Uzol maternice 29 ročnej ženy

O. Ondič, P. Martínek, J. Bouda, V. Eret, N. Ševčovičová

Sklíčkový seminár

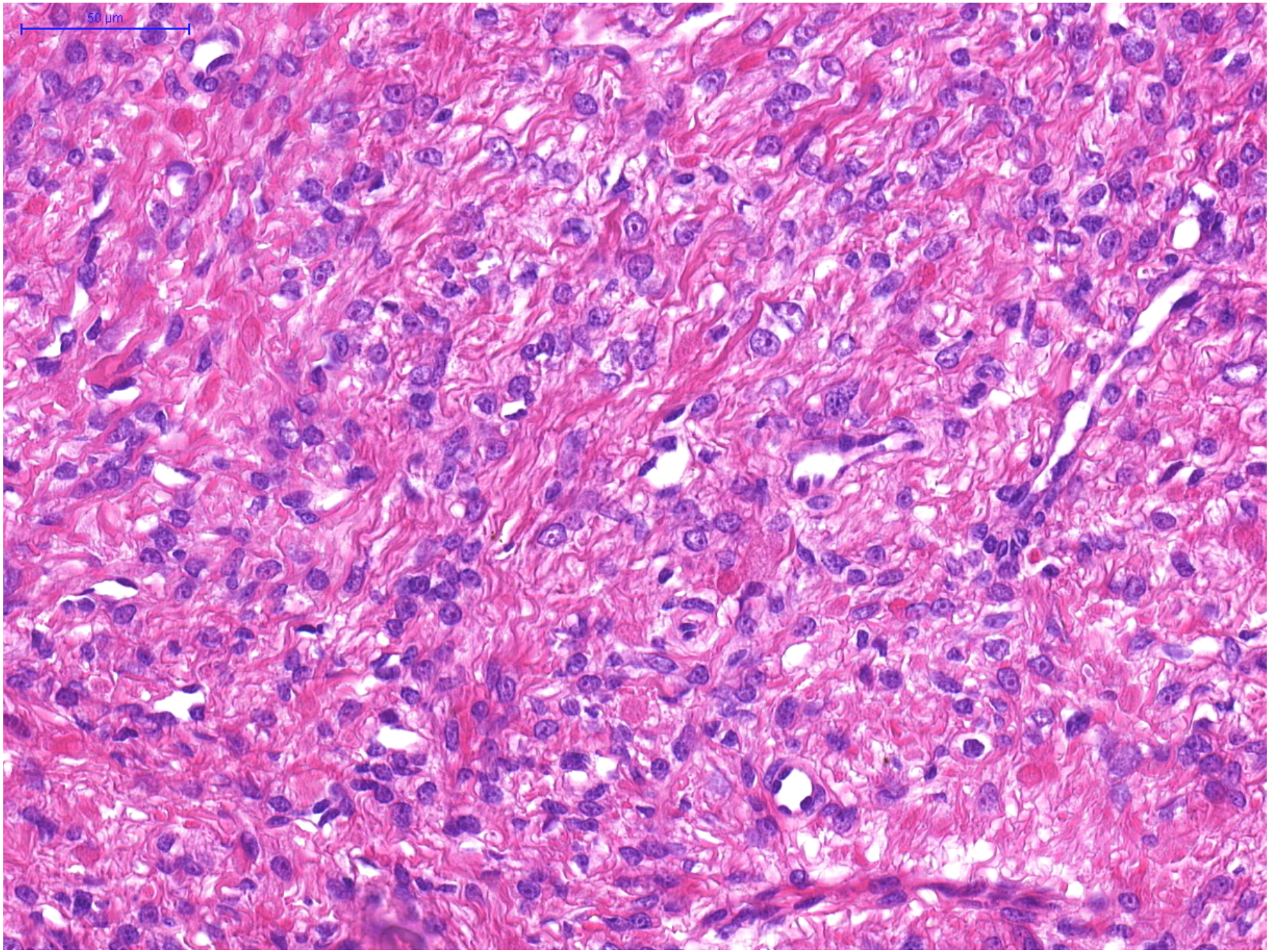
Senec, SR

2016

Klinické údaje

- 2009 USG - v ľavej hrane uzol 17 mm, v pravej hrane uzol 21 mm. Pre obezitu nemožno vylúčiť sy. PCO.
- 05/2011 USG - v pravej hrane intramurálne a subserózne uložený myom 44x39 mm, ďalší myóm v ľavom rohu, subserózne uložený, cca 35x34 mm.
- 25.11.2011 – enukleácia myómov.

