An 81-year-old female with a bladder tumor

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Clinical history:

The patient is an 81-year old female with a history of hypothyroidism, hypertension and knee replacement. She presented to her primary care physician complaining of vague right abdominal pain and minor weight loss. She reported normal micturition. Lab investigations found no abnormalities. A CT-abdomen was performed, revealing a highly suspicious burgeoning 1.6cm inferolateral right bladder tumor. Urine cytology showed acute inflammation. She was referred to urology, where a transurethral resection of the bladder tumor (TURBT) was performed. The specimen was described as a 1.0cm submucosal nodule on the right anterolateral bladder wall, clinically suspicious for a leiomyoma.

Grossly, multiple fragments of tissue were seen, with no distinct tumor nodule. On histologic examination, the fragments were largely comprised of tumor (80%). A low-power view of one of the tissue fragments shows a normal urothelium overlying a well-circumscribed, densely cellular tumor invading the lamina propria (Fig. 1), as well as the muscularis propria (Fig. 2). Perineural invasion was present but no lymphovascular invasion was identified.

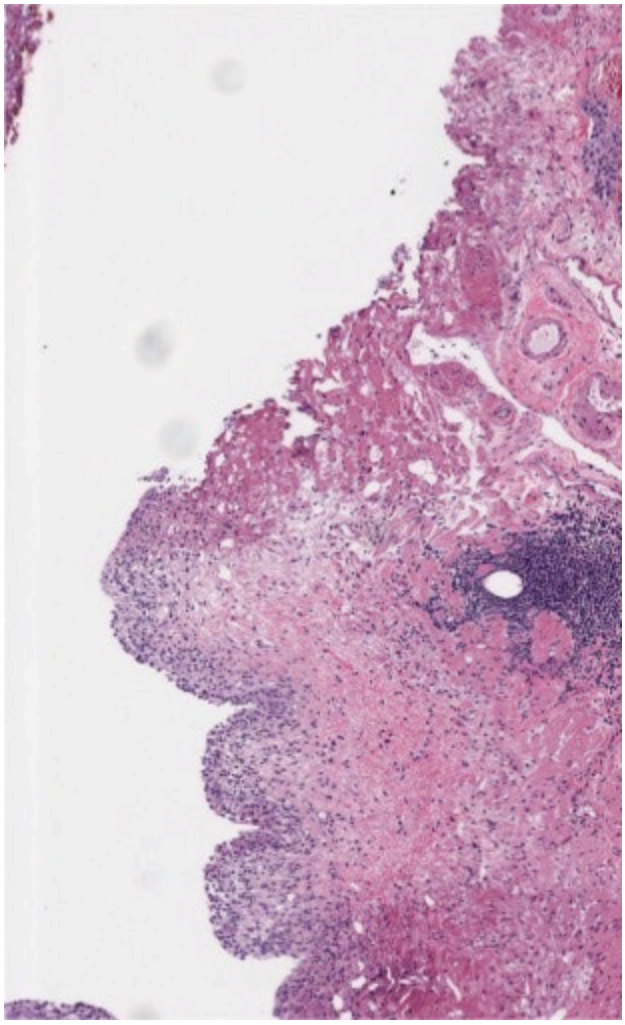

Fig. 1: Dense, well-circumscribed tumor underlying the urothelium

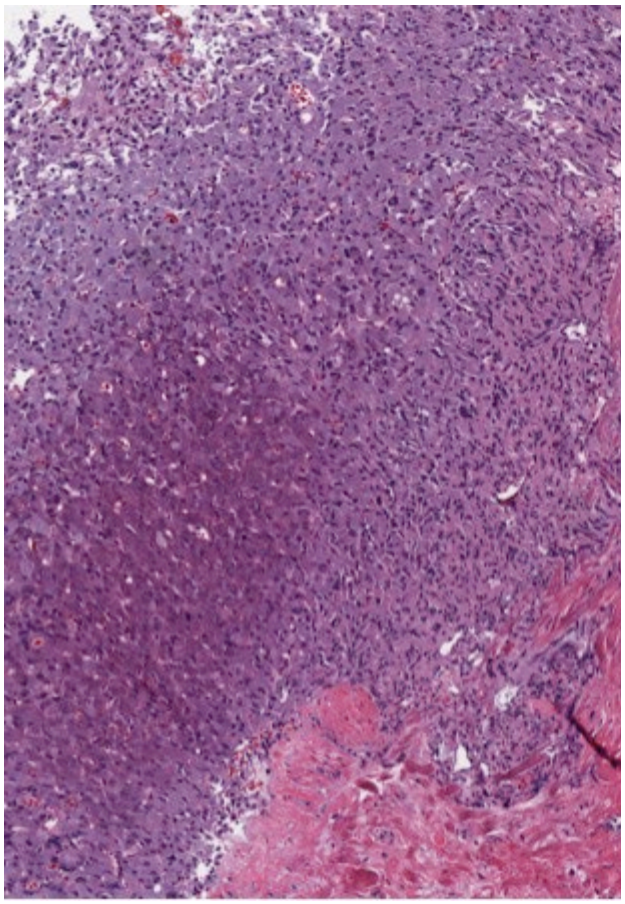

Fig. 2: Tumor involving the muscularis propria.

