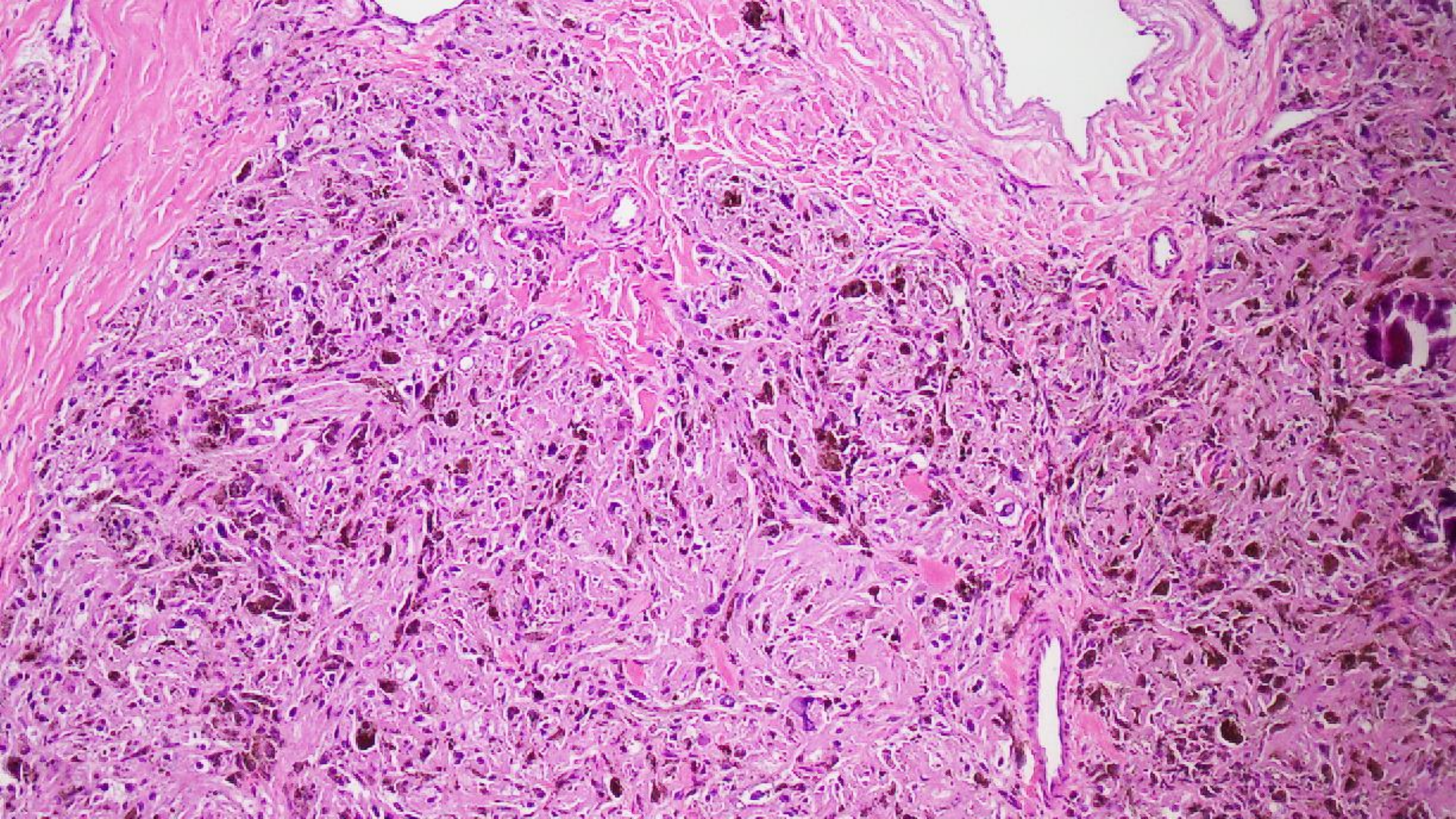


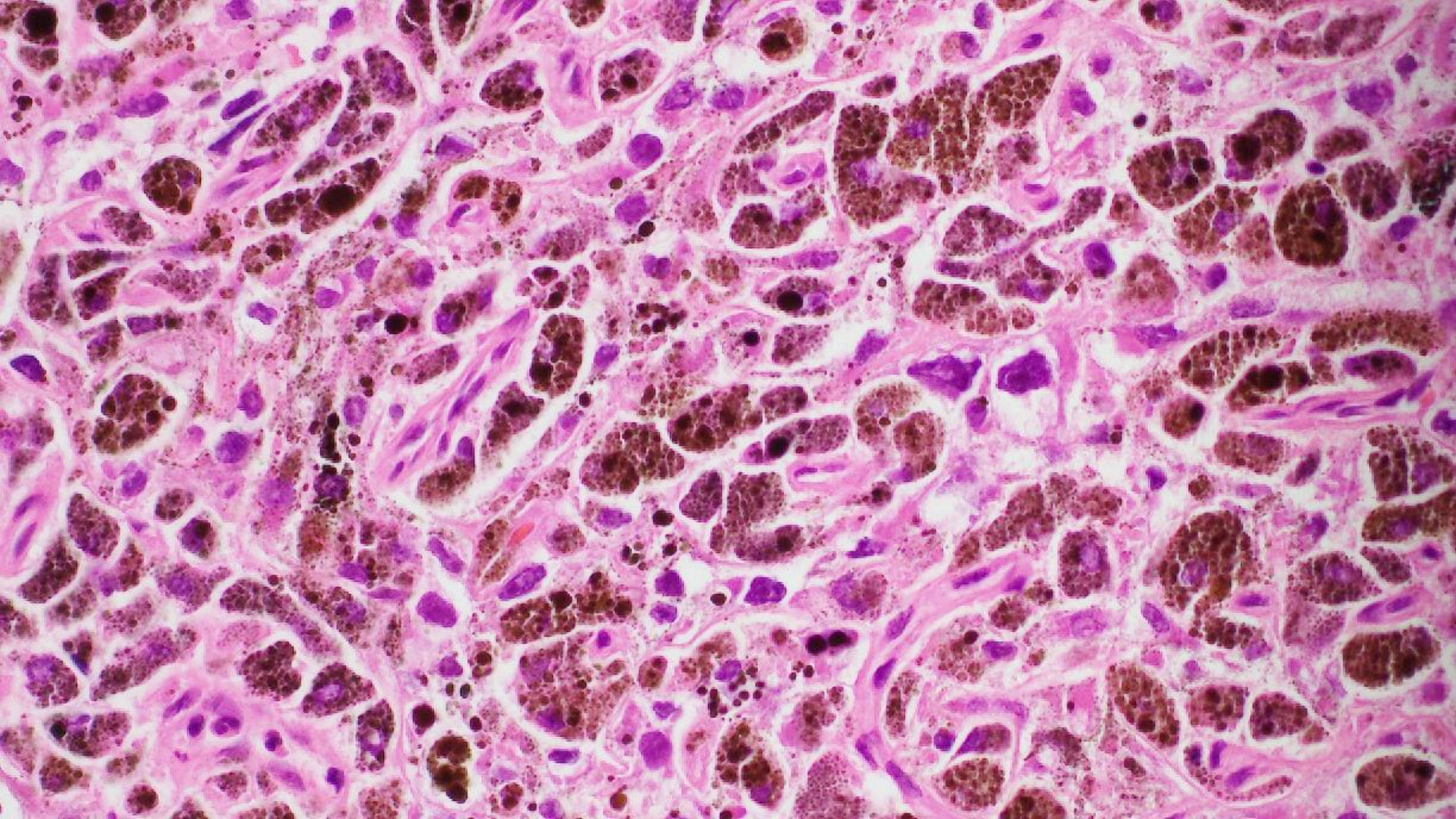
Metastatic melanoma of unknown primary: differential diagnosis

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Professor of Pathology, Harvard Medical School
Massachusetts General Dermatopathology Service
Boston, MA, USA

