NOVEDADES EN PROLIFERACIONES VASCULARES CUTÁNEAS

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Intravascular histiocytosis

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- **Erupción macular en la pierna izquierda.**
- **Histopatologia: estructuras vasculares de la dermis dilatadas conteniendo células mononucleares que no expresan marcadores endoteliales (CD34 y factor VIII), pero si marcadores histiocitarios (MAC-387 y CD68).**
- **Denominaron el proceso *histiocitosis intravascular* y discutieron el diagnóstico diferencial histopatológico con el linfoma intravascular.**

Intralymphatic Histiocytosis. A Clinicopathologic Study of 16 Cases

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*Sonia Segura, MD,‖ Mirjana Ziemer, MD,** Mark A. Hurt, MD,¶*
Omar P. Sangüeza, MD,‡§ and Heinz Kutzner, MD††

Abstract: Intralymphatic histiocytosis is a rare condition characterized by the presence of dilated lymphatic vessels containing aggregates of mononuclear histiocytes (macrophages) within their lumina. The phenomenon seems to occur almost exclusively within the reticular dermis. Although its pathogenesis remains uncertain, there has been speculation about the possible relationship between intralymphatic histiocytosis and intravascular reactive angioendotheliomatosis. In addition, several examples historically have been associated with rheumatoid arthritis. We describe our experience with 16 cases of intralymphatic histiocytosis. Clinically, the lesions were located predominantly on the upper and lower limbs, and they consisted of asymptomatic and poorly demarcated erythematous plaques and livedo reticularis–like lesions. They were characterized histopathologically by dilated vascular structures involving the reticular dermis. Some of these dilated vessels had empty lumina, whereas others contained variable number of mononuclear histiocytes. An inflammatory response of variable intensity from case to case was also present in the adjacent dermis. The dilated vessels exhibited thin walls with irregular shapes, and a single discontinuous layer of flat endothelial cells lined their lumina. Immunohistochemically, the endothelial cells lining the dilated lumina expressed immunoreactivity for CD31, CD34, podoplanin, D2-40, Lyve-1, and Prox-1, which confirmed their nature as lymphatic endothelial cells. Intralymphatic mononuclear histiocytes expressed CD68 (PGM1), although some cases also had variable immunoexpression for myeloperoxidase, CD31, and podoplanin. In the 4 cases that employed double immunohistochemistry, with podoplanin + CD68 (PGM1) or with Lyve-1 + CD68 (PGM1), each marker highlighted their specific target cells unequivocally; the endothelial cells expressed podoplanin or Lyve-1 immunoreactivity, and intralymphatic histiocytes showed CD68 (PGM1) immunoexpression. Our findings expand on the previously described morphologic and immunohistochemical features of intravascular histiocytosis. We also discuss the possible relationship between intralymphatic histiocytosis and the so-called reactive intravascular angioendotheliomatosis.

Key Words: intralymphatic histiocytosis, intralymphatic macrophages, reactive intravascular angioendotheliomatosis, intravascular lymphoma, lymphatic endothelial cell markers, immunohistochemistry, rheumatoid arthritis, breast carcinoma, joint prosthesis inflammatory reaction, CD31, CD34, D2-40, podoplanin, Lyve-1, Prox-1, CD68

(*Am J Dermatopathol* 2009;31:140–151)

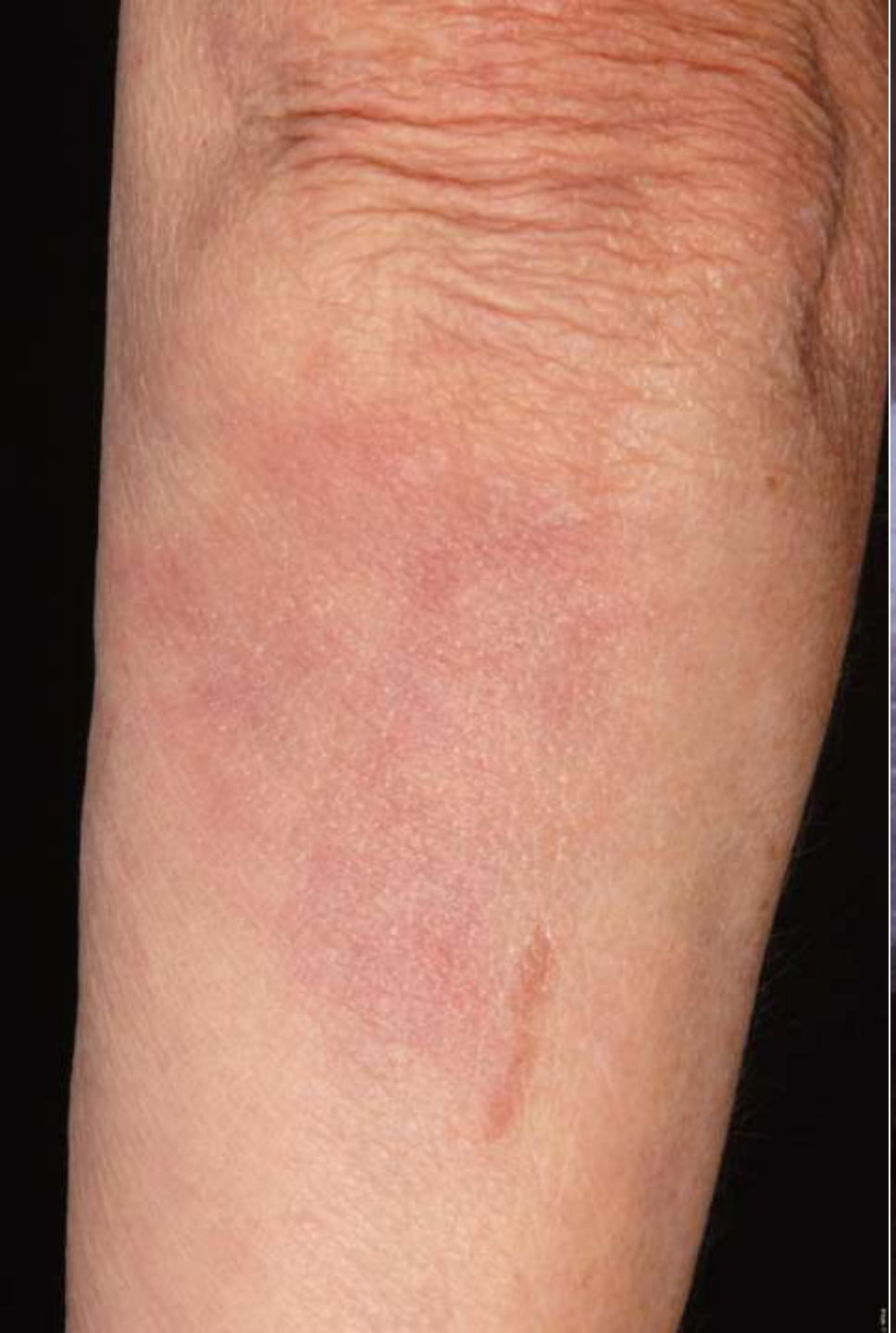
The condition known as intravascular histiocytosis was first documented in 1994 by O'Grady et al.[1] They described an otherwise healthy 77-year-old woman with a nontender erythematous rash below the left knee, which was histopathologically characterized by dilated dermal vessels, some of them containing collections of mononuclear histiocytes (macrophages) within their lumina. The intravascular cells expressed immunohistochemical markers for macrophagic histiocytes (Mac 387 and Kp1), whereas the endothelial cells of the dilated vessels stained positively with antibodies to factor VIII–related antigen. Thus, those authors named the condition "intravascular histiocytosis" and discussed the histopathologic differential diagnosis with intravascular lymphoma.

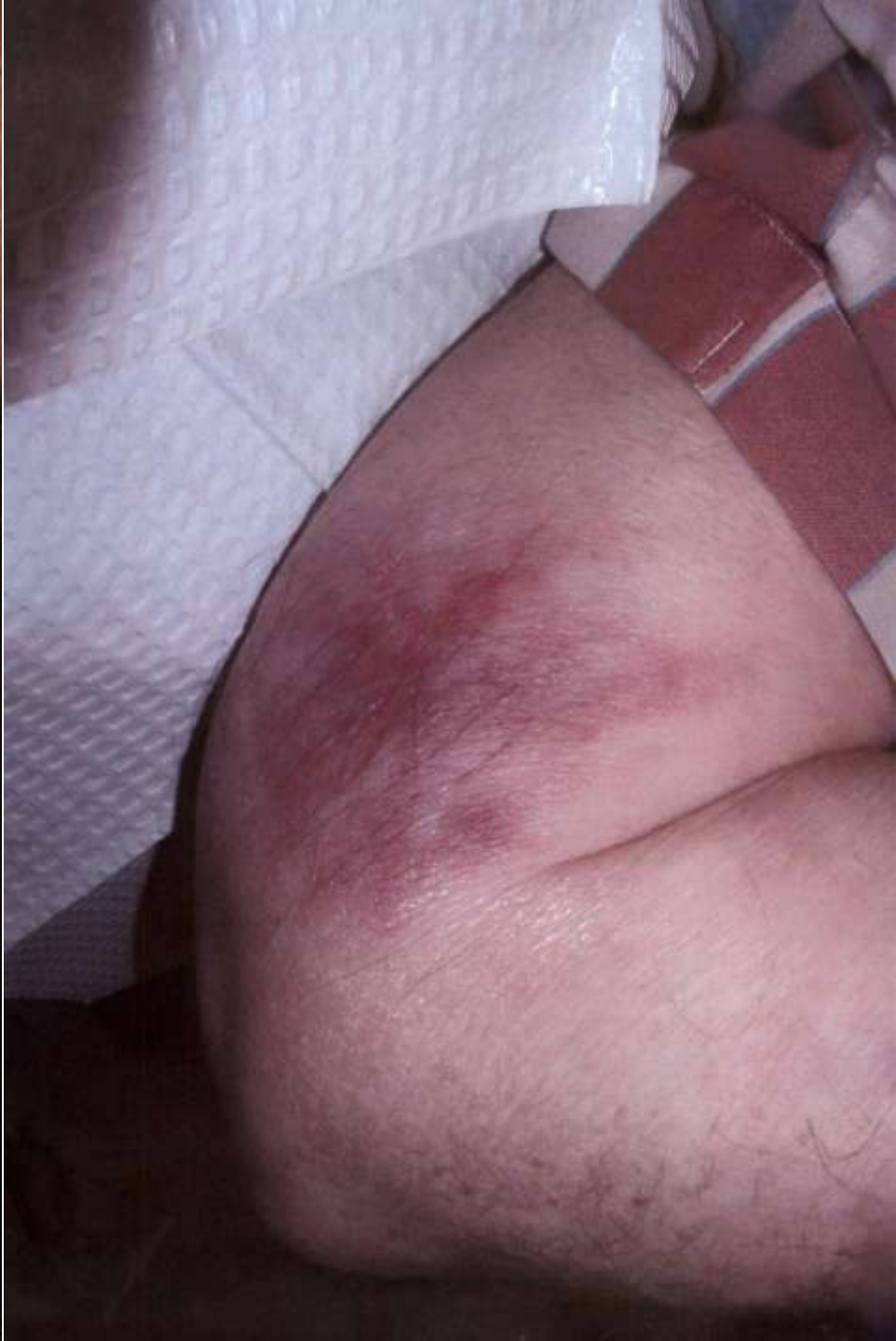
Five years later, in 1999, Rieger et al[2] described 2 similar patients, one of them with history of rheumatoid arthritis, and speculated about the possible relationship between

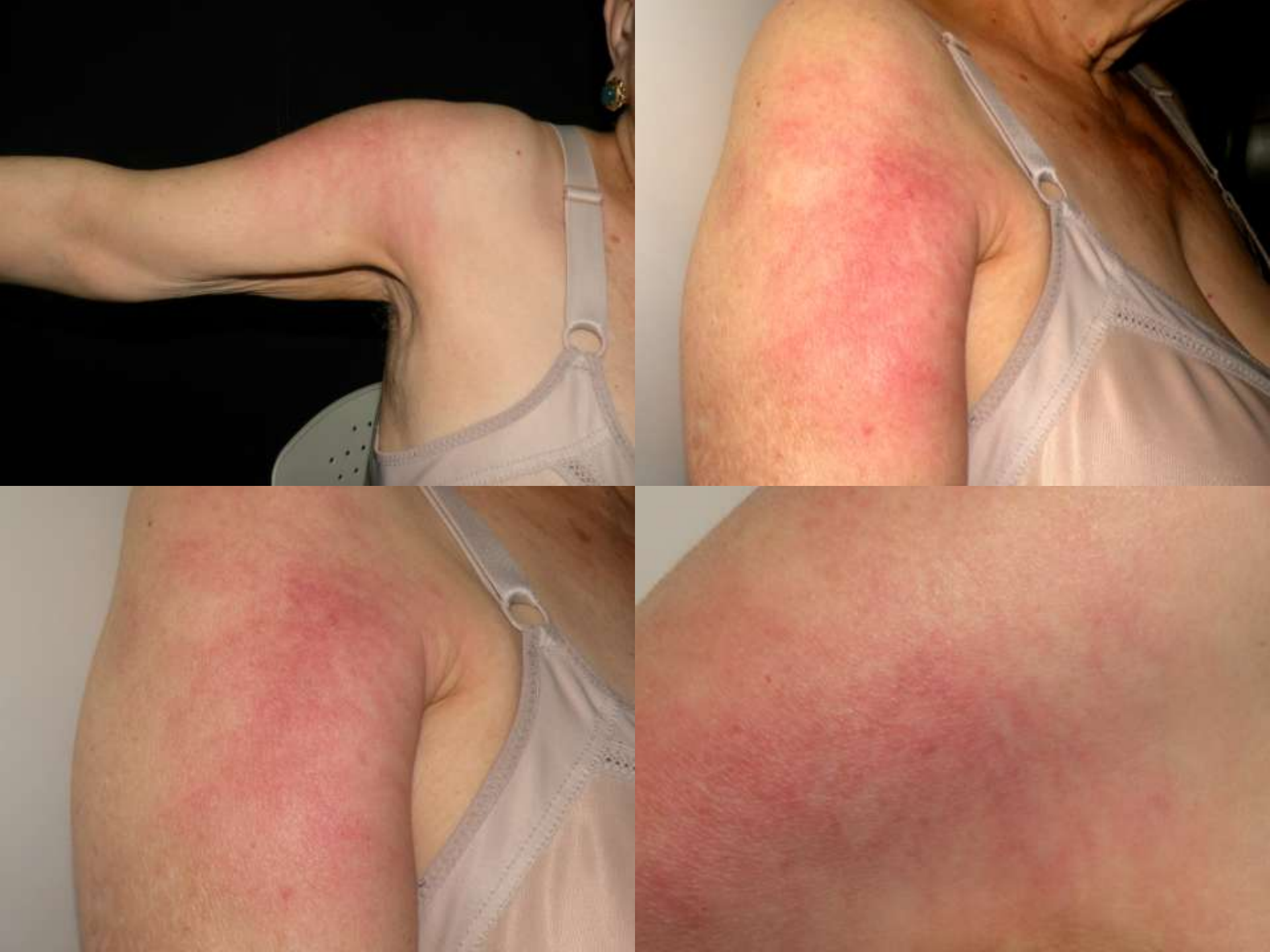
HISTIOCITOSIS INTRALINFÁTICA

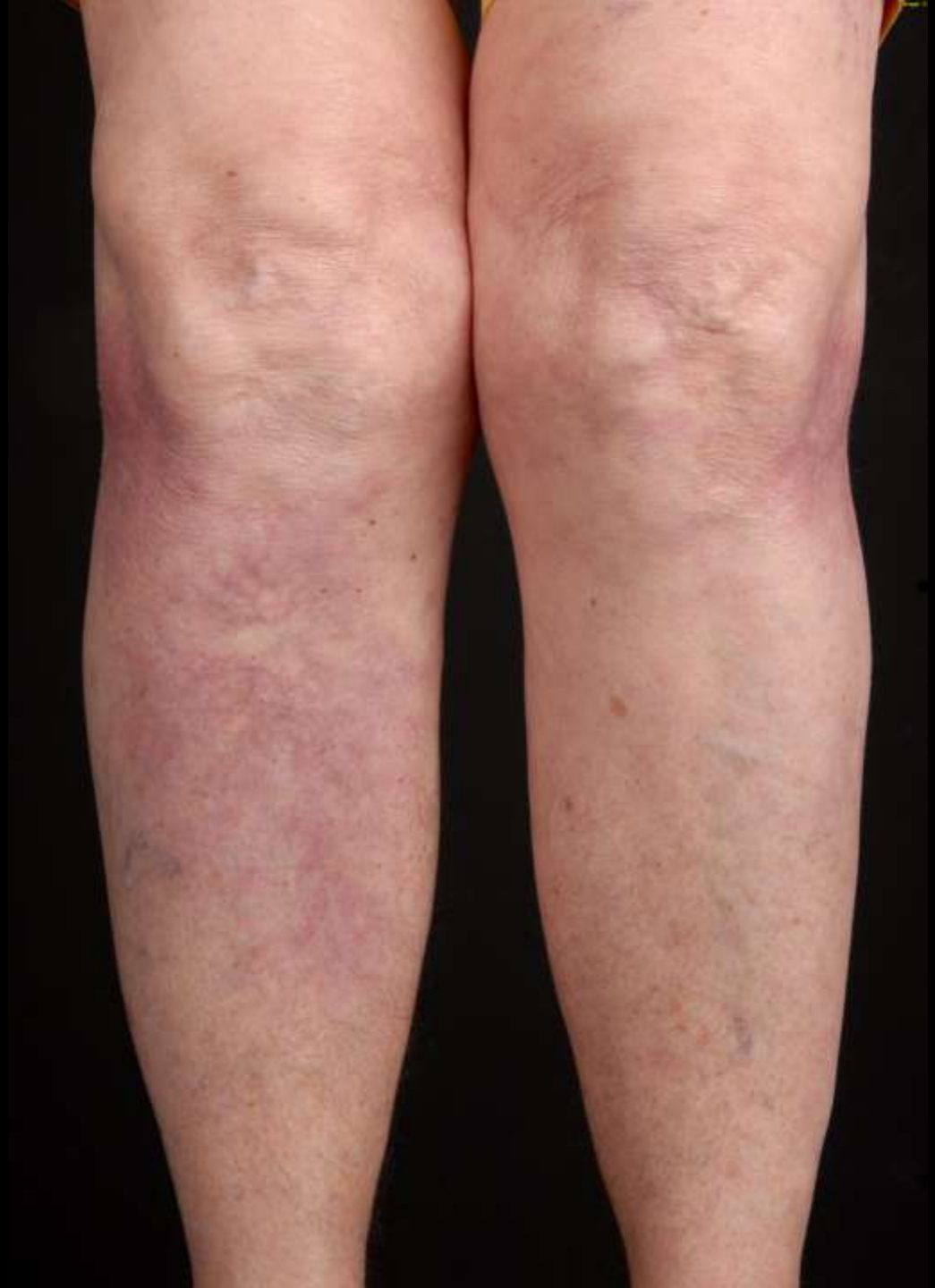
Características clínicas

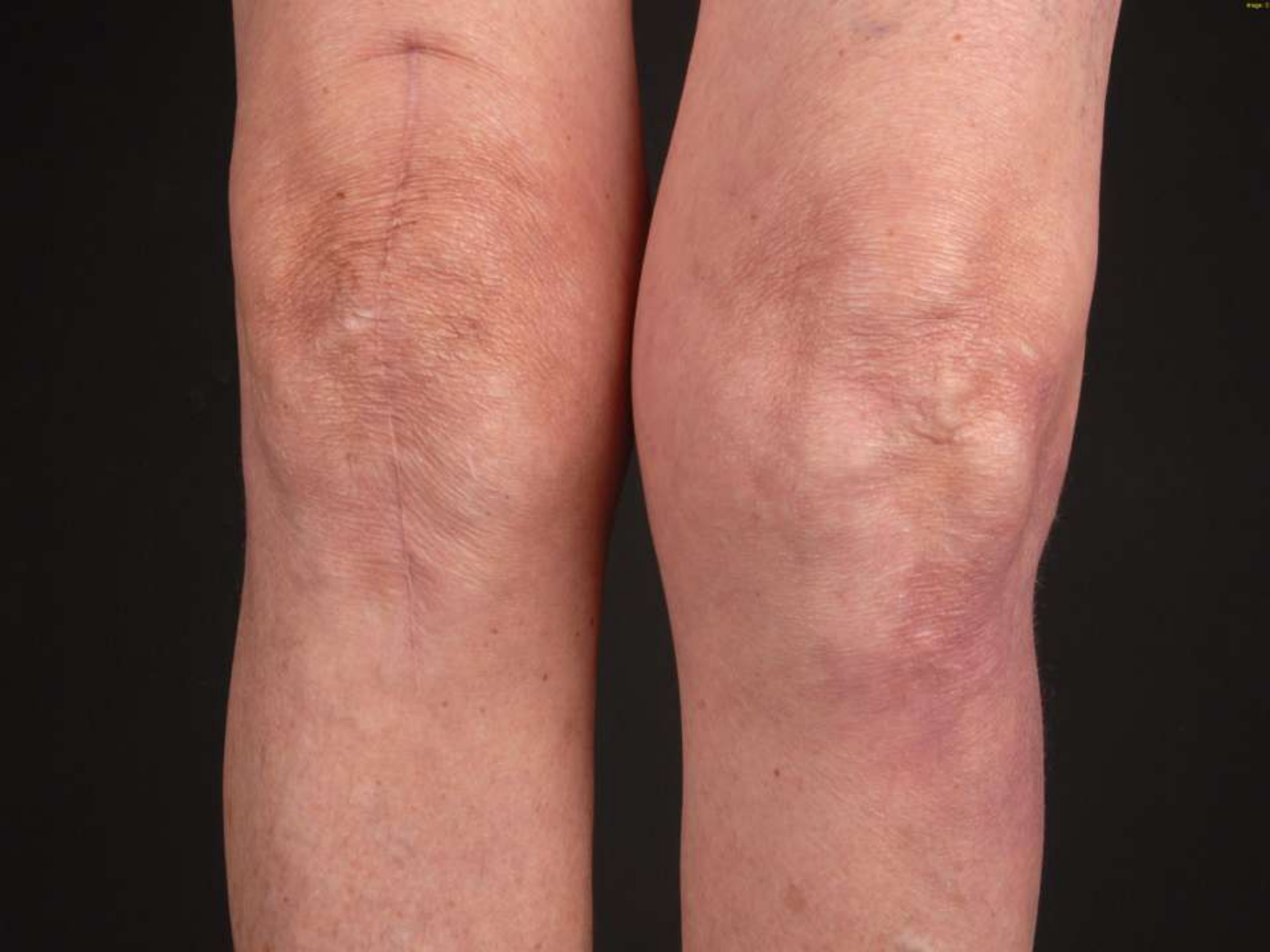
- 16 pacientes: 6 hombres y 10 mujeres.
- Edad: 46-85 años (media 70 años).
- Lesiones preferentemente localizadas en extremidades superiores e inferiores.
- Apariencia clínica: Placas eritematosas mal delimitadas y *livedo reticularis*.
- Enfermedades asociadas:
  - 5 pacientes con artritis reumatoide
  - 2 pacientes con cáncer de mama
  - 1 paciente con melanoma
- 2 pacientes con lesiones en cicatriz de prótesis de cadera.
- 2 pacientes con lesiones en cicatriz de mastectomia.
- 1 paciente con lesiones bilaterales en las piernas, que desaparecieron espontánemente en la extremidad en la que se colocó una prótesis de rodilla, permaneciendo sin cambios en la otra extremidad.

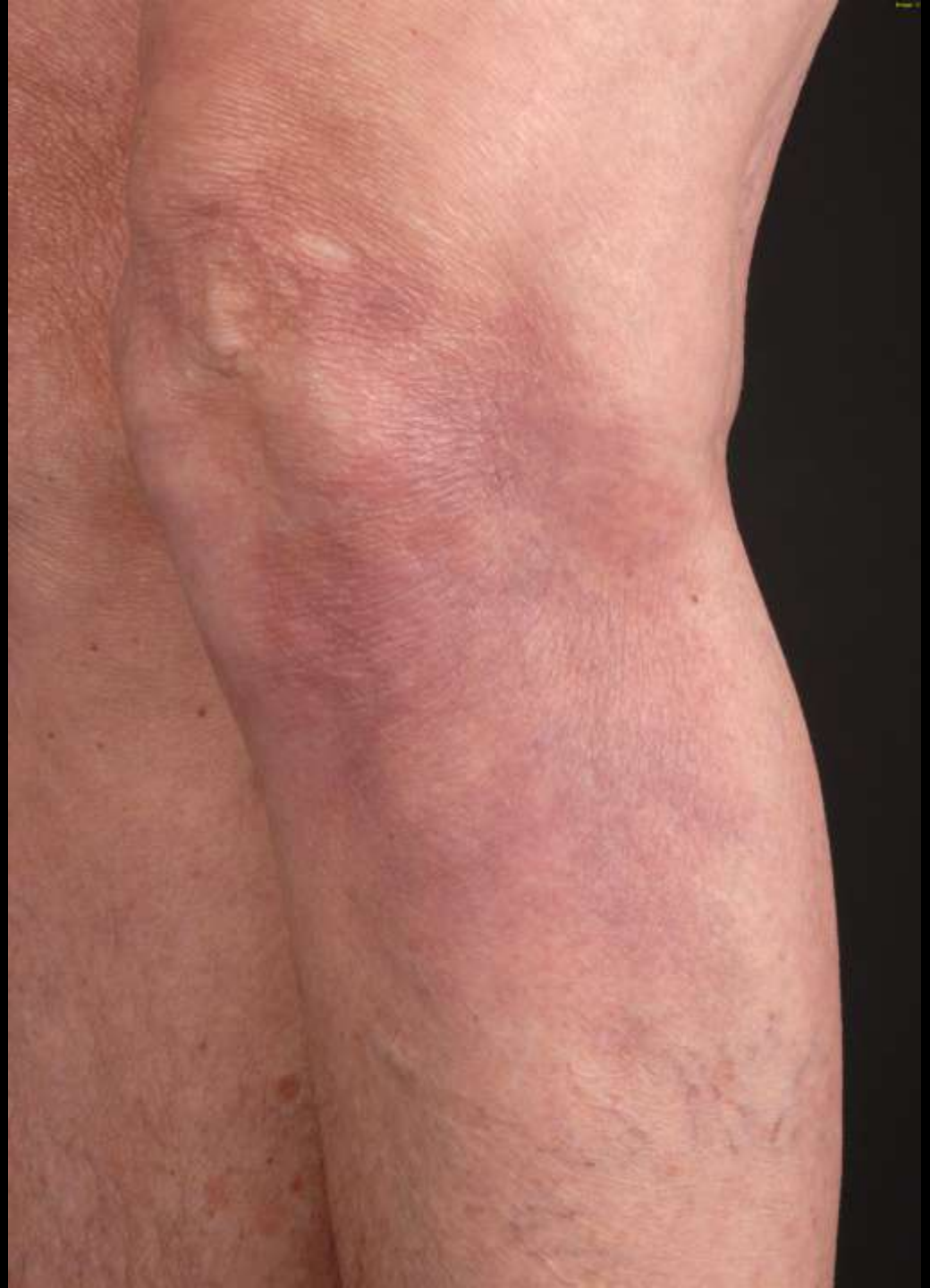


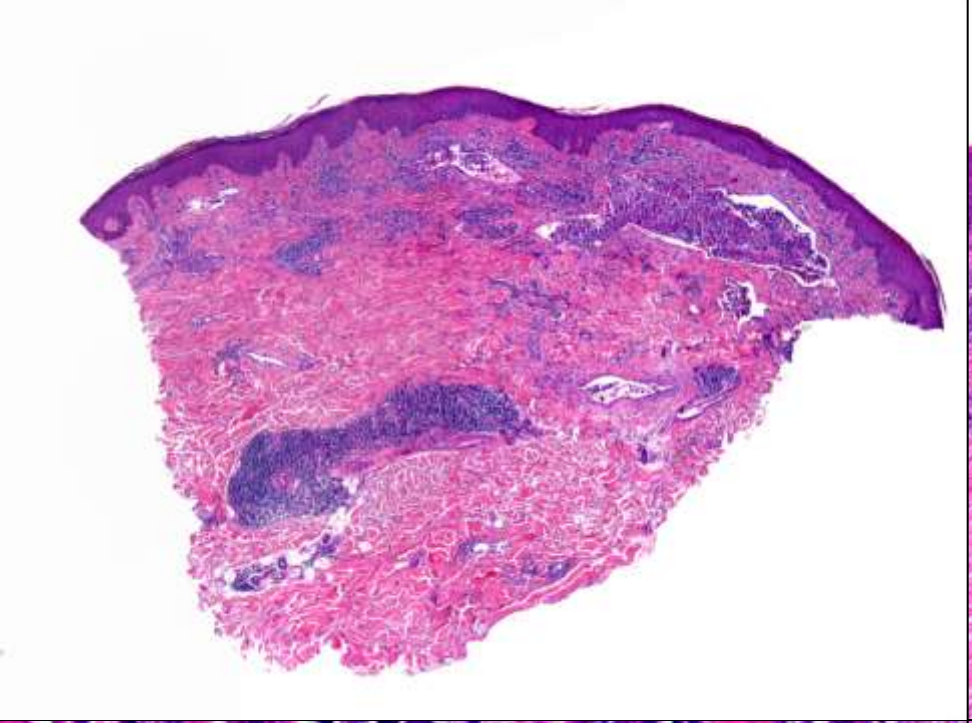
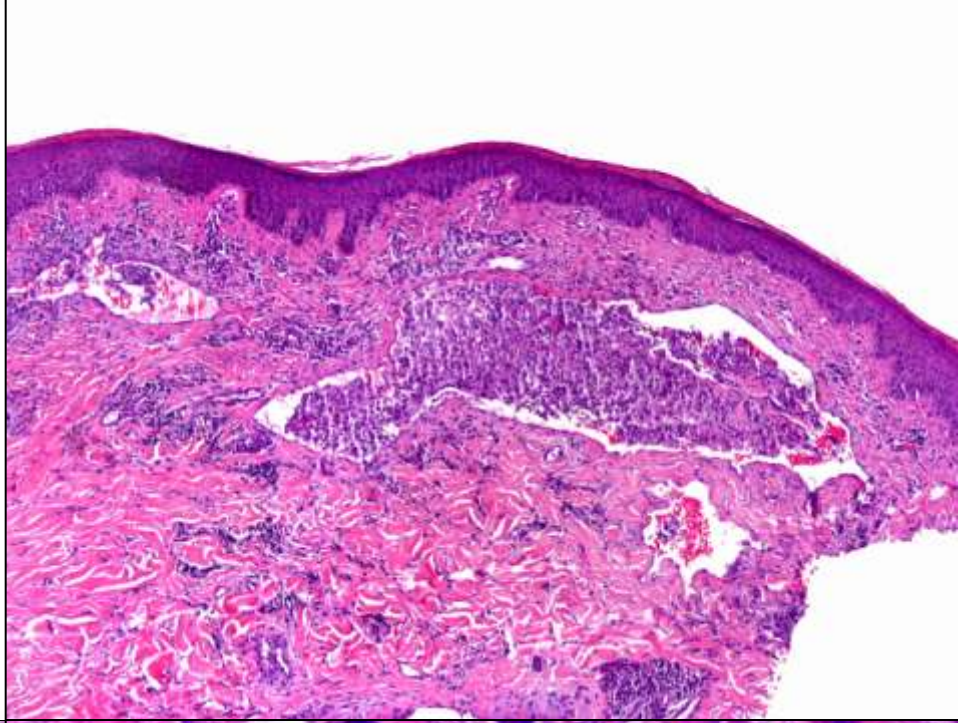
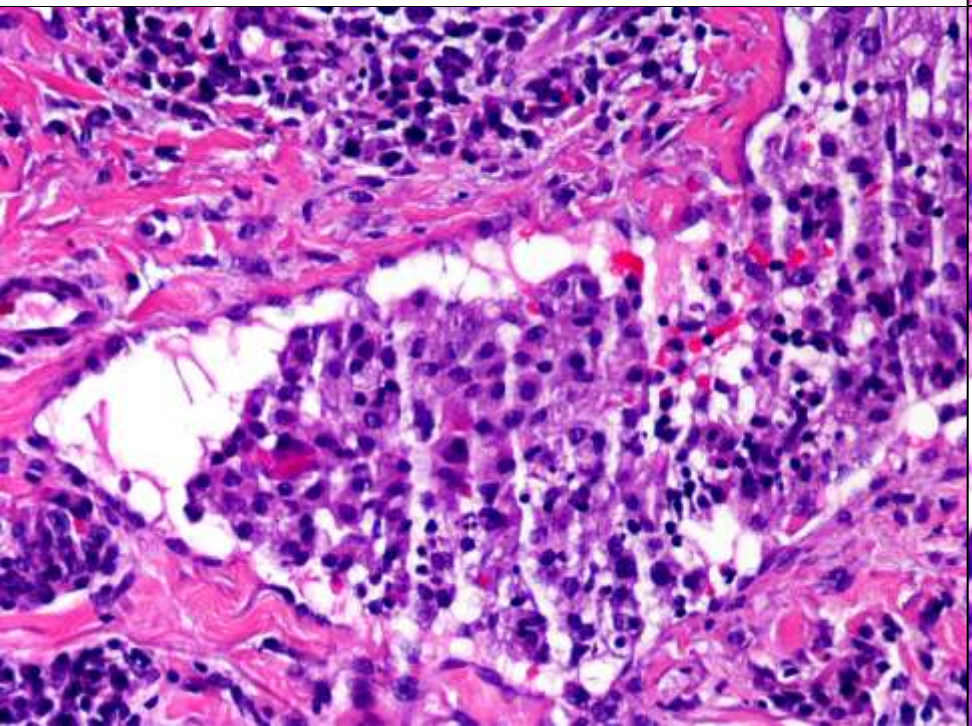
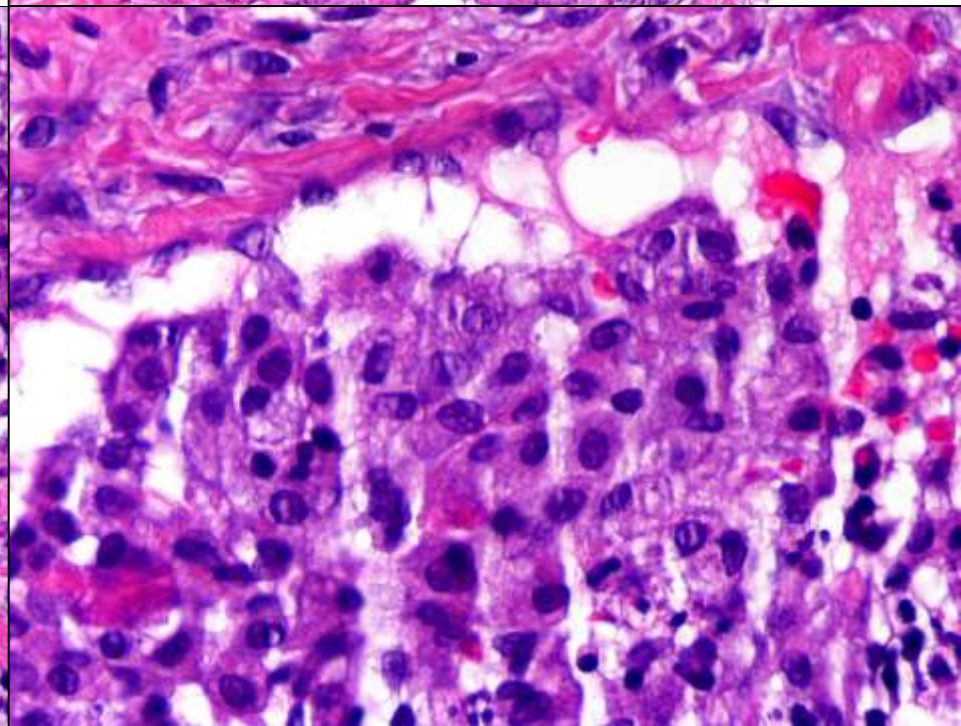










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CD3	F7.2.38	1:200	Dako
CD4	IF6	1:10	Novocastra
CD8	DK25	1:50	Dako
TIA-1	2G9	1:600	Immunotech
CD20	L26	1:500	Dako
CD79a	JCB117	1:50	Dako
CD45	PD7/26	1:400	Dako
S-100	S-100	1:4000	Dako
Ki-67	MIB-1	1:40	Dako
CD68	PGM1	1:200	Dako
Mieloperoxidasa	MPO-7	1:2000	Dako
Actina músculo liso	IA4	1:300	Dako
CD34	Qbend/10	1:100	Dako
CD31	JC/70A	1:10	Dako
Podoplanina	Policlonal	1:200	Acris
Prox- 1	Policlonal	1:200	Relia Tech
LYVE-1	Policlonal	1:200	BmT
D2-40	D2-40	1:100	Dako

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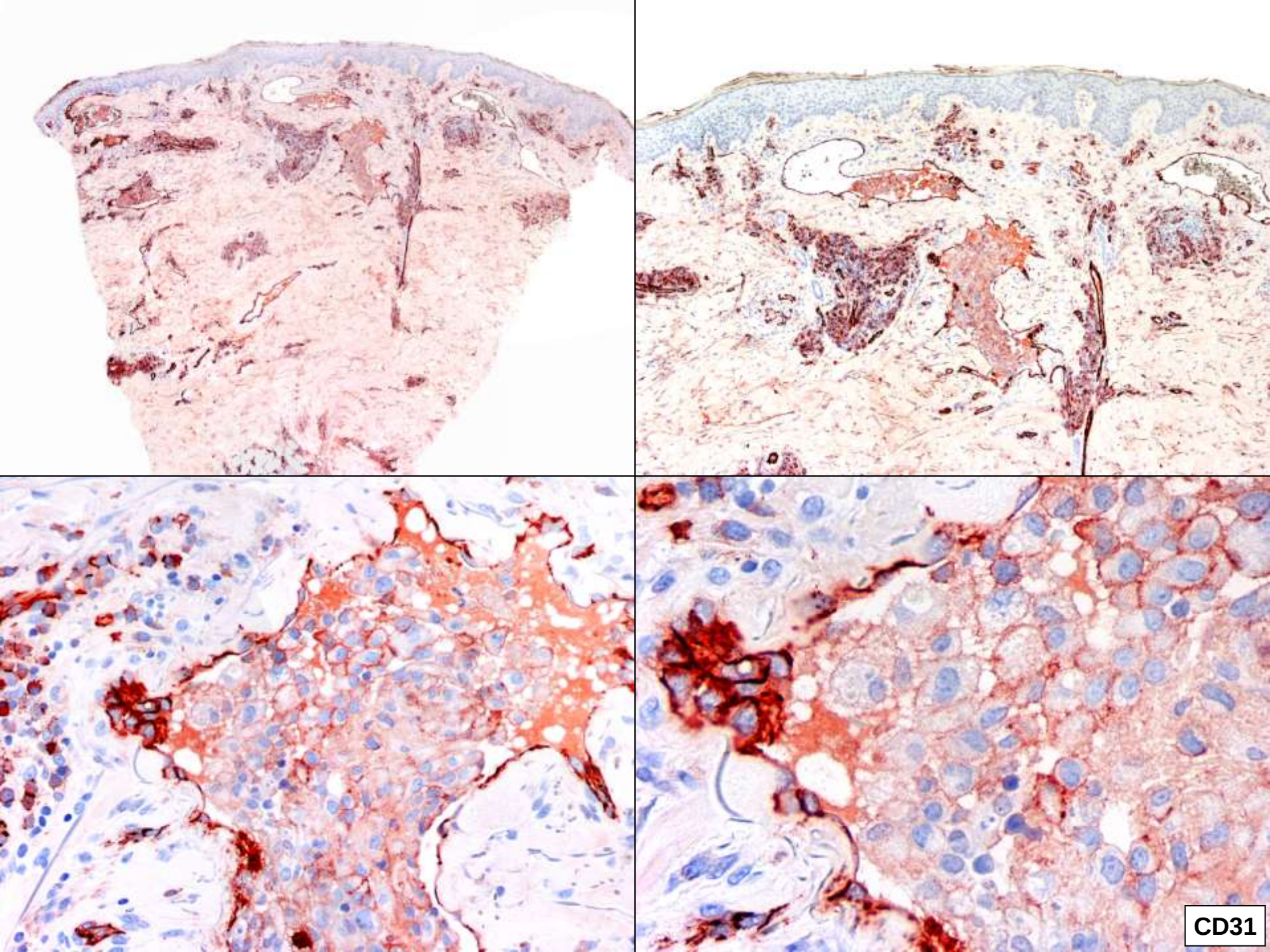
CD20	L26	1:500	Dako
CD79a	JCB117	1:50	Dako
CD45	PD7/26	1:400	Dako
S-100	S-100	1:4000	Dako
Ki-67	MIB-1	1:40	Dako
CD68	PGM1	1:200	Dako
Mieloperoxidasa	MPO-7	1:2000	Dako
Actina músculo liso	IA4	1:300	Dako
CD34	Qbend/10	1:100	Dako
CD31	JC/70A	1:10	Dako
Podoplanina	Policlonal	1:200	Acris
Prox- 1	Policlonal	1:200	Relia Tech
LYVE-1	Policlonal	1:200	BmT
D2-40	D2-40	1:100	Dako