At higher power, the tumor is composed of a vaguely nested pattern of polygonal cells separated by a delicate, vascular stroma (Fig 3.) The cells have abundant amphophilic cytoplasm, which is homogeneously dense and granular. The nuclei are both central and eccentric, and round to oval in shape with smooth nuclear borders. The nucleoli are inconspicuous. Other areas of the tumor show increased nuclear variation with very slight atypia and a more prominent vascular network (Fig. 4). The tumor has focal areas with a more sheet-like, diffuse architecture, with vaguely salt-and-pepper chromatin in the nuclei (Fig. 5.). Mitoses were exceedingly rare, with just one figure seen. Tumor necrosis was not seen.

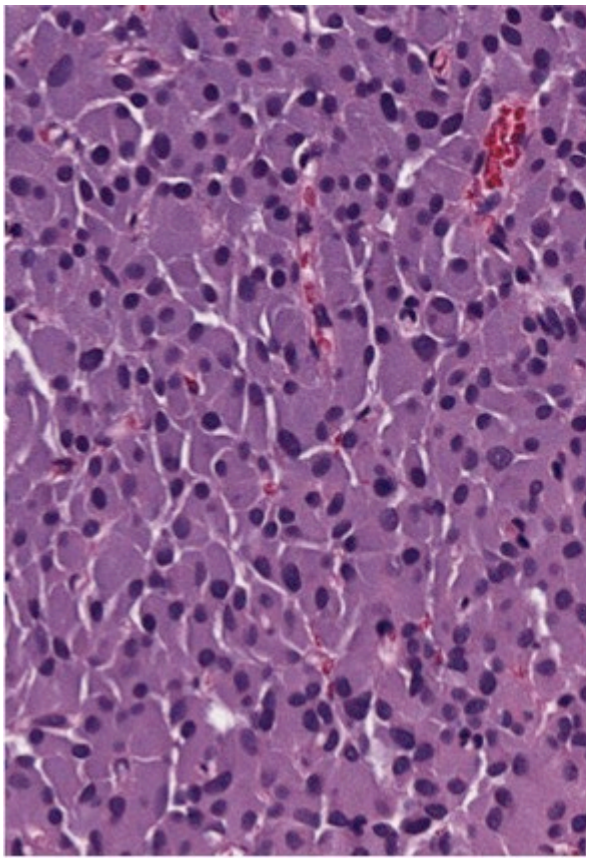

Fig. 3: Nested architecture of polygonal cells with amphophilic cytoplasm surrounded by delicate, vascular stroma.

