Cancer precursor project - characteristics of premalignant precursors, part 3a (dermatopathology)

6 May 2024

MAY 06, 2024

Our Cancer precursor project is intended to better understand how cancer arises by compiling a regularly updated spreadsheet of all distinct human cancers (now 1,232) and their precursors (now 191).

In part 1, we noted that the percentage of identified precursors varies widely by pathology subspecialty (see table below) and we discussed precursors for subspecialties with epithelial sites (breast, head & neck, gyn, GI/liver, GU/adrenal and thoracic).

	Cancers	Precursors	%
Neuropathology	114	1	0.9%
Dermatopathology	79	6	7.6%
Bone, joints and soft tissue	143	11	7.7%
Hematopathology	207	19	9.2%
Breast	58	8	13.8%
Head & neck	128	19	14.8%
Gyn	96	20	20.8%
GI / liver	203	47	23.2%
GU / adrenal	141	34	24.1%
Thoracic	63	26	41.3%
Grand total	1232	191	15.5%

Epithelial malignancies, whether carcinomas or melanomas, typically have known risk factors associated with chronic inflammation (microorganisms, parasites, autoantigens, trauma, excess weight, diet, aging), DNA changes (carcinogen exposure, germline changes, radiation or aging), constitutive hormone production (estrogens, androgens or insulin) or immune system dysfunction (Pernick 2021). These risk factors promote changes in molecular pathways that produce intraepithelial neoplasia or dysplasia, in situ carcinoma and ultimately invasive malignancies.

In part 2, we discussed neuropathology-related malignancies and their lack of precursors and speculated that contrary to current thinking, most non-epithelial malignancies may lack precursors. These non-epithelial malignancies often have no known risk factors and may arise from random processes or “bad luck” (Pernick 2022).

In the skin, of the 79 distinctive malignancies identified to date, only 6 malignancies have known precursors (5 melanocytic, 1 nonmelanocytic):

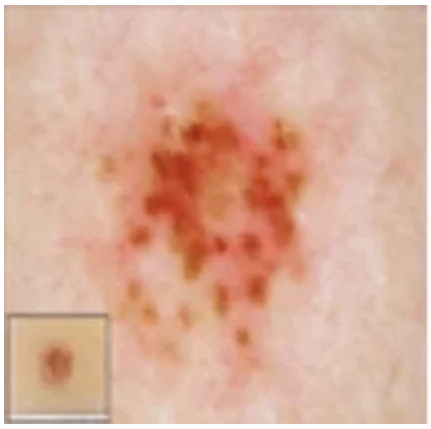
1. Invasive melanoma: precursor is dysplastic nevus
2. Superficial spreading melanoma (low CSD [cumulative sun damage] melanoma): precursor is also dysplastic nevus
3. Lentigo maligna melanoma: precursor is lentigo maligna
4. Acral melanoma: precursors are acral lentiginous melanoma in situ and acral nevus
5. Melanoma arising in giant congenital nevus: precursor is giant congenital nevus
6. Squamous cell carcinoma: precursors are actinic keratosis / keratinocytic dysplasia and squamous cell carcinoma in situ

These 6 malignancies with known precursors are all epithelial. We speculate that the cell-cell connections and the presence of basement membranes in epithelial cells may force malignancies to go through a premalignant, intraepithelial neoplasia process because the cell-cell connections make inappropriate cell division more difficult and the basement membrane limits invasion unless additional DNA changes are present. However, at non-epithelial sites, a stem or progenitor cell can acquire malignant properties, divide and invade adjacent tissues without any intervening precursor lesion.

