PAX8 Expression in a Subset of Malignant Peritoneal Mesotheliomas and Benign Mesothelium has Diagnostic Implications in the Differential Diagnosis of Ovarian Serous Carcinoma

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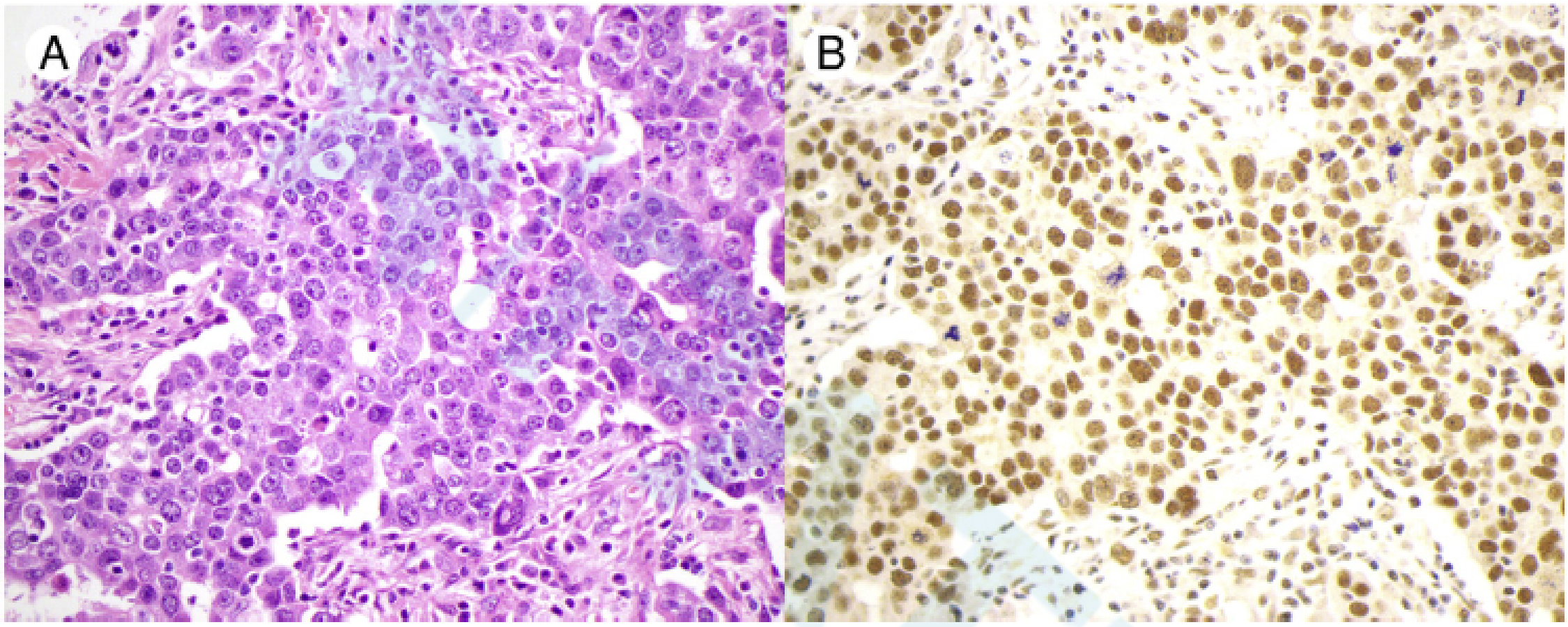

Fig. 1 Serial H&E (A)– and BAP1 (B)–stained section from a high-grade serous carcinoma demonstrated diffuse strong positive nuclear expression of BAP1 (original magnification ×400).