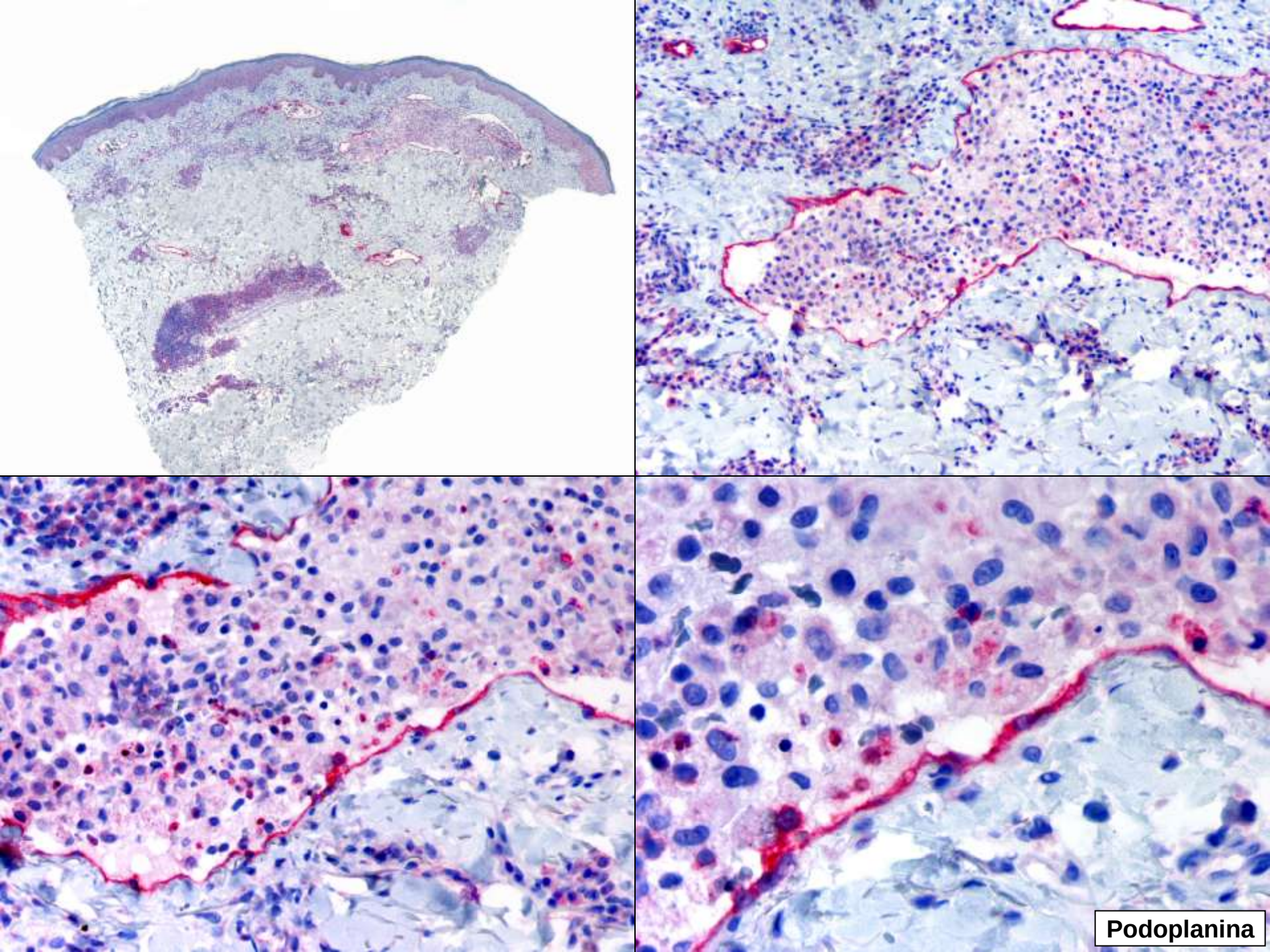

CD31

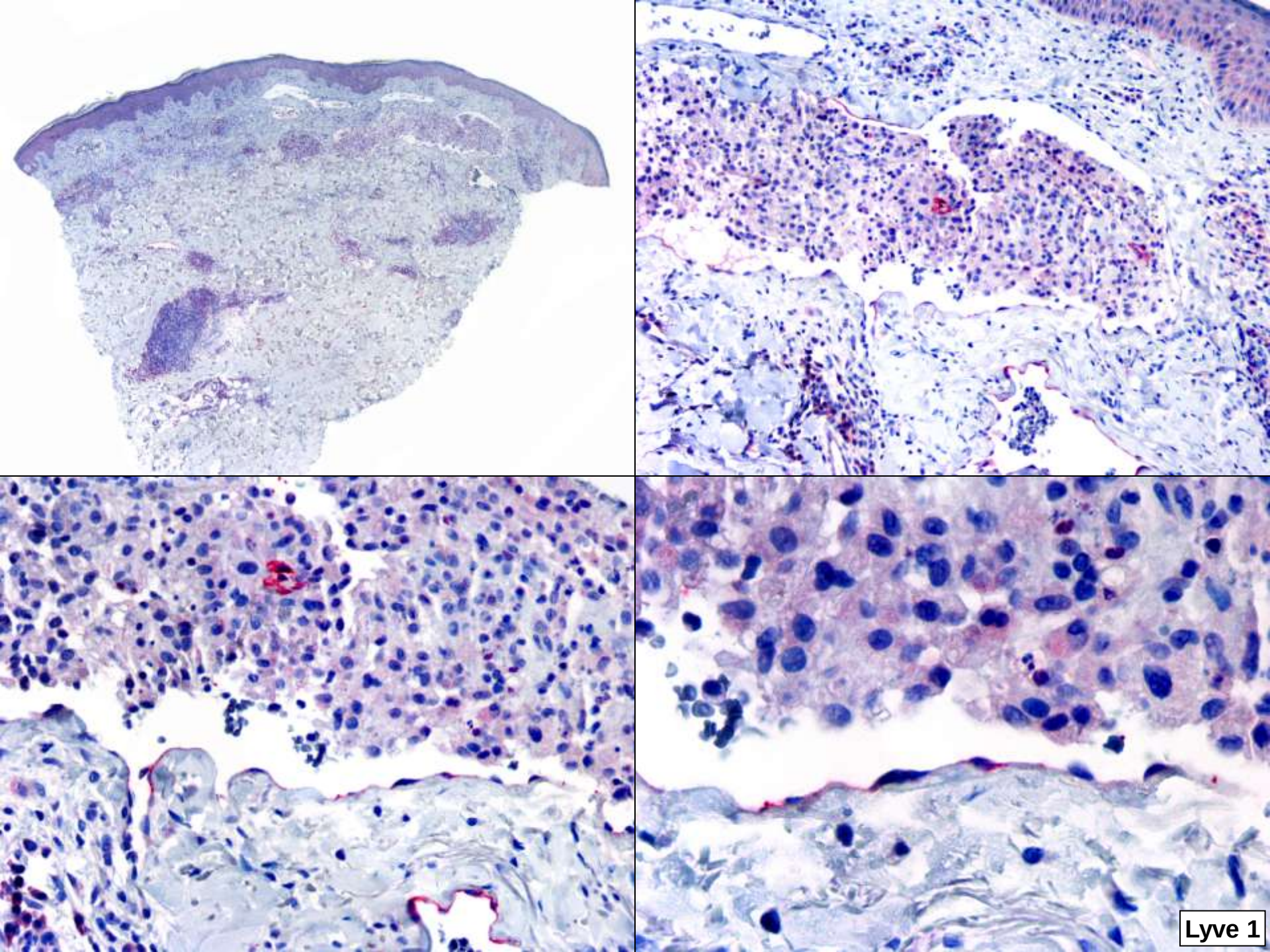
The American Journal of Surgical Pathology *25(9): 1167–1173, 2001*

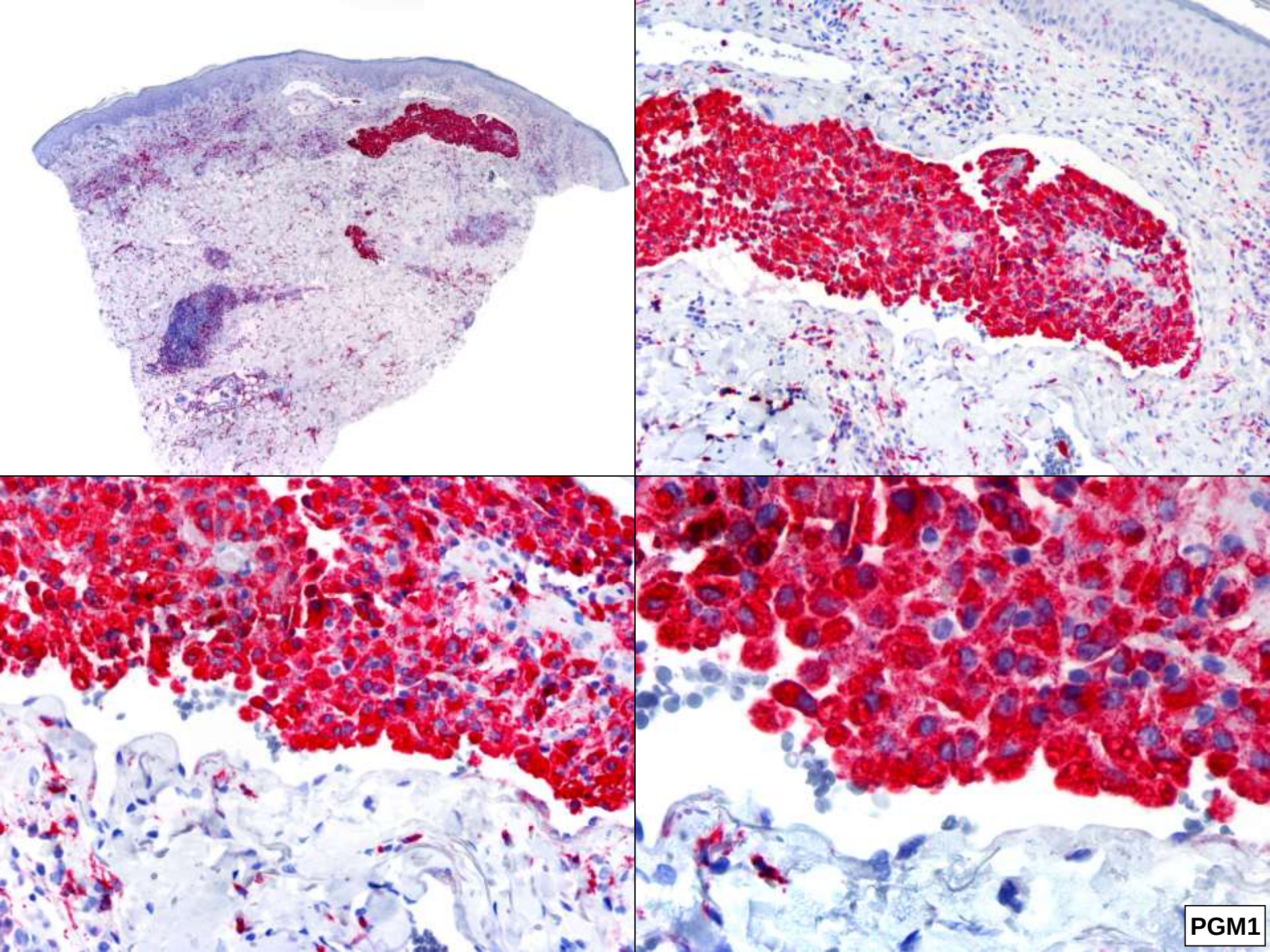
CD31 Expression in Intratumoral Macrophages

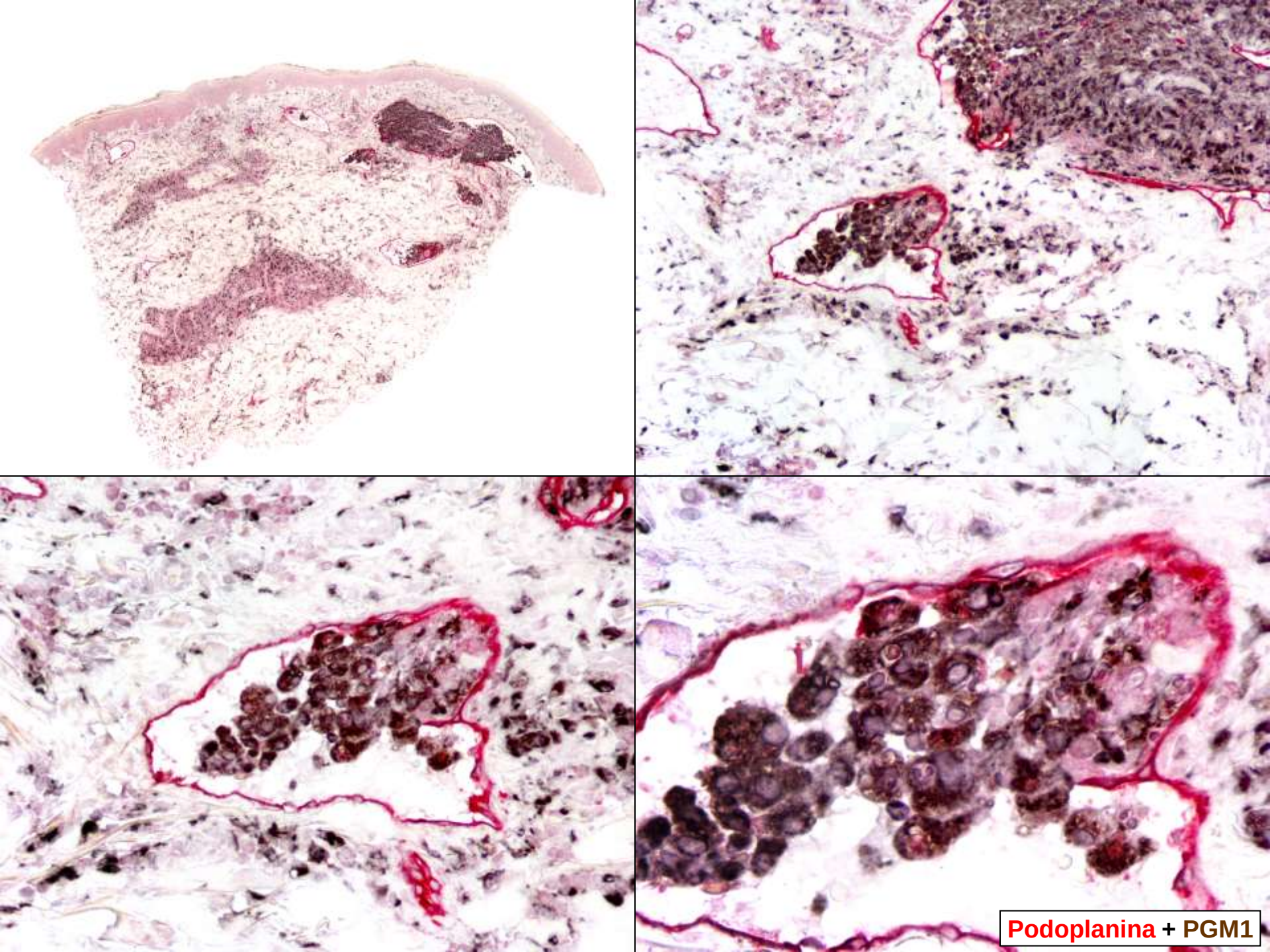
A Potential Diagnostic Pitfall

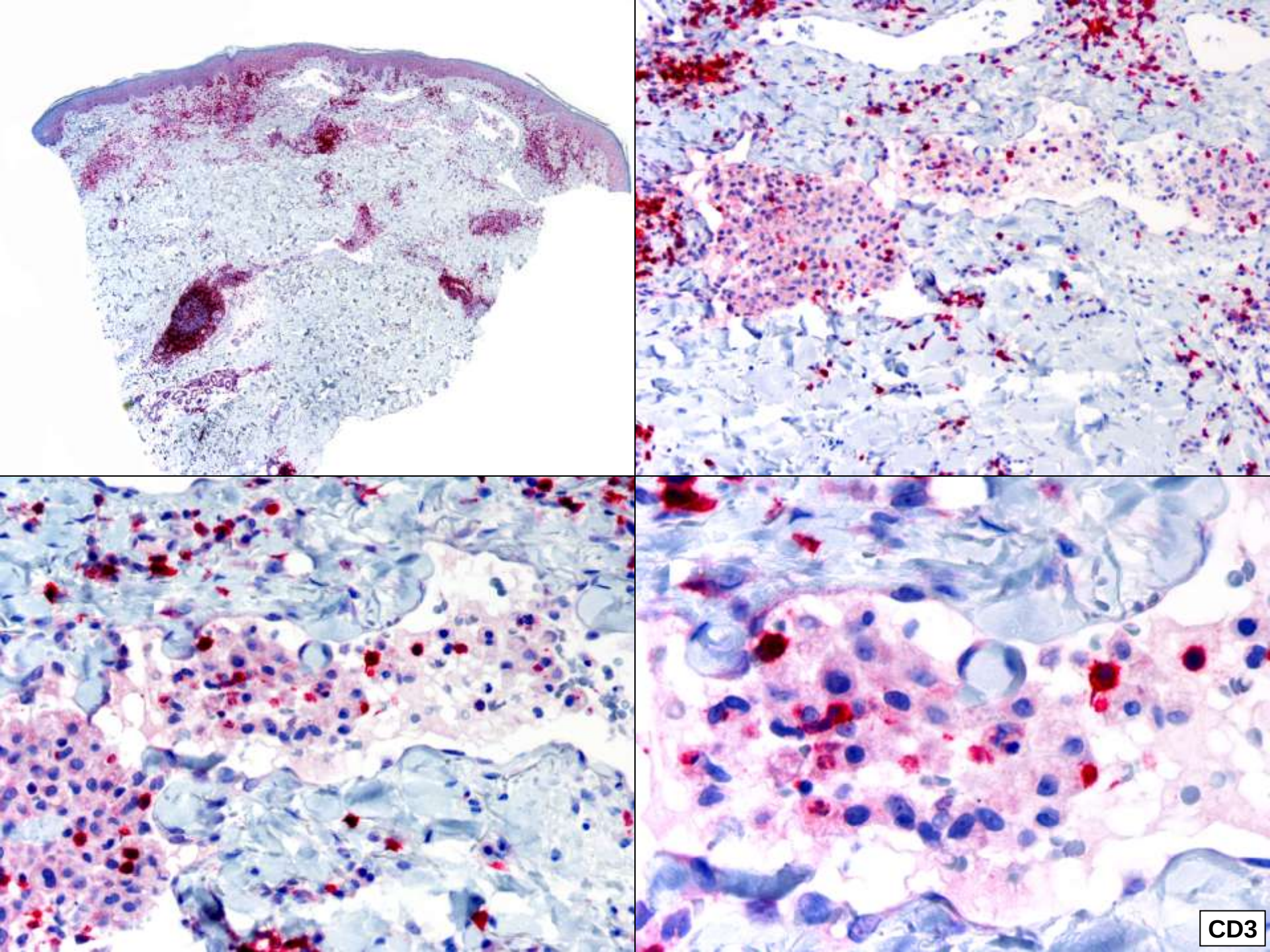
Jesse K. McKenney, M.D., Sharon W. Weiss, M.D., and
Andrew L. Folpe, M.D.


Podoplanina


Lyve 1


PGM1


Podoplanina + PGM1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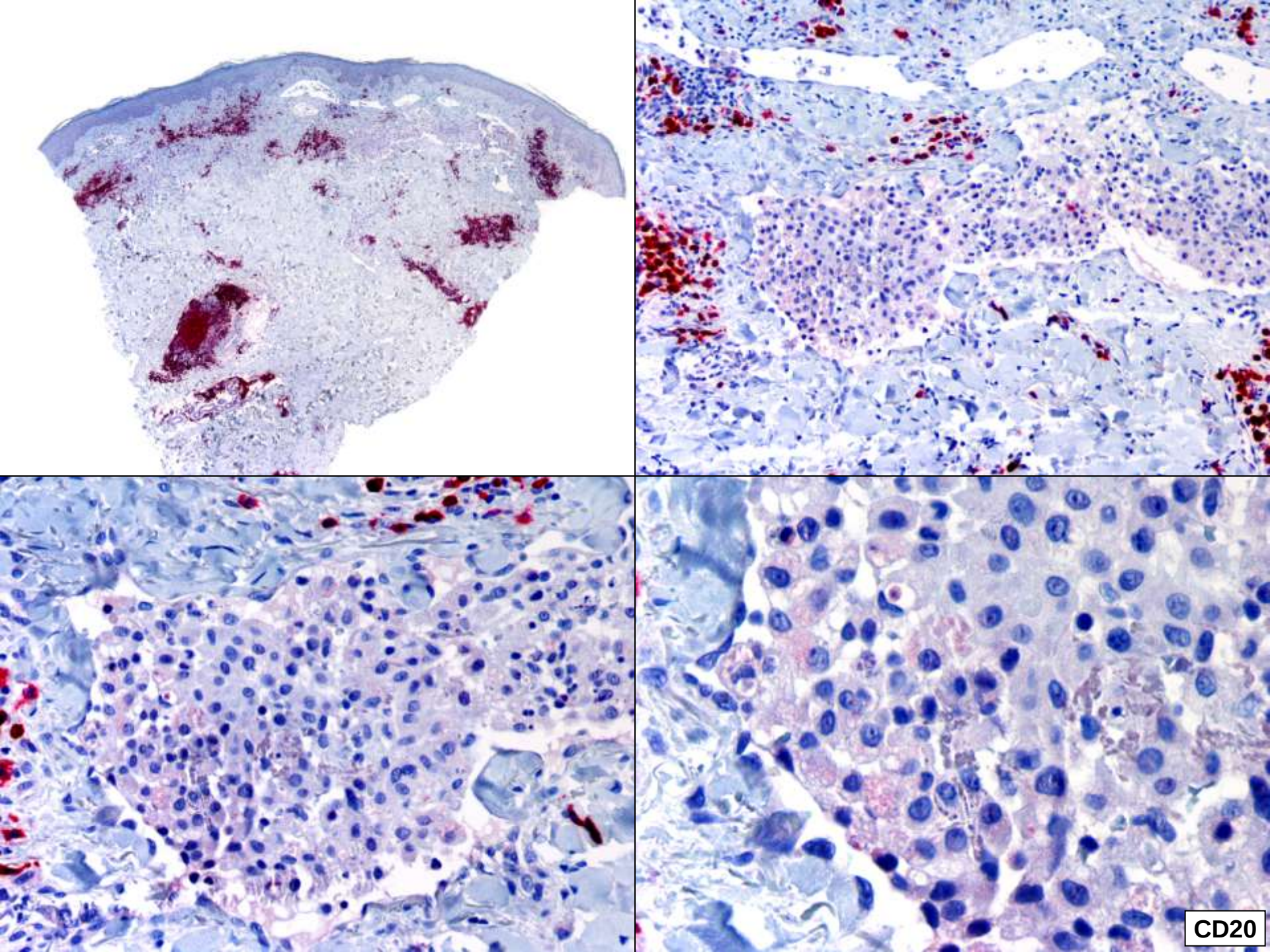
CD20

British Journal of Dermatology 1999; **140**: 497–504.

Reactive angioendotheliomatosis or intravascular histiocytosis? An immunohistochemical and ultrastructural study in two cases of intravascular histiocytic cell proliferation

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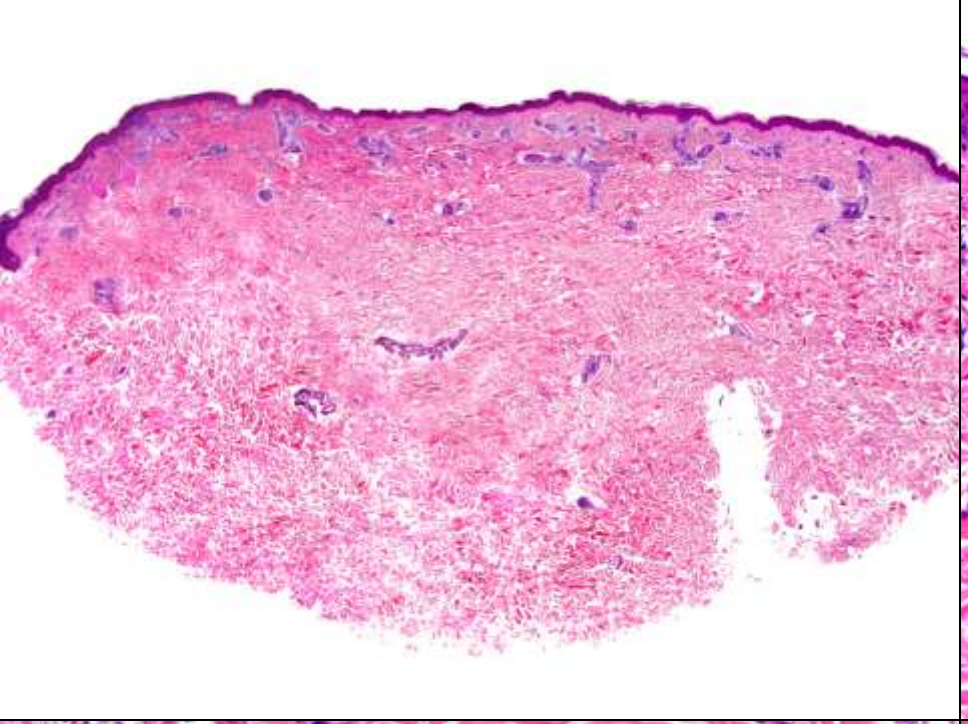
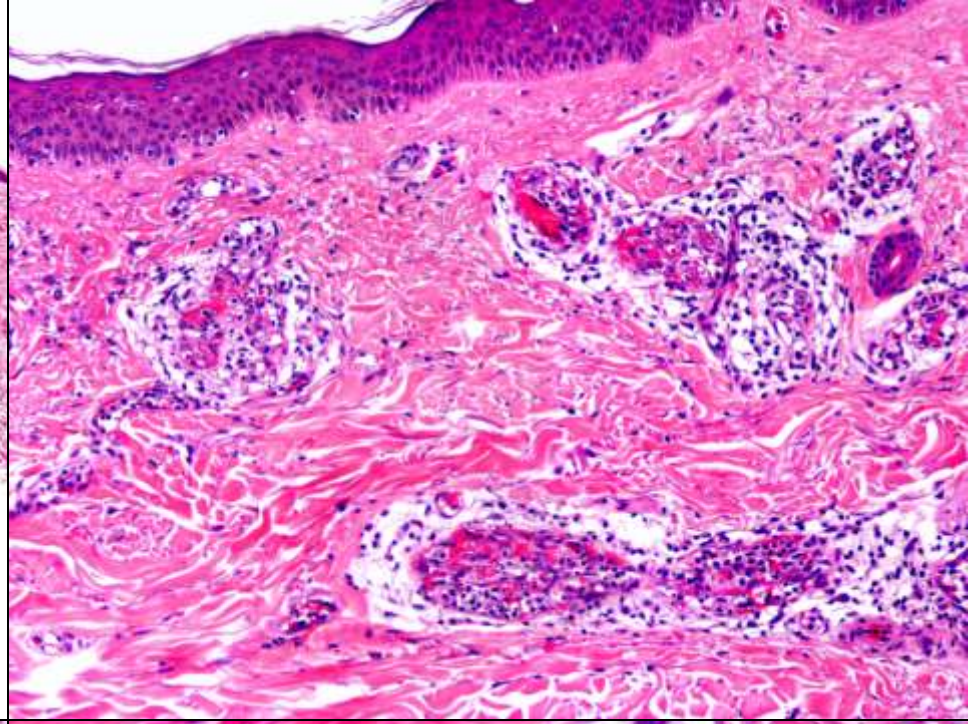
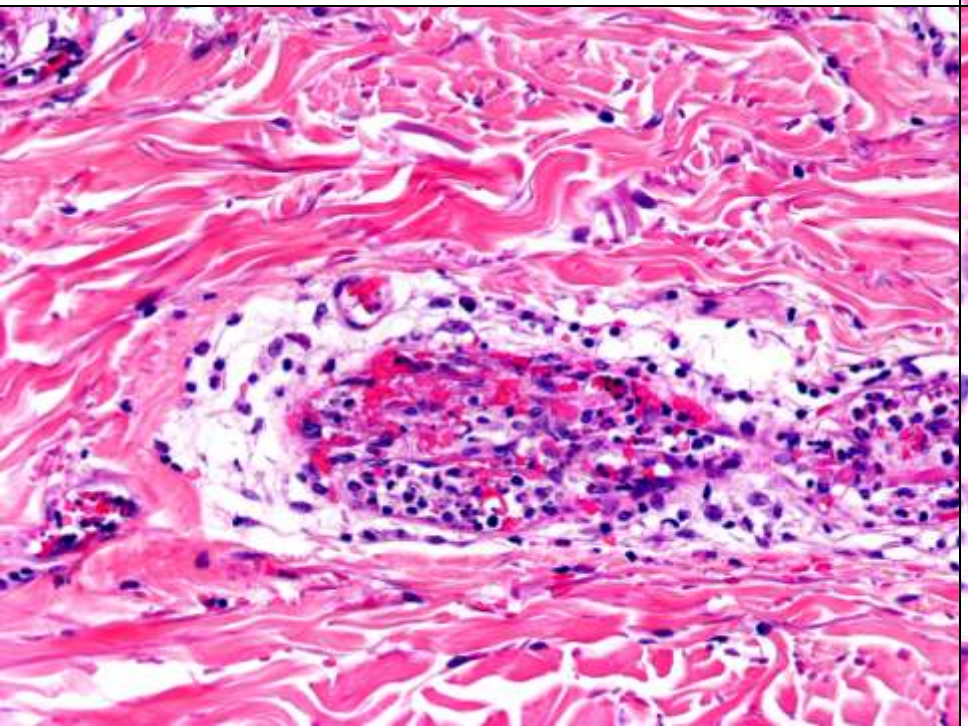
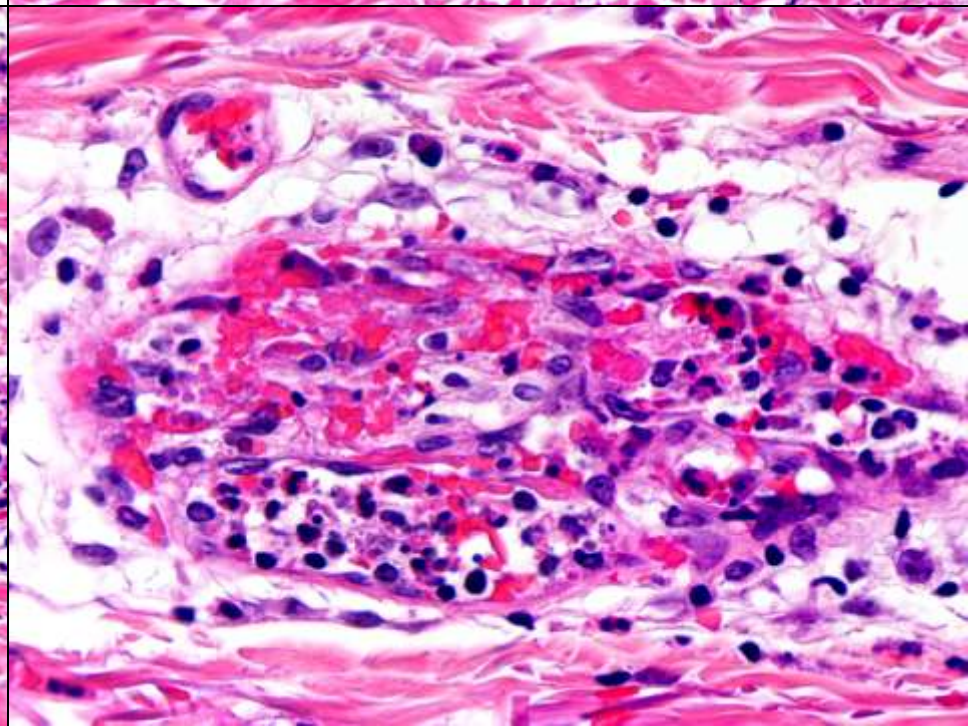
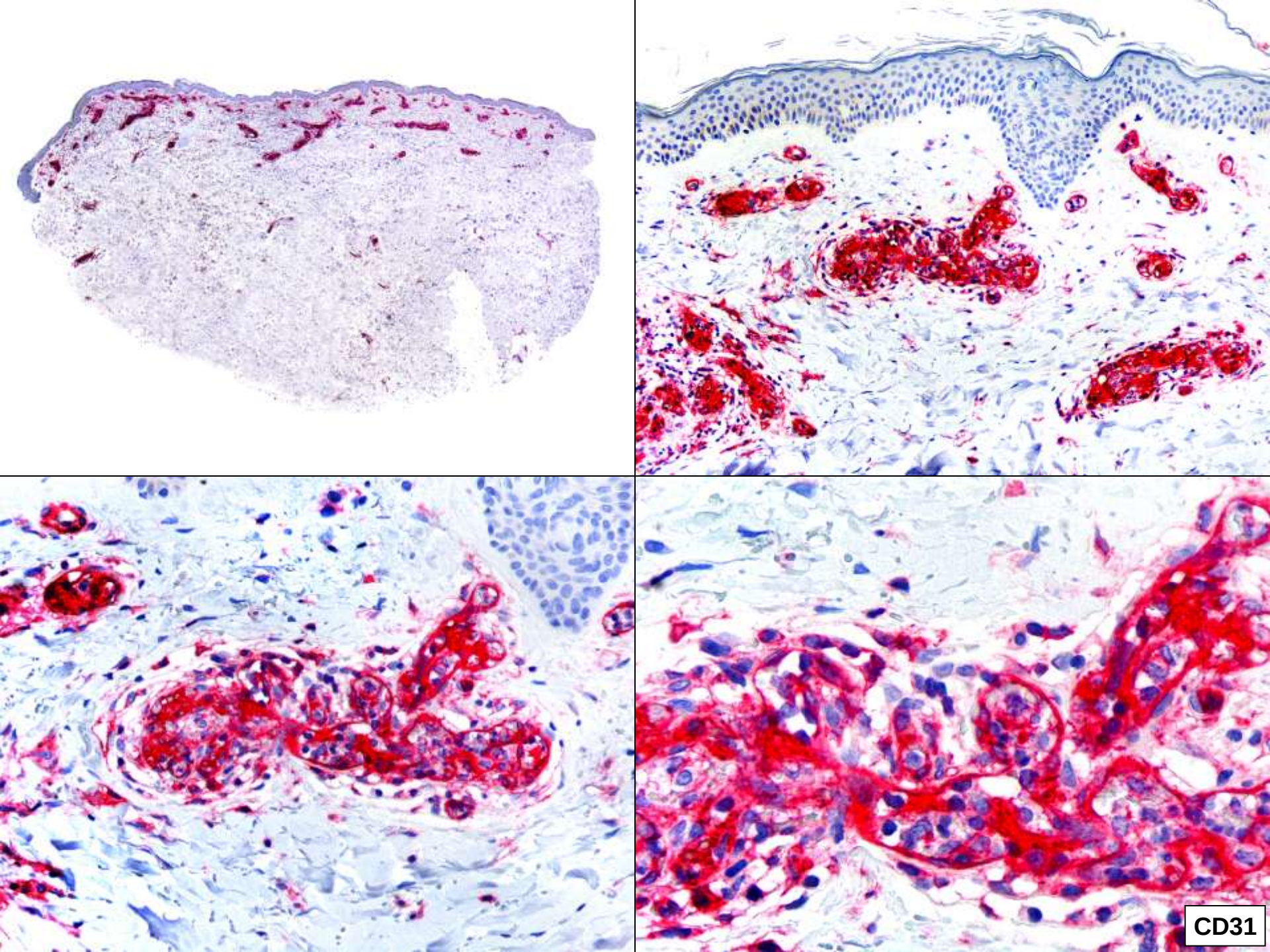
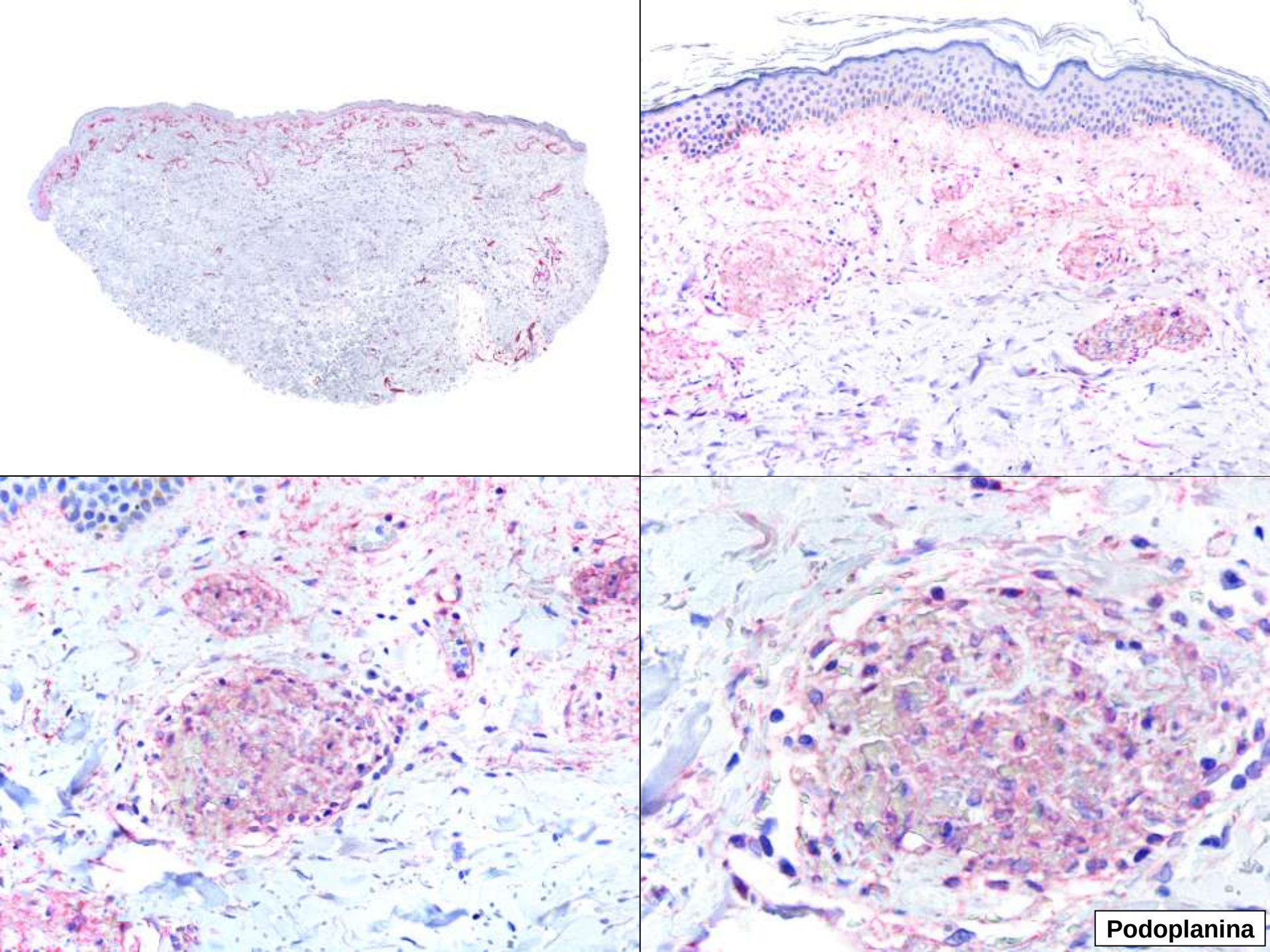
- **Desde el trabajo de Rieger et al., todos los autores han considerado la histiocitosis intravascular como un estadio inicial de la angioendoteliomatosis reactiva intravascular.**
- **Los histiocitos intravasculares aparecerían en las fases iniciales del proceso y posteriormente serían reemplazados por una proliferación intravascular de células endoteliales.**


CD31

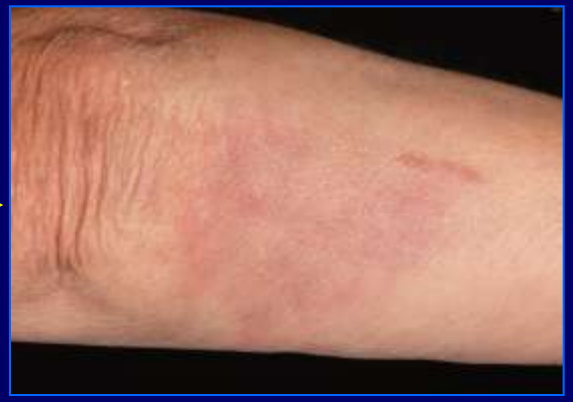

Podoplanina

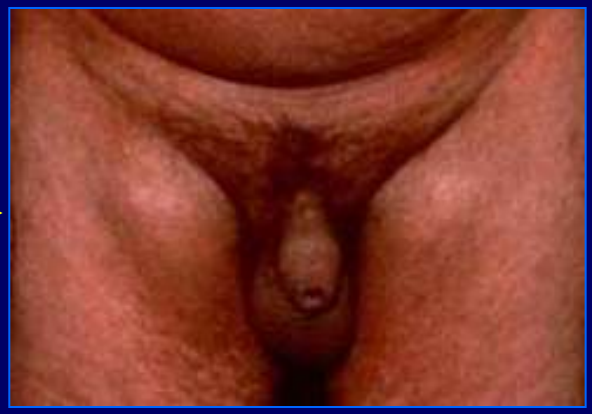
HISTIOCITOSIS INTRALINFÁTICA Y ANGIOENDOTELIOMATOSIS REACTIVA INTRAVASCULAR

- La angioendoteliomatosis reactiva intravascular se desarrolla en vasos sanguíneos.
- La histiocitosis intralinfática se desarrolla en vasos linfáticos.

