Case of the Month -September

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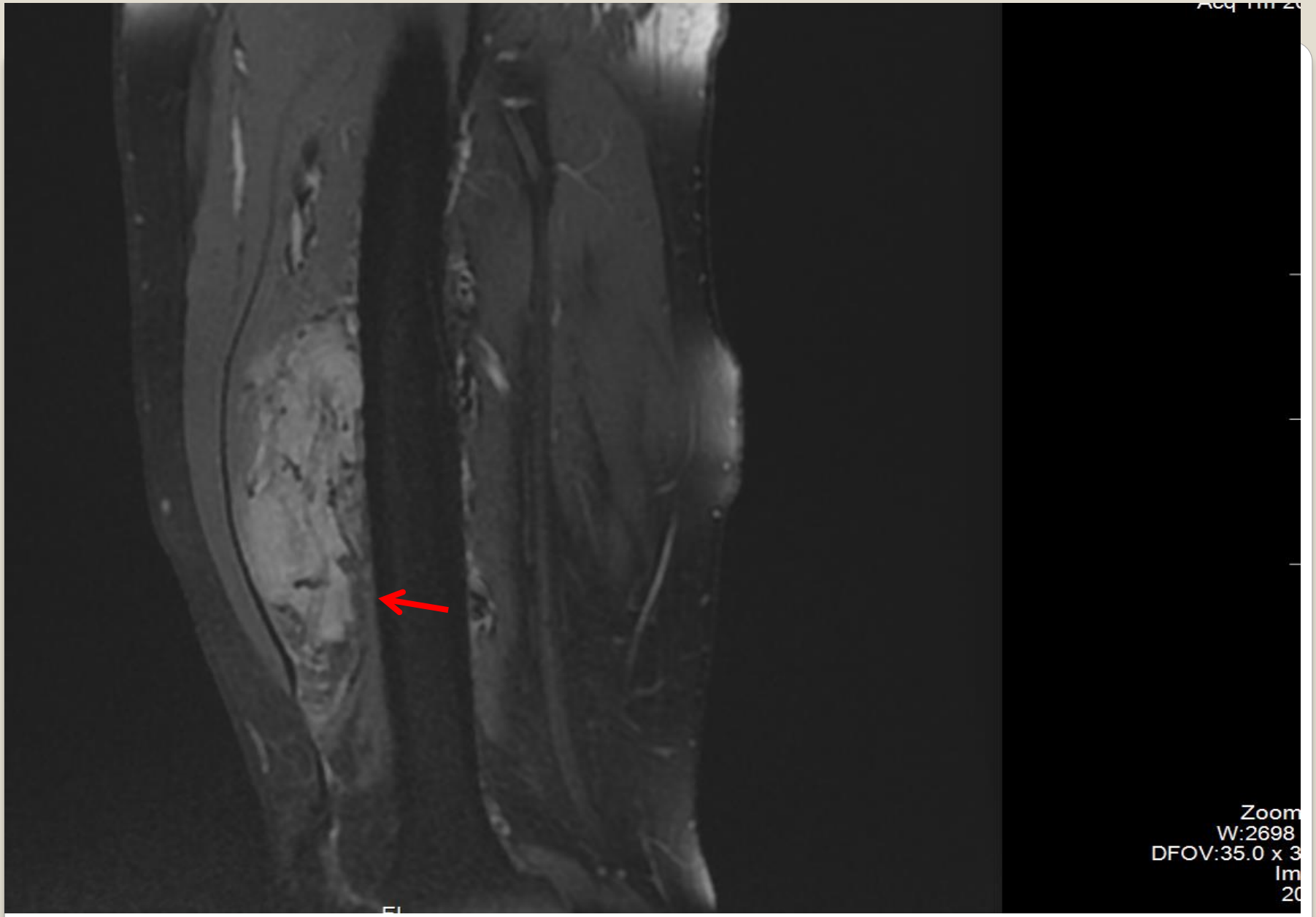
A 25-years-old male with no significant past & family history presented with C/0:

- Swelling right thigh x 2 years
- Gradually increasing in size
- Pain while walking x 2months
- Routine Laboratory investigations were within normal limits.

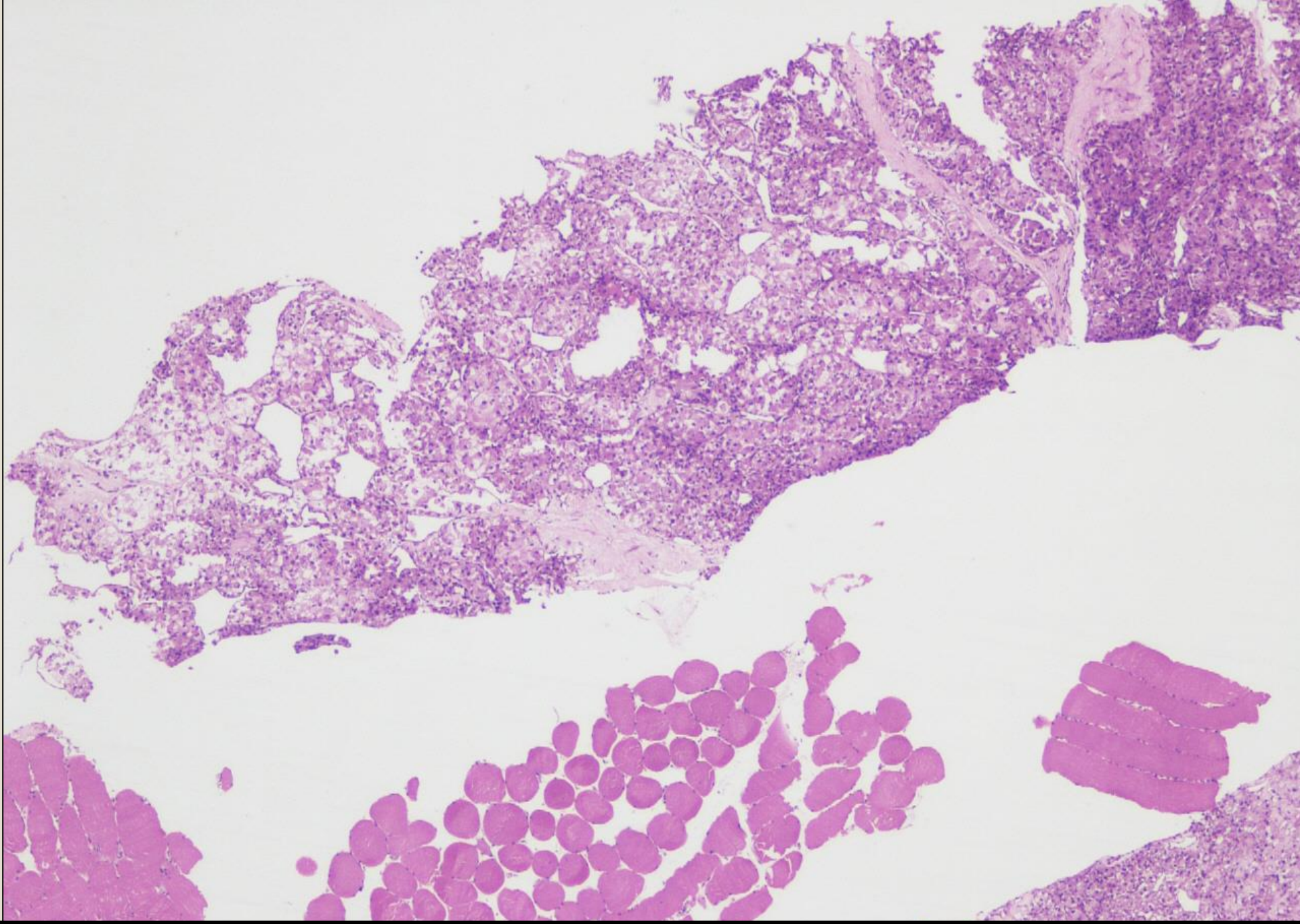
Radiology Findings

- A PET scan done revealed:
  - Metabolically active soft tissue lesion involving anterior compartment muscles of midthird region (7.7 x 3.8 x 10.9 cm, SUV max 5.2)
  - Underlying femur was free.

