

Renal Hemangioblastoma with Mixed Mullerian tumor of endometrium: A tale of two rare primary tumors

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Case report

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Abstract

Introduction: Renal hemangioblastoma (RH) is a very rare benign tumor. Hemangioblastoma most commonly occur in the central nervous system (CNS) and only few cases of RH have been reported as they occur most commonly as asymptomatic masses found incidentally. Mixed Mullerian Tumor (MMT) of the uterus is a rarer and aggressive form of uterine malignancy. The detection of two primary rare tumors incidentally is a rare entity.

Case presentation: A 50 years female presented with abnormal uterine bleeding which on endometrial sampling was diagnosed as a rare variety of endometrial cancer i.e., MMT or uterine carcinosarcoma. On preoperative imaging, a renal mass was also detected which was highly vascular and was mimicking Renal Cell Carcinoma (RCC). Fine needle aspiration cytology (FNAC) was done from the renal mass to differentiate between RCC and metastasis but it showed only blood cells. Patient underwent staging laparotomy for endometrial cancer and frozen section examination of the renal mass which was inconclusive with few atypical cells and thus patient underwent radical nephrectomy too. Histopathological examination revealed it to be a RH which is a very rare benign tumor.

Discussion: RH is a rare benign tumor which doesn't require any treatment in majority of the patients. Only 26 cases of RH outside the CNS have been reported till date. MMT is a rare aggressive uterine tumor with an incidence of 1-2 % of all uterine neoplasms, which metastasizes early and thus early identification and treatment is the key. RH needs to be differentiated from RCC to avoid over treatment. Morphological findings are similar in both, preoperative FNAC, PET scan and intraoperative frozen section can be utilized to differentiate in between two in well circumscribed tumors and in high suspicion. Occurrence of renal mass as an incidental finding in the preoperative work up of uterine malignancy directed us to the differentials of metastasis or another histologically distinct primary tumor. The presence of two rare primary tumors i.e., RH and MMT in the same patient which are unrelated is a rare entity.

Introduction:

Hemangioblastoma, a rare benign tumor is more commonly associated with Von Hippel Lindau (VHL) syndrome and its most common site is CNS. Hemangioblastoma can occur in other sites such as kidney. To date, only 26 cases of a RH have been reported in literature thus it is a very rare benign tumor^{1,2} occurring as a sporadic tumor and is mostly as an incidental finding. MMT of uterus, also known as carcinosarcoma is also rare and aggressive variety of uterine cancer with high chances of early metastasis. The incidence of MMT is 1 to 4 per 100,000 women.^{3,4} We present a rare case of two rare primary tumors occurring in the same patient.

Case Presentation:

A 50-year-old woman presented to our Gynecology OPD with chief complaints of bleeding per vaginum for 4 months, pain lower abdomen and dyspareunia for 2 months. Patient had regular menstrual cycles lasting for 6 days, occurring every 28 days till 4 months back when she developed vaginal bleeding, associated with passage of clots, pain and sexual discomfort. She never used oral contraceptive pills or any other method of contraception. She has two children, both normal vaginal delivery with last childbirth 17 years back. Patient was detected with hypothyroidism 2 years ago and was maintaining euthyroid status on thyroxine 50 microgram daily. There was no significant history of any genital, colonic or renal malignancy in her family.

On examination, patient was average built, afebrile, pulse 76/min, blood pressure 110/74mmhg, mild pallor was present. Abdomen was soft and didn't reveal any mass. Per speculum examination revealed hypertrophied cervix and slight bleeding through external os. On per vaginal examination, cervix appeared firm, uterus was bulky, firm, mobile with no palpable adnexal mass through fornices. Per rectal examination had normal rectal mucosa and soft parametrium.

Patient had an endometrial sampling which was reported as a high-grade endometrial adenocarcinoma (villos-nodular type). Her haemoglobin was 8.9 gm%, kidney and liver function tests were within normal limits. S.TSH was 2.6 uIU/ml, Ca-125 was 165 IU/L. Pap smear was reported as negative for intraepithelial lesions or malignancy. On Ultrasonography (USG) of pelvis, uterus was anteverted, bulky with increased endometrial thickness with a growth within the endometrial cavity. Computed tomography revealed bulky uterus showing heterogenous attenuation of myometrium with foci of heterogenous enhancement in central part and a heterogeneously enhancing mass lesion towards lower pole of left kidney suggestive of mitotic etiology most likely RCC. Contrast enhanced MRI of abdomen and pelvis was done and it revealed a bulky uterus with an ill-defined myometrial based lobulated mass lesion extending into the endometrium measuring 2.4 x 1.1 x 2.0 cm with distorted endometrial cavity with adenomyosis. (Fig 1) It also picked up a 4.8 x 4 x 3.2 cm heterogeneously enhancing lesion in lower pole of left kidney reaching upto hilum and no lymphadenopathy. (Fig. 2,3)

USG guided FNAC from the renal lesion was done (twice) however it yielded only blood and no tissue in both attempts. The renal mass was radiologically enhancing and vascular, so it was presumed to be a highly vascular RCC. Patient did not agree for Positron Emission Tomography- Computed Tomography (PET-CT) which could have been helpful and was thus planned for staging laparotomy for endometrial cancer and frozen section for renal mass with due counselling. She underwent extra fascial hysterectomy and bilateral salpingo-oophorectomy with pelvic lymphadenectomy and infracolic omentectomy with frozen section from renal mass. There was no ascites, omental or peritoneal deposits. As frozen section report was doubtful and inconclusive radical nephrectomy was performed; the counselling and consent was obtained prior for the same.