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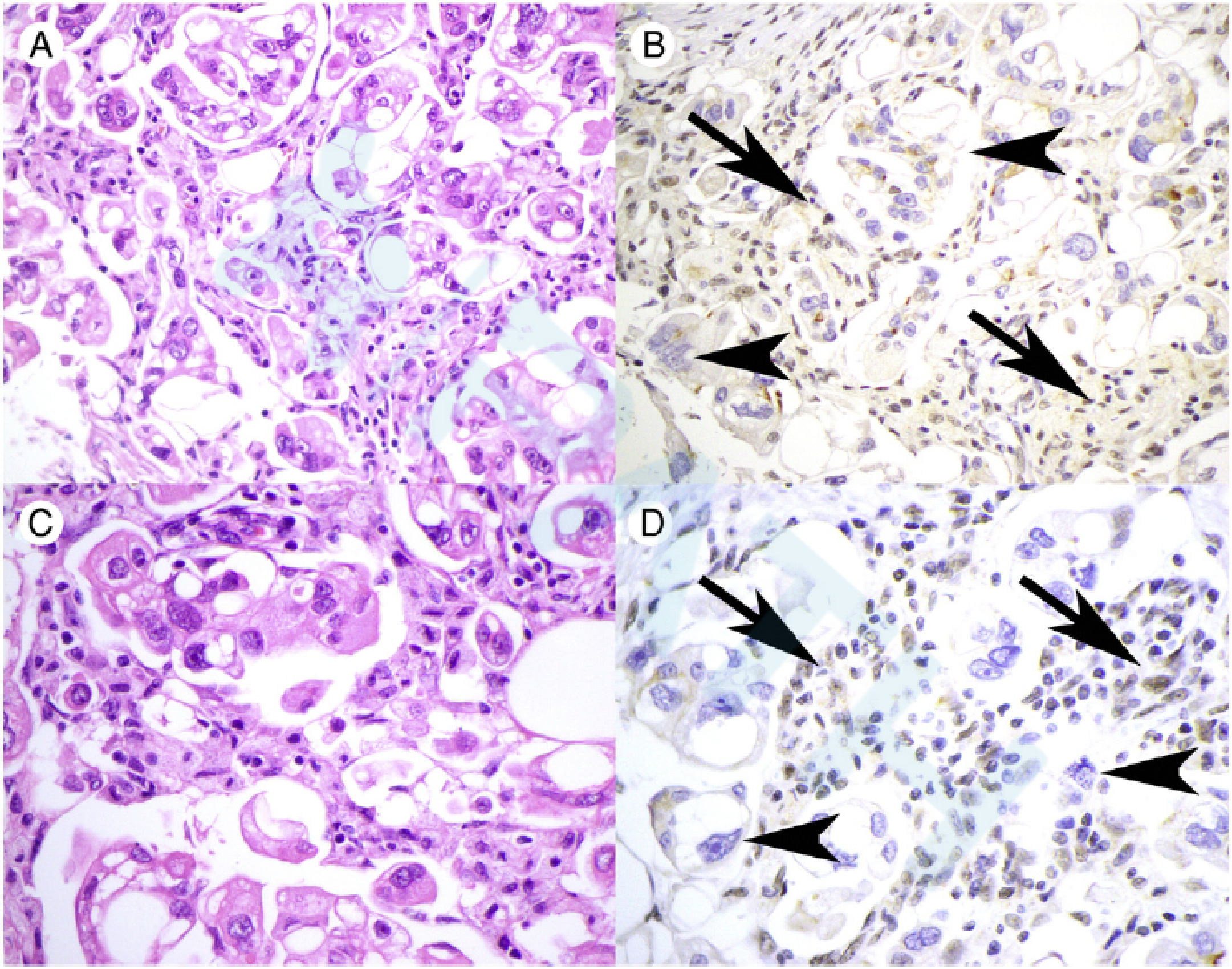