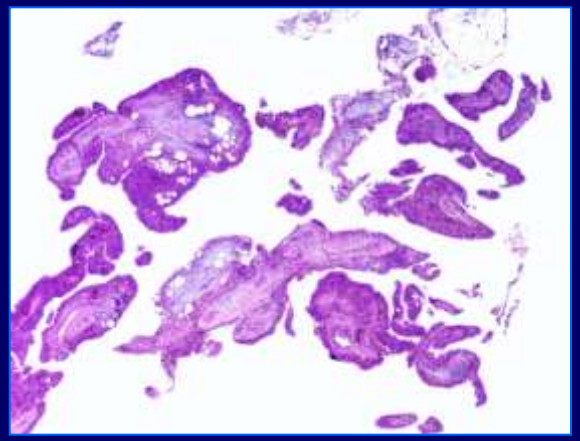
Angioendoteliomatois reactiva intravascular ≠ Histiocitois intralinfática

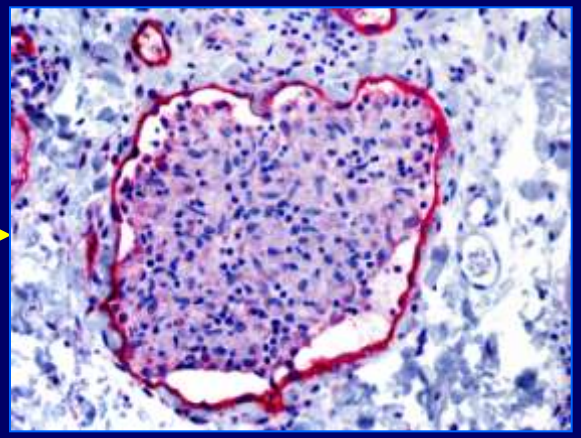
HISTIOCITOSIS INTRALINFÁTICA: PATOGENIA

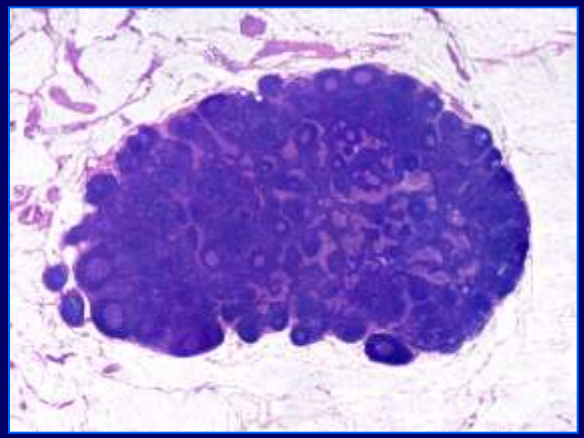




ARTRITIS REUMATOIDE → HISTIOCITOSIS INTRALINFÁTICA → GANGLIOS LINFÁTICOS







Unique Histologic Variants of Cutaneous Kaposi Sarcoma

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Background: Kaposi sarcoma (KS) is a low-grade angioproliferative neoplasm derived from lymphatic endothelium. Lesions progress from early patch stage into plaques that ultimately form tumor nodules. Several histological variants of KS have been described. The aim of this study is to describe 5 new histopathologic variants of cutaneous KS.

Method: Skin biopsy material submitted to a South African dermatopathology practice diagnostic of KS was reviewed. Formalin-fixed, paraffin-embedded tissue was routinely processed and stained with hematoxylin and eosin. Confirmatory immunohistochemical stains included CD31 and latent nuclear antigen-1 (human herpesvirus 8).

Results: All biopsies were procured from HIV-positive patients with a clinical diagnosis of cutaneous KS tumor. Five distinct histologic KS variants, not previously well characterized in the literature, were identified including glomeruloid KS, telangiectatic KS, ecchymotic KS, KS with myoid nodules, and pigmented KS. Tumor cells in all of these variants were immunoreactive for CD31 and latent nuclear antigen-1.

Conclusions: These unique cases highlight the ability of KS to exhibit variable histomorphology. Their clinical significance requires further study. Dermatopathologists should be aware of these newly described variants to avoid the potential for their misdiagnosis.

Key Words: AIDS, HIV, Kaposi sarcoma, pathology, skin, variant

(*Am J Dermatopathol* 2010;32:244–250)

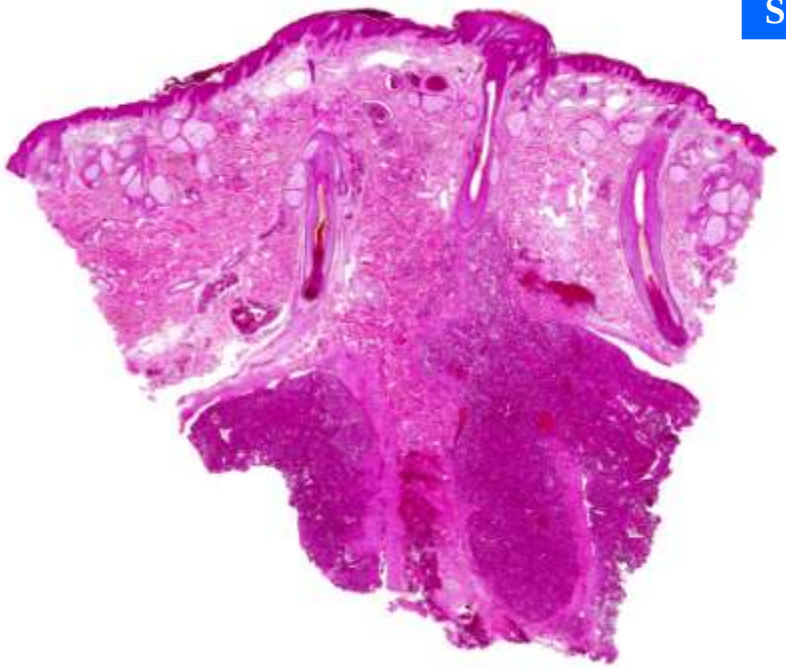
be problematic for the histopathologist. Fortunately, the availability of immunohistochemical stains, such as latent nuclear antigen-1 (LNA-1), for identifying latent HHV8 infection within KS lesional cells serves as a valuable diagnostic tool.[5] The detection of LNA-1 has proved diagnostically helpful in recognizing some KS variants.[6]

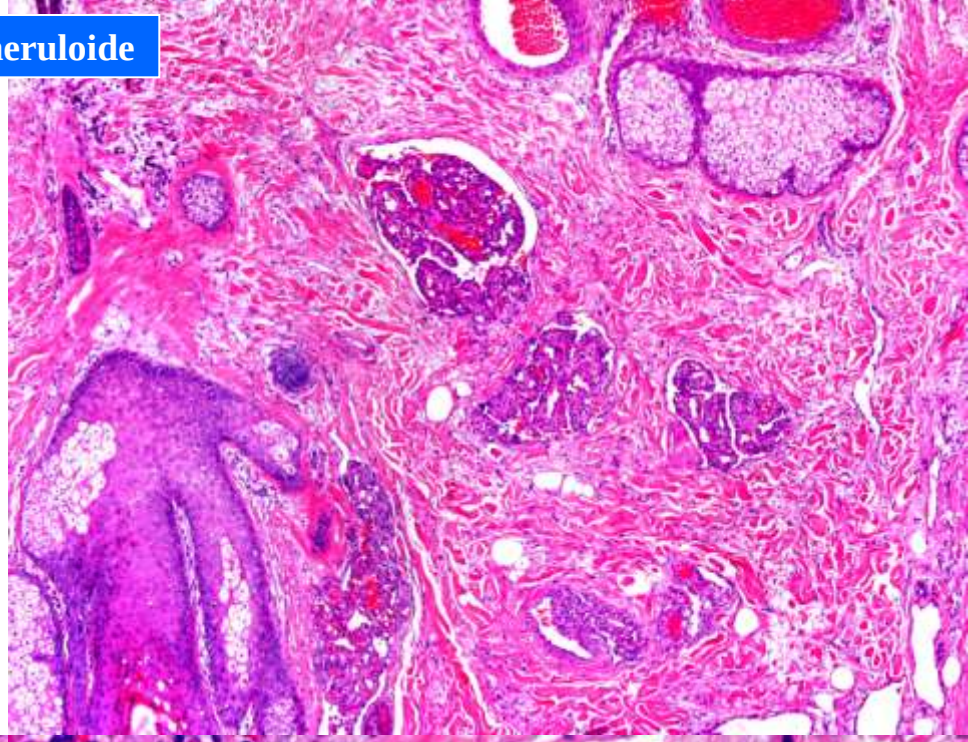
Recently, there have been reports suggesting a much broader spectrum of cutaneous KS, and as a result many clinical and/or histologic variants of KS have been described in the literature. Previously described KS variants include anaplastic (pleomorphic) KS, several lymphedematous variants (lymphangioma-like, lymphangiectactic, and bullous KS), and hyperkeratotic (verrucous), keloidal, micronodular, pyogenic granuloma-like, and intravascular KS.[7–10] An in situ form of KS has been described,[11] and the histopathology of involuting KS lesions as a result of treatment-related regression has also been documented.[12] Herein, we describe 5 unique histologic variants of cutaneous KS.

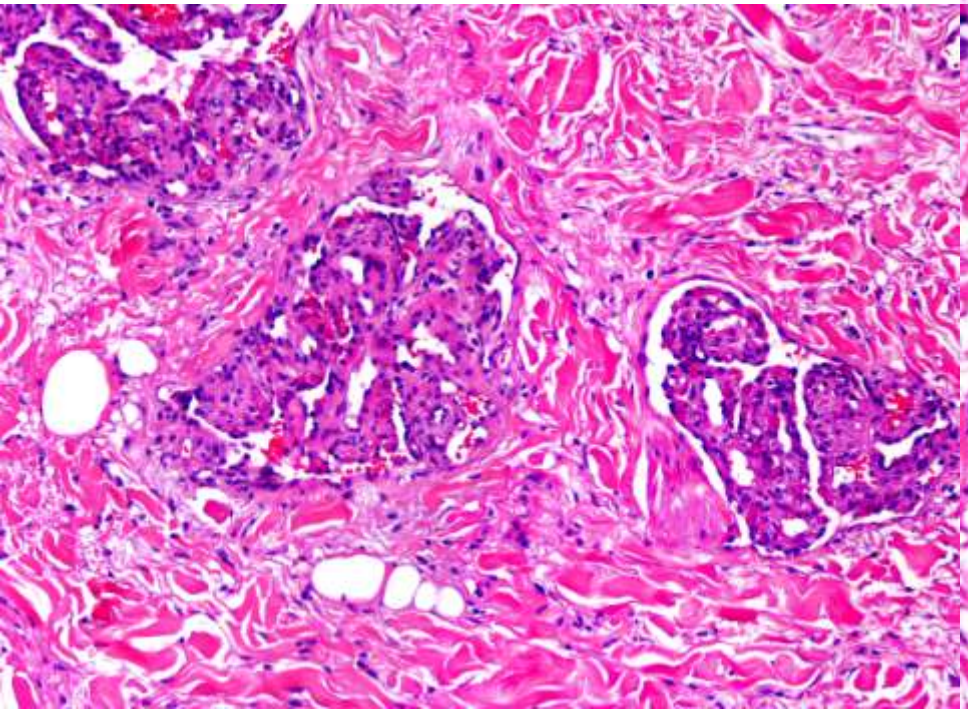
METHODS

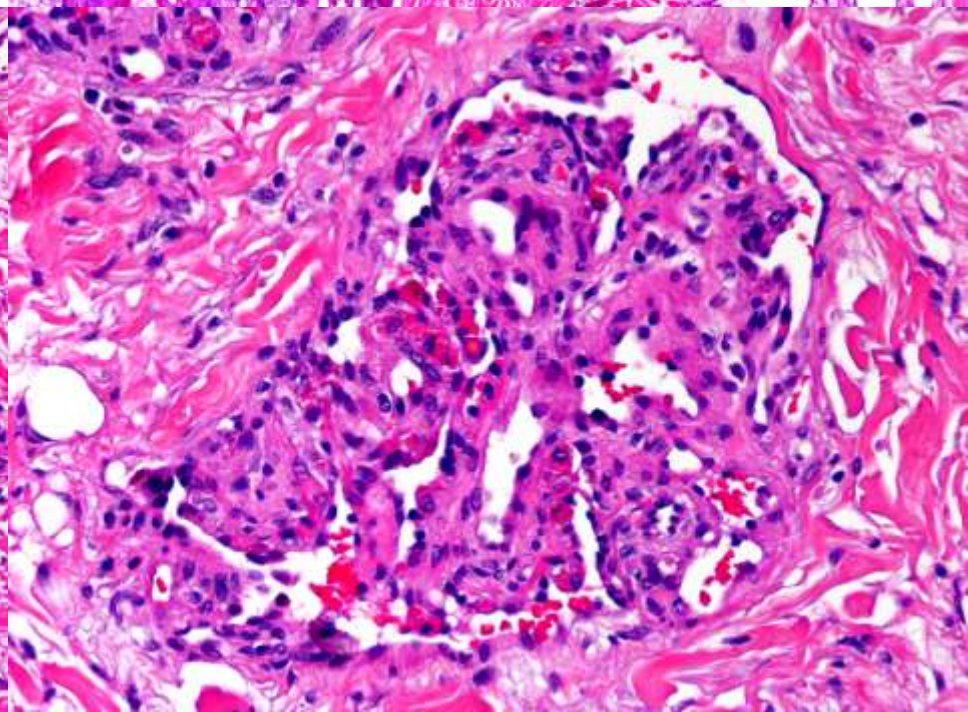
Skin biopsy material submitted to the Division of Anatomical Pathology, National Health Laboratory Service and the University of the Witwatersrand, Johannesburg, South Africa, that were all clinically diagnostic of AIDS-associated KS was reviewed. Formalin-fixed, paraffin-embedded tissue was routinely processed and stained with hematoxylin and eosin (H&E). Histochemical stains for hemosiderin (iron–Prussian blue) and melanin (Fontana Masson) were performed in one

SK glomeruloide

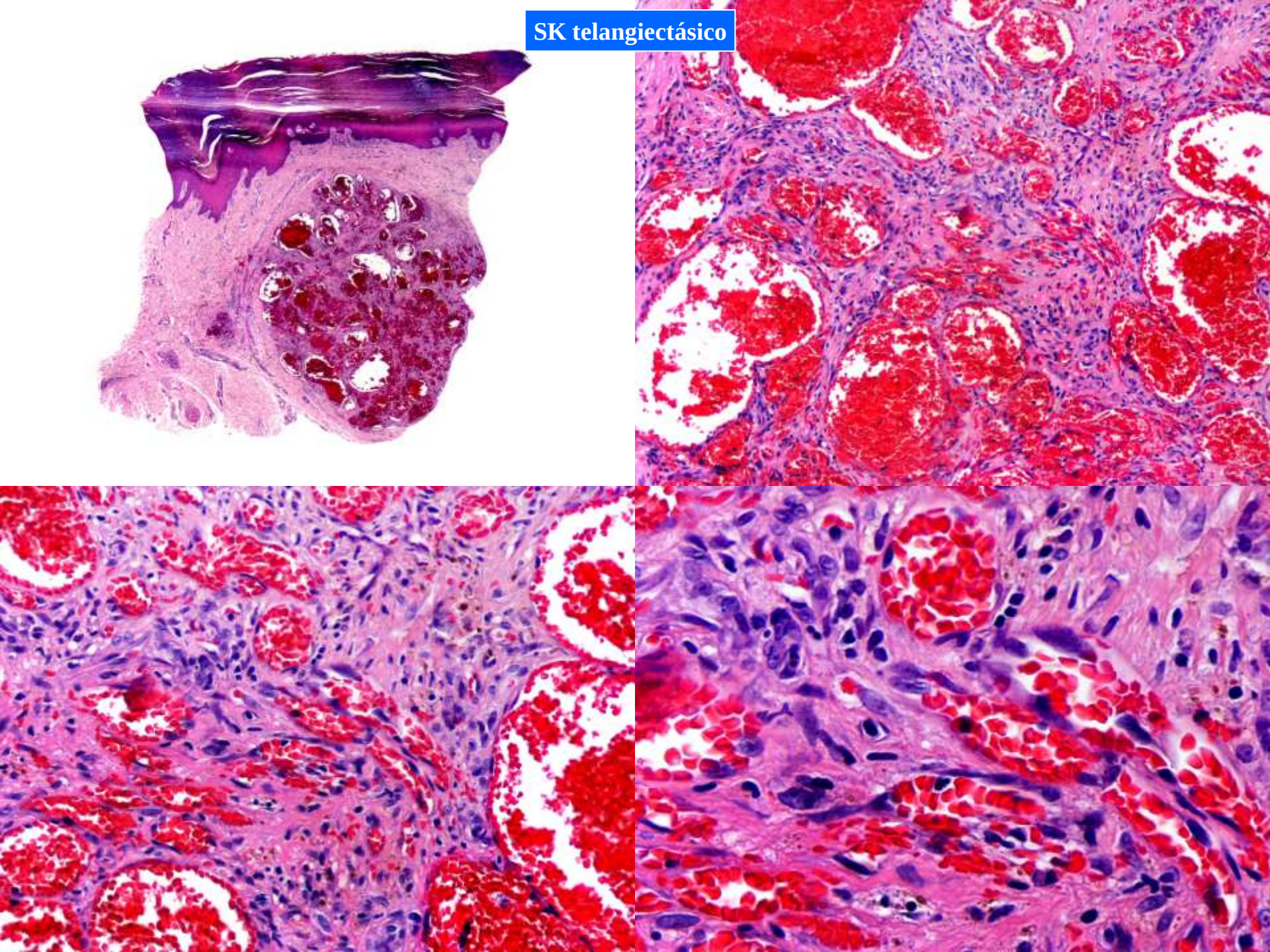




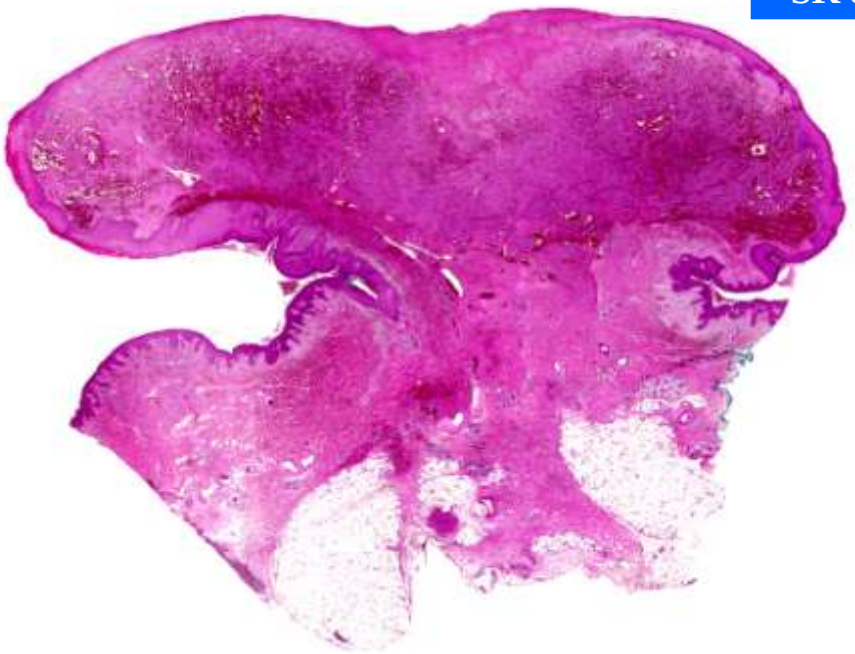


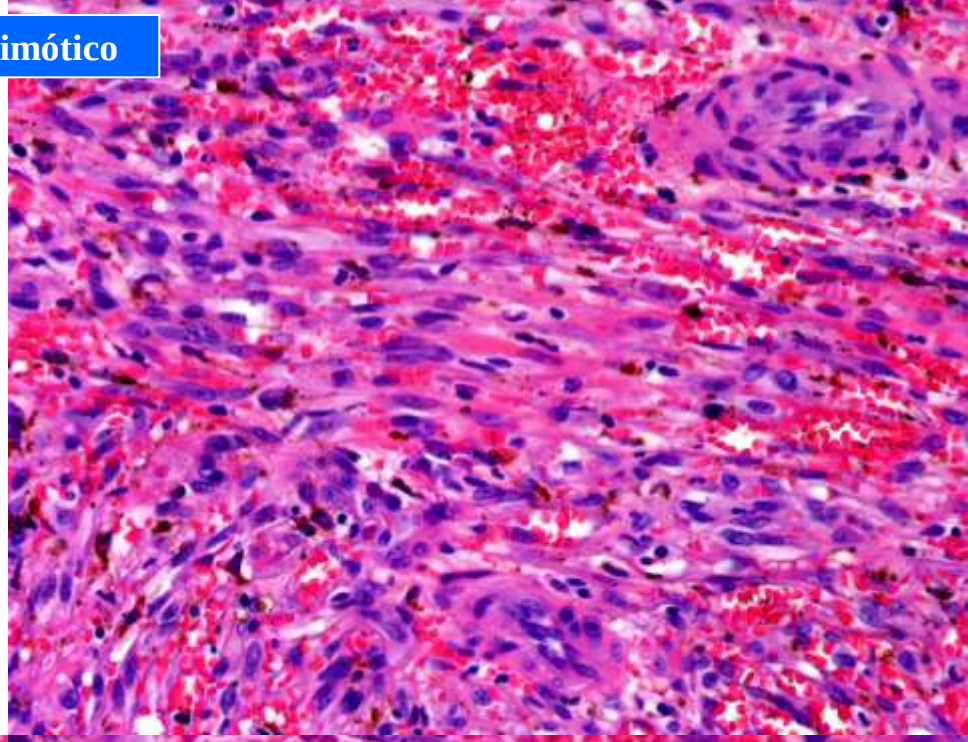


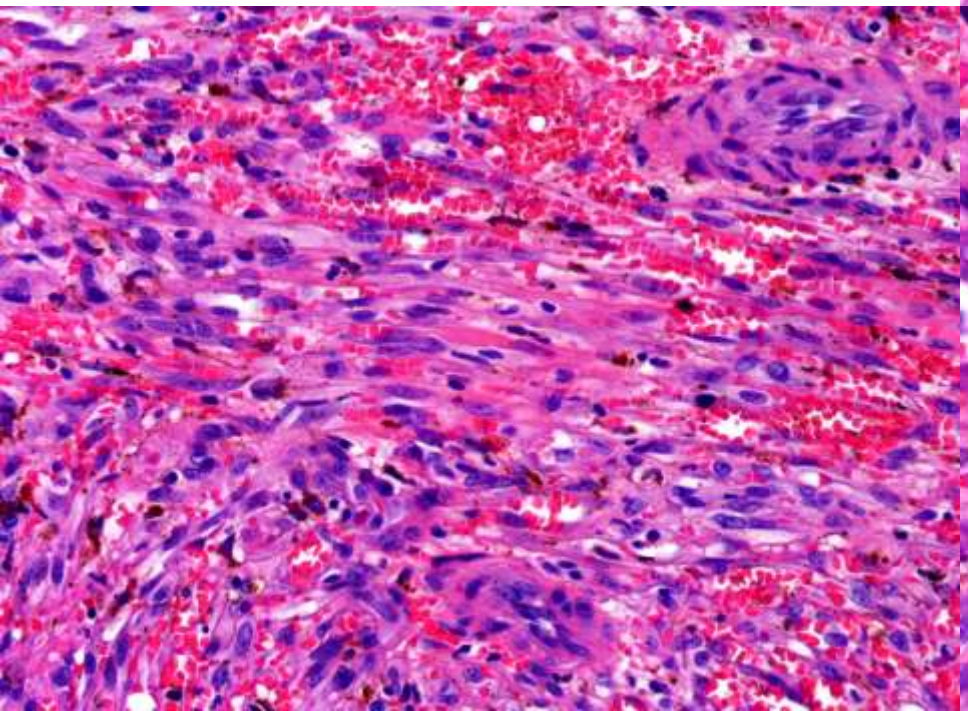
SK telangiectásico

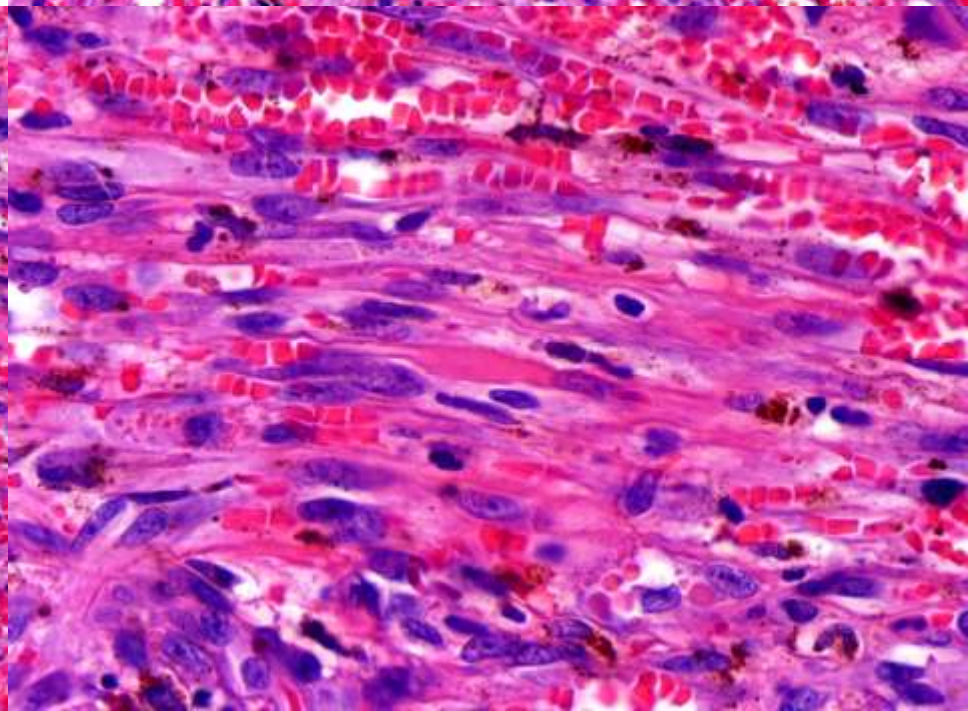


SK equimótico

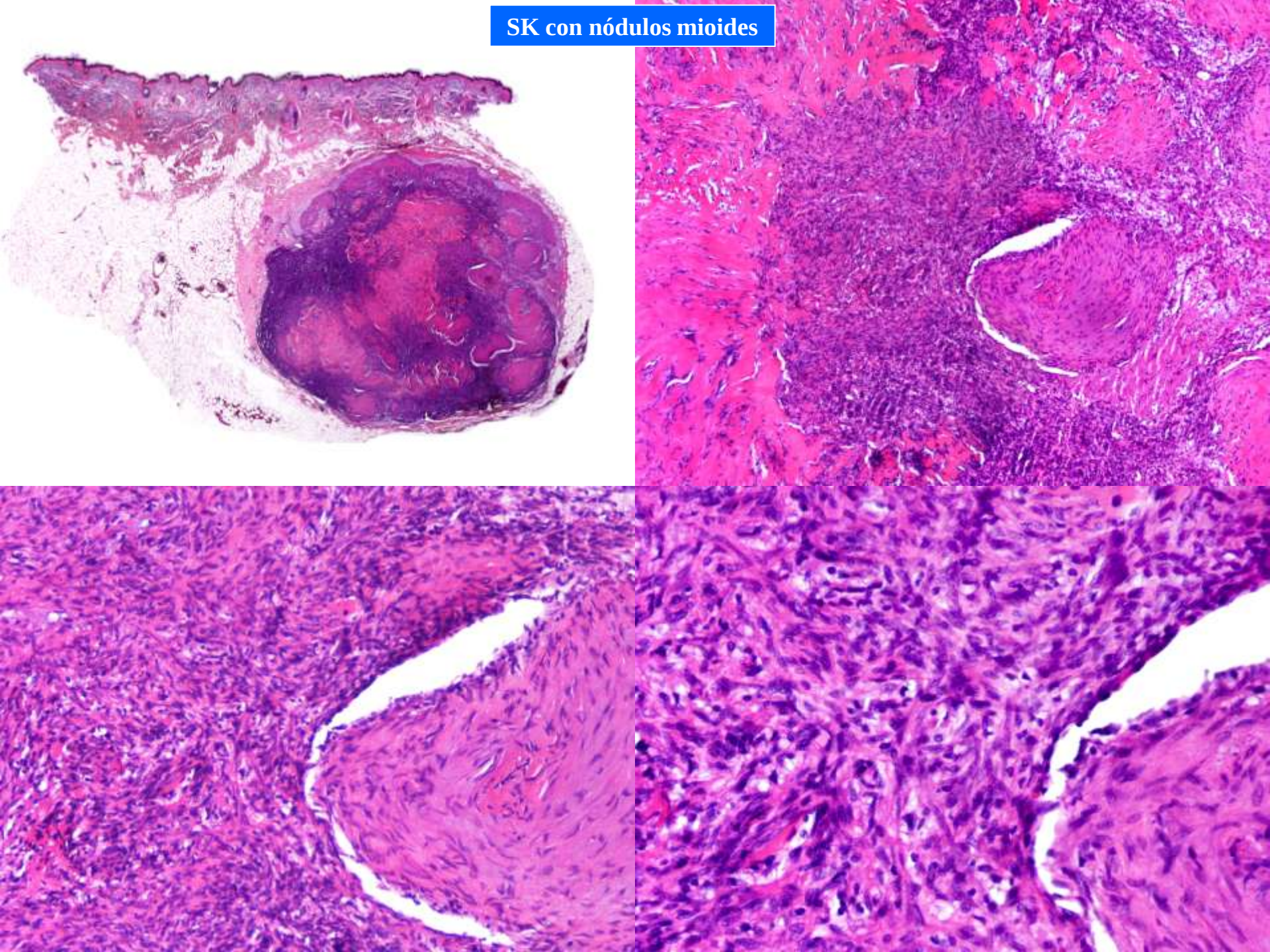








SK con nódulos mioides



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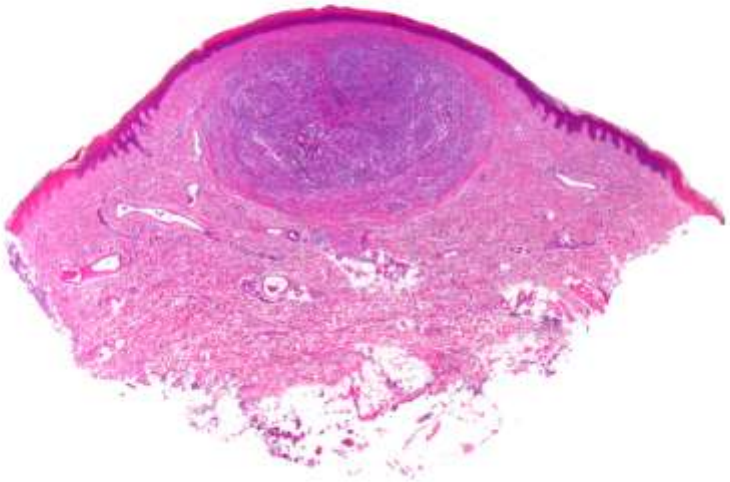

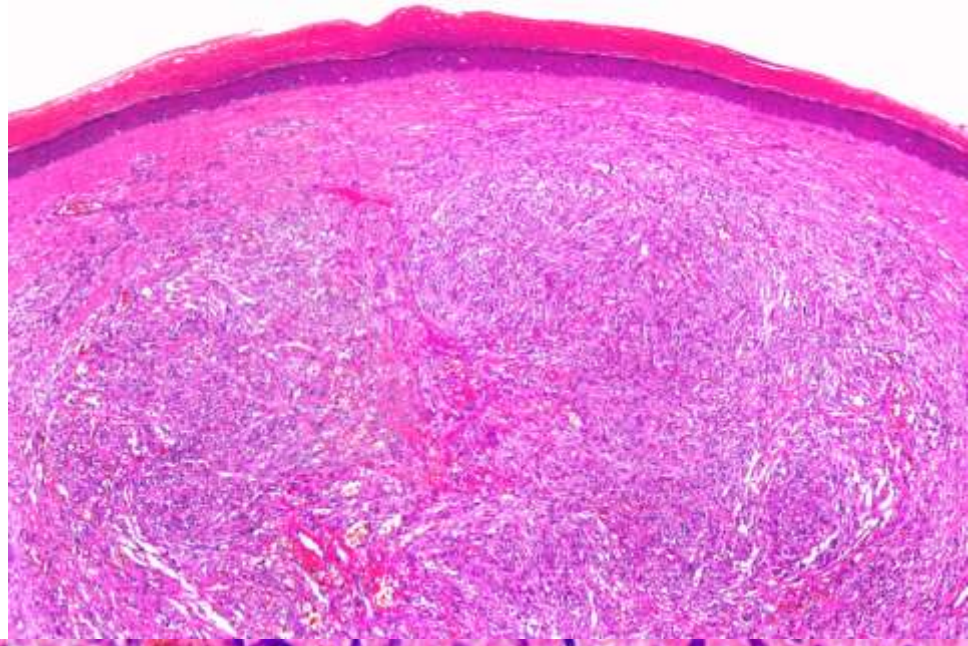

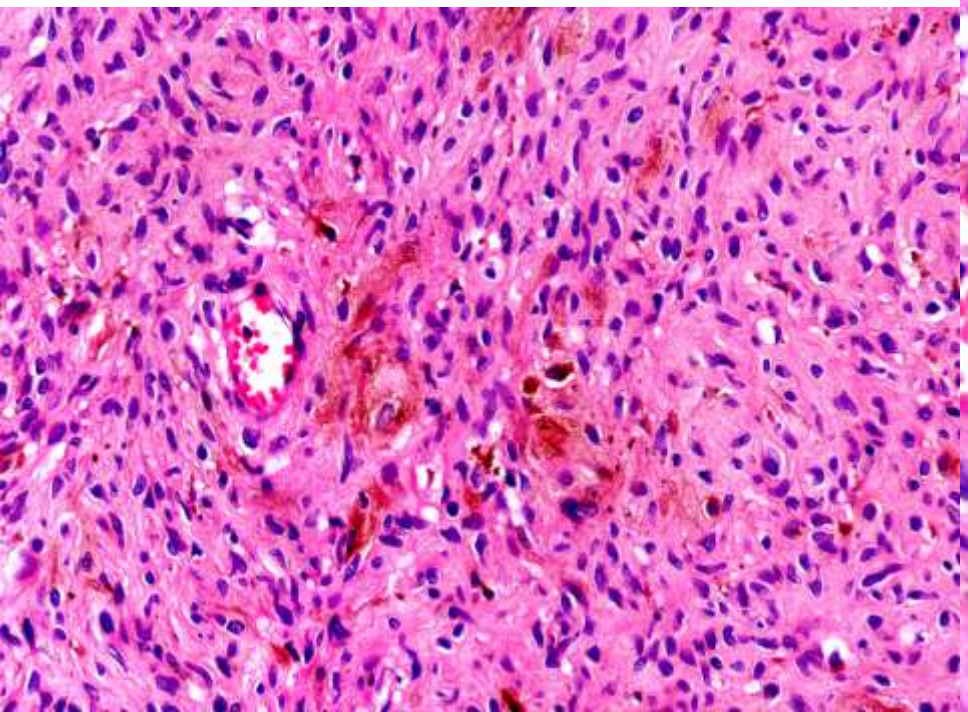

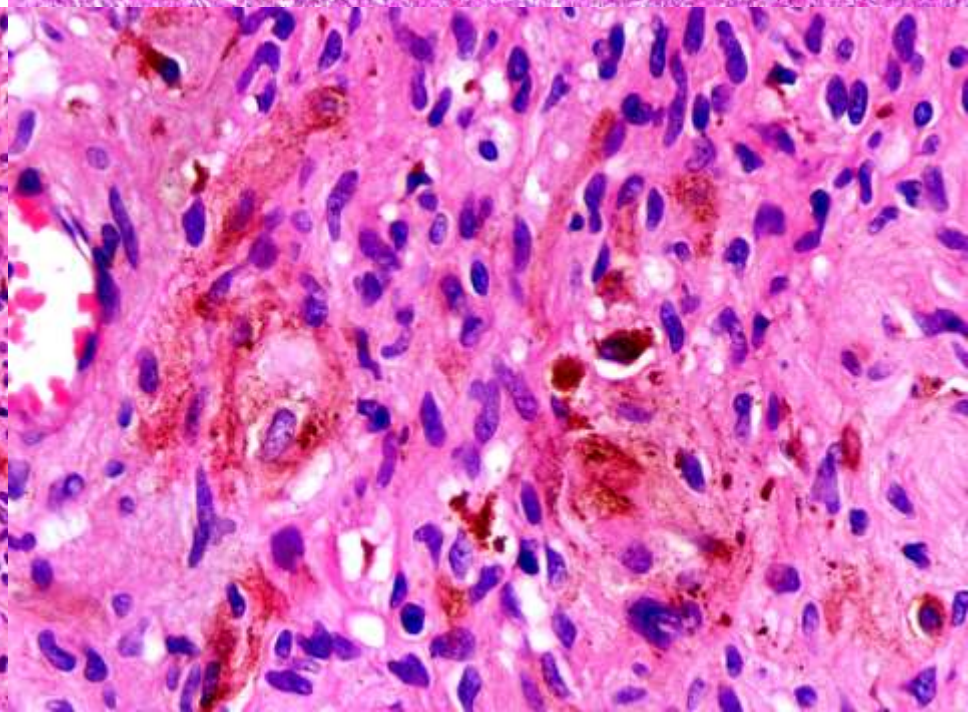

O´Donnell PJ et al. Unique histologic variants of cutaneous Kaposi sarcoma. Am J Dermatopathol 2010;32:244-50.

- **Cinco nuevas variantes histopatológicas de sarcoma de Kaposi asociado a SIDA:**
  - **Glomeruloide: Areas de vasos con patrón glomeruoide en la vecindad de sarcoma de Kaposi nodular clásico.**
  - **Telangiectásico: Vasos dilatados y congestivos**
  - **Equimótico: Gran cantidad de hematíes extravasados**
  - **Con nódulos mioides: Nódulos mioides en el espesor de sarcoma de Kaposi nodular**
  - **Pigmentado: Células dendríticas S100 positivas con pigmento melánico (Fontana-Masson positivo y azul de Perls negativo).**
- **El diagnóstico en todos los caso fue confirmado inmunohistoquímicamente por la positividad del CD31 en las células neoplásicas y por la intensa positividad de la proteína LNA-1 del HHV8.**

Pseudomyogenic Hemangioendothelioma: A Distinctive, Often Multicentric Tumor With Indolent Behavior

Jason L. Hornick, MD, PhD and Christopher D.M. Fletcher, MD, FRCPath

Abstract: A 1992 report described 5 keratin-positive spindle cell neoplasms with multifocal presentation in a single limb, which were proposed at that time to be a variant of epithelioid sarcoma. This tumor type is not widely recognized and is incompletely characterized. We examined 50 cases of this distinctive tumor to evaluate histologic, immunophenotypic, and clinical features. There was a 4.6:1 male predominance (mean age, 31 y; 82% ≤40 y). Half of the patients presented with painful nodules and the other half with painless nodules. Mean tumor size was 1.9 cm (range, 0.3 to 5.5 cm). Tumors arose in the lower limb (54%), the upper limb (24%), trunk (18%), or head and neck (4%). Thirty-three (66%) were multifocal lesions (ranging from 2 to 15 lesions), including 32 cases with involvement of multiple tissue planes. Of 205 total lesions, 64 (31%) involved the dermis, 42 (20%) involved the subcutis, 70 (34%) lesions involved muscle, and 29 (14%) lesions involved bone; all the lesions had infiltrative margins. The tumors were composed of loose fascicles and sheets of plump spindle cells with vesicular nuclei, variably prominent nucleoli, and abundant brightly eosinophilic cytoplasm, some with a strikingly rhabdomyoblast-like appearance. In all cases, a minority of cells were epithelioid. Twenty-seven tumors contained a prominent neutrophilic inflammatory infiltrate. Most tumors showed only mild nuclear atypia; 6 tumors contained foci of notably pleomorphic cells. The median mitotic rate was 1 per 10 HPF (range, 1 to 10). Seven tumors showed vascular invasion; 7 tumors had areas of necrosis. By immunohistochemistry, all tumors were diffusely positive for AE1/AE3 and FLI1; 22 of 47 tumors were variably positive for CD31. Focal positivity was seen for CAM5.2 (21 of 35), smooth muscle actin (14 of 42), epithelial membrane antigen (7 of 49 weak), and PAN-K (MNF116) (1 of 47). All were negative for CD34, desmin, and S100 protein and showed intact INI1 expression. Follow-up was available for 31 patients and ranged from 9 months to 17 years (mean, 4 y). Most lesions were treated by local excision. Eighteen (58%) patients had local recurrence or developed additional nodules in the same region, all but one, within 1 year of first presentation. Eight patients had postoperative radiation therapy and 6 patients had chemotherapy. Four patients had amputations for multifocal disease. One patient had a regional lymph node metastasis, and, thus far, only 1 patient has developed distant metastases (disseminated), 16 years after primary tumor excision. At the time of the last follow-up, 27 patients were alive with no evidence of the disease, 1 patient was alive with unknown disease status, 2 patients were alive with recurrent disease, and 1 patient died of the disease. In summary, we describe a distinctive type of rarely metastasizing ("intermediate") tumor affecting mainly young men and usually characterized by multifocality in different tissue planes of a limb. Although sharing some features with epithelioid sarcoma (skin/soft tissue of distal extremities, young adults, keratin positive), it differs by having predominantly myoid-appearing spindle cell morphology, expression of FLI1, common reactivity for CD31, lack of epithelial membrane antigen, CD34, and PAN-K expression, and intact INI1. The overall immunophenotypic findings favor endothelial differentiation. Despite the ominous presentation, follow-up thus far suggests an indolent clinical course with a small risk of distant metastasis. Although the precise nosologic status of this tumor type is uncertain, we propose the interim designation "pseudomyogenic hemangioendothelioma."

