



Umbilical Melanoma: An Entity to Approach Thoughtfully: A Literature Review And Case Series

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Abstract

Umbilical melanoma is an extremely rare and underreported disease with a complex underlying anatomy and the requirement for a tailored, specific approach. Embryological remnants in this region render this tumor more prone to metastatic spread via these structures. Inadequate treatment of this specific tumor can therefore result in a more devastating prognosis. This makes a more radical approach, compared to other melanoma, a necessity. Our aim is to provide an in-depth insight into the unique characteristics of this disease, the underlying anatomy and pathophysiology, and the required approach in order to be able to adequately manage this tumor. In this respect, we performed a detailed literature search for this rare disease as well as presented a case series from our tertiary center.

Keywords: Pathophysiology; Embryological; Immunotherapy; Umbilical Melanoma

INTRODUCTION

Malignant melanoma is currently the most lethal form of skin cancer with 287.723 new cases reported in 2018 worldwide, and over 60.000 deaths [1].

The incidence of cutaneous melanoma varies between countries because of differences in skin phenotype and sun exposure. Overall, over the past decades its prevalence has been steadily rising in the western world [2], resulting in increased morbidity and mortality. Despite the omnipresence of these tumors, melanoma located in the umbilical area are rare and often underestimated. In literature only very few articles have been published on this topic since its first report in 1916 [3], most of them being case reports

Because of the specific anatomy and surgery of the umbilical region, inadequate treatment can result in disease progression and potentially mortality, especially in metastatic conditions [4]. Although surgical resection is considered the first-tier treatment option of all melanomas, a more complex surgical approach is required in case of umbilical melanoma. For this, a thorough knowledge of the unique characteristics of umbilical melanoma is important for both surgical treatment and aesthetic reconstruction, as well for timely referral to specialist familiar with this pathology. An extensive review based on both single-center/personal experience and literature search highlights the possible pitfalls and oncological limitations.

METHODS

Data was collected from case series at University Hospitals Leuven and literature search.

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Case series

Prospectively collected data from all umbilical melanoma patients in the UZ Leuven database until April 2020 were reviewed. Patients were included irrespectively of disease stage, treatments received or patient age. The hospital protocol for workup of these patients included lactate dehydrogenase (LDH) levels (elevated LDH may indicate distant metastases) [5] and imaging (abdominal and lymph nodes ultrasonography). The treatment protocol was based on international guidelines for the treatment of melanoma [6]: upfront surgery after biopsy, postoperative histopathological confirmation of diagnosis and extent of resection (free cutting edges), followed by radiotherapy, chemotherapy and/or immunotherapy based on disease stage.

Literature search

A literature search was conducted for all articles containing at least one case of umbilical melanoma. Inclusion criteria were clear description of the umbilical location or a picture of the lesion. Exclusion criteria were peri-umbilical location, doubt about the exact location or only mentioning the term umbilical melanoma without reporting details. An initial online literature search in MEDLINE was performed for potentially relevant articles from inception to April 2020 (search as performed on May 1st, 2020), using following search strategy: ("Umbilicus"[Mesh] OR Umbilic*[tiab]) AND ("Melanoma"[Mesh] OR "Melanom*" [tiab]). We further expanded our search by using the 'related article' function and a free-word search in Trip database, Cochrane, Embase, Dare and Cinahl. There was no journal restriction, only case reports, (systematic) reviews, datasets and observational studies were included.

The literature search yielded a total of 40 articles [7-46], while a search in the reference lists of the potentially relevant articles added another 7 articles. After reading the abstracts, 32 articles did not meet the inclusion criteria, mainly because the lesions at the umbilical site were no melanoma (Figure 1). The remaining 15 articles were selected for full-text reading. Of those, all studies were included, encompassing 22 patients.

Primary outcome

Patient characteristics (including potential risk factors for umbilical melanoma), lesion specific characteristic (including anatomical, diagnostic and histological information), therapy and follow-up of the umbilical melanoma were analyzed. A summary of the collected data items that were extracted from the text and from the associated images off the included articles is available in the appendix.