On gross examination, the endometrial cavity was filled with papillary growth 2.2 x 2 x 1.5 cm which was grossly infiltrating the outer half of myometrium with areas of necrosis. (Fig 4) There was a 4 x 5 cm well circumscribed encapsulated growth at lower pole of kidney reaching renal hilum. Histopathological

examination of the uterine growth showed a biphasic tumor with malignant epithelial component with pleomorphism, in the form of glands showing atypia and stromal component in the form of spindle cells suggestive of MMT. There was no lymph vascular space occlusion and immunohistochemistry (IHC) markers such as vimentin, keratin, desmin, myogenin, S-100, and epithelial membrane antigen were positive suggestive of MMT.

The renal mass showed sheets of polygonal cells with haemorrhage with minimal atypia suggestive of RH. (Fig. 5) The tumor was positive for markers like inhibin, CD34 and Neuron-Specific Enolase (NSE) by IHC and negative for vimentin and cytokeratin which are markers of RCC. (Fig. 6,7) No vascular invasion or capsular breach was seen. Patient had uneventful recovery and was discharged on day 6. In view of RH, computed tomography head was done to rule out VHL disease and the study came out to be normal. Medical oncologist started the patient on chemotherapy for the MMT and she was given paclitaxel 175 mg/m² and carboplatin AUC 5 once in 3 weeks for 6 cycles. Patient is healthy at present and is on regular follow up for 15 months.

Discussion:

Capillary hemangioblastoma, is a benign tumor which consists of a network of small blood vessels along with lipid-laden stromal cells.⁵ The stromal cells may exhibit significant nuclear pleomorphism, mimicking cancer tissues. It can occur either sporadically, or in association with VHL disease in around 25% of the patients.⁶ The common age of presentation is between 20 to 50 years with a male: female ratio of 2:1. This tumor most commonly occurs in the CNS, predominantly in the cerebellum, but can occasionally occur in the meninges, retina, spinal cord, corpus callosum, lateral ventricle, pituitary gland, and the optic nerve. Rarely, hemangioblastoma can be seen in other sites, such as retroperitoneum, skin, liver, pancreas, lung, adrenal, peripheral nerve, soft tissue, and urinary bladder, usually in association with VHL syndrome. VHL is an autosomal dominant syndrome associated with germline mutation in the VHL tumor suppresser gene located on chromosome 3p.^{7,8} There are only few reports on sporadic hemangioblastoma occurring outside the CNS, including kidney.⁹⁻¹⁴ Till date only 26 cases of sporadic RH have been reported. RH are asymptomatic masses generally found incidentally as in our case. Rarely, they may present with loin pain or haematuria.

MMT also known as uterine carcinosarcoma is a rare uterine malignancy occurring in postmenopausal females in 5th to 6th decade of life. It comprises of only 1–2% of all uterine neoplasms.¹⁵ It is a dedifferentiated and aggressive form of endometrial carcinoma having poor prognosis.¹⁶ They have high chances of metastasis commonly to the lung (49%), peritoneum (44%), pelvic or para-aortic lymph nodes (35%), adrenal gland or bone (19%), heart or pericardium (9%), and/or brain (7%). Other rare sites include the pancreas, liver, eye thyroid gland and skin.¹⁷ The clinical presentation of carcinosarcomas is nonspecific and is similar to other pelvic neoplasms. Patient may present with pyometra with vaginal bleeding, bloody or watery discharge, abdominal pain, or with a polypoid mass in a postmenopausal woman. A “symptom triad” has been defined favouring carcinosarcoma over endometrial

adenocarcinoma which includes pain, severe vaginal bleeding, and the passage of necrotic tissue per vaginum. MMT doesn't have pathognomonic appearance on MRI. However, there should be a suspicion of MMT in the presence of a large heterogenous infiltrative tumor or when tumor enhancement is equal to or greater than the myometrium. The diagnosis is made by doing endometrial sampling and HPE of the sample.

On HPE there are both epithelial and mesenchymal elements suggestive of MMT. PET scan useful to identify unsuspected disease, extra-pelvic site or rule out metastasis ^{18, 19, 20} Surgical management should include extra fascial hysterectomy with bilateral salphingo-oophorectomy, infracolic omentectomy, bilateral pelvic and in some cases para-aortic lymphadenectomy.

Based on the GOG 161 study, Ifosfamide/ Paclitaxel is considered the treatment of choice²¹ and paclitaxel/carboplatin is equally effective ²² as adjuvant treatment and was used by our medical oncology team.²³ There is increasing role of adjuvant chemo-radiation now with significant overall survival however multiple demographic and clinical factors influence the choice of adjuvant therapy.^{24, 25} Despite the use of aggressive therapy, only modest improvement in overall survival is noted over the last few decades with a five-year overall survival rate of approximately 20–30%.²⁶

The occurrence of rare tumors like sporadic RH and MMT in the same patient is very rare entity. When a new tumor is found in a patient with one existing tumor we need to differentiate it from metastasis to determine the further management and prognosis. To differentiate, a combination of history, clinical, radiological and pathological investigation will be needed. The most appropriate way to distinguish is by HPE as it will show different cells of origin.

RCC needs to be differentiated from RH as the former is malignant and the latter is essentially benign. Each of them has a different prognosis and differentiating the two will help avoid over-diagnosis and unnecessary treatment.