Key Words: hemangioendothelioma, epithelioid sarcoma, soft tissue tumor

(*Am J Surg Pathol* 2011;35:190–201)

In 1992, Mirra et al[17] described 5 seemingly distinctive soft tissue tumors characterized by multifocal presentation in a single limb, often including osseous involvement, consisting of bland keratin-positive spindle cells with "fibrohistiocytic" or "myoid" cytomorphology. The investigators proposed that this tumor type was a variant of epithelioid sarcoma (the "fibroma-like" variant). No clinicopathologic series describing this tumor has been published until now. This tumor type is not widely recognized and its features are incompletely characterized. Furthermore, its relationship with epithelioid sarcoma remains uncertain.

In the mid-1990s, we began to recognize a group of tumors with distinctive histologic features and clinical presentation, which, over time, we realized were likely related to (or the same as) the tumors reported by Mirra et al.[17] We presented preliminary data with regard to such lesions, under the rubric "pseudomyogenic (fibroma-like) variant of epithelioid sarcoma"[10] at the United States and Canadian Academy of Pathology meeting in Denver, Colorado in March 2008. Since that time, after accruing

From the Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Presented in part at the 97th annual meeting of the United States and Canadian Academy of Pathology in Denver, CO, March 1 to 7, 2008.

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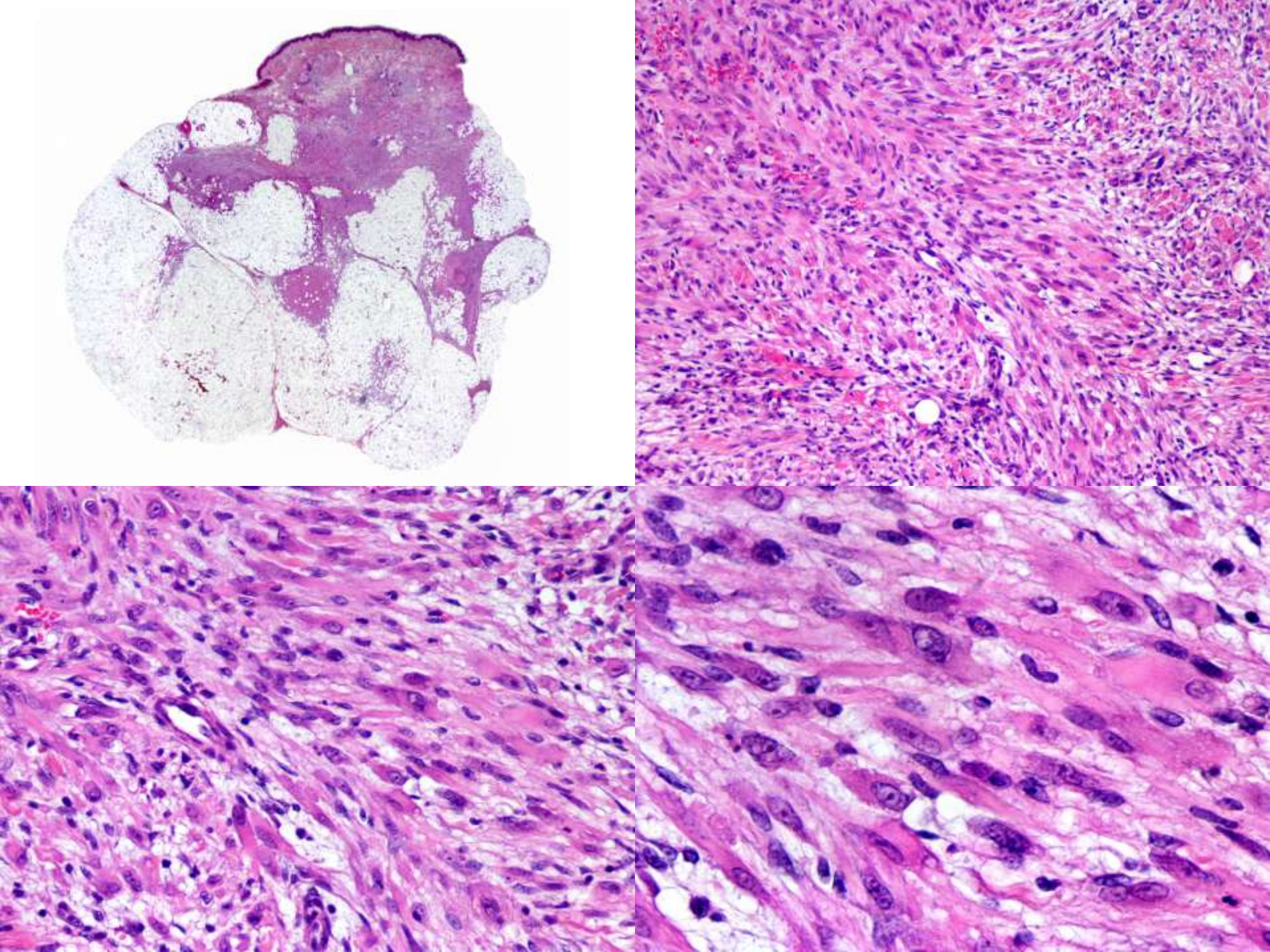

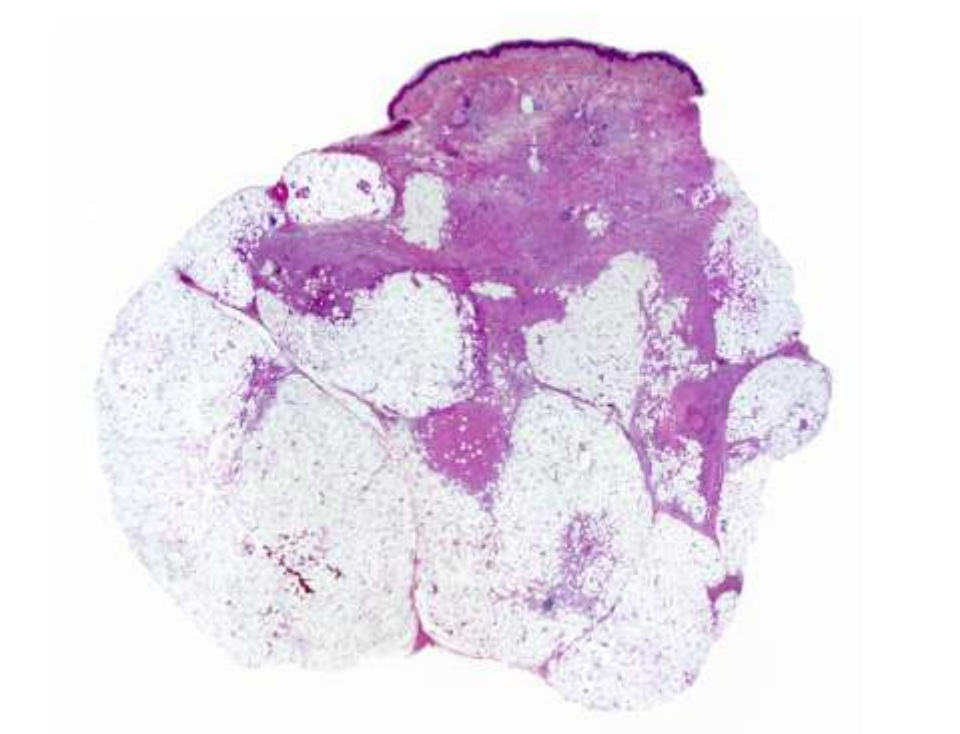
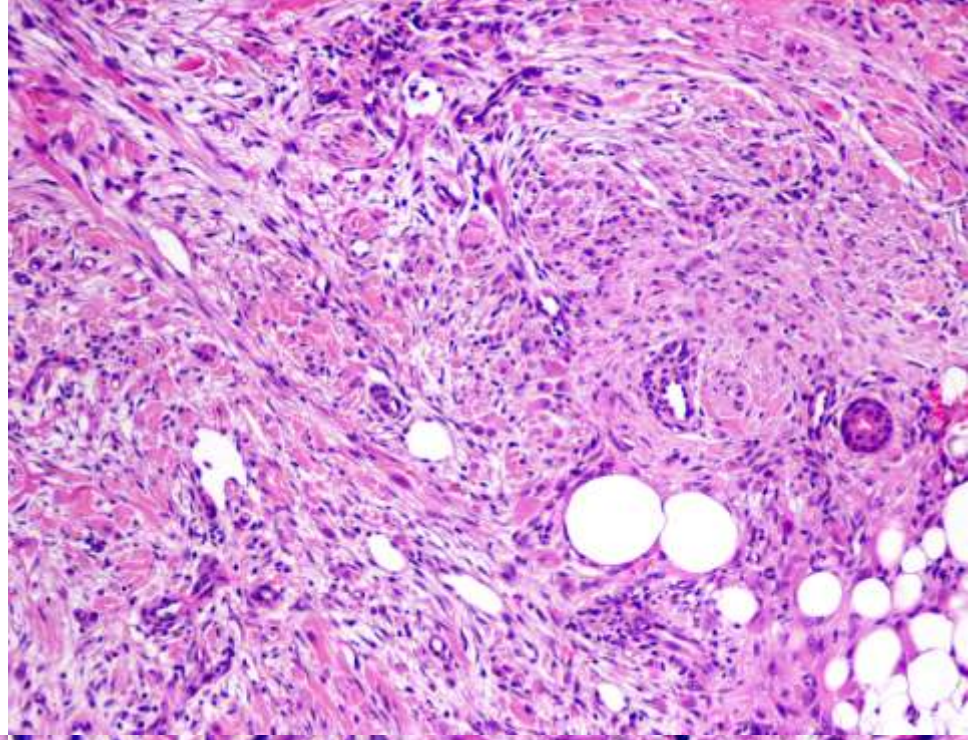
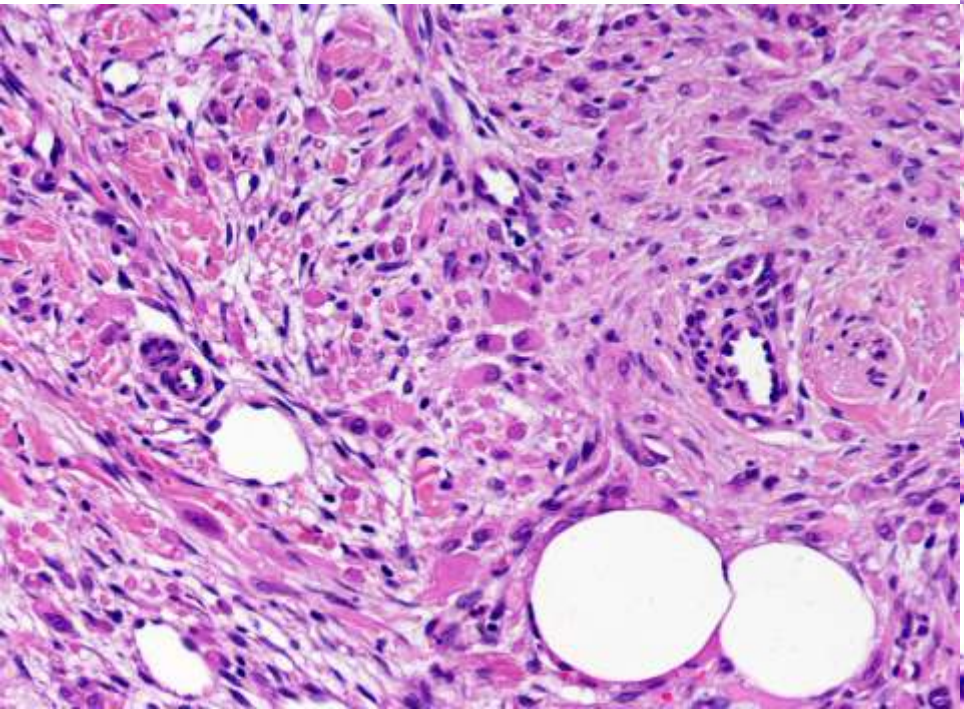
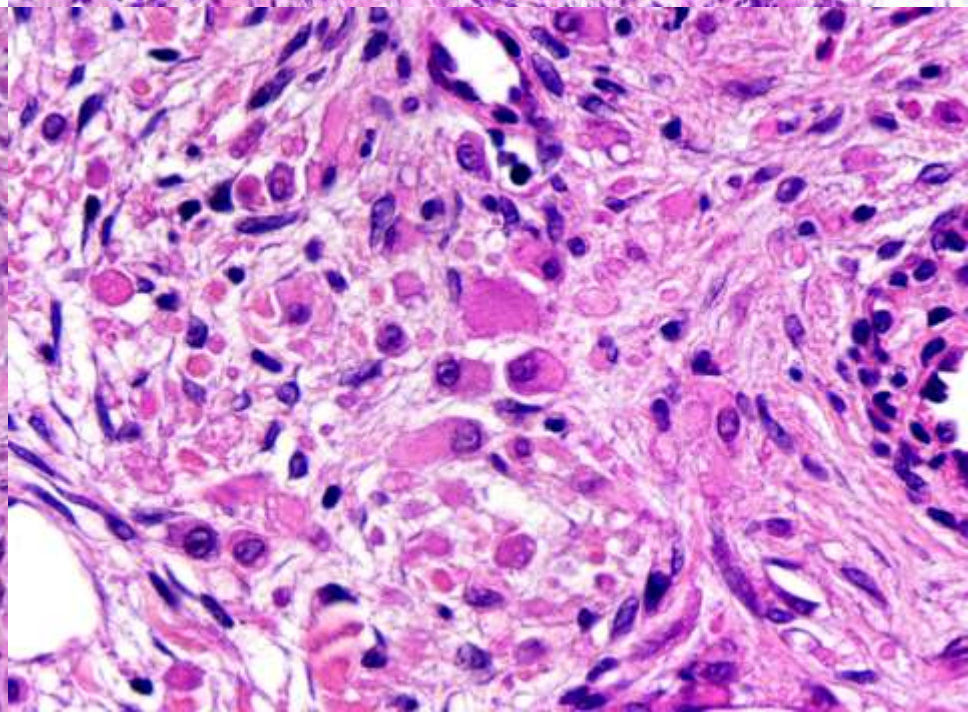

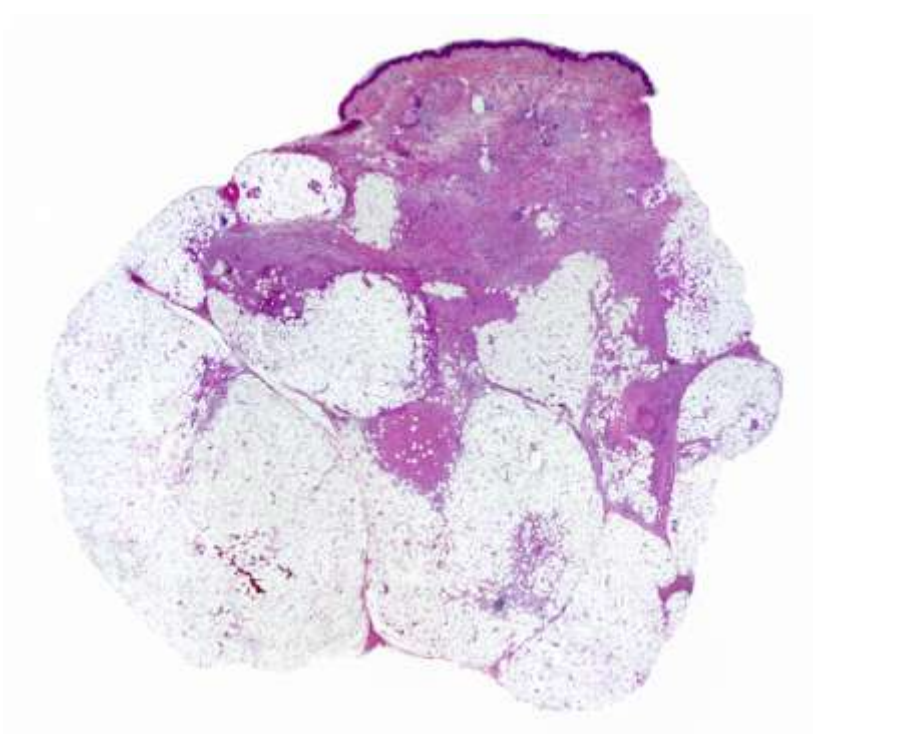
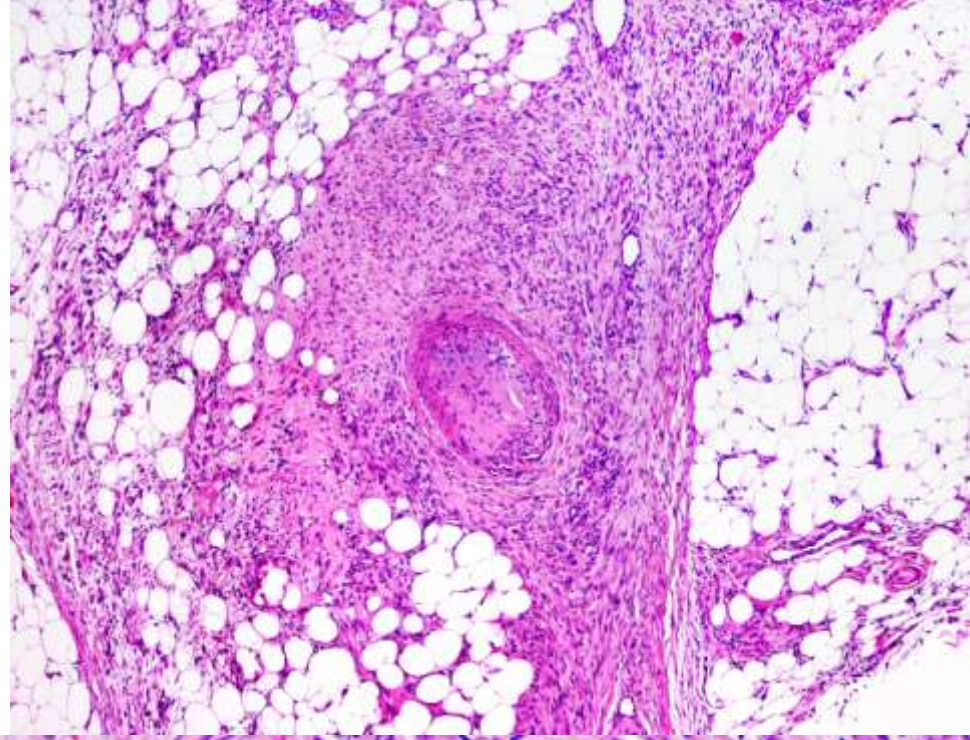
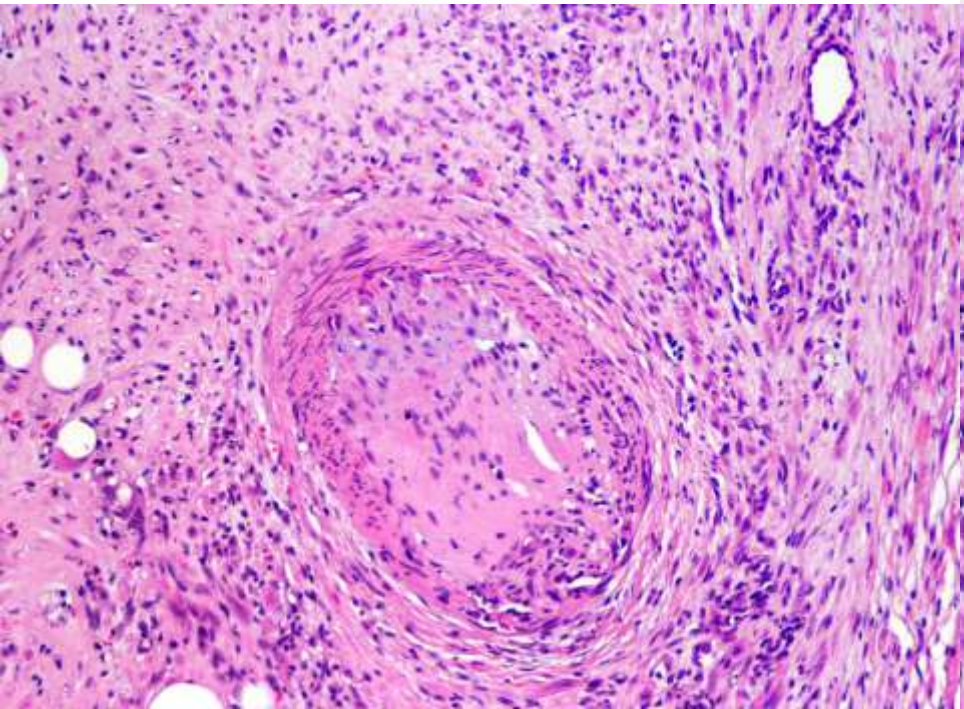
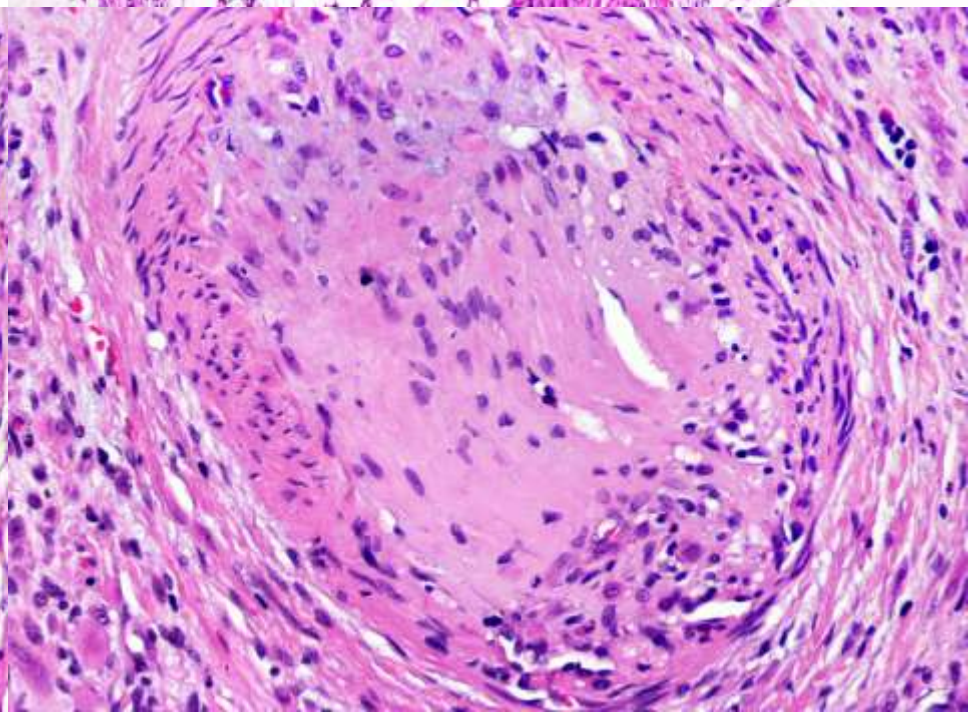

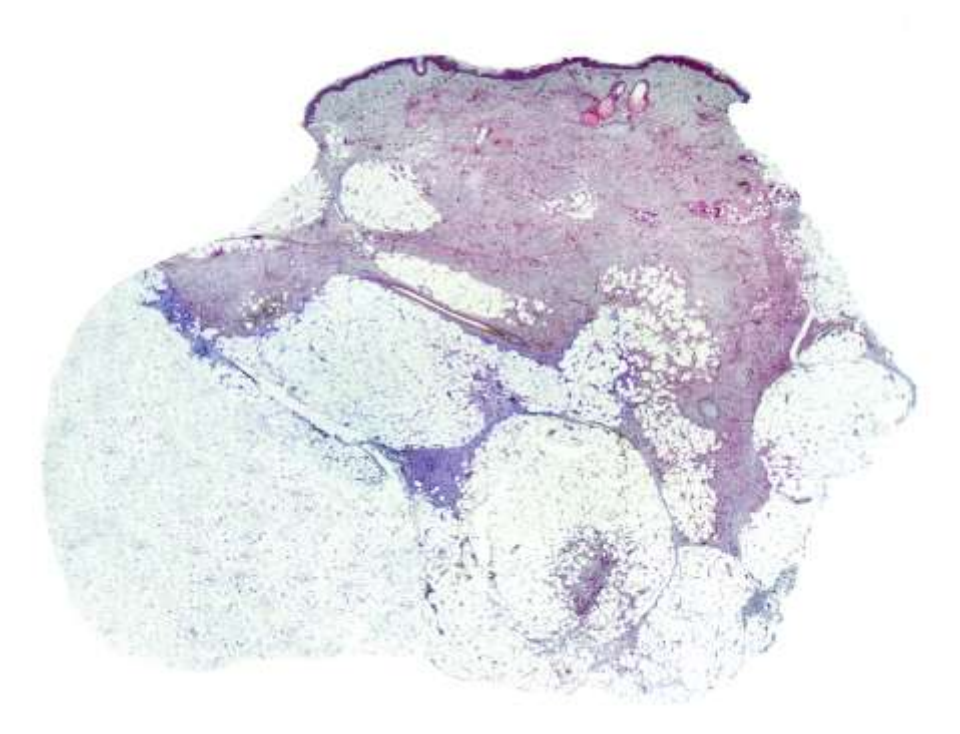

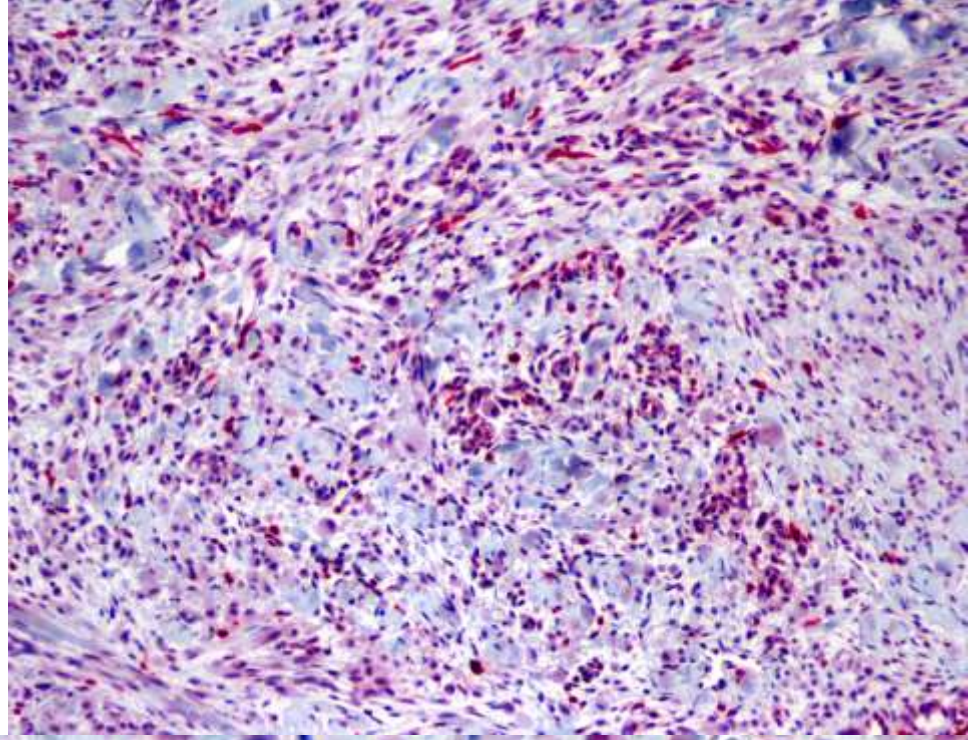

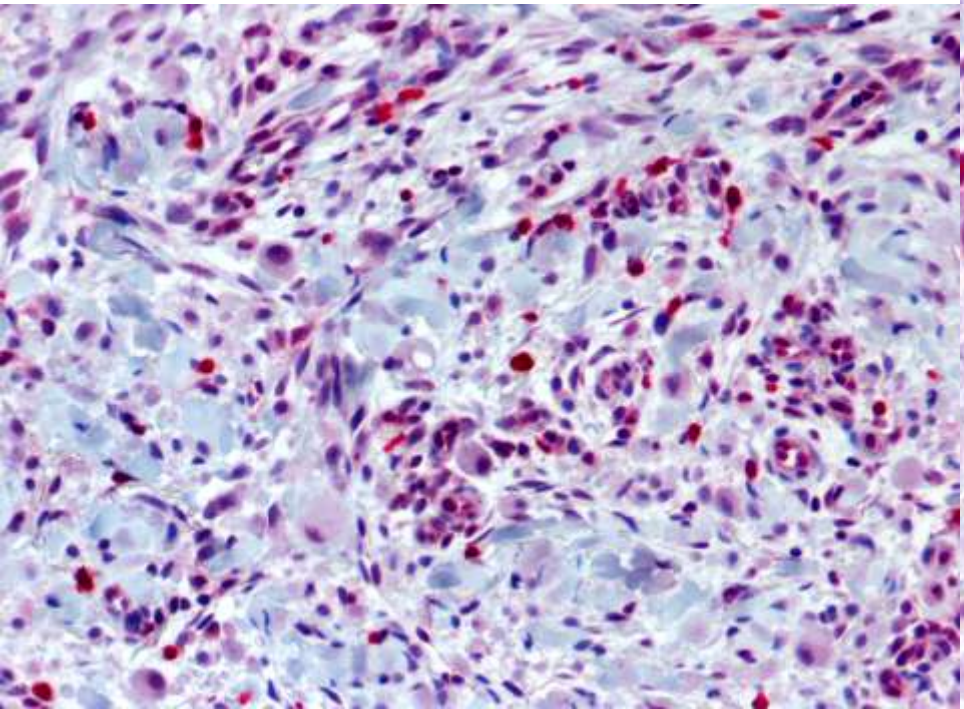

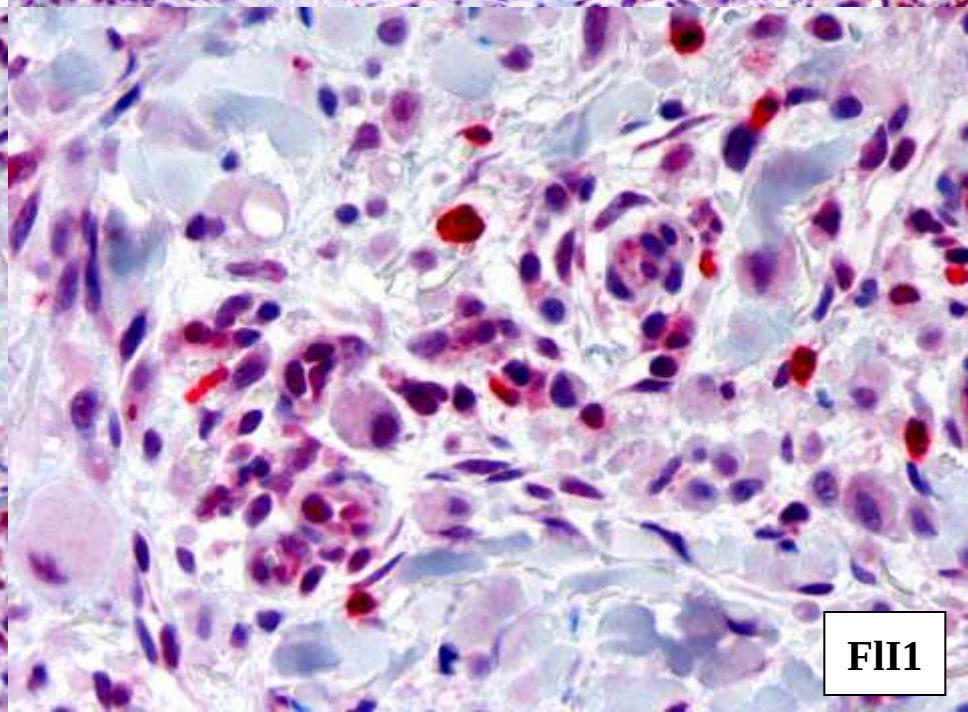
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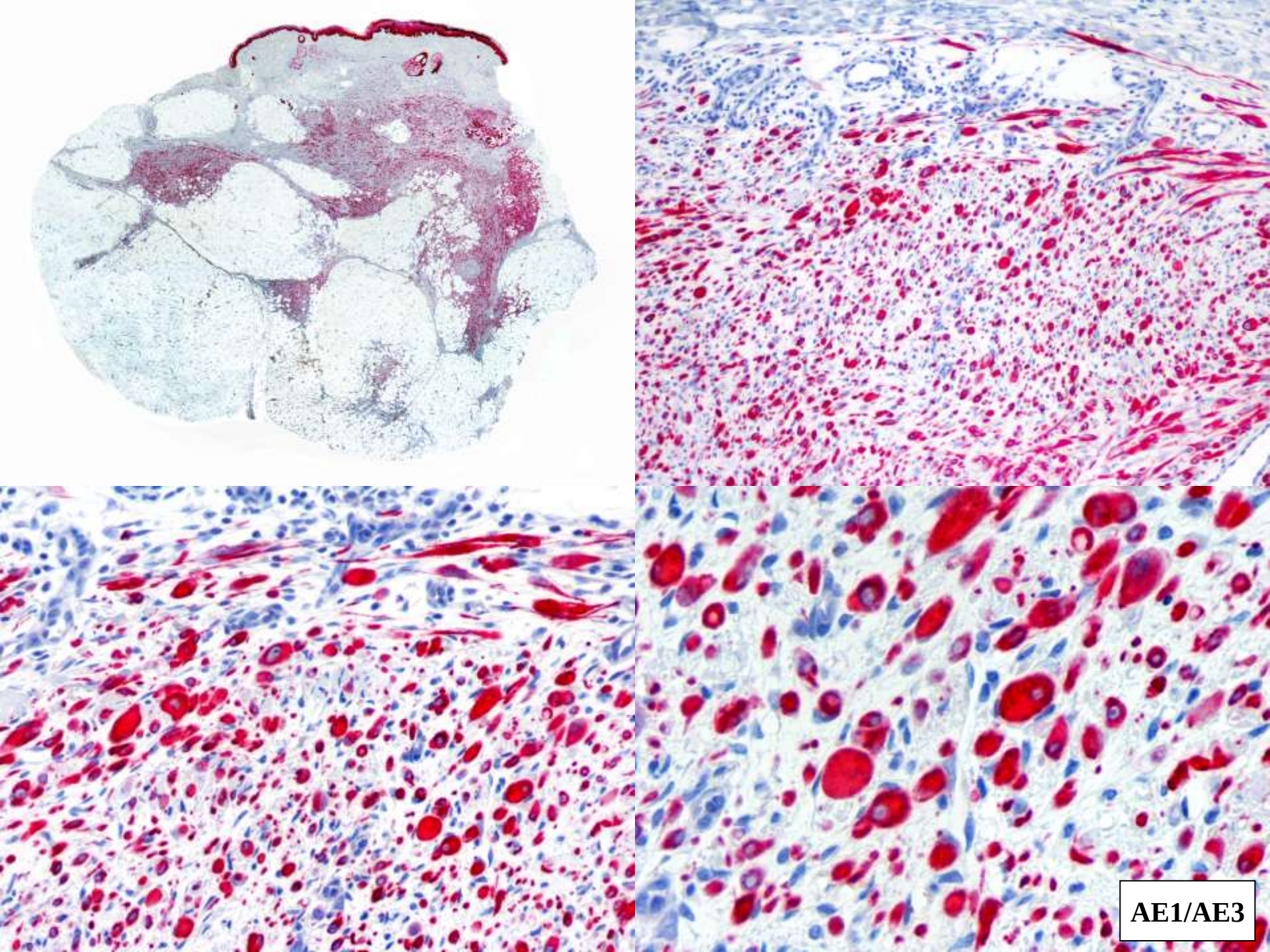
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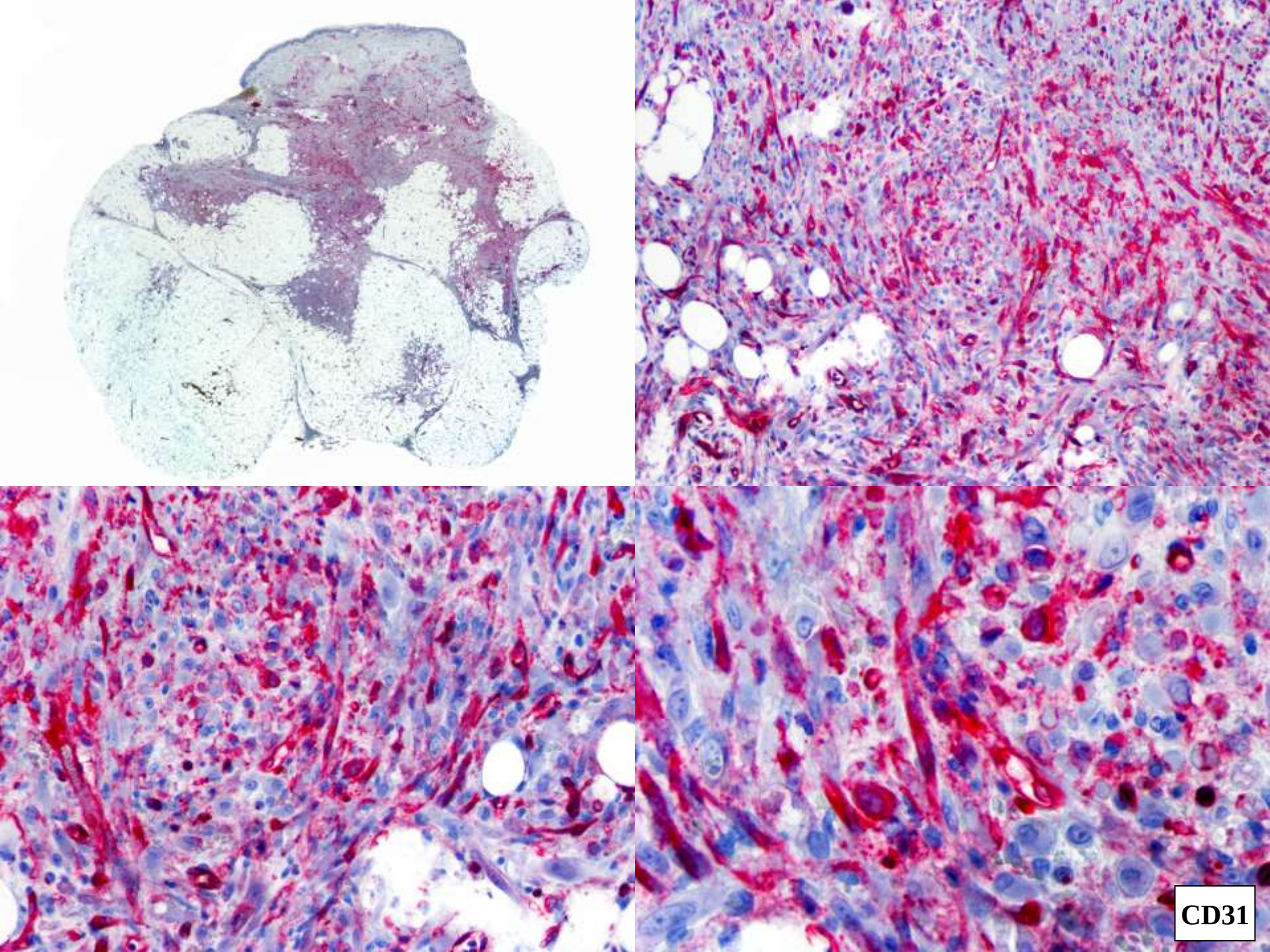
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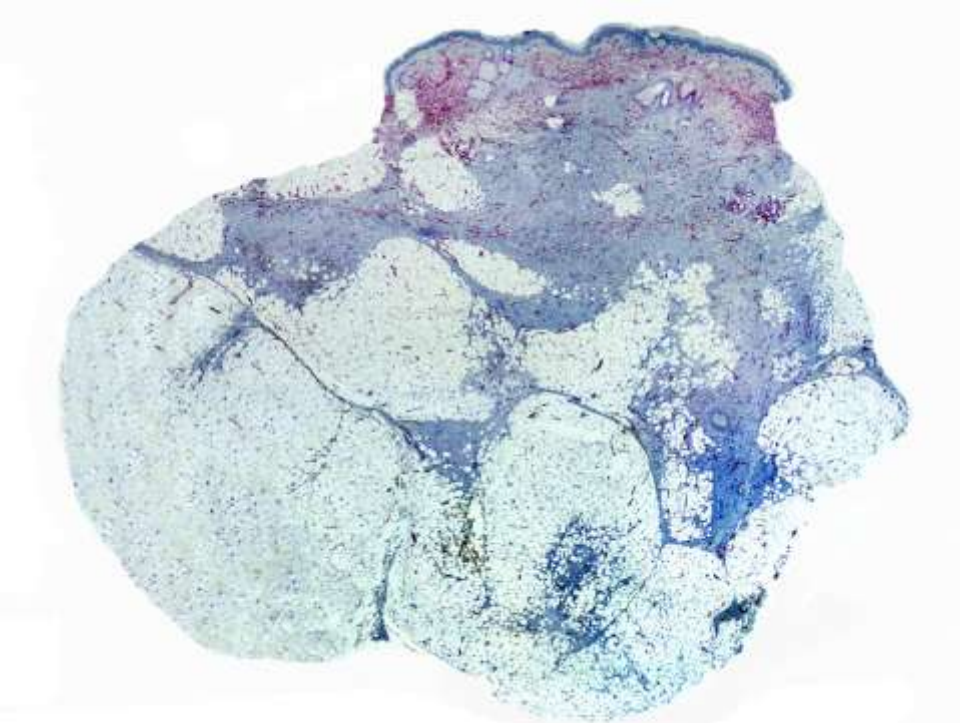

