lavage with antiseptics and drainage of the Douglas' pouch. Postoperative evolution is uneventful, with complete recovery, the patient being discharged on the 8th post-operative day.

The histopathology on paraffin embedded sections and hematoxylin-eosin stain reveals a small cells malignant proliferation, considered initially as a MALT-lymphoma with a high degree of malignancy. The malignant melanoma diagnosis is established on immunohistochemical examination: positivity for HMB-45, S-100, vimentine, Melan A, and negativity for CK AE1/AE3, LCA, C-kit, CD30, CD34, actine, desmine, chromogranine, bcl2; p53 was positive (35-40%) and PCNA also positive (70-75%). (Fig. 3) No lymph node metastases were identified on nine examined lymph nodes.

The repeated general clinical examination, oncologic examination, dermatological examination, upper digestive endoscopy and colonoscopy were normal, without any

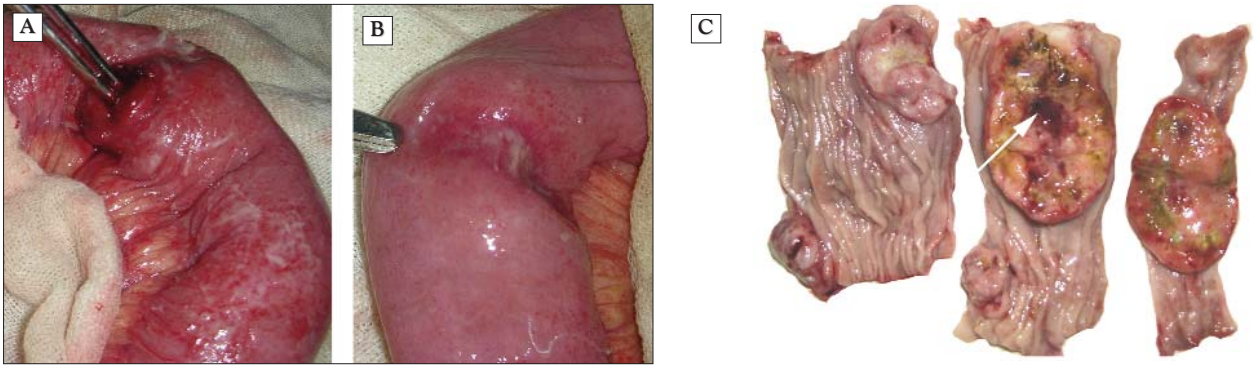

Figure 2. *Small bowel tumors.* ***(A)*** *Perforated jejunal tumor (intraoperative detail, with the clamp showing the perforation site);* ***(B)*** *Another small bowel stenosing tumor located below the previous one (intraoperative detail);* ***(C)*** *All the resected tumors - fresh resection specimen (the white arrow indicates the perforation site)*

suspected lesions of the skin, esophagus or ano-rectum. An ophthalmologic examination was performed, but the result was also normal.

Fourteen months after the initial diagnosis (without a specific adjuvant treatment) the patient is diagnosed and operated for two subcutaneous firm tumors, with reddish, inflamed skin over the tumors, which were histologically diagnosed as malignant melanoma hypodermic metastasis. On the same admission a plain thoracic X-ray discovers three pulmonary and mediastinal metastasis, confirmed by CT examination. (Fig. 4)

The patient is submitted again to oncology and receives two series of Sindovine (2 mg), Daltrizen (800 mg) and Sinplatin (120 mg) (CVD regimen) (7). The disease continues to evolve and multiple similar subcutaneous tumors appear; eighteen months after the initial diagnosis, the patient died due to the melanoma dissemination.

Discussion

The small bowel represents a preferential site of the skin malignant melanoma metastases (50-60% in autopsy series) but there is a 4-9% of cases in which the primary lesion could not be identified (malignant intestinal melanoma with unknown origin), with three possible explanations: a) the spontaneous regression of the primary lesion; b) the primary lesion is too small to be diagnosed; c) the gastrointestinal tract is a site for primary melanomas, with origin in the melanoblastic cells of the neural crest or by the APUD cells (occasionally melanocytic cells were, also, found in the alimentary tract) (1, 8, 9). The incidence of the primary intestinal melanomas is only 2.3% in the SEER series (3); the ano-rectum, the esophagus, the stomach, the colon and the gallbladder were also reported as metastatic sites (10,11,12,13), as well as a primary topography for

