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Roberta Tutino*/**, Giuseppe Clerico**, Alberto Realis Luc**, Gaetano Gallo***/**, Mario Trompetto**

**Department of Surgical, Oncological and Oral Sciences, University of Palermo, General Surgery and Emergency O.U., Policlinico Universitario "P. Giaccone", Palermo, Italy*
***Coloproctology O.U., Clinica Santa Rita, Policlinico di Monza, Vercelli, Italy*
****Department of General Surgery, University of Catanzaro, Italy*

Polypoid anal melanoma. A case report and review of the literature

INTRODUCTION: *Ano-rectal melanoma is an uncommon finding in patients complaining of rectal bleeding and/or anal mass often misinterpreted as a haemorroidal pile.*
CASE REPORT: *A 55-years-old woman, complaining of rectal bleeding, frequent anal pain and anal mass suspected for haemorroidal thrombosis was referred for evaluation and possible treatment. A brown polypoid mass arising from the anal canal/lower rectum with a maximum diameter of 6 cm was diagnosed. The hystological examination of the neoplasm, transanally removed, revealed the presence of a polypoid melanoma partially involving the resection margin. Nor metastases nor limph-node involvement were found at the total-body CT scan and at a CT-PET. C-KIT examination was negative. Multidisciplinary evaluation recommended an abdominoperineal resection followed by an adjuvant chemotherapy as the only possible salvage treatment. To date the patient has refused it.*
DISCUSSION: *The delay in the diagnosis of an anal melanoma is well-known, bringing frequently to treat advanced stages of the disease that to date has no clear guidelines for the treatment.*

KEY WORDS: Ano-rectal melanoma, Mucosal melanoma, Rectal bleeding

Introduction

The anal region is an unusual site for melanoma even if it is the most frequent mucosal one; among anal cancers it accounts for 1% of cases and among melanomas for 0.4%-1.6% with an incidence of 0.3 cases/million in the USA [1,2]. Its frequency is increasing faster than any other type of cancer (by 2%-7% annually), particularly in the last decades [1]. The anal location is encountered mostly at an early stage whereas rectal or ano-rectal areas have often a delayed diagnosis. Its main symptoms are bright ano-rectal bleeding, pain and an anal mass often misinterpreted as a hemorroidal pile. Irrespective to the location, long-term prognosis remains poor with a 5-years survival rates ranging from 6% to 22% [2]. To date its low incidence has not permitted the possibility to have specific guidelines for its management.

Case Report

A 55-years-old woman, complaining of rectal bleeding, anal pain and an anal mass, attended to a coloproctology unit for the management of a suspected hemorroidal thrombosis. The patient complained of a protruding mass during defecation, accompanied by occasional

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Correspondence to: Roberta Tutino, MD,Department of Surgical, Oncological and Oral Sciences, University of Palermo, General Surgery and Emergency O. U., Policlinico Universitario "P. Giaccone", Palermo, Italy (e-mail: la.tutino@gmail.com)

bleeding and anal pain. At examination a small pile and an enhanced anal tone was noted. A severe anal pain did not allow nor an accurate digital rectal examination nor a proctoscopy. The prompt evaluation in anesthesia revealed a dark red polypoid mass arising from the anal canal/lower rectum with a maximum diameter of 6 cm (Fig. 1); another small lesion with similar features was noted at the anal verge (Fig. 2). A transanal removal of the mass including the nodule close to the biggest lesion was performed. Histologic examination revealed the presence of a pigmented, ulcerated, polypoid melanoma with epithelial cells showing an area of central necrosis; the margin of resection was partially involved by the tumor. Also the other removed nodule presented infiltration from melanoma. Mitotic index was 16/10HPF. Positive immunostaining by using monoclonal for antibodies S-100 and HMB45 was evidenced while Melan-A/Mart-1 and KER pan resulted negative. BRAF analysis showed a wild type without mutations. c-KIT examination was negative. Total-body CT scan was negative for metastasis. A spherical pelvic lymph-node of 10 mm suspected for tumor involvement was ascertained through a PET-CT examination that resulted negative. The following multidisciplinary consultation suggested an abdominoperineal amputation followed by adjuvant chemotherapy that has been refused by the patient.