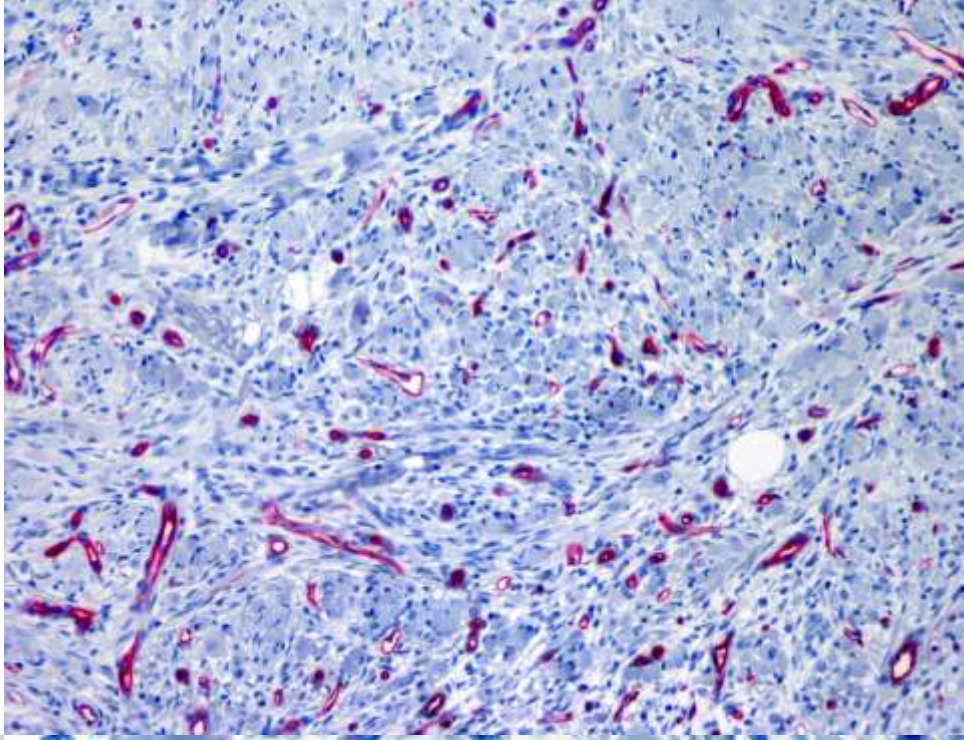

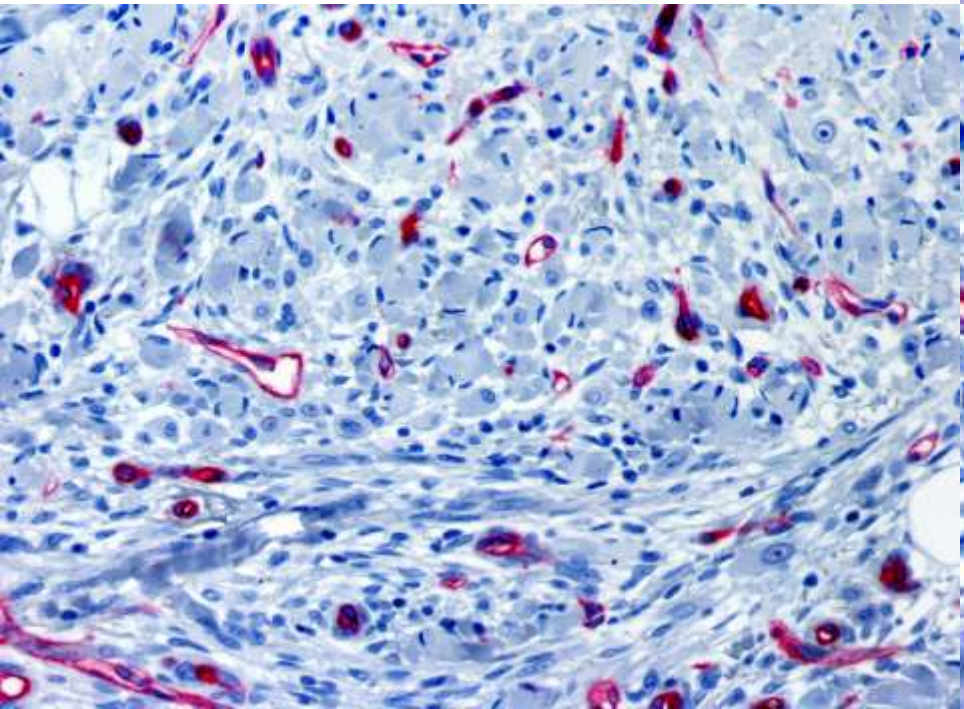

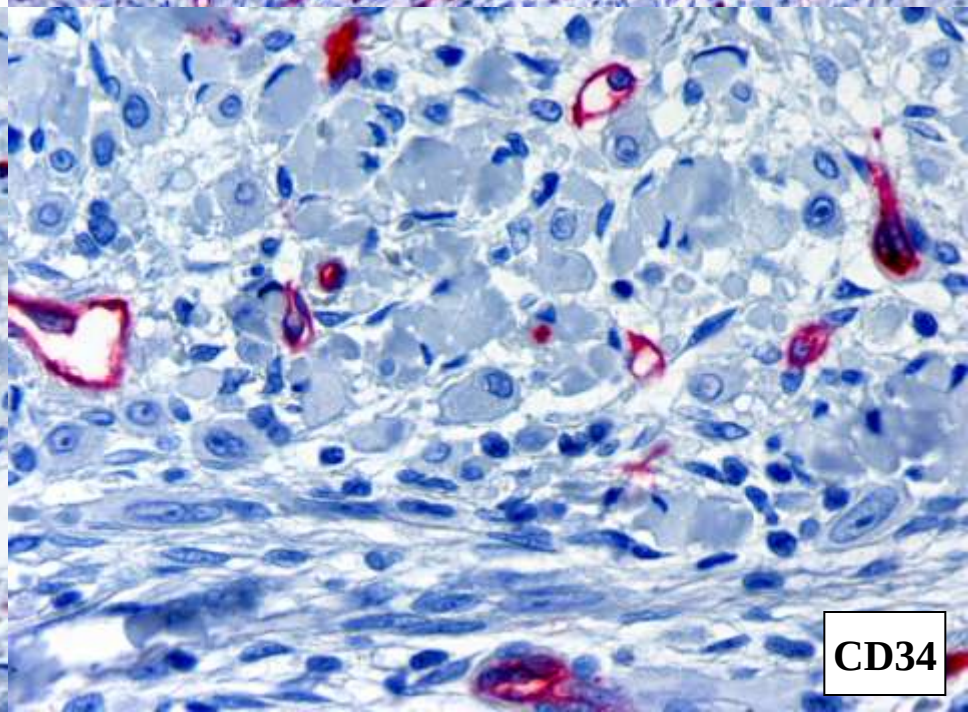
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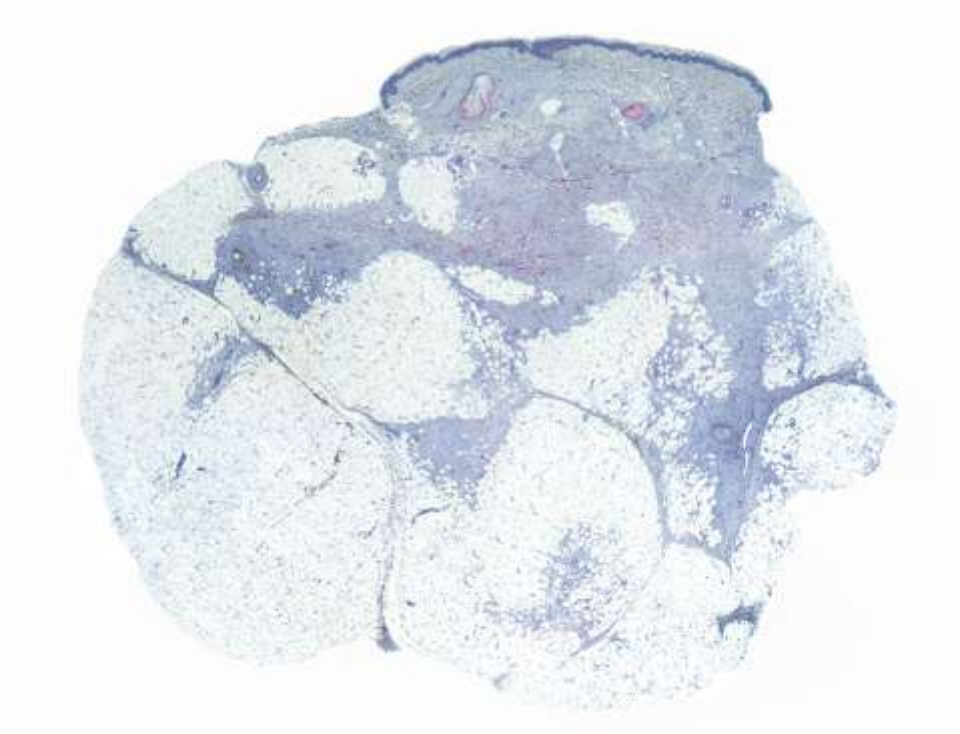

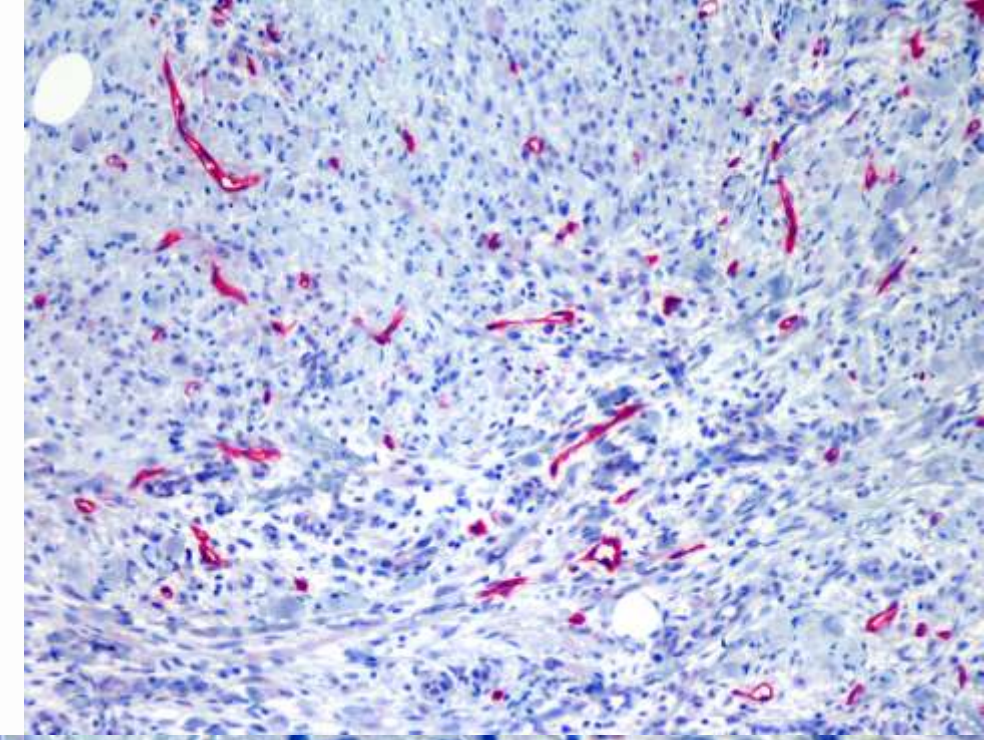

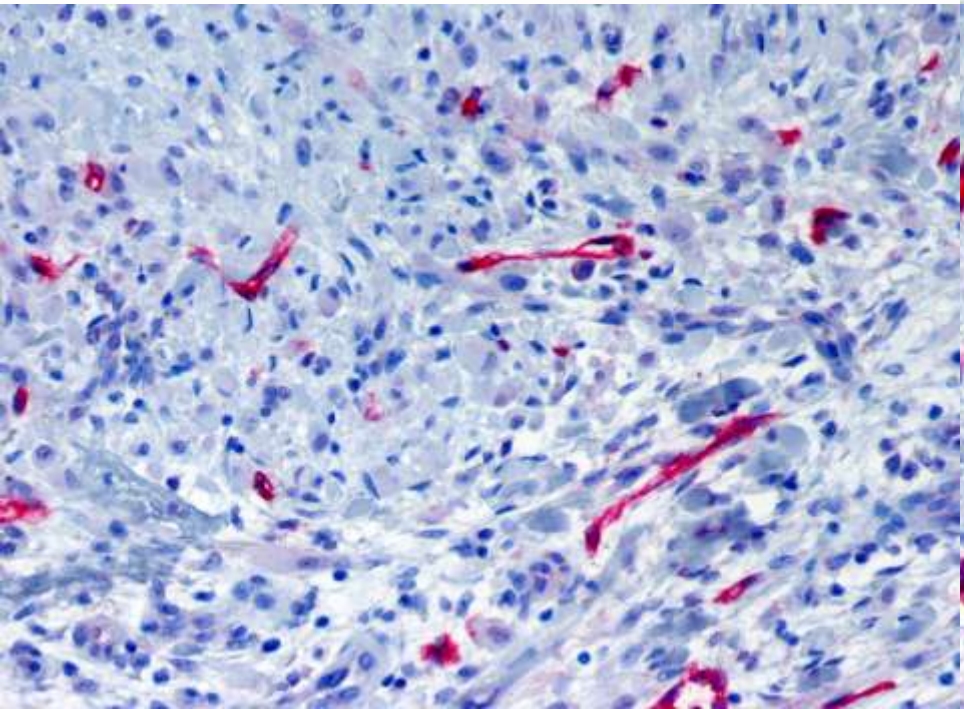

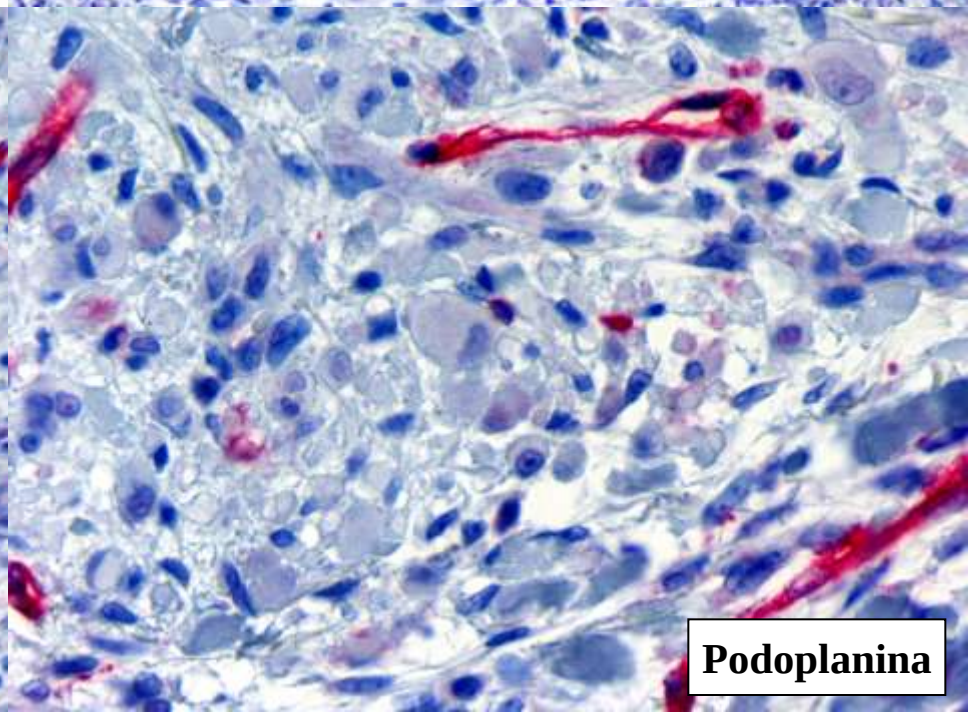

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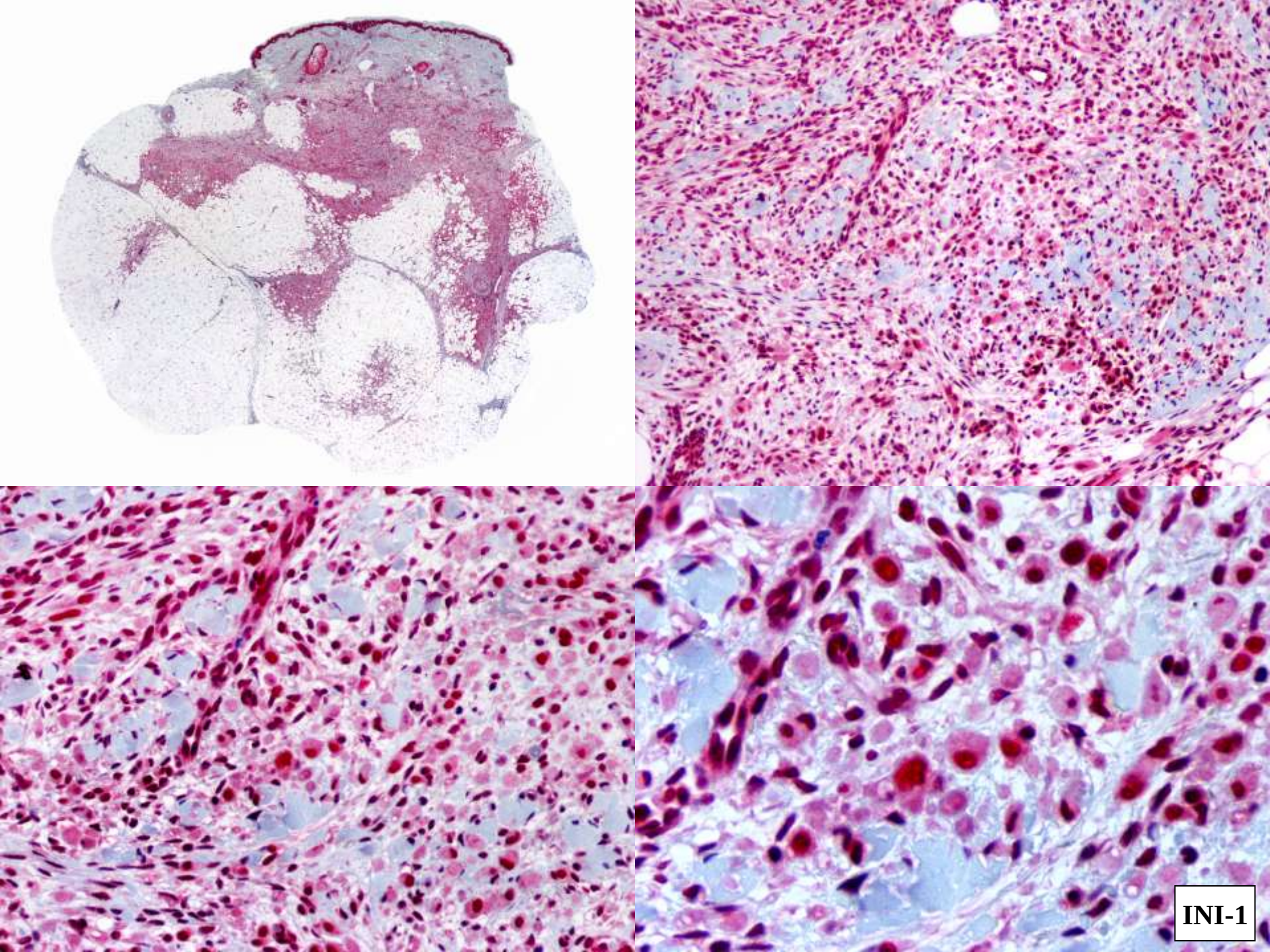

INI-1

Hornick JL, Fletcher CDM. Pseudomyogenic hemangioendothelioma: A distinctive, often multicentric tumor with indolent behavior. Am J Surg Pathol 2011;35:190-201.

- 50 casos. Nódulos dérmicos y/o subcutáneos, a menudo múltiples, en extremidades.
- Bordes infiltrativos
- Fascículos de células fusifomes u ovaladas con núcleo vesiculoso, nucléolo prominente y amplio citoplasma llamativamente eosinófilo, que confiere a algunas de estas células una apariencia de rabdomioblastos. Escaso número de mitosis.
- Inmunohistoquímica: Positividad intensa de FlI1 y AE1/AE3. Expresión variable de CD31, CAM5.2, SMA y EMA. Negatividad de CD34, MNF116, S100 y desmina. Expresión intacta de INI-1.
- 58% de los pacientes con recurrencia local o nuevos nódulos en la misma región. 1 paciente con metástasis a ganglios linfáticos regionales y 1 paciente con metástasis diseminadas y muerte.

Hemangioendotelioma pseudomiogénico: Diagnóstico diferencial

	AE1/AE3	FLI1	CD31	CAM5.2	SMA	EMA	MNF116	CD34	S100	INI1
HE	+	-	+	-	+/-	-	+	+	-	+
SE	+	-	-	+	-	+	+	+	-	-
HSM	+	+	+/-	+/-	+/-	+/-	-	-	-	+

HE: Hemangioendotelioma epitelioide
SE: Sarcoma epitelioide
HSM: Hemangioendotelioma pseudomiogénico

ELSEVIER

Cancer Genetics 204 (2011) 211–215

Cancer Genetics

BRIEF COMMUNICATION

Translocation t(7;19)(q22;q13)—a recurrent chromosome aberration in pseudomyogenic hemangioendothelioma?

Domenico Trombetta [a,b], Linda Magnusson [b], Fredrik Vult von Steyern [c], Jason L. Hornick [d], Christopher D.M. Fletcher [d], Fredrik Mertens [b,*]

[a] *Department of Genetics and Microbiology, University of Bari, Bari, Italy;* [b] *Department of Clinical Genetics, University and Regional Laboratories, Lund University Hospital, Lund, Sweden;* [c] *Department of Orthopedics, Clinical Sciences, Lund University and Skåne University Hospital, Lund, Sweden;* [d] *Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*

Pseudomyogenic hemangioendothelioma is a recently described morphologic entity among soft tissue tumors. It is more common in young individuals, shows a male predominance, is often multifocal and involves different tissue planes, and shows a high propensity for local recurrence. To our knowledge, no genetic characteristics of this tumor type have been presented before. Here, we describe the finding of a balanced t(7;19)(q22;q13) as the sole anomaly in three lesions from a 14-year-old girl. By means of fluorescence in situ hybridization, the breakpoints could be delineated, but reverse transcriptase–polymerase chain reaction for putative fusion genes did not reveal any fusion transcript. Interphase fluorescence in situ hybridization on sections from nine other pseudomyogenic hemangioendotheliomas indicated the presence of an unbalanced der(7)t(7;19) in one of them. Thus, the translocation between chromosomes 7 and 19 seems to be a recurrent phenomenon and is likely to be of pathogenetic significance in at least a subset of pseudomyogenic hemangioendotheliomas.

Keywords Pseudomyogenic hemangioendothelioma, translocation, t(7;19)(q22;q13), SERPINE1

ERG Transcription Factor as an Immunohistochemical Marker for Vascular Endothelial Tumors and Prostatic Carcinoma

Markku Miettinen, MD, Zeng-Feng Wang, PhD,* Anders Paetau, MD,† Shyh-Han Tan, PhD,‡§ Albert Dobi, PhD,‡§ Shiv Srivastava, PhD,‡§ and Isabell Sesterhenn, MD**

Abstract: ERG, an ETS family transcription factor, is known to be expressed in endothelial cells, and oncogenic *ERG* gene fusions occur in subsets of prostatic carcinoma, acute myeloid leukemia, and Ewing sarcoma. In this study, we immunohistochemically investigated nuclear ERG expression using a new monoclonal antibody, CPDR ERG-MAb, that is highly specific for detecting ERG protein and ERG-expressing prostate carcinomas. A broad range of vascular endothelial (n = 250), other mesenchymal (n = 973), and epithelial tumors (n = 657) was examined to determine the use of ERG immunohistochemistry in surgical pathology. Only immunostains with ERG-positive normal endothelia (internal control) were considered valid, and only nuclear staining was considered to be positive. In adult tissues, ERG was restricted to endothelial cells and to a subset of bone marrow precursors, but early fetal mesenchyme and subpopulations of fetal cartilage were also positive. In vascular tumors, ERG was expressed in endothelia of all hemangiomas and lymphangiomas, and typically extensively expressed in 96 of 100 angiosarcomas, 42 of 43 epithelioid hemangioendotheliomas, and all 26 Kaposi sarcomas. Among nonvascular mesenchymal tumors, only blastic extramedullary myeloid tumors (7 of 10) and rare Ewing sarcomas (2 of 29) were positive. Among epithelial tumors, 30 of 66 prostatic adenocarcinomas showed focal-to-extensive ERG positivity, with no immunoreactivity in the normal prostate. Other carcinomas and epithelial tumors (n = 643) were ERG negative, with the exception of 1 of 42 large cell undifferentiated pulmonary carcinomas and 1 of 27 mesotheliomas, each of which showed focal nuclear ERG positivity. On the basis of the above observations, ERG is a highly specific new marker for benign and malignant vascular tumors. Among epithelial tumors, ERG shows a great promise as a marker to identify prostatic carcinoma in both primary and metastatic settings.

Key Words: ETS-family transcription factor, ERG, angiosarcoma, hemangioendothelioma, hemangioma, immunohistochemistry, prostate carcinoma

(*Am J Surg Pathol* 2011;35:432–441)

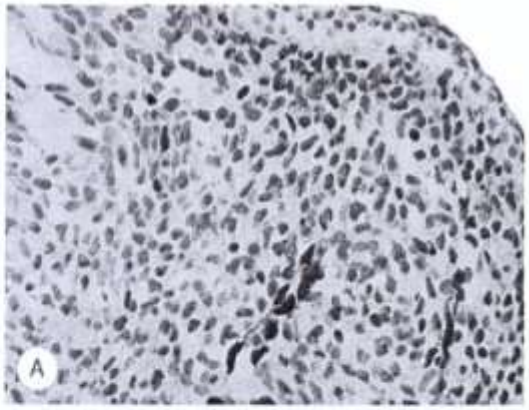


TABLE 1. Endothelial Nuclear ERG Expression in Vascular Tumors

Hemangioma, total	61/61
Juvenile	8/8
Lobular capillary	8/8
Cavernous	10/10
Miscellaneous capillary	12/12
Papillary endothelial hyperplasia	5/5
Epithelioid hemangioma	4/4
Spindle cell hemangioma	14/14
Lymphangioma	11/11
Lymphangioendothelioma	2/2
Kaposiform hemangioendothelioma	3/3
Retiform/Dabska hemangioendothelioma (3 + 1)	4/4
Epithelioid hemangioendothelioma	42/43
Angiosarcoma, total	96/100
Angiosarcoma of the scalp or face	21/21
Other cutaneous angiosarcoma (nonradiation associated)	6/6
Postradiation angiosarcoma of the breast/chest wall	6/6
Lymphedema-associated angiosarcoma	5/5
Angiosarcoma of the deep soft tissue, peripheral	15/16
Angiosarcoma, intra-abdominal/mediastinal	12/13
Angiosarcoma of the breast parenchyma	1/1
Hepatic angiosarcoma	1/1
Splenic angiosarcoma	5/5
Angiosarcoma of bone	2/2
Other visceral angiosarcomas	22/24
Angiosarcoma of epithelioid cell type (included above)	15/15
Kaposi sarcoma (including 3 AIDS associated)	26/26
Total for vascular tumors	250

TABLE 2. Nuclear ERG Immunoreactivity in Nonepithelial Mesenchymal, Neuroectodermal, and Hematopoietic Tumors, Other Than Vascular Endothelial Tumors

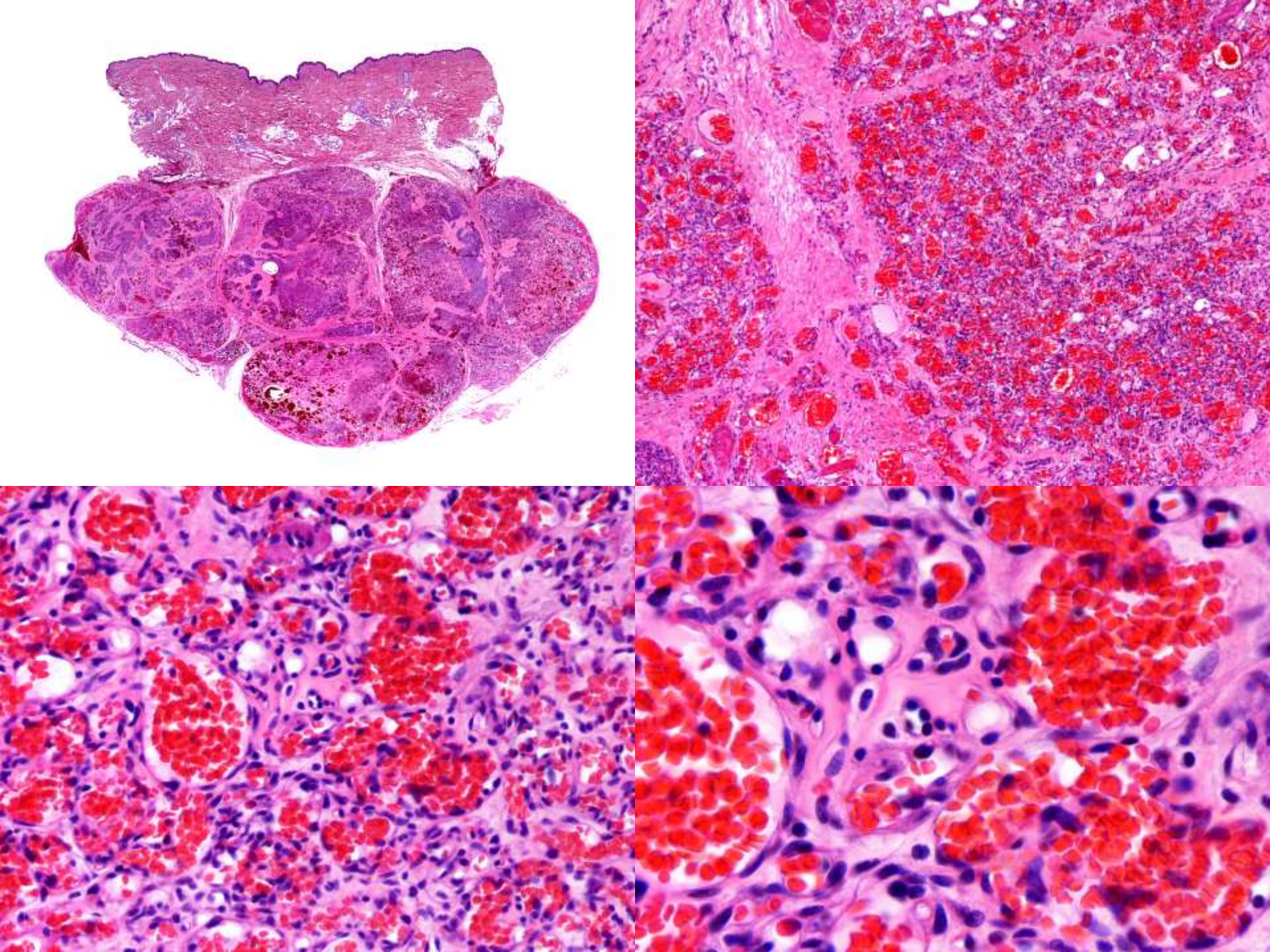
Alveolar soft part sarcoma	0/13
Angioleiomyoma	0/4
Angiomyolipoma	0/9
Astrocytoma, cerebellar	0/7
Chondrosarcoma	0/8
Chondrosarcoma, extraskeletal myxoid	0/17
Chondrosarcoma, dedifferentiated	0/6
Chondrosarcoma, mesenchymal	0/7
Chordoma	0/22
Desmoid fibromatosis	0/19
Dermatofibrosarcoma protuberans	0/32
Endometrial stromal sarcoma	0/6
Ependymoma	0/4
Epithelioid sarcoma	0/8
Ewing sarcoma	2/29
Extramedullary myeloid tumor, blastic	7/10
Fibrous histiocytoma, angiomatoid	0/20
Fibrous histiocytoma, benign, cutaneous	0/18
GIST (50 gastric, 38 small intestinal)	0/88
Glioblastoma multiforme	0/17
Glomus tumor	0/18
Granular cell tumor	0/20
Granulosa cell tumor of ovary	0/9
Hemangioblastoma of cerebellum	0/6
Hemangiopericytoma, meningeal	0/24
Hemangiopericytoma/SFT, soft tissue	0/51
Leiomyosarcoma	0/26
Liposarcoma, well differentiated	0/9
Liposarcoma, dedifferentiated	0/14
Liposarcoma, myxoid/round cell	0/25
Liposarcoma, pleomorphic	0/17
Low-grade fibromyxoid sarcoma	0/12
Lymphoma, anaplastic large cell	0/7
Lymphoma, diffuse large B cell	0/9
Lymphoma, T-cell lymphoblastic	0/7
Lymphoma, mantle cell	0/9
Malignant peripheral nerve sheath tumor	0/12
Medulloblastoma	0/19
Melanoma, metastatic	0/34
Meningioma	0/65
MFH, pleomorphic	0/35
Myofibroma	0/9
Neuroblastoma	0/19
Neurofibroma	0/6
Nodular fasciitis	0/29
Oligodendroglioma	0/17
Osteosarcoma	0/12
Paraganglioma	0/14
Perineurioma, sclerosing	0/6
Rhabdomyosarcoma, alveolar	0/16
Rhabdomyosarcoma, embryonal	0/15
Schwannoma	0/14
Synovial sarcoma	0/36
Total	9/973

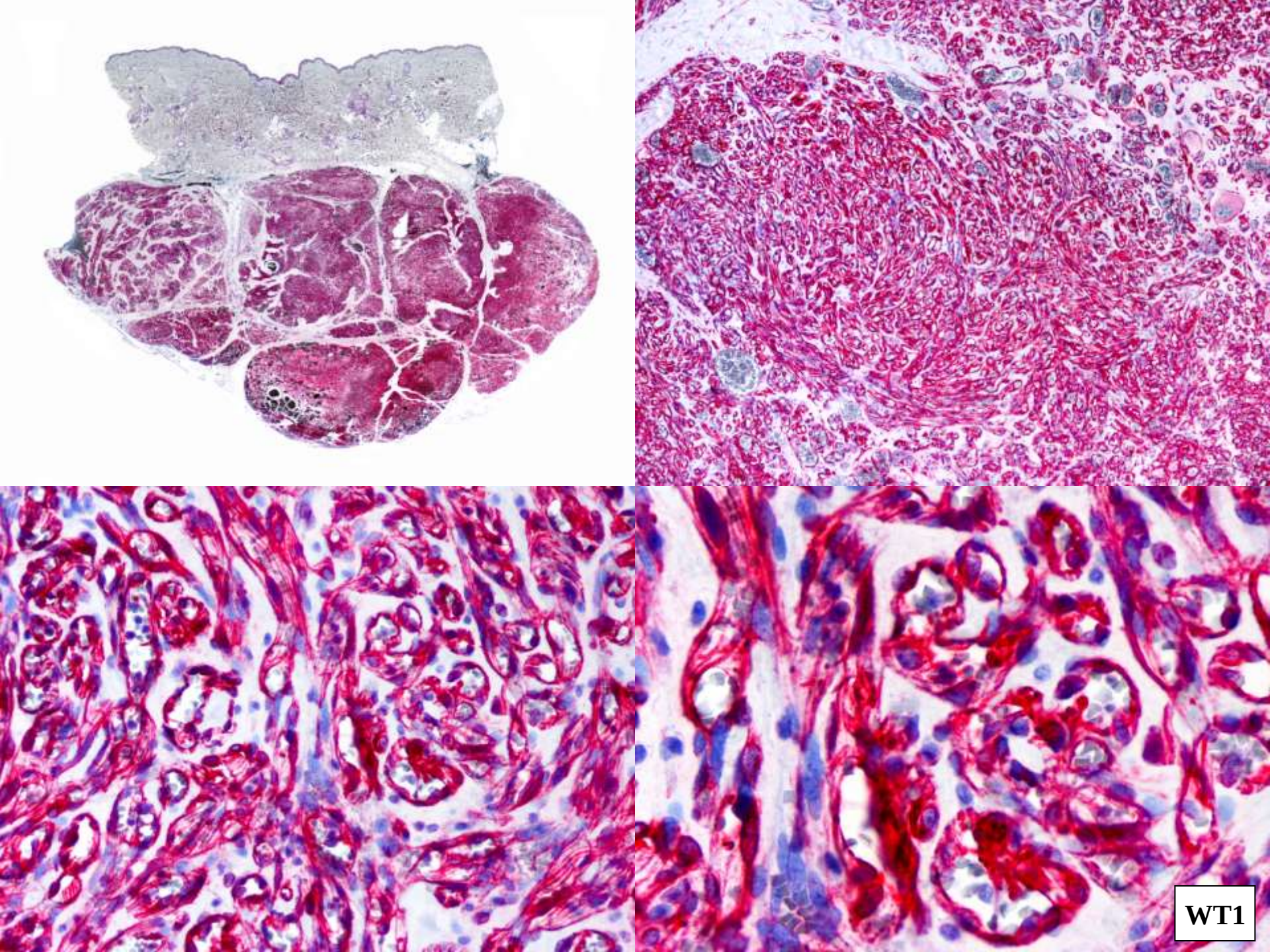
MFH indicates malignant fibrous histiocytoma; SFT, solitary fibrous tumor.

TABLE 3. Results on ERG Immunoreactivity in Epithelial Neoplasms

Adenocarcinoma, ductal, breast	0/26
Adenocarcinoma, colon	0/45
Adenocarcinoma, endometrium, differentiated	0/14
Adenocarcinoma, endometrium, sarcomatous (Malignant mixed mullerian tumor)	0/9
Adenocarcinoma, lung	0/27
Adenocarcinoma, pancreas	0/13
Adenocarcinoma, prostate	30/66
Adenocarcinoma, stomach (14 signet ring cell)	0/24
Adenoid cystic carcinoma, major/minor salivary glands	0/16
Ca of basal cell, skin	0/5
Cholangiocarcinoma, hepatic	0/6
Hepatocellular carcinoma	0/7
Renal cell carcinoma	0/52
Ca of serous papillary, ovary or peritoneum	0/29
Ca of small cell, lung	0/26
Ca of squamous cell, lung	0/20
Ca of squamous cell, esophagus	0/8
Ca of squamous cell, larynx	0/24
Ca of squamous cell, uterine cervix	0/12
Ca of transitional cell, urinary bladder or renal pelvis	0/21
Ca of undifferentiated large cell, lung	1/42
Ca of Merkel cell	0/4
Ca of thyroid, anaplastic	0/13
Ca of thyroid, follicular	0/12
Ca of thyroid, medullary	0/7
Ca of thyroid, papillary	0/14
Carcinoid, intestinal/Islet cell tumor	0/14
Ca of small intestine, undifferentiated	0/9
Malignant mesothelioma, pleura/peritoneum	1/27
Mixed tumor/myoepithelioma	0/31
Embryonal carcinoma, testis	0/8
Seminoma, testis	0/10
Wilms tumor	0/16
Total	32/657

Ca indicates carcinoma.