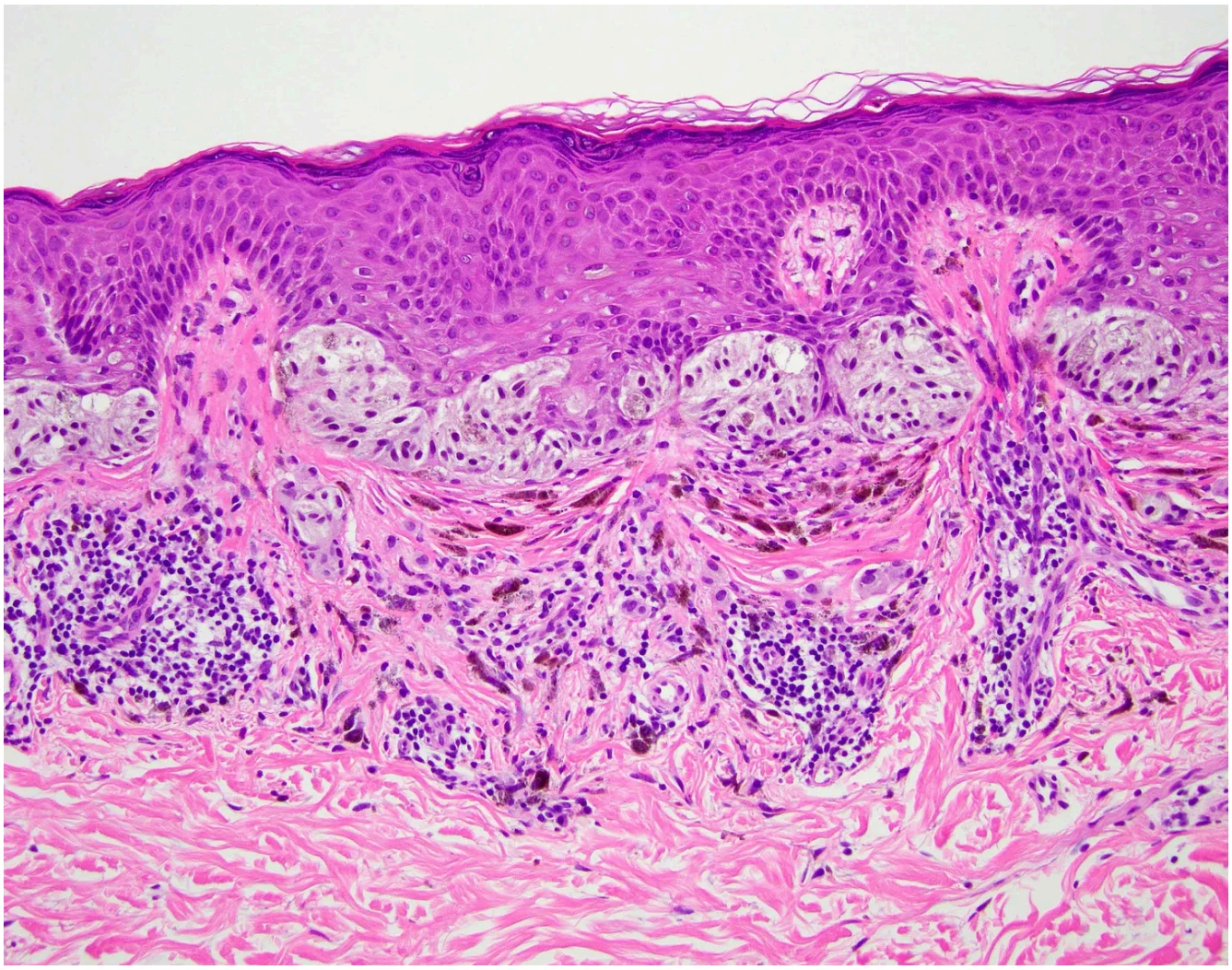
In this essay, we discuss the first 3 dermatologic malignancies with known precursors:

