The British Association of Gynaecological Pathologists

Lecturer – Dr Kat Vroobel

Kat Vroobel is a consultant histopathologist specialising in gynaecological pathology and haematopathology at the Royal Marsden Hospital. She reports almost exclusively oncological specimens and experiences a high proportion of complex cases as a result. Her interests include uterine mesenchymal tumours and high grade/ambiguous endometrial carcinomas. She has published on a range of topics and contributed to the RCPath Datasets for carcinomas of the ovaries, fallopian tubes and peritoneum and the upcoming revision to uterine sarcomas. She enjoys teaching at a local and national level and is Educational Lead for the department and a Councillor for the BAGP.

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Syndromic Tumours in Gynaepath
Diagnoses not to be missed by Pathologists

- A case-based discussion
- Dr Katherine Vroobel
- The Royal Marsden NHS Foundation Trust
- 14th November 2025

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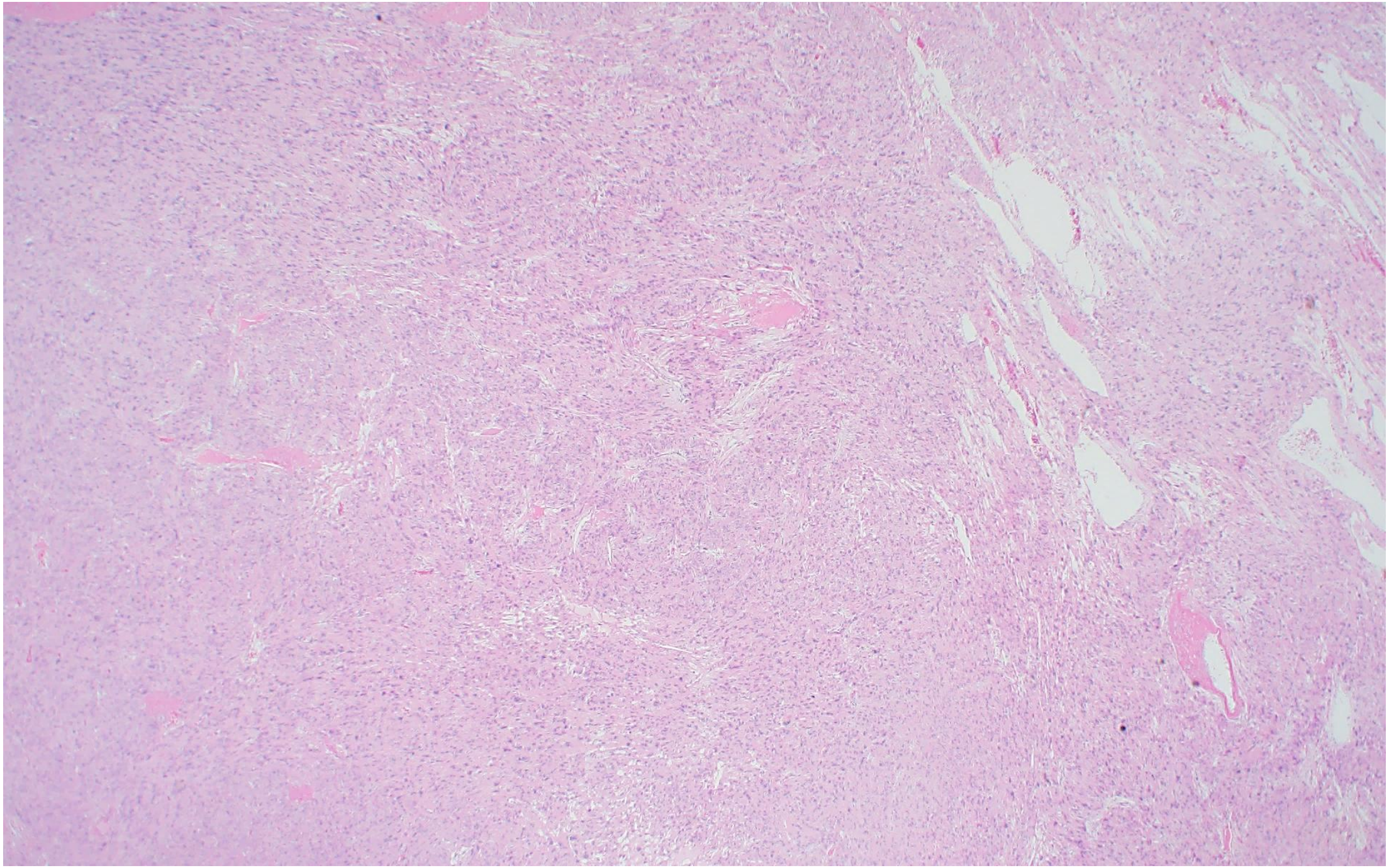
Speaker disclosures