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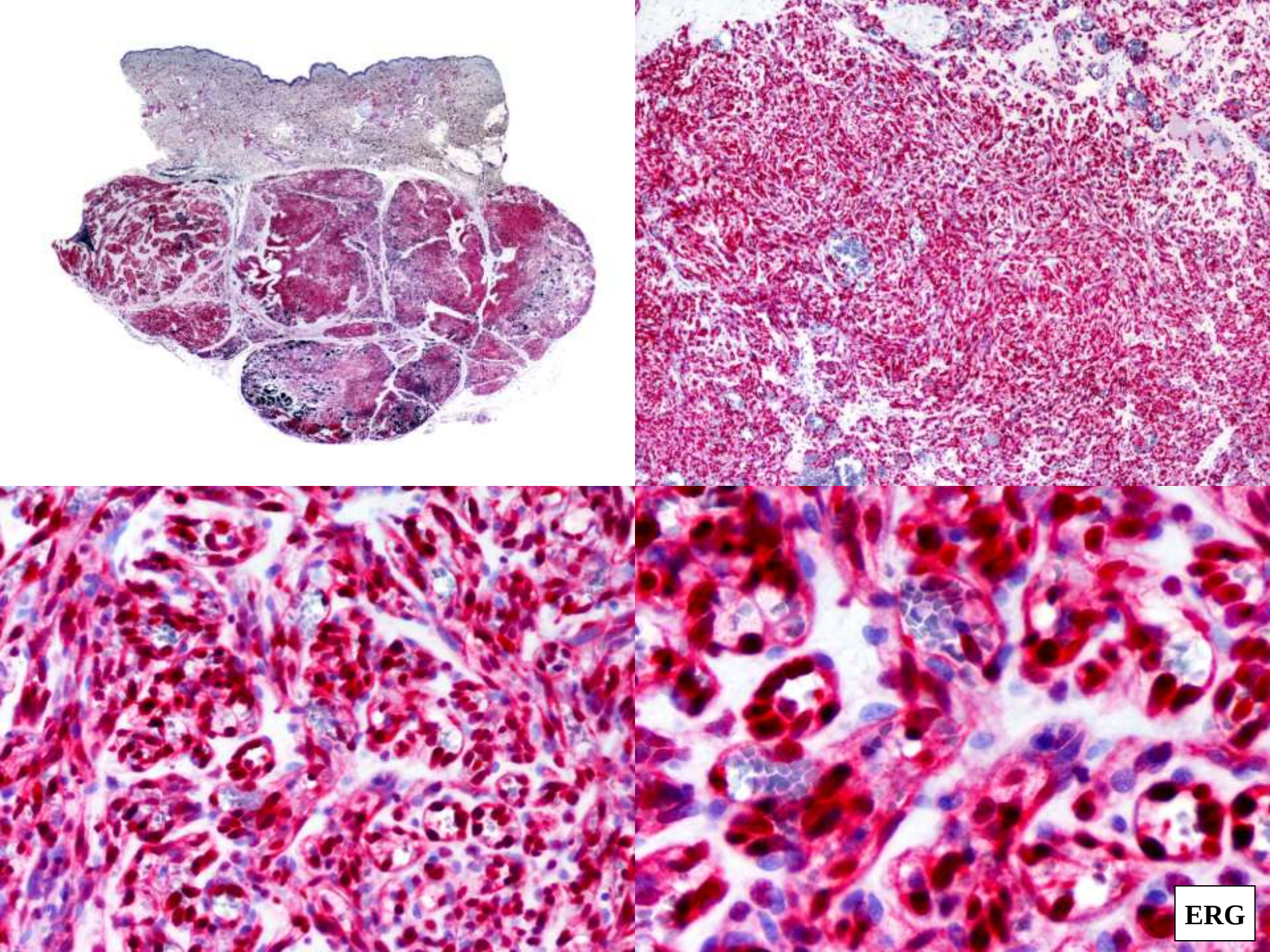
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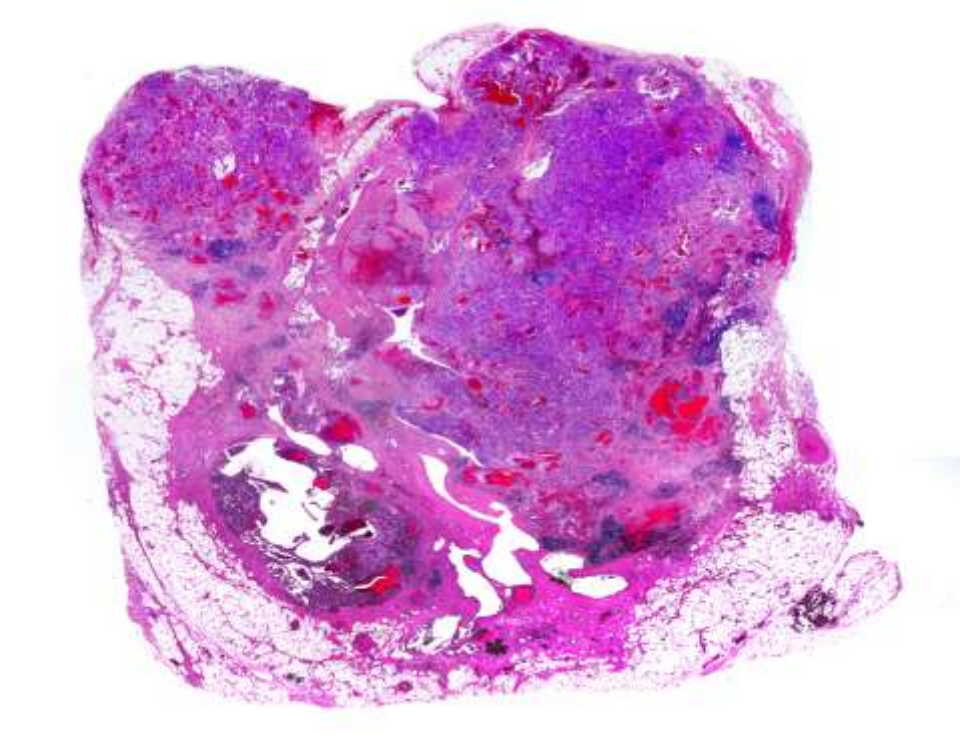
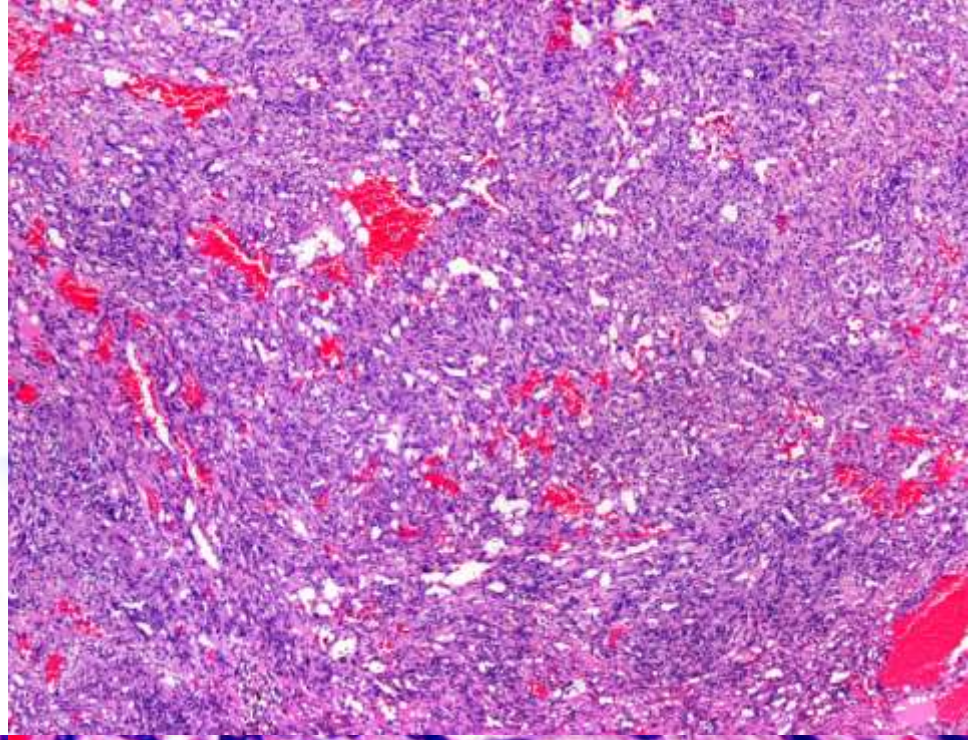
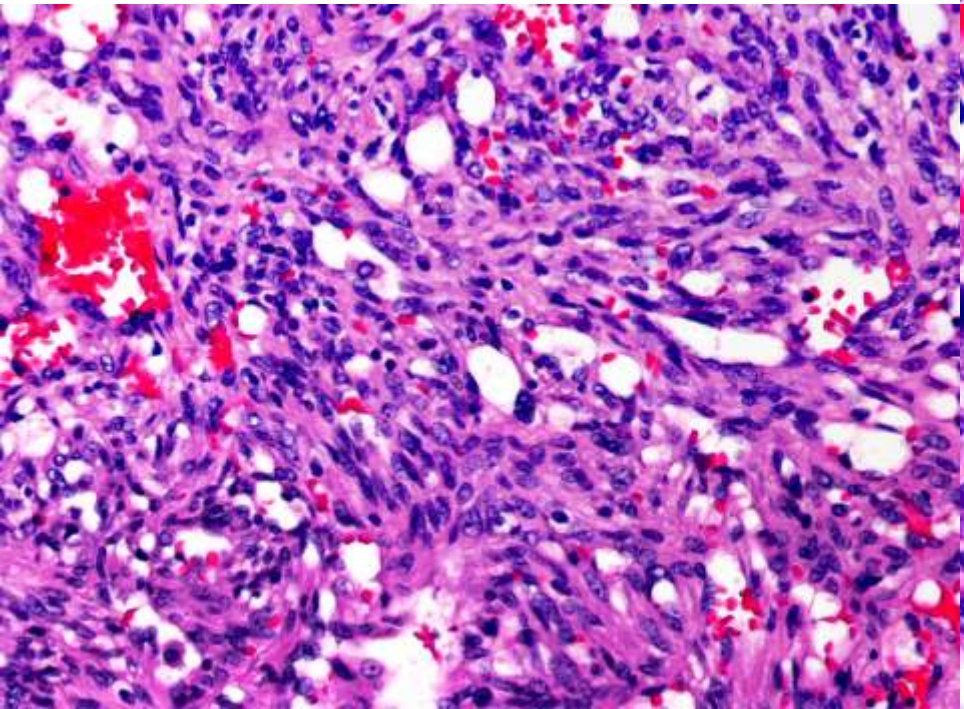
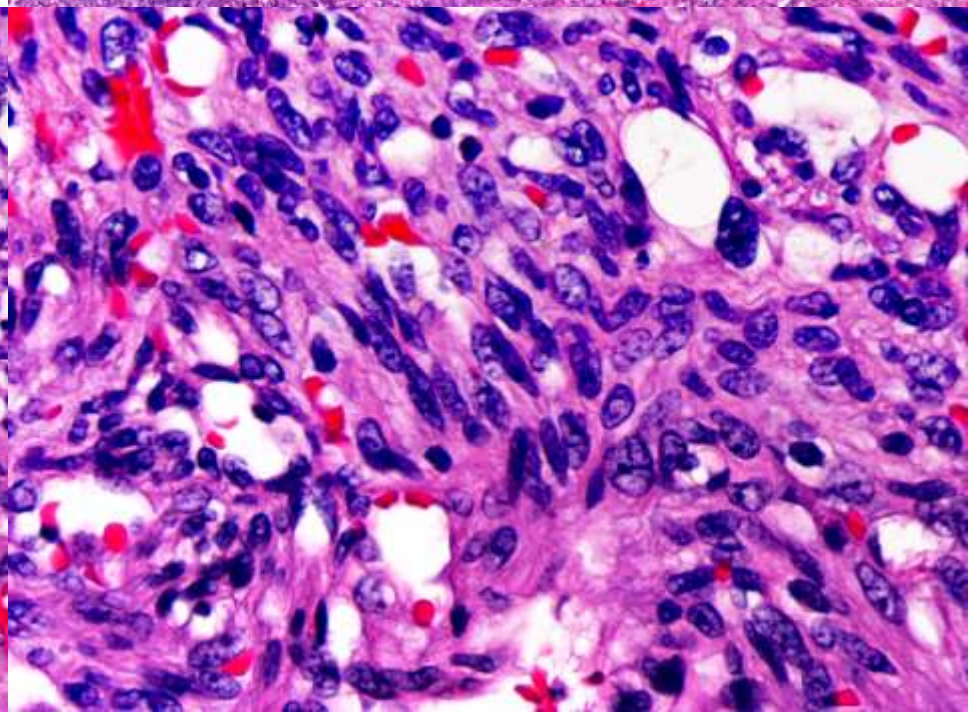

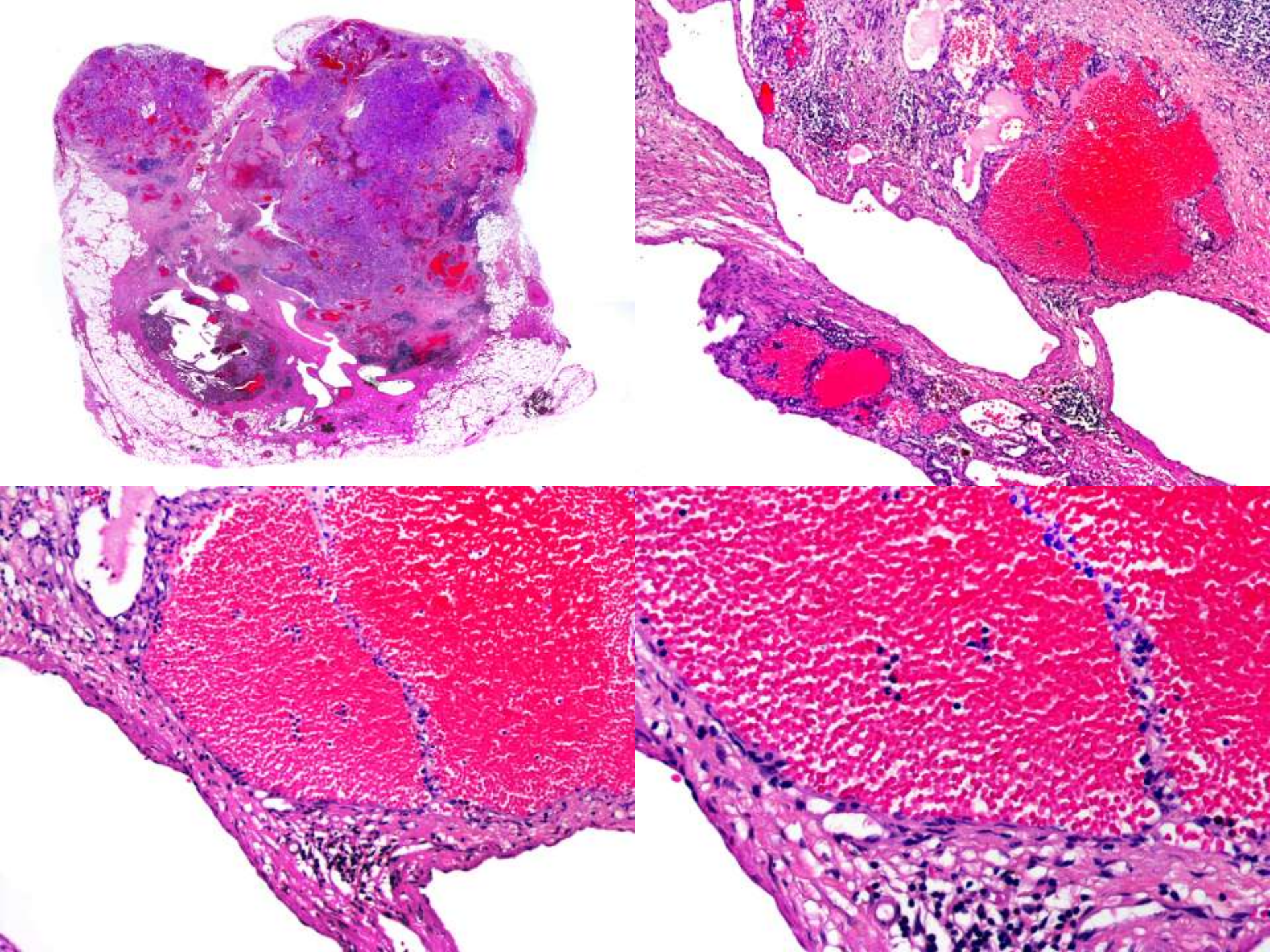

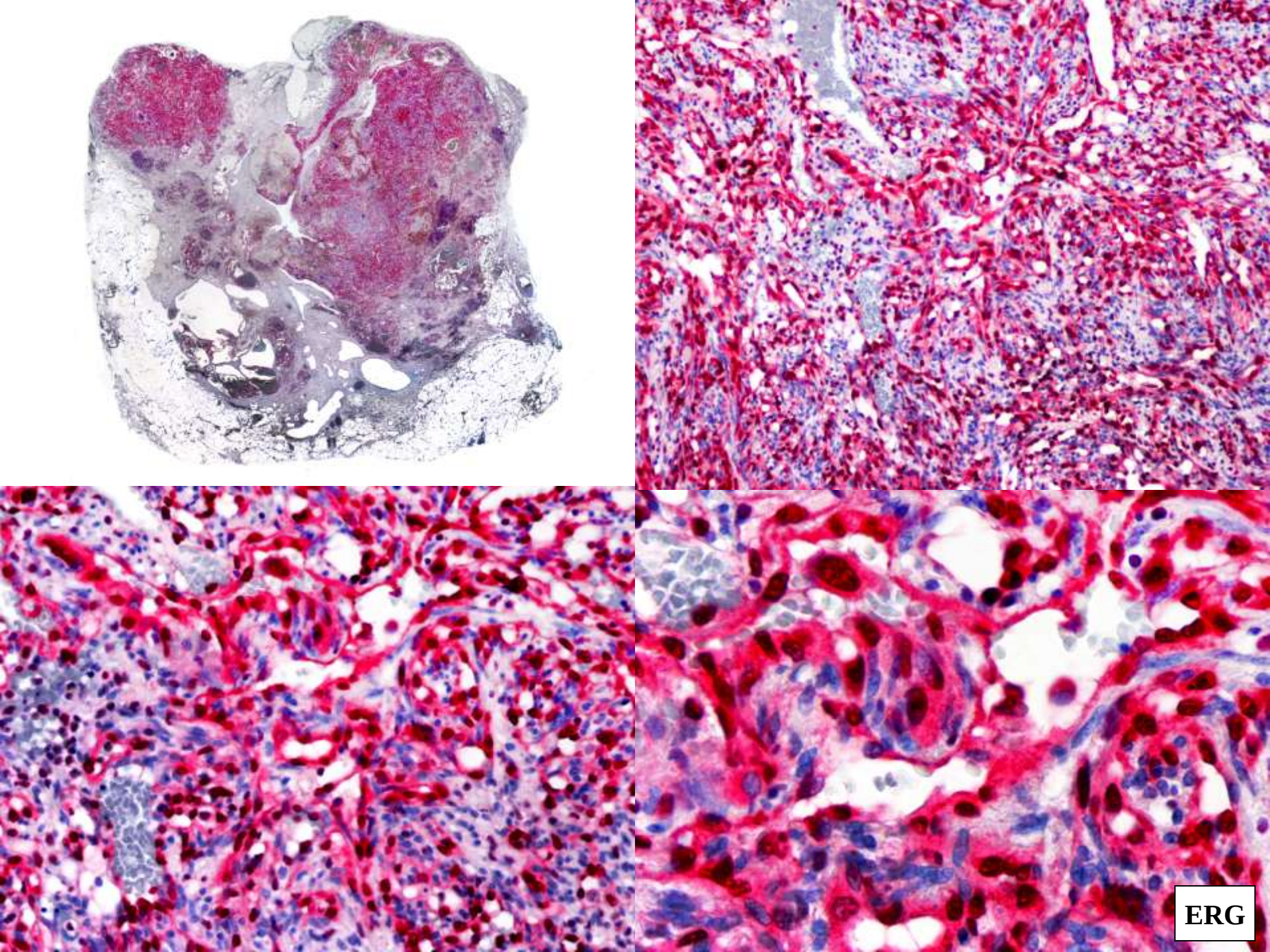
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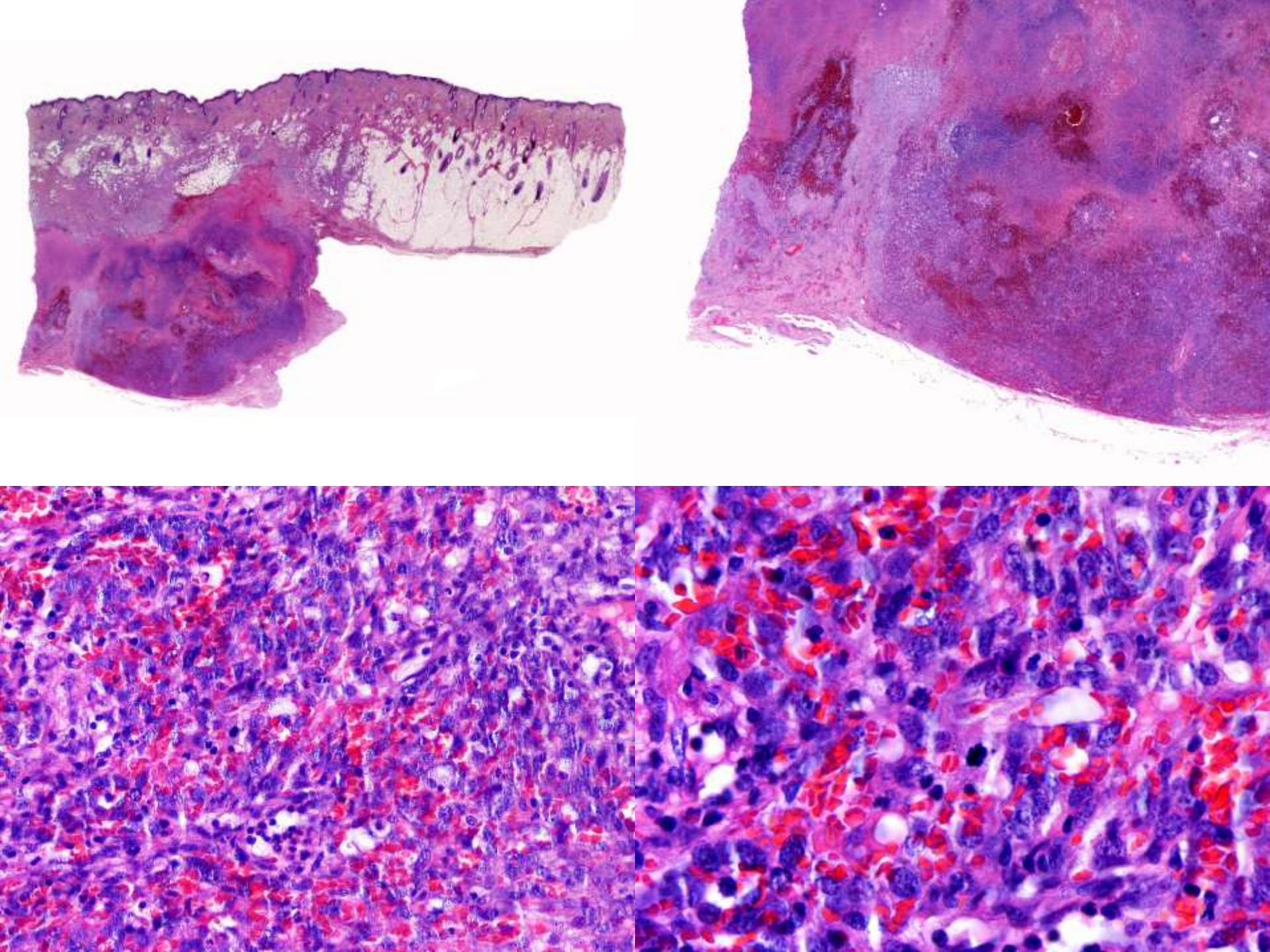

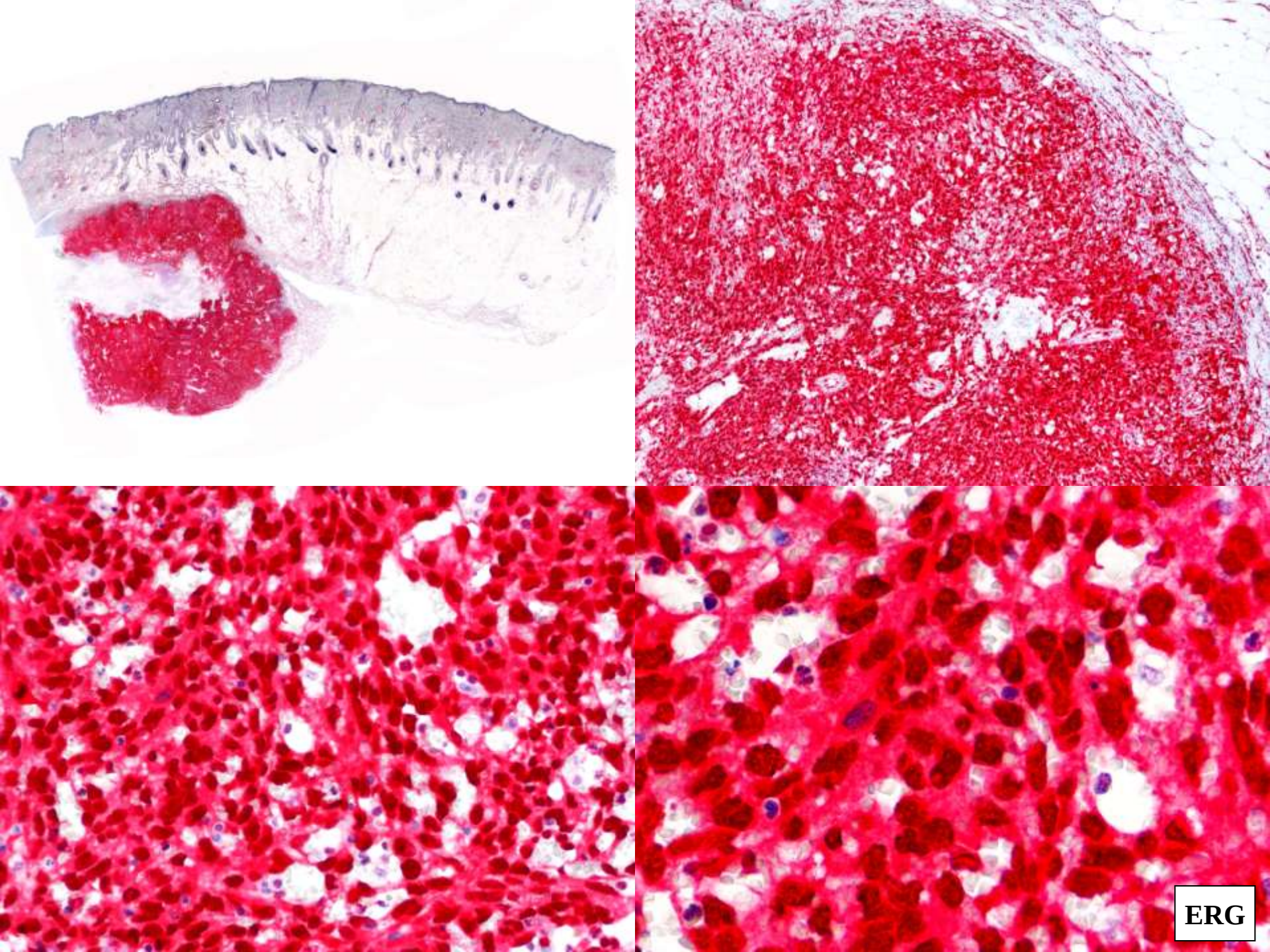
ERG

Miettinen M et al. ERG transcription factor as an immunohistochemical marker for vascular endothelial tumors and prostatic carcinoma. Am J Surg Pathol 2011;35:432-41.

- **ERG (*avain v-ets erythroblastosis virus E26 oncogen homolog*) es un factor de transcripción de la familia ETS.**
- **Positividad en los núcleos de las células endoteliales de vasos sanguíneos y linfáticos normales.**
- **Positividad en los núcleos de las células endoteliales de neoplasias benignas y malignas de endotelio sanguíneo y linfático.**
- **Los pericitos y las fibras musculares lisas son ERG negativo.**
- **Además de células endoteliales, ERG se expresa en las células epiteliales del 50% de los casos de cáncer de próstata (no en tejido prostático normal), células mieloides inmaduras de médula ósea, células de leucemia mieloide crónica y células de sarcoma de Ewing.**

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Short Communication

MYC High Level Gene Amplification Is a Distinctive Feature of Angiosarcomas after Irradiation or Chronic Lymphedema

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ary to irradiation, 2 tumors secondary to chronic lymphedema) confirmed high level amplification of *MYC* on chromosome 8q24.21 as a recurrent genetic alteration found exclusively in 55% of AS secondary to irradiation or chronic lymphedema, but not in primary AS. Amplification of *MYC* did not predispose to high grade morphology or increased cell turnover. In conclusion, despite their identical morphology, secondary AS are genetically different from primary AS and are characterized by a high frequency of high level amplifications of *MYC*. This finding may have implications both for the diagnosis and treatment of these tumors. *(Am J Pathol 2010, 176:34–39; DOI: 10.2353/ajpath.2010.090637)*

Angiosarcomas (AS) are rare sarcomas with morphological and functional properties of endothelial cells.[1] AS represent <1% of all sarcomas.[2] Roughly 35% of cases arise in the skin, 25% in soft tissue and the rest in various other locations including breast, liver, spleen, and bone.[1] The prognosis of AS has generally been considered to be poor with unpredictable clinical behavior. However, several publications clearly showed that prognosis depends on the primary site with a particularly poor prognosis for tumors arising in liver, spleen, heart, and bone with a 5-year-survival rate of 0%, as compared with approximately 50% for skin and soft tissue AS.[3,4] Other factors

GENES, CHROMOSOMES & CANCER 50:25–33 (2011)

Consistent *MYC* and *FLT4* Gene Amplification in Radiation-Induced Angiosarcoma But Not in Other Radiation-Associated Atypical Vascular Lesions

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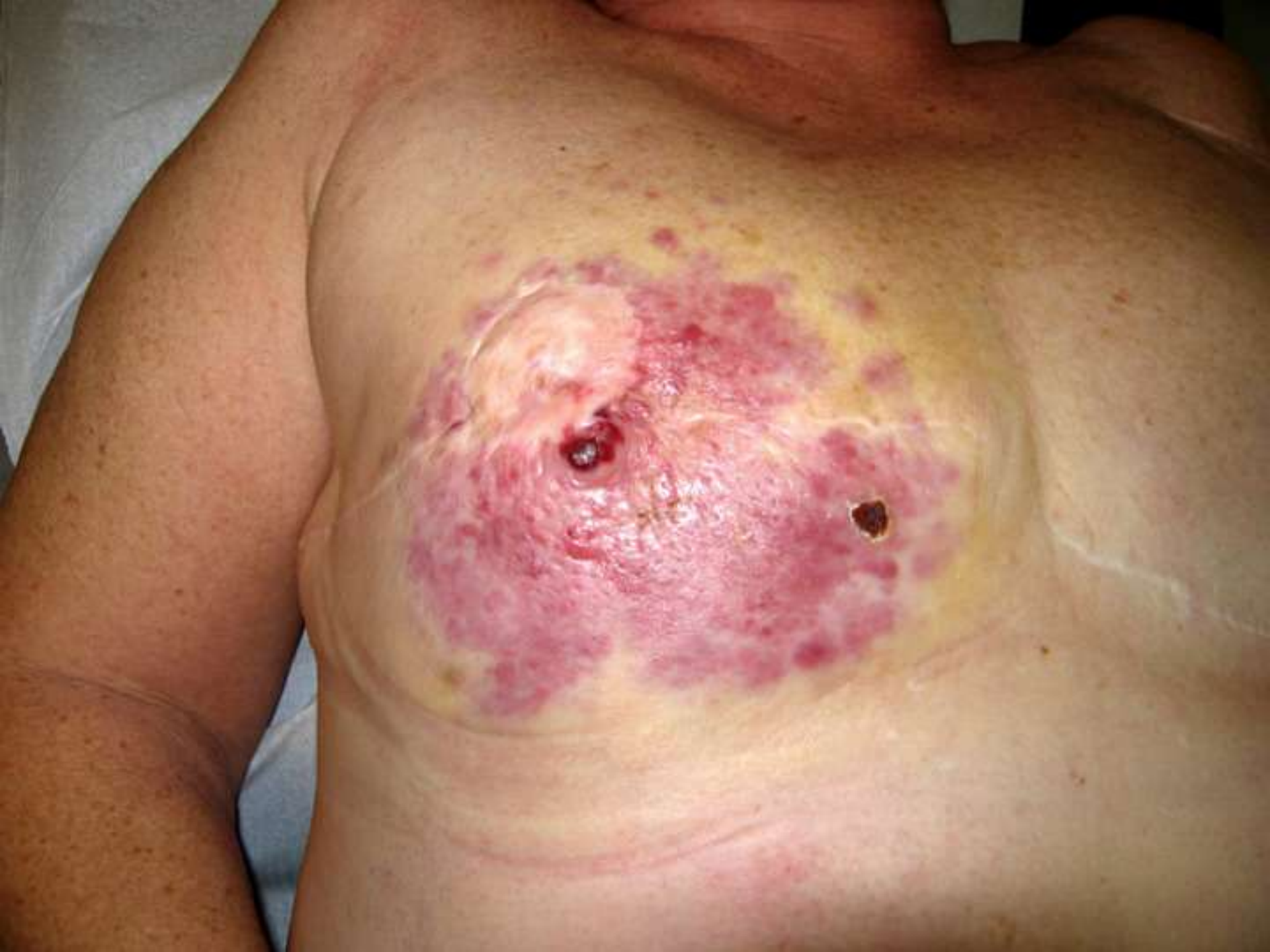
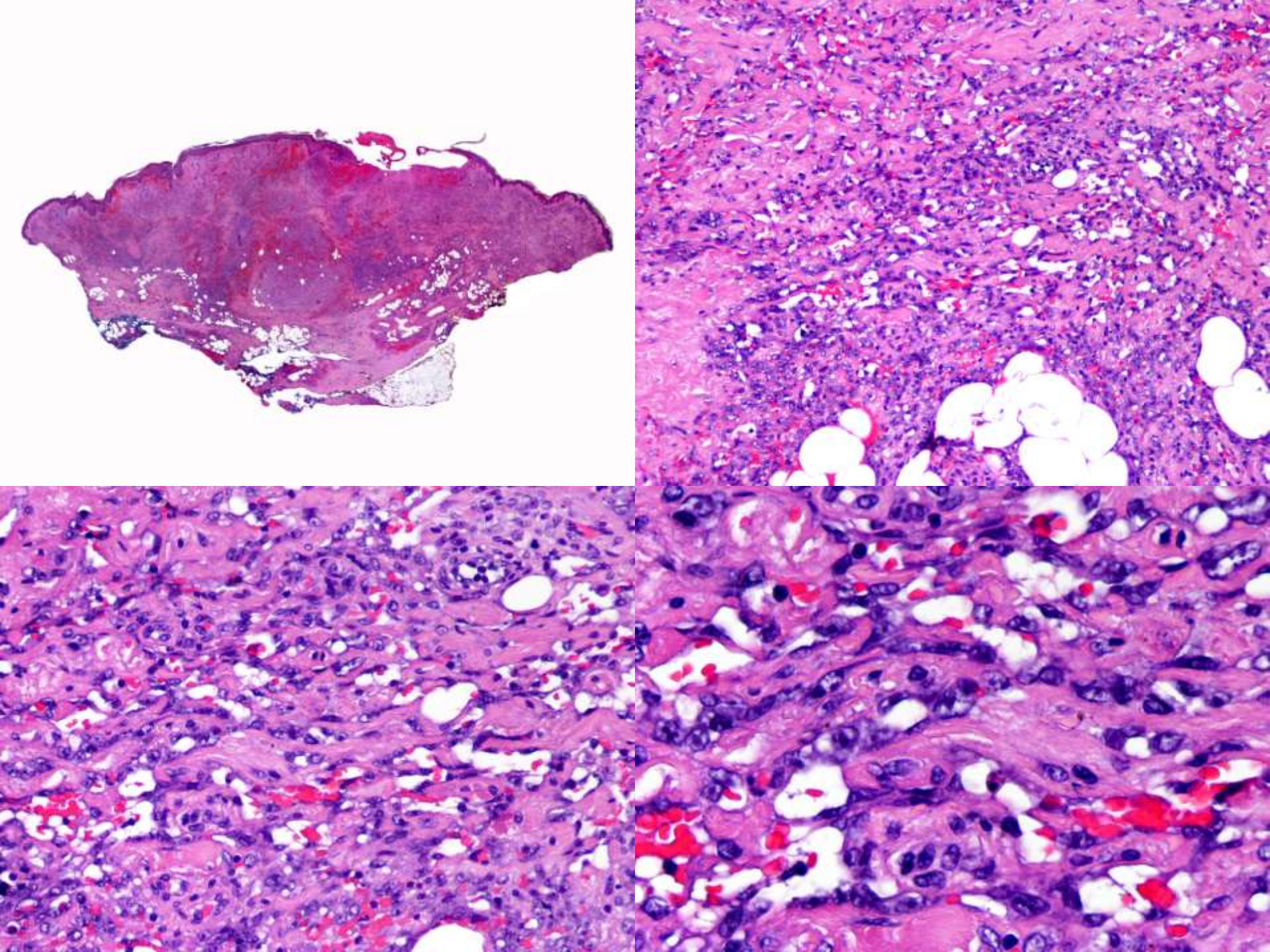
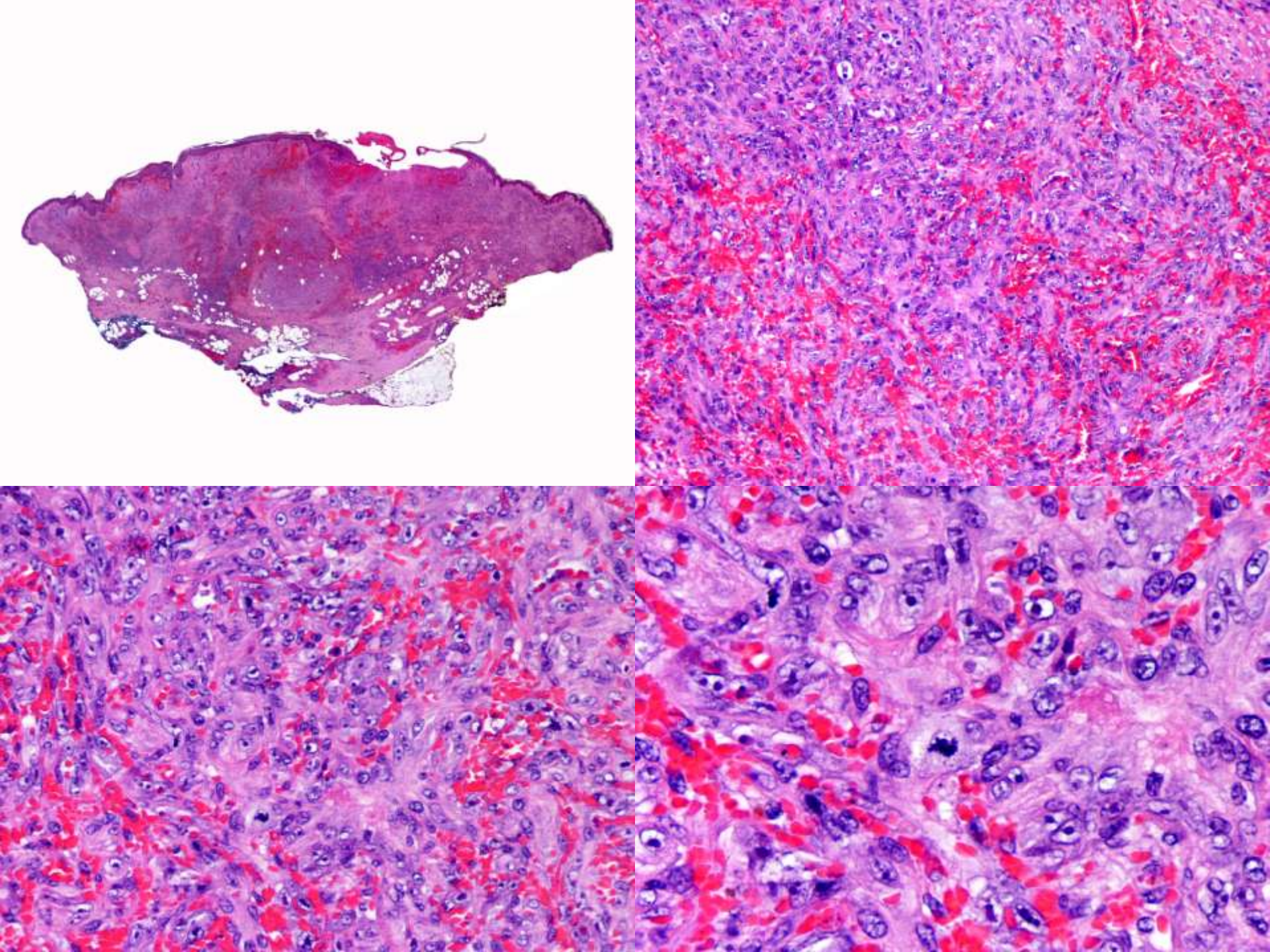
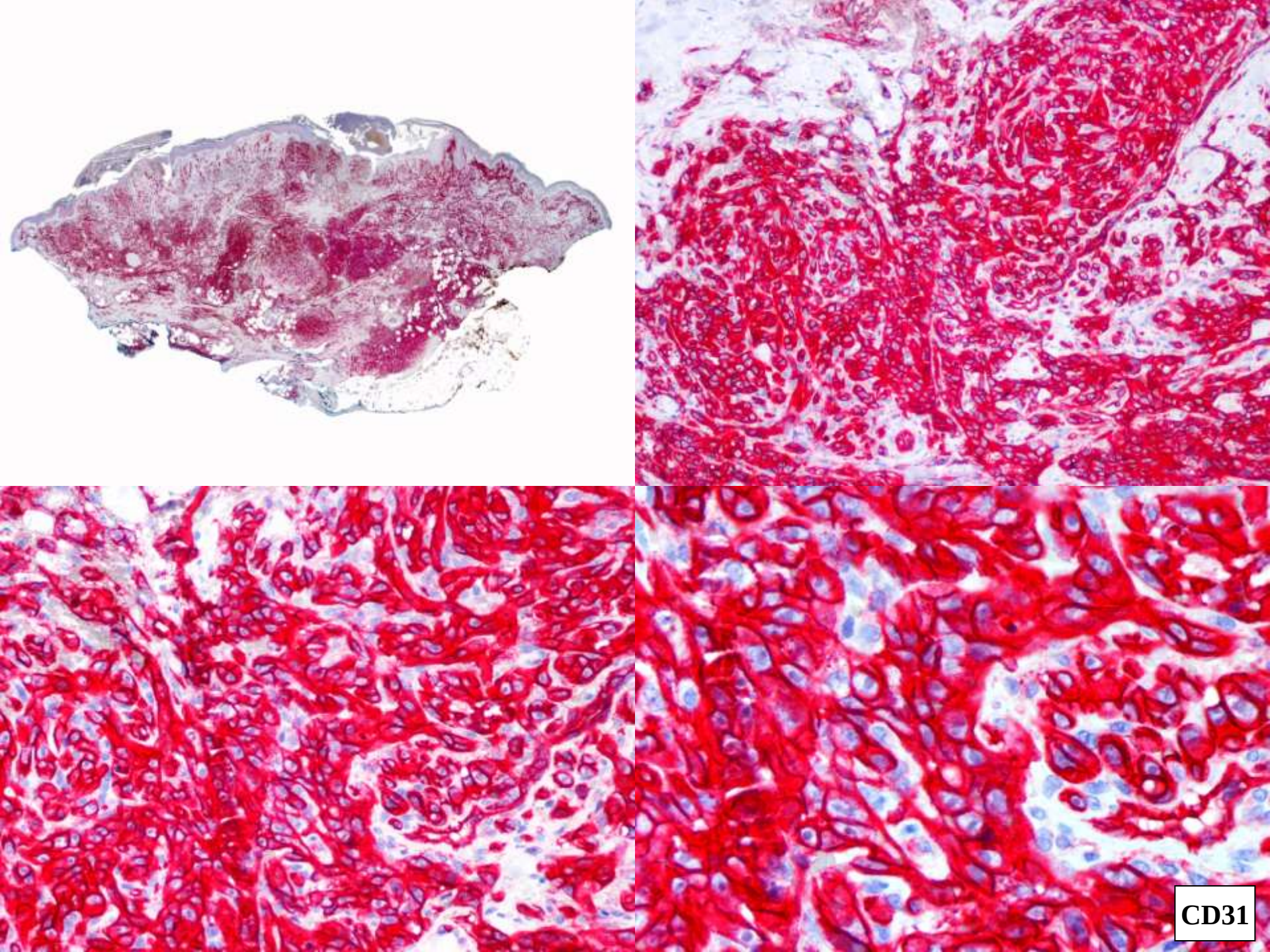
Angiosarcoma (AS) is a distinct group of sarcomas characterized by upregulation of vascular-specific receptor tyrosine kinases, including *TIE1*, *KDR*, *TEK*, and *FLT1*. In keeping with the clinical heterogeneity, gene-expression profiling distinguishes two AS genomic clusters, which correlate with anatomical location and prior exposure to radiation. Furthermore, a high percentage of secondary AS, but not primary AS, shows distinct 8q24 chromosomal gains, due to *MYC* amplification. In this study, we mined the transcriptional output of 10 secondary and 11 primary AS to better define the dichotomy in the pathogenesis of these two clinical subsets. The oncogenic role of *MYC* was investigated further in secondary AS as well as in radiation-induced atypical vascular lesions (AVL) and other radiation-associated sarcomas. High-level *MYC* amplification was found in 100% of secondary AS, but in none of the AVL or other radiation-associated sarcomas. Coamplification of *FLT4* (encoding VEGFR3) was identified in 25% of secondary AS, but not in other types. Our findings reinforce the distinct pathogenesis of AS subtypes, with *MYC* amplification being an early, but necessary event in secondary AS. Secondary genetic hits, such as *FLT4* gene coamplification or *KDR* mutations, may play a role in tumor progression as well as potential therapeutic targeting.