- On radiology and gross examination, RH mimics various renal neoplasms. Clear cell variety of RCC shares various morphological features with RH, making it the most common differential diagnosis. Thus, RCC may occasionally have a hemangioblastoma-like pattern making it nearly impossible to distinguish it from RH on morphological basis. ^{27,28}
- The clues to the diagnosis of RH are circumscribed borders, sheets of large polygonal cells with arborizing thin-walled blood vessels and pleomorphic nuclei, paucity of mitotic figures despite prominence of atypical cells. The presence of peri-cytomatous growth patterns and intracytoplasmic lipid vacuoles strongly suggests hemangioblastoma although both tumor types have similar morphological features, such as clear cytoplasm and a vascular network. ^{12,27,28}
- To confirm the diagnosis of hemangioblastoma, IHC must be done. The absence of immunostaining for cytokeratin, and positive staining for α-inhibin, S100 and NSE is diagnostic of hemangioblastoma. ^{27,28}

- Since they can be sporadic or associated with VHL syndrome a polymerase chain reaction sequencing analysis of the VHL gene is done to confirm presence of mutation in the

RH needs to be correctly diagnosed as sporadic RH does not require further treatment and it has a very good prognosis.¹⁴ Adjuvant therapy in MMT will depend on the histology of tumor in terms of local invasion, nodal status and adequacy of margins. Prognosis in case of MMT and RH depends on biological potential of MMT as RH is a benign condition.

Such cases need a multidisciplinary approach with a team of gynaecologists, onco-surgeons, urologist, radiologist, pathologist and medical oncologist. The key is to evaluate each tumor independently. They should be treated aggressively with the intent to cure each, so as to achieve maximum therapeutic benefit

Conclusion:

RH is a rare benign tumor which doesn't require any treatment in majority of the patients. MMT is a rare aggressive uterine tumor which metastasizes early, henceforth early identification and treatment is the key. RH needs to be differentiated from RCC to avoid over treatment. Morphological findings are similar in both, preoperative FNAC, PET scan and intraoperative frozen section can be utilized to differentiate in between two in well circumsised tumors and in high suspicion. The presence of two rare primary tumors i.e., RH and MMT in the same patient which are unrelated is a rare entity.

Declarations

Acknowledgements:

Nil

Declarations

Ethics approval and consent to participate

Written consent for the publication of this case report was obtained from the patient. Approval for case report by the institutional ethics committee is not required.

Consent for publication

Written informed consent for the publication of this case report and for the accompanying images was obtained from the patient.

Availability of data and materials

Not available.

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Conflict of interest

The authors declare that they have no conflicting interests.

Authors' contributions

LB, AS, DK conceptualized the manuscript. AS, DK, LB, PS, AT reviewed the literature, analysed data, and made major contribution to the writing of the manuscript. DK, LB, AS, PS performed the clinical examination, surgical treatment, and clinical follow-up. VM provided the histopathological diagnosis. All authors have read and approved the final version of the manuscript.

Abbreviations

MMT	mixed mullerian tumor
RH	renal hemangioblastoma
MRI	magnetic resonance imaging
USG	ultrasonography
HPE	histopathological examination
RCC	renal cell carcinoma
NSE	neuron-specific enolase
PET	positron emission tomography
AUC	area under curve
VHL	Von Hippel Lindau disease
IHC	immunohistochemistry