Melanoma of unknown primary

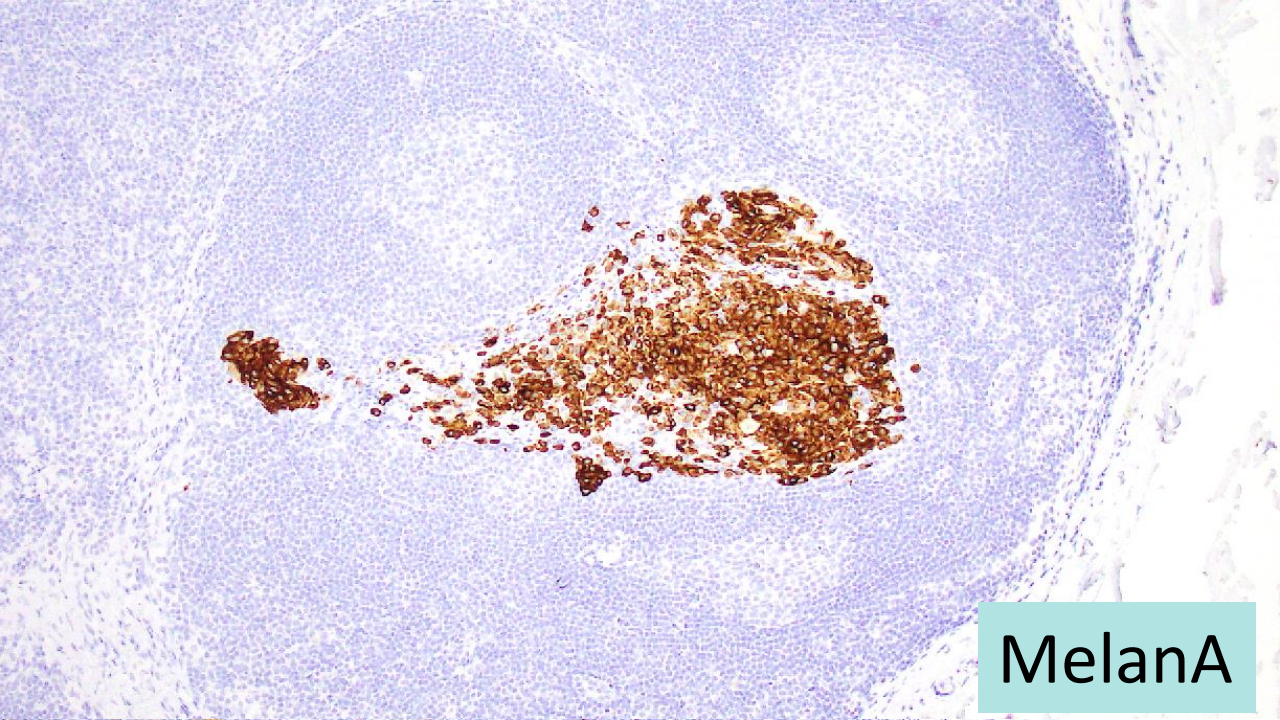
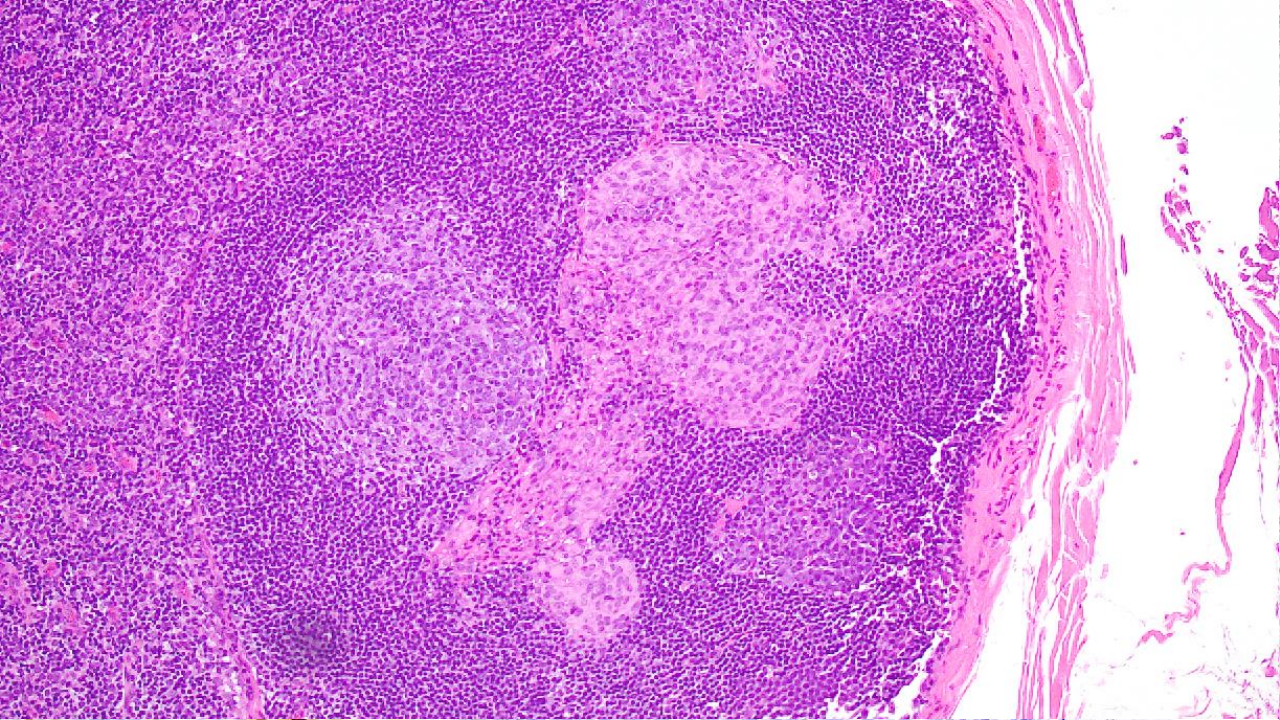
- histopathological diagnosis of metastatic melanoma
- normal dermatological, ophthalmological, otorhinolaryngology, and anogenital examinations
- normal brain magnetic resonance imaging
- normal positron emission tomography scan



