Adenocarcinoma do intestino delgado – revisão a propósito de um caso clínico
Small bowel adenocarcinoma – case report and literature review
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Resumo
Os autores apresentam uma revisão teórica sobre neoplasias do intestino delgado baseada no caso clínico de um homem de 49 anos, com os diagnósticos de Hipertensão arterial e Diabetes mellitus, seguindo dieta que incluía as principais fontes de ferro, sem cirurgias prévias. Apresentou-se com fadiga progressiva, palidez, e redução da capacidade de realizar esforços, sem modificação dos hábitos intestinais, sem perdas hemáticas visíveis nas fezes nem emagrecimento recente. Os estudos laboratoriais revelaram: Hb 8,1g/dL; VGM 66,9 fl; HCM 19,8 pg; ADE 19%; anisocitose e poiquilocitose; ferro 16 µg/dL; transferrina 404 mg/dL; ferritina 2,75 ng/mL; contagem de reticulócitos 2,8%. A endoscopia digestiva alta (EDA) e colonoscopia não revelaram lesões sangrantes. Os níveis de hemoglobina e de ferritina permaneceram baixos mesmo após administração parentérica de ferro. No estudo complementar realizado os anticorpos anti-gliadina, antiendomísio, e anti-tissue transglutaminase foram negativos, e a biopsia endoscópica da mucosa do intestino delgado foi normal; a pesquisa de sangue oculto nas fezes foi negativa. A cine-radiografia do intestino delgado revelou aspecto inflamatório ao nível do duodeno e jejuno, e a cápsula endoscópica revelou lesões em ferradura necróticas sangrantes a esse nível.

A exploração cirúrgica com enteroscopia definiu uma lesão solitária no jejuno que foi removida e cuja biopsia revelou um adenocarcinoma do intestino delgado.

Palavras chave: neoplasias do intestino delgado, adenocarcinoma do intestino delgado, anemia.

Abstract
The authors present a theoretical review of small bowel neoplasm based on a case report, of a 49-year-old man, with hypertension and diabetes mellitus, whose diet included the main sources of iron, without any previous surgeries. He presented progressive fatigue, pallor, and reduced exercise capacity, without changing bowel habits, apparent hematocult stool losses or recent weight loss. Laboratory studies showed: Hb 8.1g/dL; MCV 66.9 fl; MCH 19.8 pg; RDW 19%; anisocytosis and poikilocytosis; iron 16 mcg/dL; transferrin 404 mg/dL; ferritin 2.75ng/mL; reticulocyte count 2.8%. The upper gastrointestinal endoscopy (UGE) and colonoscopy revealed no bleeding lesions. Hb level ranged between 8 and 13 g/dL, with low levels of ferritin even after parenteral iron therapy was started. Additional tests carried out showed that antigliadin, antiendomysial and anti-tissue transglutaminase antibodies were negative, and an endoscopic biopsy of small intestine mucosa was normal; faecal occult blood test was negative. Small bowel cine-radiography showed an inflammatory aspect of the duodenum and jejunum, and a capsule endoscopy showed horseshoe necrotic bleeding lesions at that level. Surgical exploration with enteroscopy defined a solitary lesion on the jejunum that was removed, and a small bowel adenocarcinoma was identified in the biopsy.

Key words: small bowel neoplasm, small bowel adenocarcinoma, anaemia.

INTRODUCTION
Iron deficiency anemia is a common disease, caused by a change in the iron hemostasis (increase on the consumption, increase on losses or decrease of intake/uptake). Excluded the common causes (menstrual losses and increase on iron demand during pregnancy), gastrointestinal losses should be considered, and neoplasm of the small bowel a rare cause.1

Although the small bowel representing 80% of the length and 90% of the mucosal surface of the gastrointestinal tract, it presents a reduced incidence of neoplasms (1-6 % of the digestive tract neoplasms, 40 times less than in the colon) and this might be due to a higher rate of apoptosis and cell proliferation of the small bowel promoting a cell desquamation before these are transformed.2, 3

The diagnosis of the small bowel neoplasms is usually in late stages as the clinic symptoms and signs correspond more often to other pathologies.2, 3 (Table I) They should be considered on the following scenarios: a) unexplained relapsing abdominal pain;
b) recurring intestinal obstruction, mainly in the absence of intestinal inflammatory disease or previous abdominal surgery; c) adult intestinal invagination; d) chronic digestive hemorrhage with a radiologic study/negative classic endoscopic (obscure digestive hemorrhage); e) Iron deficiency anemia without an evident cause (hidden digestive hemorrhage); f) personal history of Celiac or Crohn disease; g) family history of colon neoplasm. 2, 3

CASE REPORT

49 years old man, Caucasian, born and living in Fundão (District of Castelo Branco), auto body worker, married.

