Liver metastases from a hard-to-find primary cancer

Metástases hepáticas de primário difícil de encontrar

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RESUMO
O cancro de primário desconhecido é responsável por cerca de 3-5% de todas as neoplasias malignas e é, portanto, um dos 10 diagnósticos de cancro mais frequentes. A tecnologia de imagem moderna e o estudo anatomopatológico desenvolvido (imuno-histoiquímica, microscopia eletrónica e diagnóstico molecular) resultaram na melhoria do diagnóstico; no entanto, os primários permanecem ocultos na maioria dos doentes, mesmo pós-autópsia. Os locais mais comuns de origem são os tumores do pulmão e pâncreas. O cancro de origem desconhecida é diagnosticado num estádio metastático, conferindo um prognóstico desfavorável. O fígado é um dos órgãos mais comumente envolvido na doença metastática, que surge com mais frequência de primários no cólon. A colосoscopia é o gold standard para avaliação da mucosa do cólon e reto. É apresentado um doente de 64 anos, sem história médica de relevância, que recorreu ao serviço de urgência por dor no flanco direito. A ecografia abdominal revelou metastização hepática difusa. A tomografia computadorizada referia suspeita de espessamento do cólon ascendente mas a endoscopia e coloscopia (com uma boa visibilidade da válvula ileocólica) não tinham alterações.

Palavras-chave: Coloscopia; cancro colorretal; metástases hepáticas; cancro de primário desconhecido.

INTRODUCTION
Cancer of unknown primary site (CUP) is a well recognized clinical disorder, accounting for 3% to 5% of all malignant epithelial tumors1,2,3,4,5. CUP represents a heterogeneous group of metastatic tumors for which no primary site can be detected following a thorough medical history, careful clinical examination and extensive diagnostic work-up1,5,7. Diagnostic approaches to identify the primary site include radiological assessment, modern imaging technology (computed tomography, digital mammography, positron emission tomography), detailed histopathological examination and tumor markers workup with specific immunohistochemistry2,5,7. Upon detection of a metastasis of unknown origin, extensive diagnostic work-up is undertaken to optimize the treatment6.

CUP is reported to be the seventh to eighth most frequent malignant cancer, and is the fourth most common cause of cancer death in both sexes5. Median age at presentation is 65–90 years3,4. The disorder is slightly more common in men than in women, and predominantly affects adults (less than 1% of patients with diagnosed solid CUP are children)3,4.

Most cases of CUP are carcinomas, which are divided into adenocarcinomas of well or moderate differentiation (60%), undifferentiated or poorly differentiated adenocarcinomas (30%), squamous-cell carcinomas (5%), and undifferentiated neoplasms (5%)3,7,9. CUP may occasionally present as mixed tumors, adenocarcinoma with neuroendocrine components, or sarcomatoid carcinomas5,8. Autopsy helps to understand the diagnosis and natural history of CUP1. In some analysis studies from 1944 to 2000, the primary tumour was identified in 644 (73%) of 884 patients; the most common primaries were lung (27%) and pancreatic tumours (24%); tumours in the liver or bile duct (8%), kidney or adrenals (8%), colon or rectum (7%), genital system (7%), and stomach (6%) were also reported3,4. More than 50% of CUP patients present with multiple sites of involvement, while the rest have a single site, most commonly liver, bone, lung or lymph nodes3,5,11. CUP is clinically characterized as an aggressive disease with early dissemination3,5,7. In particular, the prognosis is favorable in CUP limited to lymph nodes and with histology other than adenocarcinoma3,5,6,8.

Recent studies demonstrated familial clustering of CUP and the association of CUP with many other cancers, especially those originating from organs suspected to be responsible for many CUP diagnoses1,8. Accordingly, CUP often occurred in relatives of patients with lung, colorectal (CRC) liver, ovary and kidney cancers, among others3,6,7.

CASE REPORT
A 64-year-old man with dyslipidemia, benign prostatic hyperplasia and partial gastrectomy due to duodenal bleeding (30 years earlier) presented to the emergency department because of a right flank pain since 2 months before. The pain was colicky, moderate intensity, sometimes radiating to the
lower back, without aggravating or relieving factors. He was evaluated by several physicians who prescribed anti-viral and painkillers drugs, without achieving pain relief. Concomitantly, he complained about anorexia and weight loss (2 kg in 2 months, corresponding to 2.8% of body weight). No urinary or gastrointestinal symptoms were described, nor night sweats or blood loss in stool. On physical examination, he was well hydrated, anicteric; abdomen was painful on deep palpation of the right flank and hypogastrium, with no signs of peritoneal irritation; hepatomegaly was palpable 4 cm below the costal margin, with irregular edges.