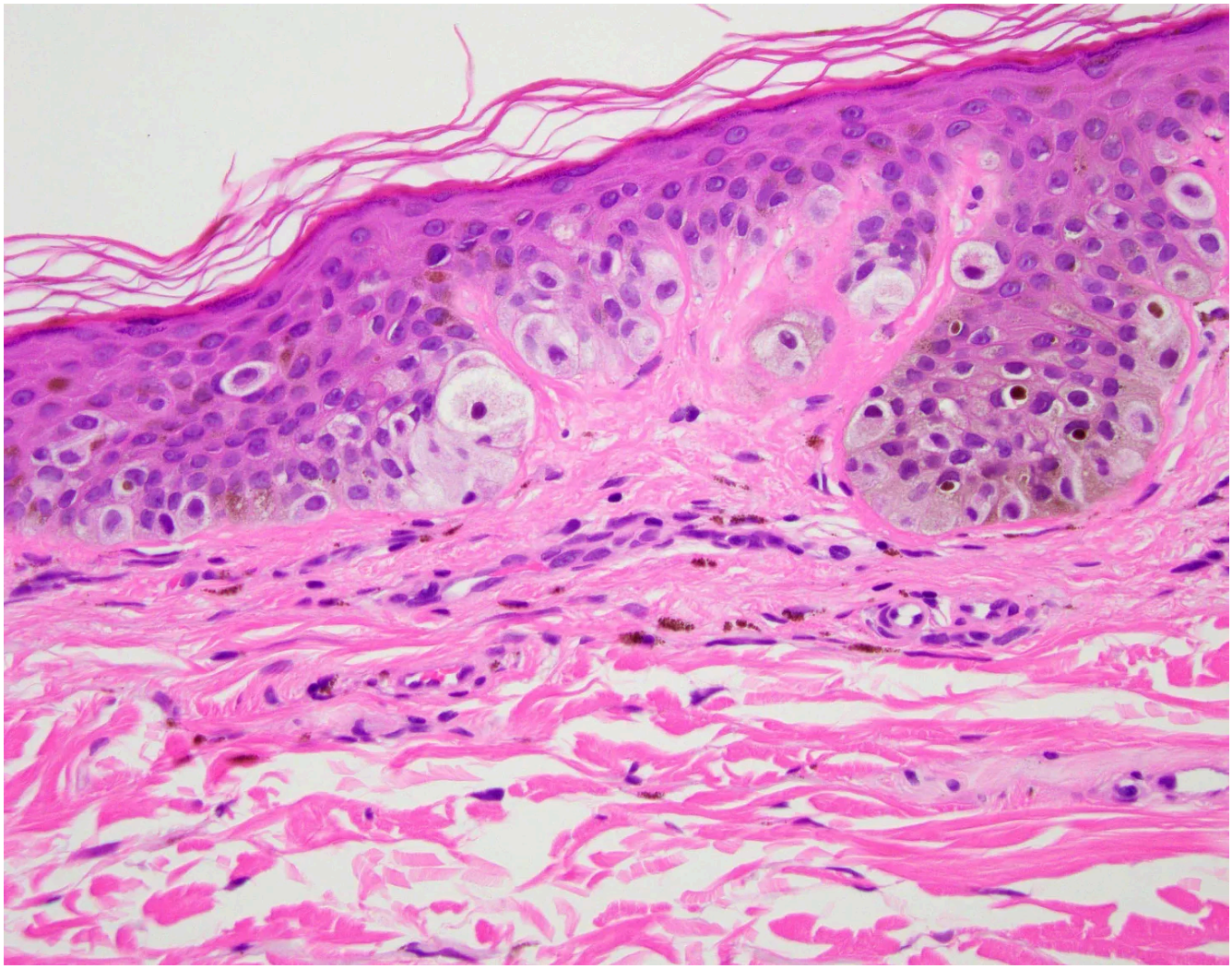
1 & 2. Dysplastic nevus is a precursor of invasive melanoma and superficial spreading melanoma (low CSD melanoma).

Dysplastic nevus



Dysplastic nevus: precursor to invasive melanoma and superficial spreading melanoma.





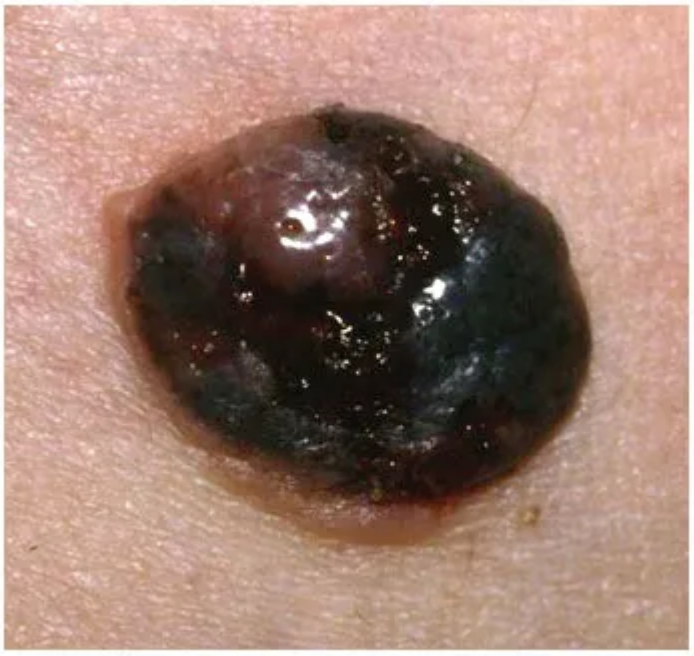
Histology of dysplastic nevus, a precursor to invasive melanoma and superficial spreading melanoma. There is bridging of junctional nests. Some nevomelanocytes are enlarged and have size variation, dusty cytoplasm and upward migration.