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Figures

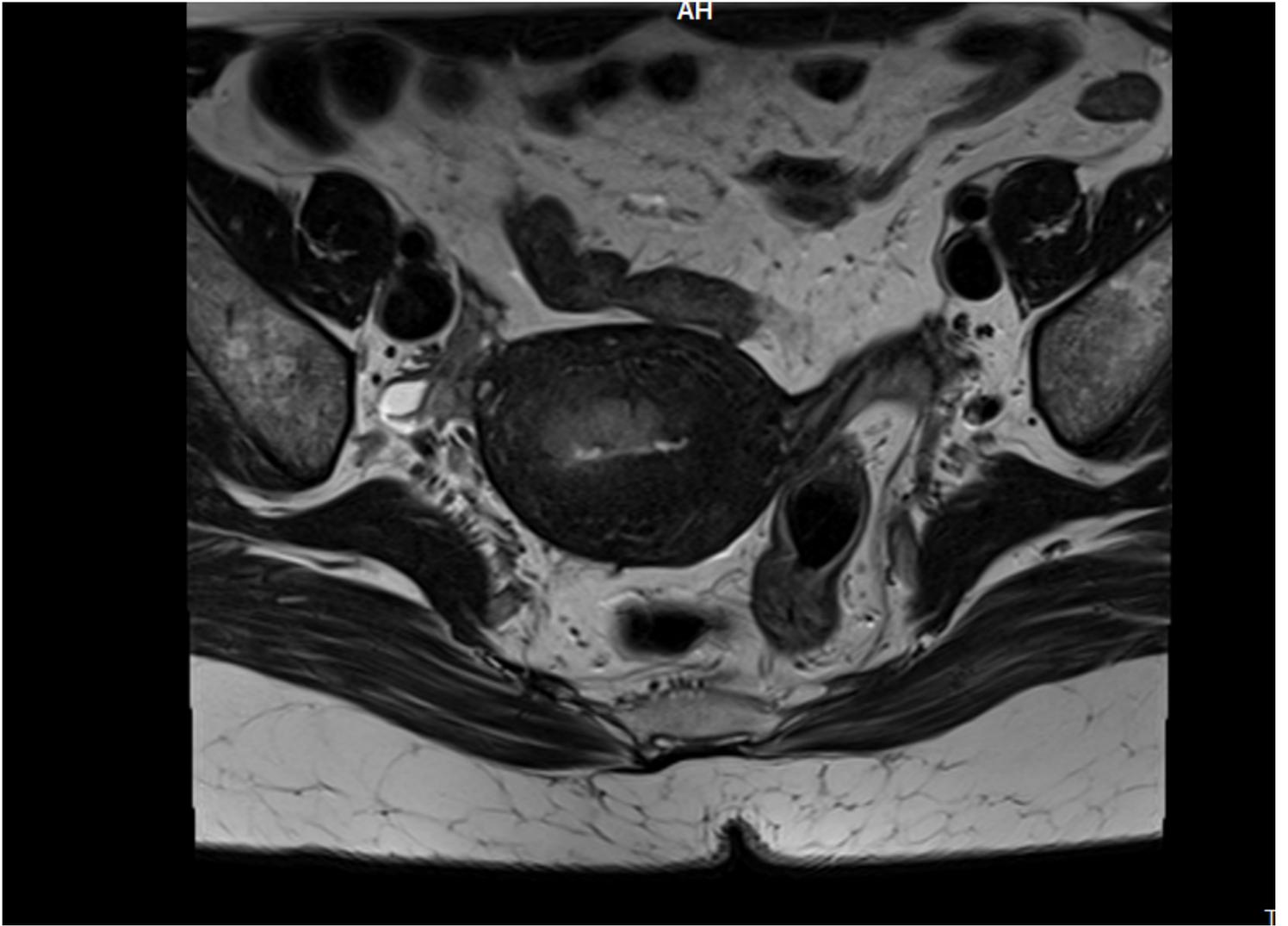


Figure 1

MRI showing enhancing lesion in the endometrium extending into the myometrium

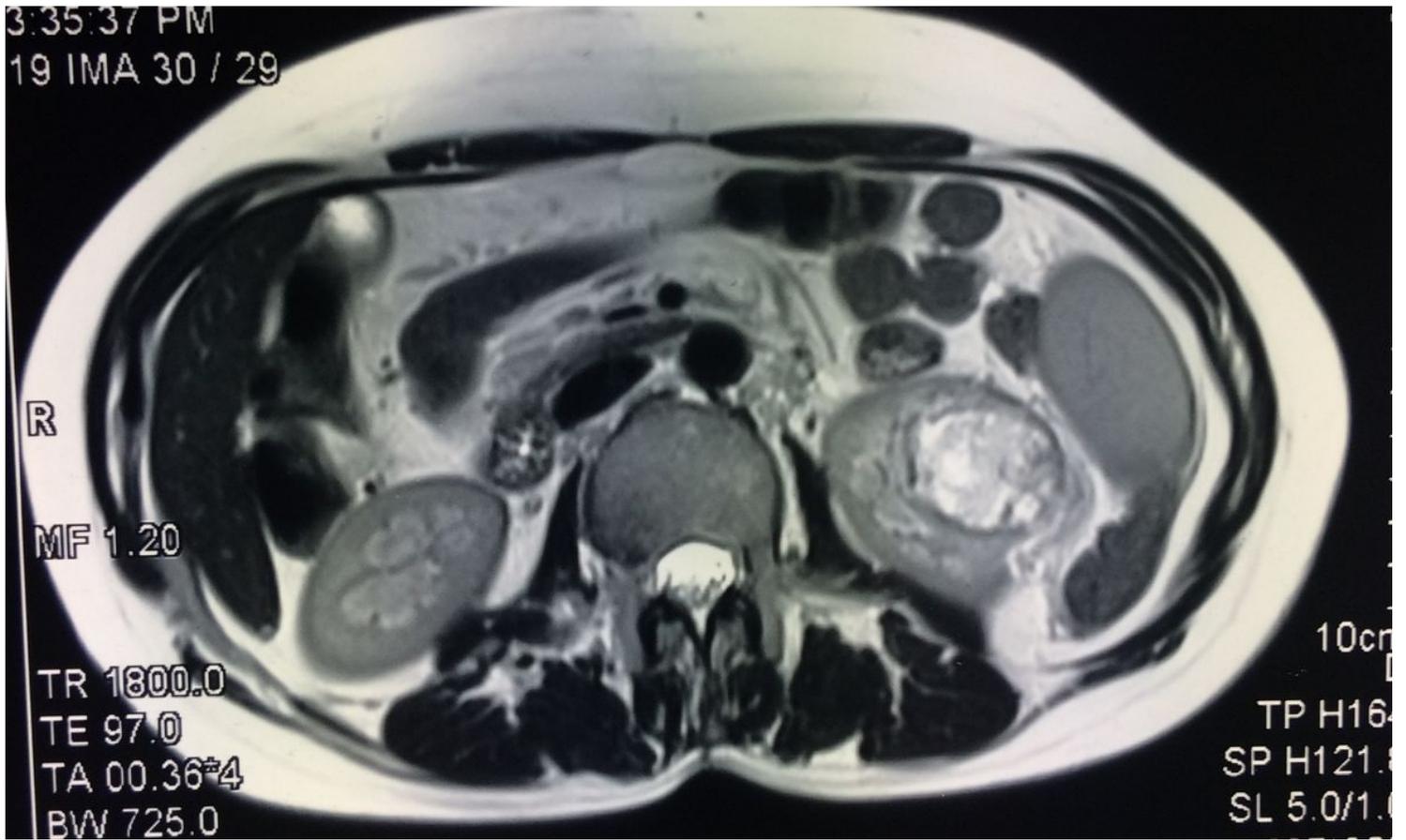


Figure 2

MRI (transverse section) showing enhancing renal mass at lower pole of left kidney

