Primary Duodenal Melanoma: Challenges in Diagnosis and Management of a Rare Entity

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ABSTRACT

Primary melanoma of the duodenum is an extremely rare, aggressive and life-threatening malignant neoplasm. Published data regarding the effectiveness of current treatment strategies is limited, and our knowledge relies mostly on sporadic case reports. The diagnosis of primary duodenal melanoma is challenging and is based on the patient's medical history and findings from physical examination and radiological and endoscopic imaging as well as proper and careful pathological examinations of the tumor. Despite the many advances in cancer treatment, the prognosis for patients with this type of melanoma remains extremely poor. Delayed diagnosis at advanced disease stage, the general aggressive behavior of this neoplasm, the technical difficulty in achieving complete surgical resection, along with the rich vascular and lymphatic drainage of the intestinal mucosa, all have a negative impact on patients' outcome. In the present review, we aimed to collect and summarize the currently available data in the literature regarding the pathogenesis, clinical features, diagnosis, management and long-term outcomes of this rare, malignant tumor, in order to expand knowledge of its biological behavior and investigate optimal therapeutic options for these patients. Additionally, we present our experience of a case involving a 73-year-old female with primary duodenal melanoma, who was successfully treated with complete surgical resection.

KEYWORDS

primary duodenal melanoma; diagnosis; management; outcome; treatment; prognosis

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INTRODUCTION

Malignant gastrointestinal (GI) melanomas, primary or metastatic, are exceedingly rare, representing just 1–3% of all malignant neoplasms located along the GI tract (1). In the absence of a screened primary cutaneous lesion, differentiation between the primary and metastatic nature of a malignant melanoma (MM) can be highly challenging to establish (2, 3). In the case of secondary localization, the metastatic site can vary greatly throughout the entire length of the GI tract; nonetheless, the most frequent metastatic site is the small bowel (4). Primary mucosal melanoma is an unusual oncologic entity, accounting for only 1% of all melanomas, being epidemiologically and molecularly distinct from the cutaneous subtype. It occurs less commonly in the small intestine and presents high malignant potential, with an estimated 5-year overall survival rate of 25%, regardless of stage (5–7). Specifically, it has been demonstrated that the primary sites of MMs originating from the GI tract were mainly the oropharynx and nasopharynx (32.8%), anal canal (31.4 %) and rectum (22.2%), while small intestine tumors accounted for only 2.3% of GI melanomas(8). Primary melanoma of the duodenum (PMD) is shown to be extremely aggressive and life-threatening. It is associated with dismal prognosis, possibly due to its insidious anatomical localization and lack of symptoms in early stages, resulting in extensive disease at the time of diagnosis (9, 10). Due to its rare occurrence, real-world data on the efficacy of existing treatments are scarce, and as there are no specific recommendations, our current knowledge relies mostly on sporadic case reports.

In this review, we aimed to summarize the limited existing evidence concerning the pathogenesis, clinical features, diagnosis and management of this infrequent but difficult malignancy in the adult population, in order to enhance the knowledge of its biological behavior and highlight the optimal treatment approach for the patients. Additionally, we describe our related clinical experience in a case of PMD successfully treated by surgical resection.

CASE PRESENTATION

A 73-year-old female patient presented to our emergency department with a five-day history of moderate epigastric pain accompanied by multiple episodes of emesis and melena. At presentation, she was hemodynamically stable but with signs of mild dehydration. Physical examination revealed a mildly distended abdomen with tenderness to palpation, especially in the epigastrium. On auscultation, bowel sounds were normal, with no sign of bowel obstruction. Laboratory evaluation revealed mild anemia (hemoglobin of 8.8 g/dL; reference range: 12.0–15.0 g/dL). Her past medical history was unremarkable. Abdominal computed tomography (CT) performed on admission revealed a large mass at the level of the third portion of the duodenum, with significant dilation of the stomach and first and second portions of the duodenum (Figure 1). Upper endoscopy confirmed a duodenal obstruction (Figure 2). A biopsy and histological examination of the lesion indicated MM (Figure 3).