Dysplastic nevi are pigmented lesions that share the clinical and histological features of common nevi and melanoma. Most never progress to melanoma. Although many melanomas arise without a detectable precursor lesion, 25% are associated with a melanocytic nevus, which may or may not be dysplastic (Cymerman 2016). The progression from dysplastic nevus to melanoma is not well understood (Asadbeigi 2023). Patients whose nevi have more severe atypia (Arumi-Uria 2003) or who have family members with melanoma (Silva 2011) have a higher risk for melanoma. The risk of melanoma increases as the number of dysplastic nevi increases (Bhatt 2016). Patients with familial atypical multiple mole melanoma syndrome (familial dysplastic nevus

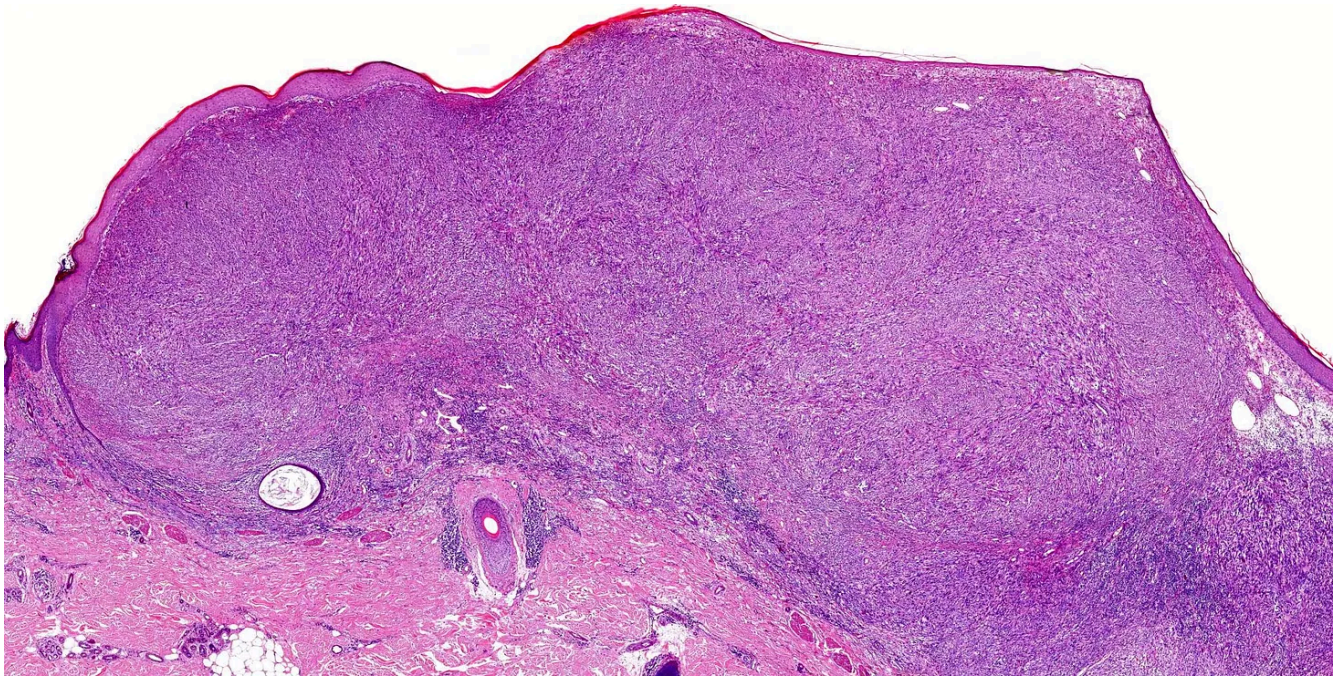
syndrome) have an increased risk of developing other malignancies, particularly pancreatic cancer (Vasen 2000).

The two types of melanoma (invasive melanoma and superficial spreading melanoma) associated with dysplastic nevi are described below:

Invasive melanoma

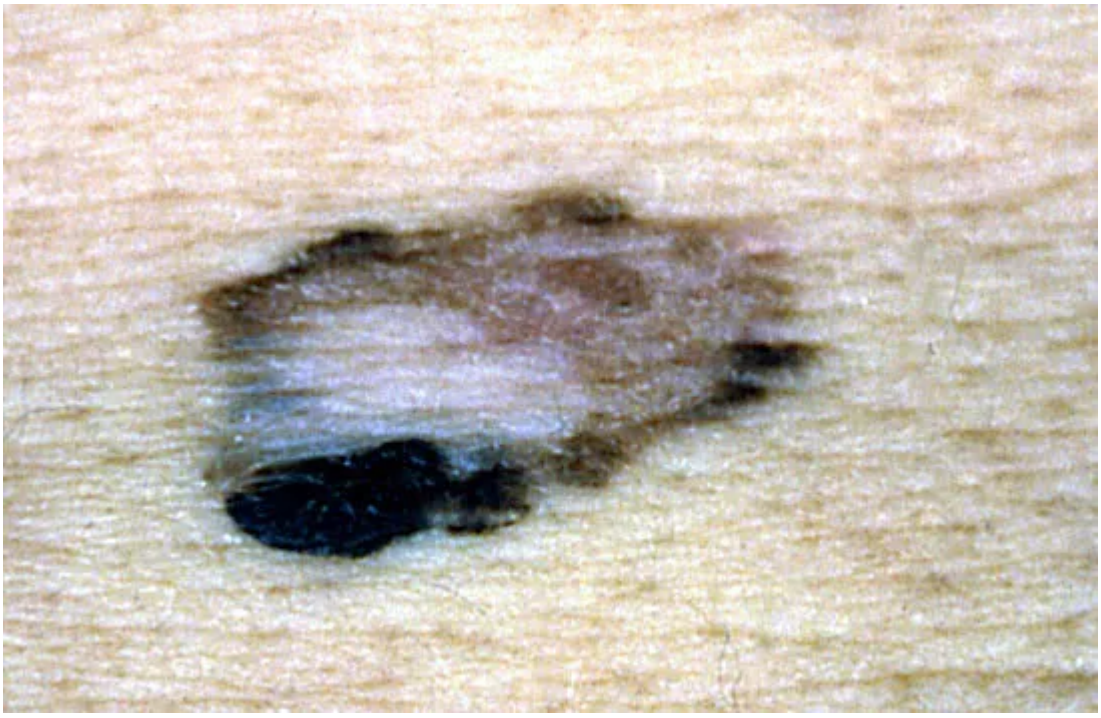


Invasive melanoma (nodular): 67 year old man with a 1.2 cm pigmented ulcerated nodule on the back.

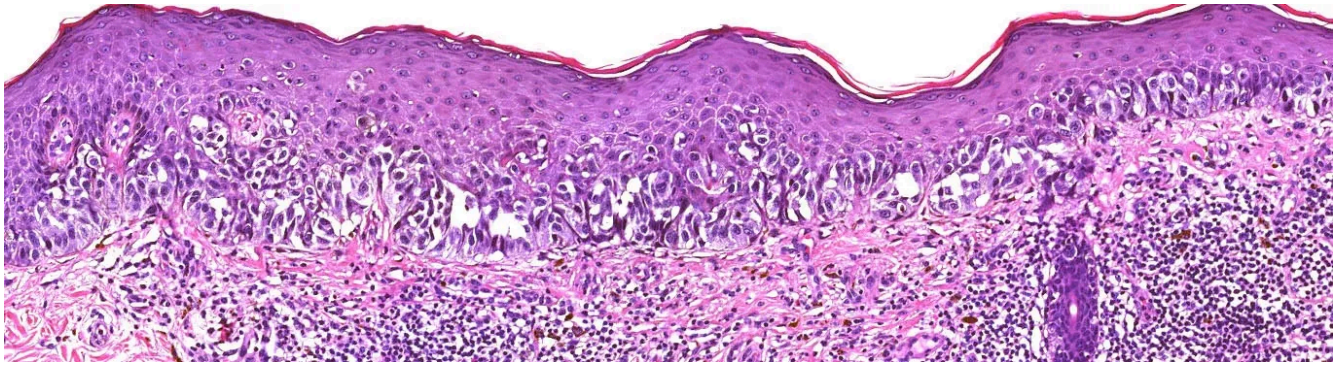


Invasive melanoma (nodular): 44 year old woman with 0.8 cm nodule on her back. There is a prominent proliferation of melanocytes.