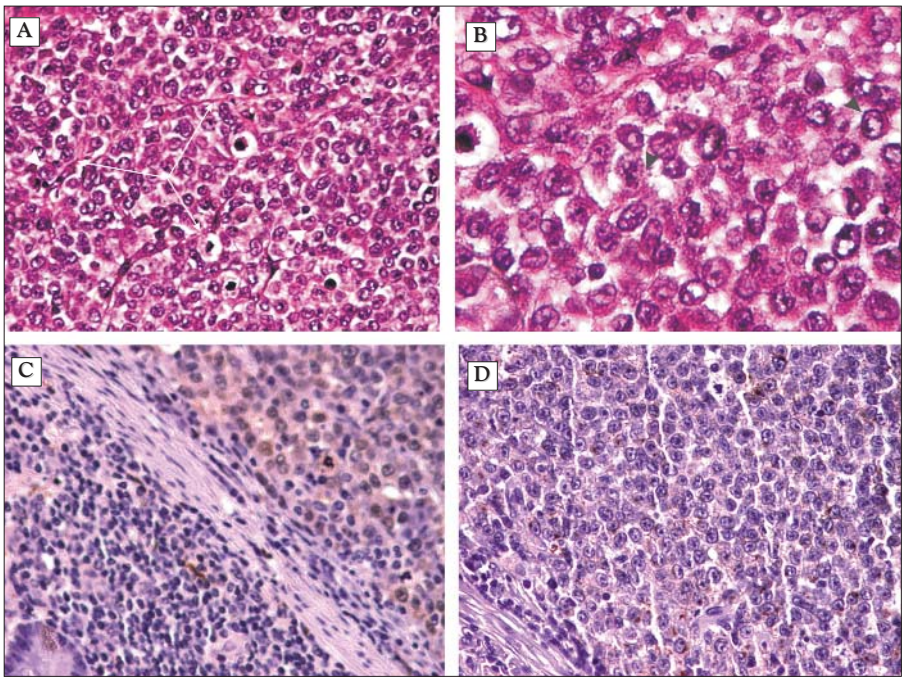

Figure 3. *Histology of the intestinal tumors.* ***(A)*** *Malignant proliferation formed by small cells with atypical nuclei and cytoplasm and atypical mitosis (arrow heads) (HE stain, x200);* ***(B)*** *Cellularity details: atypia of the nuclei and cytoplasm, and atypical mitosis in a small cell malignant tumor (black arrow heads) (HE stain, x400);* ***(C)*** *Small bowel malignant tumor S-100 positive (IHC stain, LSAB technique, x200);* ***(D)*** *Small bowel malignant tumor HMB-45 positive (IHC stain, LSAB technique, x200)*

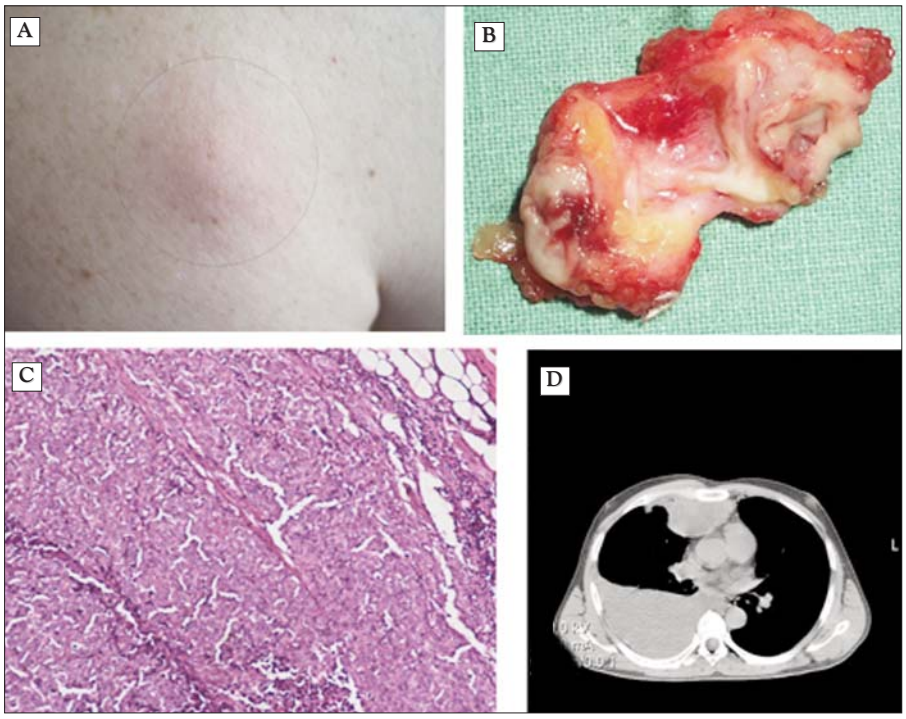

Figure 4. *Metastases developed in the intestinal melanoma evolution.*
(A) *Subcutaneous metastasis (preoperative detail);* ***(B)*** *Sectioned subcutaneous metastasis (fresh resection specimen);* ***(C)*** *Diffuse malignant proliferation, formed by atypical, small, round cells (subcutaneous melanoma metastasis) (HE stain, x100);* ***(D)*** *Big mediastinal metastasis of malignant melanoma on CT image.*

malignant melanoma (2,4,9,14). The pancreas was, also, reported as a metastatic site of an ocular melanoma (15).