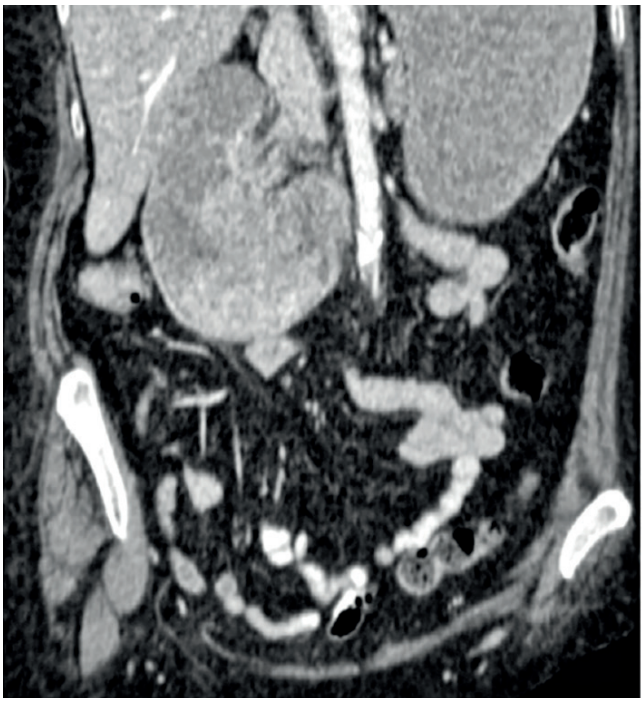

Fig. 1 Abdominal computed tomography revealed a large mass at the level of third portion of the duodenum with a significant dilation of stomach and first and second portions of the duodenum.

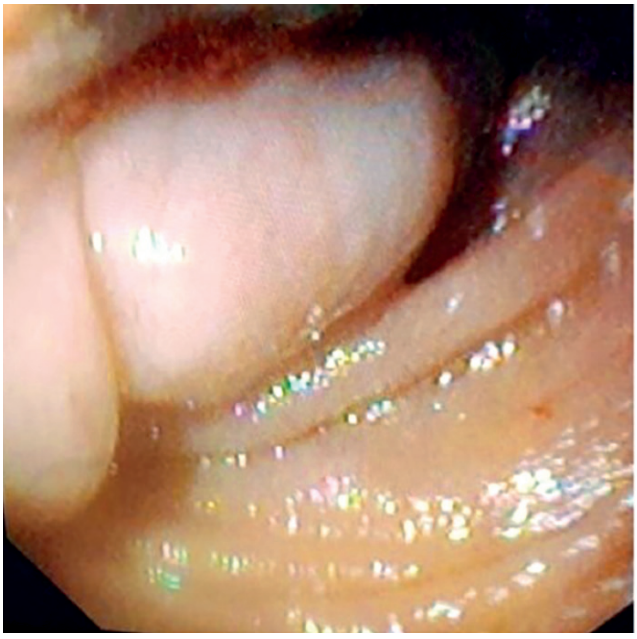

Fig. 2 Upper endoscopy confirmed a subtotal obstructing duodenal mass.

Accordingly, the patient underwent exhaustive systemic evaluation including cutaneous, retina, nasal and oral cavity examination as well as a colonoscopy, which did not detect a primary melanoma lesion. Therefore, the lesion was categorized as a PMD. After optimization of the patient's condition, a Whipple's procedure was performed. Her postoperative course was uneventful and she was discharged on postoperative day 10. At 3-year follow-up, the patient remains disease-free. Informed consent was given by the patient for publication of this case.