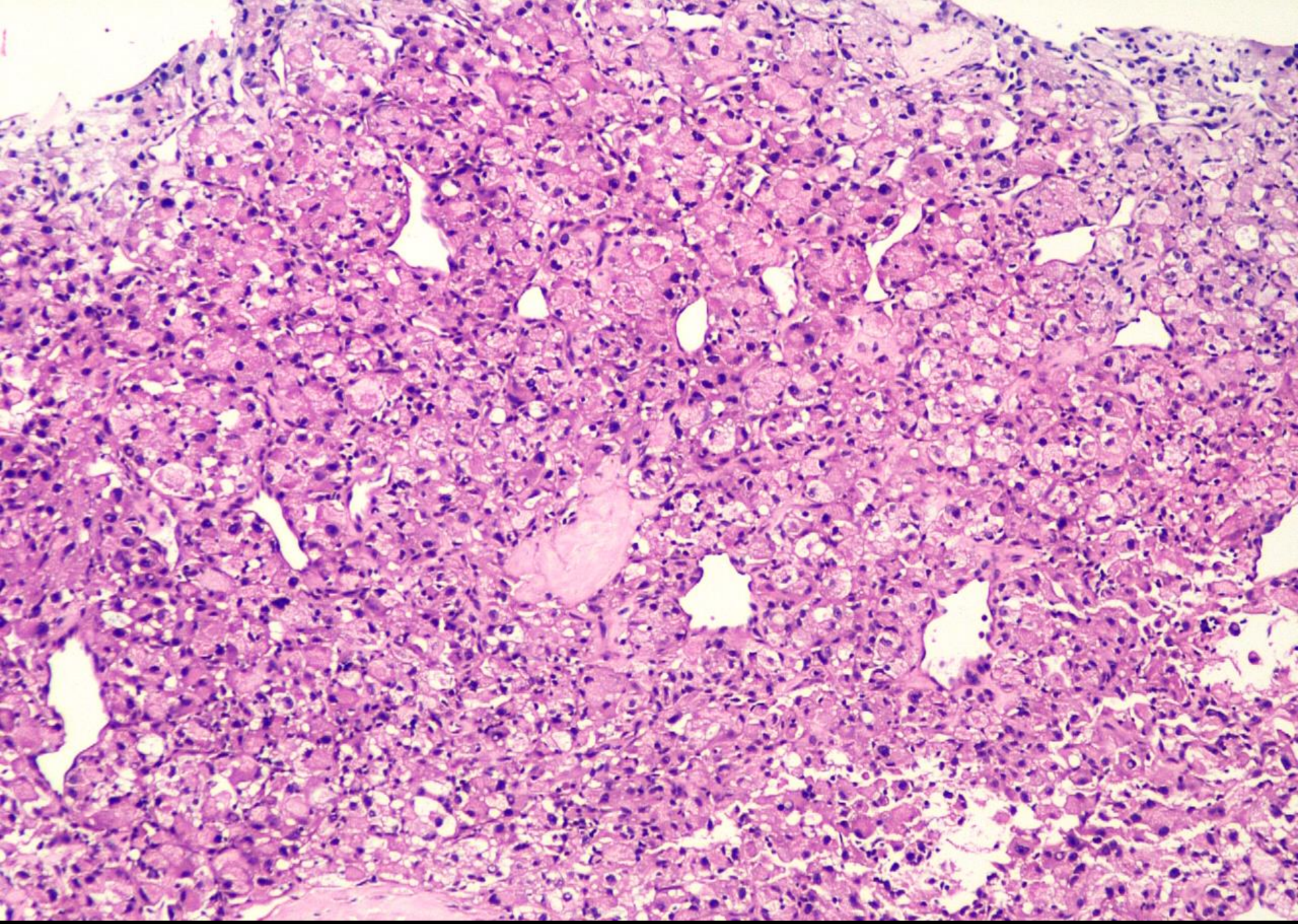


Heterogenous soft tissue mass in anterior compartment of thigh

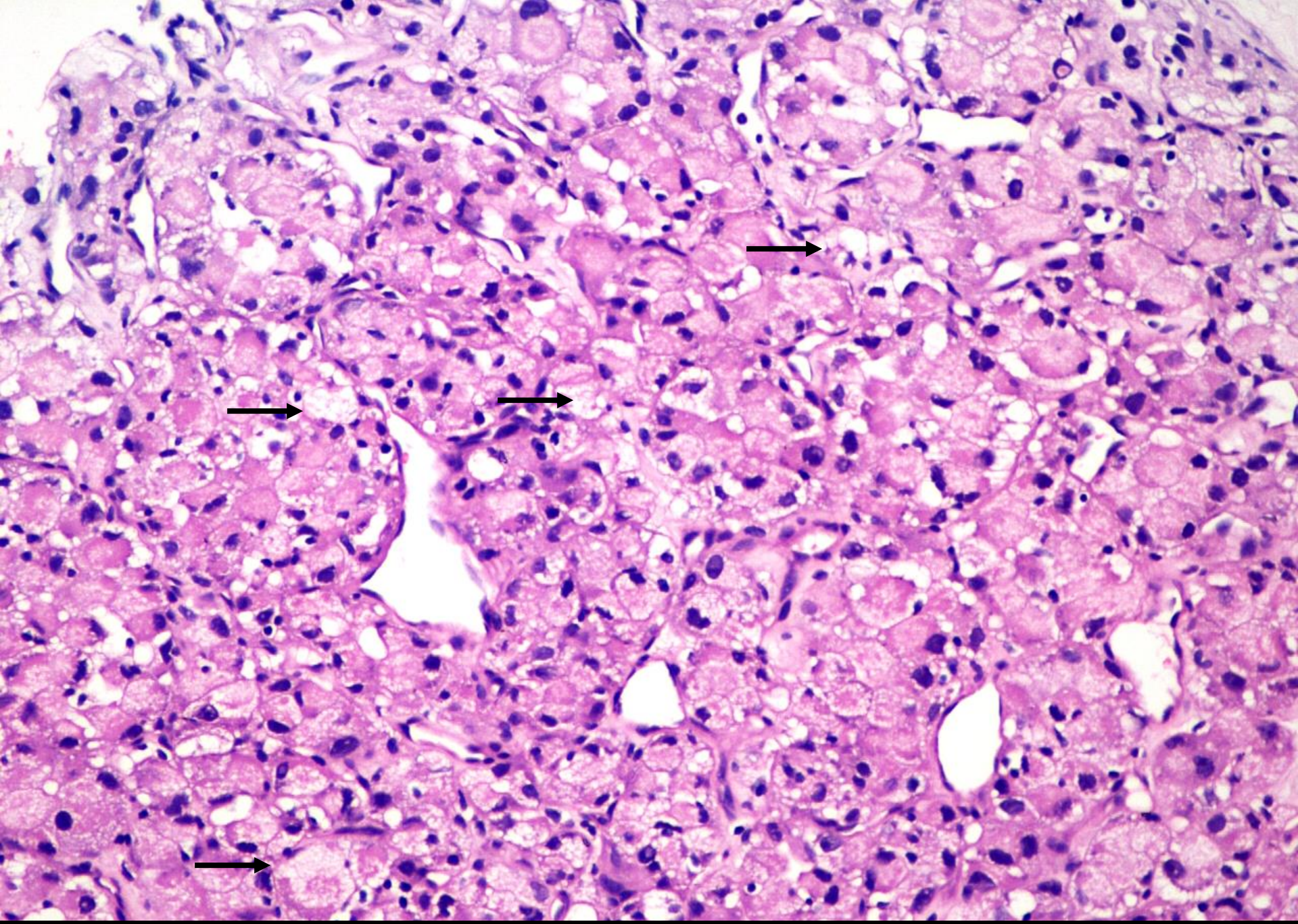
- A tru cut biopsy was performed from thigh mass.