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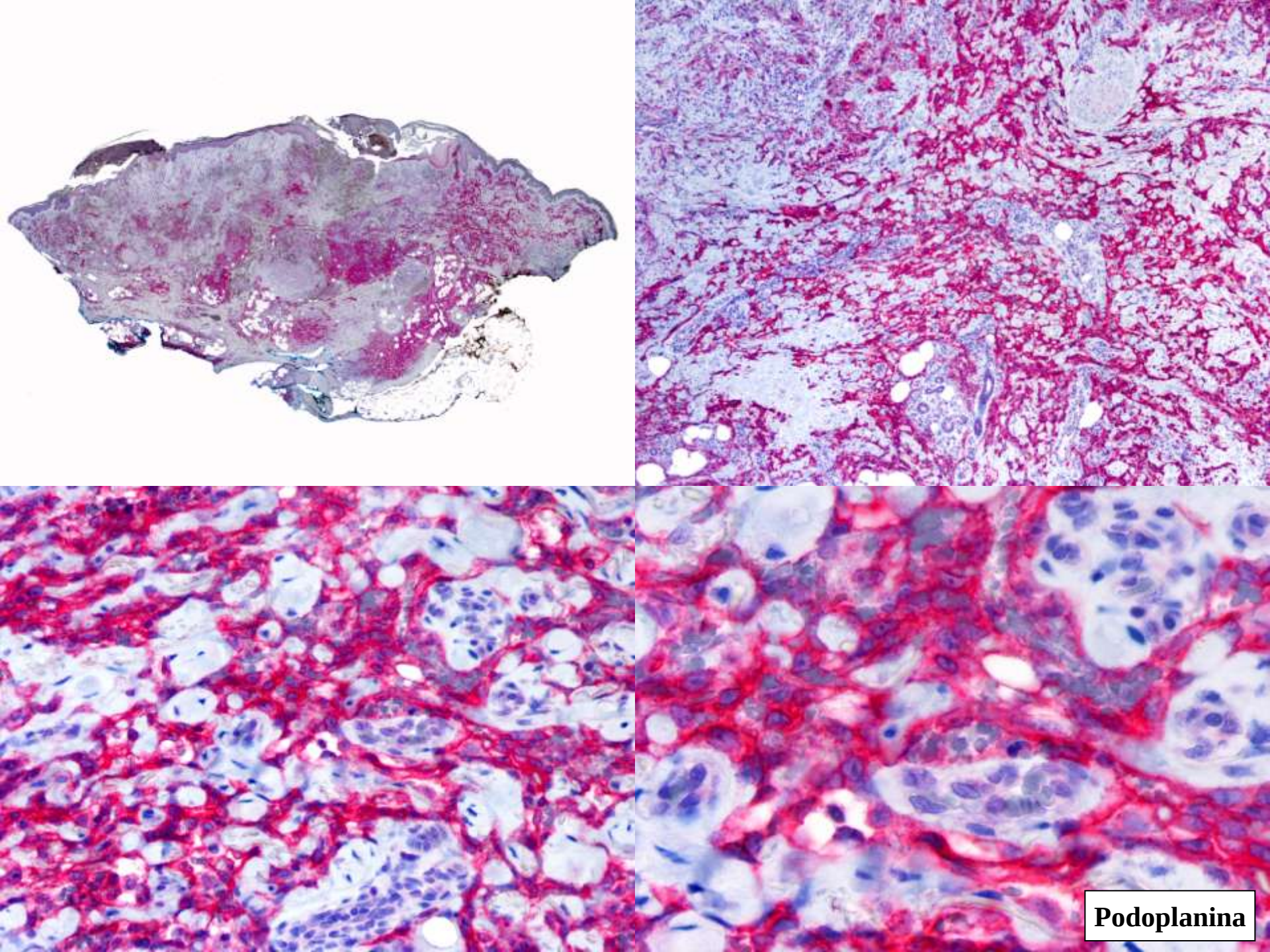
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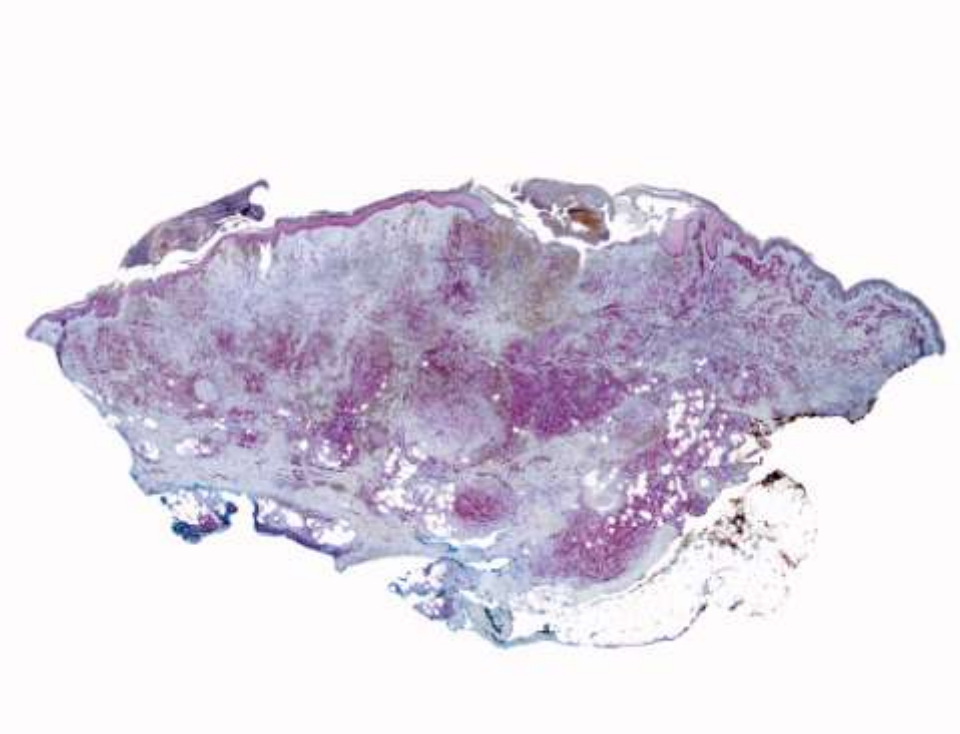

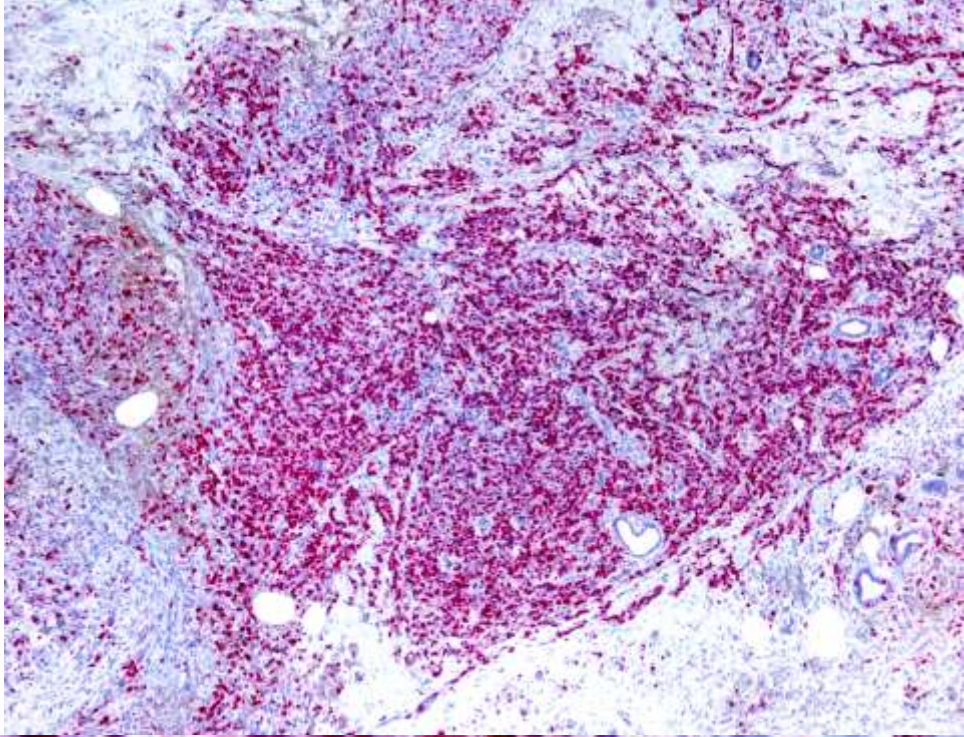

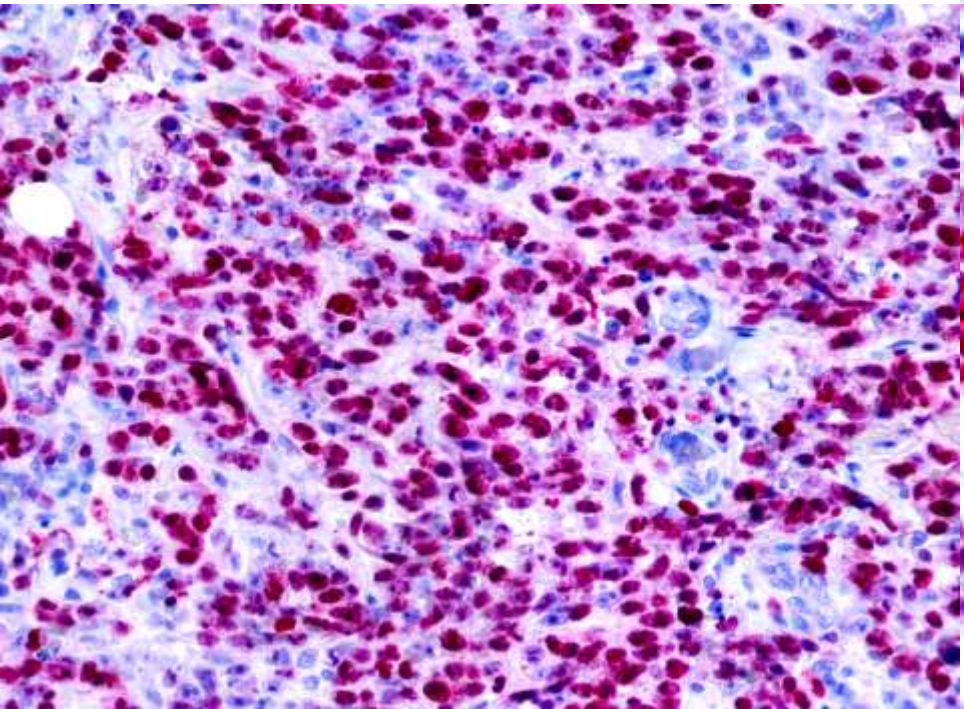

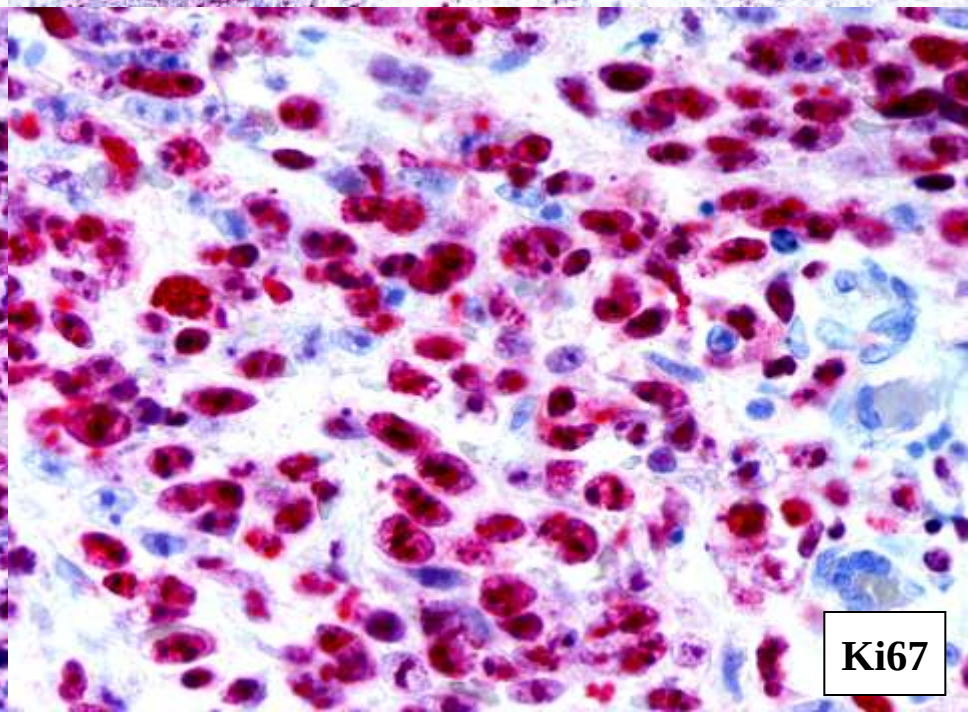
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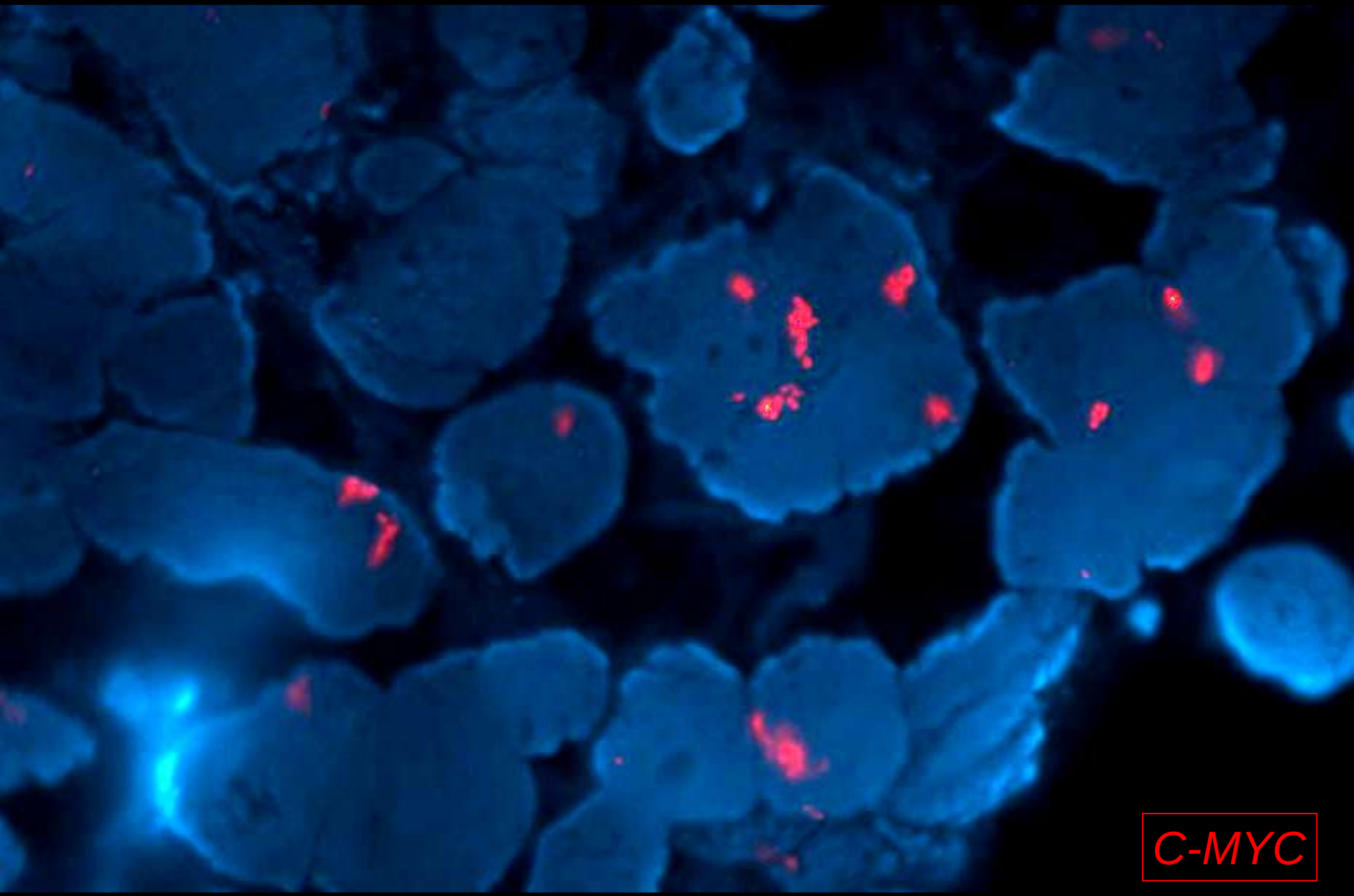
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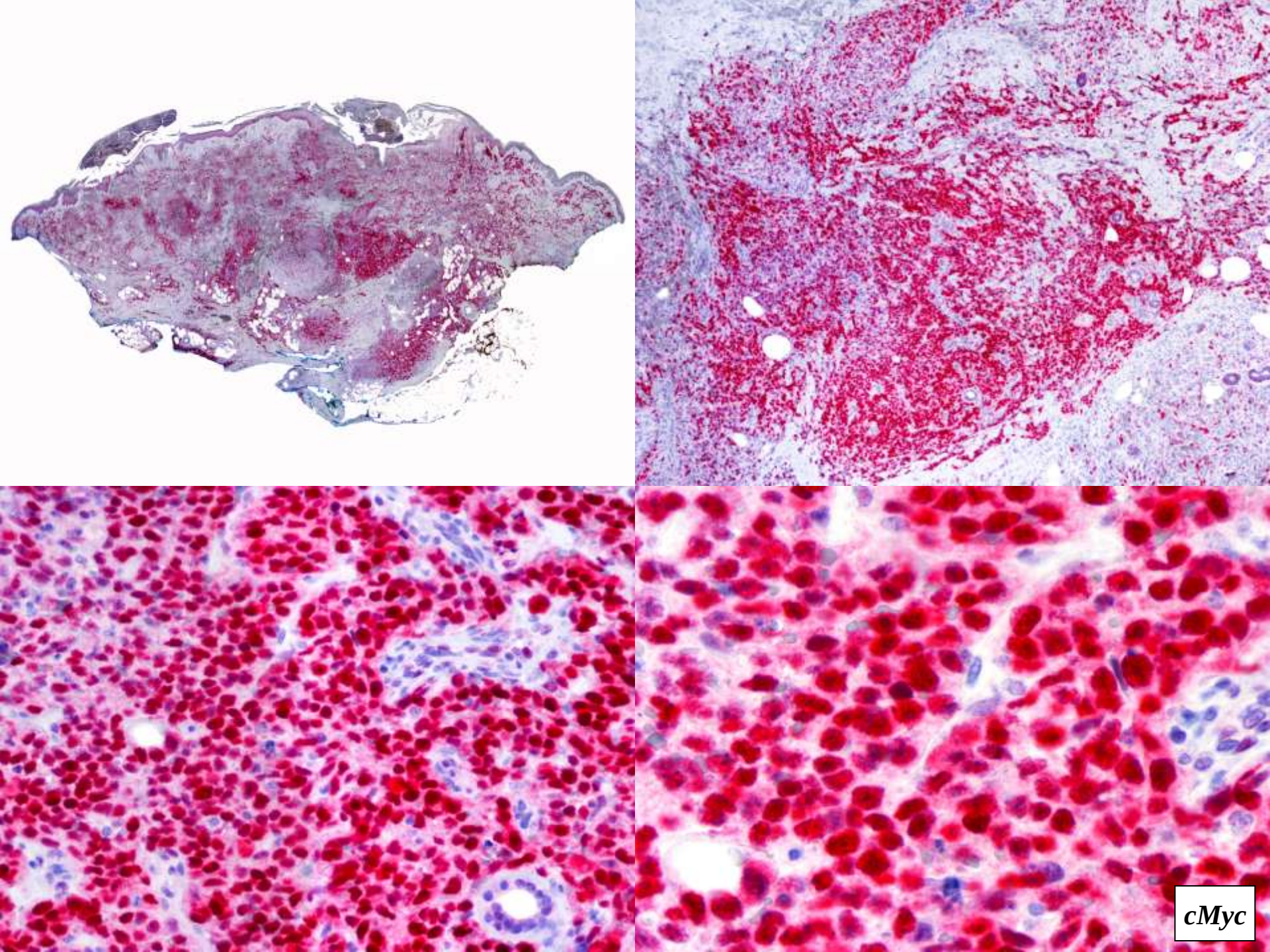
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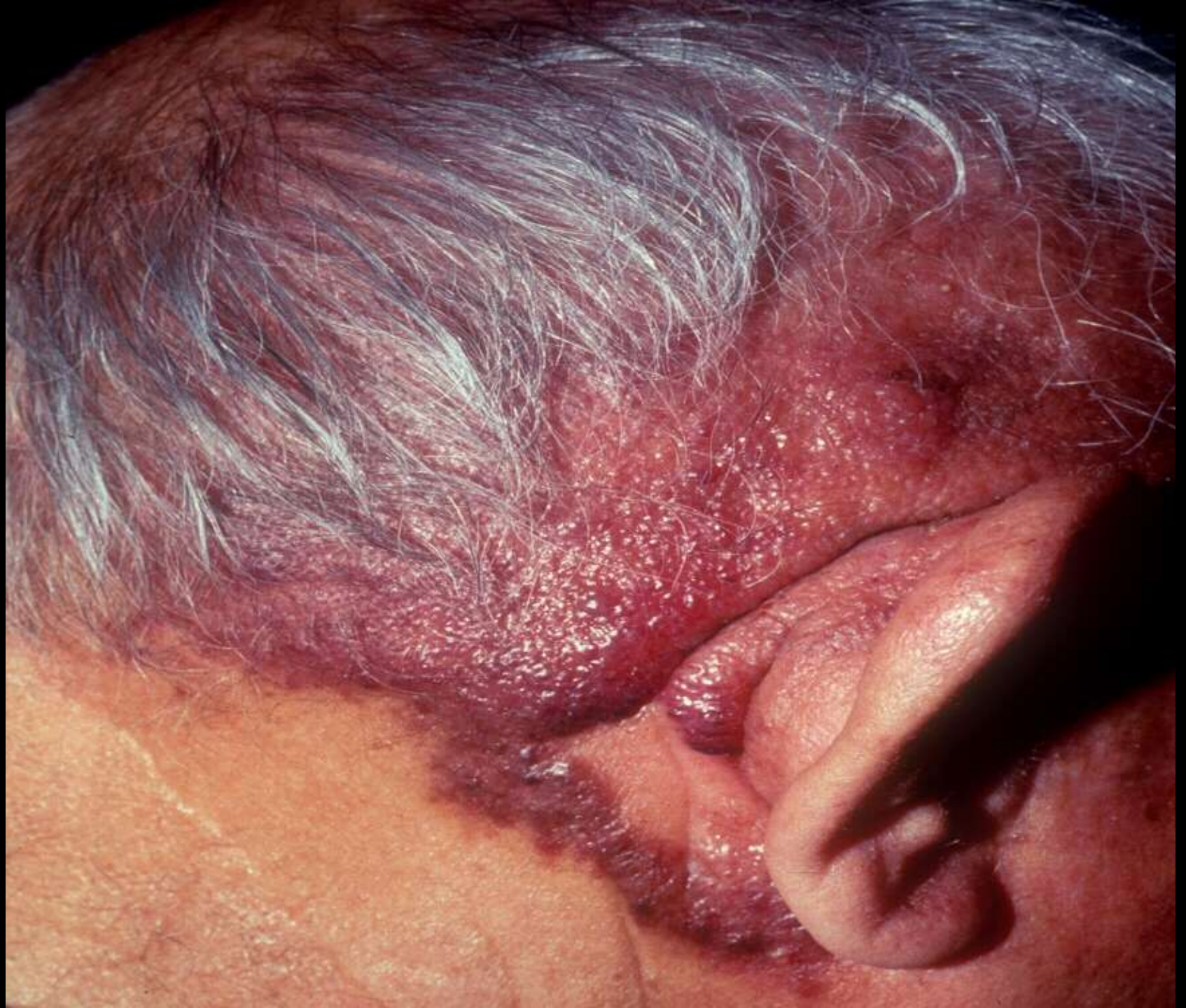

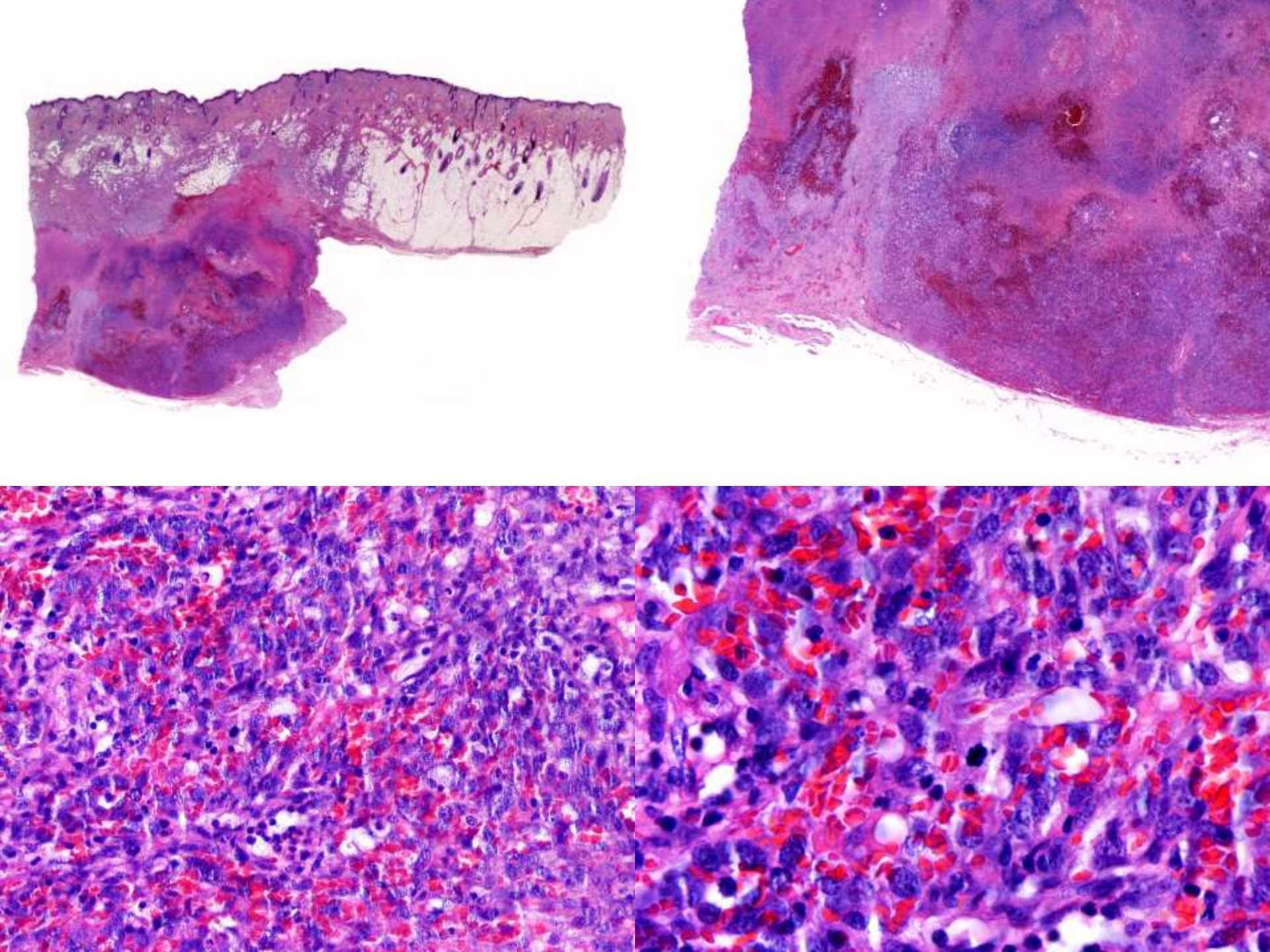

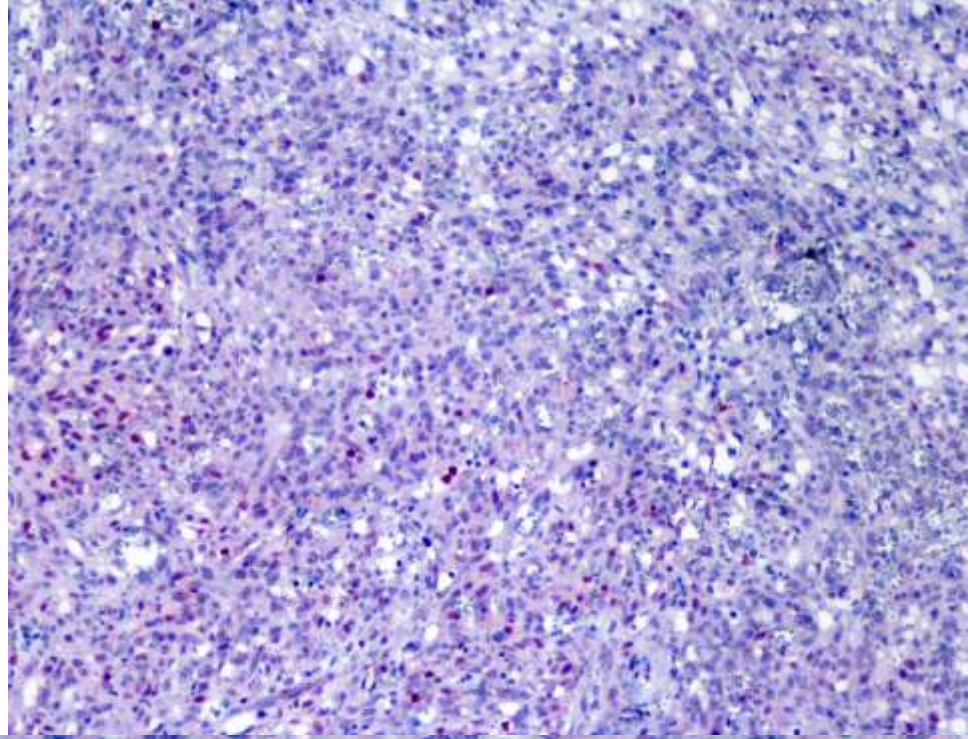

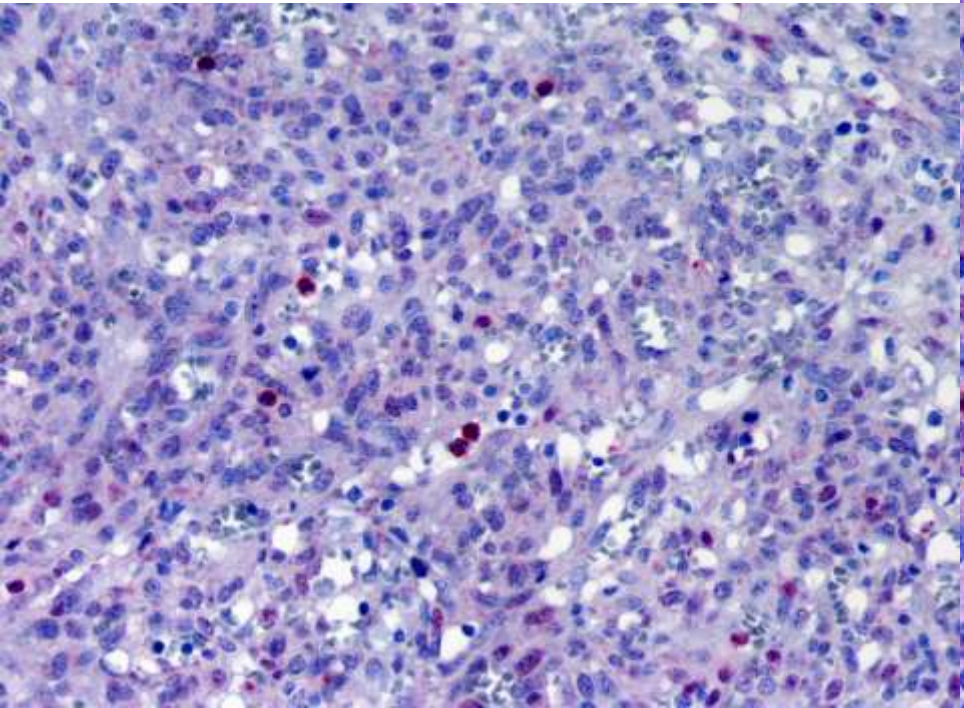

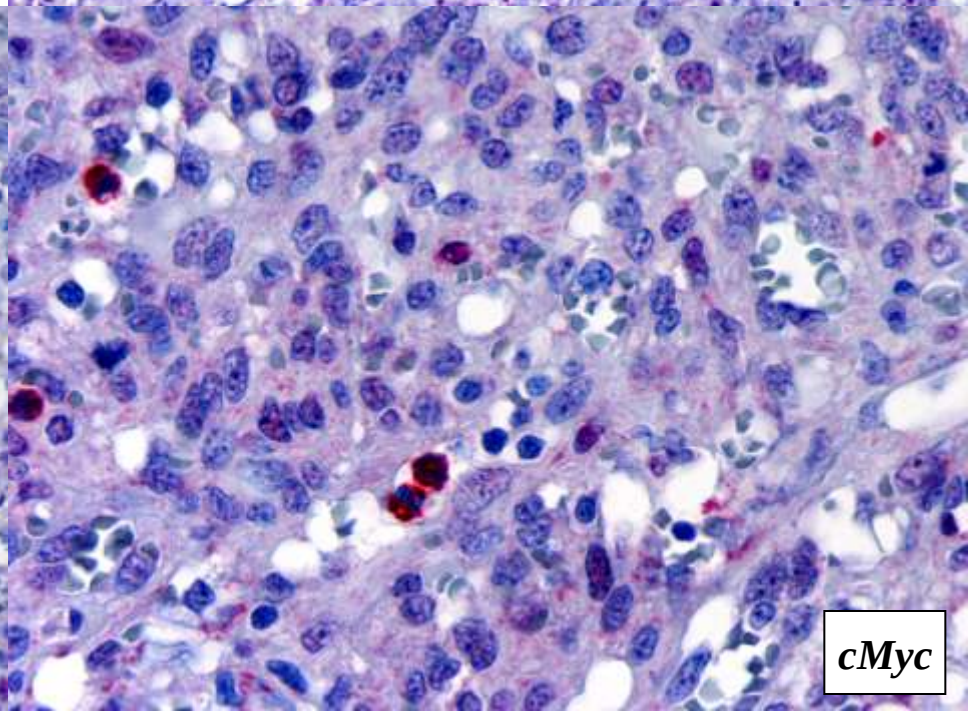
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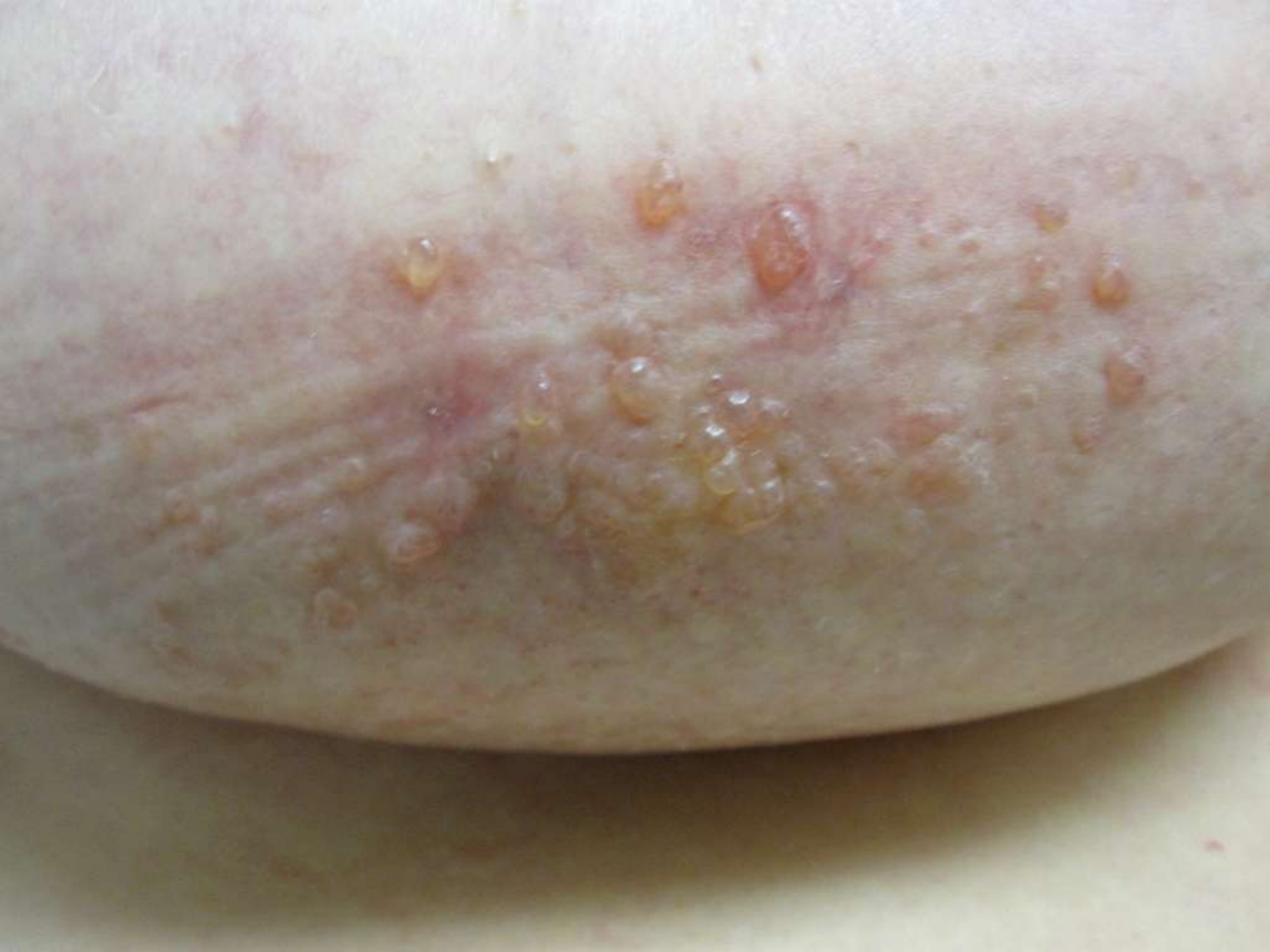