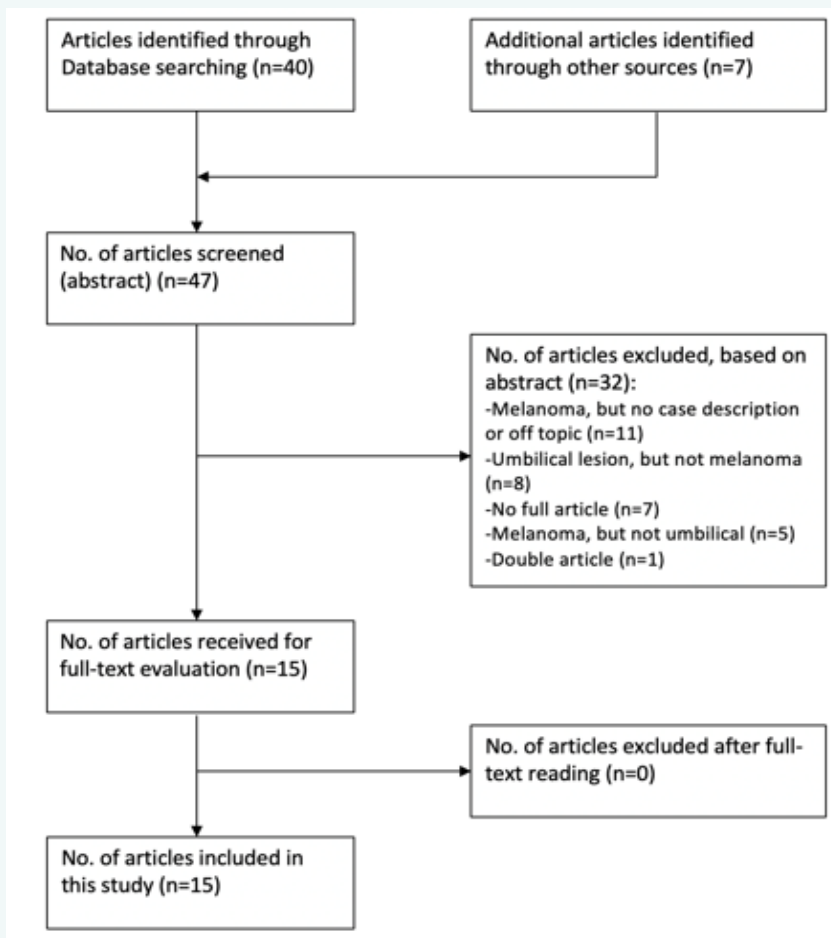


Figure 1: Overview of study selection.

RESULTS

Patient characteristics

Four patients with umbilical melanoma were identified from a total of 13550 melanomas (and 6112 patients) in the electronic medical record database (Table 1). The mean age at diagnosis was 52 years (range 17 – 71), which was comparable with average age in 22 previously described cases in literature (56 years, ranging from 30 until 83). There was an equal number of women and men, whereas in literature the men: women ratio was 5:17. Two patients presented because of a suspicious umbilical lesion (moist or bloody), while the other two were diagnosed during routine clinical examination by the general practitioner. In literature a suspicious looking lesion is found to be the most common presenting symptom, followed by discharge, pruritus and/or and bleeding. None of our patients had any first-degree relatives with cancer, nor a personal history of melanoma. Two patients were previously treated because of another malignancy (follicular adenoma of the thyroid and an adrenal adenoma). As far as the cases in literature is concerned, familial tumors were only mentioned in 11 cases (none of them had a first or second degree relative with a melanoma, one patient had family members with breast, lung and colorectal cancer). One patient of the literature cases had a personal history of breast cancer and one of stomach cancer. None of those patients had a personal melanoma history. Personal cancer history was not available in six of these patients.

Not much was mentioned regarding risk factors for melanoma

development in our patients; none of them used tanning beds. For one patient it was also known that she always used factor 50 sunscreen and was minimally exposed to sunlight. Half of the patients were regularly screened by their general practitioner for any suspicious skin lesions. One of those two also reported that she never did any form of self-examination. In literature seven cases reported regular sun burns, while nothing was written about a presence of risk factors for developing a melanoma.

Melanoma characteristics

All four patients suffered from a superficial spreading malignant melanoma with an average Breslow depth 2,51 mm (range 2,05 – 3,50 mm) and Clark depth 4 (range 3-5). An example is shown in Figure 2. None of these tumors showed perineural or lymphovascular invasion. Also, regression and ulceration were absent in all lesions. In only two cases the amount of lymphocyte invasion (one brisk and one non-brisk) and the growth phase (one vertically and one both vertically and radially) were given. For the most recent case both a picture and a description of the umbilical location were available; for all other cases we had to rely on a detailed description of the location. No mutational analysis for BRAF V600E mutations was performed. In literature both superficial spreading as well as nodular subtype are described, with an average Breslow depth 6,31 mm (range 0,86 – 40,0 mm) and Clark depth 4 (range 3 -5). Most melanomas had no ulcerations. Only for one lesion the amount of lymphocyte invasion was given (brisk). Next to a description, the umbilical location was confirmed by a picture in all but four cases.