Laboratory tests revealed normal hemoglobin concentration 14.7 g/dL (normal range 13.0 - 18.0 g/dL); leukocyte count 8.90 x10E3/µL; platelet count 253 x10E3/µL (normal range 150 x10E3/µL to 450 x10E3/µL). Kidney function and urine analysis were normal. Alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transpeptidase and alkaline phosphatase were within normal limits. Tumor markers CA19.9, alpha fetoprotein and prostate-specific antigen were also normal. Abdominal ultrasound revealed many nodules scattered over the right and left liver lobes, suggestive of metastases. An abdominal computerized tomography (CT) scan described, in addition to liver findings, a stenotic lesion of the proximal colon compatible with probable neo-formative condition, defined like a concentric wall irregular thickening involving 4.5cm in length of colonic segment and leading to reduced colonic lumen. Pelvic magnetic resonance imaging
In this clinical case, the initial presentation was abdominal pain with ultrasound and CT revealing lesions suggestive of liver metastases. The imaging and endoscopic tests were not conclusive: the stenotic lesion of the ascending colon initially observed in abdominal CT was not visualized in both colonoscopies, considered the gold standard test for detection of CRC, with the highest sensitivity and specificity. Detection rates are highly related to the experience of the operator, adequacy of the bowel preparation, and even the time taken on examination. Otherwise, during the past 30 years, the accuracy of detecting primary cancer by CT or MRI has increased from 11–26% to 33–55%. Specifically, CT colonography and endoscopic capsule has gained much attention for its high sensitivity for CRC, in some cases.

The liver is one of the most common organs to be involved with metastatic disease of CUP, which arises most frequently from primary sites in the colon, breast, lung, pancreas, and stomach. The accurate detection of metastatic disease at the time of diagnosis or during the course of treatment remains crucial to patient management. Early identification of primary tumor, provides the opportunity for resection which, at least in cases of CRC, has been shown to prolong survival.

CRC is the fourth most common cancer (in the West) and the second most common cause of cancer-related mortality after lung cancer (in Europe and North America). More than 50% of patients will develop liver metastases during their lifespan. Presentation of liver metastasis may be either synchronous or metachronous. Synchronous disease, commonly defined as liver metastases occurring within 12 months of the diagnosis of colon or rectal primary tumor, represents 13 to 25% of newly diagnosed CRC liver metastases. Metachronous disease develops in 20 to 25% of patients. Patients with synchronous CRC liver metastases are thought to have a worse prognosis than those with metachronous disease.

Almost half of patients undergoing resection for primary CRC will eventually develop metachronous liver metastases. Thanks to improvements in chemotherapies and biological agents, survival is about 54 months. Unlike many other types of cancer, the presence of distant metastases from CRC does not preclude curative treatment. Hepatic resection is currently the most effective form of therapy for CRC metastases confined to the liver. However, only a minority of patients with liver metastases is eligible to surgery. Recent progress including new chemotherapeutic regimens, ablative techniques and interventional radiology may permit an increase in the number of patients that can be treated with curative intent.

Considering 80% of patients with CRC hepatic metastases presenting with unresectable disease, systemic chemotherapy represents the main and often the only form of therapy for many patients. Chemotherapy also plays a role in transforming patients with unresectable disease into resection candidates.

Most high-volume centers report a 5-year survival rate of 30 to 40% following resection for hepatic CRC metastases.
In this clinical case, at the time of laparoscopy, the diagnosis of CRC was unknown. Stenosis and proximal dilation of the ileum (and the absence of peritoneal carcinomatosis) were revealed during laparoscopy, leading to perform a radical hemicolectomy. Multiple liver metastases were not eligible for resection. Therefore, after colon surgery, the patient received palliative chemotherapy.

**CONCLUSION**

This clinical case and review emphasize the importance of a multidisciplinary approach for the early suspicion and diagnosis, as well as optimal management of CUP. The new endoscopic techniques along with recent developments in radiological imaging suggest that the investigation of CUP could define a new patient-based diagnostic paradigm and decision making.

**REFERENCES**