Superficial spreading melanoma



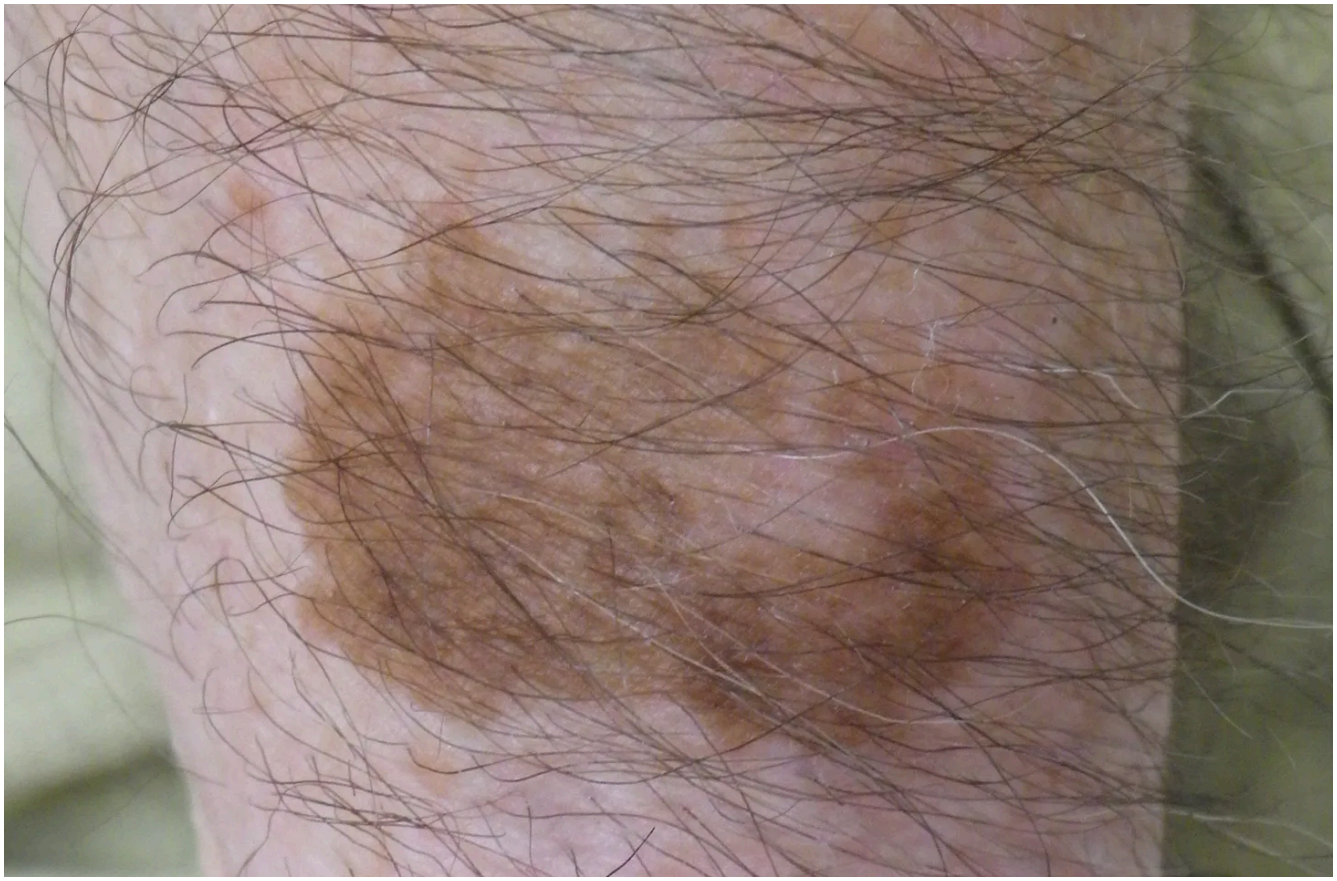
Superficial spreading melanoma: 59 year old man with a 0.9 cm pigmented flat lesion on the back. White areas suggest regression.