Table 1: Demographics

	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4
PRESENTING SYMPTOM	Routine exam	Moisty lesion	Routine exam	Bleeding
AGE	55	64	71	17
GENDER	male	female	male	female
TYPE OF MELANOMA	SSM	SSM	SSM	SSM
BRESLOW THICKNESS (mm)	2.5	2	3.5	2.0
METASTASES at diagnosis	yes	no	no	no
RESECTION TO THE PERITONEUM	No	Yes	No	Yes
SNB	No	No	No	Yes
LOCAL COMPLICATIONS	No	Infection	No	No
OUTCOME	Deceased due to distant recurrence (52 months after diagnosis)	Remission	Deceased due to distant recurrence (94 months after diagnosis)	Remission

SSM = superficial spreading melanoma; SNB = sentinel node biopsy

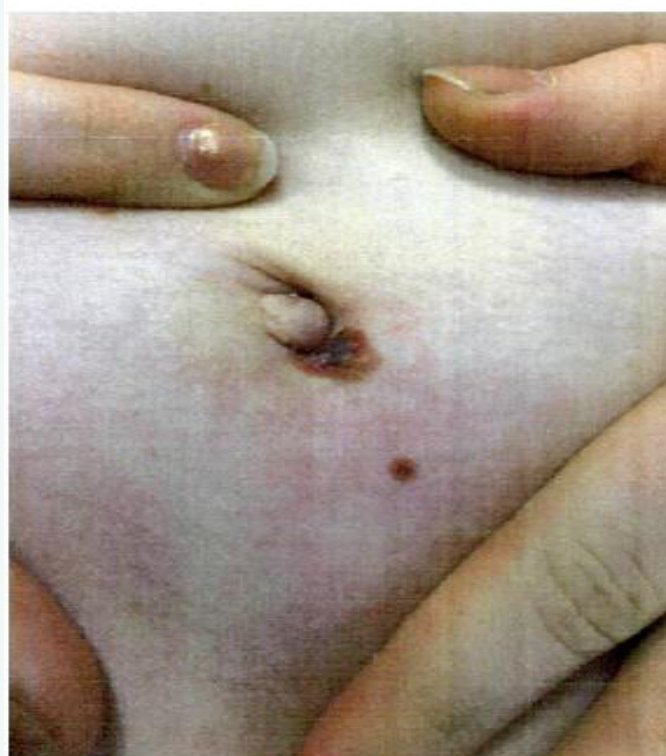


Figure 2: Umbilical melanoma of one of our patients

In eight cases a mutational analysis was performed with three of them having a BRAF mutation, in two patients the mutation was not specified and another three having no mutation.

Diagnosis

In two of our patients the initial diagnosis was delayed (up to one year) because the severity of the lesion was underestimated. This is consistent with reports in literature with average delay of 12 months

(range 2 – 48 months). Reasons for this delay were underestimation of the severity of the disease, using another first-tier treatment method (cryotherapy), refusal of any treatment by the patient and incorrect diagnosis (omphalitis).

Further disease staging was dependent of the pathological severity, including ultrasound of the lymph nodes, chest x-ray, PET-CT and/or MRI of the brain. This heterogeneity is similar to what is reported in literature: in older cases combination of CT and lymphoscintigram was often used,



whereas in more recent cases PET-CT and/or MRI of the brain were more frequent.

One case showed metastasis (occipital and shoulder) on diagnosis as well as two malignant inguinal lymph nodes, whereas in literature 4 cases with metastasis are described.

Therapy

All patients received primary surgery: after an initial marginal resection, all lesions were widely excised including removal of the entire umbilicus to the peritoneum (R_0 resection). One patient relapsed 46 months after initial surgery. In case of malignant inguinal lymph nodes a nodal clearance was performed. In the most recent case a sentinel node biopsy (SNB) was performed. A combination of radiocolloid and blue dye with immunohistochemistry staining was used and suspicious lymph nodes were found in both left (one case) and right inguinal (two cases) region. Eventually, none of those three nodes were malignant. All cases got only one biopsy before wide excision. Postoperatively 1 local infection requiring debridement, replacement of the mesh and IV antibiotics was observed.

