HHS Public Access

Author manuscript

AJSP Rev Rep. Author manuscript; available in PMC 2023 May 01.

Published in final edited form as:

AJSP Rev Rep. 2022 ; 27(3): 98–102. doi:10.1097/pcr.0000000000000503.

Nivolumab-induced peritonitis with peritoneal mesothelial hyperplasia mimicking metastatic mesothelioma

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Abstract

A 57-year-old man developed a mesothelial proliferation in the peritoneum, several months after he was diagnosed with biopsy-proven epithelioid mesothelioma of the pleura and having undergone several treatments with checkpoint inhibitor immunotherapy. The differential diagnosis was metastatic mesothelioma from the lung primary, versus a reactive process. A diagnosis of atypical mesothelial proliferation was made. Follow-up CT showed no evidence of abdominal disease 5 months later. The complication of serositis following checkpoint inhibitor therapy is reviewed, as well as the differential diagnosis between reactive mesothelial hyperplasia and epithelioid mesothelioma.

Case report

A 57-year-old male developed a cough which progressed over three months at which time he presented to urgent care, where imaging revealed a right pleural effusion. He was found also to have left external iliac vein thrombosis which was treated with Lovenox and transitioned to rivaroxaban. He underwent right video-assisted thorascopic sugary with talc pleurodesis and biopsy showed epithelioid mesothelioma, with transitional areas which some reviewers favored to be sarcomatoid (biphasic mesothelioma). (Figure 1). He elected to enroll in a clinical trial and was randomized to nivolumab immunotherapy. The patient received three doses of nivolumab neoadjuvantly and was scheduled for extended pleural decortication. A week before the scheduled pleurectomy he developed pneumonia, for which he was treated, delaying surgery. Six months after initial presentation he underwent peritoneal biopsy for biopsy of a suspicious area in the abdomen, which preoperatively was presumed to be metastatic mesothelioma based on imaging findings. The operative summary noted murky fluid in the abdomen, with significant inflammation in the right upper quadrant, overlying the liver, as well as in the right lower quadrant. There was no gross evidence of what appeared to be papillary lesions typical of mesothelioma. The area was biopsied, as well as a “phlegmon” adhered to the right colon to the right lateral abdominal wall. There was no evidence of a bowel perforation.

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The biopsies demonstrated a papillary proliferation of epithelioid mesothelial cells without definite invasive tumor. Some areas had a neutrophilic infiltrate with fibrin, and most areas were uninflamed (Figures 2–4) The primary tumor was confirmed to demonstrate MTAP and BAP-1 retention by immunohistochemical staining, as was the peritoneal proliferation. A diagnosis of atypical mesothelial proliferation was made, with a comment that a reactive process was favored, after much debate among several pathologists. The pathology slides were referred to the institution administering the immunotherapy to the patient, and a similar diagnosis was made, indicating that a metastatic mesothelioma could not be excluded. The thoracic surgery was aborted, in part because metastatic disease was suspected, and because there was debate about where the primary tumor was biphasic or epithelioid with transitional areas. The patient concluded his immunotherapy. Six months later a staging PET CT was performed. The thoracic disease was read as stable, and there was no evidence of ascites or thickening of the mesentery or peritoneum. In retrospect, it was concluded that the peritoneal biopsy was reactive, and possibly related to checkpoint inhibitor toxicity. The possibility that the peritonitis was secondary to pneumonia was rejected, based on the facts that it was several months prior, had resolved with antibiotics, and had not resulted in empyema.

Checkpoint inhibitor-induced serositis.

Checkpoint inhibitor toxicity denotes adverse autoimmune events involving almost every organ and system. The most common manifestations include dermatoses, colitis, pneumonitis, and nephritis. Serositis is a rare potential complication, usually involving the pericardium or pleura, manifest as effusions. (1) A single case of fatal mesenteritis has been reported a patient as a presumed complication to nivolumab toxicity, with histologic illustrations. (2) The current case is the second report of peritoneal inflammation due to nivolumab, and the first to document mesothelial hyperplasia mimicking mesothelioma. Checkpoint inhibitor peritonitis should be distinguished from mesenteric ischemia, which can cause secondary peritonitis, and may be mediated by checkpoint inhibitor-induced antiphospholipid syndrome. (3)

Pathologic distinction between reactive hyperplasia and epithelioid mesothelioma.

The histologic distinction between reactive mesothelial hyperplasia and epithelioid mesothelioma has been recently reviewed (4) The most definitive feature of epithelioid mesothelioma is the presence of invasion, although there are several other features helpful in the differential diagnosis if this feature is absent (Table 1).