He was referred to the appointment due to a progressive onset of fatigue, paleness and decrease on the tolerance to effort, without change in the bowel movement, without evident hematic loss and without recent weight decrease.

He had a personal background of high blood pressure and diabetes mellitus type 2, he was taking metoprolol, enalapril, and glimepiride without previous hospitalizations or previous surgical interventions. His smoking load was above 10 packs/year, with alcohol consumption quantified in around 10 gr/ day for over 10 years and diet without restriction on the main sources of iron. Irrelevant family background.

The objective examination showed a pale skin and mucosa; blood pressure - 130/70 mmHg; wide and intense peripheral pulse, heart rate of 60 bpm; axillary temperature 37.2 °C; intense heart sounds, with proto-systolic blow II/VI in the aortic focus; without lymphadenopathy, splenomegaly or petechiae; abdominal and rectal exam without changes.

Laboratorial exams reveal: 1) Severe anemia with a Reticulocytes Production Rate below 2.5 being classified as hypoproliferative (Hemoglobin – 8.1 g/dL, RPR – 1); 2) Erythrocyte rates compatible with microcytosis and hypochromia seen in the swab (Mean Corpuscular Volume – 66.9 fL, Mean Corpuscular Hemoglobin – 19.8 pg); 3 – Iron deficiency (Iron - 16 μg/dL, Transferrin – 404 mg/dL, Ferritin – 2,75 ng/mL); 4 – Possible anisocytosis with increase on the amplitude of the erythrocytary distribution (ADE/RDW - 19%), and poikilocytosis with the anemia severity.

Considering the causes of iron deficiency anemia (Table II), two hypotheses were raised: chronic hematic losses or malabsorption due to disease.

Uppergastroendoscopy and colonoscopy have revealed respectively: a) hernia of the esophagus hiatus and esophagitis without signs of recent hemorrhage; b) four sessile micro polyps (3 mm). In the gastroenterologist point of view, in spite of not having evidence of bleeding, esophagitis could justify small losses in a chronic way, and the sessile micro polyps would hardly bleed. Therefore the patient quitted smoking, reduced alcohol intake and started a proton pump inhibitor and oral iron (at different times in the day to avoid interaction with iron absorption).

On the six months reassessment, it was seen that hemoglobin has oscillated from 8 to 13 g/dL, without being able to keep the highest levels for over a few weeks, with ferritin levels oscillating from 4 to 12 ng/mL, even after therapy with parenteral iron, reason

| TABLE I |
|-----------------|-----------------|
| **Presentation signs and symptoms** | **More common causes** |
| Hemorrhage | Peptic disease, Meckel’s diverticulum, vascular abnormalities. |
| Obstructive jaundice | Coledoco-lithiasis, pancreatitis, pancreas neoplasm. |
| Obstruction | Adherence (previous surgery), internal herniation, volvulus, invagination. |

| TABLE II |
|-----------------|-----------------|
| **Causes of Iron Deficiency Anemia** |
| **Increase of iron consumption and/or hematopoiesis** |
| Quick growth – childhood / adolescence |
| Pregnancy |
| Therapy with erythropoietin |
| **Increase of iron losses** |
| Chronic hematic losses |
| Menstruation |
| Acute hemorrhage |
| Blood donation |
| Phlebotomy – with polycitemia therapy |
| **Decrease on the iron apport or absorption** |
| Inadequate diet |
| Disease mal-absorption – Sprue / Crohn |
| Post-surgical mal-absorption – post-gastrectomy |
| Acute/chronic inflammation |

Adapted from Harrison’s Principles of Internal Medicine; 17Th Edition.
why endoscopies were repeated revealing absence of esophagitis previously identified keeping polyps in the colon.