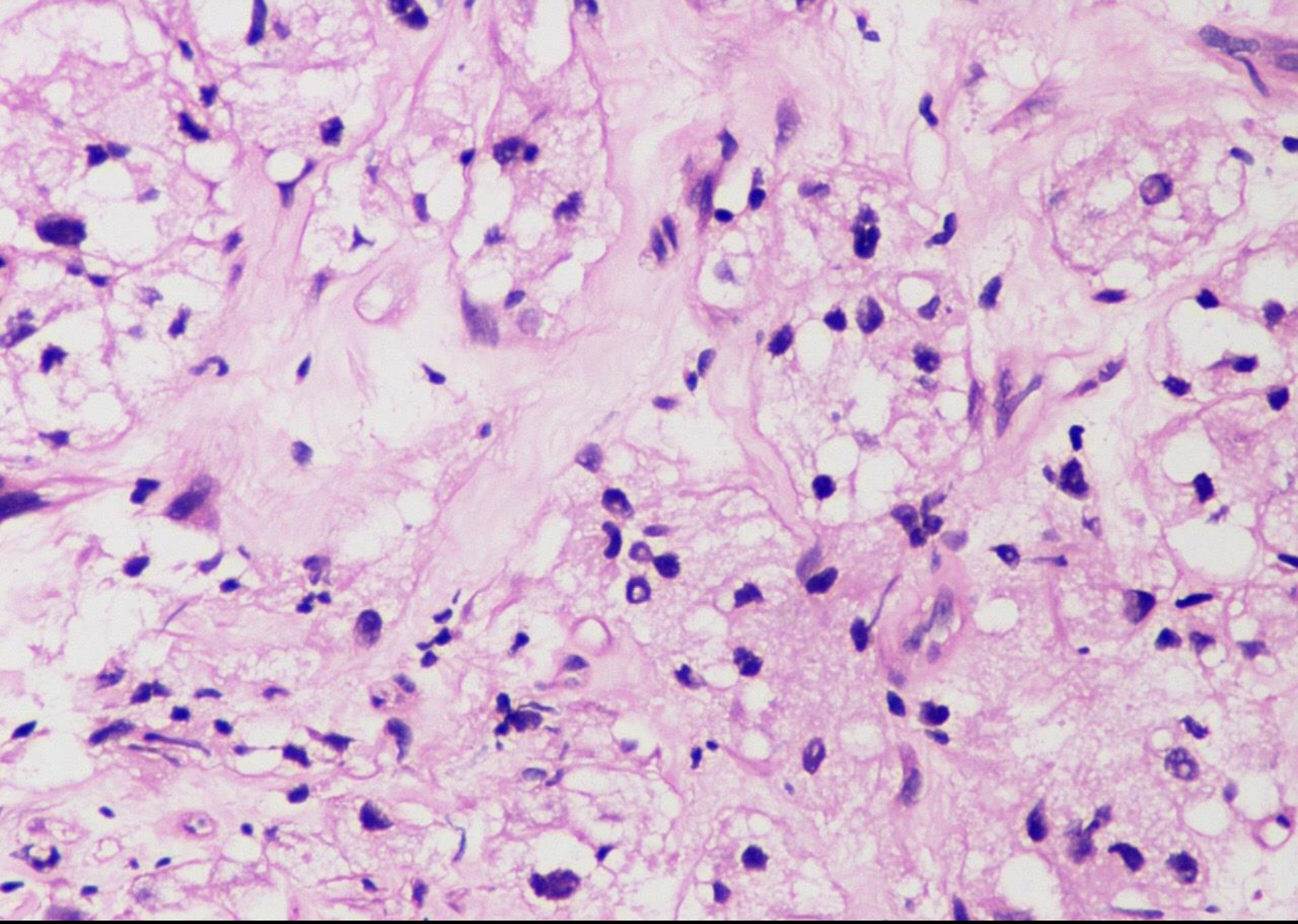
Single core of tumor tissue with adjacent skeletal muscle (H & E, 40X)



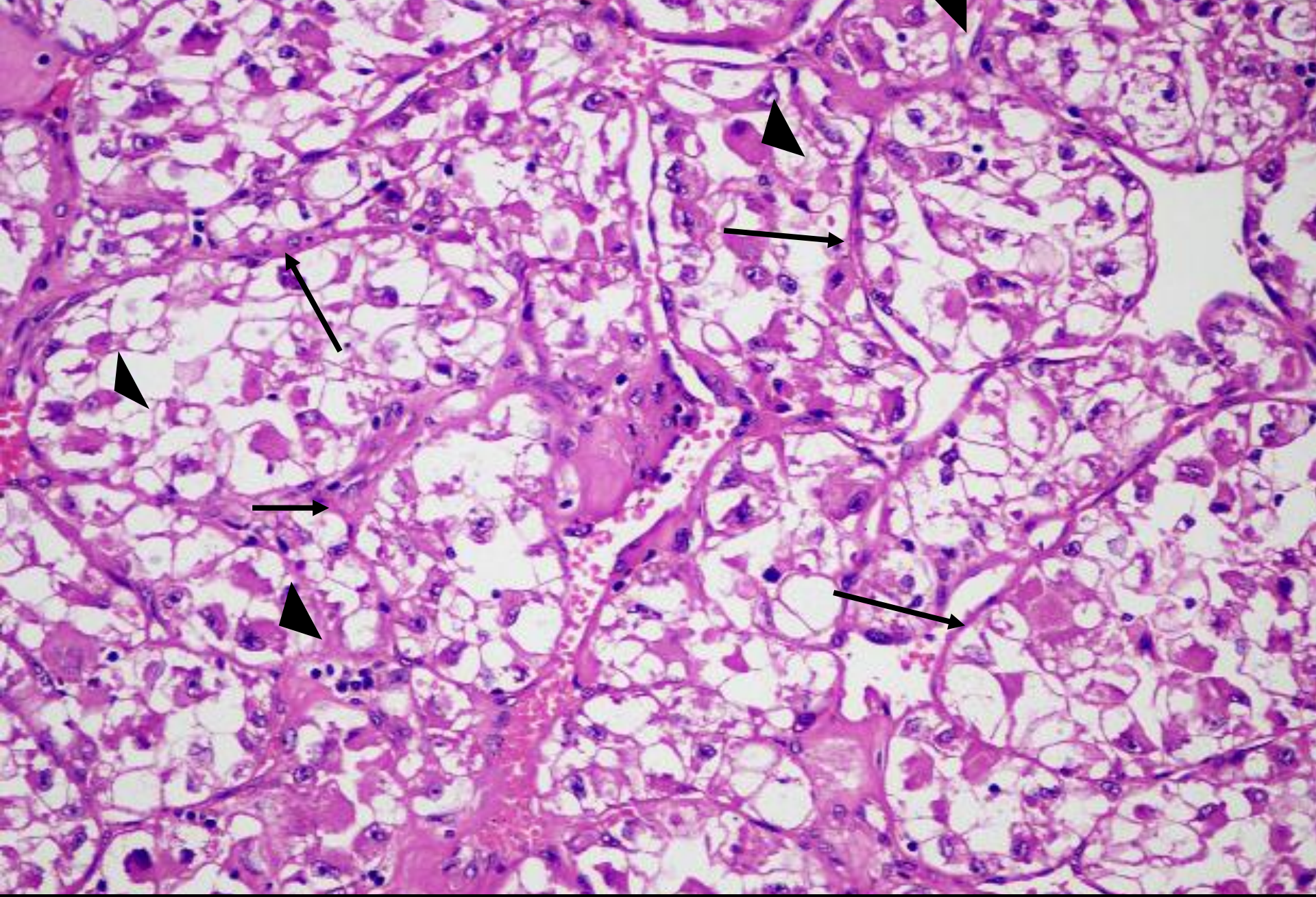
Cellular tumor composed of cells having abundant cytoplasm (H& E, 100X)



