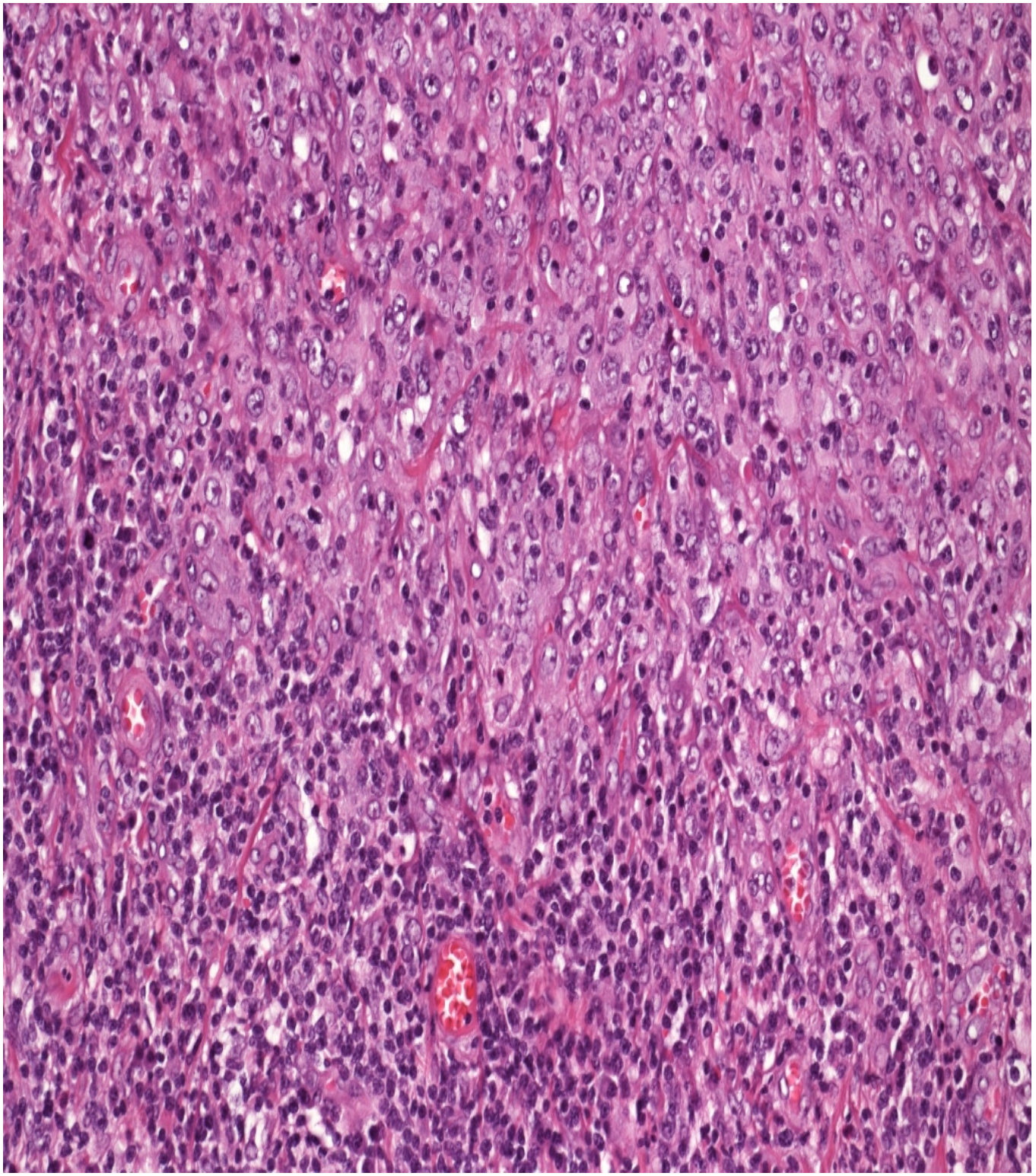
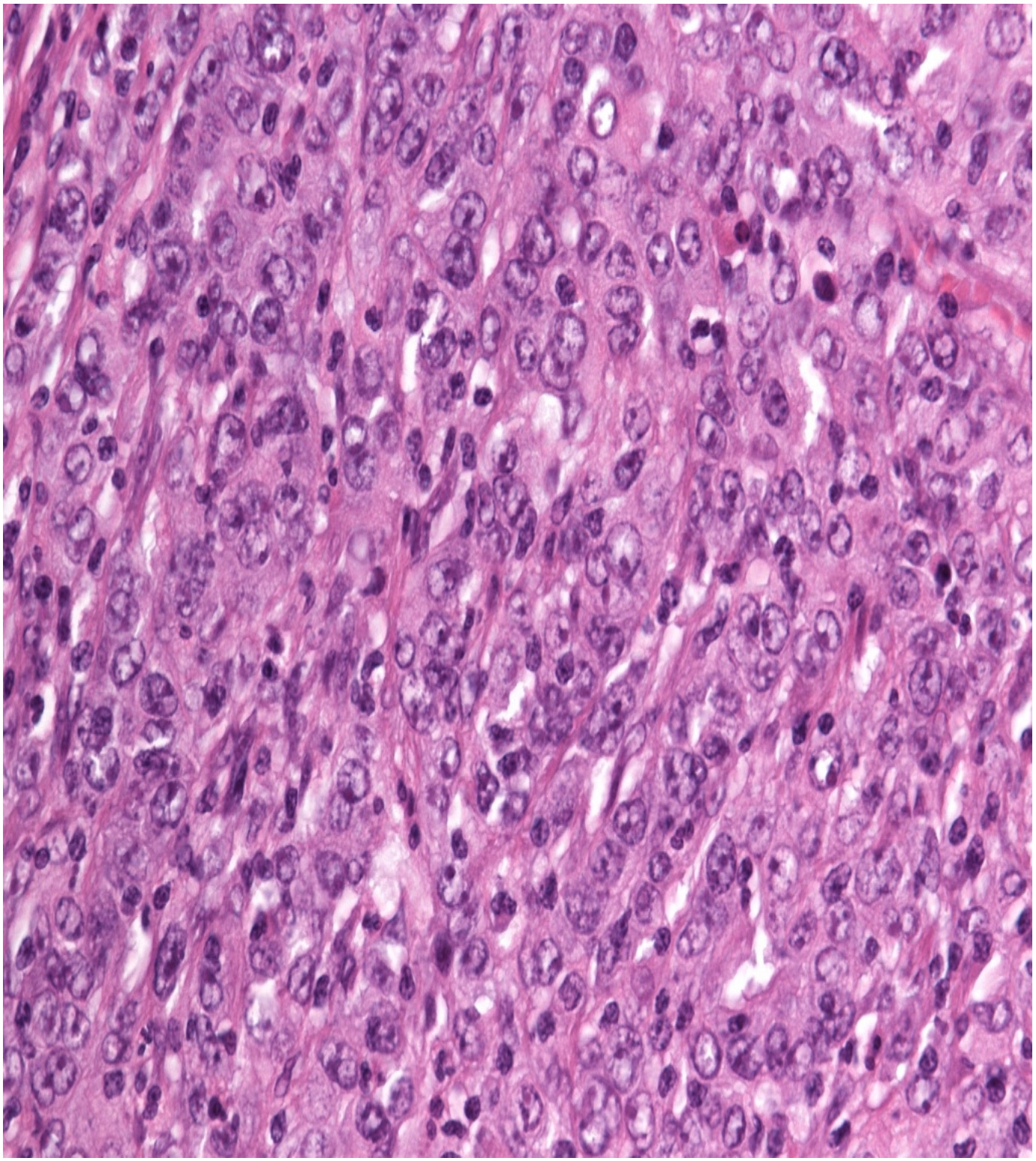