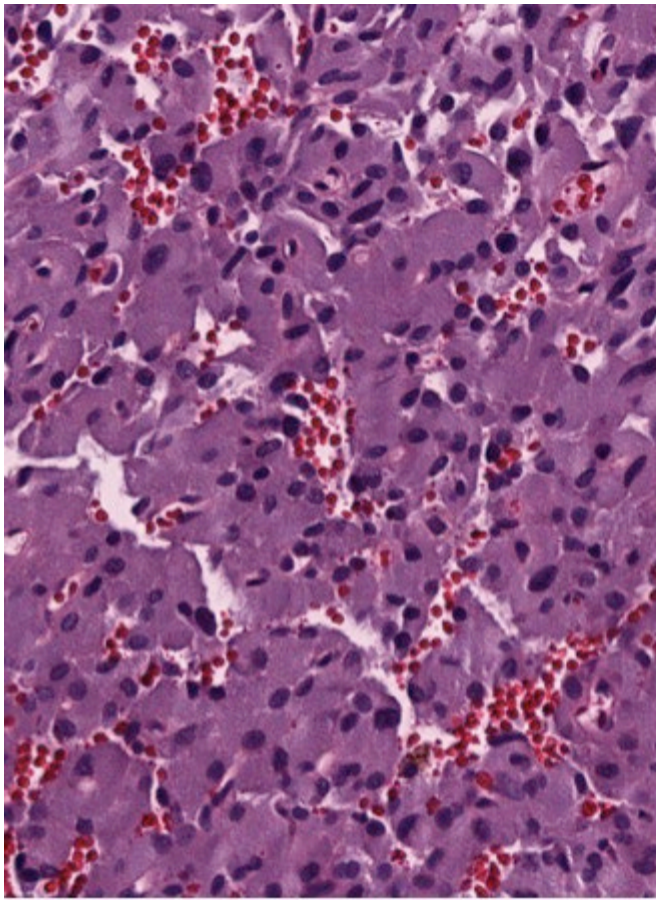

Fig. 4: Slight nuclear variation, mild atypia and prominent vascular network

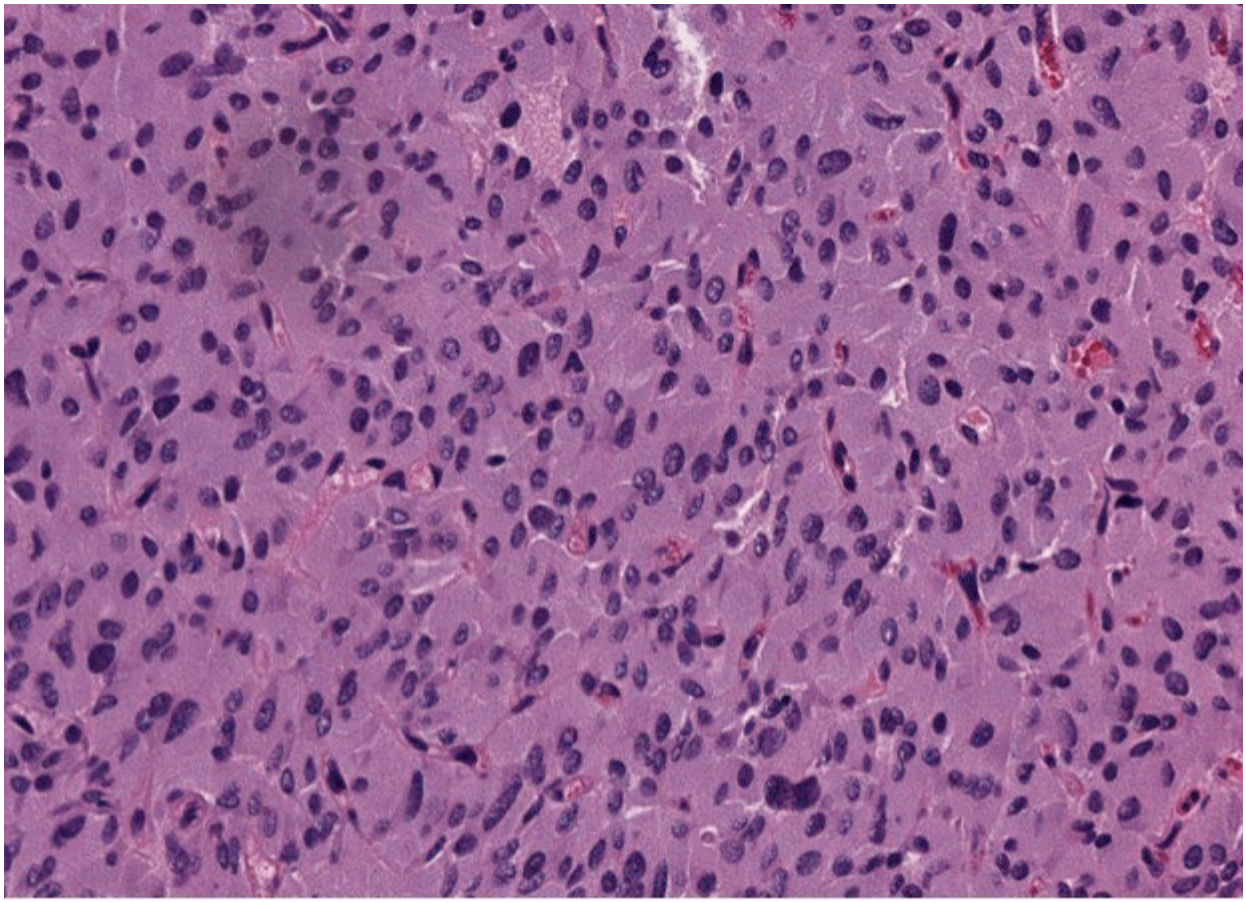

Fig. 5: Focally, there is a slightly more diffuse architecture with stippled chromatin.

Differential Diagnosis

The differential diagnosis for this bladder tumor includes the nested variant of invasive urothelial carcinoma. This is a cytologically bland and rare variant of invasive urothelial carcinoma that occurs most often in the bladder. It typically consists of irregular and confluent nests infiltrating the lamina propria or muscularis propria, helping to distinguish it from benign von Brunn nests. The histology may be purely nested variant, or it may be admixed with the more atypical cells of a usual invasive urothelial carcinoma. The stroma has a varied appearance, as it can be myxoid, focally desmoplastic, or with no reaction. An important clue to suggest this diagnosis is the association with a malignant papillary or in-situ urothelial lesion, which we do not see in this case. GATA-3 staining is expected to be positive in urothelial carcinoma, as it is in this case, however, this marker is also positive in many other neoplasms including most breast carcinomas, paraganglioma/pheochromocytoma, and a small percentage of other solid tumors (Fig. 6). Importantly, as in the conventional type, the nested variant of invasive urothelial carcinoma stains positively for pan-cytokeratin and p63, both of which were negative in this case (Figs. 7, 8).

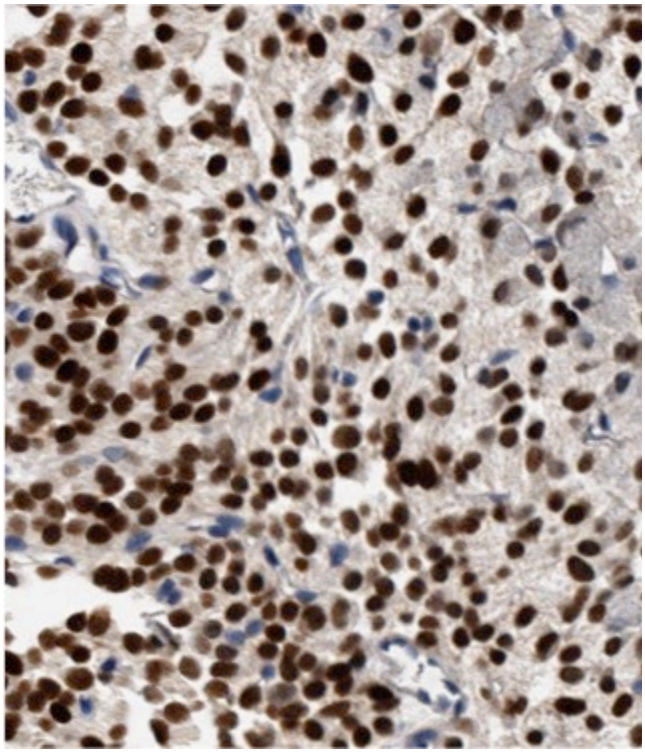

Fig. 6: Positive staining for GATA3.