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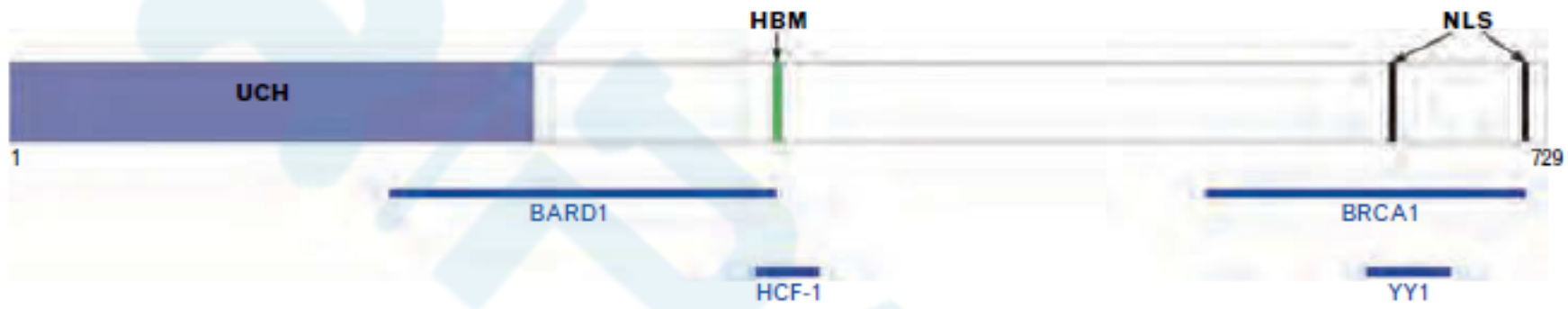

Fig. 1 Simplified structure of BAP1 protein illustrating functional domains and regions of interaction with other proteins. BAP1 is a 729 amino acid protein, consisting of an N-terminal ubiquitin carboxyl hydrolase (UCH) domain (1–250), an HCF-1-binding domain (HBM, 363–366), and a two-part nuclear localisation signal (NLS, 656–661 and 717–722). BAP1 interacts with BARD1 (182–365), HCF-1 (365–385), BRCA1 (596–721) and YY1 (642- 686).[10,88] Numbers refer to amino acid positions. Please see text for additional details.

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Table 1 Clinical and pathological characteristics of 395 serous adenocarcinoma patients and 9 abdominal mesothelioma patients

Variable	Serous adenocarcinoma, n (%)	Mesothelioma		*P*	
		Abdominal, n (%)	Thoracic, n (%)	Serous adenocarcinoma *vs* abdominal mesothelioma	Serous adenocarcinoma *vs* all mesotheliomas
Total (n)	395	9	277		
Age at diagnosis in years, mean (range)	62 (19-87)	66 (50-91)	72 (31-97)	.40	<.001
Site				–	–
Ovary	258 (65.3)	–	–		
Fallopian tubes	45 (11.4)	–	–		
Uterus	46 (11.6)	–	–		
Peritoneal	46 (11.6)	–	–		
Overall stage				–	–
1A	91 (23.9)	–	–		
1B	9 (2.4)	–	–		
1C	15 (3.9)	–	–		
2A	8 (2.1)	–	–		
2B	24 (6.3)	–	–		
2C	11 (2.9)	–	–		
3A	16 (4.2)	–	–		
3B	68 (17.8)	–	–		
3C	133 (34.9)	–	–		
4	6 (1.6)	–	–		
BAP1 status				<.001	<.001
BAP1 positive	394 (99.75)	3 (33)	146 (53)		
BAP1 negative	1 (0.25)	6 (67)	131 (47)		

