Dermatology Practical & Conceptual

Diffuse Melanosis Cutis as the First Sign of Recurrence of Low-Risk Melanoma: Case Report and Systematic Review

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ABSTRACT

Introduction: Diffuse Melanosis Cutis (DMC) is a rare and late complication of metastatic malignant melanoma (MM) characterized by progressive pigmentation of skin and sometimes mucous membranes. The distinctive feature is the widespread and progressive deposition of melanin precursors in the dermis.

Objectives: The purpose of this review is to define the clinical and demographic features of DMC and to promote a deeper insight into the clinical manifestation, histological findings, and pathophysiology behind DMC.

Methods: We have conducted a systematic review of the literature on published DMC in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis. We also reported a case of DMC secondary to low-risk melanoma.

Results: Overall, including our case report, we reported 53 articles described 62 DMC patients. Breslow level of primary melanoma was reported having a mean value of 3.3 mm. The mean survival rate from onset of DMC resulted being 4.36 months.

Conclusions: Among the most widely accepted etiopathogenetic hypotheses are deposition of melanic precursors in the dermis following tumor lysis, melanocyte proliferation induced by neoplastic growth factors, and the presence of diffuse dermal micro-metastases of MM. However, unanimous consensus on the proposed etiopathogenetic models of DMC is still lacking.

Introduction

Diffuse Melanosis Cutis (DMC) is a rare and late complication of metastatic malignant melanoma (MM) characterized by progressive pigmentation of skin and sometimes mucous membranes.

The first properly documented case with photographic finding was described by Odel et al in 1937 [1].

There are few mentions of previous work in the literature referring to various reports of "melanosis" or "melanoderma," however their exact correspondence with actual cases of DMC cannot be demonstrated.

The distinctive feature is the widespread and progressive deposition of melanin precursors in the dermis, which gives the skin a discoloration variously defined as "blue-gray", "slate-gray" and "metallic-gray". This pigmentation is almost unanimously described as more pronounced in the photo-exposed areas and with a caudo-cranial progression.

A clinical feature almost always associated with DMC is the presence of melanuria, due to the presence of melanic precursors in the urine, which typically becomes more apparent with exposure of urine specimens to open air.

The essential histological finding of DMC is the presence of melanin in the dermis which has been described predominantly within perivascular melanophages, but also as free scattered pigment.

It is essential to emphasize that in DMC the presence of neoplastic melanocytes in the dermis is never observed, making this clinical entity intrinsically different from cases of cutaneous metastases of metastatic malignant melanoma (MM).

Objective

This comprehensive review is dedicated to unraveling the clinical and demographic features of Diffuse Melanosis Cutis (DMC), aiming to provide a better understanding of its clinical presentation, histological findings, and underlying pathophysiology. In addition to a detailed analysis of existing literature, we contribute valuable insights through the inclusion of a case report detailing DMC secondary to low-risk melanoma. By offering a practical context alongside a careful exploration of various aspects, this study seeks to enrich the collective comprehension of DMC.

Case Report

A 63-year-old Caucasian man presented with a 3-week history of progressive skin and urine darkening. His past medical history included a retro-auricular melanoma (pT1a, Breslow-depth 0.39 mm, Clark-level I, mitotic rate 0/mm^2, no microsatellitosis, no regression) excised in 2014 and subsequently subjected to wide local excision with free margins.

Clinical examination revealed a diffuse slate-gray hyperpigmentation affecting the entire skin, more pronounced on sun exposed areas (Figure 1).

Oral and conjunctival mucosal membranes and nail beds were normal. No lesions suggestive of primary or recurrent melanoma were evidenced at the site of previous melanoma excision, nor on other explorable mucosae and skin.

Hepatomegaly was present. Blood tests excluded hypoaldosteronism, hemochromatosis, lead, mercury, and silver nitrate poisoning. Urine analysis showed elevated values of 5-S-Cysteinyldopa.