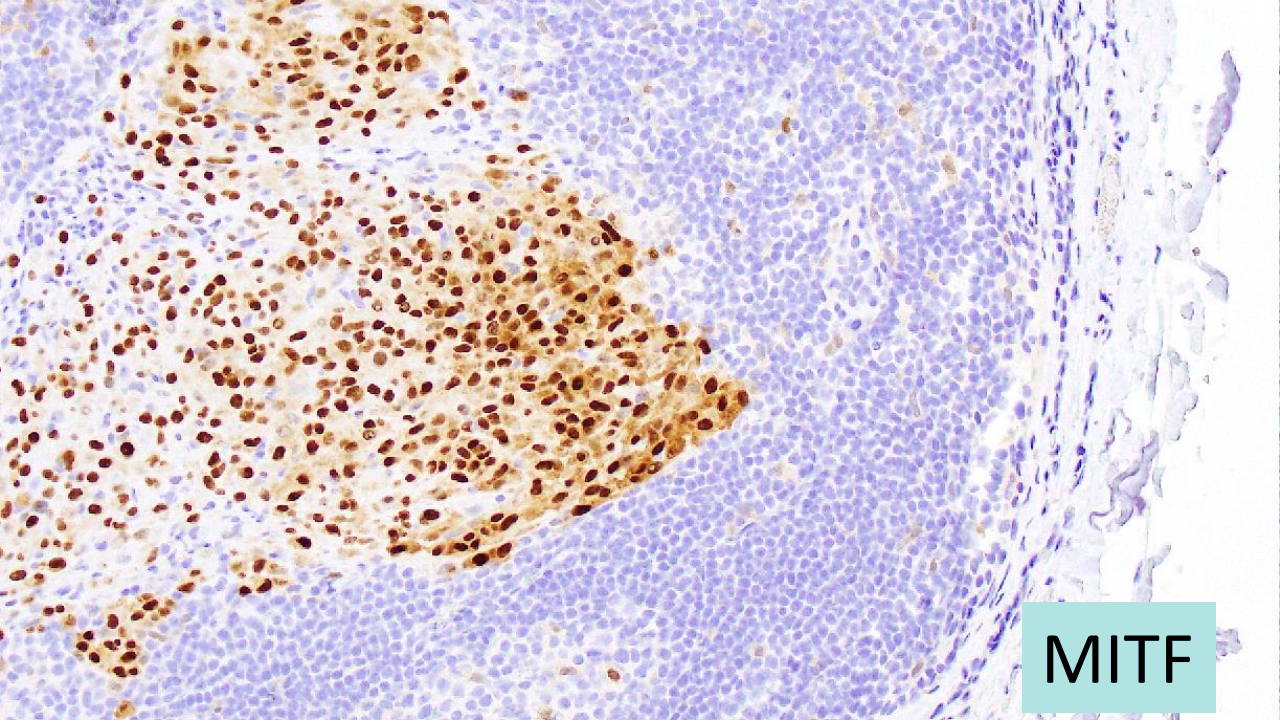


Immunohistochemistry in Differential Diagnosis

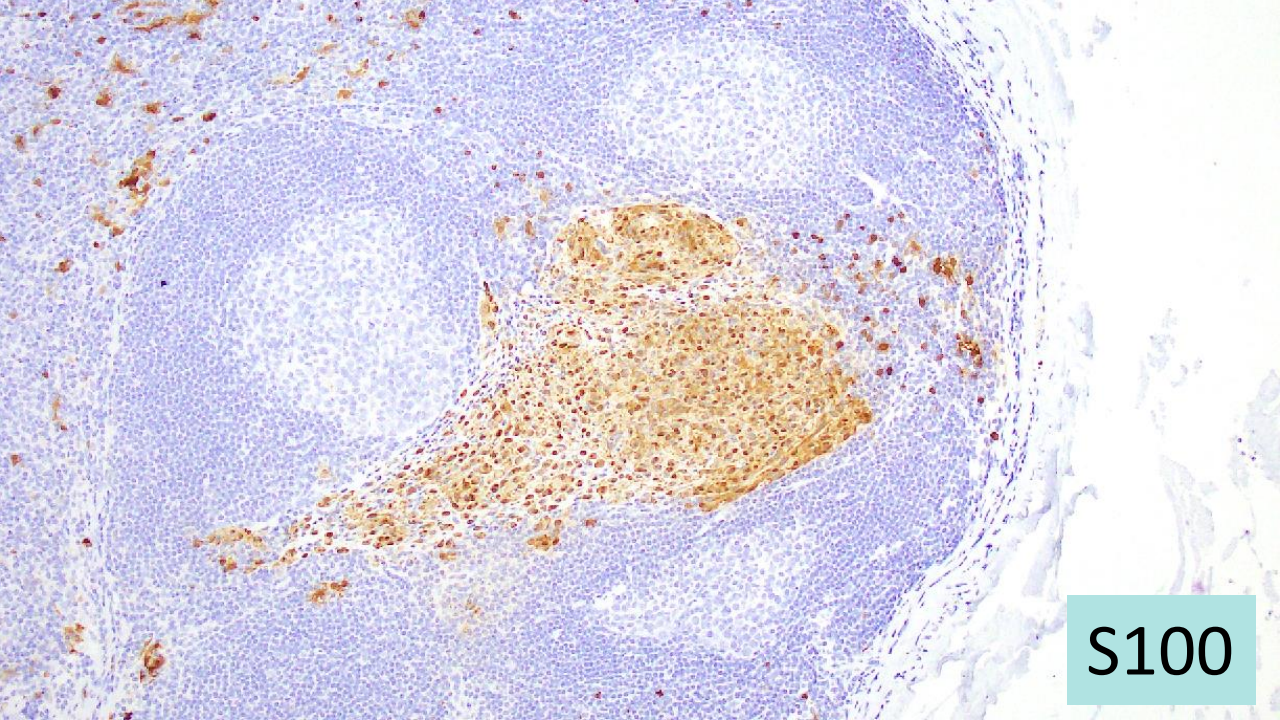
Diagnosis	Immunophenotype
Melanoma	S100, SOX10, Mart1, HMB45
Poorly differentiated Carcinoma	p63, p40, p16, cytokeratins
Diffuse large B cell lymphoma	CD20, PAX5
Malignant peripheral nerve sheath tumor	S100, SOX10 (loss of H3K27m33)
Follicular dendritic cell sarcoma	CD21, CD23, CD35, claudin-4, D2-40, SSTR2
Neuroendocrine carcinoma	INSM1, chromogranin, synaptophysin, keratins
Malignant melanotic nerve sheath tumor	S100, SOX10, Mart1, HMB45 (loss of PRKAR1A, no BRAFm)