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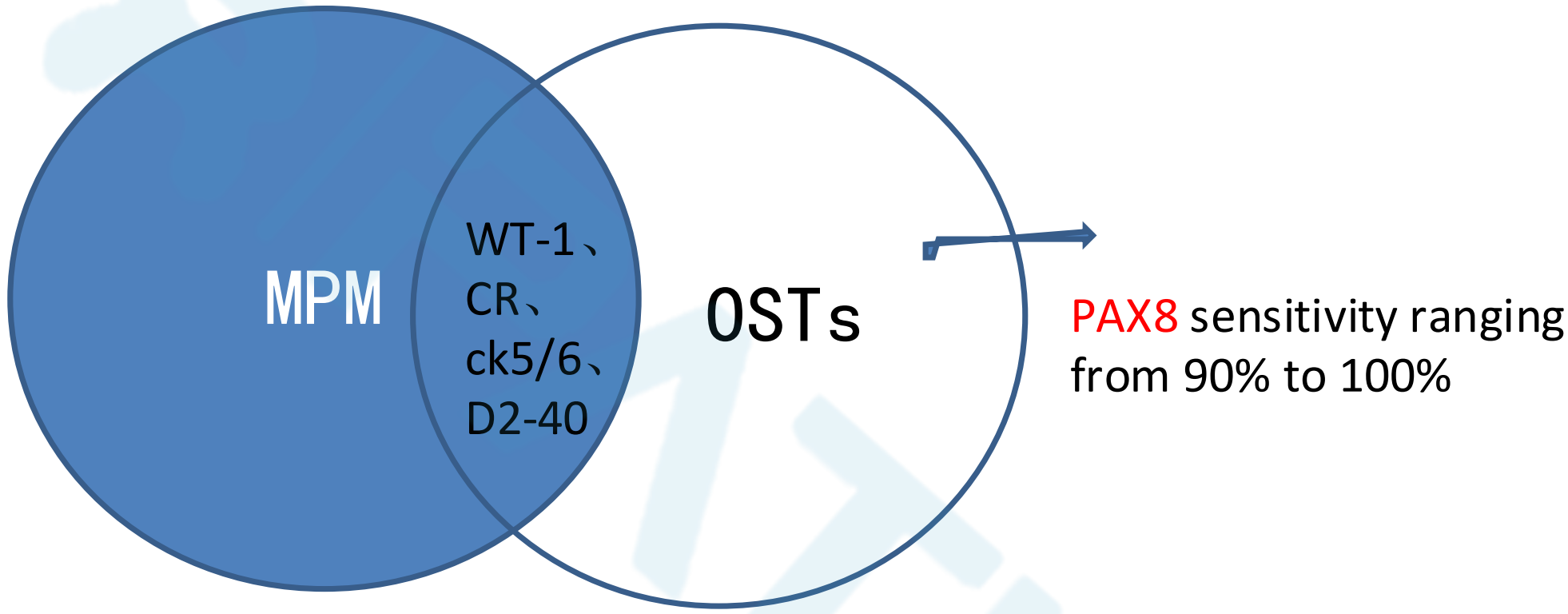


MPM： malignant peritoneal mesothelioma
OSTs： ovarian serous tumors

MATERIALS AND METHODS

- 27 cases of MPM（malignant peritoneal mesothelioma) diagnosed at the University of Chicago between January 2003 and June 2016

For purposes of comparison:

- 10 well differentiated papillary mesotheliomas (WDPMs);
- 4 benign multicystic mesotheliomas;
- 11 cases of reactive mesothelium;

- OSTs (ovarian serous tumors): 16 HGSCs, 15 LGSCs, and 14 SBTs

- IHC：polyclonal anti-PAX8 antibody；monoclonal anti-PAX8 antibody；ER；anti-BAP1 antibody

A :ER was performed only on cases of mesothelium (benign or malignant) that exhibited PAX8 expression,;

B :Loss of BAP1 expression was defined by complete absence of BAP1 staining in tumor cell nuclei, in the presence of an internal positive control (BAP1+ stromal or inflammatory cells).

RESULTS

- Sixteen MPMs exhibited BAP1 loss (16/25, 64%), while BAP1 was retained in all benign mesothelium and all OSTs.

TABLE 1. Frequency of PAX8 Expression Using Polyclonal PAX8 Antibody, in Reactive Mesothelium, Benign Mesothelial Tumors, and Malignant Peritoneal Mesothelioma in Men and Women

			Female			Male		
Diagnosis	N	$PAX8^+$ (n [%])	$PAX8^-$	Focal $PAX8^+$	Diffuse $PAX8^+$	$PAX8^-$	Focal $PAX8^+$	Diffuse $PAX8^+$
Reactive mesothelium	11	6 (55)	1	2	4	4	0	0
Benign multicystic mesothelioma	4	1 (25)	1	0	1	2	0	0
Well-differentiated papillary mesothelioma	10	1 (10)	3	0	1	6	0	0
Malignant peritoneal mesothelioma	27	5 (18)	11	0	3	11	2	0

Mesothelial expression of PAX8 was significantly more common in women than in men ($P=0.01$).