Total body computed tomography (CT) evidenced multiple osteolytic lesions of long bones, generalized lymphadenopathy and a 6 cm diameter liver mass in which an echo-guided needle biopsy disclosed the presence of protein S100+, HMB-45+ and BRAF+ (exon 15) pleomorphic cells, both epitheliomorphic

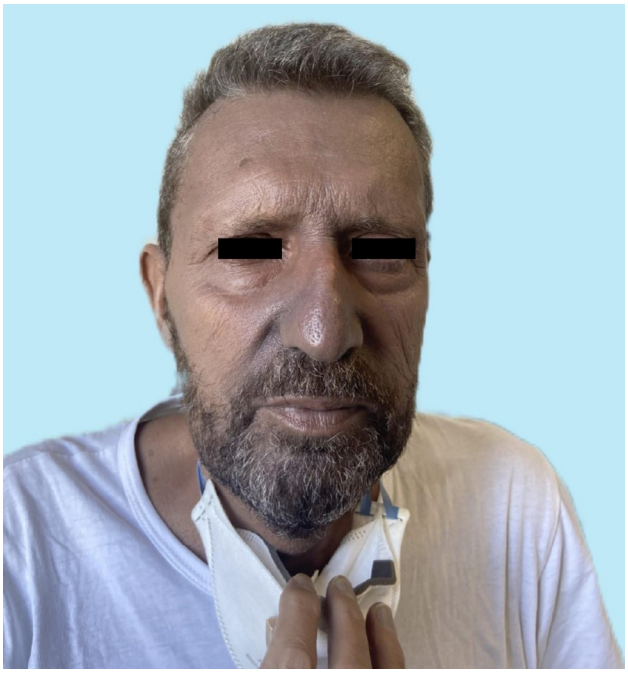

Figure 1. 63-year-old caucasian patient with intense slate-gray pigmentation.

and spindle-shaped, with eosinophilic cytoplasms and nuclei with prominent nucleoli. Also, abundant brownish pigment was observed supporting the diagnosis of metastatic melanoma. A skin biopsy showed sparse melanophages containing melanic pigment in the superficial dermis, without any neoplastic proliferation. Immunohistochemistry was negative for pS100, Sox10, HMB45; positive for CD68 pgm1, supporting the diagnosis of diffused cutaneous melanosis (Figure 2).

Combination therapy with encorafenib and binimetinib was initiated but immediately discontinued because of acute iatrogenic liver failure. After supportive therapy and restoration of liver function, second-line therapy with dabrafenib was initiated, with good tolerability.

The patient underwent disease progression, developing diffuse cerebral metastases 5 months after the diagnosis of DMC and died 8 months after the diagnosis of DMC.

Methods

A systematic review of the literature on published cases of diffuse melanosis cutis (DMC) was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis, through PubMed and Google Scholar [2].

Combinations of the following MeSH terms and keywords were used to retrieve all the relevant articles: melanosis cutis, diffuse melanosis cutis, cutaneous melanosis. To identify eligible articles, titles and abstracts were screened and full texts when necessary. Also, references of the selected articles were screened manually to include possibly left-over articles.

Inclusion criteria were: articles focusing on DMC, case reports, case series, commentaries, reviews reporting new DMC cases. Conversely, studies reporting a definitive diagnosis other than DMC, and literature reviews without new DMC reports, were excluded.

Further analyzing the described cases of initially included articles, we eventually included only cases with definite DMC diagnosis, not reporting cases just presenting cutaneous metastasis.

Evidence extrapolated from the reviewed articles (Table 1) regarded: year of publication; number of studied patients; gender, age, ethnicity of patients; site of, Breslow level, Clark level, ulceration, mitotic rate of primary melanoma; lunge