Histologický preparát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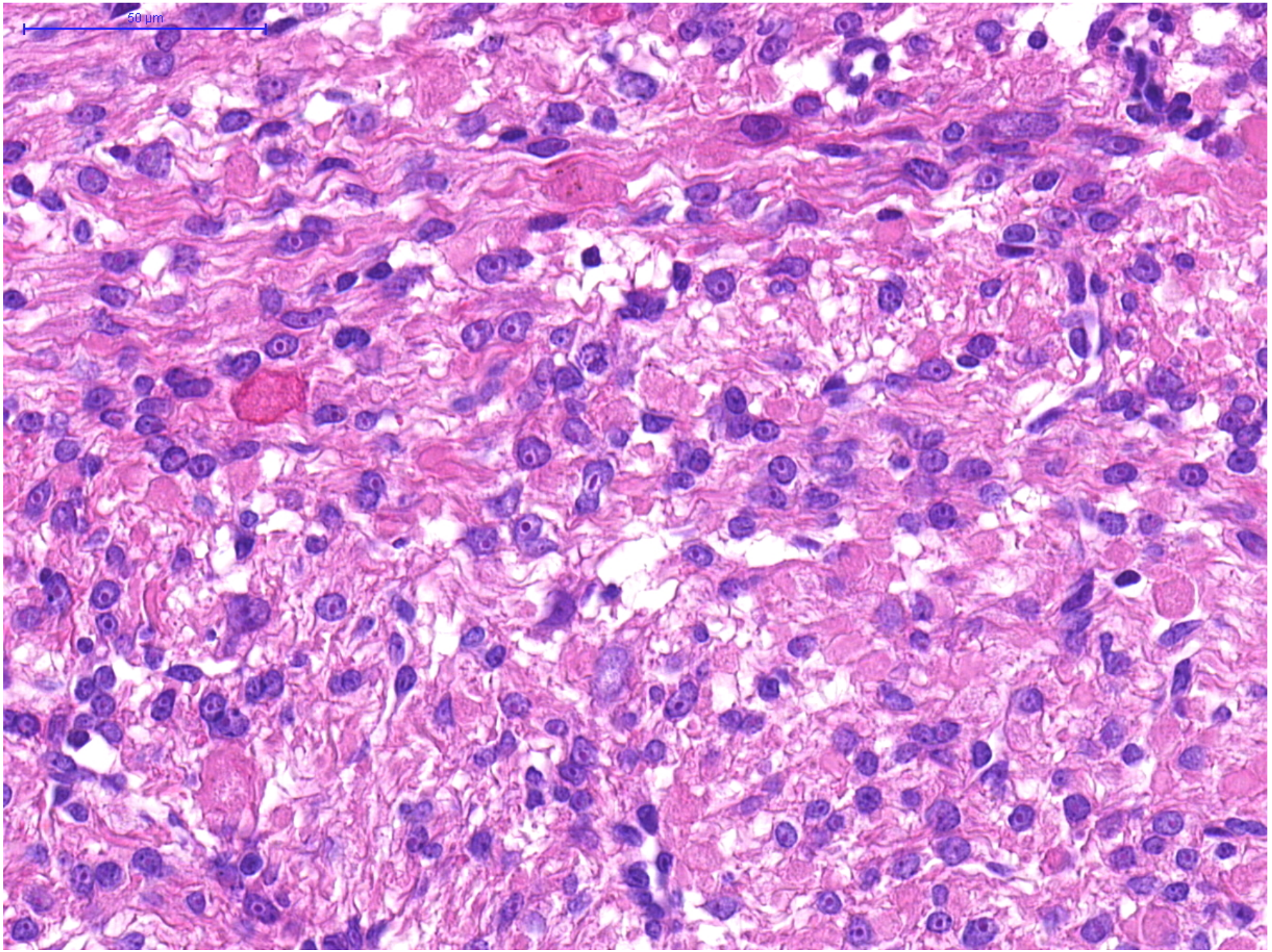
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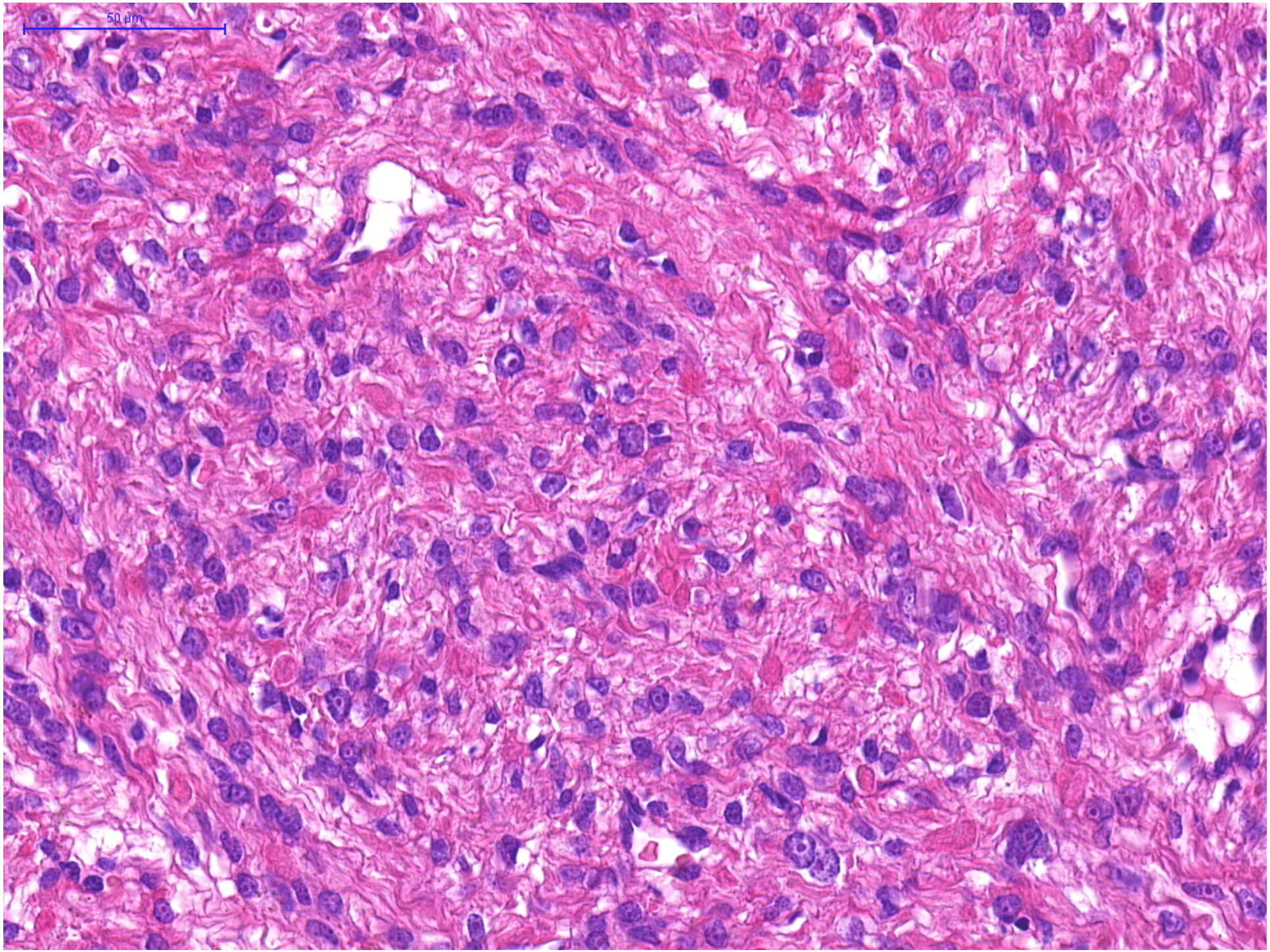
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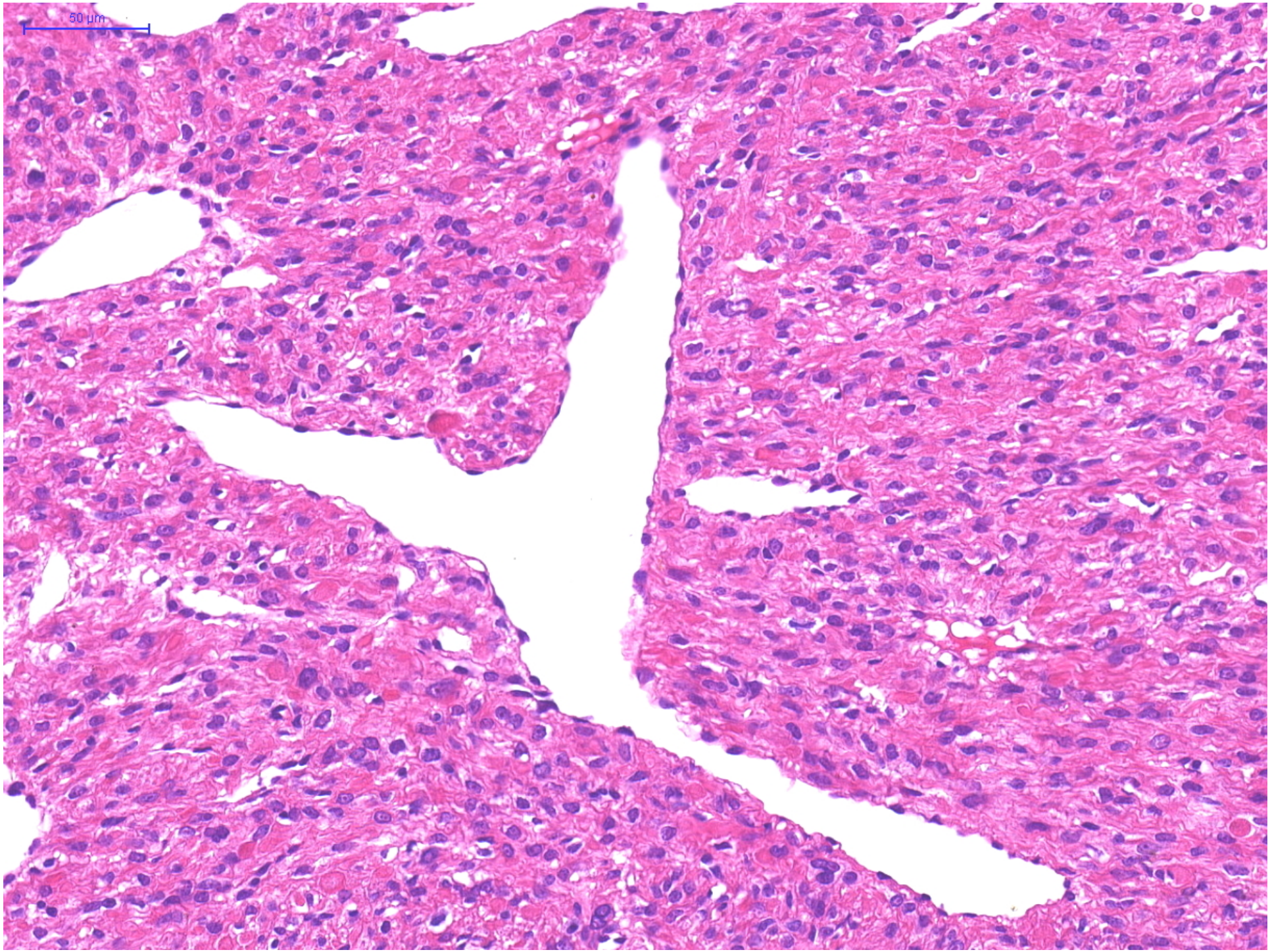
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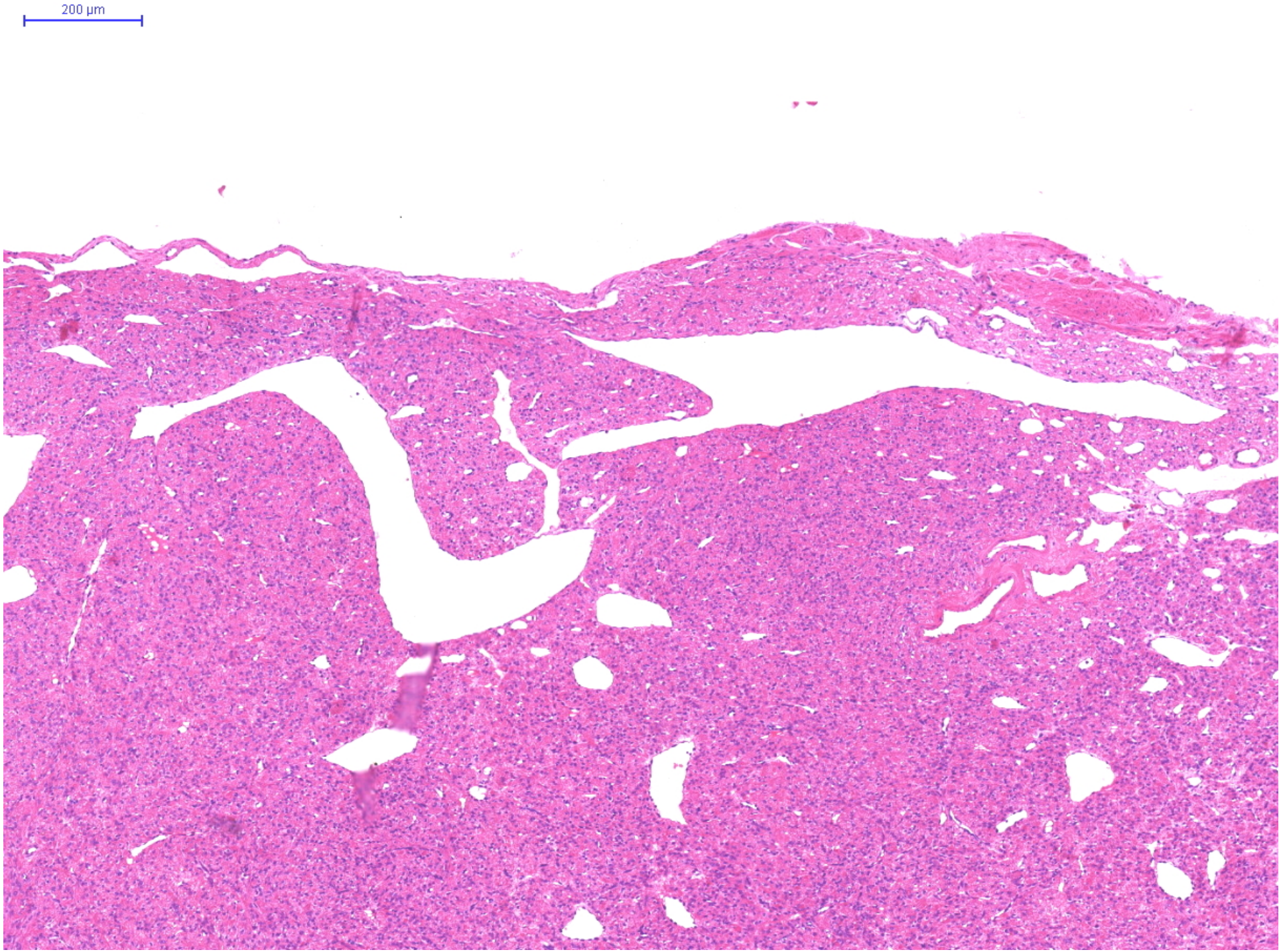