Across men and women, frequency of PAX8 expression in benign mesothelial lesions was not significantly different from PAX8 expression in malignant peritoneal mesothelioma ($P=0.34$).

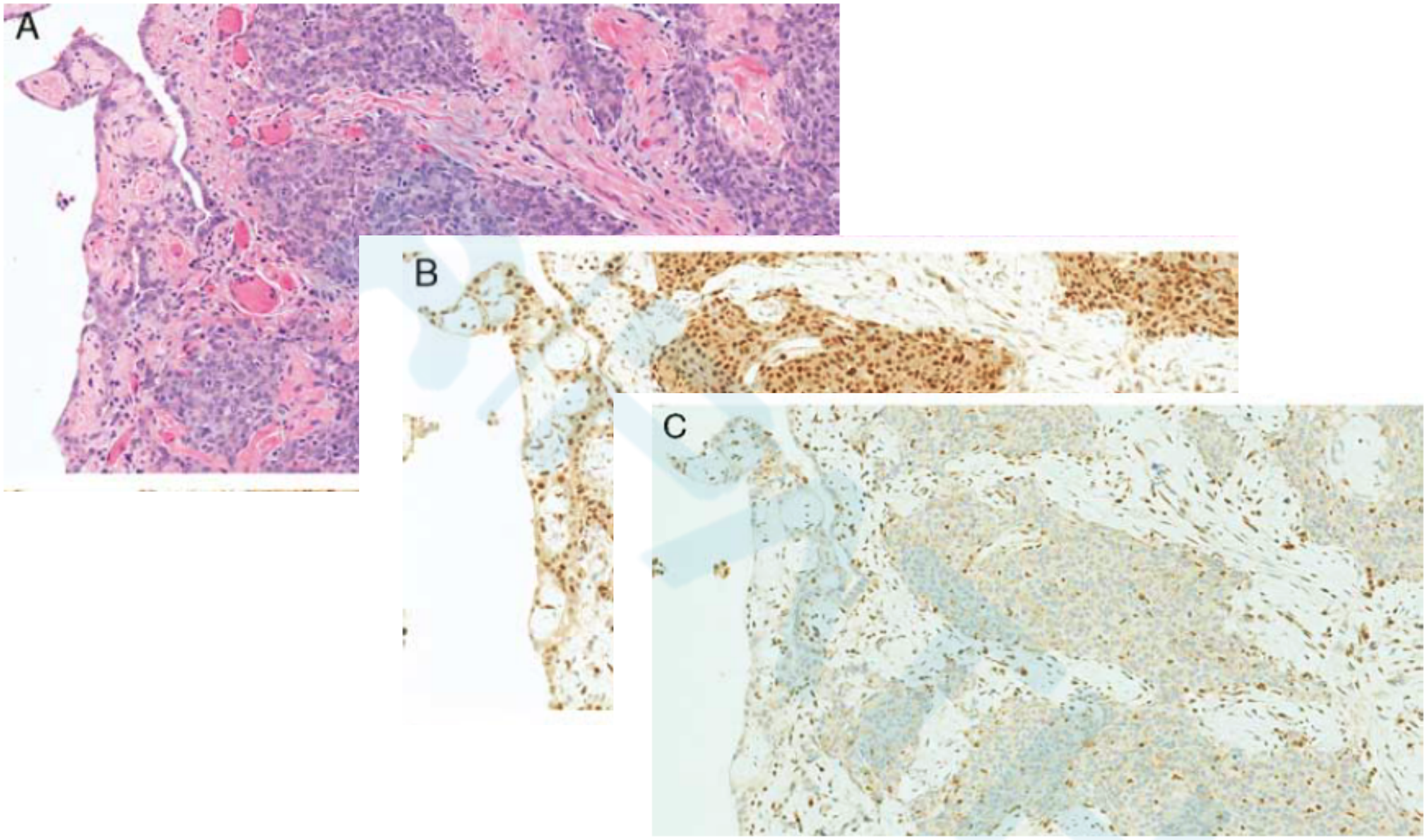


FIGURE 1. Case 1, 50-year-old woman. A, Invasive malignant peritoneal mesothelioma with stromal desmoplasia (H&E). B, Diffuse nuclear PAX8 expression by the mesothelioma cells. C, Mesothelioma cells exhibit diffuse loss of nuclear BAP1 expression. $BAP1^{+}$ stromal cells and lymphocytes provide an internal positive control.