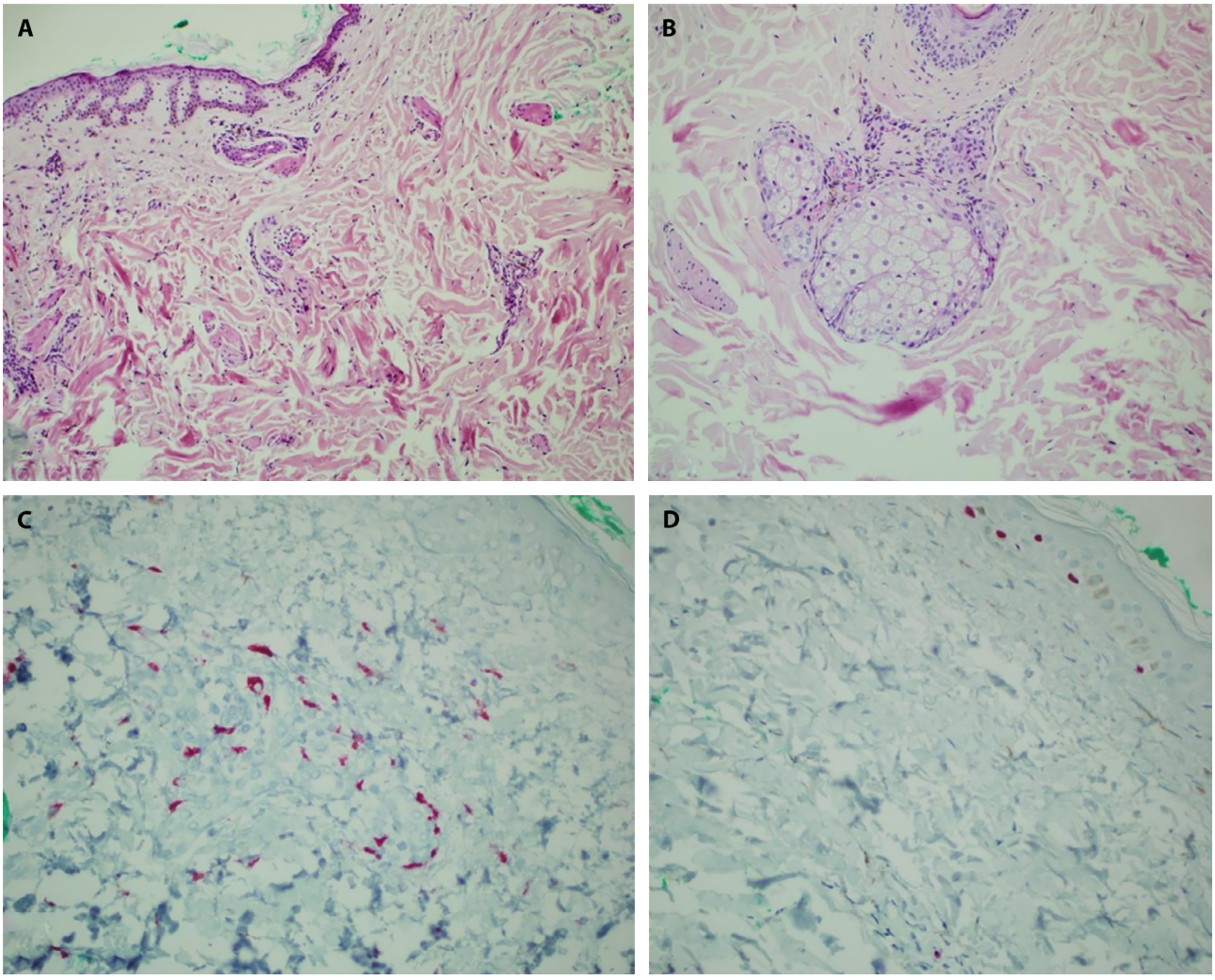

Figure 2. (A) The epidermis shows solar lentigo-like characteristics while melanophages containing cytoplasmic melanin are visible in the dermis. (B) Perivascular and peri-adnexal distribution of macrophages. (C) High expression of CD68 pgm-1 by superficial dermal melanophages. (D) Negative immunohistochemical study for SOX-10 (D).

Table 1. Summary table of clinical-demographic features of DMC cases reported in the literature.