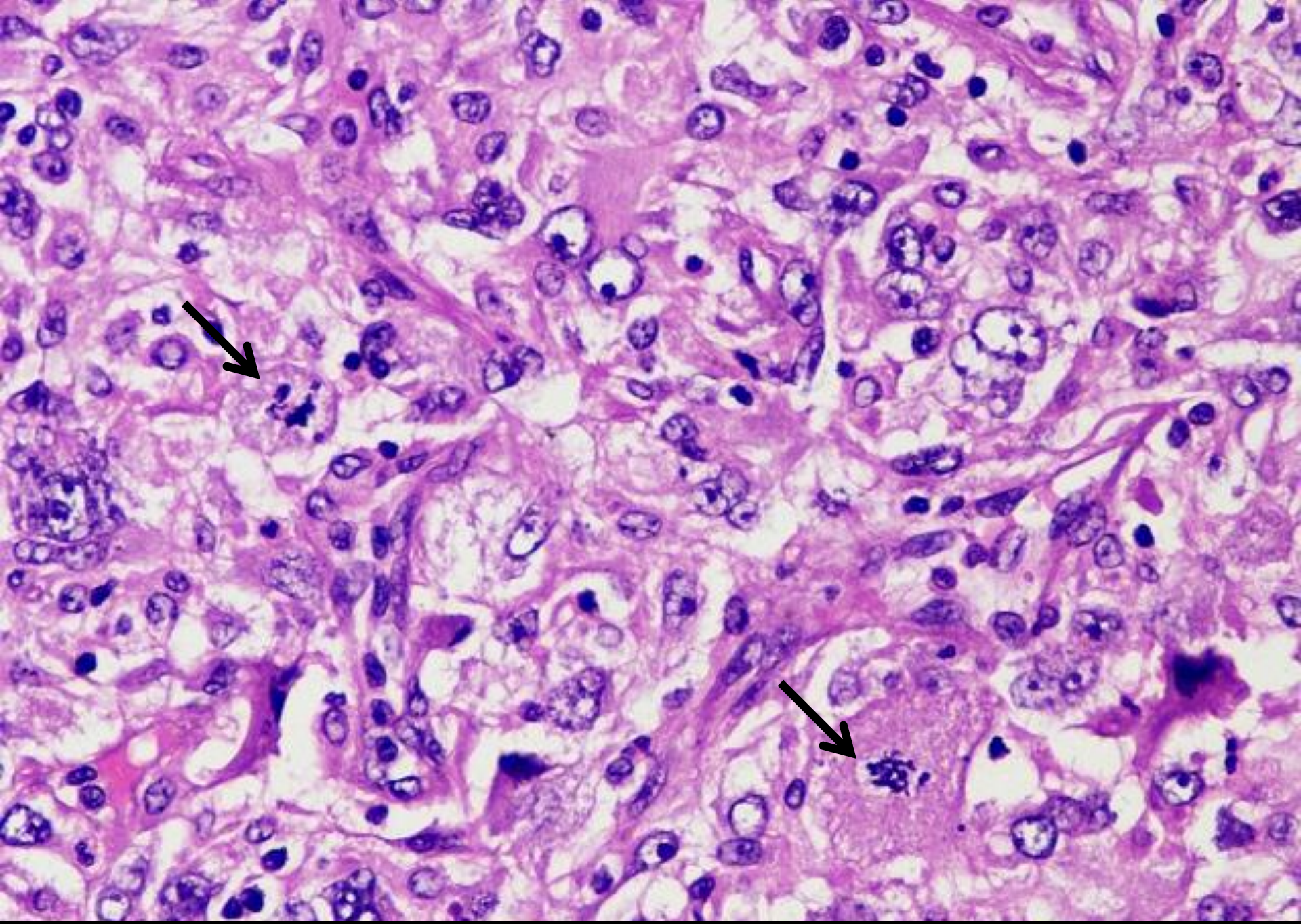
Tumor cells have eosinophilc to clear cytoplasm (arrow) (H& E,200X)



Many foci showed tumor cells having clear cytoplasm (H& E,200X)



Tumor nests separated by fibrovascular septa (arrow).
Rhabdoid differentiation (arrowhead) (H& E, 200X)



Pleomorphic tumor cells with scattered mitotic figures (arrow))(H& E, 400X)

Summarizing the Histopathological Findings

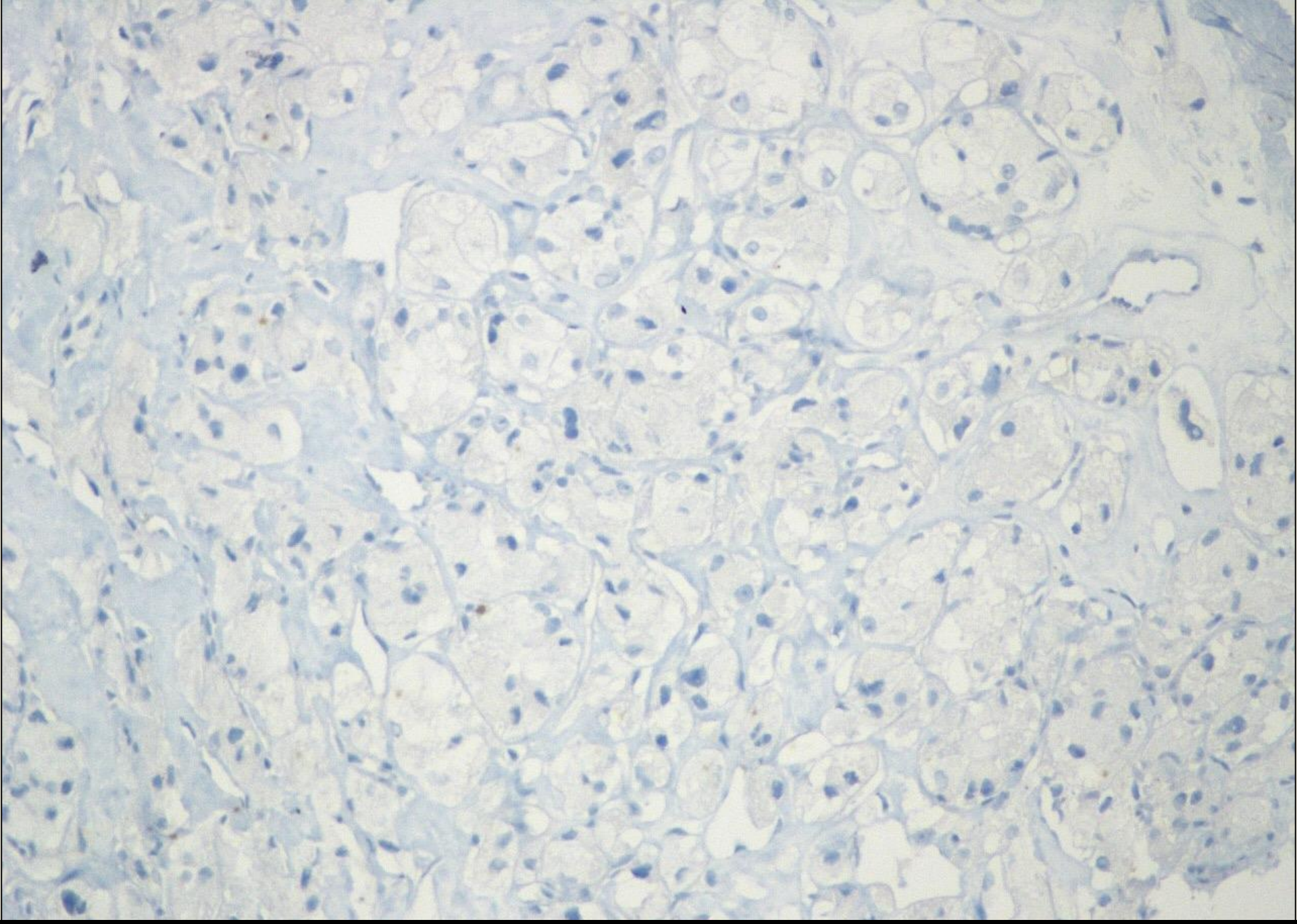
- Tumor cells arranged in small uniform nests, separated by fine fibrovascular septae.
- Polygonal to epithelioid having eccentric large vesicular nucleus, prominent nucleoli and moderate amount of eosinophilic cytoplasm.
- Cytoplasmic clearing evident in few foci
- Few mitosis seen.
- No definite necrosis evident