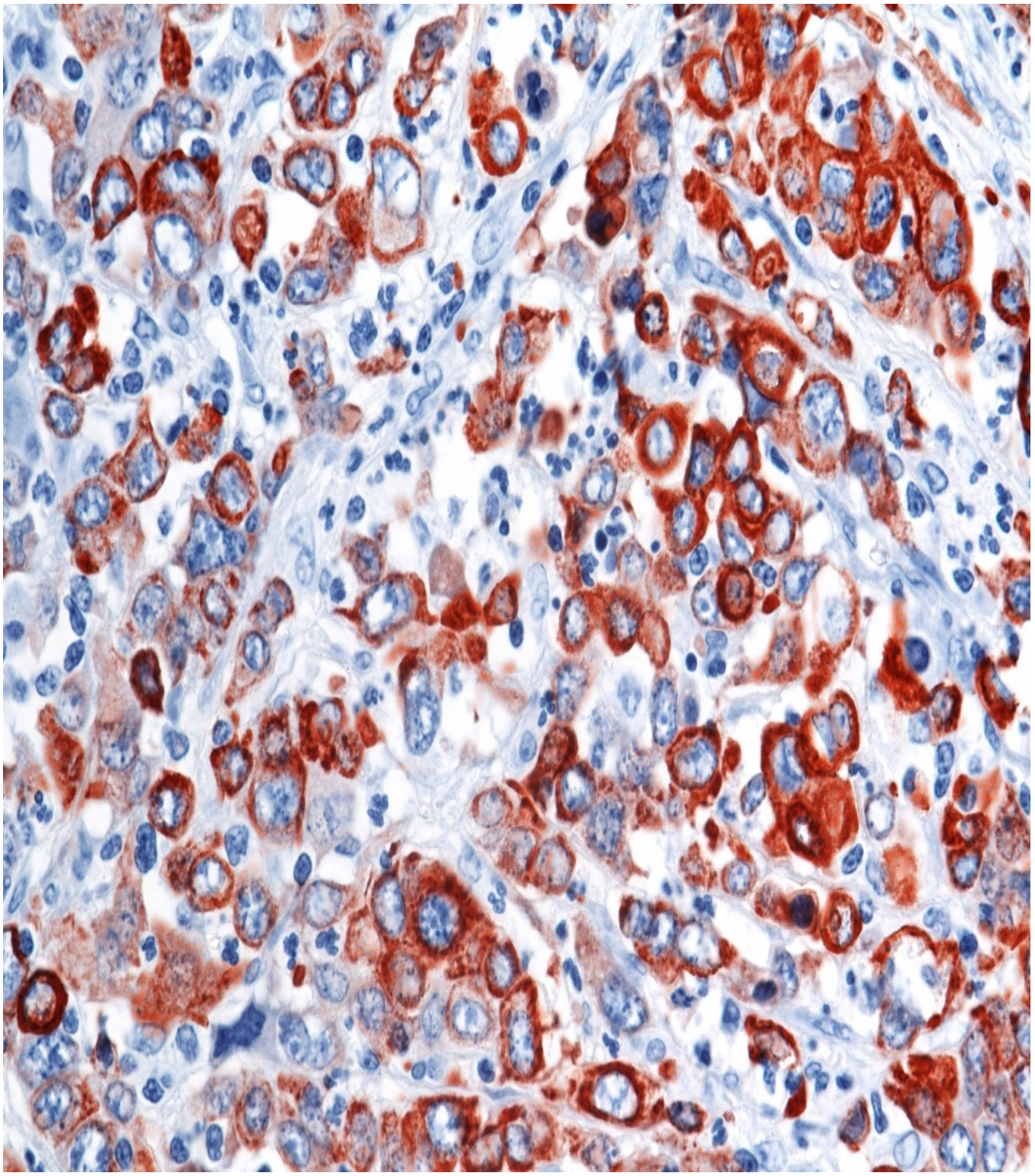
# September 2015