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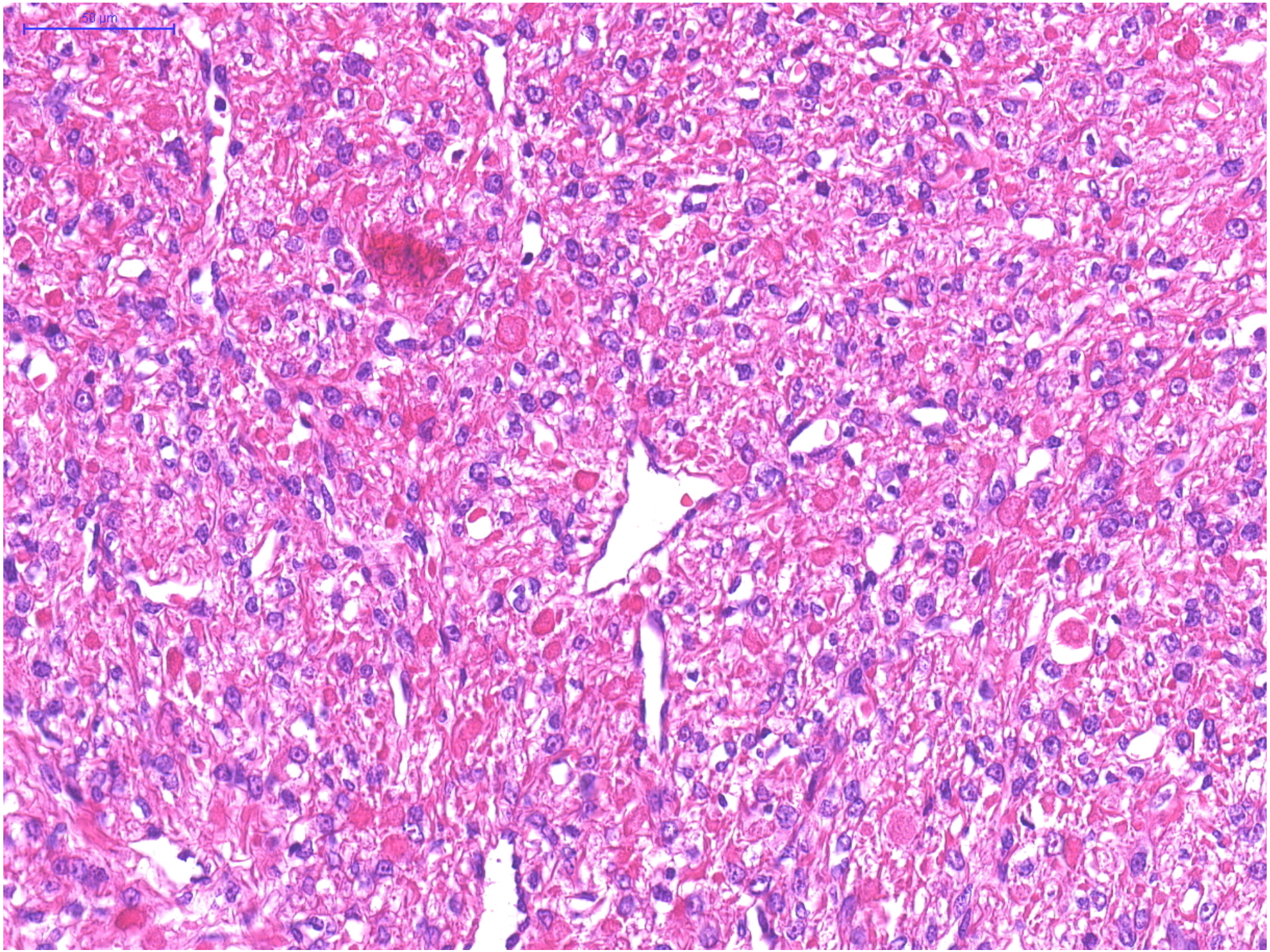
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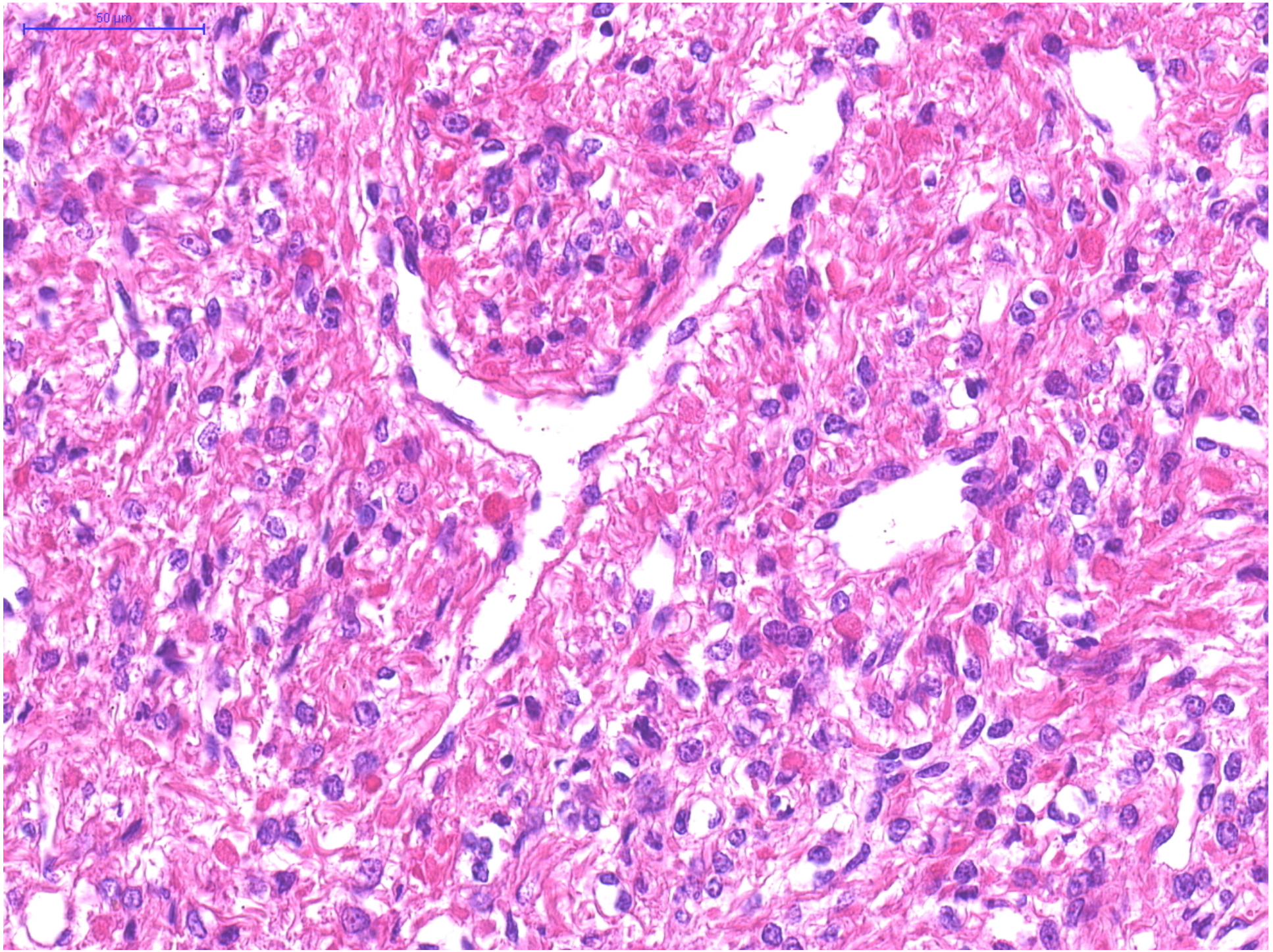
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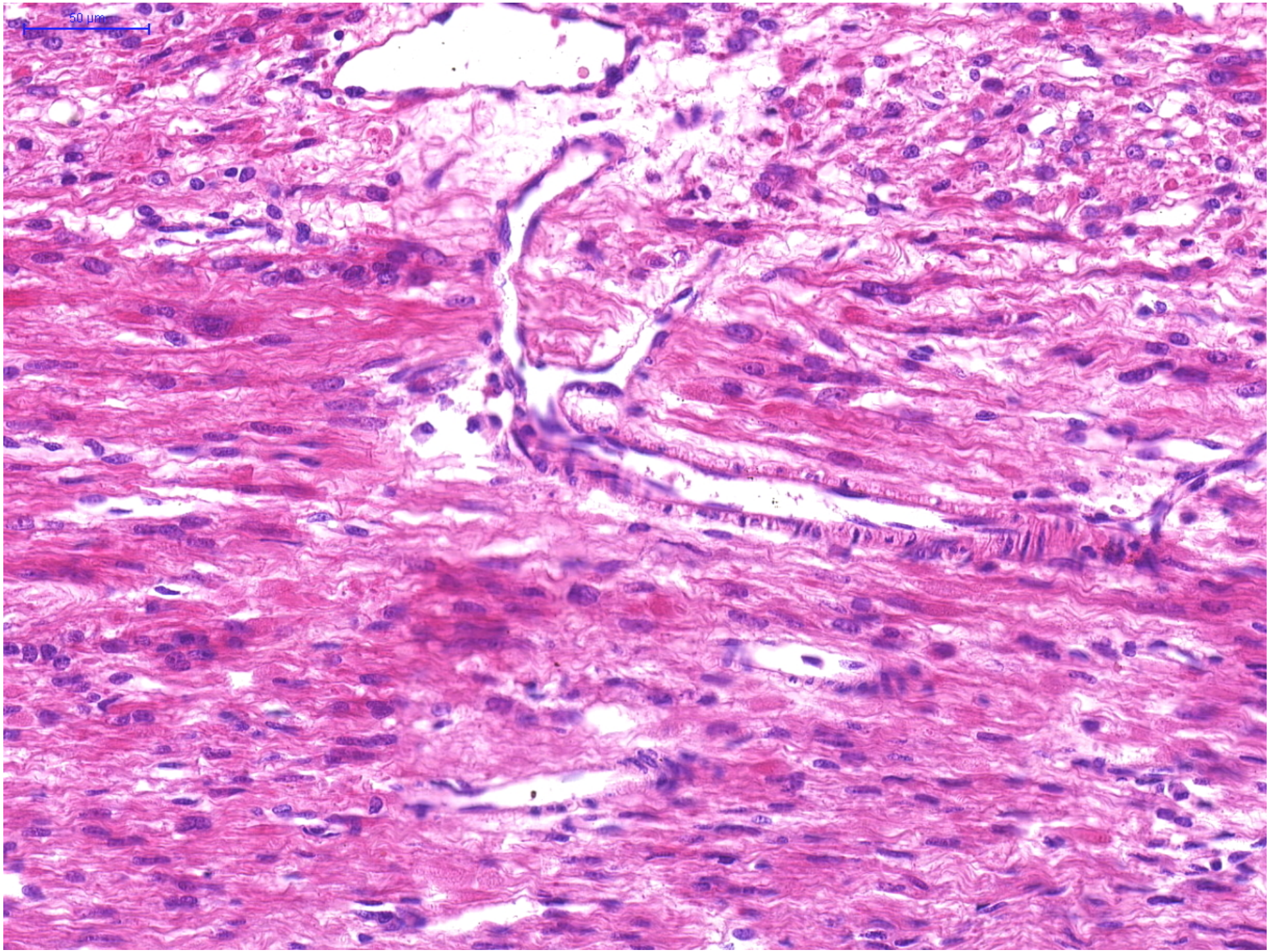
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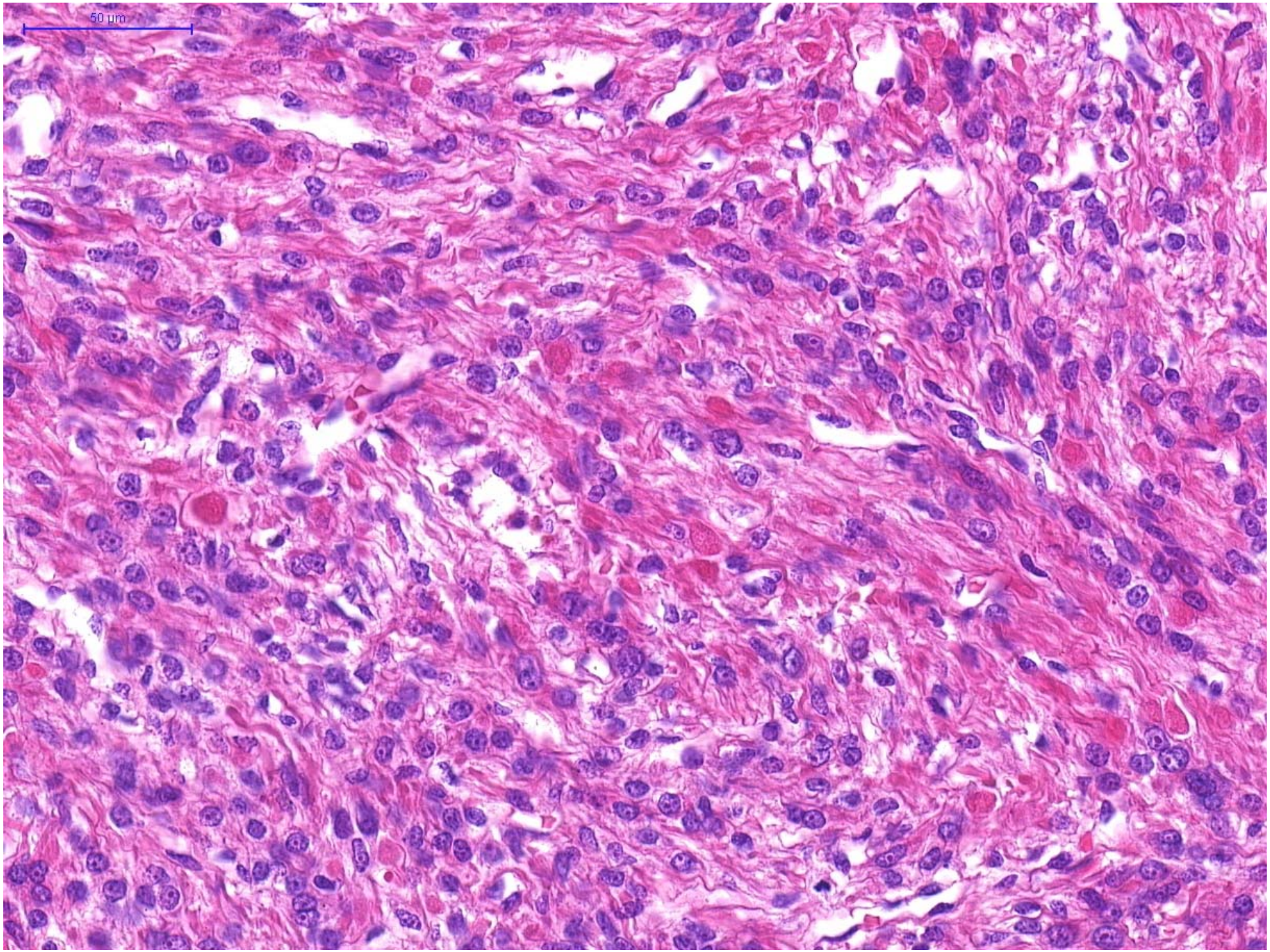