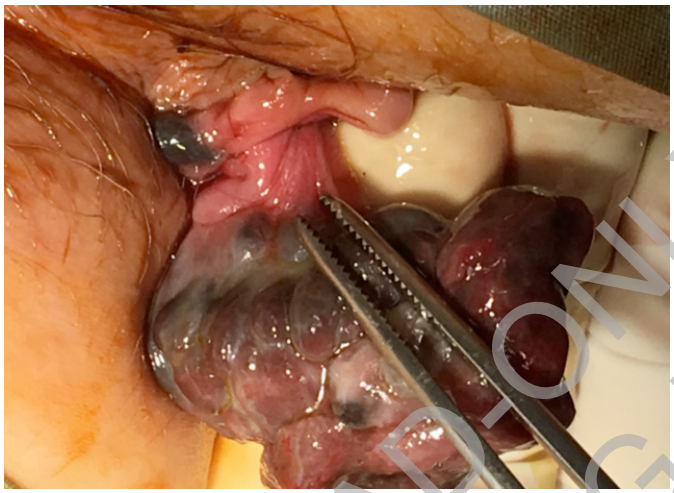

Fig. 1: Dark red polypoid mass arising from the anal canal/lower rectum (maximum diameter: 6 cm)

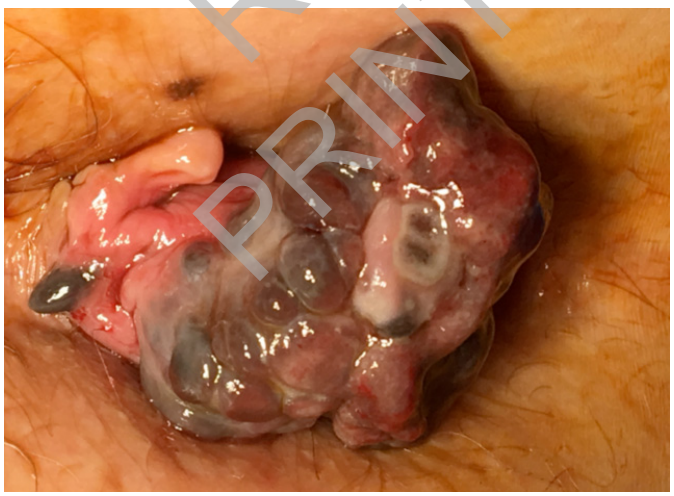

Fig. 2: Small lesion of the anal verge with similar features to the biggest one (histology: metastasis of a melanoma).

Discussion

Rectal bleeding can be related to several diagnoses, including malignancies [3,4]Chiu et al. report that although most patients with anorectal disturbances seek a prompt medical attention, 19% of them wait for more than 6 months to attend a visit. Furthermore a rectal examination is performed only in 54% of patients with a subsequent diagnosis of hemorrhoids in 27% of them. Further investigations are ordered in only 54% of patients. If a misdiagnosis of hemorrhoids is made, to obtain a diagnosis of cancer an average of 3.2 months after the first visit to a physician and 7.4 months after onset of symptoms are needed [5]. Delay in diagnosis may lead to advanced cancer stages at presentation and related worse survival [5,6]. Ano-rectal melanoma (AM) is an uncommon malignancy. The anal location is encountered mostly at an early stage whereas rectal or anorectal melanomas have often a more delayed diagnosis. Irrespective to the location, long-term prognosis remains poor in all cases [7]. In literature there are only few case series and some case reports about AM while there is a lack of guidelines or recommendations due to its very low frequency and the related difficulty to standardize treatments [8]; however some considerations can be taken into account. A simplified staging system has been proposed for AM, dividing patients into three stages: localized (I), with regional lymph-nodes involvement (II) or with distant metastasis (III) [9,10]. Recently Chae reported that TNM staging for rectal cancer can be more accurate in patients with lymph-node involvement with a significant difference in OS and DFS for patients showing stage IIIA and IIIC respectively (OS: 66.7% vs 0% and DFS: 51.4% vs 0%) [11] (Table I). Endoscopic ultrasound can be useful to plan a possible mini-invasive excision or even an endoscopic mucosal resection. Magnetic resonance (MR) can carefully assess a possible lymph nodes invasion [12-15]. PET-CT is probably more accurate than CT in evaluating the stage of the disease, identifying additional sites of metastasis [16] (Table II). Surgical treatments for AM can be a local (LEE) or a more extensive excision (MEE) including an abdomino-perineal resection with lymphadenectomy, also if the role of lymph-nodes involvement and the importance of its removal are still on debate. A population- based Surveillance, Epidemiology

TABLE I - *Staging system and data from the SEER analysis*

		OS(months)		5-years OS	
		Surgery	No surgery	Surgery	No surgery
I	Localized	27	4	17%	0%
II	Regional lymph-nodes involvement	19	3	18%	0%
III	Distant metastasis	7	5	5%	4%
If lymph-nodes involvement > Use TNM staging system for rectal cancer					
TNM		OS	DFS		
III a		66.7%	51.4%		
III c		0%	0%		