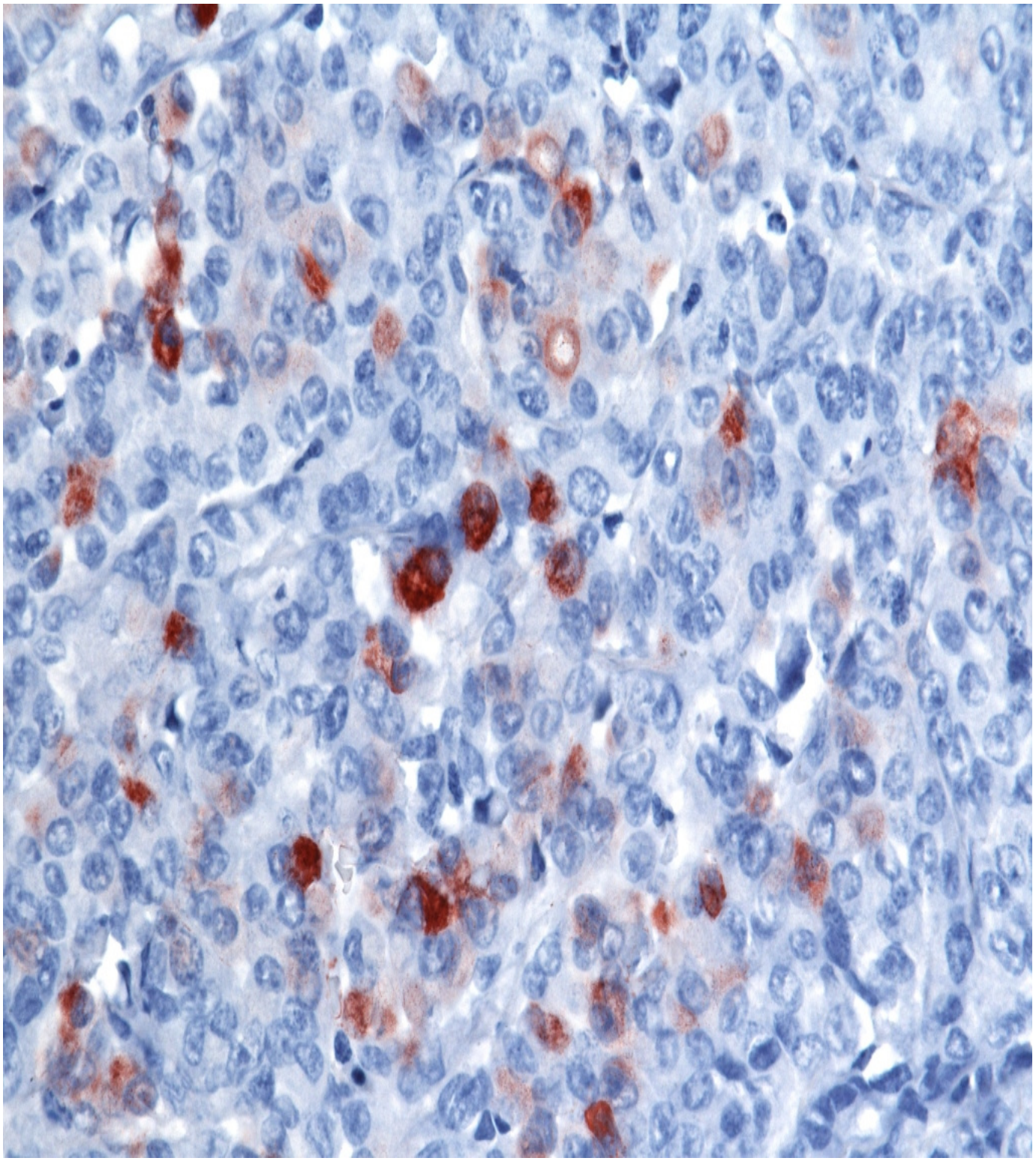
Tumour in the caecum of a 74-year-old female.