Immunohistochemical detection of differentiation antigens are of limited use in the differential diagnosis of epithelioid mesothelioma v. reactive mesothelium. GLUT1 and desmin expression have been reported to be more likely positive in mesothelioma (5). Although GLUT1 has been shown to be highly sensitive and specific in the distinction between mesothelioma and reactive mesothelial hyperplasia (6), there are few more recent studies to confirm this. Other markers, such as p53 expression, has shown promise if positive

in favoring mesothelioma (5) but current guidelines do not include immunostaining for GLUT1, desmin, or p53 in the routine workup of epithelioid mesothelioma. (4)

Immunohistochemical stains for gene loss of CDKN2A and BAP1 are, however, very useful in distinguishing mesothelioma and reactive mesothelial hyperplasia. (7,8) In the current report, the primary tumor unfortunately showed retention of both genetic alleles, so these stains were not useful. The addition of FISH for CDKN2A loss, in addition to MTAP staining, increases the sensitivity for the diagnosis. Kinoshita et al have shown that the addition of FISH for NF2 gene (lost in various malignancies), increases the sensitivity of these tests to nearly 100% (8) Chapel et el did not notice a significant difference in specificity and sensitivity between small biopsies or cell blocks and resections for MTAP staining, and found a 75% sensitivity for MTAP expression and nearly 100% specificity when compared to the FISH result. (7) Table 2 shows data from Kinoshita's study showing the combined effectiveness of immunohistochemistry for BAP1 and MTAP and CDKN2A FISH in the distinction between epithelioid mesothelioma and reactive mesothelial hyperplasia.

Noninvasive mesothelioma of the peritoneum

The major differential diagnosis in this case was a metastasis from the patient's pleural mesothelioma. Approximately 10% of patients with mesothelioma of the lung have concurrent peritoneal disease and a little over 20% of patient develop peritoneal metastasis in their disease course. (9) The histologic features of peritoneal metastases are similar to the primary tumor and are almost always the epithelioid type and are indistinguishable from primary peritoneal mesothelioma. (10,11) The mechanism of metastatic spread in these patients is unclear, and either involves direct extension across defects in the diaphragm, or lymphatic or hematogenous spread.

In this case, if there were an absence of a history of pleural mesothelioma, the main differential diagnostic consideration is primary mesothelioma of the peritoneum. Primary peritoneal mesotheliomas are broadly divided into low-grade indolent tumors, and diffuse malignant mesothelioma. The low-grade tumors are further classified as well differentiated papillary mesothelioma, and multicystic mesothelioma. Well differentiated papillary mesothelioma would be a consideration in this case, were it not for the history of pleural mesothelioma. Well differentiated papillary mesotheliomas are non-invasive and composed of bland papillae lined by a single layer of flat cuboidal epithelium (Figure 5). These tumors occur almost exclusively in women and have a prolonged clinical course over decades with very long time intervals between recurrences. Like all of the subsets of primary peritoneal mesothelioma, they are diffuse lesions that occur in multiple areas of the serosal surfaces of the peritoneum.

Diffuse malignant mesothelioma of the peritoneum is usually an aggressive tumor with clear cut features of malignancy. However, 15% demonstrate a lack of stromal invasion, have a clinical course intermediate between well differentiated papillary mesothelioma and invasive diffuse malignant mesothelioma of the peritoneum(10,11). Unlike well differentiated papillary mesothelioma, there is no sex predilection. Although the histologic distinction with

well differentiated papillary mesothelioma can be difficult, the lining cells of the papillae are more atypical, they lack the flattened cuboidal appearance, and there is usually a more exuberant papillary growth (Figure 6,7). There may be clear cut invasive areas in diffuse malignant mesothelioma that have areas without invasion (Figure 8).

In pathologic reporting of diffuse malignant mesothelioma of the peritoneum, reporting specific features such as depth of invasion, structures that are invasion, and histologic grade are optional, as there no American Joint Committee on Cancer protocols for this rare lesion. Treatment is generally hyperthermic intraperitoneal chemotherapy with meticulous surgical resection of all visible tumor, if possible. Prognosis depends largely on the degree of residual gross tumor as assessed surgically (completeness of cytoreduction), which in turn depends on preoperative peritoneal cancer index and degree of invasion into visceral organs or abdominal wall. (12)