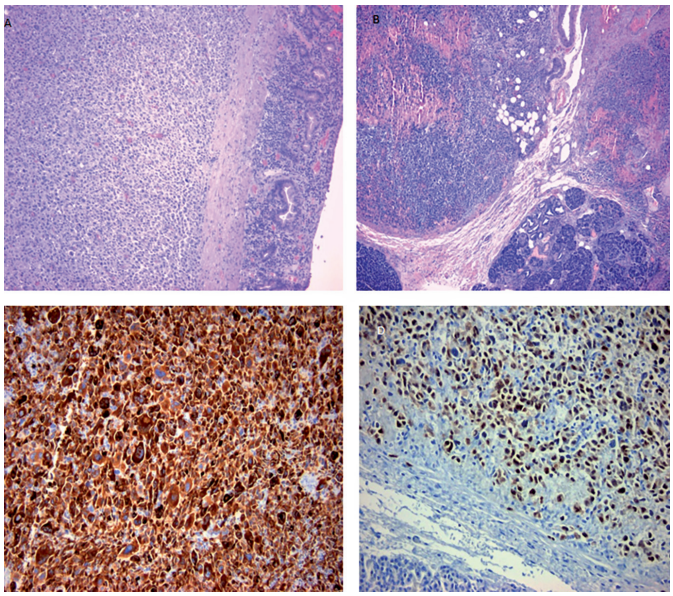

Fig. 3 Biopsied sections showed a pleiomorphic tumor infiltrating adjacent organs. A: Duodenum (hematoxylin & eosin, 200×); B: Pancreas (hematoxylin & eosin, 200×); C–D: By immunohistochemistry, the cells were positive for S100 (C; 400×) and SOX10 (D; 400×).

PATHOGENESIS

PMD is a particularly rare tumor with unclear etiology. Several theories have attempted to describe its pathogenesis in the past, but determination of its exact origin remains problematic and controversial. One hypothesis proposes that although melanocytes are not normally contained within the small and large bowel, they can be sporadically found in the mucosa epithelium of the alimentary tract and in the lymph nodes, leading to the development of primary melanomas at these sites (11). Another theory suggests that these neoplasms may arise from Schwann cells related to the autonomic innervation of the gut (12). Others have postulated that GI melanomas might originate from melanoblastic neural crest cells that migrate into the GI mucosa *via* the umbilical-mesenteric canal during embryogenesis, where they differentiate into amine precursor uptake and decarboxylation cells (13). Subsequently, amine precursor uptake and decarboxylation cells may potentially transform into neoplastic cells and produce tumors such as gastrinomas, carcinoids and melanomas (13). Furthermore, it has been presumed that melanoblasts normally exist in the small intestine and might behave as precursors to MM. Other researchers disagree with the presence of primary melanomas in the small intestine and maintain that these lesions represent metastasis from unknown or regressed primary cutaneous tumors (1, 14–16).

CLINICAL PRESENTATION

Clinical presentation of MM originating in the duodenum involves a broad spectrum of clinical features and is often elusive, as it varies between patients depending on the extent of disease (3, 10, 17, 18). Remarkably, in most cases, no specific early symptomatology has been reported The tumor becomes noticeable only when its growth presses on neighboring structures or invades surrounding tissue, or when metastasis has occurred (6, 19, 20). Since diagnosis is frequently delayed, a high index of suspicion is required to reveal its incidence. Its symptoms generally include abdominal pain, intestinal obstruction, hematemesis, melena, vomiting, weakness, weight loss, anemia, loss of appetite, constipation, malabsorption, perforated bowel, jaundice and palpable abdominal mass, which are typically identical to those of other types of duodenal tumors (3, 17, 21, 22). In comparison to duodenal adenocarcinoma, which presents more frequently with obstructive jaundice, most patients with PMD initially present with abdominal pain, anemia, upper GI hemorrhage or a palpable abdominal mass (3, 18, 21).

From the year 2000 until today, a total of only 12 cases of PMD have been reported in the literature, seven of which concerned males with a median age at diagnosis of 56.5 years-old (Table 1). No risk factors have been confirmed, possibly because PMD develops on surfaces that are not exposed to ultraviolet light (23). A detailed and accurate history often reveals several episodes of intermittent midepigastric pain, sometimes associated with vomiting and nausea, while fatigue, weakness and weight loss have also been recorded. According to the published cases, the majority of patients presented to hospital with abdominal pain (n = 8). Five patients were referred with upper GI hemorrhage, such as melena or hematemesis, and five mentioned weight loss; six out of 12 patients were diagnosed with anemia. Furthermore, as illustrated in Table one, six patients described feelings of fatigue or weakness and five reported occasional episodes of vomiting, while two patients displayed jaundice attributable to an obstructive tumoral mass in the ampulla of Vater.