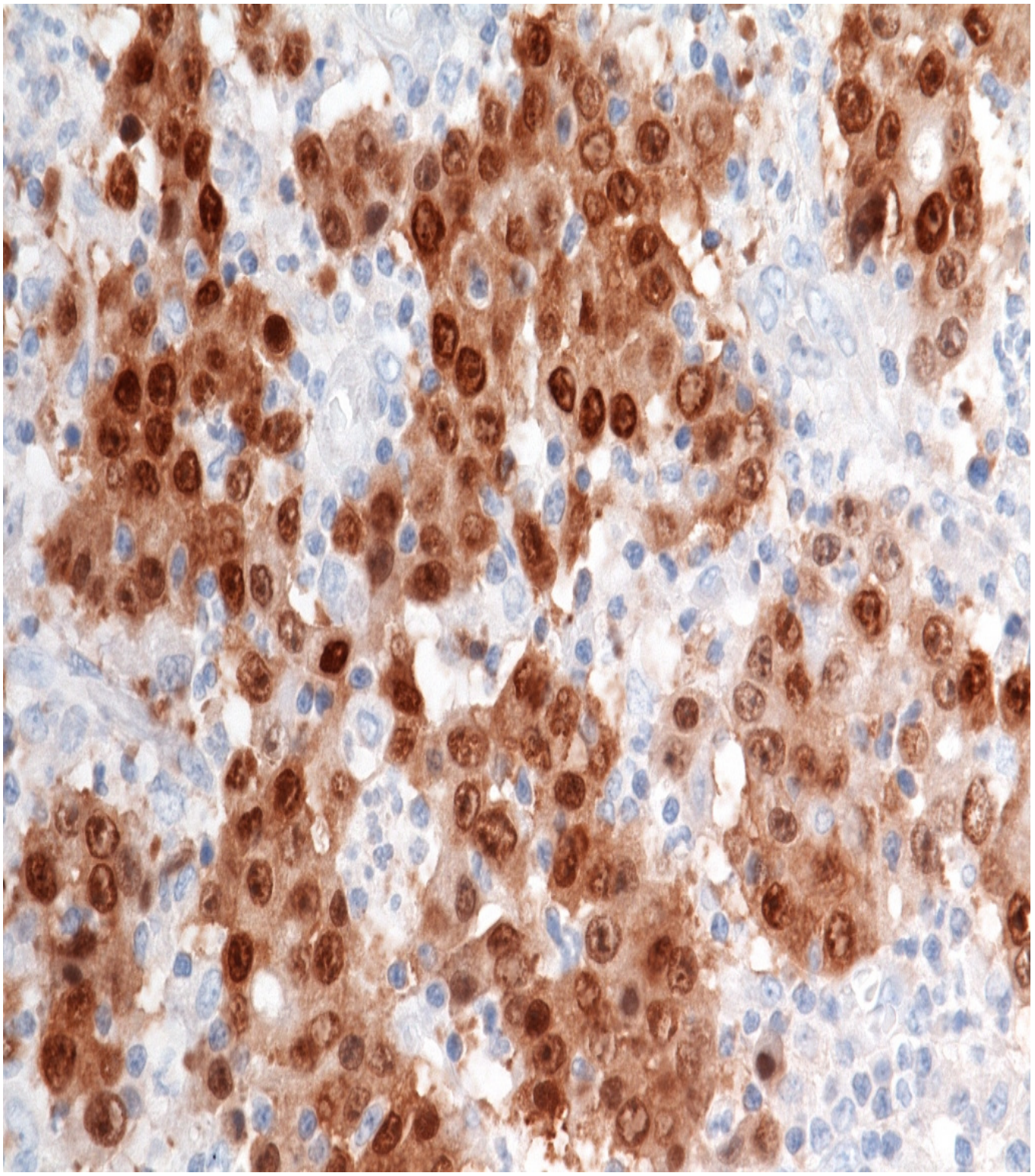
## What is your diagnosis?