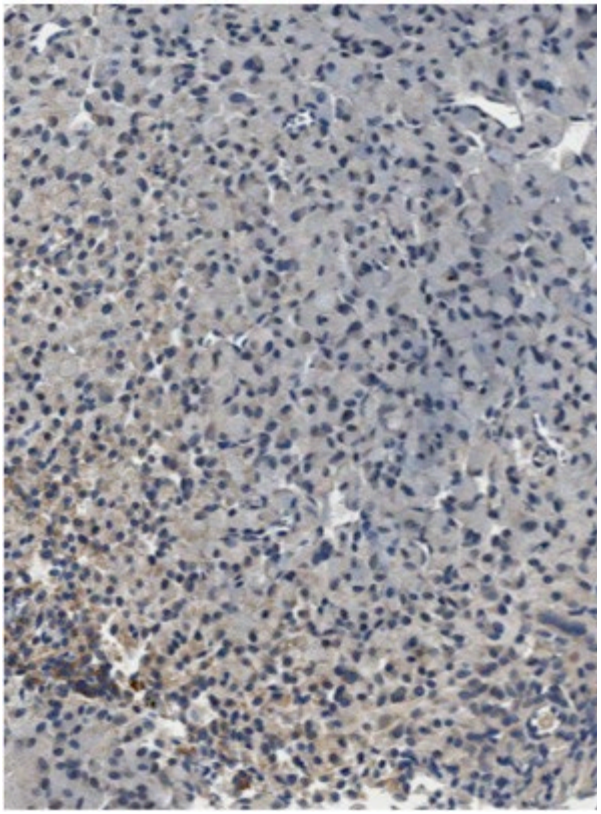

Fig. 7: Negative staining for pancytokeratin; note the reactive urothelium, a positive internal control.

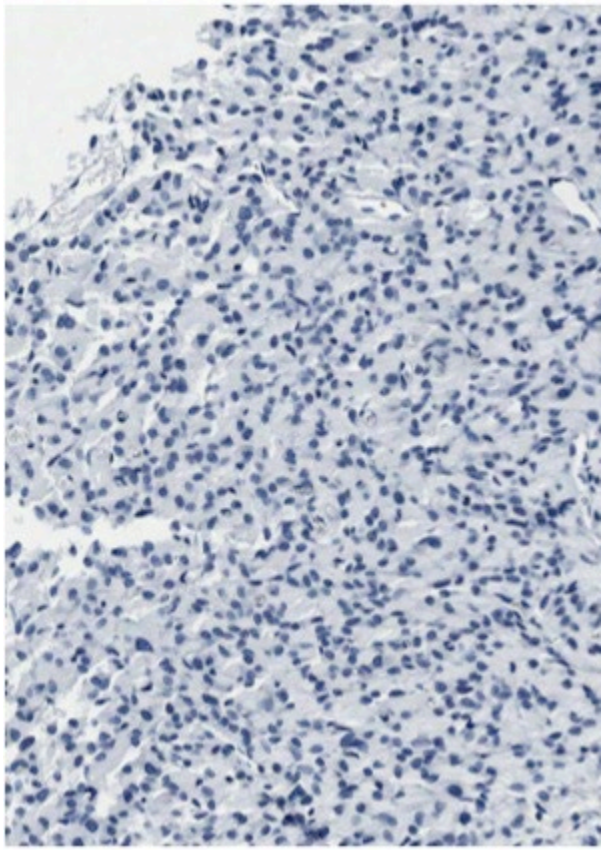

Fig. 8: Negative staining for p63.