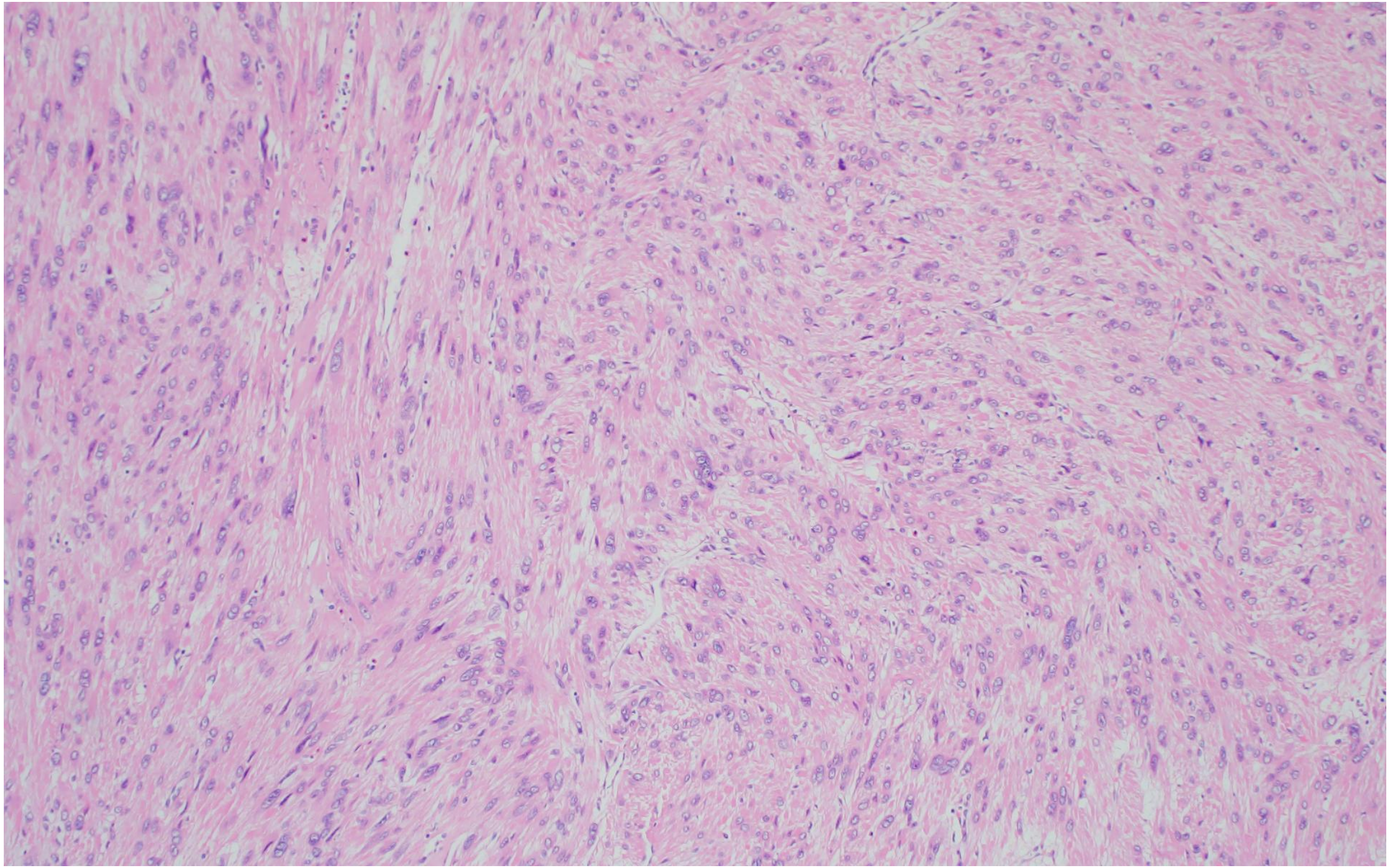
Choose one

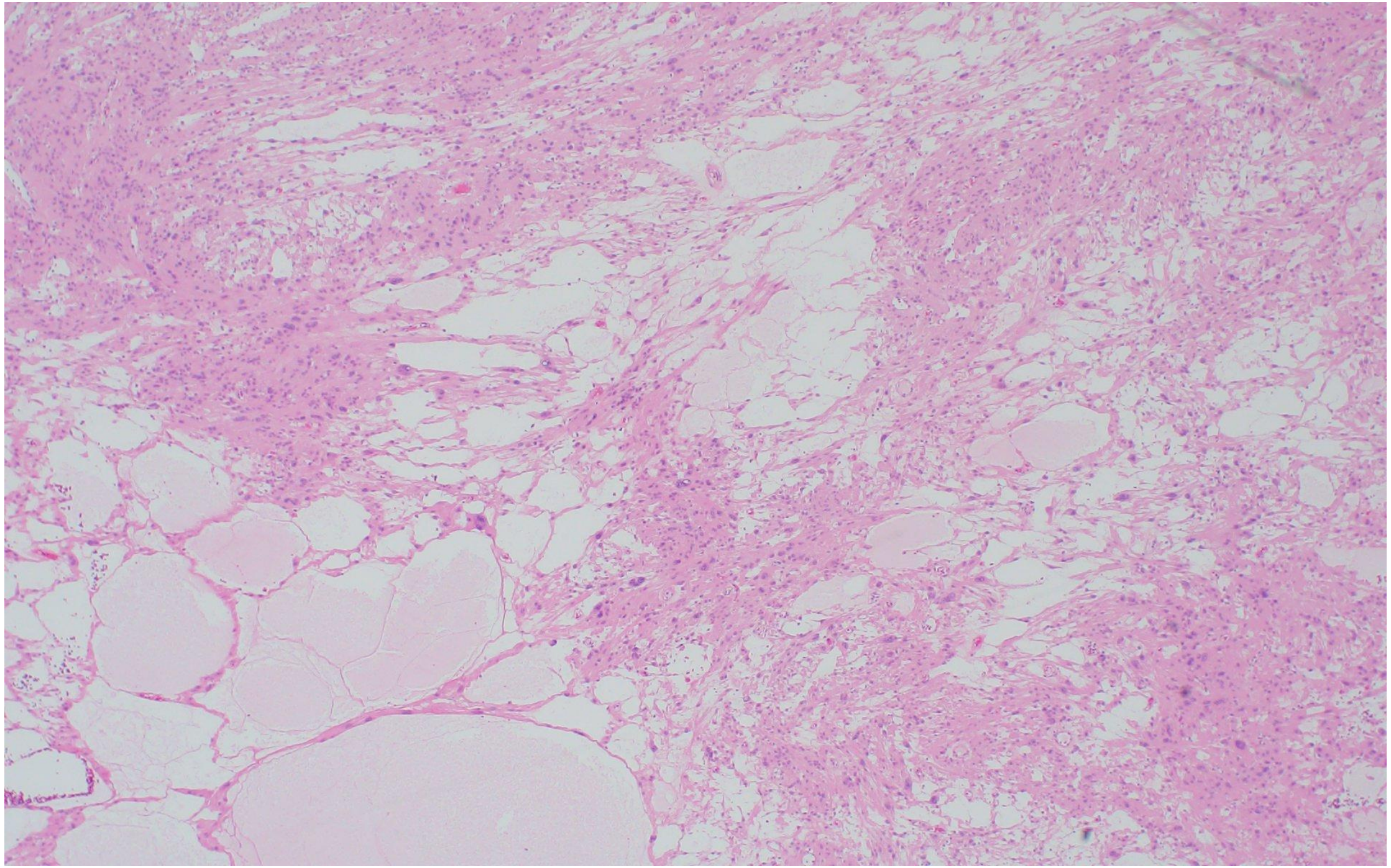
- ❑ I have no financial conflicts of interest to disclose