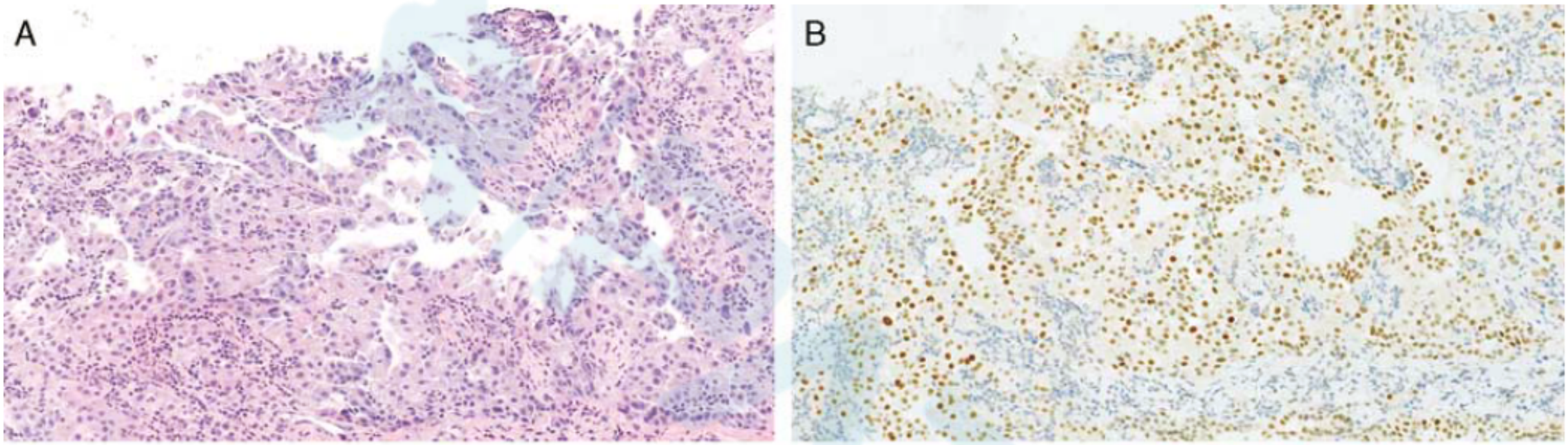