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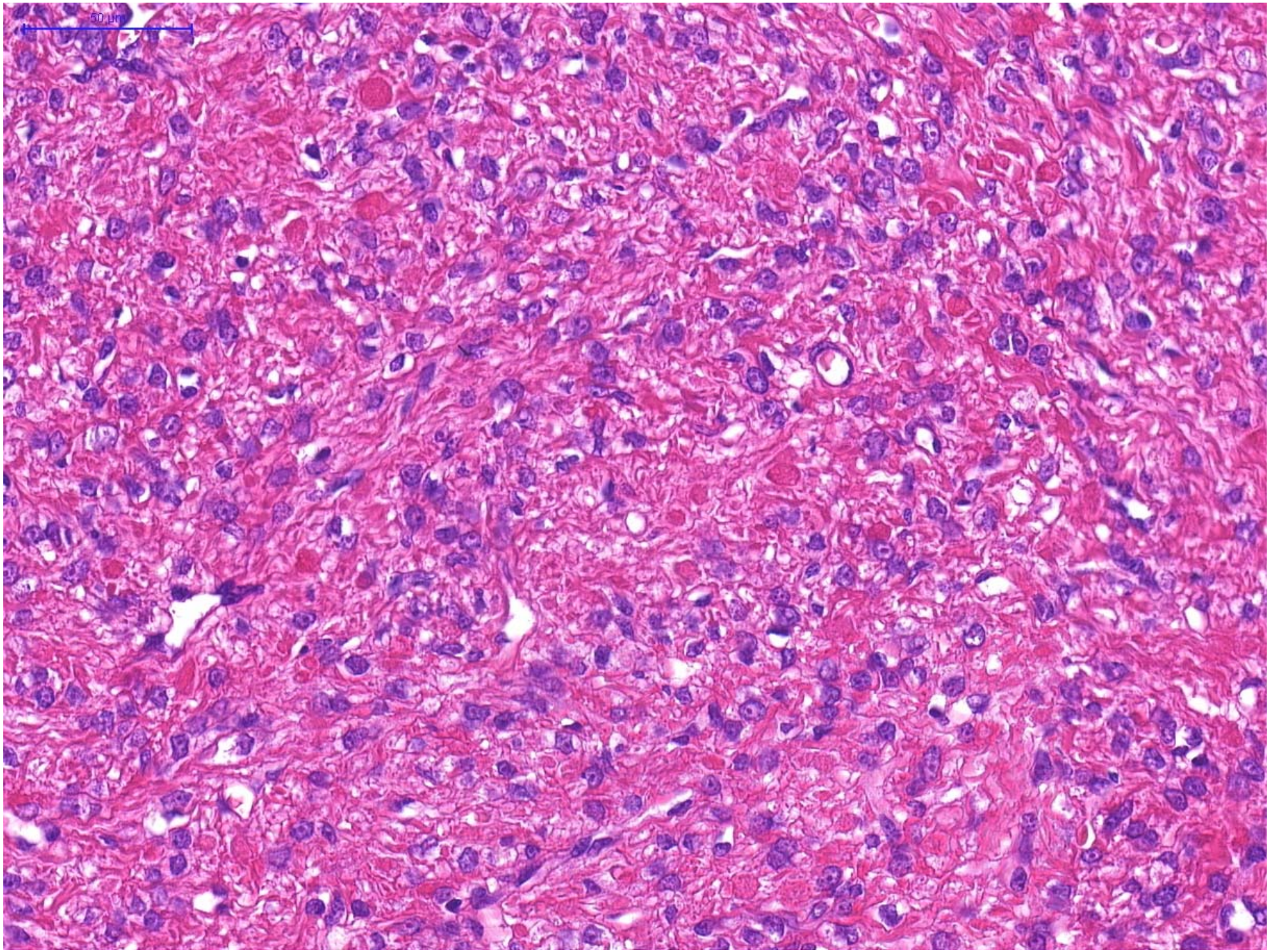
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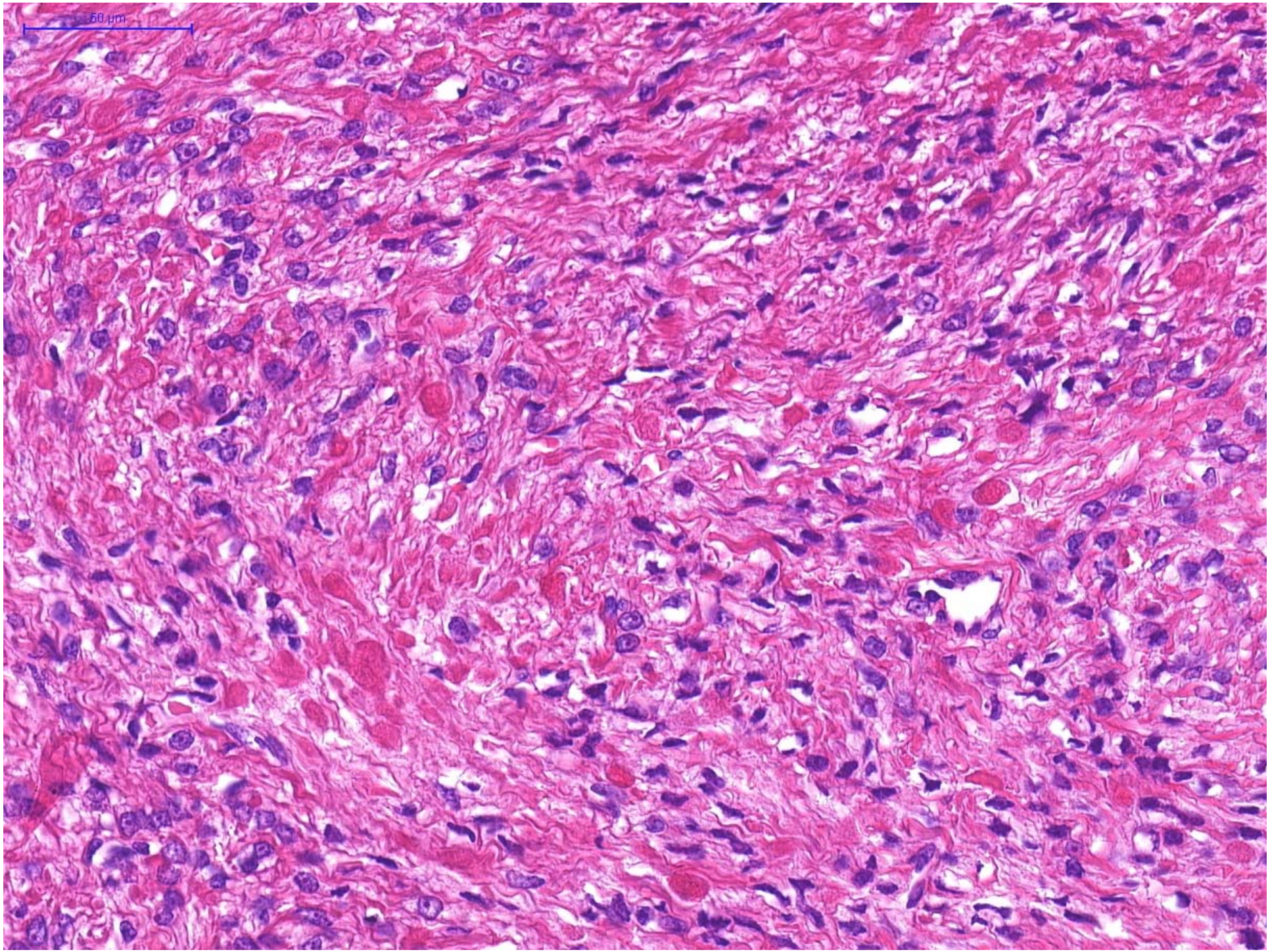
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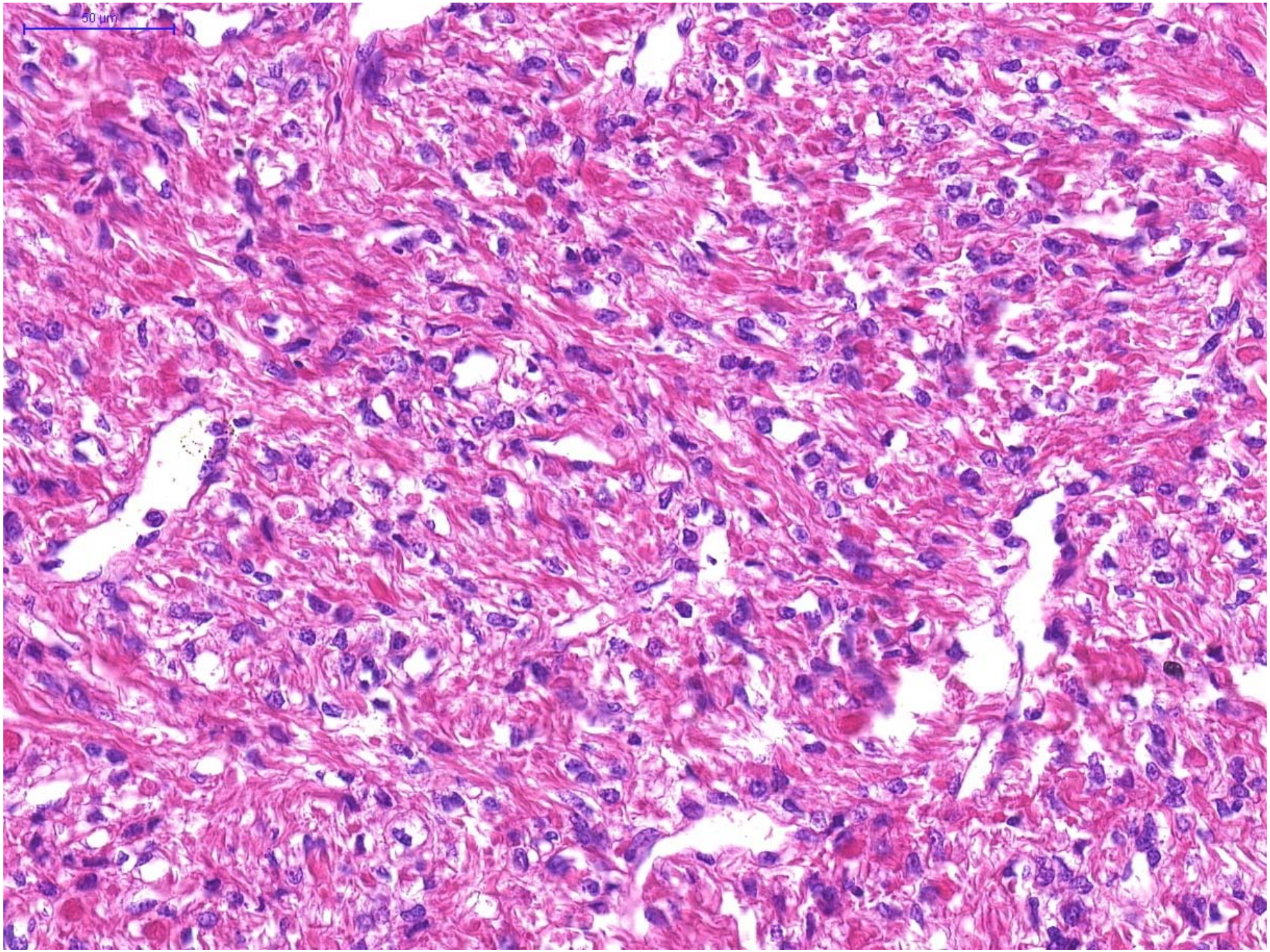
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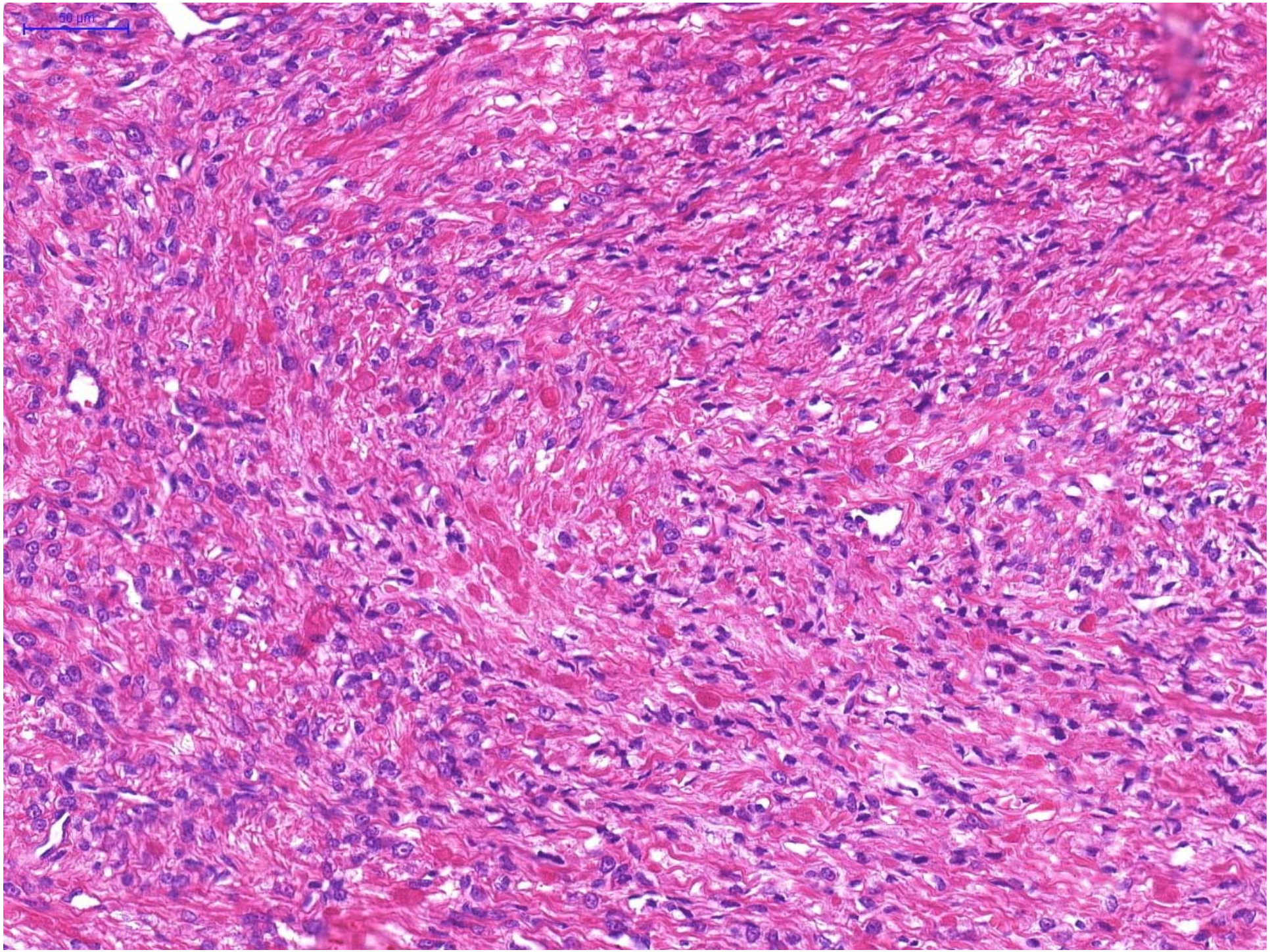