The possibility of a disease related mal-absorption was considered, but the antibody research for celiac disease was negative (anti-gliadin, anti-endomysium, and anti-transglutaminase-tissular), as well as duodenum biopsies.

Afterwards hidden blood test in the stools was carried out with a negative result, and barium cineradiography of the small bowel revealing an inflammatory aspect of the duodenum and jejunum, leading to a video-endoscopy with capsule revealing multiple necrotic lesions in horseshoe shape bleeding throughout the small bowel. The abdominal CT scan did not reveal any changes.

Subsequently he underwent surgical exploration with intra-surgical enteroscopy, being seen a solitary lesion in the proximal jejunum in horseshoe shape, bleeding, cavernous, that supposedly has motivated the recirculation of the capsule on the different cavities, leading to a diagnosis of multiple lesions. (Fig. 1 to 3)

The histology of the surgical piece has revealed a well differentiated adenocarcinoma, with mucosa infiltration up to the serosa, with metastatization in one of the fourteen nodes removed (T3N1M0).

CT scan exploration was widened to the thorax and pelvis and did not reveal any changes of value.

The patient was subject to complete surgical resection with lymph adenectomy and chemotherapy with FOLFOX (5-FU + Leucovorine + Oxaliplatin).

In the after surgery follow-up, a resolution of the hematologic condition was seen, without evidence of local recurrence or metastatization at a distance, one year after the diagnosis.

**DISCUSSION - THEORETICAL REVIEW**

Primary neoplasms of the small bowel can be benign or malignant due to a change in the epithelial cells or the stroma.\(^2,3\)

Adenocarcinoma is the most frequent (40-50%) of the small bowel malignant neoplasms, of a new or secondary to enteropathy, being often confused with chronic ulcerative disease or Crohn's disease.\(^2,3,4\)

The risk main factor is Crohn's disease with significant cumulative risk from the disease 10 years onwards (0.2% and 2.2% at 10 and 25 years) mainly after surgical “bypass”. Other risk factors are celiac disease, the hereditary syndromes of colon neoplasms (Gardner’s syndrome, - specifically for the periampullary; Peutz-Jeghers’s syndrome, - risk increasing 16 times; family adenomatous polyposis; hereditary colorectal cancer without polyposis).\(^2,3,5,6\)

It should be highlighted that: 1) in Crohn’s disease patients a suspicion of adenocarcinoma should be raised, and in youngsters with adenocarcinoma and diarrhea atypical history, Crohn's disease should be suspected; 2) a clinic exam suggesting a small bowel disease demands an endoscopic biopsy and serology for transglutaminase tissular; 3) if there is a celiac disease, particularly with a bad histologic response to a diet without gluten, neoplasms should be suspected.\(^3,5,6\)

<table>
<thead>
<tr>
<th>Neoplasm: location / type</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal neoplasms in the duodenum</td>
<td>Identical signs to peptic disease.</td>
</tr>
<tr>
<td>Peri-ampulary neoplasms</td>
<td>Obstructive jaundice.</td>
</tr>
<tr>
<td>Distal neoplasm</td>
<td>Usually asymptomatic until the occurrence of obstruction or hemorrhage.</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Occurs typically in the ileum. Early stage: identical symptoms to adenocarcinoma. Advanced stage: splenomegaly and/or peripheral lymphadenopathies. Fever and malabsorption: commons.</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>Big → perforation / massive hemorrhage.</td>
</tr>
</tbody>
</table>
It presents an incidence peak between the 6th and 7th decade of life if new, and between the 4th and 5th decade if secondary, with cases described from 15 to 93 years old, with higher prevalence in the male gender (58-61%). In Afro-Americans there is a higher incidence in young females. Incidence has been increased and there is a geographical correlation of the colon and small bowel adenocarcinoma incidence, suggesting common etiologic factors.\(^2,3,4\)

Although it is located all over the intestine, the location changes according to the age, race and presentation form: duodenal location is more frequent in the elderly, Spaniards and Afro-Americans; if new, it prefers the distal duodenum and the proximal jejunum, if secondary the ileum.\(^4\)