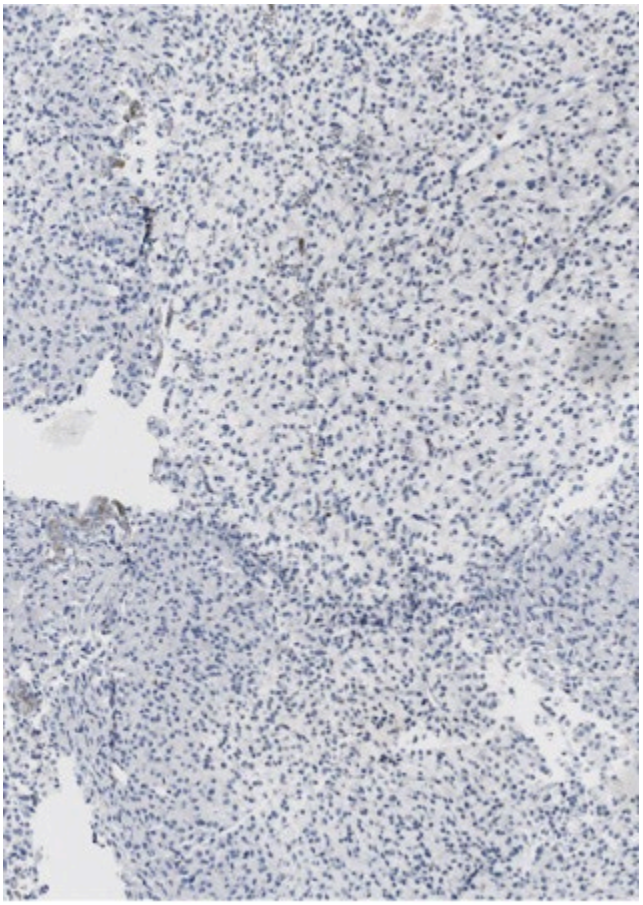

Fig. 9: Negative staining for CD68.

The tumor morphology in this case raises the possibility of a granular cell tumor. Granular cell tumors are of Schwann cell origin and grow in nests and sheets of large, polygonal cells that have abundant granular and eosinophilic cytoplasm. The nuclei, as in this case, are round, hyperchromatic and with inconspicuous nuclei. Granular cell tumors have abundant lysosomes, which are highlighted by staining for CD68. In addition, they show characteristic nuclear and cytoplasmic reactivity for S100. Both of these stains are negative in this case (Figs. 9, 10).

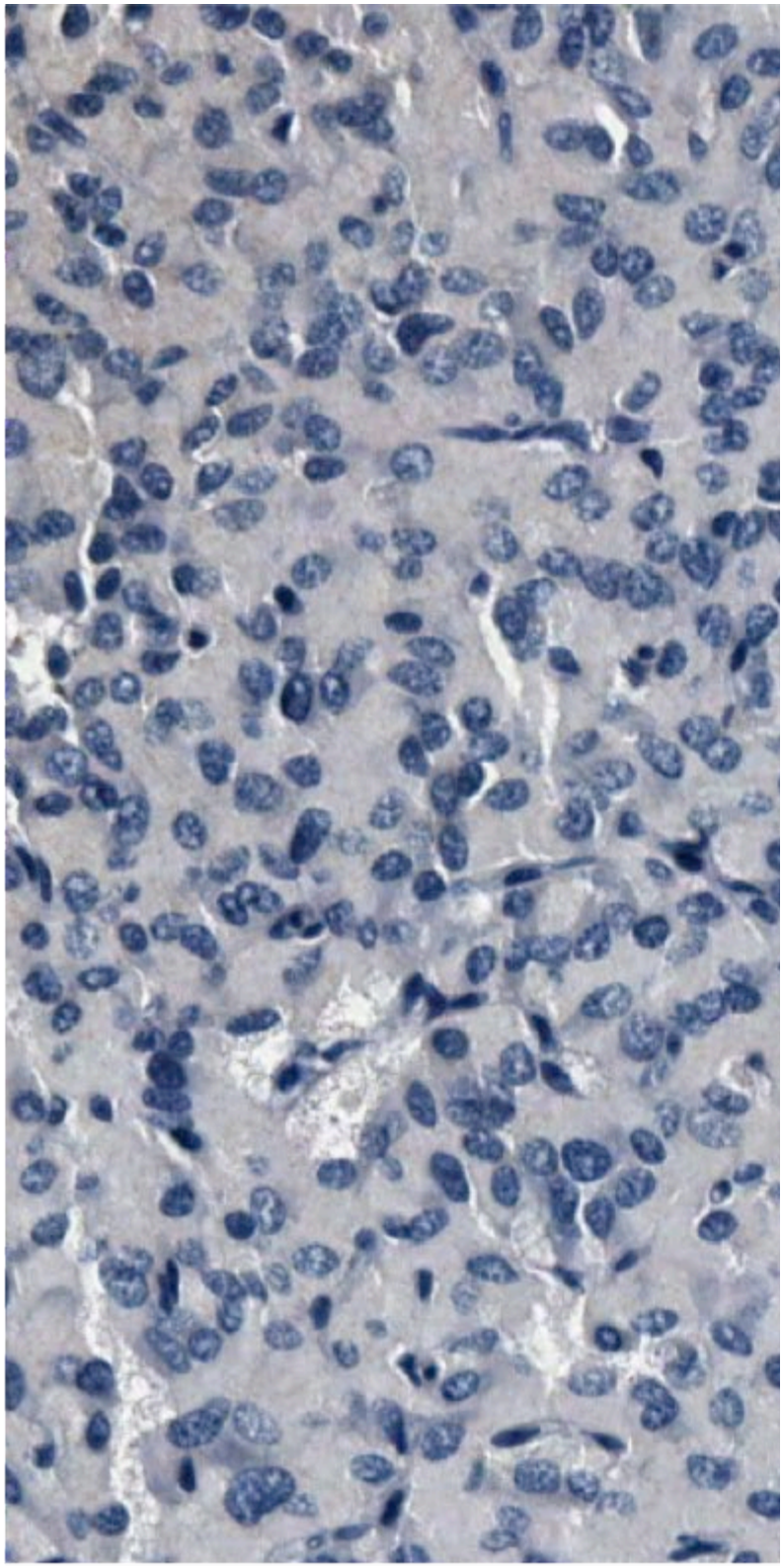

Fig. 10: Negative staining for S100.