REFERENCES

1. Brahmer JR, Lacchetti C, Schneider BJ et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018;36:1714–1768. [PubMed: 29442540]
2. Sulkes A, Kundel Y, Sadot E et al. Case Report: Fatal mesenteric and retroperitoneal serositis after pelvic chemoradiation followed by a single dose of chemotherapy and nivolumab. Current Problems in Cancer: Case Reports 2020.
3. Mintjens-Jager EMW, Vos ME, Kats-Ugurlu G, Hospers GAP, Rutgers A, van Meurs M. Severe mesenteric ischemia with multiple organ failure in a patient previously treated with a humanized monoclonal antibody against programmed death receptor-1 (pembrolizumab), a case of pembrolizumab associated catastrophic antiphospholipid syndrome? SAGE Open Med Case Rep 2020;8:2050313X20972225.
4. Husain AN, Colby TV, Ordonez NG et al. Guidelines for Pathologic Diagnosis of Malignant Mesothelioma 2017 Update of the Consensus Statement From the International Mesothelioma Interest Group. Arch Pathol Lab Med 2018;142:89–108. [PubMed: 28686500]
5. Hasteh F, Lin GY, Weidner N, Michael CW. The use of immunohistochemistry to distinguish reactive mesothelial cells from malignant mesothelioma in cytologic effusions. Cancer Cytopathol 2010;118:90–6. [PubMed: 20209622]
6. Kato Y, Tsuta K, Seki K et al. Immunohistochemical detection of GLUT-1 can discriminate between reactive mesothelium and malignant mesothelioma. Mod Pathol 2007;20:215–20. [PubMed: 17192790]
7. Chapel DB, Schulte JJ, Berg K et al. MTAP immunohistochemistry is an accurate and reproducible surrogate for CDKN2A fluorescence in situ hybridization in diagnosis of malignant pleural mesothelioma. Mod Pathol 2020;33:245–254. [PubMed: 31231127]
8. Kinoshita Y, Hamasaki M, Yoshimura M, Matsumoto S, Iwasaki A, Nabeshima K. Hemizygous loss of NF2 detected by fluorescence in situ hybridization is useful for the diagnosis of malignant pleural mesothelioma. Mod Pathol 2020;33:235–244. [PubMed: 31231129]
9. Collins DC, Sundar R, Constantinidou A et al. Radiological evaluation of malignant pleural mesothelioma - defining distant metastatic disease. BMC Cancer 2020;20:1210. [PubMed: 33298007]
10. Liu S, Staats P, Lee M, Alexander HR, Burke AP. Diffuse mesothelioma of the peritoneum: correlation between histological and clinical parameters and survival in 73 patients. Pathology 2014;46:604–9. [PubMed: 25393250]
11. Lee M, Alexander HR, Burke A. Diffuse mesothelioma of the peritoneum: a pathological study of 64 tumours treated with cytoreductive therapy. Pathology 2013;45:464–73. [PubMed: 23846294]
12. Alexander HR Jr., Burke AP. Diagnosis and management of patients with malignant peritoneal mesothelioma. J Gastrointest Oncol 2016;7:79–86. [PubMed: 26941986]

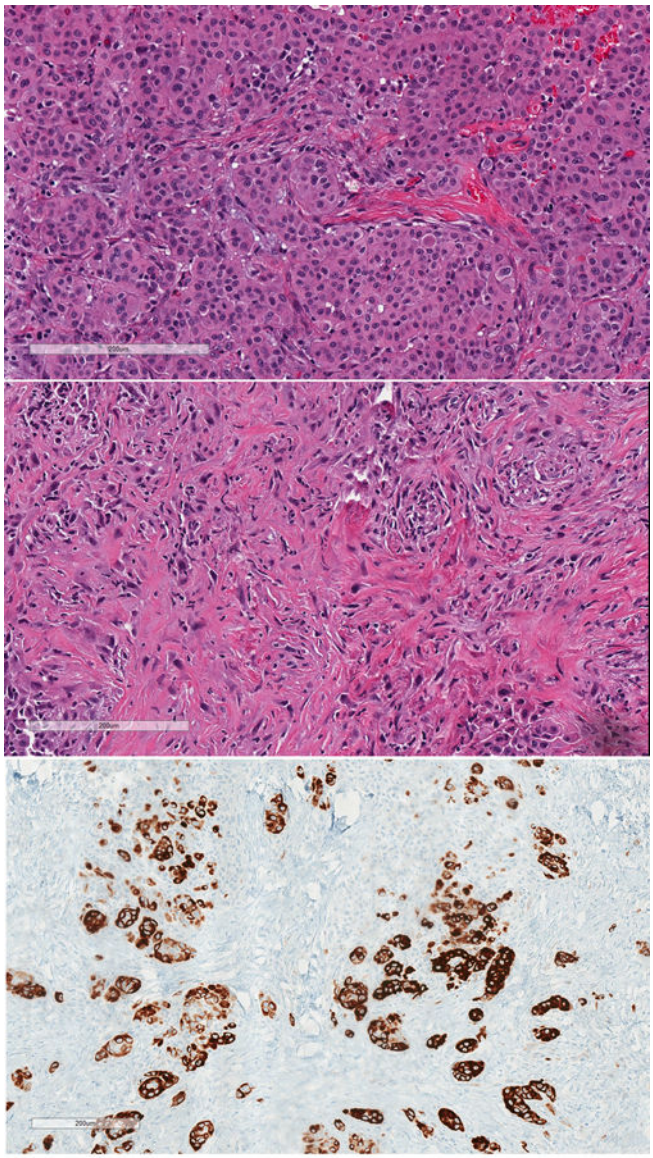

Figure 1.

Pleural tumor biopsy, diffuse malignant mesothelioma of pleura. The tumor had large sheet-like solid areas (above). There were other areas with pleomorphism and incipient spindling (middle). Immunostain for CK5,6 demonstrate positivity in tumor cells, and suggested a primarily epithelioid growth pattern.