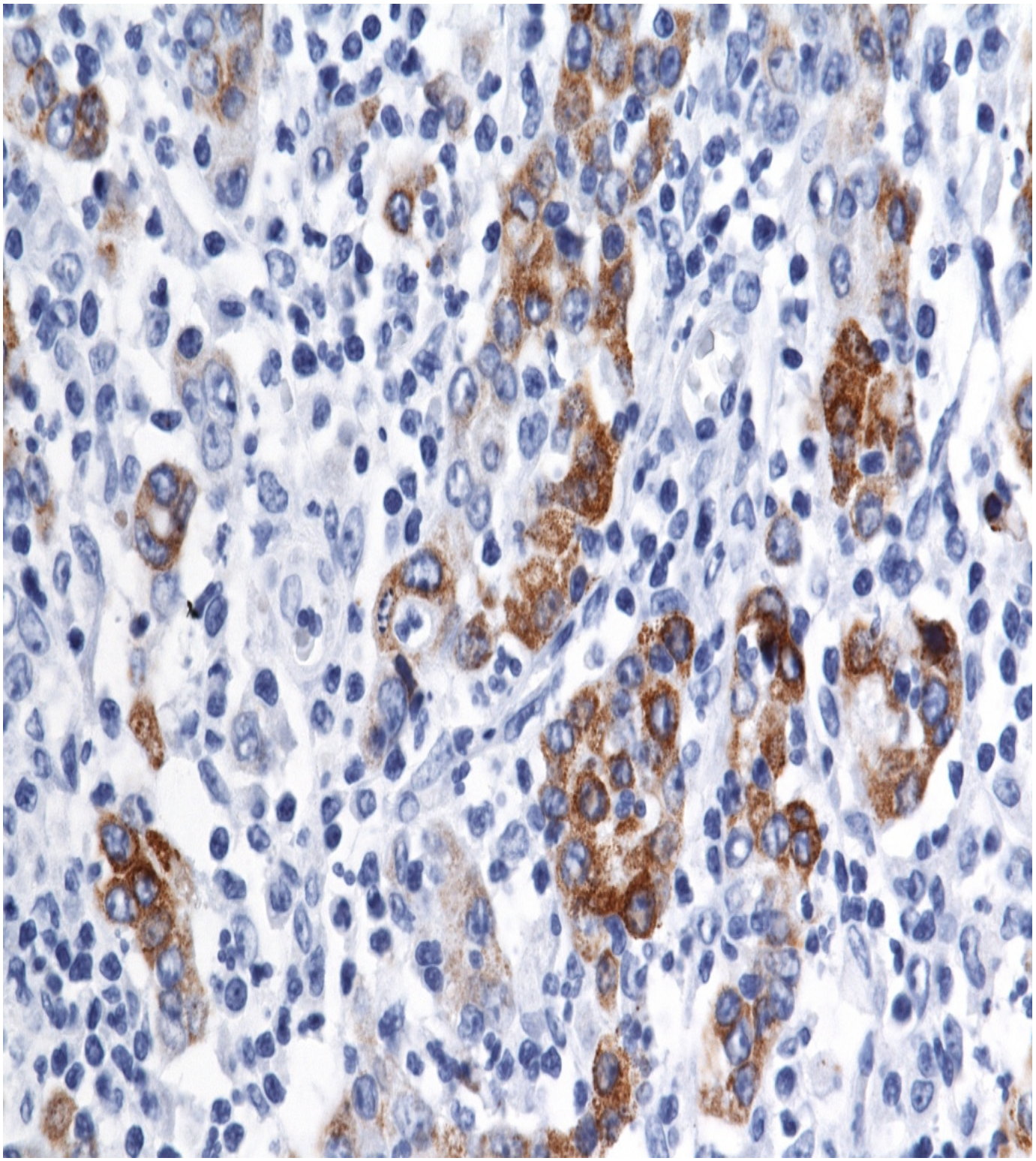