TABLE II - *Diagnostic tools*

CT scan	Lymphadenopathy
Metastasis	
MRI	Invasion depth
Lymphadenopathy	
Endoscopic ultrasound	Invasion depth
PET-CT	Additional sites of metastasis

and End Results (SEER) analysis conducted over 40 years on 485 patients reports that surgery was performed in 83.9% independently from the stage of the disease. Patients undergoing surgical resection improved survival at univariate and multivariate analysis, even if survival paralleled the stage at diagnosis with advanced stages predicting worst survival. The analysis concluded that patients at local or regional stages could benefit from surgery and that LEE or MEE do not provide statistical differences in survival conversely to patients with distant metastasis where surgery offers no benefit [2] (Table III). A retrospective study on 46 patients collected over 20 years reported a median disease specific survival (DSS) of 39 months and 5-years DSS of 34% with 53% of recurrence at 1 year are in patients submitted to curative resections unrelated to LEE or MEE (Table III). Perineural invasion was the strongest predictor of outcome with a 100% of recurrence rate (median relapse free survival of 6 months). Tumor necrosis and tumor size > than 2 cm were statistically associated with recurrence and inferior DSS. In respect to histology, epithelioid lesions seemed to recur less than spindle cell feature or mixed histology types; however these parameters were not related to survival. Regional nodal metastases were not associated with recurrences or survival even in patients submitted to LEE or MEE [17] (Table IV). Belli et al. collected 61 patients over a 35 years period, analyzing the different treatments (MEE, LEE and palliative or medical therapy). They showed that disease free survival (DFS) and overall survival (OS) were 7 months and 17 months in patients submitted to radical surgery and 5-years DFS was 20.8% for LE and 15.4% for MEE, with no differences among different types of resections. However they underlined the importance for a radical resection in achieving a longer DFS, even if with unmodified OS [18]. A Swedish retrospective study on 251 patients over a 40 years period highlighted the importance of a clear resection margins and stressed the relationship between the stage of the disease and prognosis [19]. Kiran reported similar median survival in 160 patients sub-mitted to LEE or MEE both in advanced and localized stages [20], while Choi et al. did not find any statistical differences in 19 cases over 10 years among patients similarly treated, although a statistical significant improvement in OS in patients treated with MEE compared with LEE was noted [21] (Table III). Weyandt suggests that even if OS remains unchanged for LEE and MEE in many series, including the author's one, MEE should not be underestimated being the recurrence following LEE very symptomatic with an evident worsening of the quality of life of the recurrent patients [22]. Conversely, Ballo et al. proposed a sphincter-saving local excision in order to obtain local disease control and an adjuvant radiation therapy to avoid the functional morbidity of the APR, showing no loco regional failures as the sole site of recurrence [23]. The role of sentinel node procedure (SLN) for the diagnosis of a possible lymph-node involvement in the AM is still unclear, in contrast with the cutaneous melanoma. SLN can bring to a more accurate definition of the stage of the disease in both but for AM has a minimal influence on the outcome, being the utility of a full lymph node dissection controversial because of the aggressiveness of the disease and consequent uniformly fatal outcome [24,25]. Olsha [26] highlights that in his two examined cases the nodal spread for AM is distributed only in one direction, pelvic or groin, right or left, thus giving the chance of a selected lymphadenectomy preventing the comorbidities related to the extended ones. Moreover, LSN positivity can suggest an adjuvant radio-chemotherapy. A recent systematic review of the published data on AM concluded that either in LEE than in MEE mean median survival and disease free survival were similar. However, the authors noted a wide variation in clinical data, treatment

TABLE III - *Prognosis after LEE or MEE*

Study (year)	N. of patients			MEE	LEE	P-value
Chen (2016)	485	OS(months)	Rectal melanoma			
			Stage I	13	26	0.153
			Stage II	11	7	0.087
			Stage III	7	7	0.871
			Anal melanoma			
			Stage I	35	30	0.385
			Stage II	18	23	0.583
			Stage III	9	8	0.400
Choi (2011)	19	OS (months)		66	11	0.001
		5-years survival		50%	0%	
Kiran (2010)	106	OS (months)		17	28	0.3
		5-years survival	Stage I	43.1%		
			Stage II	12.5%		
Belli (2009)	61	OS (months)		17	17	
		5-years survival		18.5%	18.5%	0.910
		DFS		20.8%	15.4%	0.969
Yeh (2006)	46	5-years survival	32%			