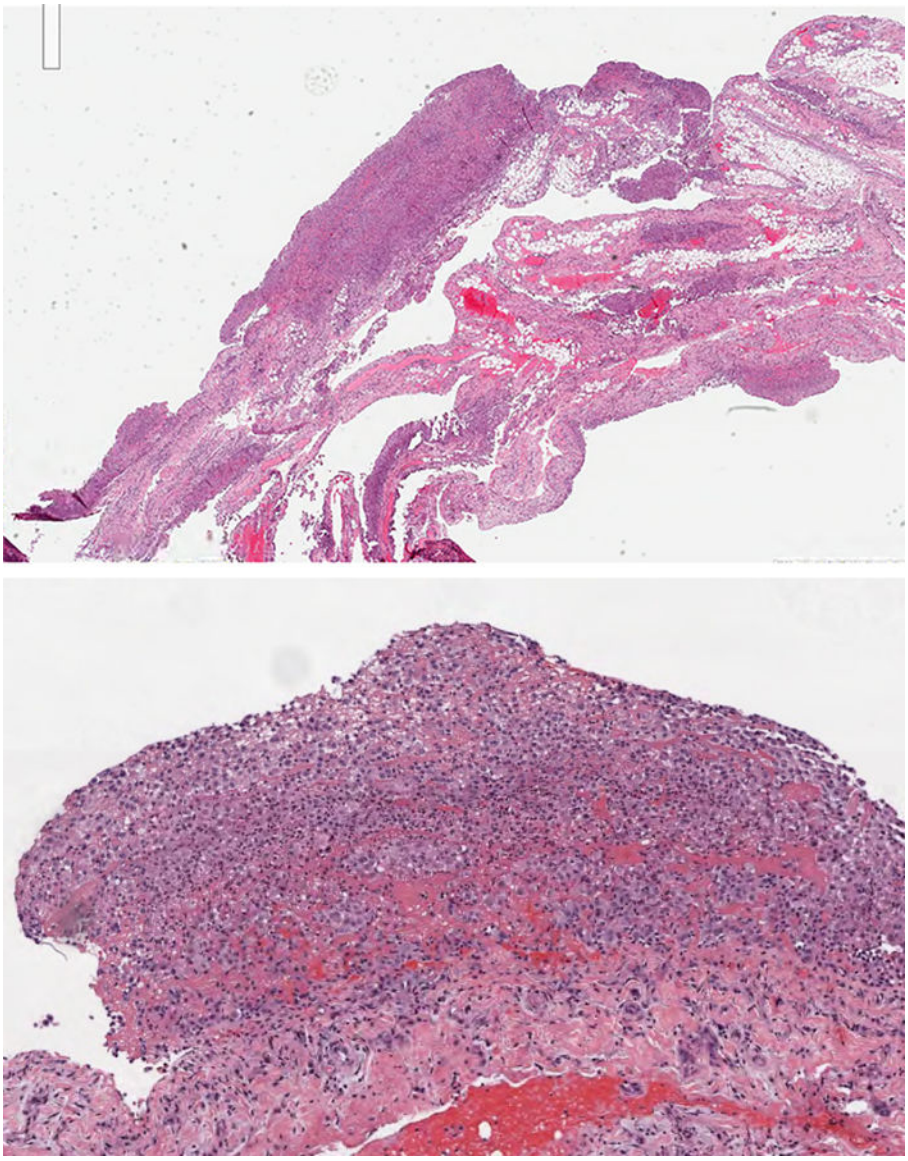

Figure 2.

Peritoneal biopsy, reactive mesothelial hyperplasia. The peritoneum is seen folded, with a several areas of thickening, one marked (above). A higher magnification (below) shows a noninvasive sheet-like growth of epithelioid mesothelial cells.