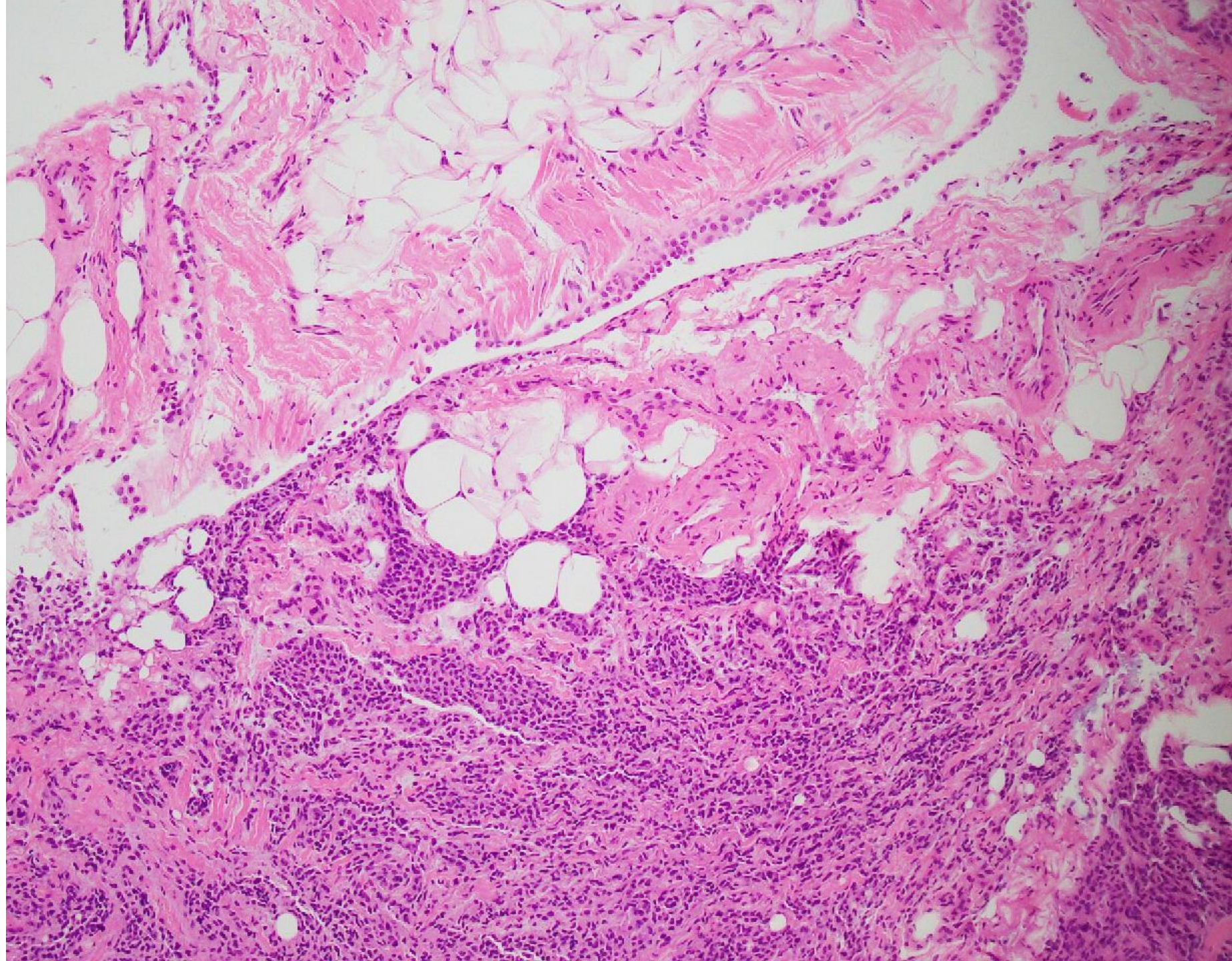
MelanA

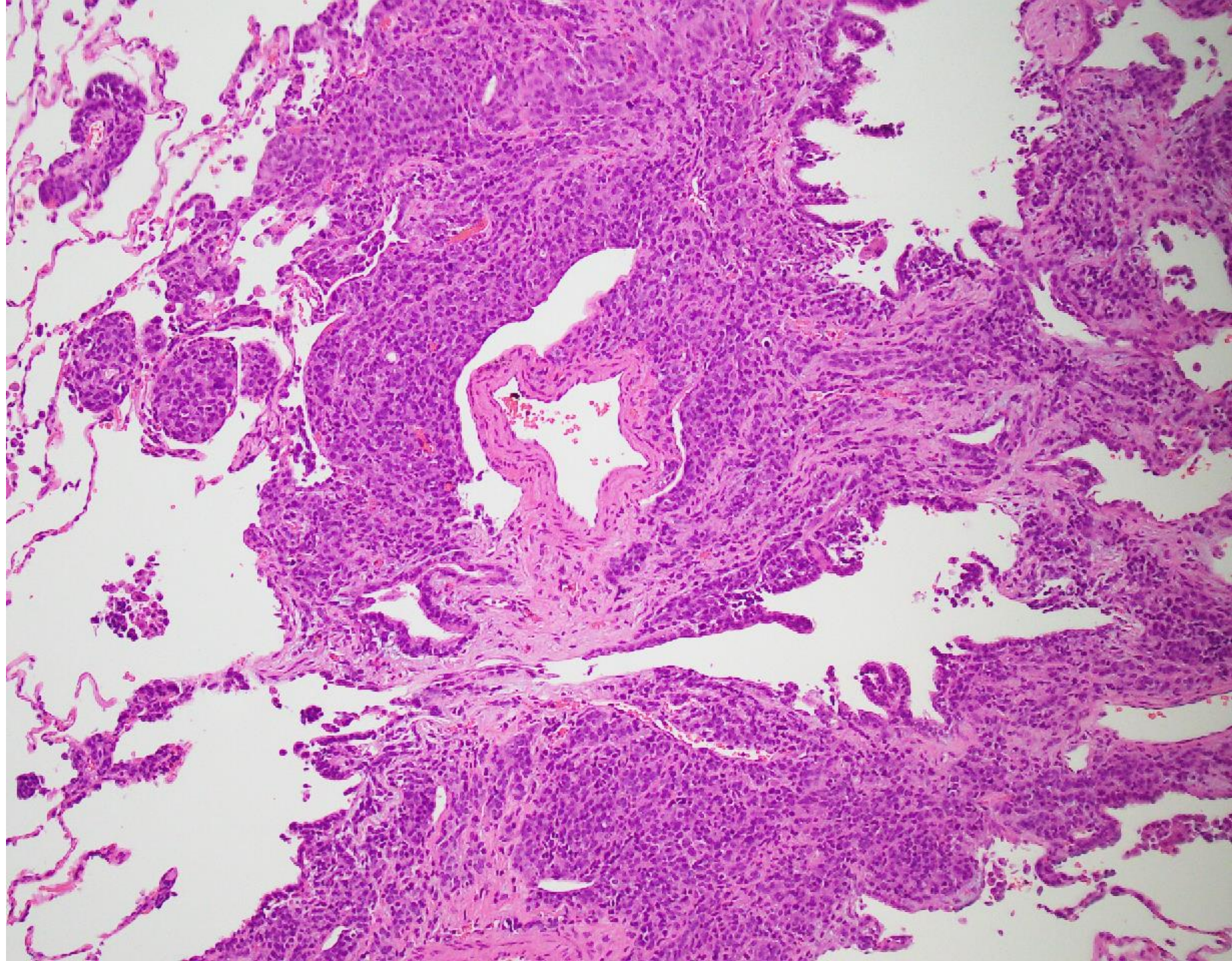


MITF



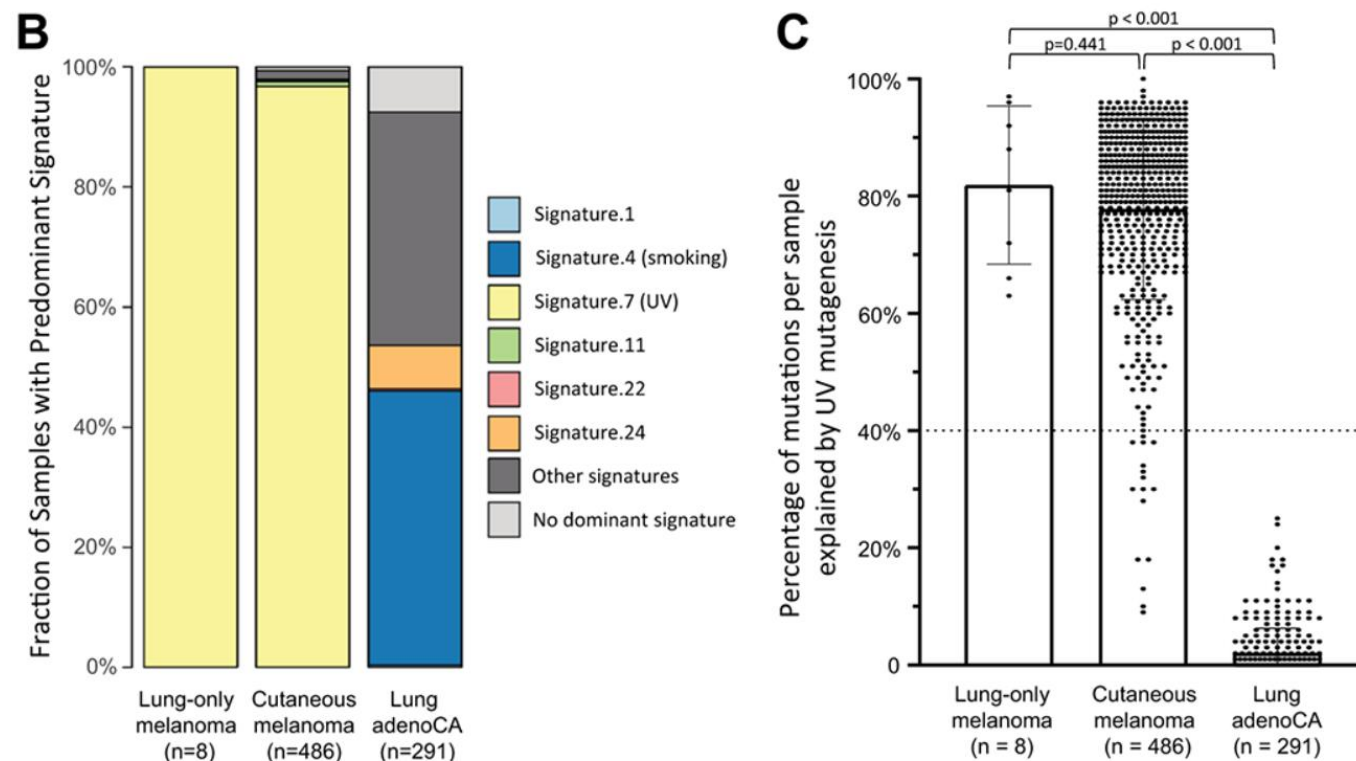
S100





Lung-only melanoma: UV mutational signature supports origin from occult cutaneous primaries and argues against the concept of primary pulmonary melanoma

Chen Yang¹, Francisco Sanchez-Vega², Jason C. Chang¹, Walid K. Chatila³, Alexander N. Shoushtari⁴, Marc Ladanyi^{1,5}, William D. Travis¹, Klaus J. Busam¹, Natasha Rekhtman¹



UV signature in lung-only melanoma with cutaneous melanoma and lung adenocarcinoma as control groups.

Dedifferentiated and Undifferentiated Melanoma

Definition

Transitional areas with dedifferentiation

Lacking histopathological features of melanoma

Negative S100, SOX10, MelanA, HMB45, Pan-mel

German report of 85 cases

- 16% (14/85) primary melanoma
- 84% metastatic melanoma
 - 66% (56/85) known prior primary
 - 18% (15/85) unknown primary

Clues to the diagnosis of melanoma

1. presence of minimal differentiated clone
2. history of melanoma
3. histology that does not fit any defined entity,
4. Site unusual for undifferentiated pleomorphic sarcoma (axilla, inguinal, neck, digestive system, etc.)
5. multifocal disease typical of melanoma spread
6. detection of a melanoma-compatible gene mutation
7. absence of a primary in other organs