In order to be considered primary and not metastatic, Heath essentially considers that tumor must be unique, with origin in the mucosal surface, with polypoid or papillary aspect, and to display junctional activity; a primary site must be firmly excluded (10).

There were no arguments for an intestinal melanoma diagnosis, preoperatively and even intraoperatively: tumors involved the mucosa and extended through the entire bowel wall and were amelanotic; the enlarged mesentery lymph node was also achromic. Bleeding, intestinal obstruction and perforation represent a usual manner of onset for intestinal tumors (6,14,16), although perforation is a rare event for intestinal melanoma (17). As a consequence, we encountered two main diagnosis difficulties: 1) to establish the positive diagnosis of an intestinal melanoma, and 2) to establish if it is a primary or a metastatic intestinal melanoma.

In an elective setting, the capsule endoscopy could have been useful for the diagnosis of the small bowel tumor (18), but the positive diagnosis of intestinal melanoma remains reserved for the pathology.

The initial pathologic examination was inconclusive, immunohistochemical analysis being mandatory for the melanoma diagnosis (S-100, HMB-45, and Melan A positivity, while immunohistochemical markers for epithelial or lymphatic proliferation were negative) (11).

Thorough examinations made repeatedly by several specialists (dermatologist, oncologist, surgeons) failed to identify a site with known specificity for malignant melanoma (skin, eyes, esophagus, anal canal); hence, the idea of a primary intestinal malignant melanoma became very interesting.

Although the small bowel may develop multiple synchronous tumors, we believe that in our case the multiplicity of the lesions (six lesions developed almost over the entire length of the small bowel) plead for metastatic origin; as an argument it is the study of Berger' et al, which demonstrates for metastatic melanoma to the gastrointestinal tract an incidence of multiple lesions of 90% (17). However, considering the absence of a primary known origin and the lack of the junctional activity assessment, we cannot debate over the primary intestinal melanoma, or a metastatic intestinal melanoma with an unknown origin.

Surgery must be offered to the patient whenever it is possible, even for metastatic lesions; in case of a primary intestinal melanoma, surgery has both, diagnostic and curative purpose, as in our case.

Although in the SEER database no significant survival improvement was recorded for the surgically treated primary melanomas of the small bowel (3), surgical resection remains the method followed by the best palliation of the symptoms (19). On the other hand, in metastatic melanoma to the gastrointestinal tract, Berger et al have demonstrated a significantly increased survival for partial resection (8.9 month) or complete resection (23.5 month), compared with inoperable cases (4.1 month) ($p < 0.0001$) (17).

One of the most important objectives of the surgery is resection with clear margins (1).

Segmental enterectomy with clear margins seem to be sufficient, no other abdominal metastasis being recorded until the moment of the patient's death. This raised again the problem of the intestinal melanoma origin: if the initial tumors were metastasis (as we considered originally), it was to be expected that other intestinal metastasis would occur in evolution, and also a shorter survival period was to be expected (below 12 month); none of the skin lesions could

be considered as a primary melanoma; the mediastinal mass was independent of any broncho-pulmonary or esophageal lesion. Thus, there are arguments for the diagnosis of the primary intestinal melanoma in our case: a longer period of survival than in case of metastatic lesions, the absence of another primary site, the aspect of the tumors, involving mucosa. Anyway, these are mainly speculations, and we cannot firmly affirm that it was a primitive intestinal malignant melanoma or a metastatic lesion with unknown primary on a scientific base.

Even though some authors recommend in case of gastrointestinal metastatic melanoma a more conservative approach over the small, non-complicated lesions (19), we preferred, in our case, to resect all the diagnosed lesions, for several reasons: the unknown diagnosis; the presence of the residual lesions may interfere with the postoperative course (a potential obstacle distal to the anastomosis); the unpredictable evolution of a tumor on long distance survival.

Intestinal malignant melanoma (primitive or metastatic) carries a poor prognosis, disease's recurrence being almost a rule; a median survival of 4-6 months was cited (5) but, surprisingly, a long distance survival (over 9 years) was also recorded (4). The median survival recorded in the SEER database in primary malignant melanoma of the gastro-intestinal tract was 17 months. In our case, the postoperative survival was similar with the SEER records; on the other hand, since both cases, ours and that of Acar et al, declined the adjuvant therapy, it seems that prognosis is mostly influenced by factors related to the tumors biology. The oncologic therapy, using interferon or a combination of cytotoxic drugs, has contradictory results and sometimes it is declined by the patient (1,4,16,17).

In conclusion, we choose to present this case due to its rarity in clinical practice, perforation of a small bowel melanoma being very rarely encountered. The diagnosis of intestinal melanoma, without an obvious primary lesion is very difficult, depending on a careful pathologic examination, with immunohistochemical specific tests (HMB-45, S-100, Melan A). Therapeutic approach is delicate, surgery being needed for solving the complication, in order to establish a correct diagnosis, for palliation of symptoms and sometimes for improvement in long distance survival or even cure.

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