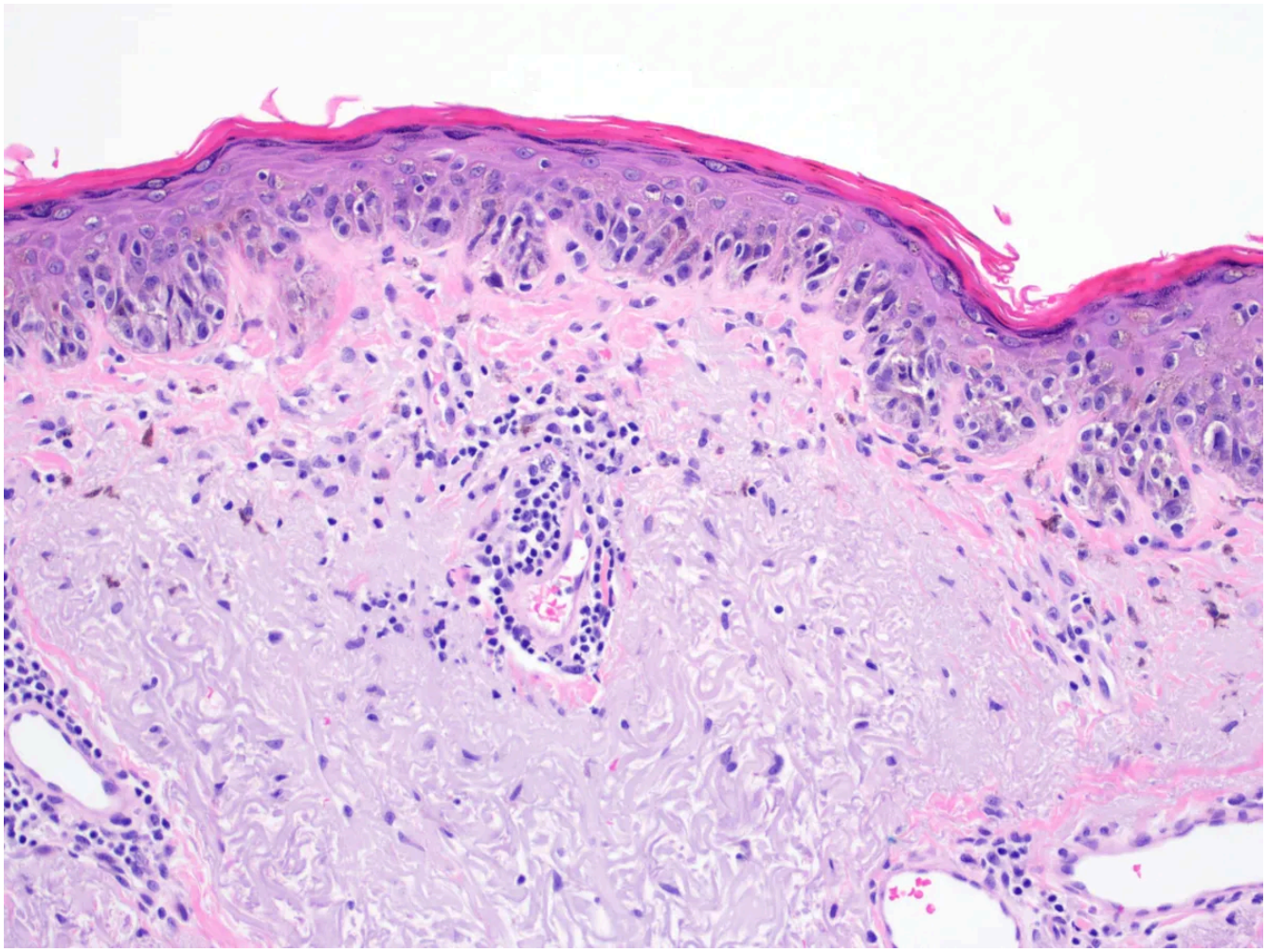
Superficial spreading melanoma: 46 year old man with a flat irregular pigmented lesion on the shoulder. Epithelioid melanocytes at the dermoepidermal junction show confluent lentiginous growth and an irregular arrangement.

3. Lentigo maligna is a precursor of lentigo maligna melanoma.

Lentigo maligna



Lentigo maligna. An irregularly pigmented macule on the forearm shows chronic actinic damage. Biopsy revealed melanoma in situ (lentigo maligna).

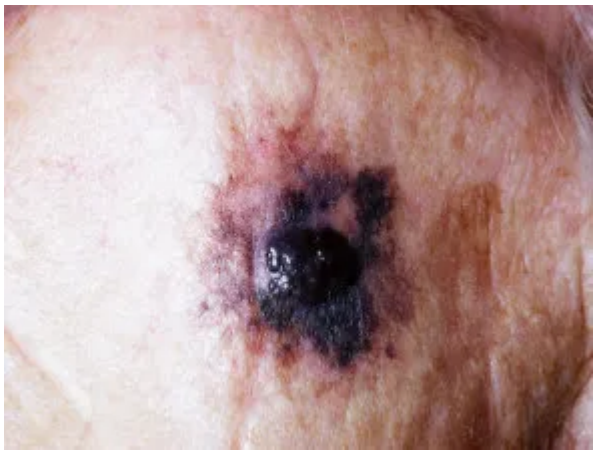


Lentigo maligna (melanoma in situ of lentigo maligna type). Atypical intraepidermal melanocytes are present with variable amounts of cytoplasm and enlarged nuclei with chromatin ranging from dense to pale and prominent nucleoli.