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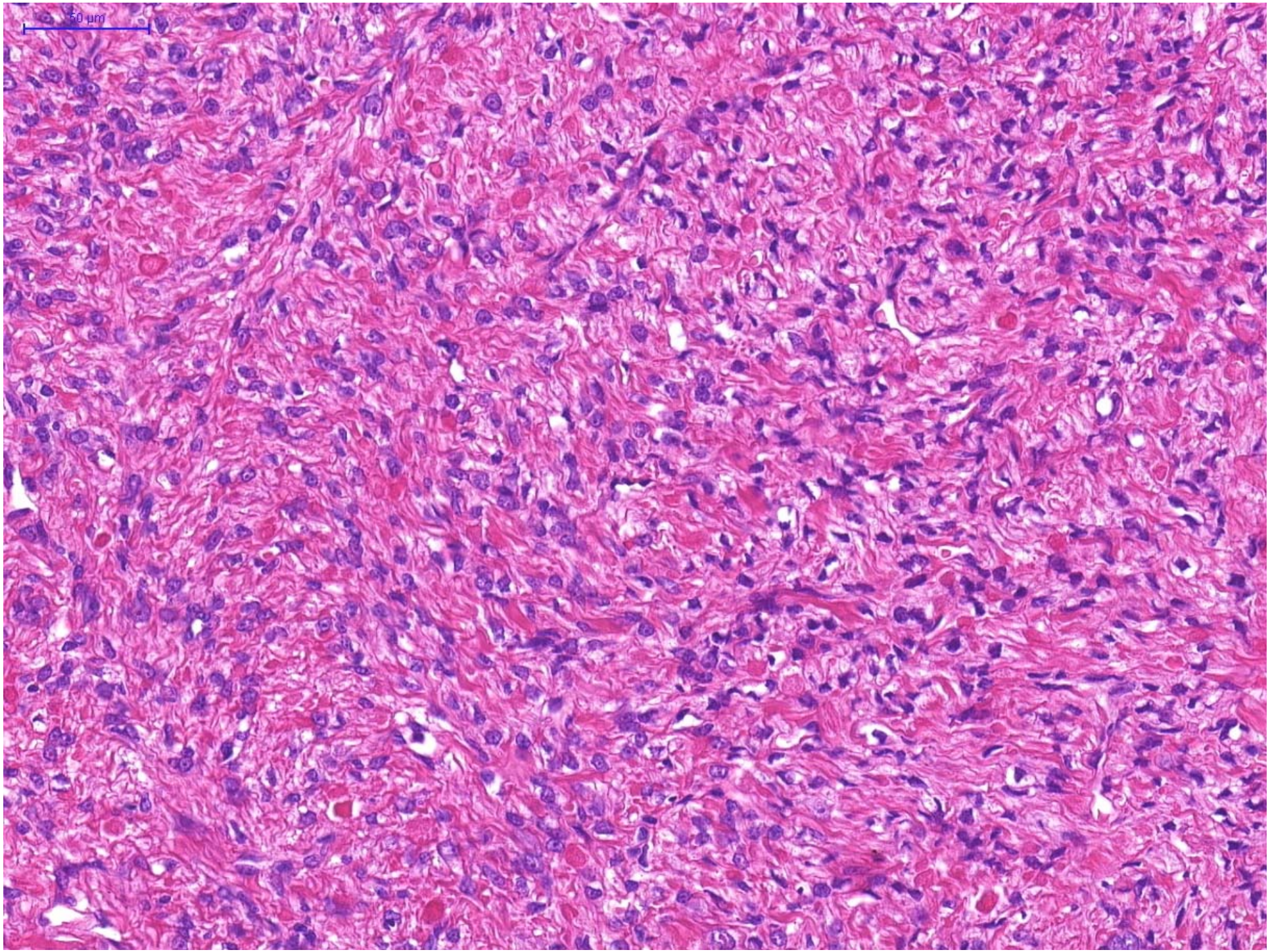
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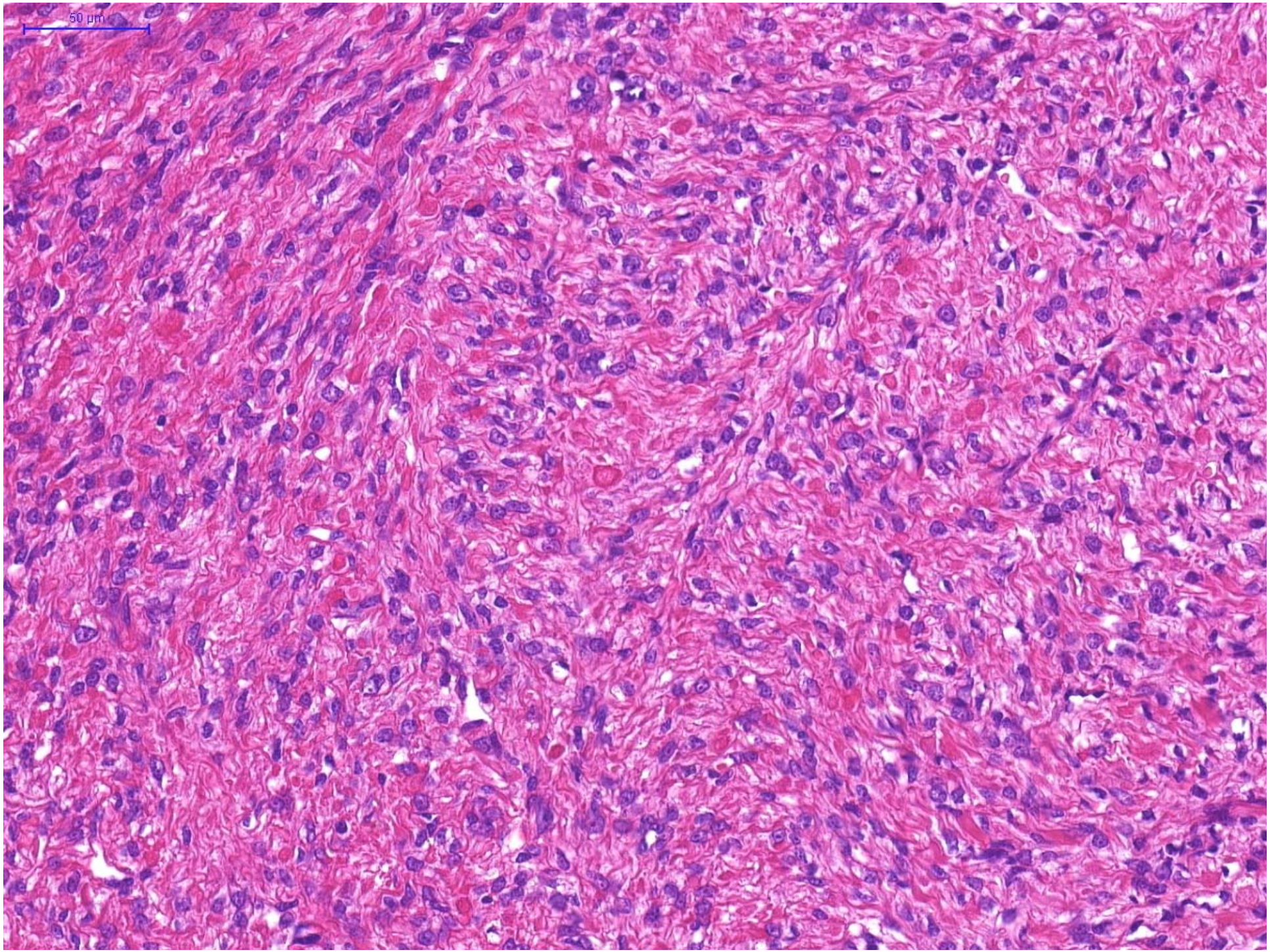
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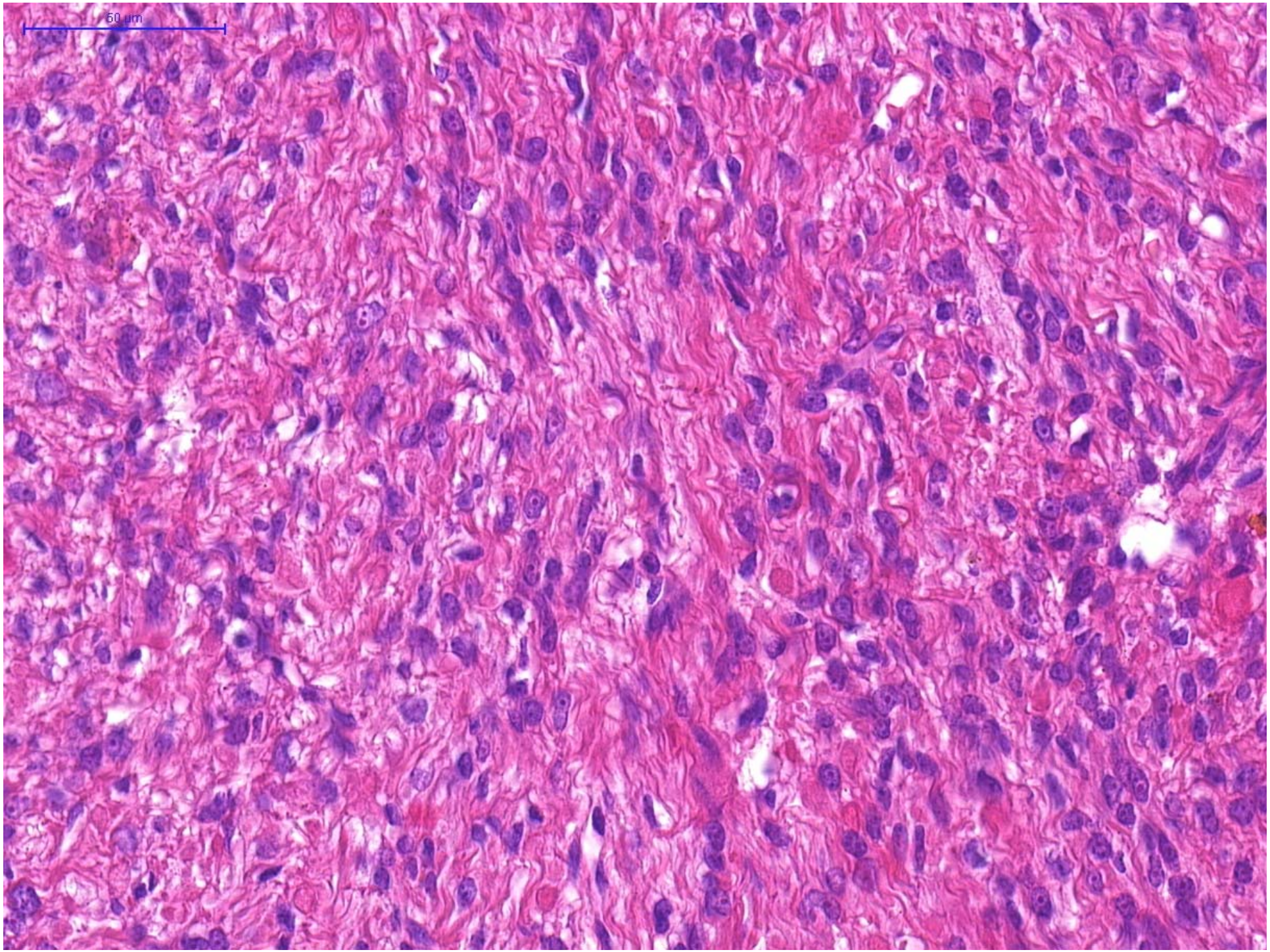
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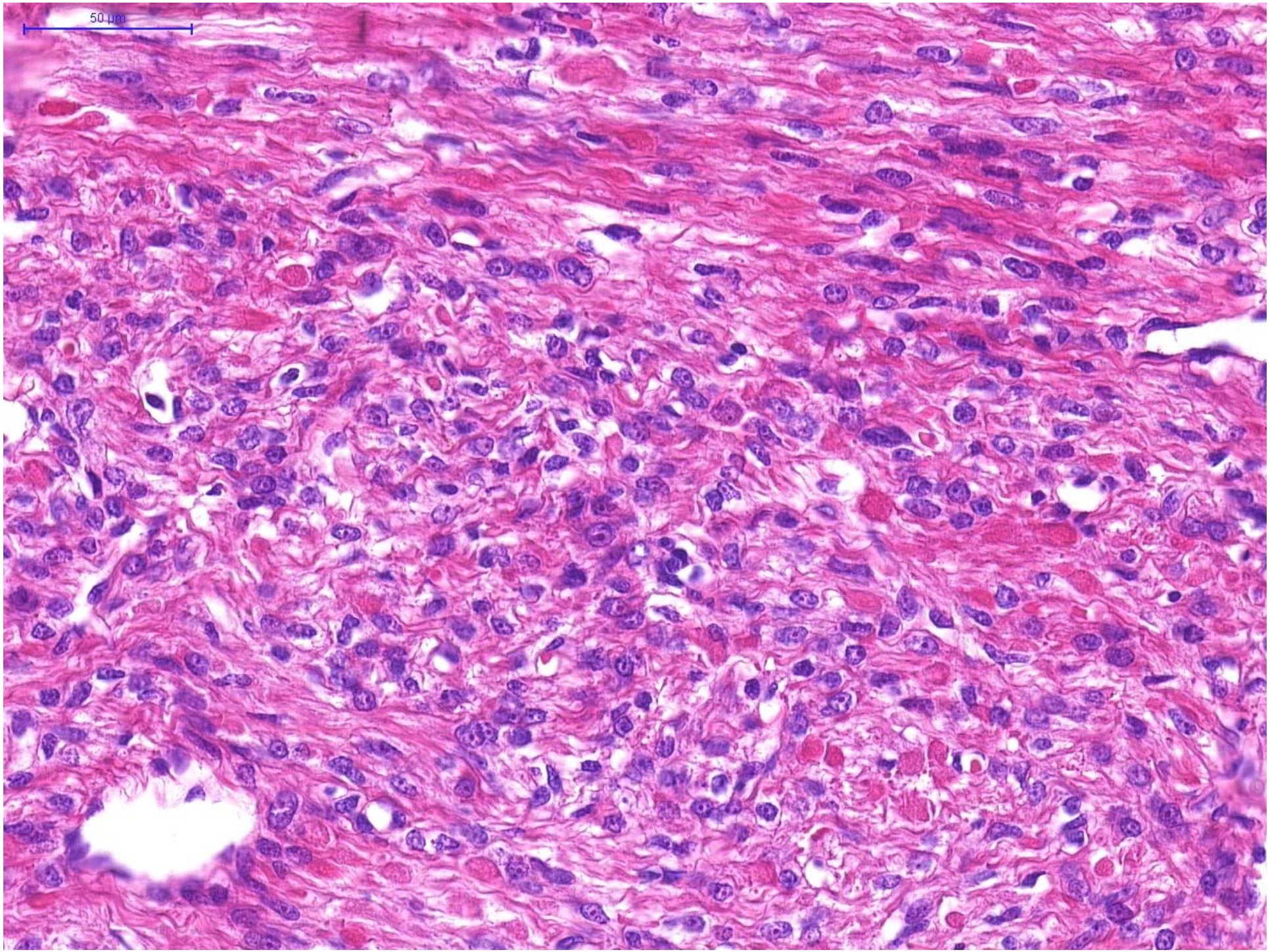
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?