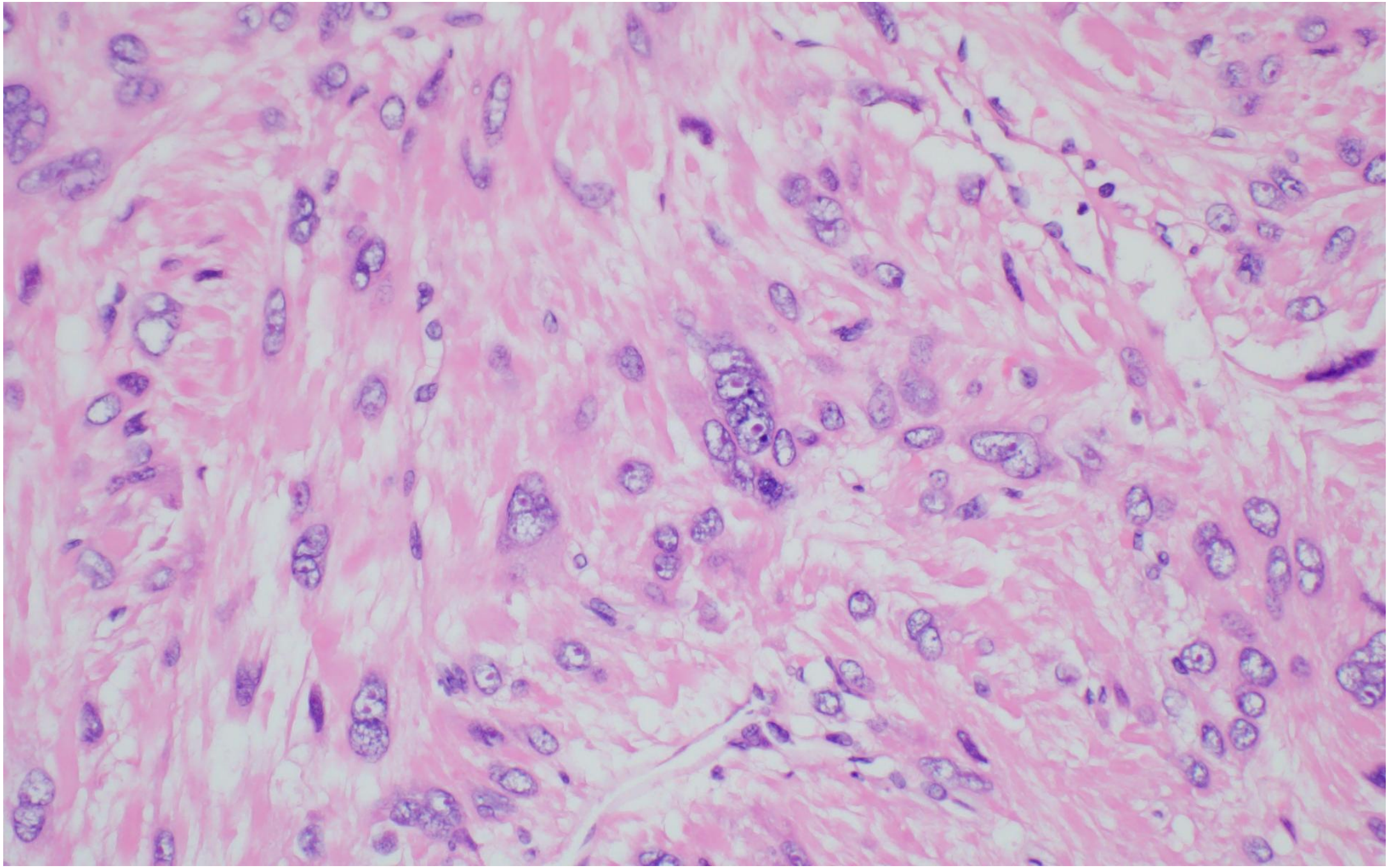
Case presentation

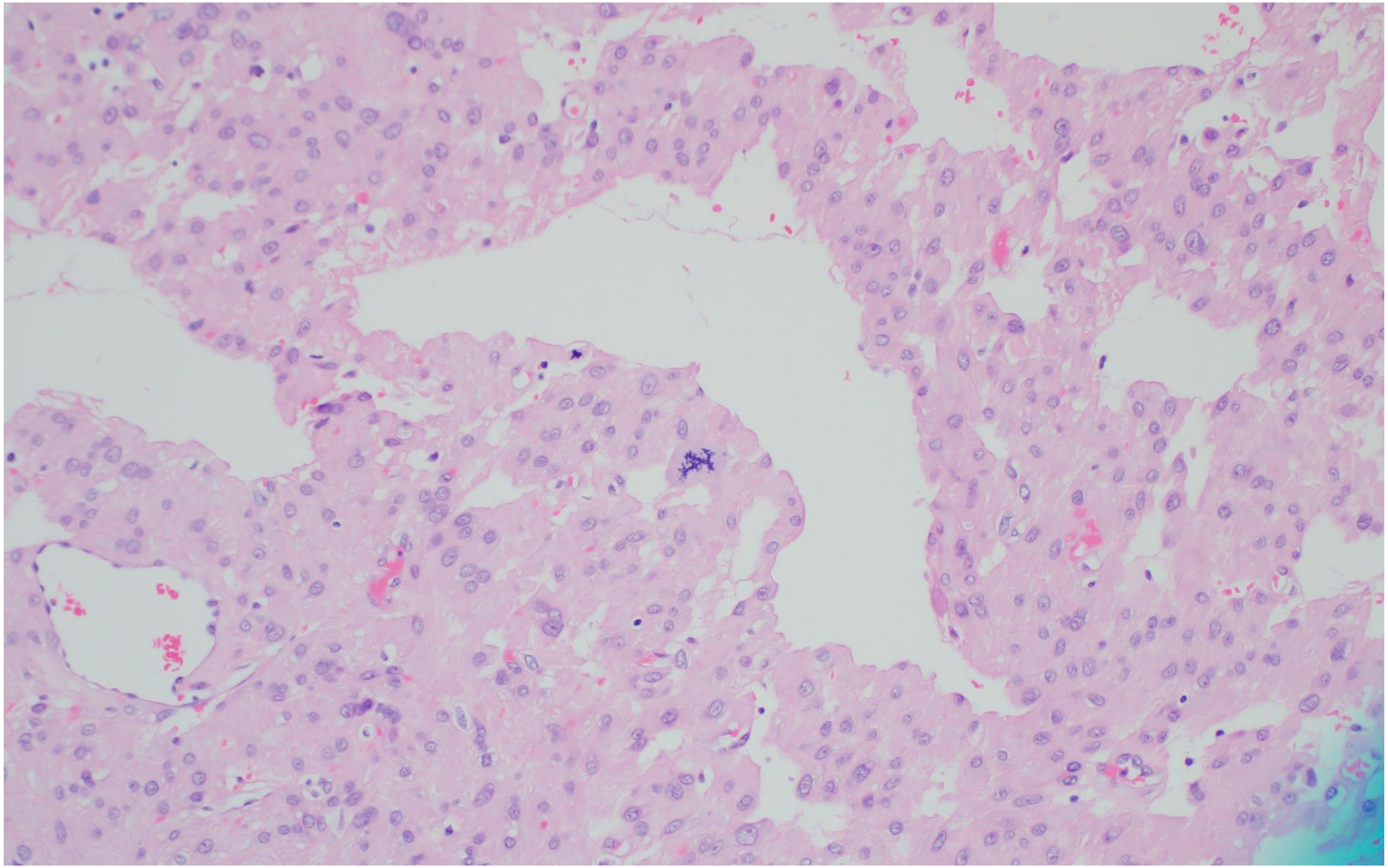
- 48F
- TAH BSO for fibroid uterus
- Macroscopy: multiple fibroids
- No other PMHx
- Histology: Multiple leiomyomata with normal morphology and one larger one with variant features…