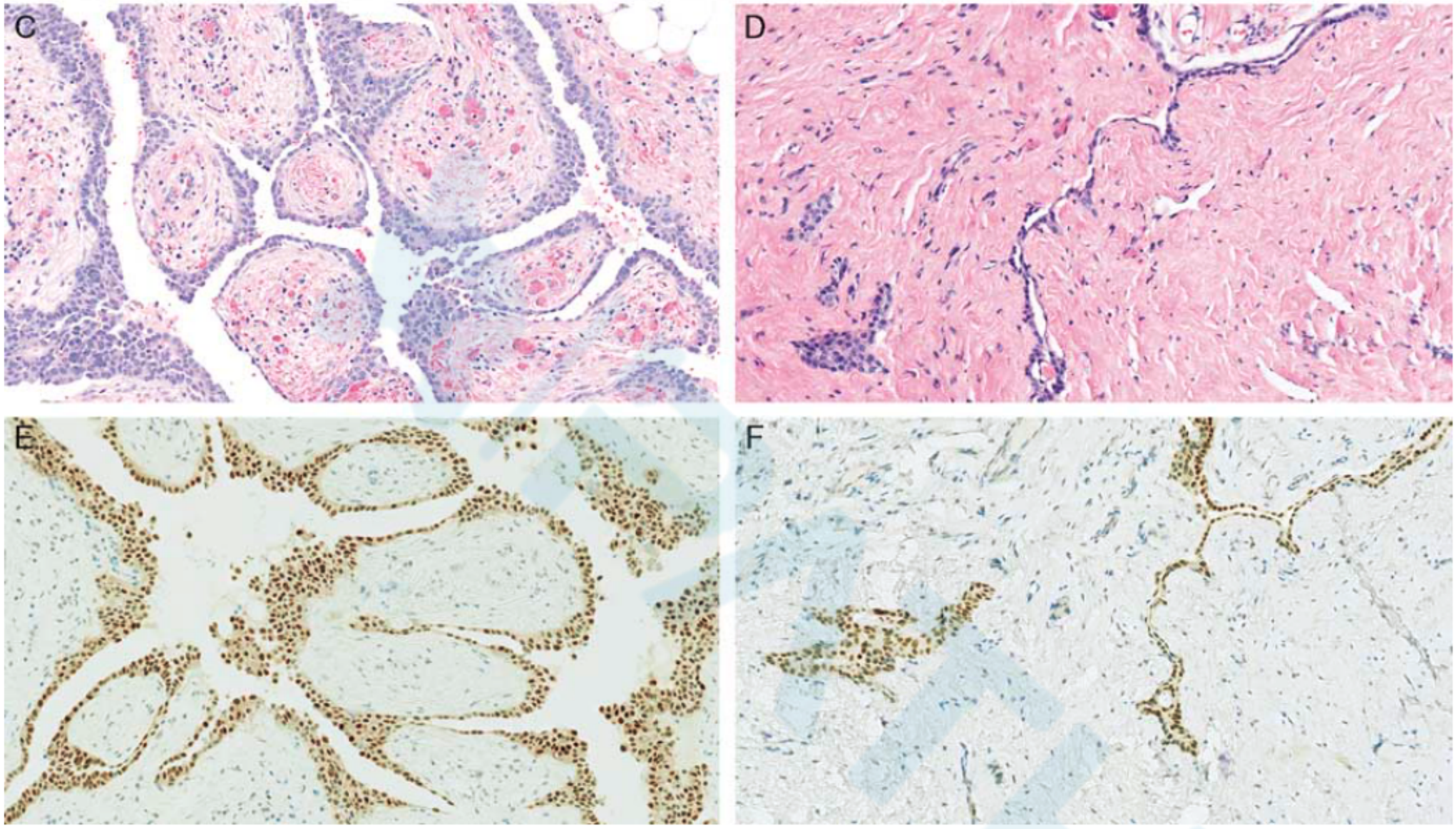