Histomorfologické znaky

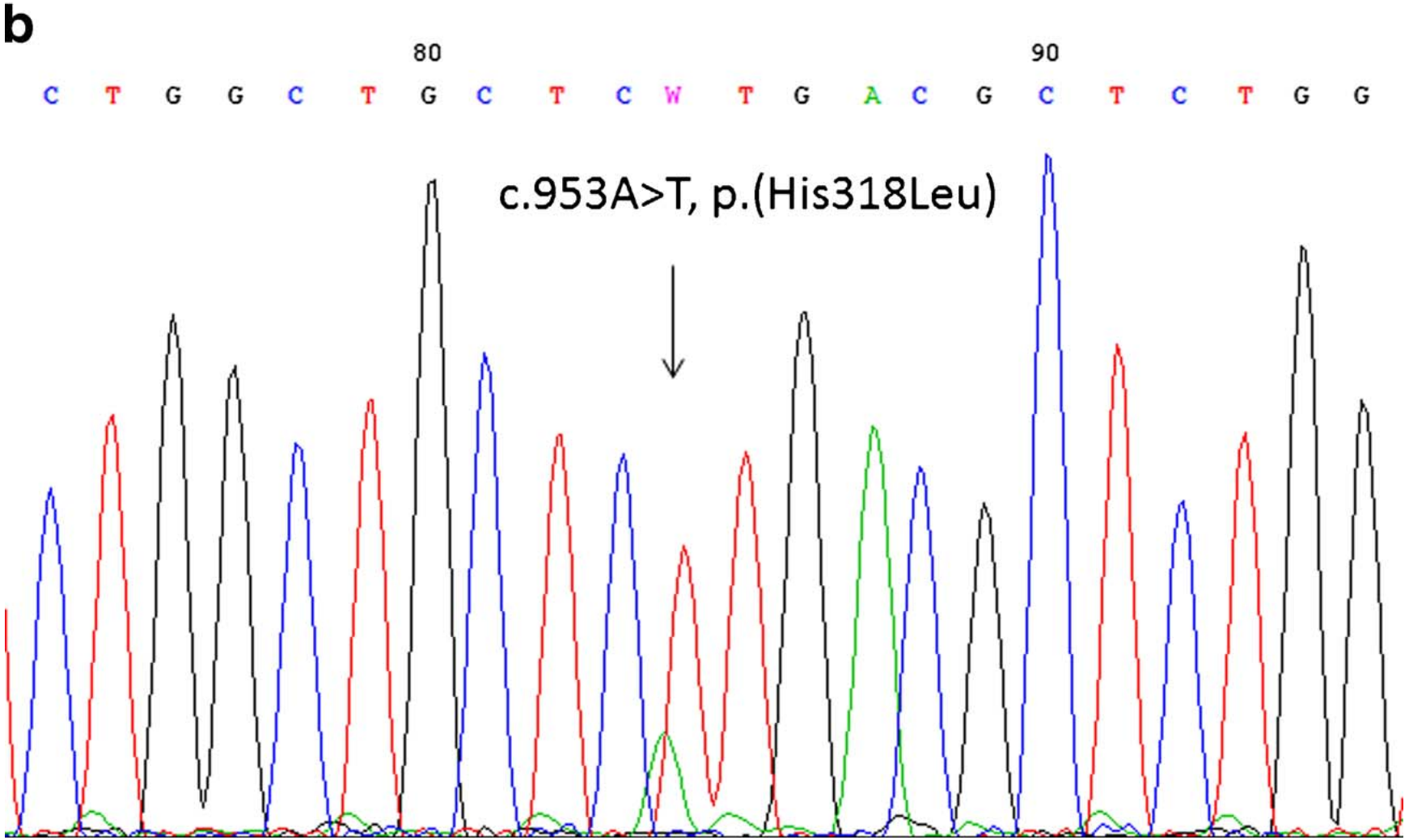
Table 2 Histomorphologic, immunohistochemical, and clinical features studied in 14 young women leiomyomas (cases tested positive for *FH* gene mutation by PCR are highlighted in red)