- Features were suggestive of a poorly differentiated tumor

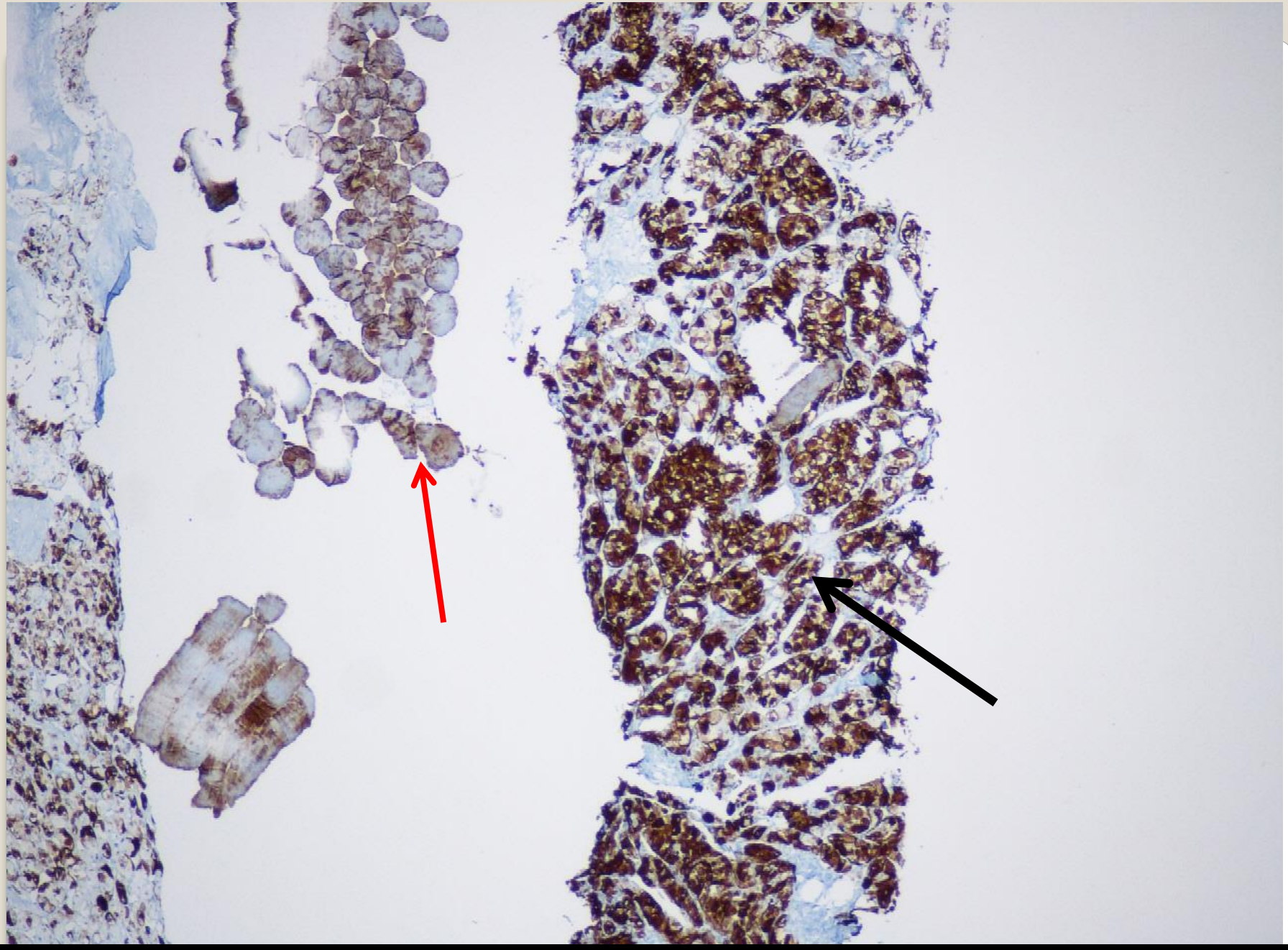
- In view of age, site, radiology and histomorphological findings, following differentials were considered:

1) Rhabdomyosarcoma (RMS)
2) Metastatic Renal Cell Carcinoma
3) Alveolar soft part sarcoma (ASPS)

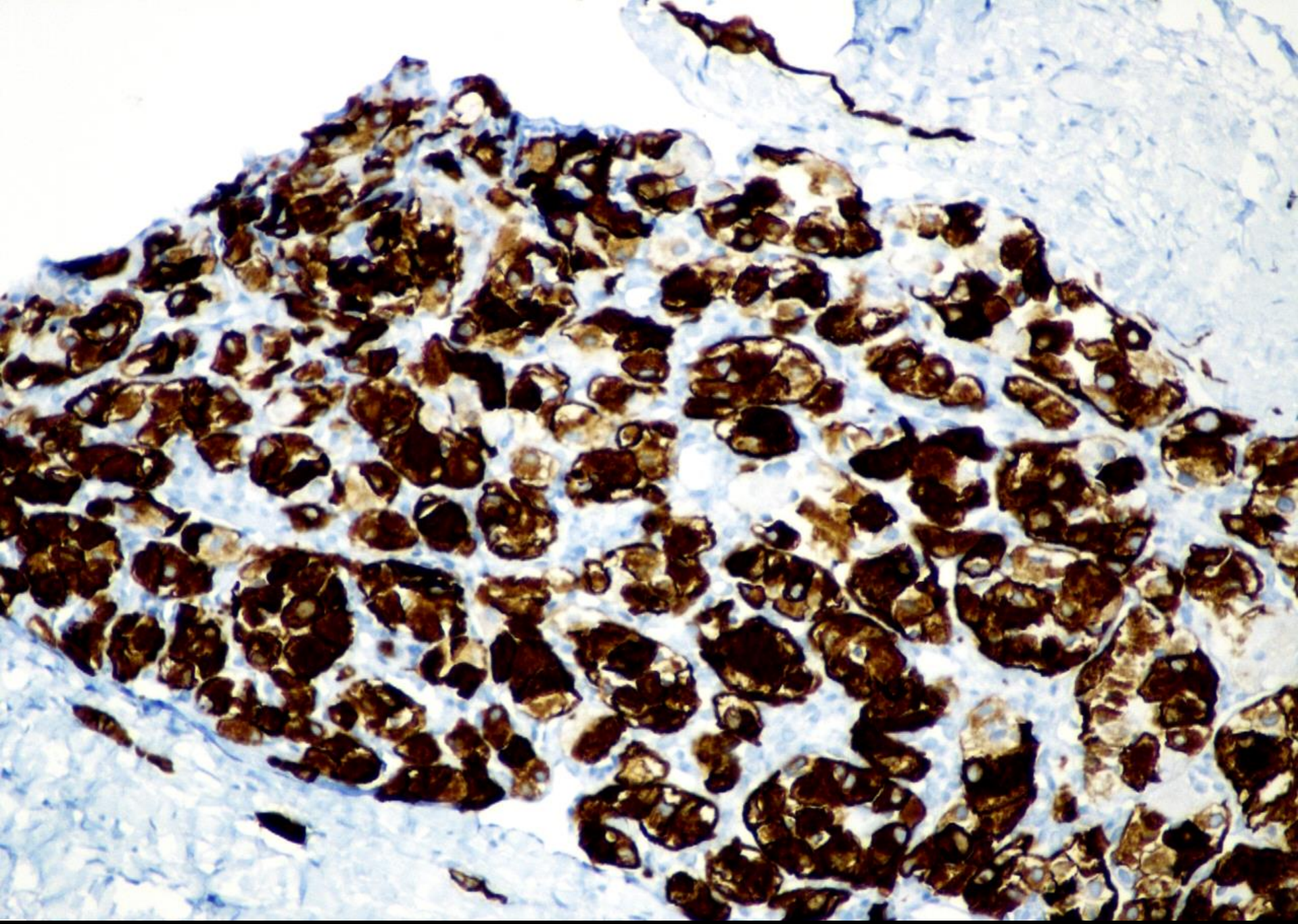
A primary panel of IHC was given comprising of CK, Desmin & S100.