A thorough physical examination may demonstrate epigastric sensitivity, a palpable, firm abdominal mass (two cases), or lymphadenopathy that indicates extensive disease. The pre-existence or coexistence of a primary lesion must also be excluded at this time (3). In our review, all patients had negative ophthalmological, otorhinolaryngeal and dermatological examination findings for other primary locations of melanoma.

DIAGNOSIS

As this type of neoplasm is rare and no typical early symptoms or signs are evident, diagnosis is invariably reached late during the disease course (6, 19). Difficult anatomical localization demanding visual detection and frequent amelanotic presentation pose a challenge to clinicians (7). Definite diagnosis relies on the combination of clinical examination, endoscopic and radiological imaging findings and careful histologic investigation with the use of proper immunohistochemical stains (9, 10). Initially, a potential metastatic spread should be excluded; although, primary or secondary origin of GI melanomas can be difficult or even impossible to establish, giving rise to much controversy (2, 3, 24, 25). Indeed, the primary site may regress

Tab. 1 Characteristics and management of reported cases with primary duodenal melanoma.

Year; Author	No of cases	Sex	Age (years)	Primary symptom	Systemic exploration for melanoma	Diagnosis-Radiogical-Biomarkers	Distant metastasis	Management	Adjuvant chemotherapy	Pathologic examination / LN+	Stains	Follow-up(months)	Recurrence	Melanoma related death	Survival
Kilambi 2017	1	M	35	Abdominal pain, weight loss	Negative	U/S, Upper GI endoscopy, CT, EUS-FNA, PET	No	Pancreaticoduodenal resection & Colectomy	Yes temozolamide	MM / Yes	HMB-45(+), S-100 protein(–)	32	No	No	Alive at 32 months
Jain 2015	1	M	35	Abdominal pain, vomiting	Negative	U/S, PET	No	Resection	Yes chemoradiotherapy	MM / Not known	HMB-45(+), S-100 protein(+)	Not known	Not known	Not known	Not known
Suganuma 2013	1	M	67	Anemia, Fatigue, dyspnea	Negative	EGD, EUS-FNA, GBS, PET, CT	Yes Stomach, left adrenal gland	Distal duodenojejunectomy, partial gastrectomy, left adreanalectomy	Yes Dacarbazine, vincristine, nimustine	AMM / No	HMB-45(–), S-100 protein(+), Melan A(+)	36	No	No	Alive at 36 months
Bendic 2013	1	M	52	Abdominal pain, hematemesis, jaundice, weakness	Negative	Upper GI endoscopy, CT, US	No	Whipple	No	AMM/ Yes	S-100(+), Melan-A(+), Vimentin(+)	6	Yes	Yes	Died at 6 months
Li 2012	1	M	60	Abdominal pain, melena, vomiting	Negative	Upper GI endoscopy, GBS, CT	No	Tumor resection	No	MM/ Yes	HMB-45(+), S-100 protein(+), vomiting-Melan-A(+), Vimentin(+)	46	No	No	Alive at 46 months
Korkolis 2008	1	M	55	Abdominal pain, massive upper GI hemorrhage, anemia	Negative	Upper GI endoscopy, CT	No	Pancreaticoduodenal resection	Yes Interferon	MM/ Yes	HMB-45(+), S-100 protein(+), Melan-A(+), Vimentin(+)	14	No	No	Alive at 14 months