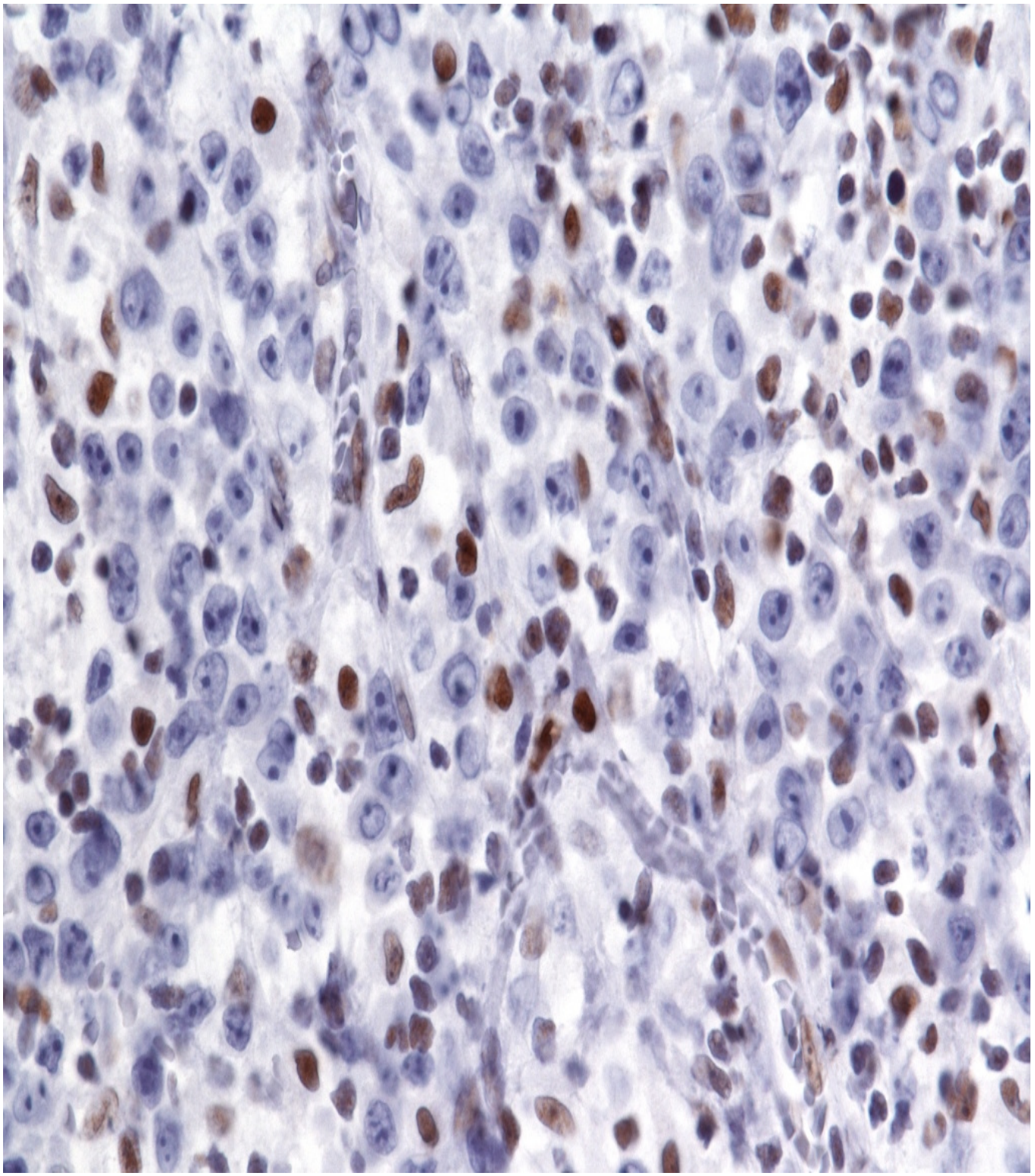


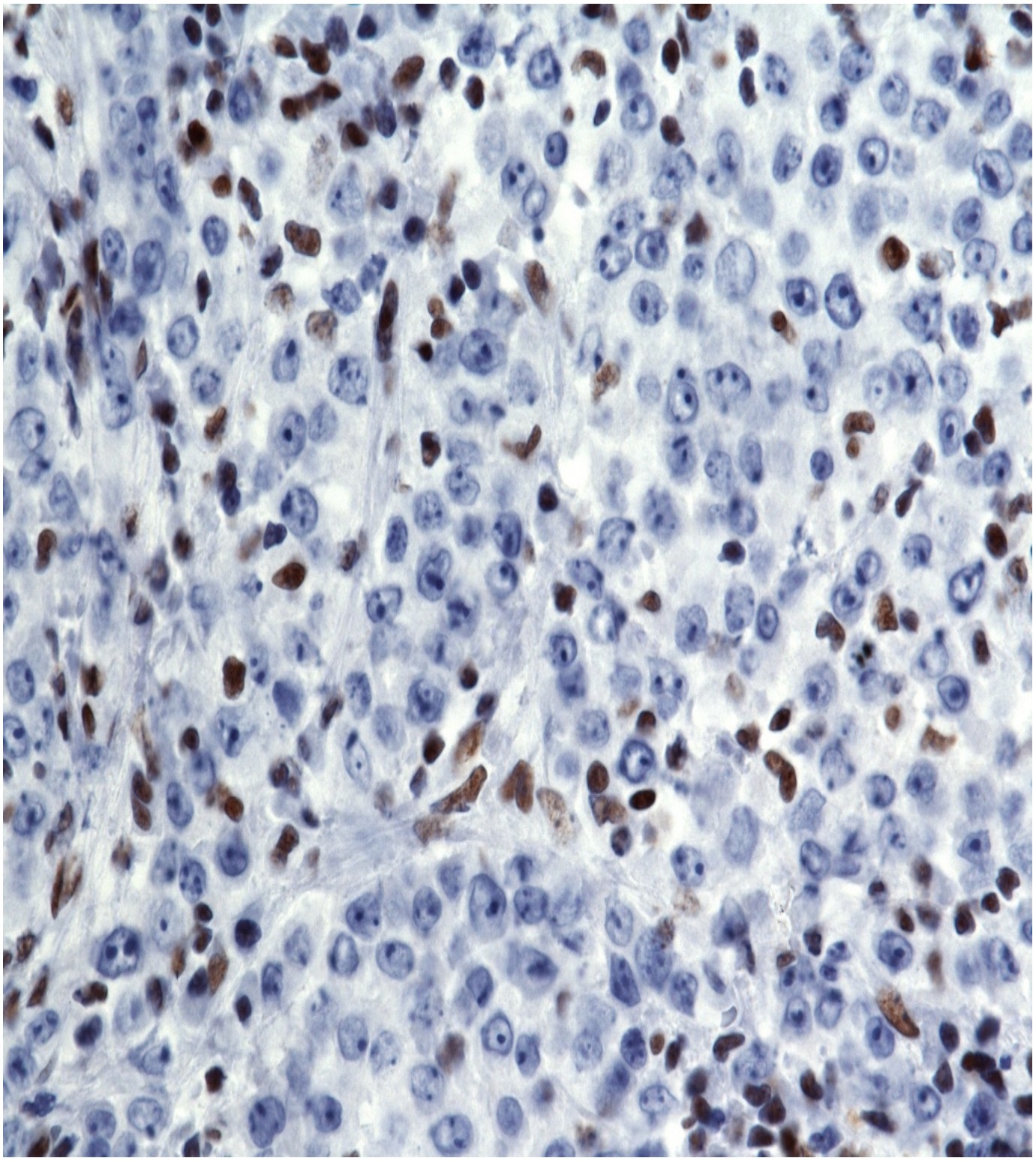












## Diagnosis:

Medullary carcinoma.