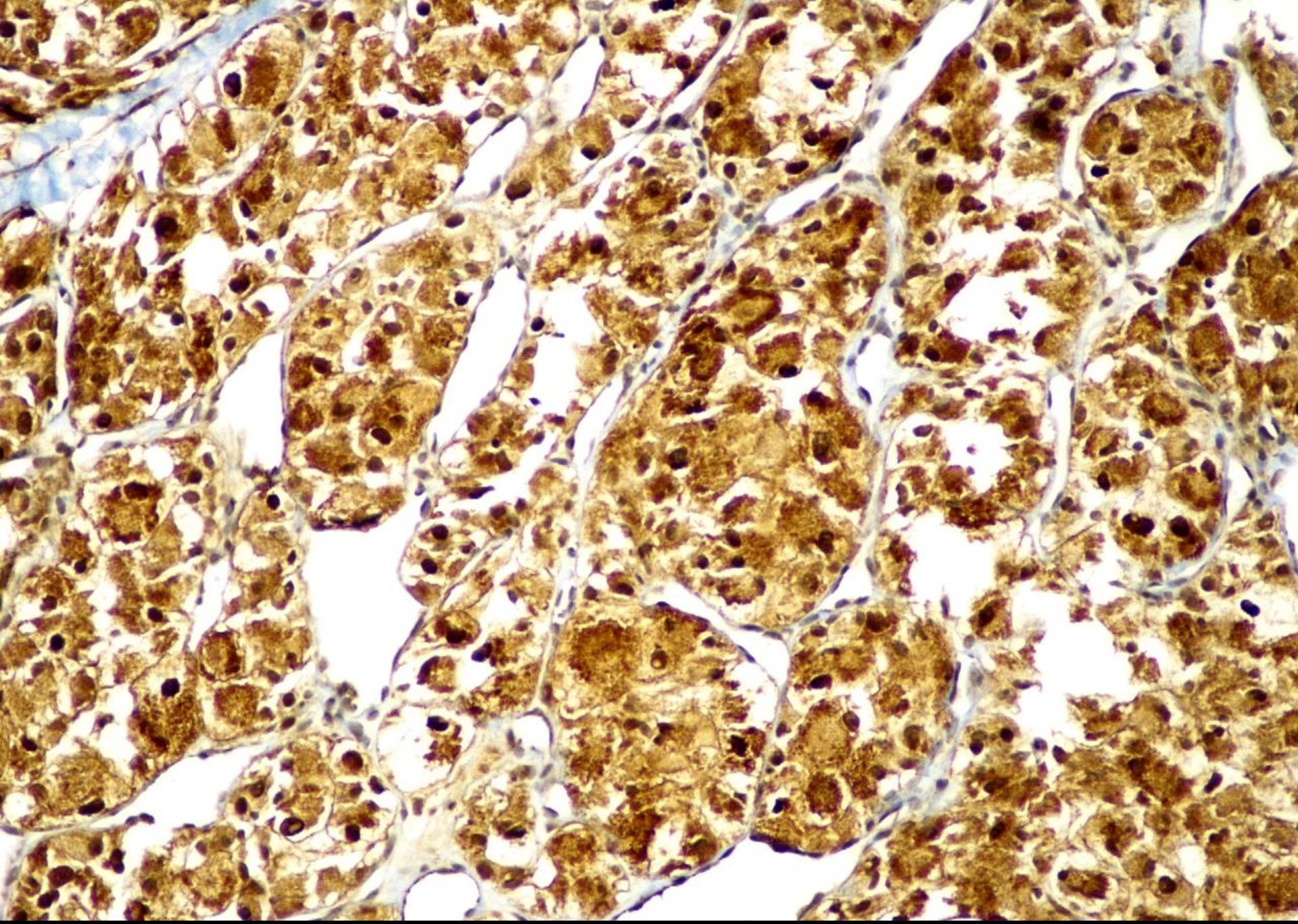
Cytokeratin (CK) ; negative (IHC)



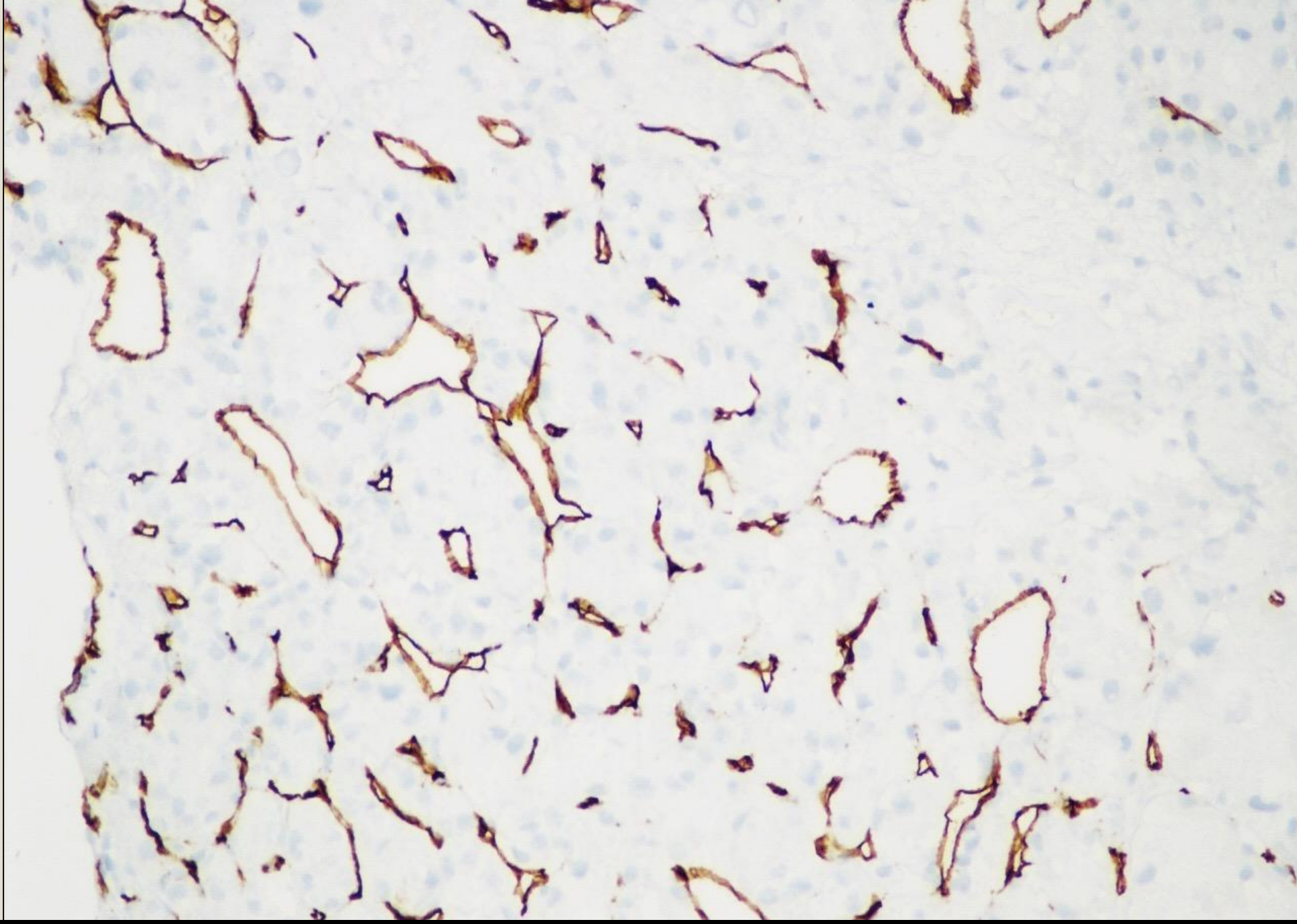
Diffuse & strong Desmin Cytoplasmic expression in tumor cells (black arrow) and native skeletal muscle (red arrow)(DAB : x10)