Year; Author	No of cases	Sex	Age (years)	Primary symptom	Systemic exploration for melanoma	Diagnosis-Radiogical-Biomarkers	Distant metastasis	Management	Adjuvant chemother-apy	Pathologic examination / LN+	Stains	Follow-up(months)	Recurrence	Melanoma related death	Survival
Houissa 2001	1	F	78	Abdominal pain, weakness, weight loss, loss of appetite anemia	Negative	Upper GI endoscopy, CT, U/S	Yes Stomach, esophagus, liver	Palliative	No	MM/Yes	HMB-45(+), Melan-A(–),	1	Not known	Yes	Died at 1 month
Flechon 2002	1	F	33	Jaundice, pruritus, vomiting	Negative	Upper GI endoscopy, CT, EUS-FNA, U/S	Yes, pancreas, interpancreaticoduodenal region	Pancreaticoduodenal resection	No	MM/Yes	HMB-45(+), S-100 protein(+), Melan-A(+), Vimentin(+)	2	Yes	Yes	Died at 2 months
Zhou 2020	1	F	58	Bone pain, fatigue	Negative	Upper GI endoscopy, CT, MDP	Yes Liver and bone	Palliative	No	MM/Not known	HMB-45(+), S-100 protein(+)	1	Not known	Yes	Died at 1 month
Anvari 2018	1	M	68	Fatigue, weakness, lethargy, weight loss, anemia	Negative	Upper GI endoscopy, CT	Yes Gallbladder, adrenal glands, mesenteric lymph nodes	Palliative chemotherapy (temozolamide)	No	MM/Yes	S-100 protein(+), Melan-A(+),	Not known	Not known	Yes	Died quickly
Surjan 2020	1	F	40	Abdominal pain, anorexia, weight loss, vomiting, melena, anemia	Negative	Upper GI endoscopy, CT	No	Pancreaticoduodejunal resection	Yes cisplatin-temozolamide	MM/No	HMB-45(+), S-100 protein(+), Melan-A(+),	36	No	No	Alive at 36 months
Coban 2013	1	F	63	Abdominal pain, melena, hematemesis, fatigue, weakness, vomiting, weight loss, anemia	Negative	Upper GI endoscopy, CT	No	Palliative	No	MM/Not known	HMB-45(+), S-100 protein(+),	1	Not known	Yes	Died at 3 weeks

AMM: Amelanotic malignant melanoma; CT: Computed tomography; EGD: Esophagogastroduodenoscopy; EUS-FNA; Endoscopic ultrasound-guided fine needle aspiration; GBS: Gastrointestinal barium study; GI: Gastrointestinal; HMD-45: Human melanoma black-45; LN+: Positive lymph nodes; Melan-A: Melanoma antigen; MM: Malignant melanoma; PET: Positron emission tomography; U/S: Ultrasound.

spontaneously without receipt of appropriate treatment, or it can be too small to be detected by conventional clinical and laboratory investigation techniques (26).

Several criteria have been suggested to distinguish whether a lesion is a PMD or a metastasis from another primary site. A biopsy-proven melanoma from the intestine at single focus, no evidence of disease in any other organs (including skin, eye and lymph nodes outside the region of drainage at the time of diagnosis) and presence of intramucosal lesions in the overlying or adjacent intestinal epithelium, may be required to support the diagnosis (4, 14). These criteria are based on the hypothesis that a metastatic melanoma would generally be multifocal. However, primary GI melanomas may present as single or multiple lesions. At least two cases have been described in the literature with primary diffuse upper GI tract melanoma with masses involving the stomach and duodenum, most likely through local hematogenous metastasis (22, 27–29). In addition, five cases with metastases to other organs have been reported, which is consistent with the aggressive behavior of mucosal melanomas (9, 22, 27–29). Even if these cases do not fulfill the above criteria, current data suggest that they are primary melanomas. Consequently, the criteria may need to be revised in order to establish a proper diagnosis.