In literature all but one case received surgery, all resulting in resection with tumor free margins. A minority was not resected to the peritoneum, while SNB was performed in 15 patients. Sentinel nodes were found in the inguinal and axillary region. In three cases adjuvant treatment was given after surgery (nivolumab, dabrafenib+trametinib with ipilimumab afterwards, and interferon). Ultrasound guided removal was done in two cases; once to remove a lymph node and once to remove an abdominal mass. In only one case a second biopsy was necessary because the first one was inconclusive.

Two of our umbilical melanoma patients passed away because of brain and lung metastasis, respectively 52 and 94 months after their diagnosis. In literature six of the 22 patients passed away because of metastases, on average 15 months after initial diagnosis (range 10-28 months).

DISCUSSION

Profound knowledge of the complex anatomy of the umbilicus is required to adequately treat umbilical melanoma. The abdominal wall at the umbilical location is formed of the following layers (from superficial to deep): skin, fat, superficial fascia, the superficial sheath of the abdominal muscle, the rectus abdominis (or linea alba in the midline, a thick cord of connective tissue), the deep sheath of the abdominal muscle, the subperitoneal connective tissue and eventually the peritoneum [47]. At birth, the umbilicus contains three umbilical vessels that obliterate later in life (one umbilical vein and two umbilical arteries) and a remnant of the urachus. These arteries will eventually form the medial ligaments, while the urachus will form the median ligament. The remnant of the umbilical vein will form the ligamentum teres.

The lymphatic drainage of the umbilical region is complex: the skin region above the umbilicus drains into the pectoral axillary lymph nodes, whereas the skin region below drains into the superficial inguinal lymph nodes. Also, for the deeper region a subdivision is made as the region above the umbilicus drains into the parasternal lymph nodes and the region below drains via the external iliac nodes to the para-aortic nodes. In literature a sentinel node biopsy (SNB) was performed in 15 cases (of which five were positive). These nodes were mostly located in the axillary region, although the inguinal region was also affected in a few cases. In one case we also detected positive sentinel nodes, which were located bilaterally in the inguinal region. Therefore, it is recommended to undertake a meticulous examination of both inguinal and axillary regions.

Understanding this complex anatomy and embryology is a necessity to understand the importance of removal of the lesion to the peritoneum, including the overlying fascia transversalis (and the sometimes-present

fascia umbilicalis which can lay in between the skin and the fascia transversalis), instead of leaving the fascia intact as in other melanomas. Spreading of the melanoma along these embryological remnants is something one should keep in mind treating melanomas in the umbilical region. Incomplete superficial resection may leave tumoral tissue on the peritoneum and facilitate recurrence and spreading of the disease.

Two of our patients had only a local incision (not preperitoneal) and died because of metastases upon recurring disease. The other two cases are in remission after 12- and 94-months follow-up. A similar pattern was observed in literature: two of the three patients with lesions that were not appropriately removed passed away because of metastatic melanoma.

Also, in this region the fascia can sometimes be absent, which implies that the umbilicus is almost directly attached to the peritoneum. Moreover, the umbilicus also represents a relatively weak point in the anterior abdominal wall. Therefore, one has to be careful when taking a deeper biopsy of lesions in this area.

Melanocytic naevus or melanoma?

One of the similarities between cases is the delay (up to 4 years) between discovery of the lesion and appropriate treatment, mostly because of an underestimation of the severity of the disease or confusion with omphalitis, an infection of the umbilicus and surrounding tissue. Therefore Song et al. recommend a careful follow-up in patients with suspected omphalitis or an umbilical nevus [37]. In case of changes such as increase in size or diabrosis on the surface a further surgical investigation should be very-low threshold to exclude infection or a Sister Mary Joseph Nodule (metastasis of abdominal or pelvic malignancy). As the majority of the cases were diagnosed by a general practitioner or a dermatologist, knowledge of the unique treatment method (extensive resection to the peritoneum) is of tremendous importance for both specialties.

One of the major limitations is the fact that only retrospective data were available. Also, the small number and heterogeneity of patients hampers the possibility to draw general conclusions. Nevertheless, our 4 patients represent the second largest case series regarding umbilical melanoma.

CONCLUSION

Umbilical melanomata represent a challenging subentity of malignant melanoma due to its unique localization. Adequate knowledge of the specific anatomy and subsequent treatment method are therefore of tremendous importance when treating these lesions. Also, timely referral of patients with umbilical melanoma is crucial to avoid more advanced stage and/or metastasis.

DECLARATIONS

Ethical Approval

Studies were conducted according to ethical guidelines (Declaration of Helsinki). The project was approved by the Ethical Commission of the University Hospitals Leuven (S65568)

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