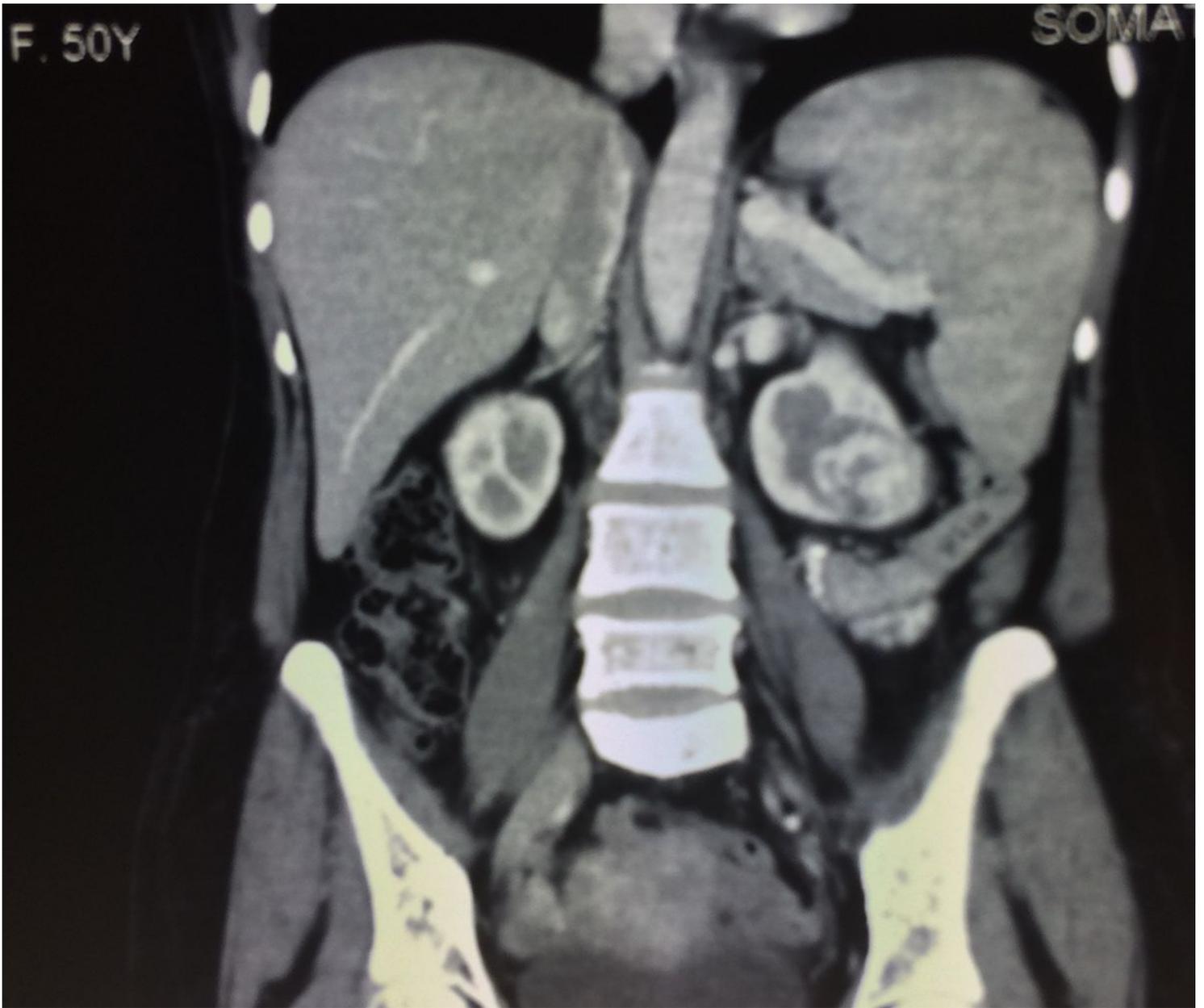


Figure 3

MRI (coronal section) showing renal mass reaching to pelvicalyceal system

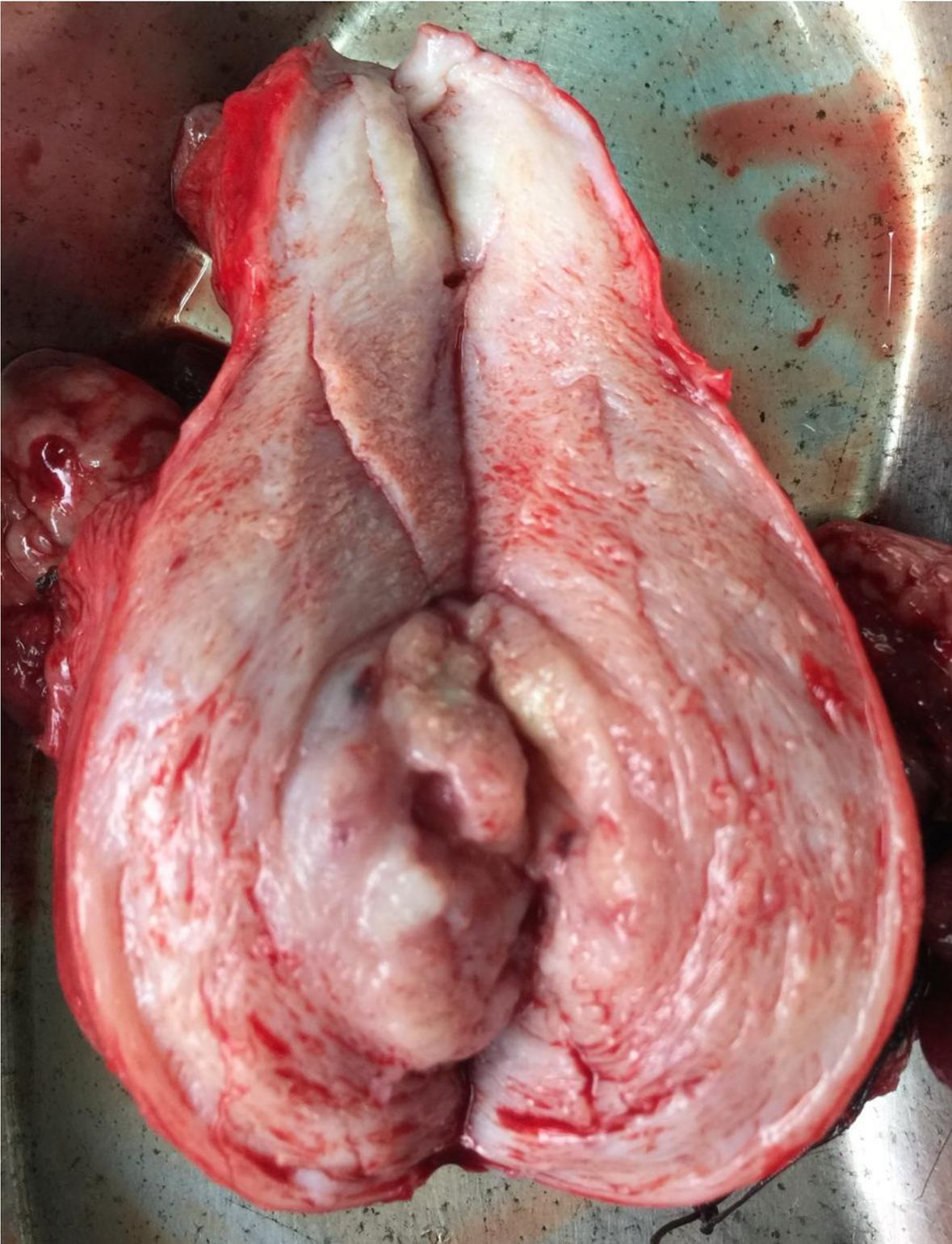


Figure 4

Uterus and cervix measured 9 X 5.5 X 4.0 cm; the