The more frequent symptoms are: abdominal pain (48-75%), vomiting – under occlusion conditions (33-72.5%), weight loss (44-52.5%), hemorrhage (23-39%). Other symptoms are: fever, abdominal mass, increase on proximal peristalsis; and in advanced forms, cachexia, hepatomegaly, ascites and jaundice, and it may vary regarding the location and the neoplasm stage.\(^2,3,4\)

Survival, trend to ulcerate, causing hemorrhage or obstruction is similar both in new as secondary neoplasms. Opposite to the colon adenocarcinoma, the distribution along the small bowel has been stable in the last six decades.\(^2,3,4\)

There are no consensus in the diagnosis, treatment and prognosis of malignant neoplasms in the small bowel. These rarities limits the available information, which usually refers to the small bowel adenocarcinoma based in isolated cases or very limited series and there are some therapeutic extrapolations from the colon adenocarcinoma experience.

**DIAGNOSIS**

It demands the rational and supplementary use of the image methods of the small bowel, in consequence of the specific condition and limited sensitivity to image tests.
There are no defined algorithms but some aspects should be highlighted: 1) classic endoscopy studies are often negative; 2) performing small bowel cine-radiography and abdominal CT scan are considered by several authors as the minimum compulsory search; 3) often cineradiography is not conclusive and should be complemented with Capsule Endoscopy video in a double balloon; 4) in spite of the advantages presented by some of these new modalities, the availability is limited, 5) seldom scintigraphy with marked erythrocytes and angiography are used in the research of digestive hemorrhage.

**Laboratorial evaluation**

Hypochromic microcytic anemia (iron deficiency) is the most frequent laboratorial change. Usually the endoscopic studies are negative, persisting an obscure digestive hemorrhage diagnosis (with visible hemorrhage) or hidden (without visible hemorrhage), demanding excluding of these neoplasms, mainly when the search of hidden blood in the stools is positive.\(^3\)

Other laboratorial changes can indicate the kind of neoplasm: 1) increase of the alkaline phosphatase and bilirubin (cholestasis) suggest duodenum periampullary neoplasms (extra-hepatic cholestasis) or hepatic metastization (intra-hepatic cholestasis); 2) increase of the serial serotonin and 5 hydroxyindolacetic acid in the urine indicating a carcinoid syndrome; 3) dysproteinemia caused by fragments of IgA heavy chains indicates Mediterranean lymphoma.\(^2,3\)

**Neoplasm locating studies**

The upper gastro endoscopy has high sensitivity (90%) for proximal lesions (duodenum), and some technical modifications increase the distal sensitivity: 1) enteroscopy with pediatric colonoscope enables to view the jejunum and proximal ileum; 2) colonoscopy through ileocecal valve (“push enteroscopy”) enables to view the terminal ileum.\(^2,3,7\)

A barium cineradiography (small bowel transit) has the highest sensitivity although limited (80-84.6%) for distal lesions by the duodenojejunal flexure, causing a high exposure to radiations.\(^2,3\)

Enteroclysis is a modification of the previous exam with a higher sensitivity for the placement of a tube in the duodenum which is infused by a marker. Enteroclysis with CT scan image acquisition has a 84.7% sensitivity, after administration of a marker or water, detecting thickening, mass or stenosis of the intestinal wall, stretching or adenopathies in the mesenterium and visceral metastases. Enteroclysis with ultrasound image acquisition (Sonoenteroclysis), consists in performing the abdominal ultrasound before and after nasojejunal infusion of electrolytic isotonic solution, non-absorbable with glycol polyethylene with a sensitivity identical to the cineradiography with lower exposure to radiations.\(^2,3,8,9\)

Endoscopic video capsule is recommended for obscure or hidden hemorrhage, suspicion of tumor, chronic abdominal pain and atypical diarrhea. In a bleeding condition it is more effective than enteroscopy with pediatric colonoscope. It is contraindicated in suspicion of intestinal stenosis (retention risk), therefore it should be preceded by cineradiography. The main limitation is the inability of an immediate therapeutic intervention, and the main advantage is the non invasive character.\(^10\)