## Comment:

The resection specimen (right hemicolectomy) shows a solid tumour, measuring 5 cm in largest diameter within the caecum. Upon histology, the tumour shows a syncytial growth pattern, characterized by sheets of malignant cells with vesicular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm. There is a considerable infiltration by tumour-associated lymphocytes (intraepithelial lymphocytes and lymphocytes within the stroma) that prevails at the tumour periphery (Panels A-B). The tumour is strongly positive for keratin 7 (Panel C), whereas only weakly positive for keratin 20 (Panel D). The tumour cells express CDX-2 (Panel E),

while only single cells or small clusters of cells express MUC2 apoprotein (Panel F). Nuclear staining for MLH1 (Panel G) and PMS2 (Panel H) is lost in the tumour cells. Molecular analysis proves the tumour to be high level microsatellite instable (MSI-H). The morphological and molecular changes qualify for a histological diagnosis of medullary colon carcinoma.

In the gastrointestinal tract, tumours with a prominent inflammatory component have been described under different terms, such as lymphoepithelioma-like (which mainly occurs in the stomach) and medullary carcinoma (which mainly occurs in the large bowel). The latter is more common than previously reported, accounting for 2.8% of all large bowel cancers. Medullary carcinoma is more likely to arise in females than males and the elderly, and on the right side, often with locally advanced disease. The tumours almost invariably show MSI-H due to sporadic epigenetic silencing of the MLH1 gene, usually in conjunction with a BRAF mutation. Distant metastasis is rare at presentation, and overall survival is favourable when compared with colorectal adenocarcinomas with equivalent demographic and pathological characteristics.

Differential diagnosis may be challenging. The characteristic inflammatory infiltrate may be scarce in biopsy specimens. In these cases, the syncytical growth of rather monomorphic “undifferentiated” cells with vesicular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm may give the decisive clue. Several immunohistochemical markers are often necessary to separate medullary carcinoma from poorly differentiated non-medullary colon carcinoma, as the immunophenotypes are overlapping.  Pathologists need to be aware of the fact that negativity for keratin 20 and CDX-2 does not rule out primary colon cancer. In my eyes, in the appropriate histopathological setting, the loss of MLH1 (and PMS2) is a major argument for the diagnosis of medullary-type cancer.

## For further reading:


- Wick MR, Vitsky JL, Ritter JH, et al. Sporadic medullary carcinoma of the colon: a clinicopathologic comparison with nonhereditary poorly differentiated enteric-type adenocarcinoma and neuroendocrine colorectal carcinoma. Am J Clin Pathol. 2005; 123: 56-65.
- Winn B, Tavares R, Fanion J, et al. Differentiating the undifferentiated: immunohistochemical profile of medullary carcinoma of the colon with an emphasis on intestinal differentiation. Hum Pathol. 2009; 40: 398-404.
- Thirunavukarasu P, Sathaiah M, Singla S, et al. Medullary carcinoma of the large intestine: a population based analysis. Int J Oncol. 2010; 37: 901-7.
- Cunningham J, Kantekure K, Saif MW. Medullary carcinoma of the colon: a case series and review of the literature. In Vivo. 2014; 28: 311-4.
- Fiehn AM, Grauslund M, Glenthøj A, at al. Medullary carcinoma of the colon: can the undifferentiated be differentiated? Virchows Arch. 2015; 466: 13-20.
- Knox RD, Luey N, Sioson L, et al. Medullary Colorectal Carcinoma Revisited: A Clinical and Pathological Study of 102 Cases. Ann Surg Oncol. 2015;22:2988-96.
- Max N, Cathomas G, Langner C. Carcinomas with Lymphoid Stroma within the Gastrointestinal Tract: Histology and Molecular Pathology. J Surg Mol Pathol, in press


## Presented by: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