Desmin; cytoplasmic expression (DAB ; x 40)

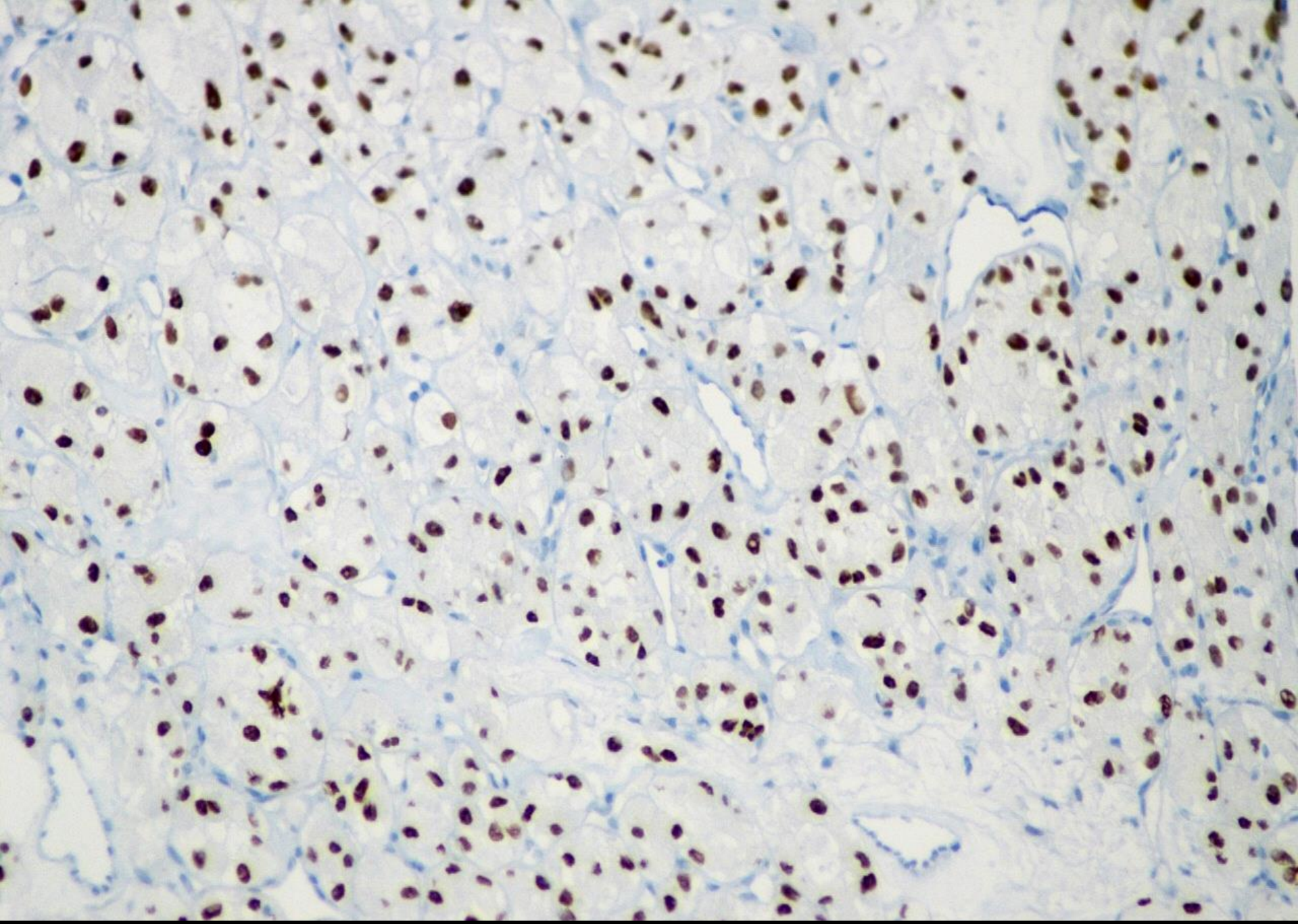


S-100; nuclear & cytoplasmic expresion (IHC)

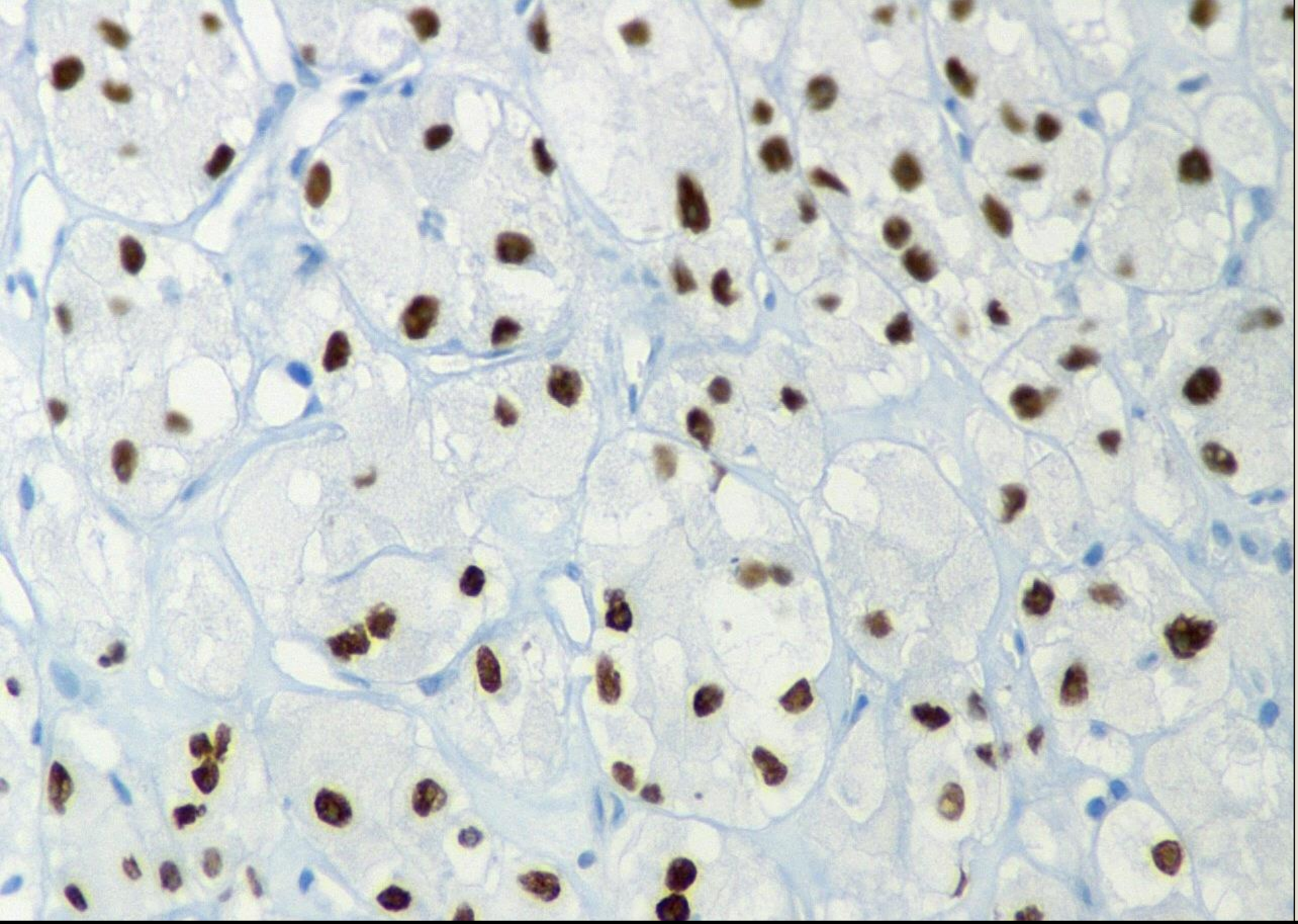


CD31; highlighted in the intervening vessels (IHC)