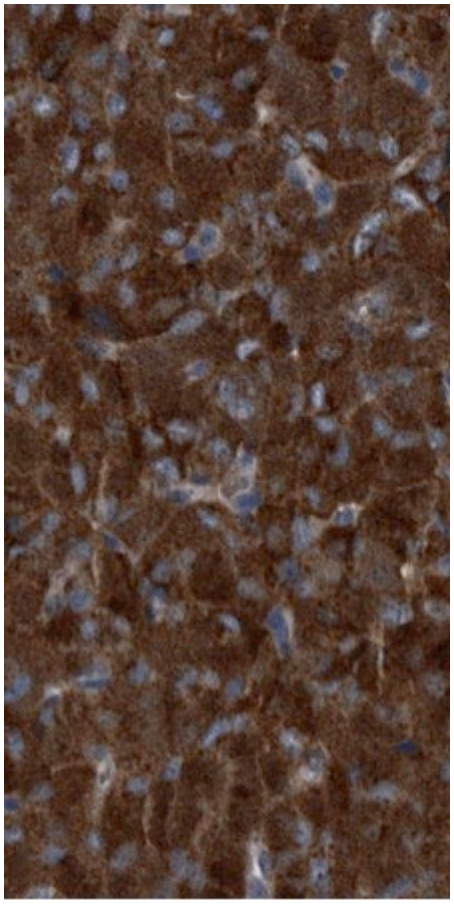

Fig. 11: Strong cytoplasmic reactivity with synaptophysin

Negative S100 staining also helps to rule out melanoma (Fig. 10). Additional melanocytic markers Sox-10, HMB-45, and Melan-A are also negative. Typically, melanoma of the bladder would also show some degree of anaplasia and prominent nucleoli, as well as admixed nested and spindled components.

Other differential diagnoses that need to be considered for this entity, but are less plausible and easily ruled out in this particular case, include Large Cell Neuroendocrine Carcinoma (LCNC), alveolar soft parts sarcoma (ASPS) and metastatic renal cell carcinoma (RCC). LCNC is a very rare tumor of the bladder. In addition to neuroendocrine cytological features, it also has high-grade features with abundant mitoses, necrosis, and cellular anaplasia, none of which are appreciated in this case.[i] LCNC stains positively for neuroendocrine markers and cytokeratins and is negative for S100. ASPS is also a nested tumor with sinusoidal vascular channels and abundant eosinophilic granular cytoplasm and minimal pleomorphism. However, ASPS has cytoplasmic vacuoles and prominent nucleoli. Both ASPS and metastatic RCC can be ruled out by the presence of strong reactivity for chromogranin, synaptophysin and CD56 (Figs. 11, 12, 13).

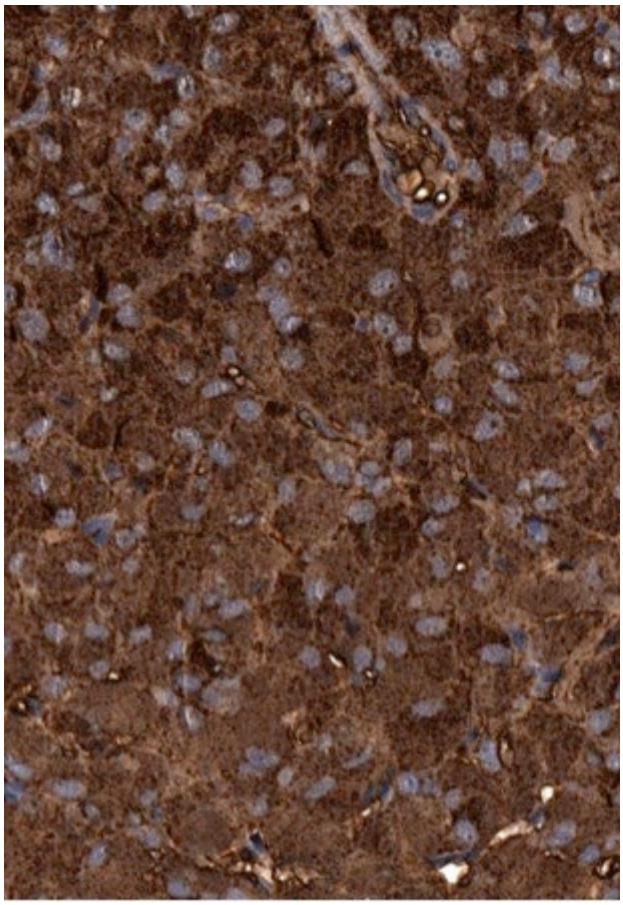

Fig. 12: Strong cytoplasmic reactivity for chromogranin.