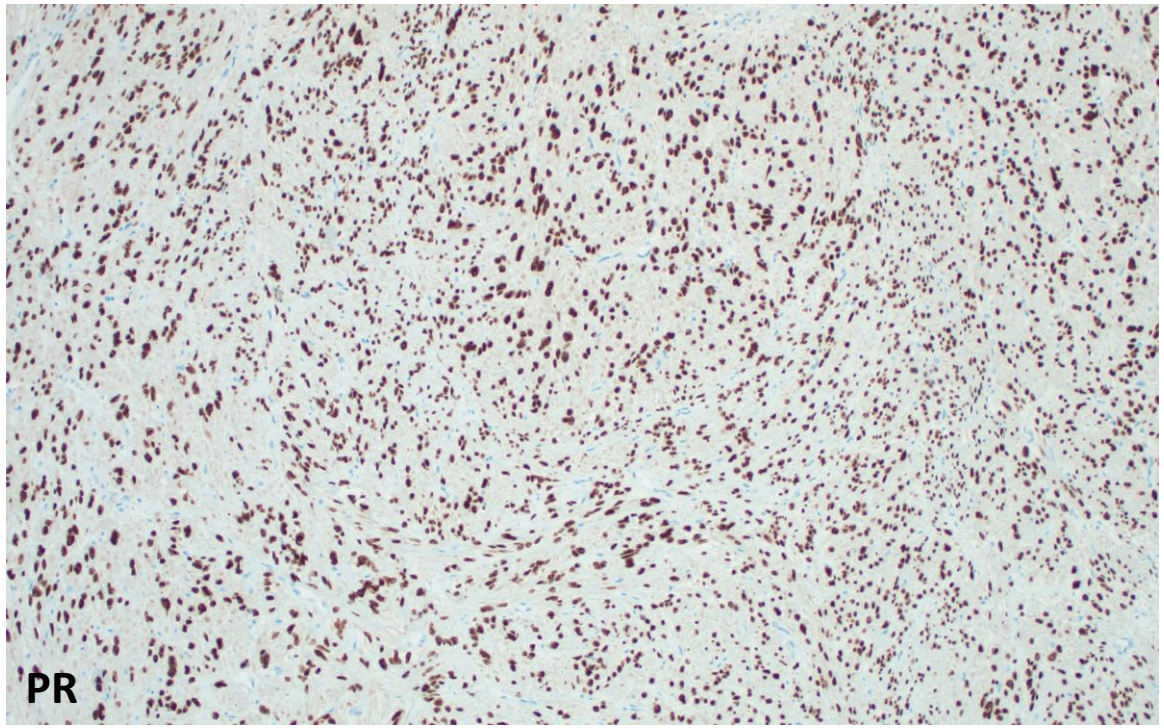








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