Case no.	Cytoplasmic fibrillarity	Staghorn vessels	Eosinophilic globules	Nucleoli	FH expression	2SC expression	Leiomyoma number/type	Para/gravida status
1	−	−	−	+	+	−	1/SM	0/1
2	−	−	−	+	+	−	Multiple - X	0/0
3	+	−	+	+	+	−	1/S	1/1
4	−	+	+	+	−	+	Multiple - 7	0/0
5	−	−	−	+	+	−	1/SM	0/0
6	−	−	−	−	+	−	1/S	1/1
7	−	+	−	−	+	−	1/S	0/0
8	−	−	−	−	+	−	1/IM	0/0
9	−	−	−	+	+	−	1/SM	0/0
10	+	−	−	+	+	−	1/IM	0/0
11	−	−	−	+	+	−	1/IM	1/4
12	+	+	−	+	+	−	1/S	0/0
13	−	−	−	+	+	−	1/S	0/0
14	+	+	−	+	+	−	1/IM	1/1

FH deficientný leiomyóm

Mutačná analýza FH génu

(germinálna missense mutácia v exóne 7 , Dr. Martínek, PhD, Bioptická laboratoř, Plzeň)



Leiomyóm asociovaný s HLRCC syndrómom

4 Launonen V, Vierimaa O, Kiuru M, *et al.* Inherited susceptibility to uterine leiomyomas and renal cell cancer. Proc Natl Acad Sci USA 2001;98:3387–3392.

Kiuru M, Lehtonen R, Arola J, Salovaara R, Järvinen H, Aittomäki K, Sjöberg J, Visakorpi T, Knuutila S, Isola J, Delahunt B, Herva R, Launonen V, Karhu A, Aaltonen LA (2002) Few FH mutations in sporadic counterparts of tumor types observed in hereditary leiomyomatosis and renal cell cancer families. Cancer Res 62(16): 4554–4557

WHO 2014

Mesenchymal tumours

E. Oliva
M.L. Carcangiu
S.G. Carinelli
P. Ip
T. Loening
T.A. Longacre
M.R. Nucci
J. Prat
C.J. Zaloudek

Leiomyoma

Definition

A benign, smooth-muscle tumour that has several variant morphological features.

ICD-O codes

Leiomyoma	8890/0
Cellular leiomyoma	8892/0
Leiomyoma with bizarre nuclei	8893/0
Mitotically active leiomyoma	8890/0
Hydropic leiomyoma	8890/0
Apoplectic leiomyoma	8890/0
Lipomatous leiomyoma (lipoleiomyoma)	8890/0
Epithelioid leiomyoma	8891/0
Myxoid leiomyoma	8896/0
Dissecting (cotyledonoid) leiomyoma	8890/0
Diffuse leiomyomatosis	8890/1
Intravenous leiomyomatosis	8890/1
Metastasizing leiomyoma	8898/1

Synonym

Symplastic leiomyoma (leiomyoma with bizarre nuclei)

Epidemiology

Leiomyomas, including variants, are the most common uterine tumour and usually affect women in their fourth and fifth decades. Variant forms account for approximately 10% of cases. Patients with hereditary leiomyomatosis and renal cancer syndrome present at a younger age. Those with metastasizing leiomyoma usually have a history of prior hysterectomy for leiomyomas.

Clinical features

Most patients are asymptomatic but

WHO 2014 – názvoslovie (hereditary?)

Leiomyomatosis and renal cancer syndrome

This autosomal dominant disorder is associated with a germline mutation in the fumarate hydratase (*FH*) gene. It is characterized by multiple leiomyomas that frequently have increased cellularity, multinucleated and atypical nuclei with prominent red to orange nucleoli

surrounded by a clear halo, as well as haemangiopericytoma-like vessels {1682}.

1682. Sanz-Ortega J, Vocke C, Stratton P, Linehan WM, Merino MJ (2013). Morphologic and molecular characteristics of uterine leiomyomas in hereditary leiomyomatosis and renal cancer (HLRCC) syndrome. Am J Surg Pathol 37: 74-80.

Histologické znaky leiomyómu asociovaného s HLRCC syndrómom

- eozinofilné jadierka s perinukleolárnym halo
- „vláknitá“ cytoplazma
- eozinofilné globuly
- „rohaté cievy“ - staghorn vessels

Histologické poznámky

- Žiadny zo znakov nie je špecifický.
- Znaky nemusia byť u HLRCC asociovaného leiomyómu prítomné všetky.

Histologické poznámky - veľké eozinofilné jadierka s perinukleolárnym halo

- Epiteloidný leiomyom.
- Leiomyóm s hormon-asociovanými zmenami (apoplektický leiomymom, hemoragický celulárni leiomyom).
- Leiomyóm s bizarnými jadrami.
- Low grade leiomyosarkóm.

Histologické poznámky – perinukleolárne halo

- Subjektívne, časovo náročné hodnotenie

Histologické poznámky – vláknitá cytoplazma

- Subjektívne hodnotenie

Histologické poznámky – rohaté cievy

- Subjektívne hodnotenie

Histologické poznámky – eozinofilné globuly

- Subjektívne hodnotenie.

Biochemické poznámky

- FH - fumarát hydratáza je významný enzým Krebsovho cyklu (fumarát - malát)
- Hromadenie fumarátu má antiapoptotický účinok.

2SC... S-(2-sukcino) cystein

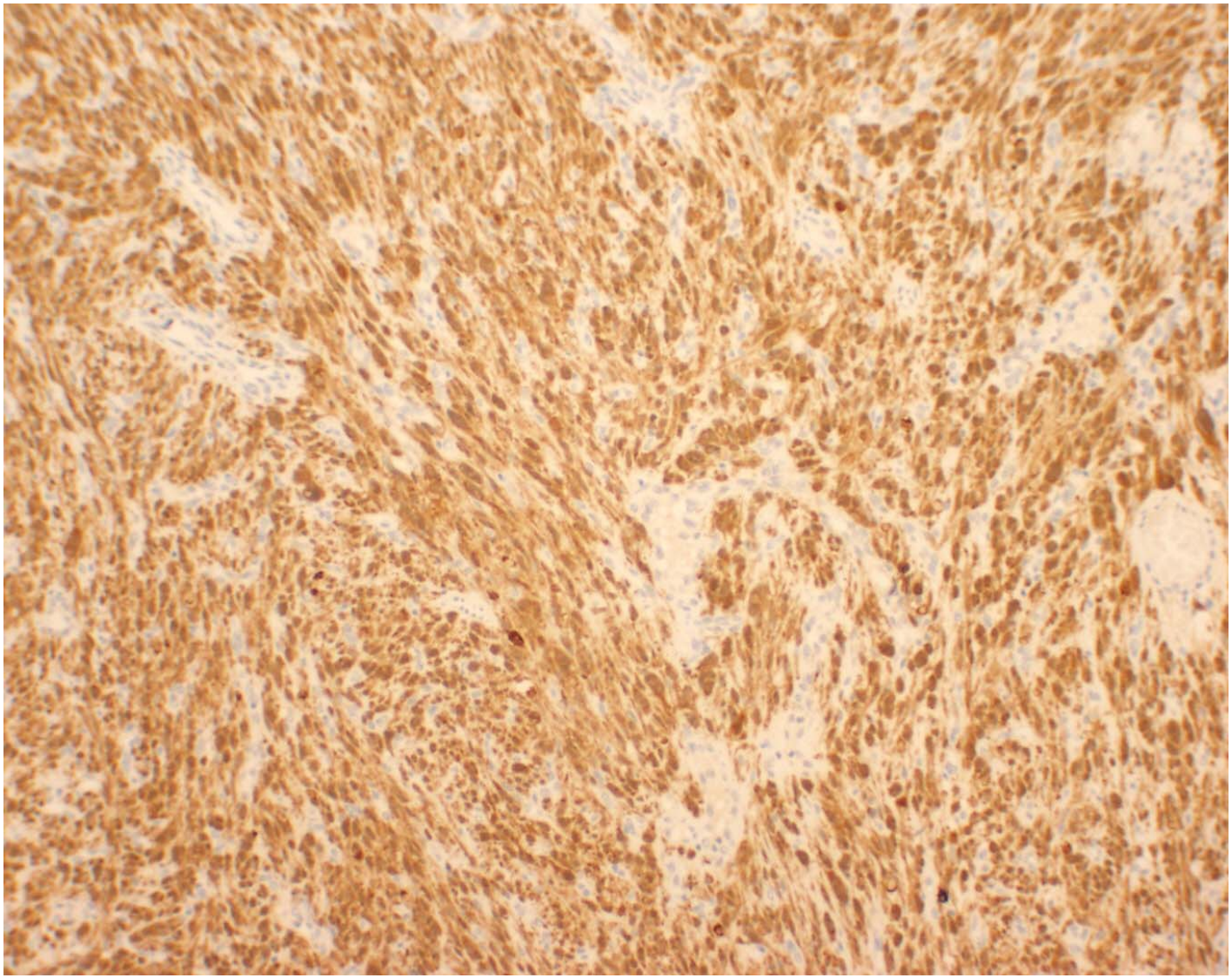
- Nahromadený fumarát indukuje proces „sukcinácia proteínov“
- Tak vzniká 2SC
- Norma Frizzell, Columbia, S.Carolina, USA (Sukcinácia proteínov v rámci Diabetes mellitus)

- Robust detection of 2SC was observed in Fh1 (murine FH)-deficient renal cysts and in a retrospective series of HLRCC tumours (n = 16) with established FH mutations. Importantly, 2SC was undetectable in normal tissues (n = 200) and tumour types not associated with HLRCC (n = 1342). In a prospective evaluation of cases referred for genetic testing for HLRCC, the presence of 2SC-modified proteins (2SCP) correctly predicted genetic alterations in FH in every case. In two series of unselected type II papillary renal cancer (PRCC), prospectively analysed by 2SCP staining followed by genetic analysis, the biomarker accurately identified previously unsuspected FH mutations (2/33 and 1/36).