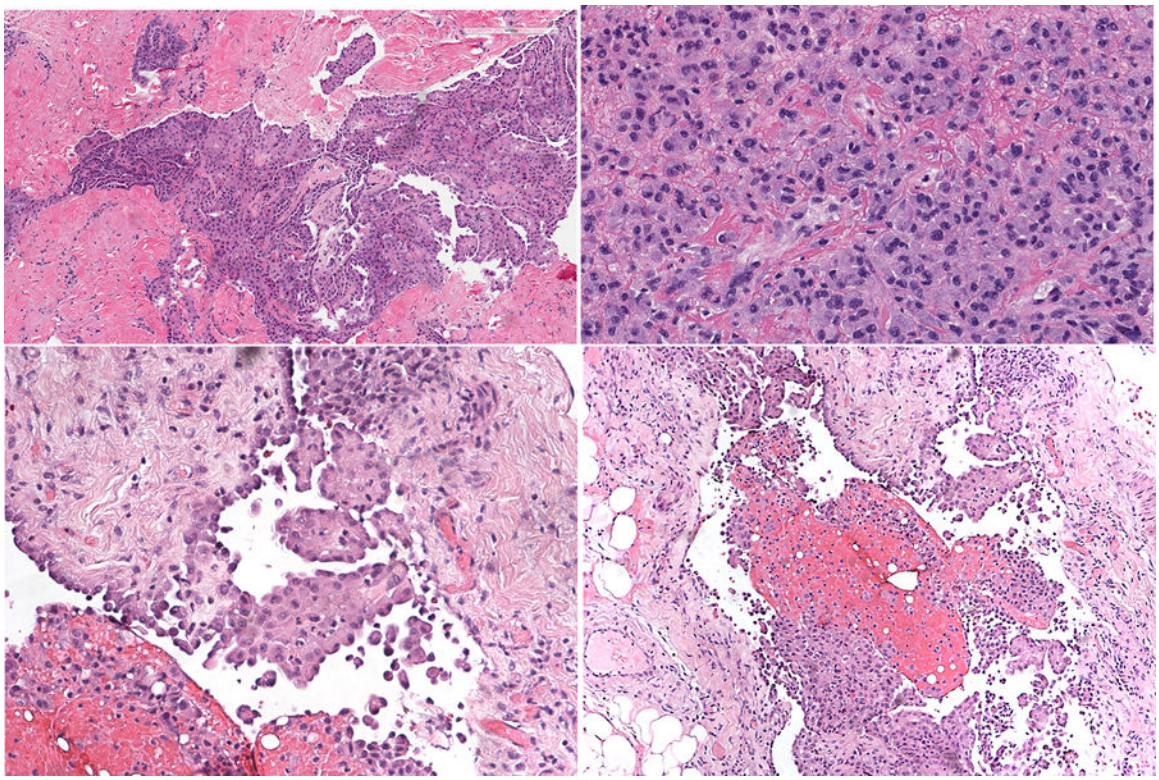

Figure 3.
Peritoneal biopsy, reactive mesothelial hyperplasia. A different area shows a papillary surface proliferation (top left), with areas of solid sheets, with interspersed fibrin (top right). The bottom panel shows two areas of reactive papillary hyperplasia, unusually proliferative for a reactive lesion.

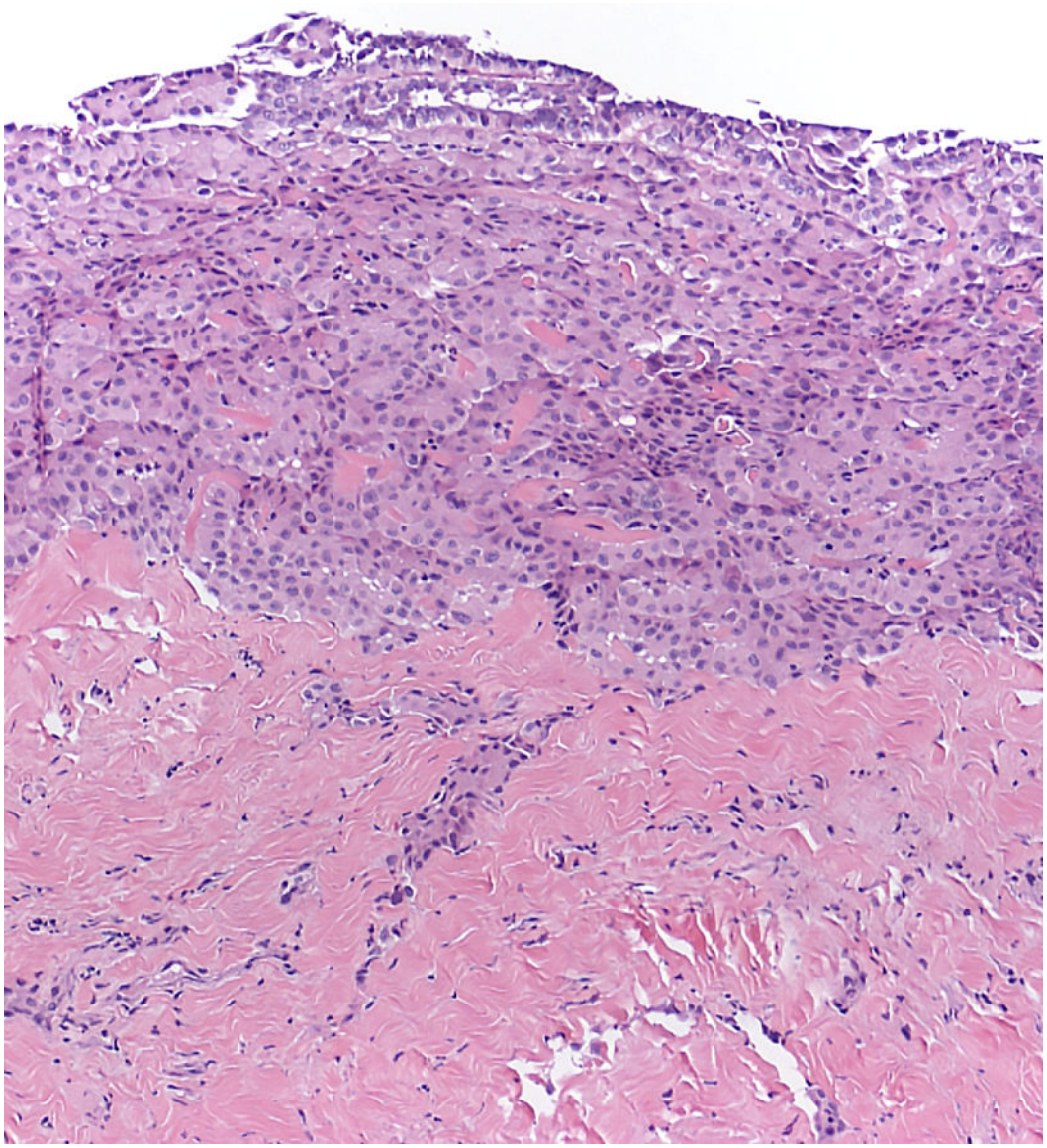

Figure 4.
Peritoneal biopsy, reactive mesothelial hyperplasia. In some foci, there were areas of papillary projections mimicking mesothelioma, with areas of pseudoinvasion.