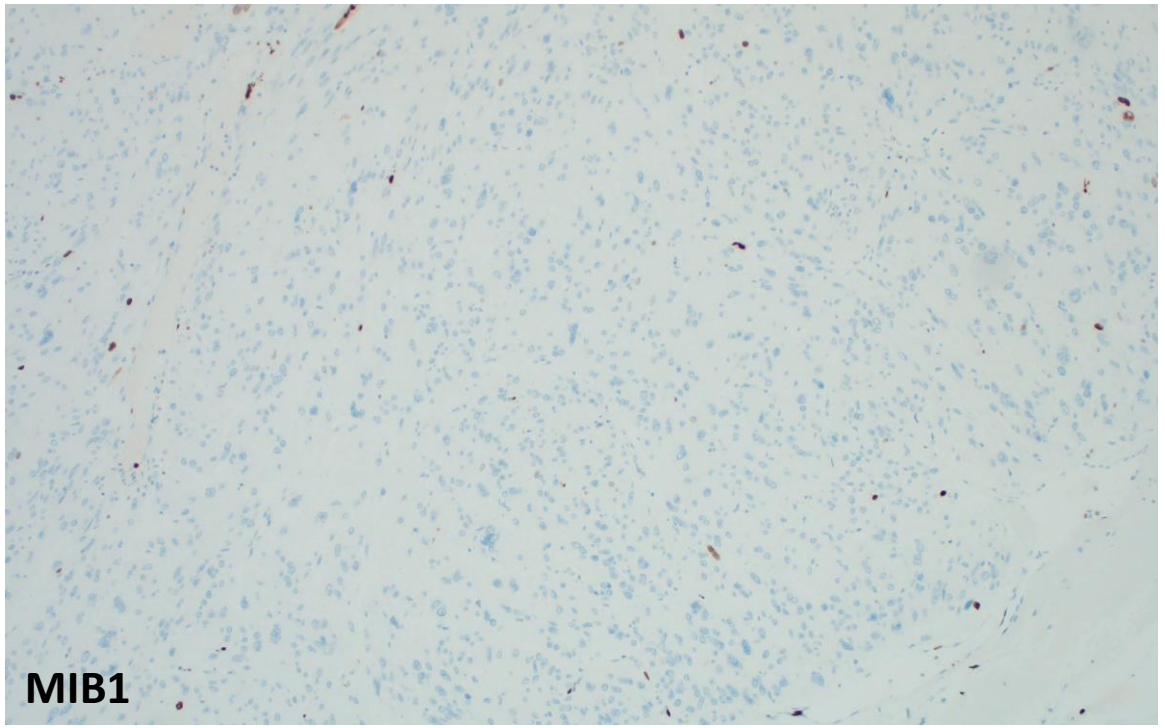
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