endometrial cavity filled with papillary growth

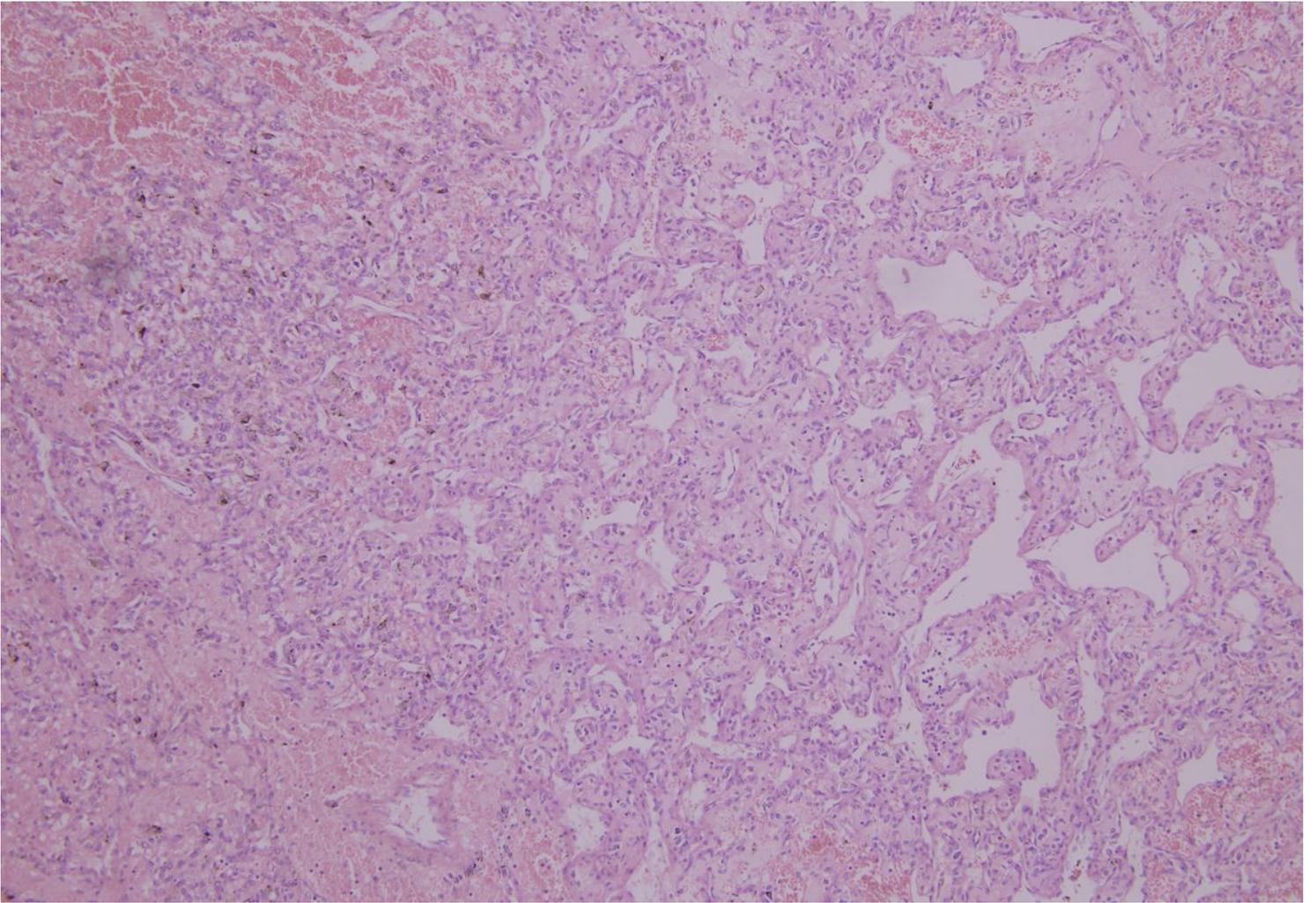


Figure 5

Photomicrograph of RH showing proliferation of capillaries with neoplastic stromal cells having clear to foamy cytoplasm (HE, X100)