YEAR	ARTICLE	NUMBER OF PATIENTS	AGE (YEARS)	GENDER	ETHNICITY	BODY SITE	BRESLOW (mm)	LUNG METASTASIS	LIVER METASTASIS	BRAIN METASTASIS	MELANURIA	THERAPY	SURVIVAL SINCE DMC DIAGNOSIS
2019	[53]	1	47	F	CAUCASIAN	HEAD-NECK	NA	NO	YES	YES	NA	Vemurafenib, Cobimetinib, Pembrolizumab	12
2019	[52]	1	47	NA	CAUCASIAN	TRUNK	NA	YES	YES	YES	YES	Dabrafenib And Trametinib	0,5
2018	[51]	2	78	M	CAUCASIAN	HEAD-NECK	7	NO	YES	NO	YES	Pembrolizumab	1,2
2018	[51]		85	M	CAUCASIAN	TRUNK	5.5	NO	YES	NO	YES	Pembrolizumab	2
2017	[50]	1	54	F	CAUCASIAN	NA	NA	YES	YES	NO	YES	Dabrafenib, Trametinib	NA
2017	[49]	1	64	M	CAUCASIAN	TRUNK	NA	YES	YES	NO	YES	None	1
2017	[48]	1	72	M	CAUCASIAN	TRUNK	> 3	NO	NO	NO	YES	None	8
2016	[47]	1	76	M	CAUCASIAN	NA	NA	NO	YES	NO	NA	Dacarbazine, Ipilumumab	16
2016	[46]	1	77	M	CAUCASIAN	NA	NA	YES	YES	NA	YES	None	0,5
2015	[45]	1	35	M	CAUCASIAN	TRUNK	0.8	YES	YES	YES	YES	Dabrafenib, Ipilimumab	NA
2015	[44]	1	43	F	CAUCASIAN	TRUNK	3	NO	YES	NO	NA	Vindesine/Cisplatin	4
2011	[43]	1	45	F	CAUCASIAN	TRUNK	NA	YES	YES	YES	YES	Polichemotherapy	11
2010	[42]	2	49	M	NA	NA	NA	NO	YES	NO	YES	Carboplatin-DTIC, YES-Ray Treatment	3
2010	[42]		52	M	NA	TRUNK	0.82	YES	YES	YES	YES	Carboplatin-DTIC	2
2010	[41]	1	62	M	CAUCASIAN	TRUNK	9	NO	NO	NO	YES	Dacarbazine	12
2009	[40]	1	54	M	CAUCASIAN	NA	NA	NA	YES	NA	YES	None	NA
2008	[39]	1	48	M	CAUCASIAN	TRUNK	0.75	NA	YES	NA	YES	Dacarbazine	3
2007	[38]	1	49	M	CAUCASIAN	HEAD-NECK	NA	NA	NA	NA	YES	NA	NA
2004	[37]	1	36	F	NA	TRUNK	NA	YES	YES	NO	NA	Temozolomide	11
2004	[36]	1	29	F	CAUCASIAN	TRUNK	2.8	YES	NA	YES	YES	Interferon Alfa	2
2004	[35]	4	43	F	NA	HEAD-NECK	3.2	NA	YES	NA	YES	Dacarbazine, Carboplatin, Cisplatin	7