The double balloon endoscopy uses a narrower endoscope to visualize the small bowel, with oral approach (anterograde) or anal (retrograde), enable to inspect, make biopsies and treat lesions usually inaccessible. It is recommended in the obscure or hidden hemorrhage, suspicion of a tumor, suspicion of an intestinal inflammatory disease, chronic abdominal pain, atypical diarrhea, changes identified in cineradiography or endoscopic video capsule, polyp removal in the small bowel, confirmation and treatment of angiodysplasia and the evaluation of Roux anastomoses in Y. It is more effective than the endoscopic capsule mainly in the hemorrhage, therefore it should be carried out when there is a high degree of suspicion of a neoplasm and the research with endoscopic capsule is negative.\(^11\)

Laparoscopy or exploratory laparotomy are used when other studies are inconclusive (66% adenocarcinomas; 73%-80% lymphoma (with/without celiac disease); 93% carcinoids), mainly when coexisting with iron deficiency anemia and abdominal pain.\(^2,3\)

**Evaluation studies of the degree of neoplasm invasion**

The echoendoscopy enables to evaluate the intestinal wall degree invasion, might be useful to define the form of resection of localized neoplasms.\(^3\)

Abdominal CT scan has a reduced sensitivity
(57%) while detecting primary neoplasm, but it is useful to evaluate the intra-abdominal and retroperitoneal involvement.\textsuperscript{2,3}

**TREATMENT**

It is based on segmental surgical resection with a curative intent which is performed in a different way depending on the location: a) segmental resection with lymphadenectomy in distal duodenum, jejunum and ileum neoplasm; b) cephalic duodenum-pancreatectomy in Vater’s ampoule and the duodenum second portion neoplasms. Local resection is an option in advanced forms to relieve symptoms.\textsuperscript{2,3}

The endoscopic resection can be an alternative for the early forms (without submucosa invasion), although it is a rare situation (0 – 3% Tis, 3 – 10% T1). It is not associated to the development of major complications (massive hemorrhage or perforation), and it is associated with the cost reduction and morbidity and mortality comparatively to the surgical resection.\textsuperscript{12}

Chemotherapy does not have a neo-adjuvant recommendation, although it has an adjuvant indication in advanced/metastasized disease, increasing the general survival. Such grounds are extrapolated from the knowledge acquired in the colon carcinoma but without support in small bowel trials, there is no consensus regarding the ideal regime, although some patients respond to more than one. Traditional regimes based in 5-fluoruracyl and platinum (cisplatin / carboplatin / oxaliplatin) have general responses of 21% - 36% as first or second line regimes (9% of total answers, and 27% of partial answers), with associated low toxicity. The new regimes based in the 5-fluoruracyl and gemcitabine / irinotecan enable a better general response.\textsuperscript{13}

Radiotherapy is used in big dimensions masses to ease surgery or in local recurrences.\textsuperscript{3}

**PROGNOSIS**

Small bowel adenocarcinomas have a reduced survival even after resection with curative intent: 25 to 52% at 5 years and 27 to 47% at 10 years; with general average survival of 18-20 months, (50.1 months in stages I and II, 11-22.2 months in stage III and 8.6 months in stage IV).\textsuperscript{14}

Factors of a better prognosis are an early diagnosis (stages I and II), and the early resection with curative intent. Factors of a worst prognosis are: 75 years of age or more, a duodenal location, positive surgical margins, ganglionic metastization at the time of resection (related with tumor local recurrence and distance metastatization after resection), distance metastatization, Crohn’s disease history.\textsuperscript{15}

**PREVENTION**

It assumes: a) regular endoscopic monitoring of hereditary polyposis to early detection of periampullary neoplasms; b) early diagnosis of the celiac disease and no gluten diet are related with lower incidence lymphoma, but it is not known the effect on the adenocarcinoma incidence.\textsuperscript{3}

**CONCLUSIONS**

1) Iron deficiency anemia is a common disease, caused by changes in iron homeostasis: consumption increase, increase on iron losses (the most common), or decrease in the supply or absorption.

2) In an adult man, the gastrointestinal hemorrhage will be the cause until different evidence emerges.

3) Small bowel neoplasms, in spite of rare (1 to 6% of the digestive tract neoplasms) should not be forgotten.

4) Adenocarcinoma represents 40-50% of small bowel neoplasms, with a reduced associated survival.

5) If the classic endoscopic studies are not revealing, the use of small bowel marked cineradiography and/or endoscopic video capsule can be very useful.

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