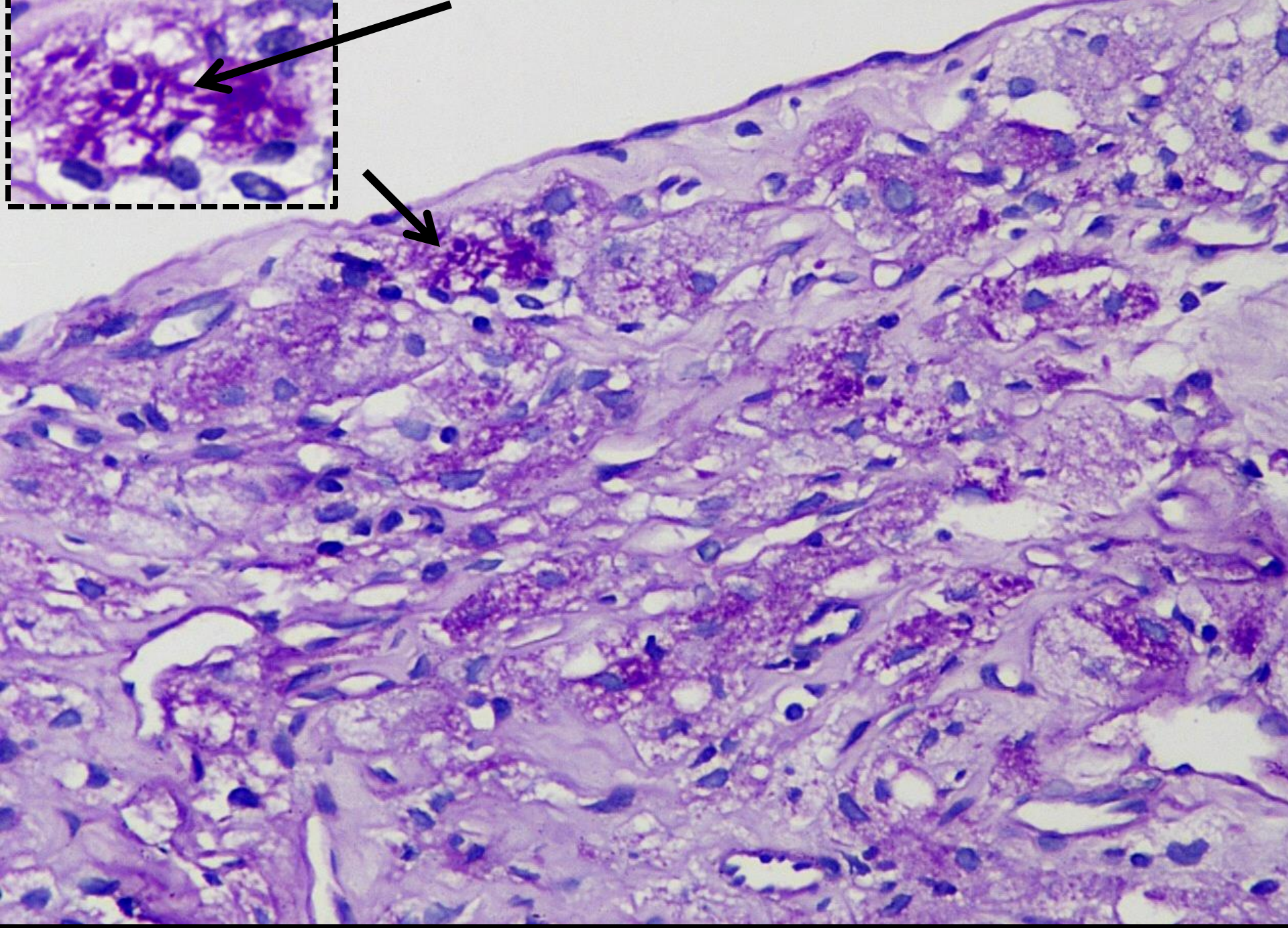
- Diffuse & strong desmin positivity pointed towards RMS.
- Myogenenin and MyoD1 were given to confirm RMS , which were negative.
- Subsequently TFE3 was given which showed strong and diffuse nuclear positivity.



TFE3; strong nuclear expression (DAB ; x20)



TFE3; strong nuclear expression (DAB ; x40)



PAS stain highlighted needle like crystalloid structures (arrow ; inset)

Summarizing IHC Findings

Positive markers	***Negative markers***
Desmin (diffuse & strong)	CK
S100 (diffuse & moderate)	EMA
TFE3 (diffuse & strong)	CD31
	Myogenin & MyoD1
	Synaptophysin

Final Diagnosis

- ***Alveolar Soft Part Sarcoma (ASPS)***

- A staging PET CT was subsequently done for staging which revealed in addition, few subcentimetric bilateral lung and subpleural nodules suggestive of metastasis.

Follow-up

- A local excision of thigh mass was done
- Patient underwent adjuvant chemotherapy (IFOS +Adriamycin).

Comments

- Alveolar soft-part sarcoma (ASPS) is a rare,distinctive sarcoma, typically occurring in young patients with female predominance (2:1)
- In adults ASPS most commonly involves soft tissue of thigh/gluteal region while in children head & neck region is involved
- ASPS usually presents as slowly growing, painless soft tissue masses.
- Metastasis to lung & brain is common and quite often the first manifestation of the disease.

IHC Findings

- ASPSs are **negative** for epithelial (CK,EMA) , specific neuroendocrine & melanocytic (HMB45) markers which helps to rule out the pertaining differentials.

- Desmin positivity has been reported in upto 50% of cases although the expression is always focal , patchy and of variable intensity.

- In the presented case desmin was strong & diffuse which was very unusual and may prompt an erroneous diagnosis of RMS. Hence myogenin and Myo D1 expression is essential to stamp the diagnosis of RMS as desmin expression is not specific for RMS.

- The histogenesis of ASPS is controversial and there is prevailing theory that ASPS representing an unusual form of myogenic tumor in view of desmin positivity.

- However ASPS are negative for truly specific markers of skeletal muscle differentiation, such as the myogenic nuclear regulatory proteins: MyoD1 and myogenin.

- As shown in the presented case, S100 can be positive in ASPS, but in contrast to melanoma and Pecomas; HMB45 is always negative in ASPS.

- Epithelioid MPNST also show diffuse expression of S100, however on morphology uniform nesting pattern or pseudoalveolar pattern evocative of ASPS, is not seen.

- Recently, an antibody directed against the C-terminus of the **TFE3** has emerged as a highly sensitive and specific marker of the ASPS .

- The expression of TFE3 has also been described in granular cell tumors, epithelioid hemangioendothelioma and in unique subsets of Pecomas and Renal cell Carcinoma.

Genetics

- ASPS is characterised by an unbalanced translocation: der(17)t(X:17)(p11;p25). This translocation results in the fusion of a gene of unknown function, ASPL, on chromosome 17 to the TFE3 gene on the X chromosome

- FISH for TFE3 rearrangement is robust method for molecular diagnosis.

- It has been suggested that the female predominance seen in patients with ASPS is because of the presence of two X chromosomes in these patients, increasing their chances of a translocation on this chromosome

To Conclude

- ASPS is a rare distinctive sarcoma characterized by an ASPSCR1-TFE3 fusion which can be misdiagnosed due to overlapping and heterogenous IHC profile.
- Careful clinical, histomorphological assessment and judicious IHC panel helps in accurate diagnosis.
- Despite a relatively indolent clinical course, the prognosis is poor and is often characterized by late metastases.