2004			52	M	CAUCASIAN	LIMBS	> 5	NA	YES	NA	YES	Dacarbazine	1,2
2004			71	M	NA	TRUNK	4	NA	YES	NA	NO	None	0,2
2004	[35]		62	F	NA	NA	NA	NA	YES	NA	YES	Dacarbazine, POLICHEMOTERAPY	1,6
2002	[34]	1	65	M	NA	NA	NA	NA	NA	NA	NA	NA	7
2001	[33]	1	35	F	CAUCASIAN	TRUNK	2	YES	YES	NO	YES	DBCT Regimen	6
2001	[32]	1	62	M	CAUCASIAN	LIMBS	3.1	NO	YES	YES	YES	Dacarbazine	1
1999	[31]	1	77	M	CAUCASIAN	LIMBS	5.5	NO	YES	NA	NA	Combination Chemotherapy	7
1998	[30]	1	78	M	JAPANESE	LIMBS	NA	YES	YES	NO	YES	DAV Regimen	4
1997	[29]	1	86	F	CAUCASIAN	NA	NA	NO	YES	YES	NO	Fludrocortisone	0,3
1996	[28]	1	58	M	CAUCASIAN	TRUNK	NA	YES	YES	NA	YES	DTIC, Cisplatin, BCNU, And Tamoxifen	6
1993	[27]	1	57	M	CAUCASIAN	TRUNK	3.5	NA	NA	NA	NA	Dacarbazine, Interferone	5
1993	[26]	1	60	F	CAUCASIAN	LIMBS	2.9	NO	NO	YES	YES	DTIC, CCNU And Vincristine	6
1993	[25]	1	79	M	CAUCASIAN	HEAD-NECK	NA	NA	YES	NA	NA	None	2
1992	[24]	1	37	M	CAUCASIAN	TRUNK	0.8	YES	YES	NA	YES	Interferone, Dacarbazine	5
1991	[23]	1	56	M	CAUCASIAN	TRUNK	NA	NO	NO	NA	YES	Interferon Alfa and Cimetidine	4
1990	[22]	1	65	F	CAUCASIAN	NA	NA	NA	NA	NA	NA	NA	NA
1990	[21]	1	60	M	CAUCASIAN	LIMBS	NA	NA	NA	NA	NA	NA	NA
1989	[20]	1	34	F	CAUCASIAN	NA	NA	NA	NA	NA	NA	None	6
1987	[19]	1	49	M	CAUCASIAN	TRUNK	1.5	YES	NA	NA	YES	None	0,5
1986	[18]	2	31	M	CAUCASIAN	LIMBS	NA	NA	YES	NA	YES	Dtic	3,2
1986	[18]		67	F	NA	TRUNK	NA	YES	YES	NA	YES	Interferon + Cimetinide	1,2
1984	[17]	1	44	M	CAUCASIAN	NA	NA	NA	NA	NA	YES	NA	2
1981	[16]	1	59	M	NA	TRUNK	NA	YES	YES	NA	YES	Acarbazine And Lomustine	4
1980	[15]	1	23	M	CAUCASIAN	TRUNK	NA	NA	YES	NA	YES	Dacarbazine, Vincristine, Lomustine	12

Continued

Table 1. Summary table of clinical-demographic features of DMC cases reported in the literature. *(Continued)*

YEAR	ARTICLE	NUMBER OF PATIENTS	AGE (YEARS)	GENDER	ETHNICITY	BODY SITE	BRESLOW (mm)	LUNG METASTASIS	LIVER METASTASIS	BRAIN METASTASIS	MELANURIA	THERAPY	SURVIVAL SINCE DMC DIAGNOSIS
1980	[14]	1	70	M	CAUCASIAN	NA	NA	YES	YES	YES	YES	NA	2,5
1979	[13]	1	43	M	CAUCASIAN	NA	NA	NA	YES	NA	YES	Dtic + Bleomycin	3
1975	[12]	1	20	F	CAUCASIAN	TRUNK	NA	NA	YES	NA	YES	BCNU, Hydroxyurea, DIC, And Vincristine	0,5
1974	[11]	1	58	M	CAUCASIAN	TRUNK	NA	YES	YES	YES	YES	Telecobalt, Strontium and X-Ray Irradiation	0,8
1973	[10]	1	39	F	CAUCASIAN	LIMBS	NA	NO	YES	NO	YES	NA	8
1972	[9]	1	39	F	CAUCASIAN	LIMBS	NA	NO	YES	NO	YES	None	8
1969	[8]	1	48	F	CAUCASIAN	HEAD-NECK	NA	YES	YES	YES	YES	Triethylene-Thiophosphoramide	3
1968	[7]	1	50	M	CAUCASIAN	TRUNK	NA	NA	YES	NA	NA	Lomustine, Dacarbazine, Actinomycin-D	9
1968	[6]	1	47	F	CAUCASIAN	HEAD-NECK	NA	YES	YES	YES	YES	Thiophosphoramide	1,2
1961	[5]	1	33	F	CAUCASIAN	TRUNK	NA	YES	YES	YES	YES	None	5
1954	[4]	3	41	M	CAUCASIAN	TRUNK	NA	NO	NA	NA	YES	NA	NA
1954			33	M	CAUCASIAN	TRUNK	NA	NA	NA	NA	YES	NA	3
1954	[4]		43	F	CAUCASIAN	NA	NA	NA	NA	NA	YES	NA	NA
1949	[3]	1	47	M	CAUCASIAN	LIMBS	NA	YES	YES	NA	YES	None	1
1937	[1]	1	36	M	CAUCASIAN	TRUNK	NA	NA	NA	NA	NA	NA	NA

NA = Not Available

metastasis; brain metastasis; melanuria; therapy, survival since DMC onset (in months); DMC in skin biopsy.