A plethora of imaging studies has been used for the preoperative diagnosis of PMD. Since patients mostly present to the hospital with vague abdominal symptoms, transabdominal ultrasonography is typically the first diagnostic tool, as (18, 21), as it could detect a large mass arising from the region of the duodenum or dilatation of the main or intrahepatic bile ducts due to obstruction of the ampulla of Vater (18, 22). Barium examination can improve intestinal imaging but is not appropriate for extraintestinal findings (10, 29). CT allows for better visualization of the duodenum and can define extraluminal and metastatic disease, although the reported sensitivity of CT for detection of intestinal melanoma is only 60–70% (30–32). Sensitivity and specificity are higher with 18-fluorodeoxyglucose whole-body positron emission tomography imaging (FDG-PET), which can offer a dual advantage by excluding other primary tumors and by staging the disease (21, 33). The most valuable diagnostic procedure is the esophagogastroduodenoscopy, as the presence of an ulcerative pigmented lesion is a pathognomonic finding, and biopsies can also be obtained at the same time (9, 32). However, endoscopic appearance may be deceptive since PMD can also present as multiple nodular lesions or as a non-pigmented lesion (18, 27, 28, 31). Indeed, in our review, two cases of amelanotic melanoma were described that complicated the diagnosis (18, 31). In addition to demonstrating the lesion and tissue acquisition, endoscopic ultrasonography is able to assess the status of the vessels entering into the mass, the layer of the duodenal wall from where the tumor originates, and the extraluminal extent (18, 22, 29). In our study, upper GI endoscopy, CT and abdominal ultrasound were the most frequently used modalities, followed by PET, endoscopic ultrasound-guided fine needle aspiration and GI barium study (Table 1).

Careful differential diagnosis is essential, as GI melanomas mimic other neoplasms, such as carcinomas, lymphomas and neuroendocrine or GI stromal tumors (10, 19, 32). Definite diagnosis of PMD is confirmed by pathological examination and several immunohistochemical markers, such as human melanoma black-45, S-100 protein, melanoma antigen (referred to as Melan-A) and vimentin (10, 20). Of note, regarding published PMD cases, seven out of 12 patients had positive lymph nodes after pathological analysis. Finally, findings from laboratory investigations are usually unremarkable, apart from anemia and abnormal hepatic biochemistry caused by the obstruction of bile ducts or metastatic disease to the liver (22, 27, 31).

STAGING

Currently, there is no universal staging system for mucosal melanomas, including PMD. However, a simplified staging system can be utilized, which was firstly applied for melanomas of the head and neck (34). Specifically, stage I involves clinically localized disease, stage II is defined as regional lymph node metastases and stage III describes the presence of distant metastatic disease (3). Nevertheless, further studies are necessary in order to establish an accurate staging system that could determine prognosis and suggest preferable and more efficient treatment, thereby improving survival.

TREATMENT

Curative surgical resection remains the gold standard treatment in patients with PMD, although its hidden and atypical presentation prevents early diagnosis, making the process challenging, morbid or even impossible (1, 3). Whether open or laparoscopic, the procedure must involve wide local excision of the neoplasm with negative margins accompanied by a subtended wedge of the mesentery to remove regional lymph nodes (3, 26). Consequently, cautious patient selection for surgery is fundamental, taking into consideration findings from imaging studies that indicate the extent of disease and patient's performance status and preference, in order to precisely predict postoperative morbidity and benefits (3, 20). With regard to the reviewed case reports, eight cases underwent surgical resection and four received palliative treatment due to metastatic disease, poor patient condition or non-acceptance of the surgical approach. The most frequent intervention was pancreaticoduodenectomy with regional lymphadenectomy (five cases). Two patients underwent tumor resection only, while one case was subjected to a distal duodenojejunostomy along with partial gastrectomy and left adrenalectomy in order to achieve complete disease excision (Table 1). In all reported cases, patient outcome was good after surgery, and no postoperative complications were recorded.

According to the published cases, two patients suffered from obstructive jaundice caused by tumors involving the ampulla region. One patient was treated with percutaneous transhepatic biliary drainage and the other underwent a pancreaticoduodenectomy (22, 31).

Published data on systemic adjuvant therapy in patients with PMD are limited, and there are no definite guidelines supporting this choice, as no improvement in the OS rate has been shown (8). The only available evidence originates from a phase II randomized trial of interferon *vs.* chemotherapy, including temozolamide and cisplatin, which showed progression-free survival in patients with resected mucosal melanoma and significantly elevated OS rates in the second group (35). However, further clinical trials with a larger patient population are needed, in order to advance adjuvant chemotherapy in accordance with general recommendations. In this context, adjuvant therapy with temozolamide alone, temozolamide-cisplatin, interferon or dacarbazine-nimustine hydrochloride-vincristine was administered to five patients with PMD with prolonged progression-free survival (Table 1) (18, 19, 21, 29, 32).