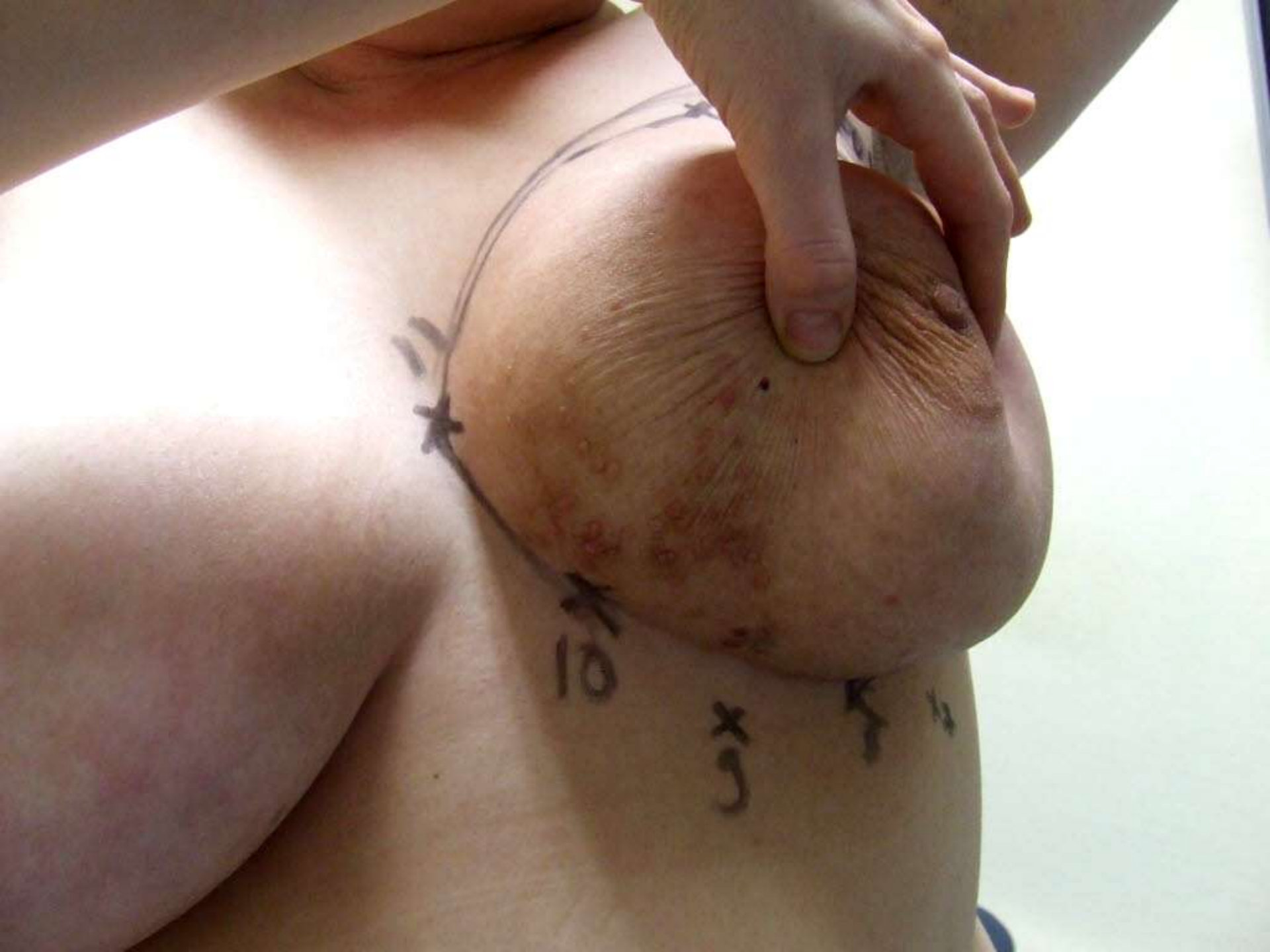
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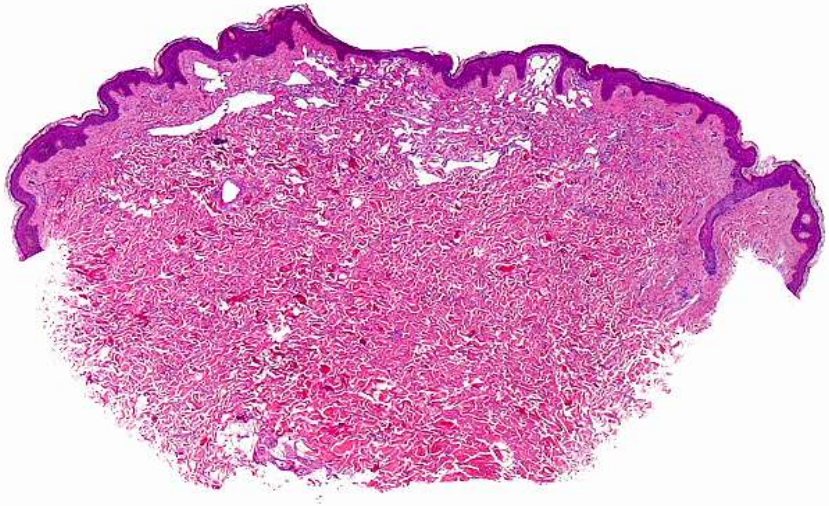

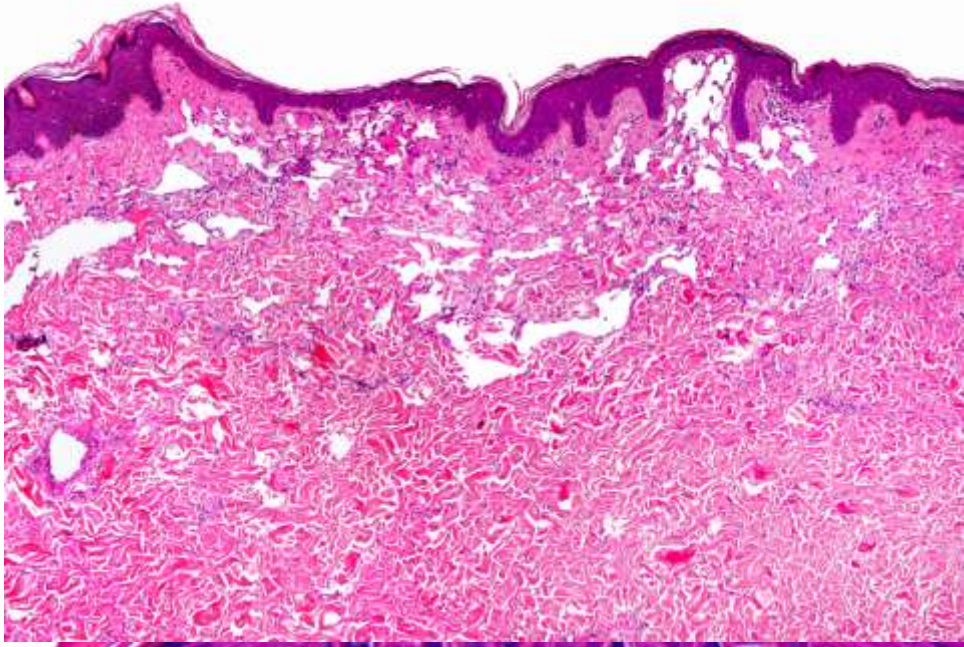

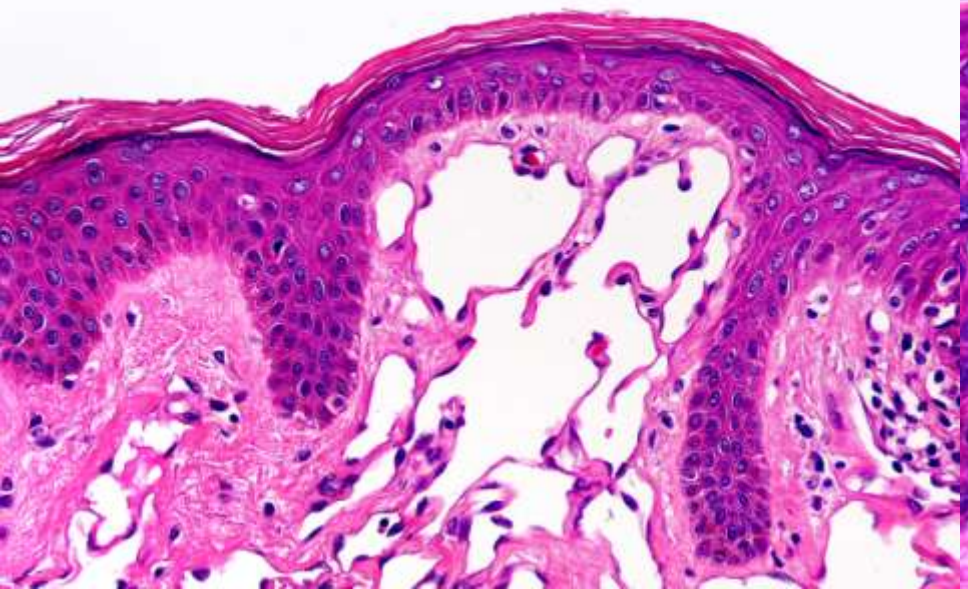

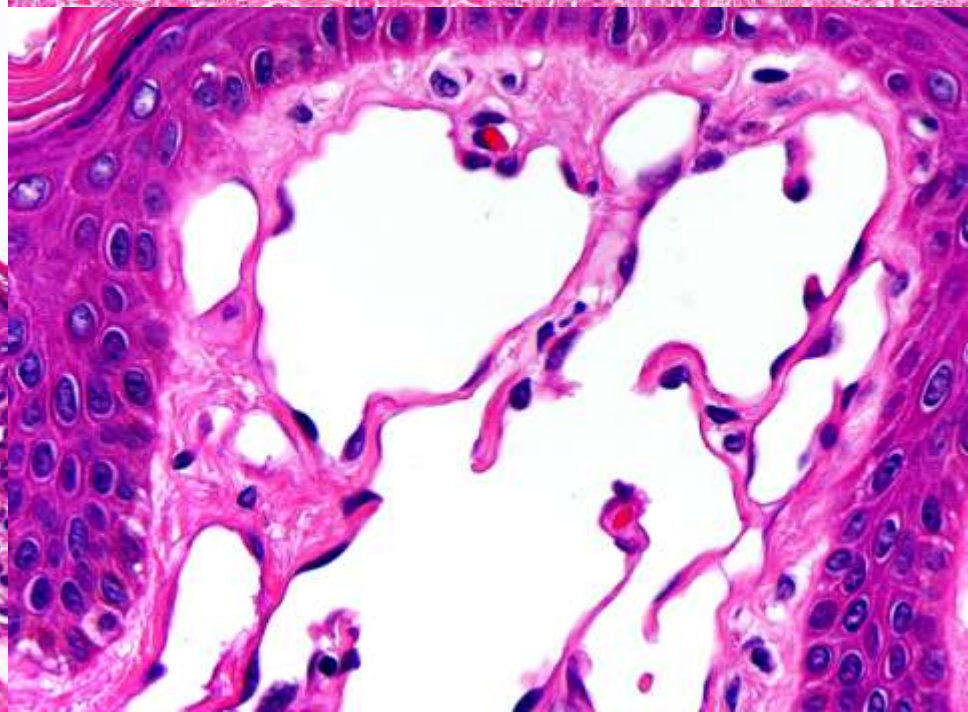

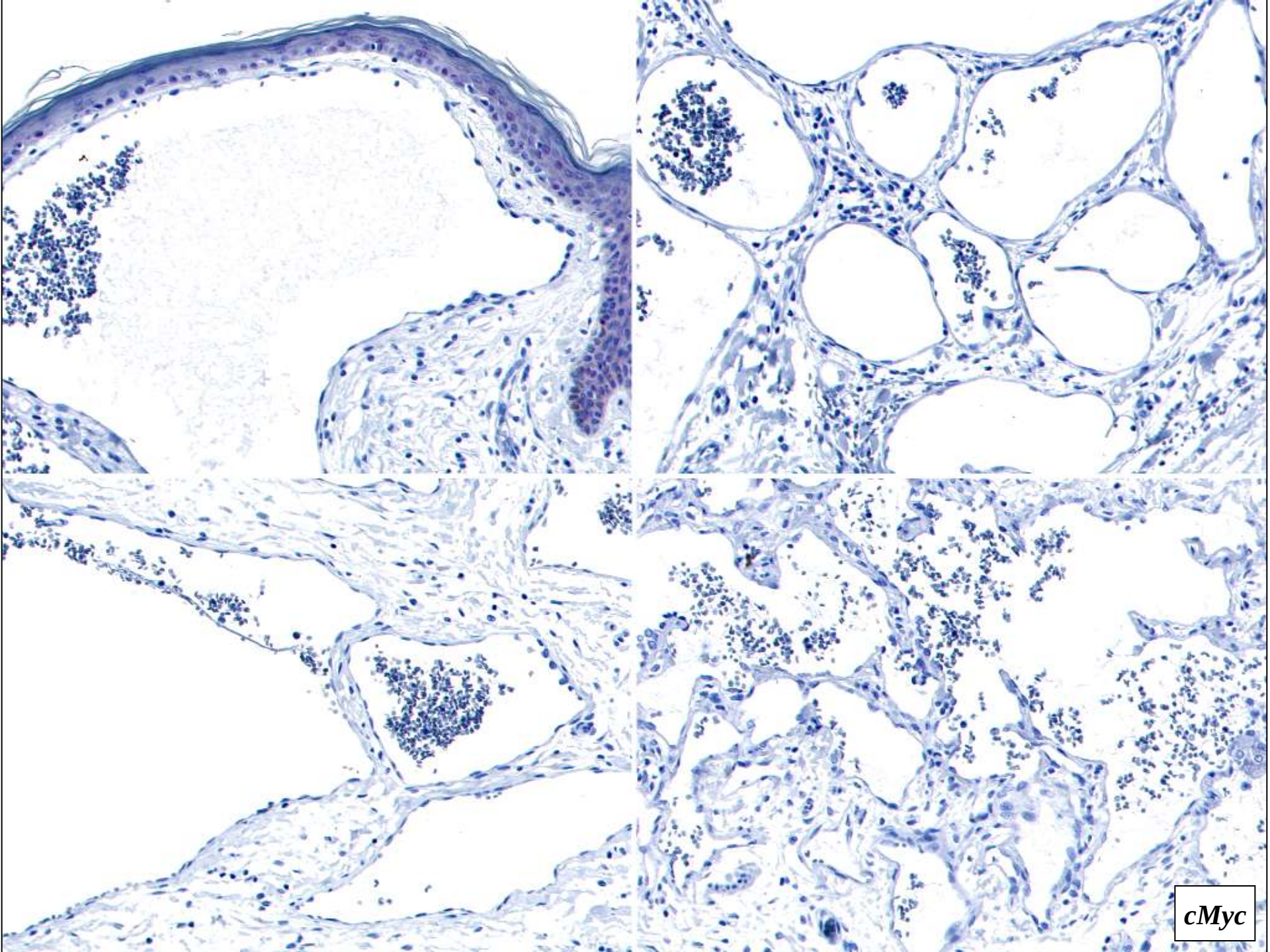
cMyc

Radiation-Associated Cutaneous Atypical Vascular Lesions and Angiosarcoma

Clinicopathologic Analysis of 42 Cases

Thomas Brenn, MD, PhD and Christopher D. M. Fletcher, MD, FRCPath

Abstract: Cutaneous angiosarcoma is a rare but well-recognized complication after radiation therapy. Atypical post-radiation vascular lesions (AVLs) with a benign course have been described recently, but few cases with limited follow-up have been studied so far. A total of 42 cases diagnosed as either radiation-associated cutaneous vascular lesions or angiosarcoma were retrieved from departmental and consultation files from 1993 to 2003. Hematoxylin and eosin-stained sections and clinical as well as follow-up data were evaluated. All patients were female with a median age of 59 years (range, 36–90 years). Presentation ranged from small erythematous/violaceous papules or nodules to large plaques with discoloration located on the chest wall (35), abdomen (2), shoulder, groin, flank, axilla, and lower leg (1 each). Reasons for radiation included breast carcinoma (35 cases) and a variety of other lesions (mainly malignant disease). Size range was 0.1 to 20 cm. Angiosarcomas presented as larger lesions (median, 7.5 cm) compared with AVLs (median, 0.5 cm). The time interval from radiation was significantly shorter for the development of AVL (median, 3.5 years) compared with cutaneous angiosarcoma (median, 6 years). Histologic evaluation revealed 26 lesions meeting criteria for angiosarcoma, ranging from morphologically low-grade to high-grade; 16 cases were classified as AVLs. These were fairly well-circumscribed lesions confined within superficial to mid dermis and composed of complex anastomosing and focally dilated vascular spaces. Some showed prominent hyperchromatic endothelial cells, while others were characterized by areas with a dissecting growth pattern within dermal collagen. Endothelial multilayering was absent. Clinical follow-up, available for 36 patients (range, 2–84 months; median, 17 months), revealed 4 patients who died of disease, 4 patients had systemic metastasis, and 12 patients with local recurrence. All patients with systemic relapse had an initial diagnosis of angiosarcoma. One patient with an AVL had a recurrence at the same site, 3 patients developed additional new lesions, and 1 patient developed multiple small papules on the chest wall, which progressed from an AVL to angiosarcoma. This study outlines the morphologic spectrum of radiation-associated cutaneous AVLs. No adverse outcome has been observed so far in this more benign subset of cases, but longer-term follow-up is necessary.

Key Words: skin, angiosarcoma, atypical vascular lesion, radiation, breast

(*Am J Surg Pathol* 2005;29:983–996)

Cutaneous angiosarcoma is a rare but well-recognized and sinister complication following treatment of breast carcinoma, being associated with significant morbidity as well as mortality. It develops in two clinically distinct settings, either on the arm in association with lymphedema following mastectomy and axillary lymph node dissection, or in the field of prior radiation treatment, typically on the chest wall, in the setting of breast-conserving therapy. At least anecdotally, there appears to be an increasing incidence in postradiation angiosarcoma because of a change in the management of breast cancer with more frequent use of radiation in the setting of breast-conserving therapy. Postradiation angiosarcoma may also be a complication of radiation therapy for various benign as well as malignant diseases other than breast carcinoma. The morphologic spectrum of postradiation vascular lesions is, however, wide and, recently, cutaneous atypical vascular lesions (AVLs) (without frank features of malignancy) have been reported to arise after radiation in the setting of breast-conserving therapy for breast carcinoma.[17] These AVLs show morphologic overlap with well-differentiated angiosarcoma, but their clinical behavior so far is reported to be benign. However, only a few reports with limited follow-up are available. The histologic and clinical separation of AVL from well-differentiated angiosarcoma may be difficult and is further complicated by the fact that areas histologically indistinguishable from AVL may be present within a larger lesion of angiosarcoma (and our personal observations). In addition, well-differentiated angiosarcoma has been reported to develop from a preceding lesion with features of an AVL. The aim of the present study was to further characterize these AVLs clinically and histologically and to study their morphology and behavior in comparison with postradiation cutaneous angiosarcoma.

Histopathology 2006, **48**, 106–114. DOI: 10.1111/j.1365-2559.2005.02293.x

REVIEW

Postradiation vascular proliferations: an increasing problem

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Postradiation vascular proliferations: an increasing problem

The occurrence of cutaneous vascular lesions is a rare but well-documented complication of radiation treatment and may be associated with significant morbidity as well as mortality. The overall incidence is low but appears to be rising due to a change in the prevailing treatment of breast carcinoma with increased use of radiation in the setting of breast-conserving therapy for stage 1 and 2 disease. The spectrum of postradiation vascular lesions is wide and ranges from atypical vascular lesions with reportedly benign clinical behaviour to frank cutaneous angiosarcoma. There is, however, significant clinical as well as histological overlap. It is frequently difficult to classify these postradiation vascular lesions accurately and they create an emerging diagnostic and therapeutic challenge to both pathologists and clinicians. Experience with these vascular lesions is very limited, and this article aims to provide an overview of our current understanding and concept of radiation-associated vascular lesions with focus on their clinical and histological presentation as well as behaviour and treatment.

Keywords: angiosarcoma, atypical vascular lesion, breast, radiation, skin

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Post-radiotherapy vascular proliferations in mammary skin: A clinicopathologic study of 11 cases

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Background: Post-radiotherapy atypical vascular lesions (AVL) in mammary skin show significant clinical and histopathologic overlap with well-differentiated angiosarcoma (AS) and pose a considerable diagnostic and managerial challenge when encountered.

Objective: We review Stanford's experience with diagnosing AVL and formulate a clinicopathologic approach to these lesions.

Methods: We performed a clinicopathologic study on 11 cases that were initially diagnosed as AVL and examined whether there are specific clinical or histopathologic features that delineate AVLs from well-differentiated AS.

Results: Clinically, all patients were women with a mean age of 68.1 years, had a history of infiltrating breast carcinoma, and were treated by excision with postoperative radiation therapy. All lesions were located in mammary skin within the prior radiation field. The clinical presentation included erythema, telangiectasias, papules, plaques, and nodules. All patients were diagnosed with AVL on initial biopsy. Six patients showed no recurrence or progression of disease following incomplete excision with no further therapy (3/6) or re-excision with negative margins (3/6). The remaining 5 patients were shown to have AS in the re-excision specimen. The patients diagnosed with AS were older and had a shorter interval from radiation as compared to those who did not experience an adverse outcome. Histologically, all initial biopsy specimens were transected and were characterized by complex, anastomosing vascular proliferations with dilated spaces. Each case was morphologically evaluated according to the AVL criteria of Fineberg and Rosen. Three cases met all of the criteria for AVL, and these patients showed no progression of disease. The remaining cases met most but not all diagnostic criteria for AVL and showed some features of AS, but fell short of a definitive diagnosis of AS, including the 5 cases that were subsequently diagnosed as angiosarcoma.

Limitations: This retrospective study utilized a small number of cases from a single consultation service; therefore, some inherent selection bias may exist.

Conclusion: We could not identify unequivocal clinical or histologic criteria that allows for a sharp separation between AVL and AS. Dermatologists and pathologists need to be aware of the overlap between AVL and well-differentiated AS and all patients who receive a diagnosis of AVL should undergo complete excision with close clinical follow-up and biopsy of any new lesions. (J Am Acad Dermatol 2007;57:126-33.)

Atypical Vascular Lesions After Surgery and Radiation of the Breast

A Clinicopathologic Study of 32 Cases Analyzing Histologic Heterogeneity and Association With Angiosarcoma

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Abstract: We report the clinicopathologic study of 32 cases of atypical vascular lesions (AVLs) after surgery and radiation of the breast, which were referred to us in consultation over a 17-year period. The patients, all women, ranged in age from 41 to 95 years (mean 61 y). The lesions developed within the radiation field from 1 to 12 years (median 6.0 y) after therapy. They occurred as one (n = 18) or more (n = 10) flesh-colored papules or erythematous patches/plaques ranging in size from 1 to 60 mm (mean 8.0 mm, median 4.0 mm). Tumors could be divided into 2 histologic types: a lymphatic type (LT) (n = 22) and a vascular type (VT) (n = 10). LT AVLs consisted predominantly of thin-walled, variably anastomosing lymphatic vessels that were usually confined to the superficial dermis but occasionally extended into the deep dermis and even subcutis. The VT (n = 10) typically consisted of small, irregularly dispersed, often blood-filled, pericyte-invested, capillary-sized vessels involving the superficial or deep dermis. VTs were often associated with extravasated erythrocytes, hemosiderin, and a surrounding minor LT component. In 4 cases, endothelial atypia, consisting of nuclear and nucleolar enlargement, was noted. Follow-up of 21 patients with LT AVLs (1 to 106 mo; mean 47 mo) disclosed recurrence/additional lesions in 6, all of whom had additional surgery. Of the 21 patients, 17 are alive without disease, 1 is alive with disease, 1 died of breast carcinoma, 1 died of unknown causes, and 1 showed progressive histologic changes in the AVLs over a period of 5 years resulting in a well-differentiated angiosarcoma. Follow-up in 8 patients with VT AVL (2 to 181 mo; mean 40 mo) disclosed that 6 were alive and well, but 2 of the 4 patients whose lesions displayed endothelial atypia had additional complications. One patient underwent a mastectomy that revealed extensive residual AVL and the second developed a high-grade angiosarcoma after 14 months. We conclude that AVLs encompass a wider spectrum of changes than previously appreciated, ranging from superficial lymphatic proliferations to more complex lymphatic and capillary vascular lesions. There seems to be an association of AVL with angiosarcoma that differs depending on the histologic features, with the VT AVLs having the higher risk. In the 2 patients who developed angiosarcoma, morphologic evidence suggested AVLs to be a precursor rather than simply a risk factor. Future outcome and management studies should take into account these differences.

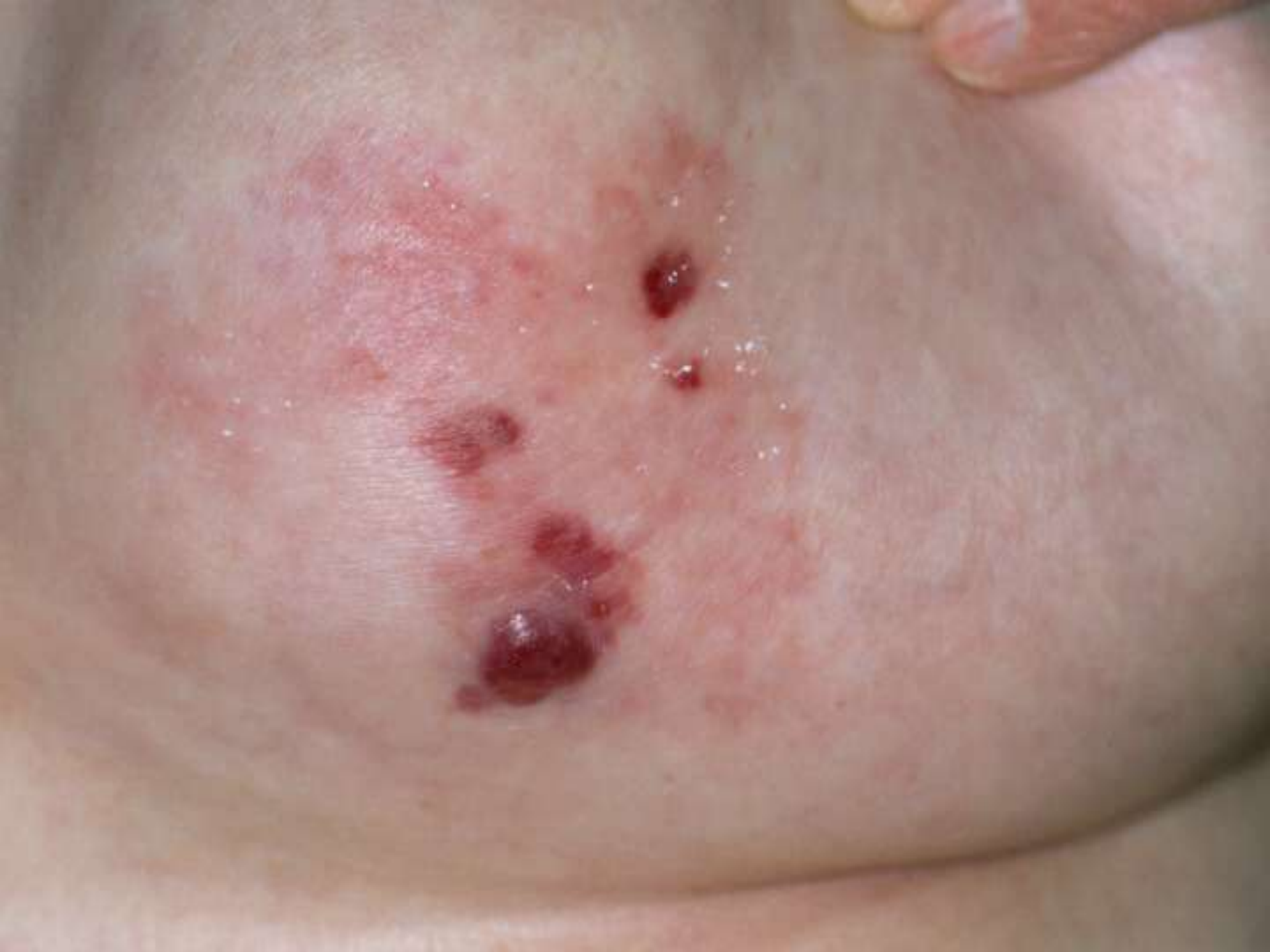
Key Words: radiation, postirradiation angiosarcoma, atypical vascular lesion, breast carcinoma

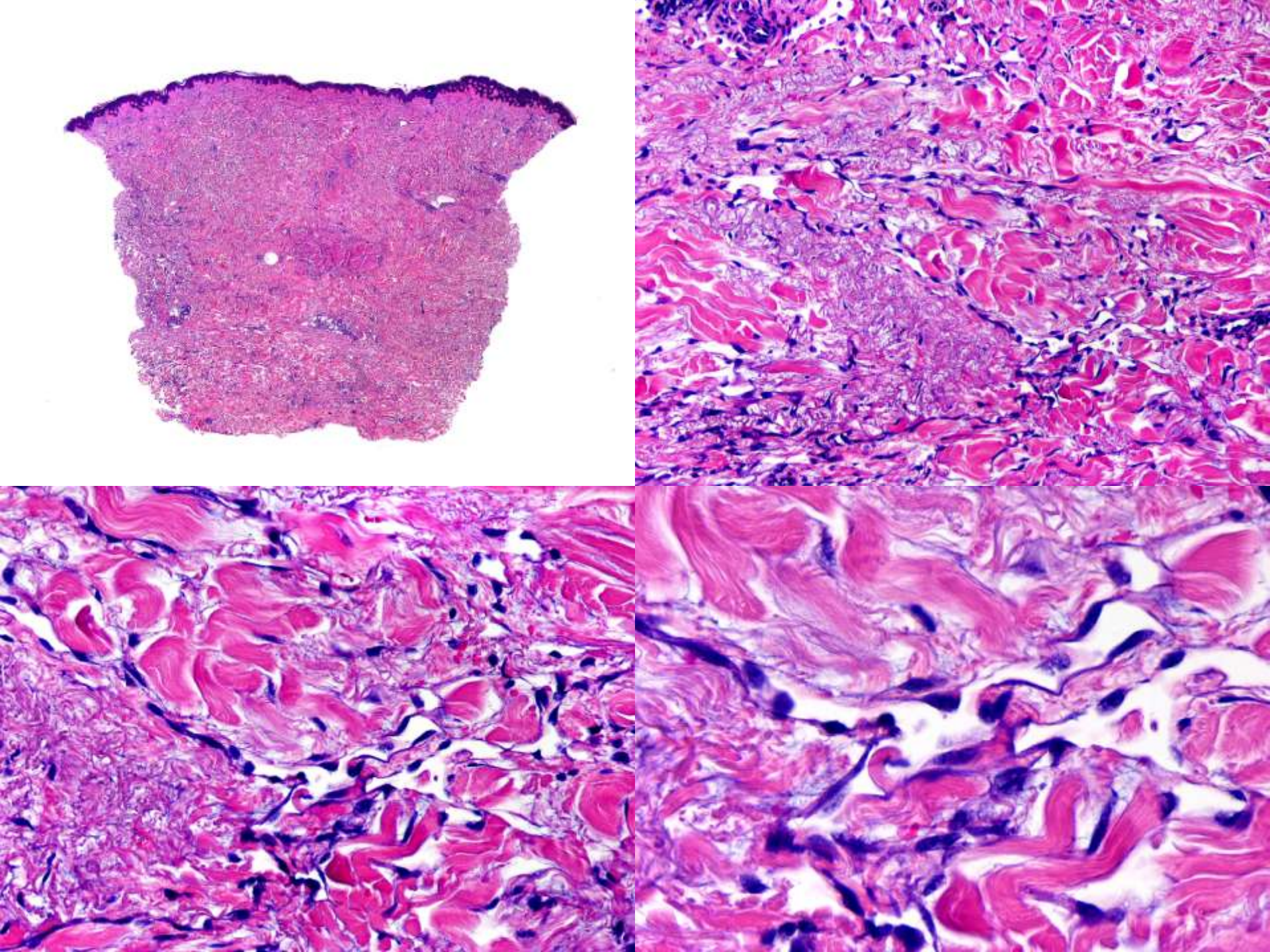
(*Am J Surg Pathol* 2008;32:943–950)

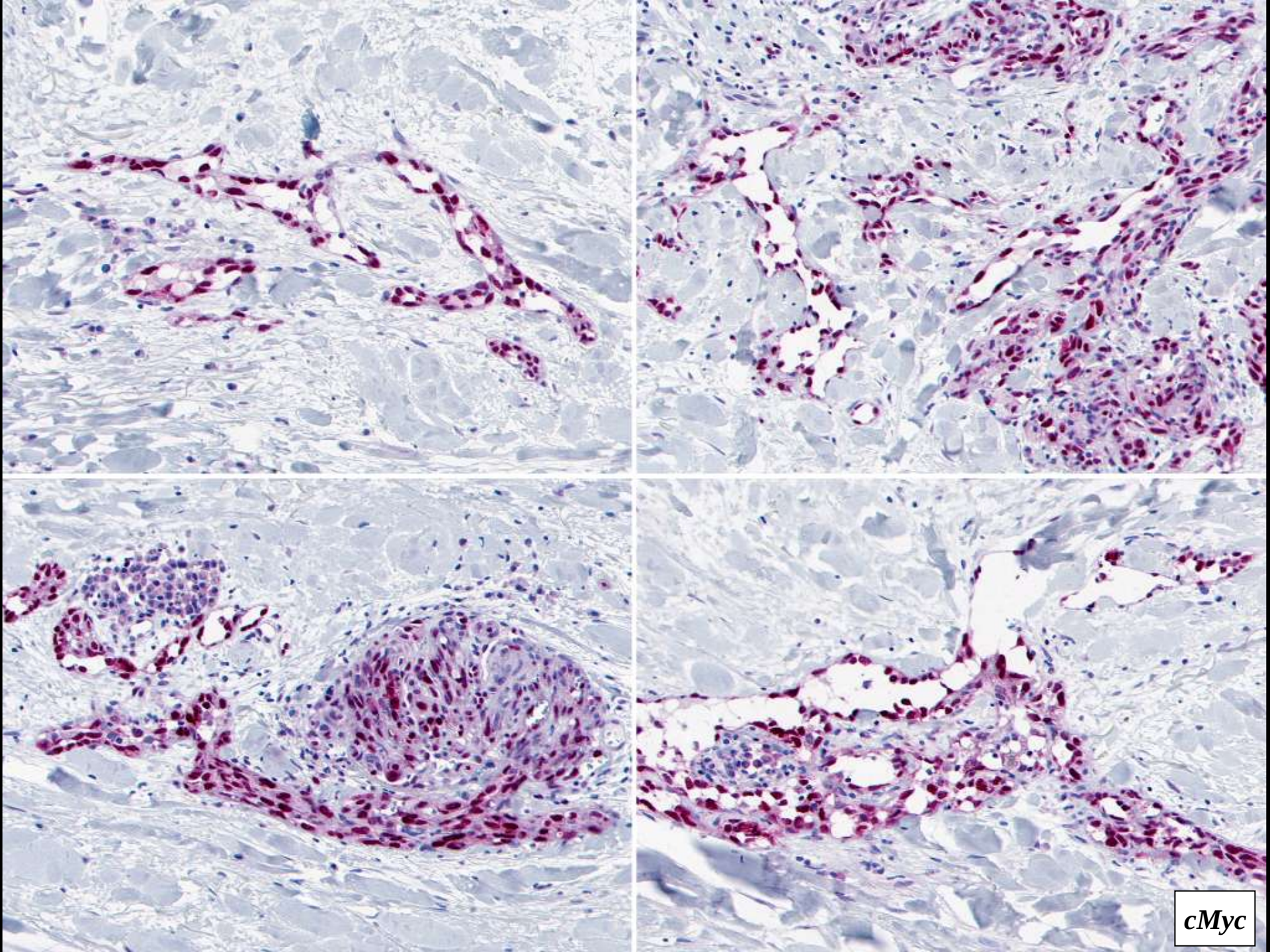
In 1994, Fineberg and Rosen[4] called attention to an unusual group of cutaneous vascular proliferations that developed in women after lumpectomy and radiation for breast carcinoma, which they labeled "atypical vascular lesions" (AVLs) whereas others used the terms "benign lymphangiomatous papules," "benign lymphangioendothelioma," and "acquired progressive lymphangioma." On the basis of 4 cases, they concluded that these were benign and unrelated to postirradiation angiosarcomas.[4] Others have challenged this concept, however, and suggested that AVLs and postirradiation angiosarcomas represent a morphologic continuum,[1] thereby implying that AVLs are a precursor to angiosarcoma. The number of reported cases with follow-up information is still small, and there have been limited efforts to evaluate the histologic heterogeneity of AVL and to correlate these features with outcome. To address these issues, we have analyzed our consultative experience with AVLs spanning a period of 17 years.

MATERIALS AND METHODS

Cases coded as "atypical vascular lesion," "atypical vascular proliferation," "hemangioma," or "vascular tumor of uncertain malignant potential" were retrieved






cMyc

Manner J et al. *MYC* high level amplification is adistinctive feature of angiosarcomas after irradiation or chronic lymphedema. Am J Pathol 2010;176:34-39.
Guo T et al. Consistent *MYC* ad *FLT4* gene amplification in radiation-induced angiosarcoma but not in other radiation-associated atypical vascular lesions. Gene Chromosome Canc 2011;50:25-33.

- **Anomalías cromosómicas en el 8q24 llevan a una amplificación del gen *MYC* en angiosarcomas secundarios a radioterapia y en angiosarcomas asociados con linfedema crónico, pero no en angiosarcomas primarios.**
- **No se demuestra amplificación del *MYC* en proliferaciones vasculares atípicas inducidas por radioterapia.**
- **La amplificación de *MYC* es no exclusiva del angiosarcoma: La proteína LANA del HHV8 del sarcoma de Kaposi estabiliza y activa el *MYC* y un incremento en el número de copias de *MYC* se ha descrito también en el histiocitoma fibroso maligno de hueso, el condrosarcoma de alto grado y osteosarcoma resistente a metotrexato.**