Results

A total of 185 articles were identified from the literature search since 1937 up to date. Ultimately, 52 articles about DMC, describing 61 DMC patients, satisfied above-described inclusion criteria and were included in the review (Table 1) [1,3-53].

Articles reported in previous literature reviews not satisfying the above-mentioned inclusion criteria were excluded. Overall, a female: male ratio of 1:1.8 and mean age at diagnosis of 53 years, median age of 50 years (86 and 20 years being the extremes) were reported.

Ethnic origin was reported for 52 patients: 98% were Caucasian, 2 % Japanese.

Regarding the primary melanoma, the most frequently affected site was the trunk (65%), followed by the limbs (21%) and head-and-neck (14%).

Breslow level of primary melanoma was reported in only 20 cases, with a mean value of 3.3 mm.

Clark level also was reported in only 20 cases, 45% had Clark level IV, 30% level III and 25% level V.

Ulceration was not reported in the great majority of cases: only 2 articles mentioned ulceration. 100% of these had no ulceration.

Mitotic rate was reported only for two cases: 21/mm^2 and <1/mm^2.

Overall, 40 patients were screened for lung metastasis: 58% had lung metastasis, 42% had not.

Overall, 49 patients were screened for liver metastasis: 92% had liver metastasis, 8% had not.

Overall, 29 patients were screened for brain metastasis: 48% had brain metastasis, 52% had not.

Of 49 patients screened for melanuria, 96% had melanuria, 4% had not.

The mean survival rate from onset of DMC was reported in 52 cases and resulted 4.36 months.

Of DMC patients 36 underwent skin biopsy to confirm the diagnosis.

Conclusions

Low-risk melanoma is defined as melanoma with a tumor thickness of 0.8 mm or less or stage I melanoma. This group includes 70% of patients with cutaneous melanoma, and most of these patients is unlikely to develop recurrences [54,55].

DMC is a rare, late-term manifestation of MM.

To date, approximately 65 DMC cases have been described in the literature all of which, when described, report a Clark level of primary melanoma of III, IV or V. This is a documented case of DMC secondary to pt1a melanoma (Clark Level I).

Several pathogenetic mechanisms of DMC have been proposed among which, the most widely accepted, is that it is derived from circulating precursors of melanin, produced by melanoma, which are deposited at the dermal level and subjected to autoxidation. This hypothesis would also explain the presence of melanuria, frequently associated with DMC, in which the presence of melanic precursors in urine is extensively documented [56,57].

However, unanimous consensus on the proposed etiopathogenetic models of DMC is lacking.

Some authors suggest that skin pigmentation is secondary to melanocyte proliferation induced by growth factors such as alpha-melanocyte stimulating hormone, hepatocyte growth factor and endothelin-1 released by neoplastic melanocytes [58].

Others, hypothesize that neoplastic cell lysis induced by anticancer therapies would release melanic precursors with subsequent dermal deposition [59].

The latter hypothesis is not applicable to our case, as the onset of DMC was prior to therapy initiation. Also, the presence of cutaneous MM micro-metastases has been advocated as responsible for DMC [48]. However, this pathogenetic hypothesis is disproved in our case by negative immunohistochemistry indicating pigmentation is attributable only to the presence of dermal melanin and melanophages and not to neoplastic melanocytic clones.

DMC is to date considered a paraneoplastic manifestation of MM, burdened by a very poor prognosis. The average survival described in the literature from the onset of DMC is 4 months, significantly lower than that of patients diagnosed with stage IV MM, but without DMC [56,60].

The reasons for the prognostic gap remain unclear to date; some authors speculate that MM complicated by DMC may be characterized by specific genetic mutations [61].

This would likely account for both the tendency of these MM to develop DMC and the worse prognosis, probably due to greater biological aggressiveness and less responsiveness to therapies.

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