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Metastatic Malignant Melanoma of the Gastrointestinal Tract: Too Dark to be Seen?

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Melanoma maligno metastático do trato gastrointestinal: demasiado escuro para ser visto?

Palavras Chave
Melanoma · Metastases · Gastrointestinal

Malignant melanoma (MM) is the most common cause of mortality due to skin cancer worldwide and its incidence is increasing [1]. The majority of MM are from cutaneous origin, and most gastrointestinal (GI) tract melanomas are a result of metastasis, although MM can, less frequently, arise primarily from GI origin [2].

Metastasis of MM in the GI tract is common (estimated in up to 60% of all patients with advanced disease), but in practice only a small proportion are clinically significant. Indeed, only about 1–5% are clinically diagnosed antemortem [2, 3]. In this issue of GE – Portuguese Journal of Gastroenterology, two case reports are published reporting interesting GI involvement of MM, highlighting the sometimes difficult task of diagnosing them.

Firstly, Soares-Santos et al. [4] described a case of an elderly woman with no previous history of melanoma who presents with a set of non-specific symptoms, including GI symptoms. The initial imaging study was negative for malignant disease and endoscopy with biopsies of dark-coloured polypoid lesions allowed the diagnosis of gastric metastasis from MM, which is a rare finding in metastatic MM. The prognosis, due to the patient's comorbidities which rendered her unfit for chemotherapy, was poor. This case highlights the role of endoscopy (the key to solve the mystery) in the diagnosis and management of this patient.

The second case by Pinto et al. [5] highpoints the fundamental role of histology in conjugation with endoscopic findings. A more distracted eye could have easily missed the darker area found in endoscopy or misinterpreted it as a non-significant lesion, and tissue acquisition in adjacent areas possibly lead to the initial misdiagnosis. Repeat endoscopy and biopsies proved to be the right choice of action, and this should be considered when clinical history, endoscopic and histological findings do not match. This case is also a reminder to never forget the previous medical history of a patient, namely, of previous malignant disease, as it might just be the clue needed for final diagnosis.

MM is among the most common carcinomas to metastasize to GI tract and can be spread throughout. Even so, it appears to have particular affinity to the small bow-

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el, specially to the jejunum and ileum [3, 6]. At a molecular level, the greatest expression of CCL25 in the small bowel, which is a ligand to CCR9 expressed in the melanoma cell surface, may somehow explain the typical (atypical) metastasis to this part of the GI tract [3, 7].

On the other hand, primary GI melanomas can arise from various GI segments, more commonly from the anal canal, rectum, and oesophagus and accounts for a minority of MM, with an estimated incidence of 0.58 cases per million people. They are more frequently encountered in elderly women and tend to be more aggressive and diagnosed at an advance stage – 36% versus 4% comparing to cutaneous melanoma, respectively [8, 9]. A primary GI melanoma might be suspected in the absence of prior history of cutaneous melanoma or if the lesion is isolated without other extraintestinal metastasis, and it can be inferred histologically if a precursor lesion is present in tissue sample [10].

Patients with metastatic MM of the GI tract may experience generalized non-specific GI symptoms such as abdominal pain or constipation, depending primarily on the place affected. Cases of GI occlusion and active bleeding have also been described [2, 3]. Clinical diagnosis of GI primary melanoma or secondary involvement can be challenging, especially if symptoms are mild and non-specific. The time between primary excision and metastatic disease can also be a confounding factor, since most metastases are diagnosed within the first 3 years, but there are some cases reporting metastatic disease 15 years after initial treatment [11].

Imaging studies such as computed tomography or positron emission tomography (PET) may be useful in identifying sites of possible metastatic melanoma and can be ordered during follow-up, particularly in advanced disease. Nevertheless, mainly for computed tomography scan, the sensitivity for detecting metastases is about 60–70% [3].

Endoscopic evaluation, as seen in the 2 case reports explored in this issue, is an irreplaceable tool to obtain a diagnosis and can, with the exception of videocapsule endoscopy, acquire tissue for histological appraisal, which is vital in confirming the diagnosis [2, 3, 12]. Endoscopic appearance is variable and metastatic lesions might be misleading. Polypoid or excavated lesions may be observed, and even though colour could be helpful, they may present themselves as amelanotic, so biopsy of suspected lesions should be performed [3, 12, 13], as seen in the case reported by Pinto et al. [5]. However, as stated previously, it is important to note that metastatic melanoma to the GI tract is much less frequently diagnosed in clinical practice than post-mortem, suggesting that most of the times metastasis is asymptomatic [3, 11]. Thus, if metastatic disease is already present, endoscopic and histological diagnosis of MM metastasis of the GI tract should only be pursued if it modifies management of the patient.

In cases of melanoma of unknown primary (that corresponds to about 3% of all cases of MM), i.e., cases in which, according to Das Gupta criteria [14], cutaneous, ophthalmologic, anal, and genital melanoma have been excluded, the true value of endoscopic evaluation is difficult to establish and more recent consensus argues that it may not be useful to search for the primary tumour in mucosal membranes, eyes, or other organs [15, 16]. In case presented by Soares-Santos et al. [4], the symptoms presented by the patient motivated the endoscopic study and lead to the diagnosis of metastatic MM.

Prognosis of MM has dramatically been transformed since the introduction of new therapeutical targets. Before the introduction of target agents, such as BRAF inhibitors and immunotherapy, MM in advanced stage had a median survival time of 6.2 months, with only 25.5% of the patients alive at 1 year [17]. In the era of immune checkpoint inhibitors and targeted BRAF/MEK inhibitors, the clinical management of metastatic MM has fortunately changed. Most immune checkpoint inhibitors are now being used in the treatment of metastatic MM with or without surgery, improving overall survival. Nivolumab, for instance, had a 1-year survival rate of 73% in patients with non-operable or metastatic MM, with a good safety profile [18]. Immune-related adverse events that can urge with this therapy, and may occur in almost every organ, are usually mild and treatable [3, 18].

Surgery also plays a role in the management of these patients, and so a multidisciplinary approach is recommended. An increase in quality of life and survival is, likewise, seen in patients undergoing resection of GI metastases of MM. Despite this fact, the decision to recommend a surgical procedure must take into account patients' comorbidities, age, and melanoma disease burden [19].

In conclusion, even if metastatic MM of GI tract is not an uncommon condition, its clinical diagnosis is far from optimal. The GI tract may be just too dark to be seen (potentially due to non-specific symptoms and the need for invasive procedures), or the lesions may be just too "white" to be deceptive. A high clinical suspicion must be present in patients presenting with GI symptoms and history of MM. Treatment options are increasing, so is the survival of these patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Jéssica Chaves performed the literature search and wrote the manuscript. Diogo Libânio reviewed the manuscript and made critical corrections.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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