Currently, cancer immunotherapy is a hot topic that has a recognized role in cutaneous and non-cutaneous melanoma postoperatively or later in disease evolution, with substantial effects on survival (36, 37). Nevertheless, compared with skin melanomas, mucosal melanomas differ biologically; they have a lower mutational burden, less immunogenicity, and have reduced expression of programmed death-ligand 1, all of which could possibly weaken the efficacy of immunotherapy (38–40). Although there are no randomized clinical trials indicating the effectiveness of immunotherapy in patients with PMD, existing evidence illustrates that in metastatic or unresected mucosal melanomas, combination therapy with programmed cell death protein 1 and cytotoxic T-lymphocyte antigen 4 antibodies or concomitant radiotherapy and immunotherapy may be of particular benefit to OS (7, 40, 41). That being the case, broader clinical trials are warranted to clarify the role of immunotherapy on mucosal melanomas.

GI melanomas also have distinct mutational and molecular profiles compared with cutaneous subtypes (40, 42, 43). Specifically, mutations in the proto-oncogene B-Raf are rare in GI melanomas (less than 5%), whereas mutations in the proto-oncogene c-KIT are more frequent (40, 42, 43). Some clinical trials demonstrated an improved response in patients with advanced mucosal melanomas that received either c-KIT or B-Raf inhibitors, depending on the tumor's gene mutations, but further investigation is necessary (44, 45).

PROGNOSIS

Despite the many advances in cancer treatment over the past few decades, the prognosis for patients with primary GI melanomas remains extremely poor, with a median OS of up to 17 months after curative surgical intervention (8). Commonly delayed diagnosis at advanced stages, the general aggressive behavior of these neoplasms and the technical difficulty in achieving complete surgical resection, along with the rich vascular and lymphatic drainage of the intestinal mucosa, are all considered major determinants of prognosis (5, 46, 47). Microinvasion or distant metastasis have already occurred at the time of diagnosis, and current therapies are unable to offer definite treatment outcome (6, 18). According to our results, the median OS was 10 months and the longest reported survival was 46 months. Notably, no recurrence was recorded during the follow-up period of three patients (32, 36 and 36 months, respectively), who underwent surgery and received adjuvant therapy postoperatively (temozolamide, dacarbazine/vincristine/,nimustine and cisplatin/temozolamide, respectively) and of one patient (follow-up period of 46 months), who refused chemotherapy after tumor resection, choosing to use Chinese traditional medicine treatment instead (10, 18, 19, 29) (Table 1). The limited number of included cases and restricted follow-up data may significantly affect the results, and prognosis cannot be accurately calculated. Larger clinical trials are required to determine the precise morbidity and mortality of PMD. The rare nature of the disease and highly malignant potential with low survival rates pose challenges to this task.

CONCLUSION

In conclusion, PMD is a very rare, aggressive oncologic entity of the alimentary tract with an extremely devastating prognosis. As its clinical manifestation is not specific, detection of this neoplasm remains particularly demanding and definite diagnosis depends on the combination of detailed history, thorough clinical examination, advanced imaging modalities and cautious histological investigation. Differential diagnosis between primary and secondary origin of the tumor is crucial since complete surgical resection can be achieved in the case of PMD, which could lead to a significant increase in OS, contrary to patients with secondary duodenal melanoma. In the literature, however, this subject remains controversial. Given the absence of significant knowledge about this malignancy, management of PMD is unclear. A methodical, multimodal and individualized approach is required, including surgical and non-surgical options, to achieve long-term survival (> 2 years) in these patients. Although complete surgical resection is the treatment of choice, the impressive advancements in systemic therapies may open up new avenues with adequate therapeutic effect, especially in the context of advanced unresected disease. Further research is needed to understand the underlying and complex pathogenetic nature of this neoplasm in order to target it specifically and design preferable and more efficient strategies.

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