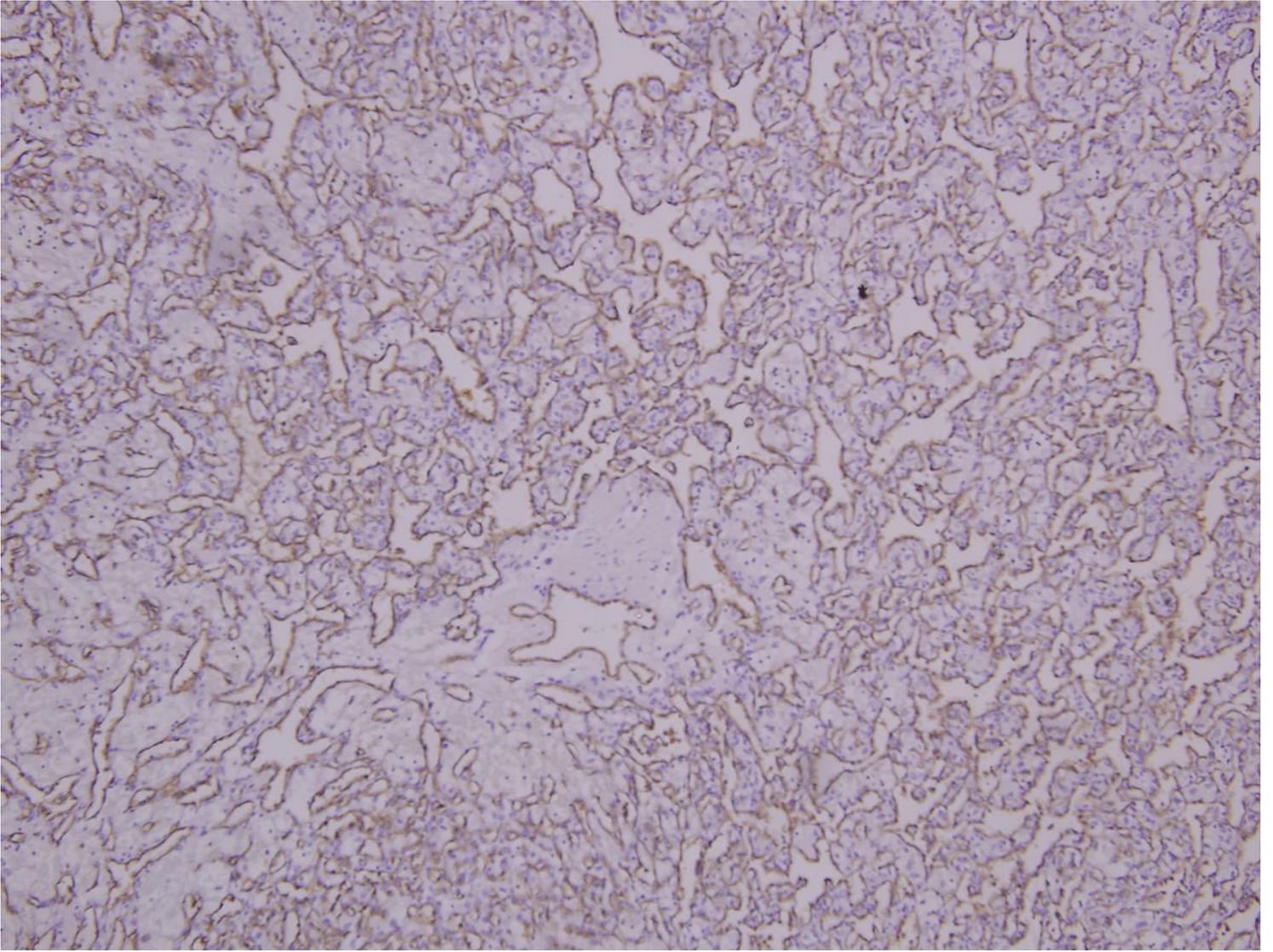


Figure 6

Photomicrograph of RH showing tumor cell positivity for CD34 (IHC, X200)