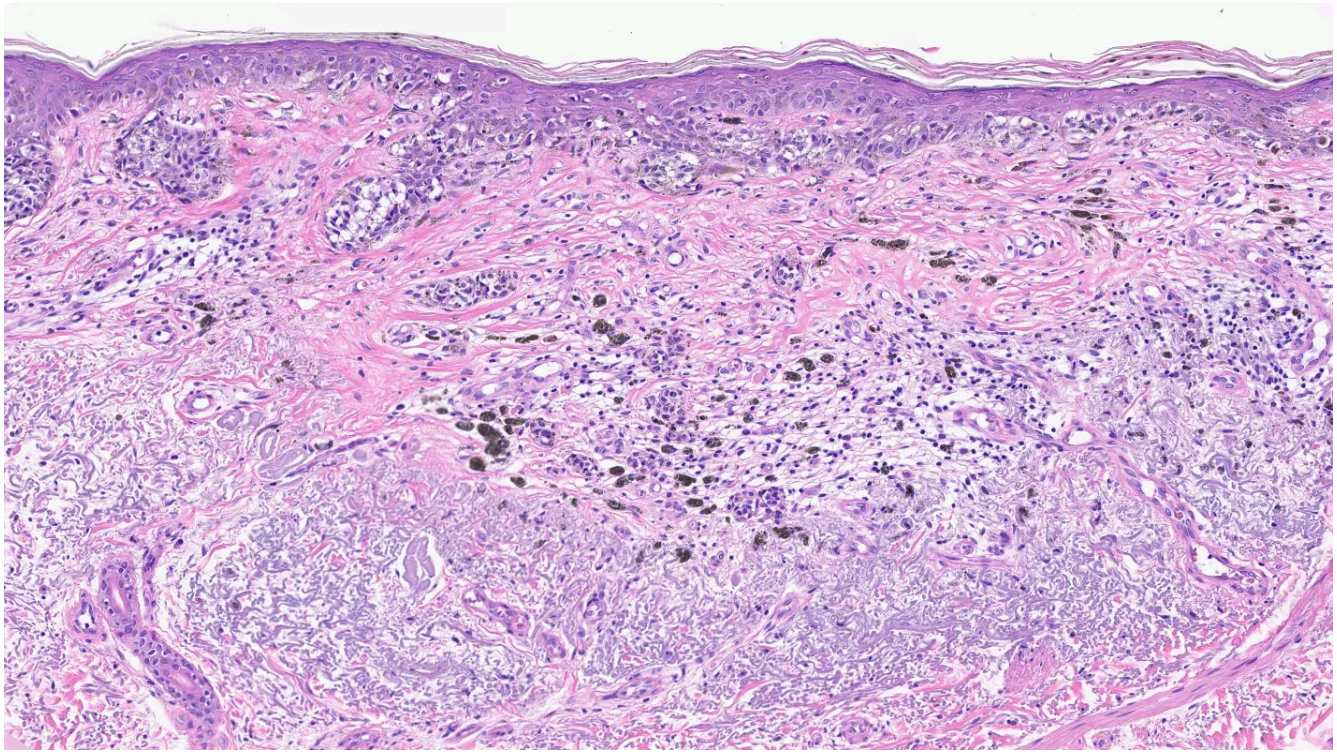
Lentigo maligna refers to the in situ (precursor) form of this disease, while lentigo maligna melanoma designates invasive disease. The precursor arises on the chronic sun damaged skin of patients on the face, neck, ears, scalp not covered by hair, forearms and dorsal hands of patients 50+ years. It presents as an irregularly pigmented macule, corresponding to an intraepidermal proliferation of atypical melanocytes.

Lentigo maligna appears to arise due to the acquisition of genetic mutations by chronic ultraviolet light exposure (Bastian 2014).

Lentigo malignant melanoma



Lentigo malignant melanoma (DermNet).



Lentigo maligna melanoma (malignant melanoma of lentigo maligna type). A compound proliferation of melanocytes with an intraepidermal component shows an irregular distribution of nests, pagetoid scatter and focal effacement of rete and a dermal component consisting of nests with associated fibrosis and lymphocytic inflammation, indicative of dermally invasive melanoma.

In part 3b, we will discuss the last 3 dermatologic malignancies with known precursor lesions.

If you like these essays, please subscribe or **share them** with others.

Click here for the Index to Nat's blog on Cancer and Medicine

Follow us on Substack, LinkedIn, Threads and Instagram (npernickmich) and Tribel (@nat385440b).

Follow our Curing Cancer Network through our Curing Cancer Newsletter, on LinkedIn or Twitter or the CCN section of our PathologyOutlines.com blog. Each week we post interesting cancer related images of malignancies with diagnoses plus articles of interest. Please also read our CCN essays.

Latest versions of our cancer related documents:

- Strategic plan to substantially reduce cancer deaths
- American Code Against Cancer (how you can prevent cancer)
- Cancer Precursor Project spreadsheet and General Overview

Email me at Nat@PathologyOutlines.com - Unfortunately, I cannot provide medical advice.

I also publish Notes at https://substack.com/note. Subscribers will automatically see my Notes.

Comments

Write a comment...