TABLE IV - *Recurrences associated risk factors*

Perineural invasion
Tumor necrosis
Tumor size > 2 cm.
Hystologic spindle cell feature or mixed types

outcomes and pathologic features as well as in the reports of the node status [27]. Even if 70% of patients have a localized disease at diagnosis, most of them will develop brain, lung or liver metastasis that need treatments based on drugs developed for skin melanoma including cisplatin, vinblastine, dacarbazine, interferon alfa and inter-leukin [2]. A regimen of temozolomide, cisplatin and doxorubicin was proposed as well as one including dacarbazine, nimustine, cisplatin and tamoxifen plus interferon-beta promising good survival in a case of metastatic AM [28, 29]. However, complete response rates range only from 5% to 20% with a poor 10% of 5-years survivals [30]. New targeted and immunologic therapies have been recently developed but, despite promising results on the overall survival in metastatic cutaneous melanoma, are not clearly beneficial in the same mucosal disease [30]. BRAF mutations can allow therapy with specific BRAF inhibitors that showed a tumor regression in up to 70% of patients. Unfortunately it is more frequent in cutaneous melanomas than in mucosal ones. Conversely, c-Kit mutations can be found up to 39% of AM. Testing tumors for c-Kit mutations may allow to introduce tyrosine kinase inhibitors such as imatinib, sunitinib, dasatinib or sorafenib in patients with recurrent or metastatic disease [31-33]. Radio and brachytherapy are still on debate also if some case reports show their possible role in the prevention of local recurrences [34, 35].

Conclusions

This case report highlights the possible clinical difficulty in differentiating an anal cancer from an anal benign disease, presumably because symptoms and features are similar. So, a high index of suspicion for malignant disease has always to be maintained. An international database of the cases of AM seem to be mandatory to better understand the natural history of the disease and to allow possible common strategies of medical and surgical care.

Riassunto

Il melanoma ano-rettale è una patologia rara, rappresentando l'1% dei tumori anali e lo 0.4-1.6% dei melanomi. I suoi sintomi sono simili a quelli delle più comuni malattie benigne della regione anorettale, portando spesso a diagnosi in stadi avanzati, in particolare se la sede del tumore è a livello del canale anale. In ogni caso la prognosi del melanoma anorettale rimane severa con una sopravvivenza a 5 anni che non supera il 22% negli stadi più precoci.
La letteratura presenta saltuarie serie monocentriche ed alcuni case report e a tutt'oggi non vi sono linee-guida per il suo management.
La classificazione più usata divide la malattia in tre stadi a seconda del coinvolgimento o meno dei linfonodi regionali e della presenza di metastasi a distanza. Un'analisi di popolazione ha mostrato una sopravvivenza a 5 anni del 17%, 18% e 5% rispettivamente per i tre stadi di malattia dopo chirurgia e dello 0%, 0% e 4% in assenza di trattamento. La risonanza magnetica e

l'ecoendoscopia sono utili per la valutazione di operabilità locale mentre la TAC e la PET sono indicati per la valutazione di eventuali metastasi a distanza. I fattori di rischio per recidiva sono l'invasione perineurale, la necrosi tumorale, dimensioni superiori a 2 cm ed un'istologia con cellule fusate o miste. I protocolli poli-chemioterapici utilizzati sinora per il melanoma anorettale hanno purtroppo portato a risultati meno soddisfacenti di quelli ottenuti nel trattamento del melanoma cutaneo. La mutazione del c-KIT ed i trattamenti con i suoi inibitori sembrano dimostrare risultati promettenti mentre la radioterapia non sembra attualmente rivestire alcun ruolo terapeutico rilevante. Abbiamo riportato il caso di una donna di 55 anni visitata presso un ambulatorio di coloproctologia per rettorragia saltuaria ed un dolore anale che ha reso impossibile la valutazione clinica locale. La valutazione in anestesia ha rivelato la presenza di una massa polipoide di colorito brunastro del canale anale, risultata poi all'esame istologico un melanoma pigmentato con indice mitotico di 16/10HPF e positività per S-100 e HMB45 e negatività per Melan-A/Mart-1 e KER pan e margini parzialmente coinvolti. L'analisi del BRAF ha dimostrato la presenza di un wild type senza mutazioni. Il c-KIT è risultato negativo. La TC e la PET non hanno dimostrato secondarismi. Per la presenza di margini di resezione positivi e l'impossibilità di asportazione radicale con preservazione degli sfinteri, è stata proposta alla paziente una amputazione addomino-perineale sec. Miles, seguita da una chemioterapia adiuvante, che questa ha rifiutato. Questo report dimostra la difficoltà nel corretto management di questa neoplasia che necessita della creazione di un database internazionale per ottenere una maggior conoscenza della sua storia naturale che porti ad una scelta terapeutica condivisa.

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