Melanoma of Unknown Primary

3 % of all melanomas

More common in males than females

Peak in fourth and fifth decades of life

Hypotheses

Malignant transformation of ectopic melanocytes

Unknown traumatic removal of cutaneous primary tumor

Complete immune-mediated regression of cutaneous primary tumor

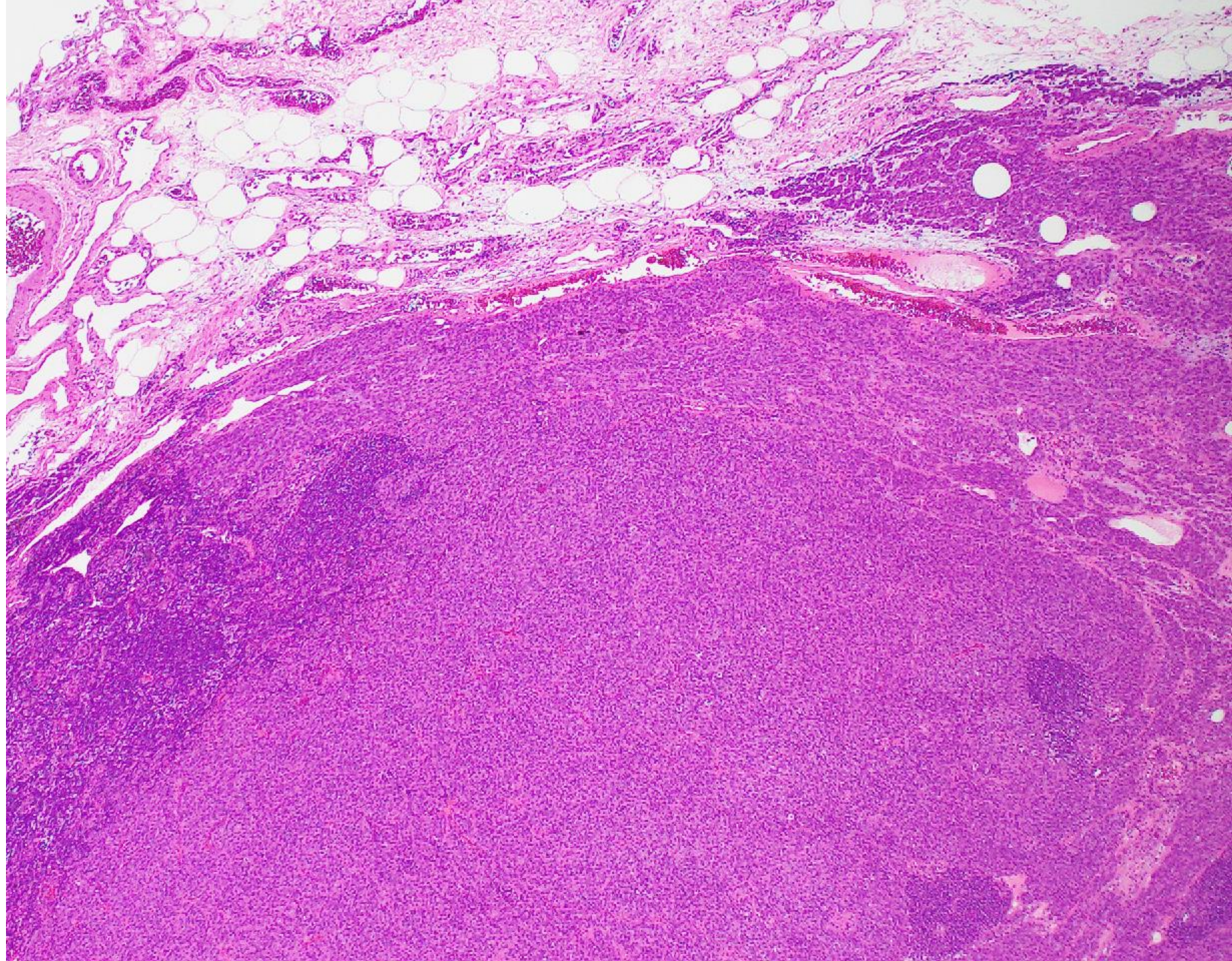
Molecular signatures

Mutational pattern similar to that of melanoma with known cutaneous primary

- high mutational burden consistent with UV signature
- similar rates of BRAF, NRAS mutations
- TERT may serve as driver mutation
- KIT mutations are rare

Prognosis

Contradictory findings in retrospective analyses before advent of novel therapies



Cutaneous Melanoma with Brain Metastasis: Report of 193 Patients with New Observations

**Alenka Gugger¹, Raymond L. Barnhill², Burkhardt Seifert³, Silvia Dehler⁴, Holger Moch¹,
Claire Lugassy², Ewerton Marques-Maggio¹, Elisabeth J. Rushing⁵, Daniela Mihic-
Probst^{1*}**

- 17% (32 of 193) primary melanoma was unknown
- 63% (20 of 32) male

French National Cancer Institute: MelBase

Initial prognostic factors

<ul style="list-style-type: none">2013 to 2021Stage III/IV Melanoma14 % (265/1882) unknown primary		Melanoma unknown primary	Melanoma with cutaneous primary	P=
	Stage IV	97%	85%	< 0.01
	≥ 3 metastatic sites	48%	39%	0.01
	CNS metastasis	38%	18%	< 0.01
	LDH > 2x NL	12%	8%	0.01

More unfavorable initial prognostic factors in patients with unknown primary

Dutch Melanoma Treatment Registry (DTMR)

- 2012 to 2017
- Stage IIIc^{unresectable} or IV
- Treatment with immune checkpoint inhibition and/or targeted therapy
- 14 % (385/2706) unknown primary

Initial prognostic factors	Melanoma unknown primary	Melanoma with cutaneous primary	P=
Initial presentation at Stage IIIc ^u or IV	73%	7%	< 0.01
CNS metastasis	32%	26%	< 0.01
ECOG performance ≥ 1	48%	40%	<0.01

More unfavorable initial prognostic factors in patients with unknown primary

North American Intergroup trial E1609 adjuvant ipilimumab vs. high dose interferon-alfa

- 13 % (214/1669) unknown primary
- Patients with melanoma of unknown primary had significantly better outcomes (recurrence free survival and overall survival) than those with known cutaneous primary tumors
- Enhanced immune activation in tumor microenvironment and the circulation

In the era of modern therapy—
patients with melanoma of unknown
primary present with more advanced
prognostic factors but have a similar or
better prognosis than patients with known
cutaneous primary

Diagnostic approach to Melanoma of Unknown Primary (MUP)



Clinical findings

- Prior melanoma or ablated cutaneous lesions?
- Eye and skin exams
- Imaging



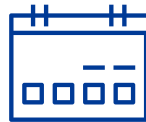
Histopathology

- Microscopic findings
- Immunophenotype



Integration

- Clinical, histopathological
- molecular and imaging



Exclude other possibilities

- MUP responds to melanoma therapies
- other tumors may not



Consultation

In diagnostically challenging cases, get input from colleagues