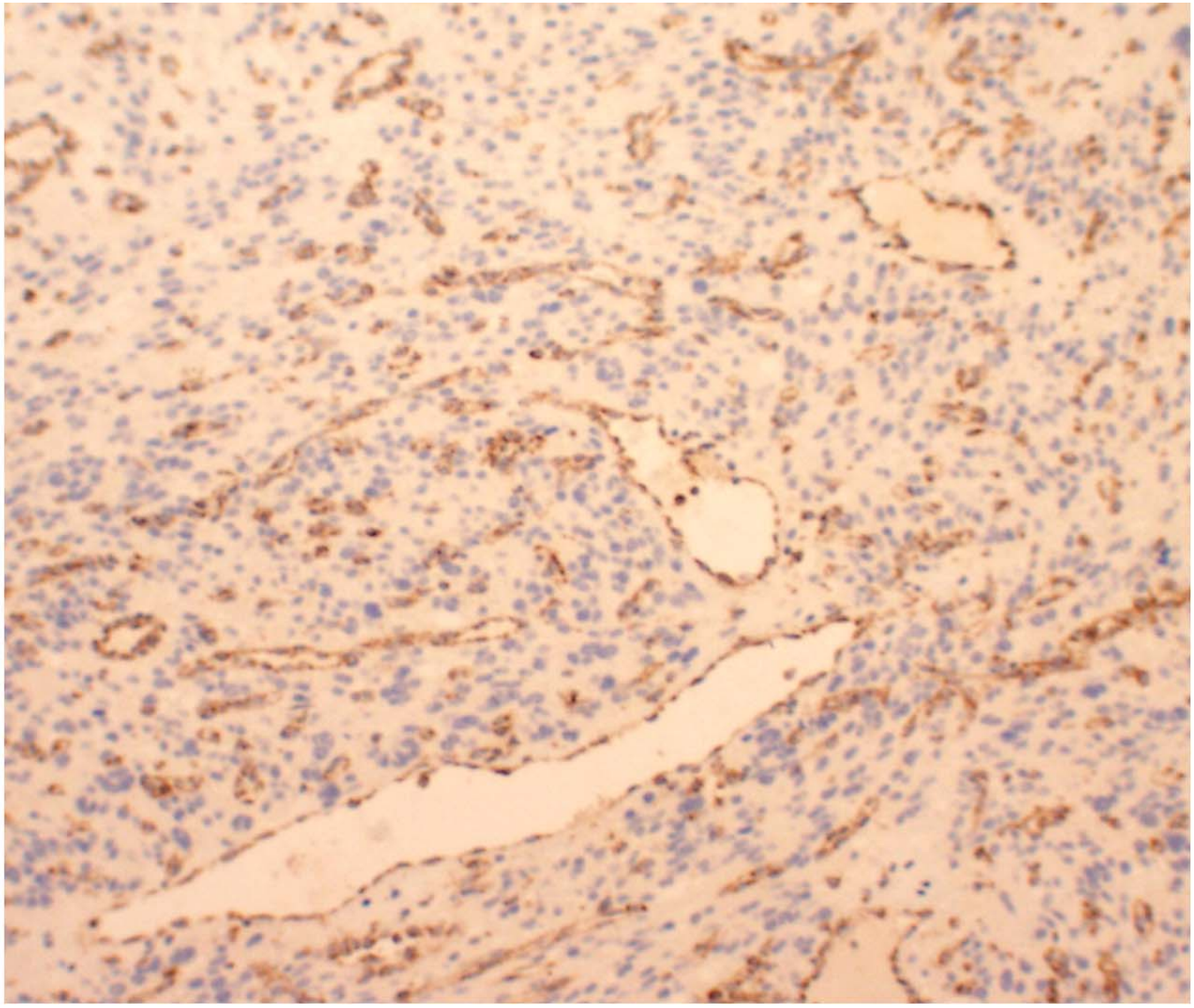
Bardella C, El-Bahrawy M, Frizzell N et al (2011) Aberrant succination of proteins in fumarate hydratase-deficient mice and HLRCC patients is a robust biomarker of mutation status. J Pathol 225:4–11

- **Frizzell N , Thomas SA, Carson JA, Baynes JW. Mitochondrial stress causes increased succination of proteins in adipocytes in response to glucotoxicity. Biochem J. 2012 Jul 15;445(2):247-54.**

IHC – 2SC pozitívna expresia (nekomerčná protilátka)



IHC - FH strata expresie (komerčná protilátka)



Možnosti skríningu?

ORIGINAL ARTICLE

OPEN

Fumarate Hydratase–deficient Uterine Leiomyomas Occur in Both the Syndromic and Sporadic Settings

Wesley J. Harrison, PhD,† Juliana Andrici, MBBS, MPhil,*† Fiona Maclean, FRCPA,‡ Raha Madadi-Ghahan, MD,†§ Mahtab Farzin, MD, FRCPA,†§ Loretta Sioson, BSc,†§ Christopher W. Toon, FRCPA,*†‖ Adele Clarkson, BSc,†§ Nicole Watson, BSc,† Justine Pickett, FRCPA,†§ Michael Field, MPhil, FRACP,¶ Ashley Crook, BA, BSc, MGenCouns[FHGSA],¶ Katherine Tucker, FRACP,# Annabel Goodwin, FRACP,** Lyndal Anderson, FRCPA, MPhil,*†† Bhuvana Srinivasan, MD, FRCPA,‡‡ Petr Grossmann, PhD,§§ Petr Martinek, PhD,§§ Ondrej Ondič, MD,§§ Ondřej Hes, MD,§§ Kiril Trpkov, MD,‖‖ Roderick J. Clifton-Bligh, FRACP, PhD,*¶¶ Trisha Dwight, PhD,*¶¶ and Anthony J. Gill, MD, FRCPA*†§*

Genetické poznámky

- Cca 1% všetkých vyšetrených leiomyómov maternice (1152) sú FH deficientné - obsahujú mutovaný gén FH.
- Častejšie ide o somatické, nie germinálne, mutácie (6/10).
- LOH lokusu 1q43 muože (v tomto prípade bola), ale nemusí byť prítomná.

Patogenéza - epidemiológia

It was found in eight women out of 46 identified by Toro et al. in the North American study [3] with median age at detection of renal tumor being 44 years. The mean age at diagnosis of renal tumor was 39 years in a study from Singapore [11].

Patogenéza -epidemiológia (svetové údaje)

Asociovaný RCC bol prítomný u probandov cca 30 % rodín s diagnostikovaným HLRCC sy.

U žien s HLRCC leiomyómy maternice (okolo 30. roku života) predbiehajú vznik RCC (okolo 40. roku života) asi o 10 rokov

Virchows Arch
DOI 10.1007/s00428-015-1783-y

ORIGINAL ARTICLE

Genetic testing of leiomyoma tissue in women younger than 30 years old might provide an effective screening approach for the hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC)

Petr Martínek[1,2] · Petr Grossmann[2] · Ondřej Hes[1] · Jiří Bouda[3] · Viktor Eret[4] · Norma Frizzell[5] · Anthony J Gill[6] · Ondrej Ondič[1,2]

HLRCC leiomyómy - plzeňská incidencia

2 zo14

symptomatických a operovaných leiomyómov u žien do 30 rokov.

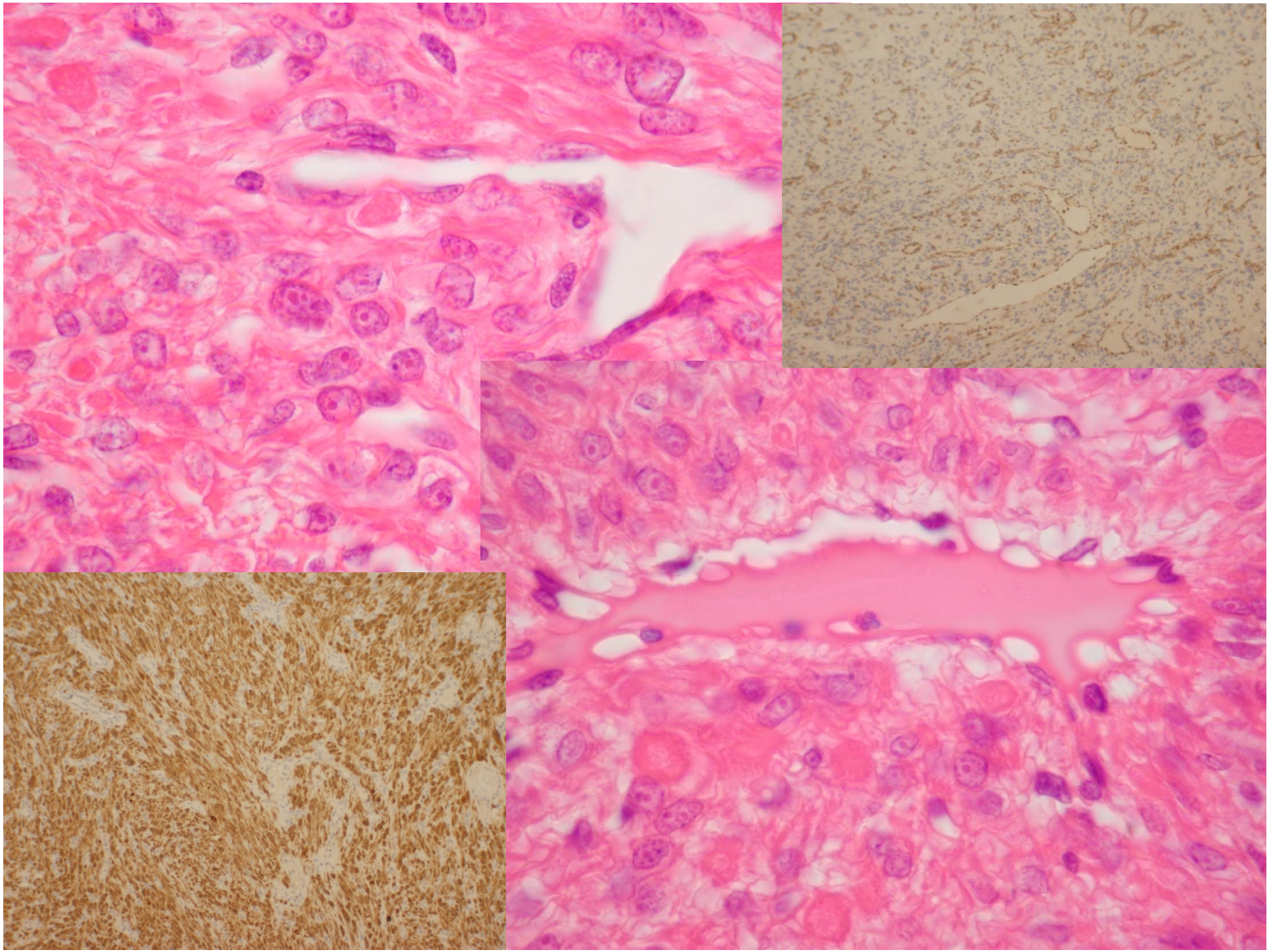
Starostlivosť o pacientov s diagnostikovaným HLRCC sy.

- USG obličiek 1x ročne.
- Doporučiť zváženie genetického poradenstva.
- Indikuje klinik (obvykle gynekológ).

Kedy myslieť na leiomyóm asociovaný s HLRCC sy?

- Mnohopočetné symptomatické myómy maternice u ženy do 30 rokov (patológ, gynekológ).
- Leiomyóm so všetkými histomorfologickými znakmi typickými pre HLRCC leiomyóm (patológ).
- Mnohopočetné kožné leiomyómy (patológ, dermatológ).

Ďakujem za pozornosť



	nádor			nenádor			výsledky	
	původní č.	č. BL	č. GL	původní č.	č. BL	č. GL	FH mutace	FH loh
1	**17750/14 - 5**	77030/16 - 5	1974/16	**14583/02**	77030/16	1975/16	neg.	NA
2	**15288/15 - C2**	77032/16 - C2	1976/16	**15288/15 - A**	77032/16 - A	1977/16	neg.	neg.
3	**9832/15 - 2**	77033/16 - 2	1978/16	**9832/15 - 2**	77034/16	1979/16	neg.	NA