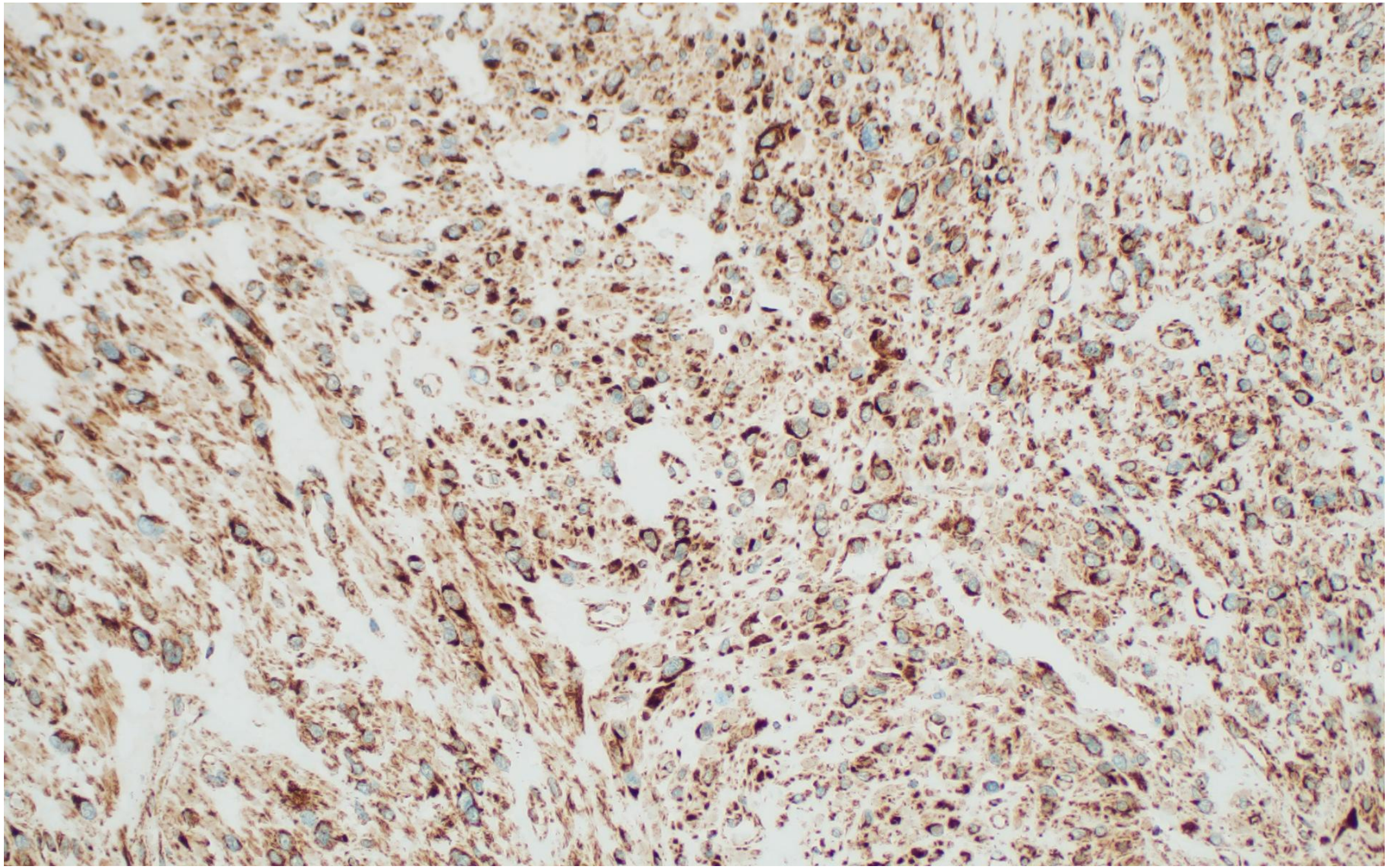
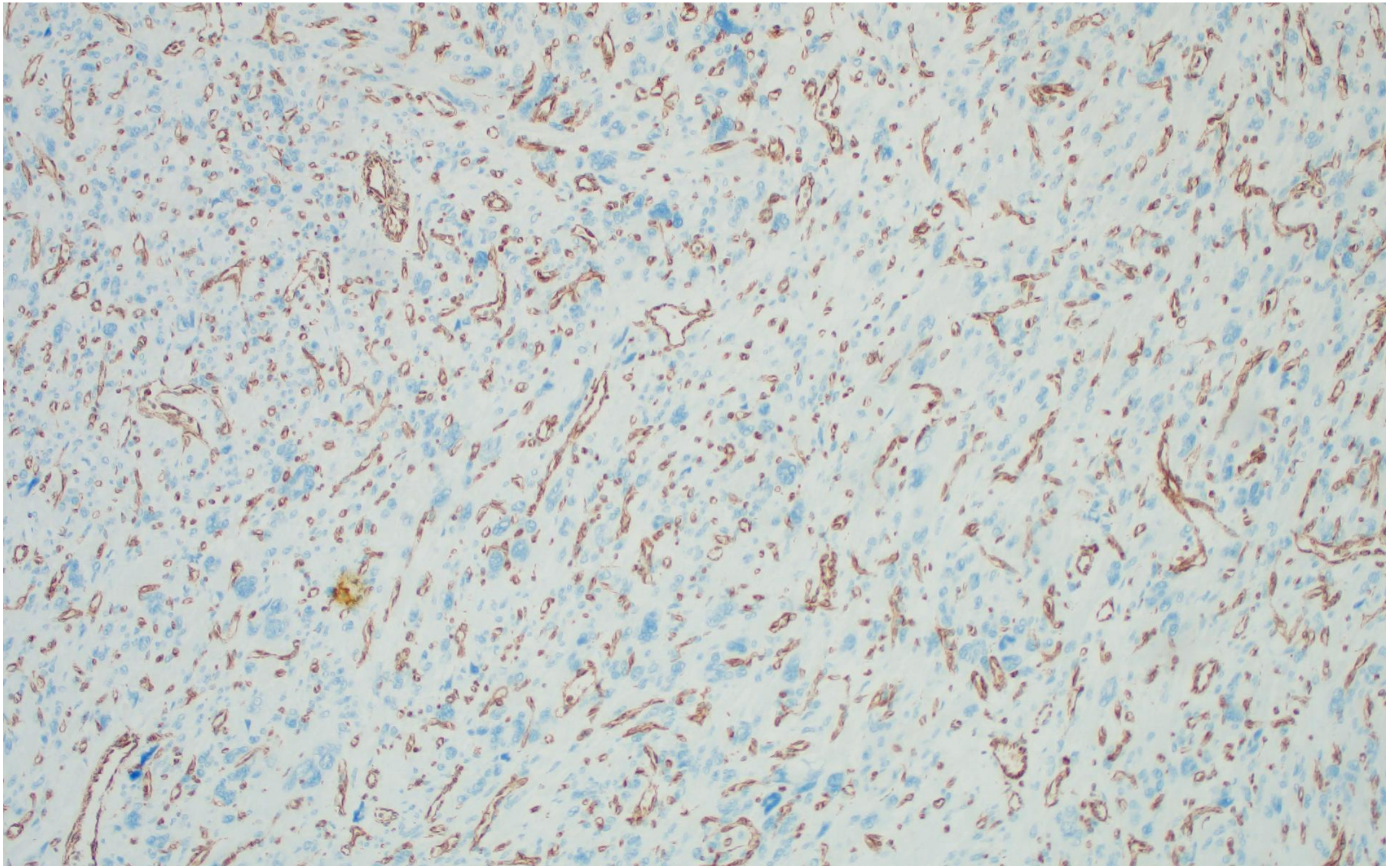