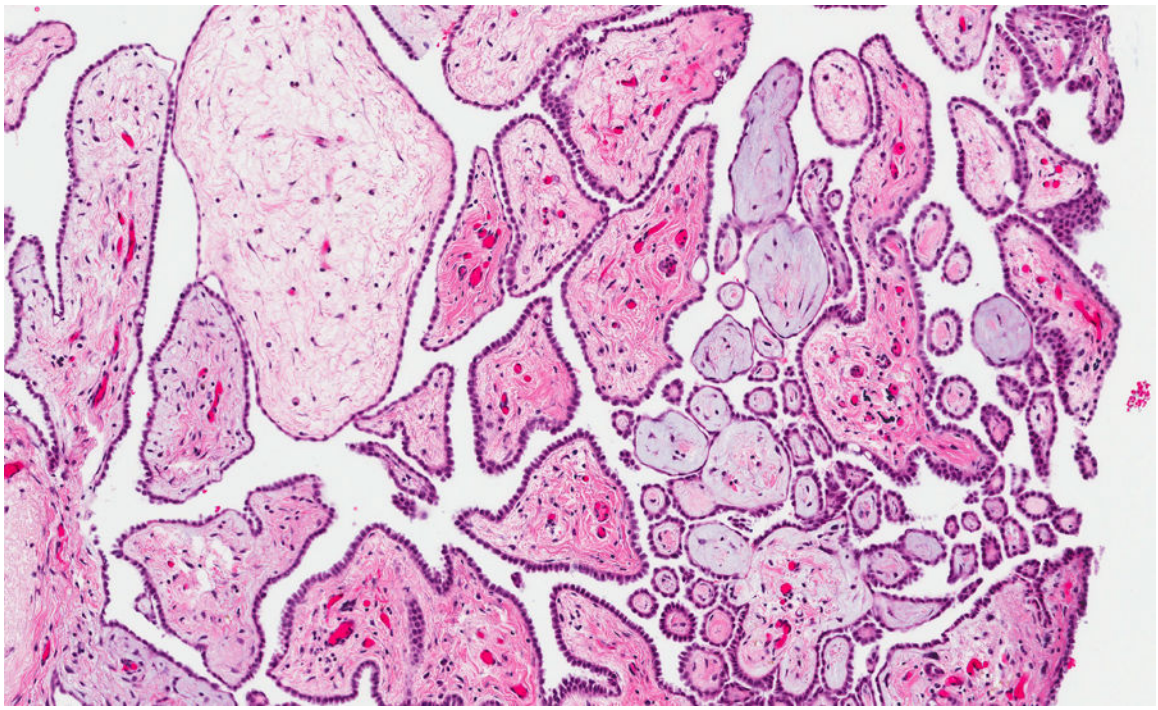

Figure 5.
Well differentiated papillary mesothelioma. The papillae have a vascular myxoid stroma and are lined by flattened cuboidal mesothelial cells with virtually no atypia.