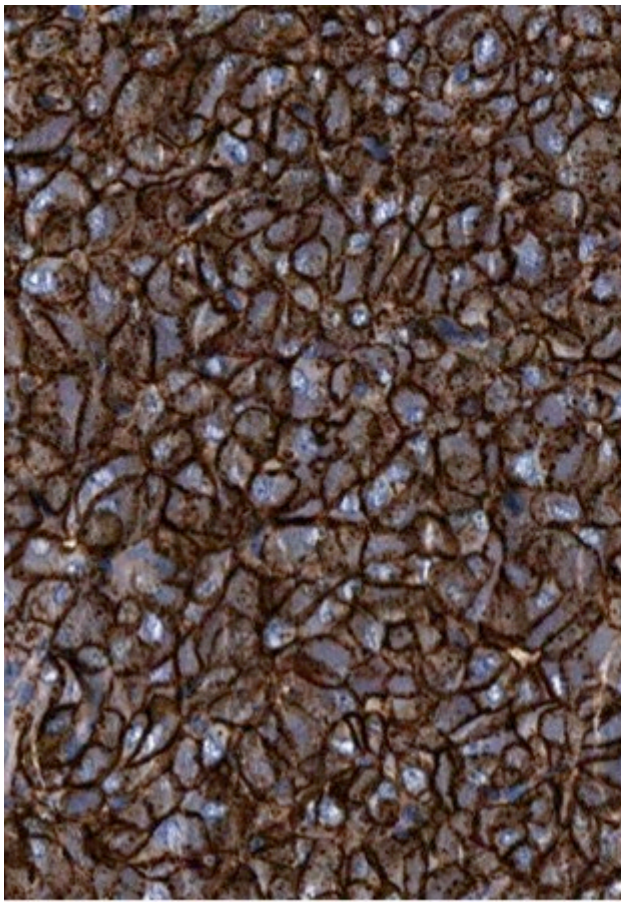

Fig. 13: Prominent, strong membranous staining for CD56.

Final Diagnosis

The **final diagnosis** in this case is a **paraganglioma of the bladder**.

Discussion

A paraganglioma (PGL), by definition, is a pheochromocytoma arising outside of the adrenal medulla. It arises from paraganglia: microscopic aggregates of cells derived from neural crest, symmetrically distributed along the paravertebral axis from the skull base to the pelvis. They are of two types: sympathetic and parasympathetic paraganglia. The sympathetic aggregates are found along the sympathetic trunk and along nerves of the retroperitoneal and pelvic organs; these typically have a neurosecretory function, releasing catecholamines.[iv] Parasympathic paraganglia cells function primarily as chemoreceptors and are found largely in the head and neck, as well as the thorax, along branches of the glossopharyngeal and vagus nerves; the most notable of the parasympathetic ganglia is the carotid body.[v]

Paraganglia may be partly or completely wrapped in S-100+ sustentacular cells, which, when present, are a useful feature for identifying PGLs.[ii,v] As in this case, which was S100 negative, they are not always apparent. In the bladder, paraganglia are a common normal finding due to the migration of chromaffin cells during embryogenesis, most commonly to the muscularis propria of the anterior and posterior walls of the bladder.[v,vi] It is important to know of their existence so that they are not mistaken for metastasis or invasive cancer.

PGLs of the bladder are exceedingly rare, comprising only 0.06% of bladder tumors and 6% of all PGLs.[iv] Clinically, they can be found in any age group, with an average age of 43 and a slight female preponderance.[i] The majority originate from sympathetic ganglia and thus release catecholamines, producing the typical symptoms of paroxysmal headache, diaphoresis, hypertension and palpitations upon micturition, as well as gross hematuria; the latter symptom may raise suspicion of urothelial carcinoma.[i,vii] Importantly, symptomatic tumors may be investigated with measures of urine and serum metabolites of catecholamines.[vii] Approximately 17% of bladder PGLs are asymptomatic, and do not generate the clinical impetus for such testing.[iv]

The vast majority of PGLs are benign, with only a 5-15% malignancy rate; recurrence occurs in around 14% of cases.[i] The only widely accepted criterion of malignancy is metastasis to a site where chromaffin cells are not normally found, such as lymph nodes, bone, lung or liver.[ii,vi,vii] Surgery, either transurethral resection, wedge resection or partial cystectomy, remains the approach to benign disease; secretory tumors require antagonism of catecholamine excess to control perioperative hemodynamic instability.[iii,vii] Metastatic disease is approached with radical cystectomy and removal of metastatic deposits, if possible.[vii]

Paraganglioma/pheochromocytoma is a highly heritable neoplasm, with up to 30% of cases occurring in the context of syndromic disease.[viii] To date, 17 germline mutations that cause PGL have been identified.[vi] The most notorious of these are in Retinoblastoma (RET), Von Hippel Lindau (VHL) and Neurofibromatosis 1 (NF1), genes well-known for causing syndromic pheochromocytoma/paragangliomas. However, half of PGL and pheochromocytoma patients harbor germline mutations in the Succinate Dehydrogenase (SDH) complex.