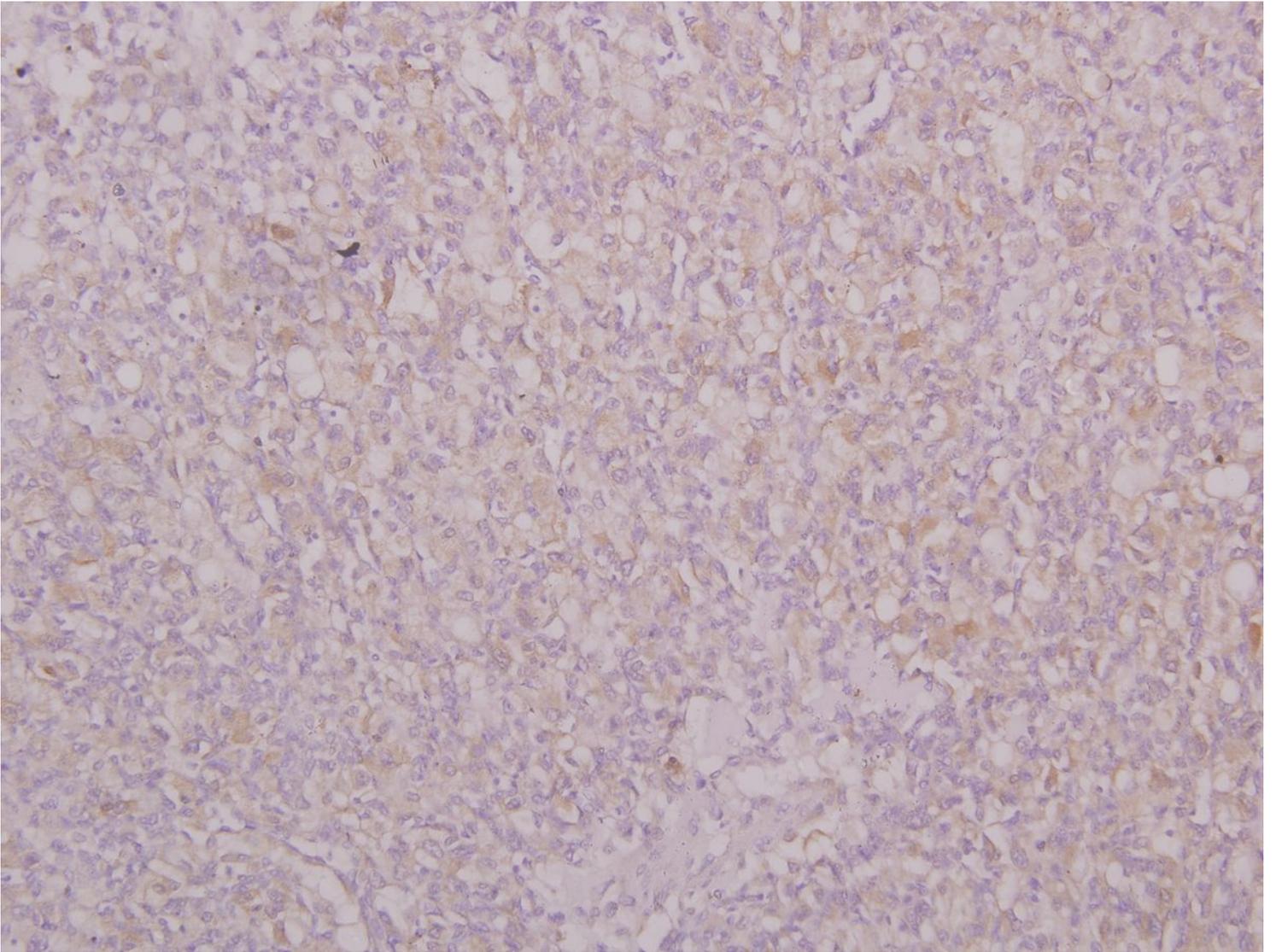


Figure 7

Photomicrograph of RH showing tumor cell positivity for NSE (IHC, X400)

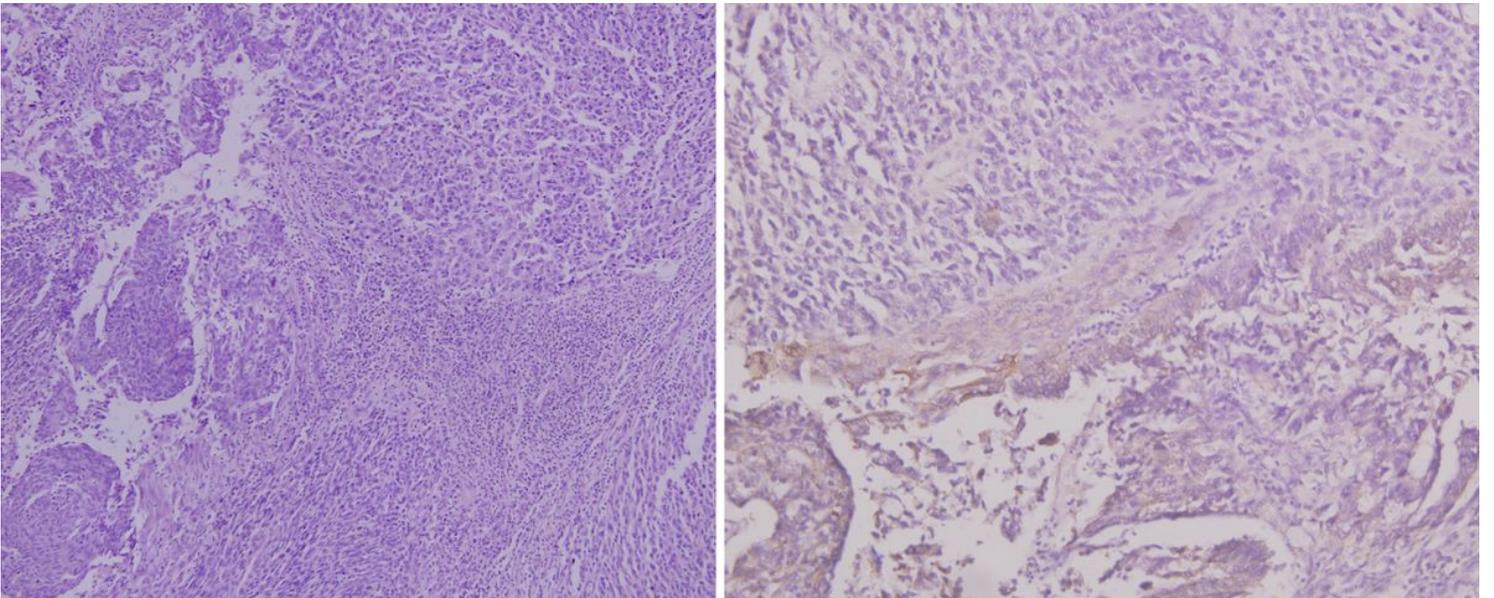


Figure 8

Photomicrograph of MMT showing a biphasic tumour composed of carcinomatous and sarcomatous component (H and E, X100) and positive CK staining (IHC, X400)

Supplementary Files

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