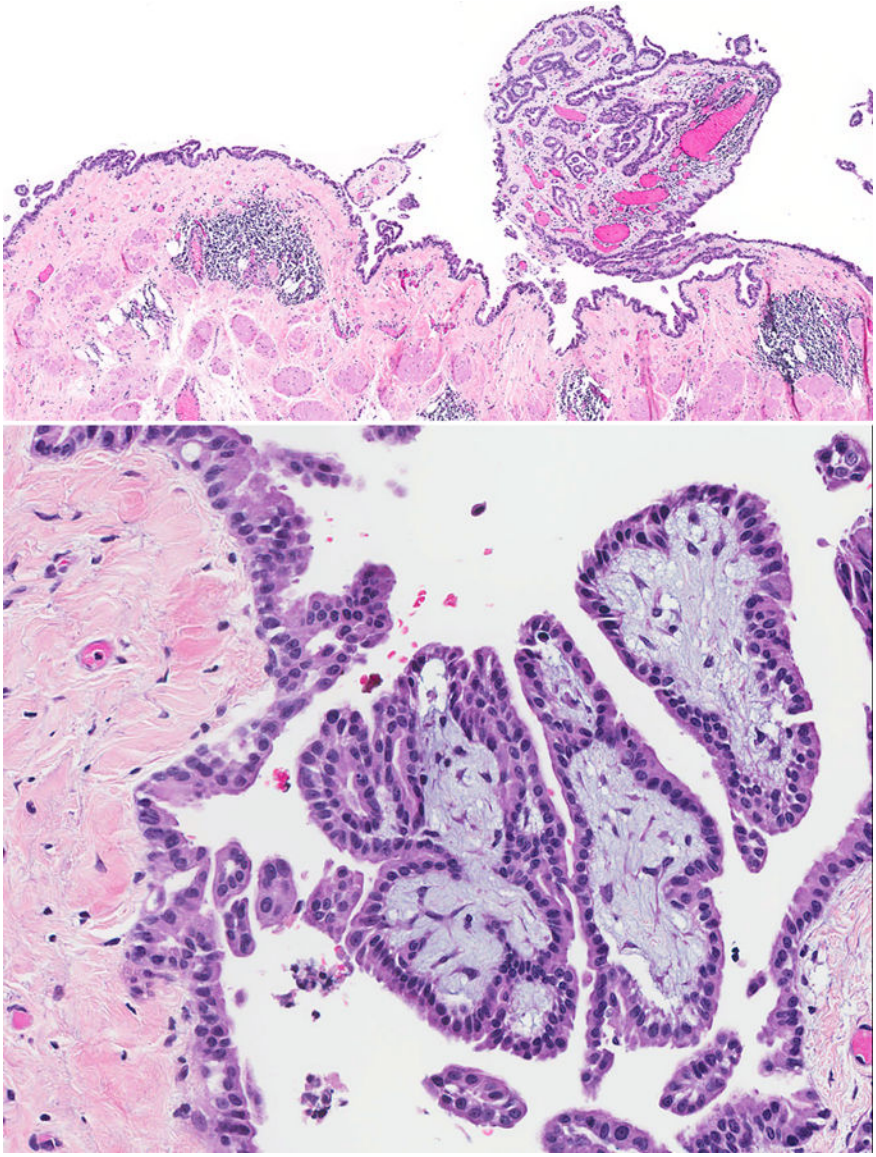

Figure 6.

Diffuse malignant mesothelioma of the peritoneum, non-invasive. The papillae have a complex structure, have a myxoid background, and the lining cells are columnar. These features all favor neoplasm over a reactive process.