The SDH complex is a unique conglomeration of five proteins encoded by nuclear DNA that links the Krebs cycle to the electron transport chain in the inner mitochondrial membrane. It is made up of four SDH proteins termed SDHA, SDHB, SDHC and SDHD, as well as an important assembly cofactor, SDHAF2. Together, these proteins form mitochondrial complex 2; its role in the Krebs cycle is to oxidize succinate to fumarate and pass electrons to the electron transport chain. Derangement in its normal functioning is hypothesized to cause tumors by two probable mechanisms: through feedback inhibition of important enzymes in the hypoxia inducible factor-(HIF) pathway due to the accumulation of succinate, and through the generation of reactive oxygen species..[ix,x]

Germline mutations in each of the five proteins of this complex are associated with autosomal dominant tumor syndromes of varying penetrance, known as familial pheochromocyoma/paraganglioma syndromes (PGL1, 2, 3, 4 and 5).[viii] Bladder and other intra-abdominal PGLs are particularly associated with mutations in SDHB, which imparts greater risk for multiple tumors and metastatic disease.[vii, x] This mutation produces the clinicopathological phenotype of PGL4, also associated with benign head and neck PGLs as well as SDH-deficient renal carcinoma, a distinct entity recently delineated by the WHO.[i, viii]

Bladder PGLs occur less commonly as part of PGL1, with mutations in SDHD, in association with head & neck PGL, adrenal pheochromocytoma and SDH-deficient GIST. The latter is a variant with distinct clinical, morphological, and immuno-histochemical properties; about 20% of cases are also seen in the context of mutations in SDHA (PGL5), SHDB or SDHC.[viii, x] The PGL2 is an exceedingly rare syndrome due to SDHAF2 that is associated with multiple benign head & neck PGLs.[viii, x] Mutations in SDHC (PGL3) are particularly associated with carotid body tumors and SDH-deficient renal carcinoma.[viii, x] Syndromic bladder PGLs also occur in the Carney-Stratakis syndrome, in which autosomal dominant mutations in any of SDHB, SDHC or SDHD produce both PGL and GIST in young patients.[x] Finally, the Carney Triad, a trio of PGL, pulmonary chondroma and SDH-deficient GIST, is a non-heritable PGL syndrome caused by promoter hypermethylation of SDHC. [ix, x]

Mutations in the SDH complex are easily and reliably detected by immunohistochemistry for the SDHB protein. Normally, staining for SDHB is positive in all cells, with granular and cytoplasmic reactivity reflecting the mitochondrial location of the complex. Loss of SDHB or any of the other four components of the SDH complex leads to instability of the whole complex, releasing the SDHB protein into the cytoplasm where it is quickly degraded.[viii] Tumors with any inactivating SDH mutations thus demonstrate loss of reactivity on immunohistochemistry, a well-established surrogate for molecular testing.[x] Immunohistochemical testing of all PGLs for SDHB is critical, given that genetic disturbances in the SDH complex are an important marker for syndromic disease and an indication for further clinical investigations.

In this particular case, the tumor was sent to an outside institution for SDHB testing, which indicated no loss of SDHB and thus no SDH complex mutation. This is a case of a non-syndromic, incidental bladder paraganglioma with no increased risk of recurrence or metastastic spread. A follow-up CT scan demonstrated no recurrence of the tumor.

In conclusion, PGL of the bladder is a rare neuroendocrine tumor derived from paraganglia. It may easily be mistaken for an invasive urothelial carcinoma, particularly with muscularis propria involvement (the usual site of paraganglia cells in the bladder wall) and GATA3 reactivity. Many cases occur in the context of germline mutations, conferring increased risk for multiple tumors. Germline mutations in SDHB, in particular, greatly increase the risk of malignancy. Immunohistochemistry for SDHB is a crucial ancillary test in this entity, as a surrogate for molecular markers of syndromic disease with important implications for patient outcome.

References:

i WHO Classification of Tumours of the Urinary System and Male Genital Organs, 4th edition, 2016.

ii MB Amin, SK Tickoo et al. Diagnostic Pathology: Genitourinary, 2nd edition. Philadelphia: Elsevier, 2016.

iii N Ordonez. Value of GATA3 immunostaining in tumor diagnosis: A review. Adv Anat Path. 2013; 20 (5): 352 – 360.

iv S Purnell, S Abhinav, M Maruf, C Grant, P Aarwal. Genitourinary paraganglioma: Demographic, pathologic, and clinical characteristics in the surveillance, epidemiology, and end results database (2000 – 2012). Urol Oncol-Semin ORI. 2017; 35: 457.e9 – 447.e14.

v SE Mills, Ed. Histology for Pathologists, 4th ed. Philadelpha: Wolters-Kluwer, 2012.

vi E Kouba, L Cheng. Neuroendocrine tumors of the urinary bladder according to the 2016 World Helath Organization classification: molecular and clinical characteristics. Endocr Pathol 2016; 27: 188 – 199.

vii JI Epstein, VE Reuter, MB Amin. Biopsy Interpretation of the Bladder, 3rd ed. Wolters-Kluwer, 2004: 318 – 323.

viii AJ Gill. Succinate Dehydrogenase (SDH)-deficient neoplasia. Histopath 2018; 72: 106-116.

ix C Bardella, PJ Pollard, I Tomlinson. SDH mutations in cancer. Biochim Biophys Acta 2011; 1807: 1432 – 1443.

x L Oudijk, J Gaal, RmR de Krijger. The role of immunohistochemistry and molecular anaylsis of succinate dehydrogenase in the diagnosis of endocrine and non-endocrine tumors and related syndromes. Endocr Pathol. 2019; 30: 64-73.