Next generation sequencing…

Two pathogenic variants (Ser419Leu, VAF 45% and Asn373Ile, VAF 40%) within the *FH* gene within lesional tissue

Both variants are reported in patients with Hereditary leiomyomatosis and renal cell cancer (HLRCC)

Diagnosis: Fumarate hydratase deficient leiomyoma

Further history and follow-up

- Patient had skin lesions on her back, father had the same
- No FHx of renal cell carcinoma (one 1st degree relative had brain cancer, one had breast cancer)
- Referred to geneticist (before molecular back!)
- Examination of skin lesions: clinically typical of cutaneous leiomyomata
- Germline testing confirmed the Ser149Leu pathogenic variant = HLRCC.

- Patient had initial renal surveillance but then lost to follow-up.

Features of FHd leiomyoma

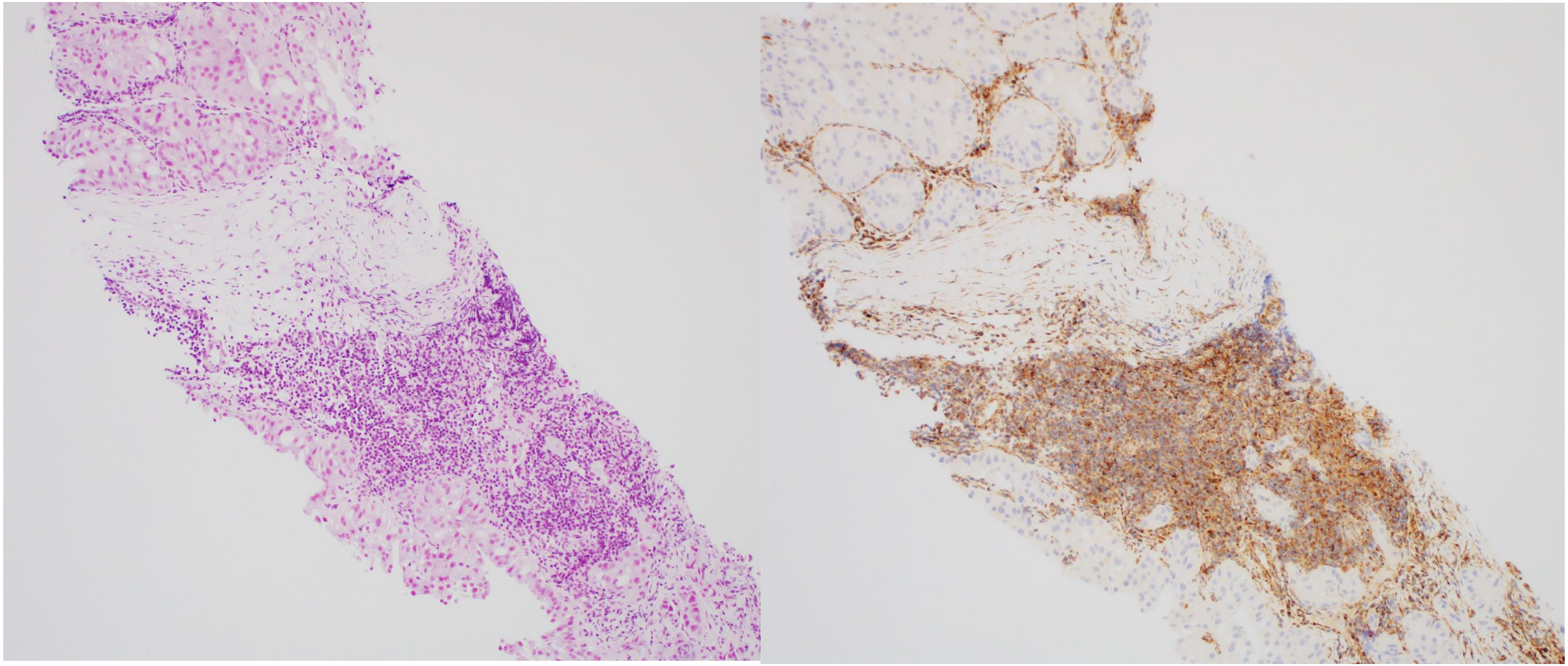
- Staghorn vessels
- Alveolar pattern oedema
- Bizarre nuclei (typically diffuse)
- Chain/ribbon-like nuclear arrangement
- Prominent, eosinophilic single nucleoli
- Perinucleolar halo
- Intranuclear inclusions
- Dense cytoplasm
- Few mitotic figures (but can occasionally be atypical)

FH deficient leiomyoma

- 0.4-1.6% of all leiomyomata are FH deficient (and up to 2% of uterine leiomyosarcoma)

- **The majority will be sporadic**
  - Estimated 2.7-13.9% associated with germline mutation based on population frequency and knowledge of pathogenic variants (Popp *et al*, Mod Pathol. 2022)
  - No good **morphological features** to differentiate
  - BUT patients with HLRCC present at **younger ages**
  - Anecdotally seems to be at the higher end of the estimate, borne out by some more recent papers…
  - 34% of tested patients (15/44, McHenry *et al*, AJSP 2025 but note in <40 only and therefore likely enriched) – median age 33 vs 44
  - 22% (Kipnis *et al*, Cancer Prev Res (Phila) 2024), median age 6 years younger

Why is it important?



Why is it important?

- Avoid diagnosis of STUMP

- FH deficient renal cell carcinoma
  - Tend to occur approximately 10-15 years after initial diagnosis of FH deficient leiomyoma
  - 25-33% of HLRCC patients will develop renal tumours
  - If HLRCC diagnosed at myomectomy, imaging surveillance can be implemented to catch at early stage
  - Aggressive with poor prognosis

FH deficiency

- Mutations in *FH* have different methods of promoting oncogenesis
  - Promotes anaerobic glycolysis
  - Induces pseudohypoxia (upregulation of HIF1alpha, HIF2alpha)
  - Impairs DNA damage repair via homologous recombination
  - Increased intracellular fumarate → oncogenic
  - Increased succination of e.g. SWI/SNF complex (Zyla *et al*, J Clin Pathol. 2021)

- **2-succinylcysteine (2SC)** = marker of protein succination…
  - 2SC immunohistochemistry 100% sensitive, 100% specific
  - FH IHC 100% specific, more like 91% sensitive (Ahvenainen *et al*, AJSP 2022)

Take home messages

- Have low threshold to do FH and/or 2SC testing
- Know morphological features that suggest FH deficiency
- Have high threshold for diagnosis of STUMP in face of diffuse nuclear atypia
- If FH IHC intact, consider another means of testing
- Recommend genetic testing if FH features especially when <40
- Contact clinician if making diagnosis of FH deficient leiomyoma.

Thank you!

Acknowledgements:

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