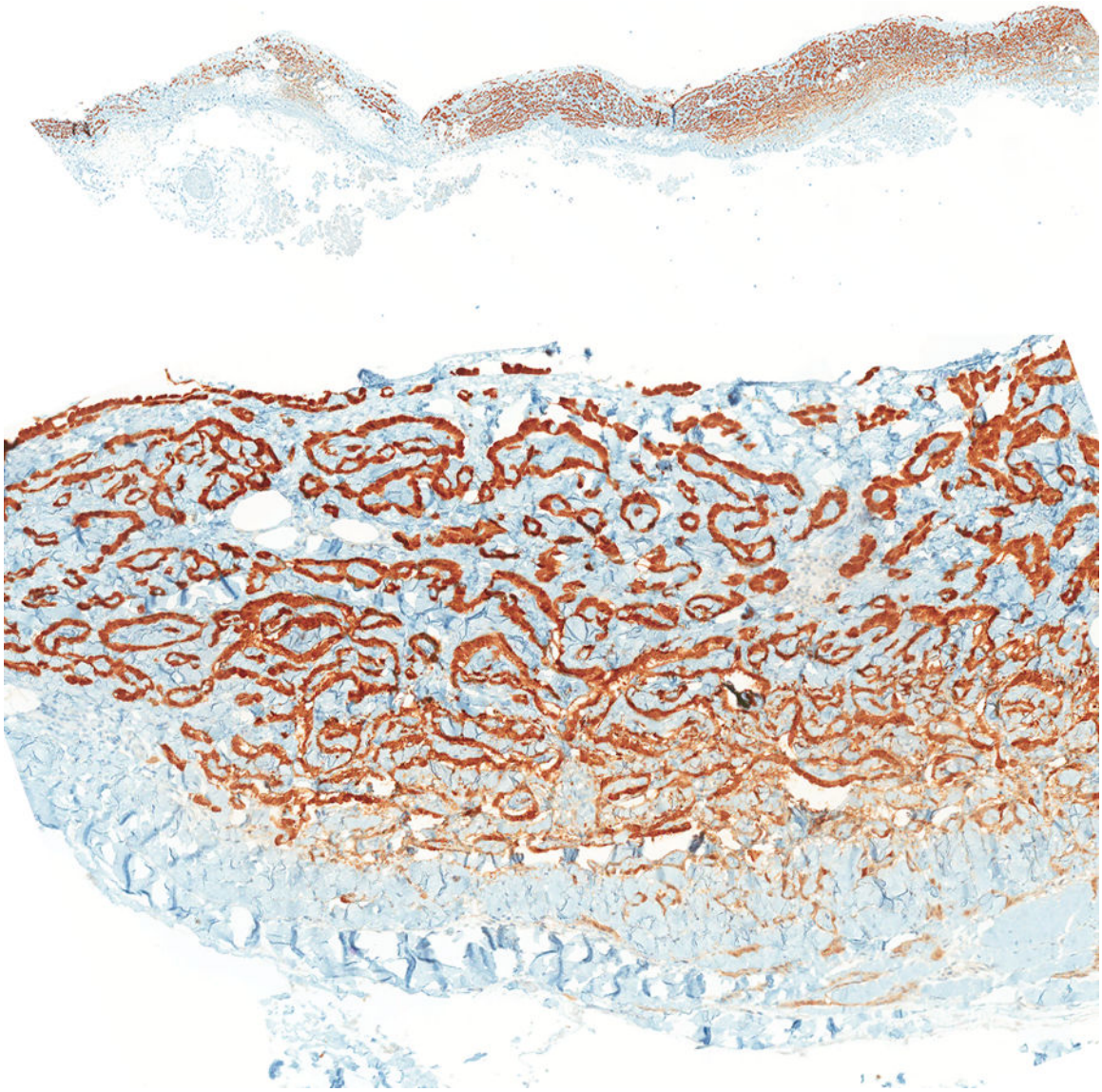

Figure 7.

Diffuse malignant mesothelioma of the peritoneum, non-invasive, calretinin immunostain. Although there is no definite invasion of the stroma, the papillae are anastomosing and complex, favoring a neoplastic process.

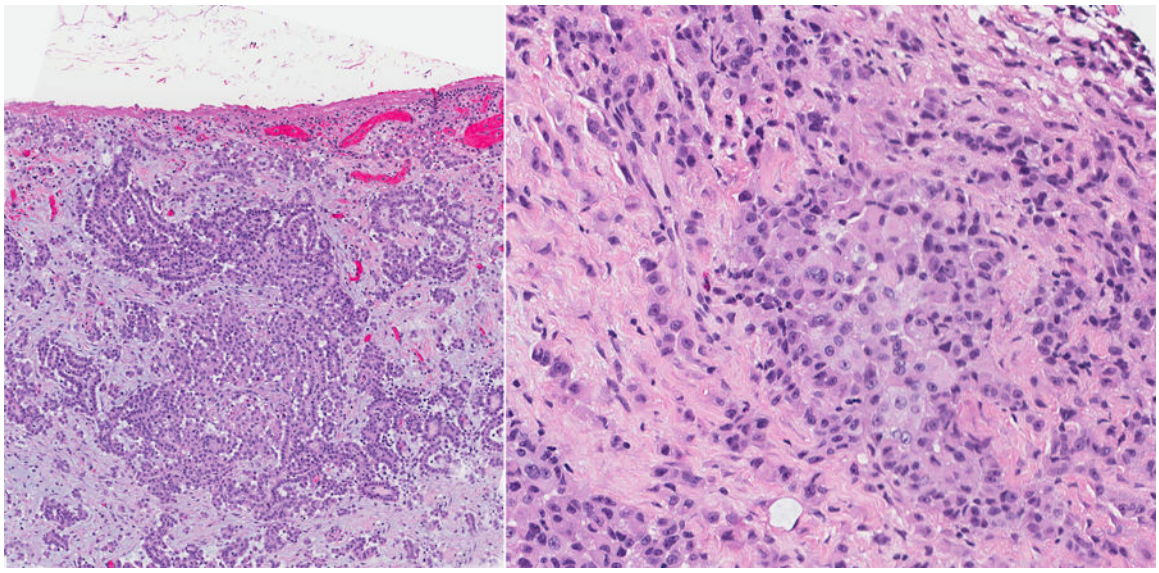

Figure 8.
Diffuse malignant mesothelioma of the peritoneum with stromal invasion. A low magnification shows a denuded serosa with fibrin coating and invasion by tumor into the stroma. A higher magnification of the stromal invasion is shown below.

Table 1,

adapted from Husain et al, 2018 (4)

Histologic features of reactive epithelioid mesothelial hyperplasia and epithelioid mesothelioma.

Histologic feature	**Reactive mesothelium**	**Epithelioid mesothelioma**
Stromal invasion	Absent	Present
Cellularity	May be prominent, but predominantly at the surface	Present at all layers, including stromal interface
Papillae	Simple, lined by single cell layer, no myxoid stroma	Complex, with tubulopapillary structures
Sheets of cells without stroma	Common	Common
Necrosis	Rare	Common
Inflammation	Common, especially neutrophilic, often mixed with fibrin	Not usually neutrophilic, fibrin may be present but not usually with admixed inflammation
Growth pattern	Uniform and linear	Asymmetric expansile nodules
Mitotic activity	Variable	Variable
Cytologic atypia	Variable, usually mild or moderate	Variable, mild to severe

Those features that are italicized are useful in the differential diagnosis.

Table 2.

Sensitivity and specificity of BAP1, MTAP, and CDKN2A testing in the distinction between reactive mesothelial hyperplasia and epithelioid mesothelioma. Adapted from Kinoshita, 2020 (8)

	Malignant mesothelioma, %	**Reactive mesothelial hyperplasia, %**	**Sensitivity**	**Specificity**
BAP1 IHC, loss of nuclear expression	57	0	57	100
MTAP IHC, loss of nuclear expression	70	0	70	100
CDKN2A homozygous deletion	79	0	79	100
Loss of either BAP1 ***or*** MTAP nuclear expression	89	0	89	100
Loss of BAP1 nuclear expression ***or*** CDKN2A homozygous deletion	94	0	94	100