FIGURE 2. A and B, Case 2, 51-year-old woman. A, Invasive malignant mesothelioma (H&E). B, Mesothelial cells exhibit diffuse nuclear PAX8 expression.



C–F, Case 3, 35-year-old woman. C, Broad papillary cores diffusely lined by a cytologically malignant mesothelial proliferation (H&E). D, Invasive malignant peritoneal mesothelioma was present at a separate site (H&E). Both superficial (E) and invasive (F) mesothelioma cells exhibit strong nuclear PAX8 expression.

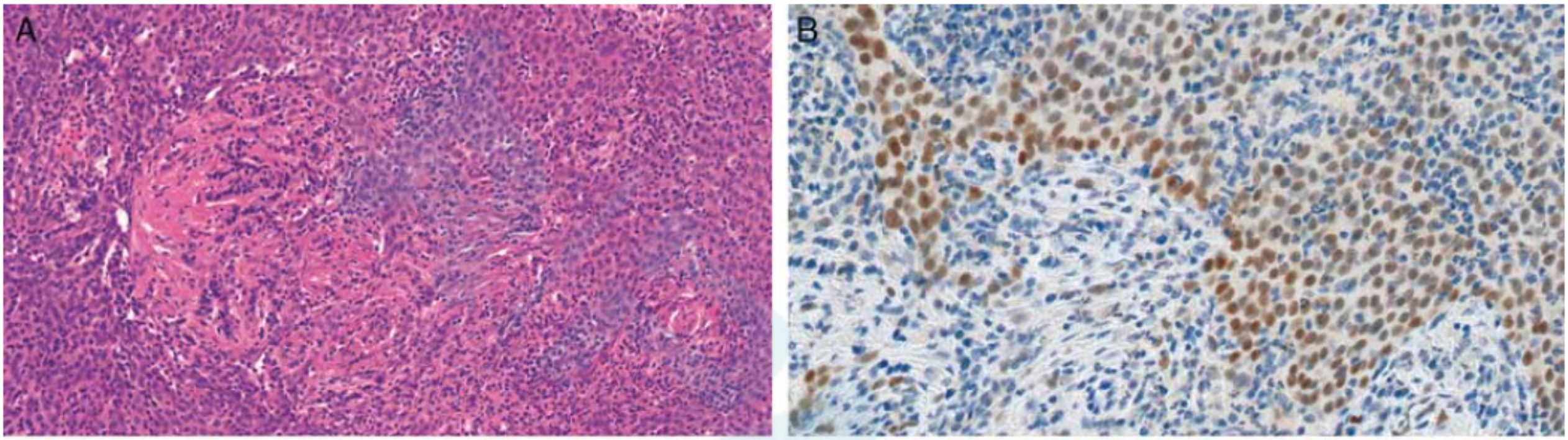
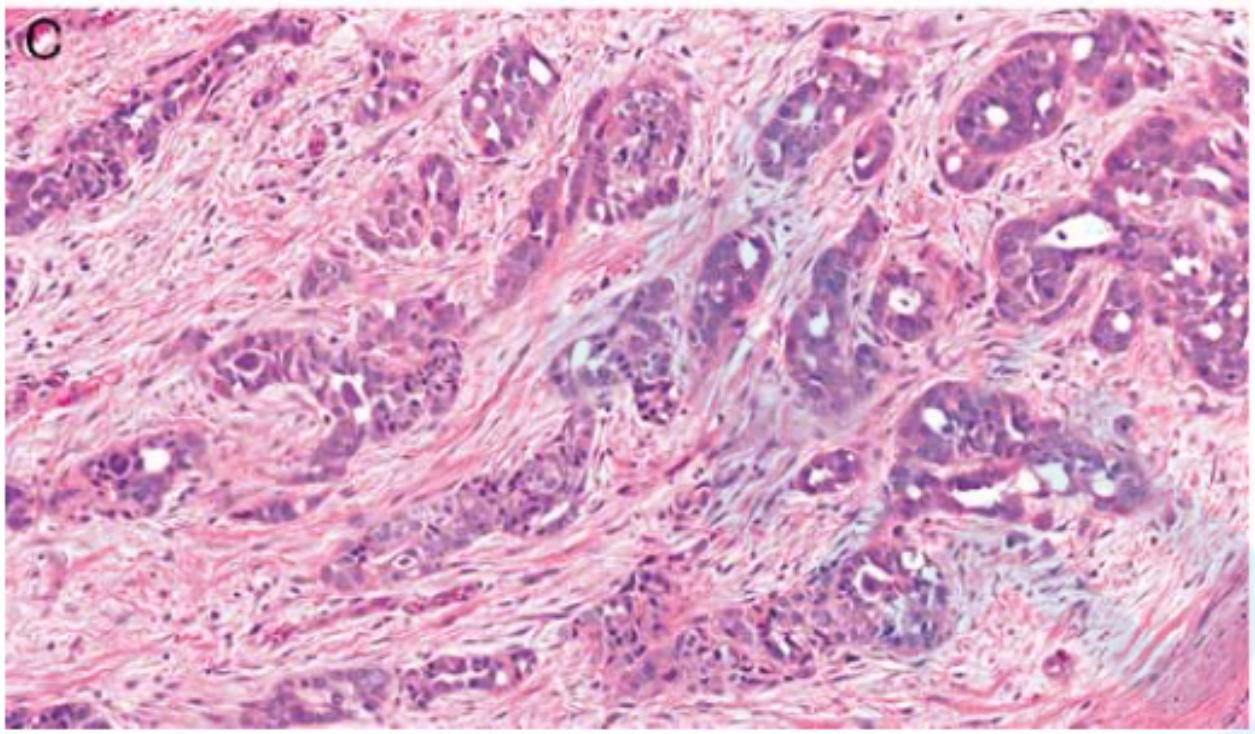
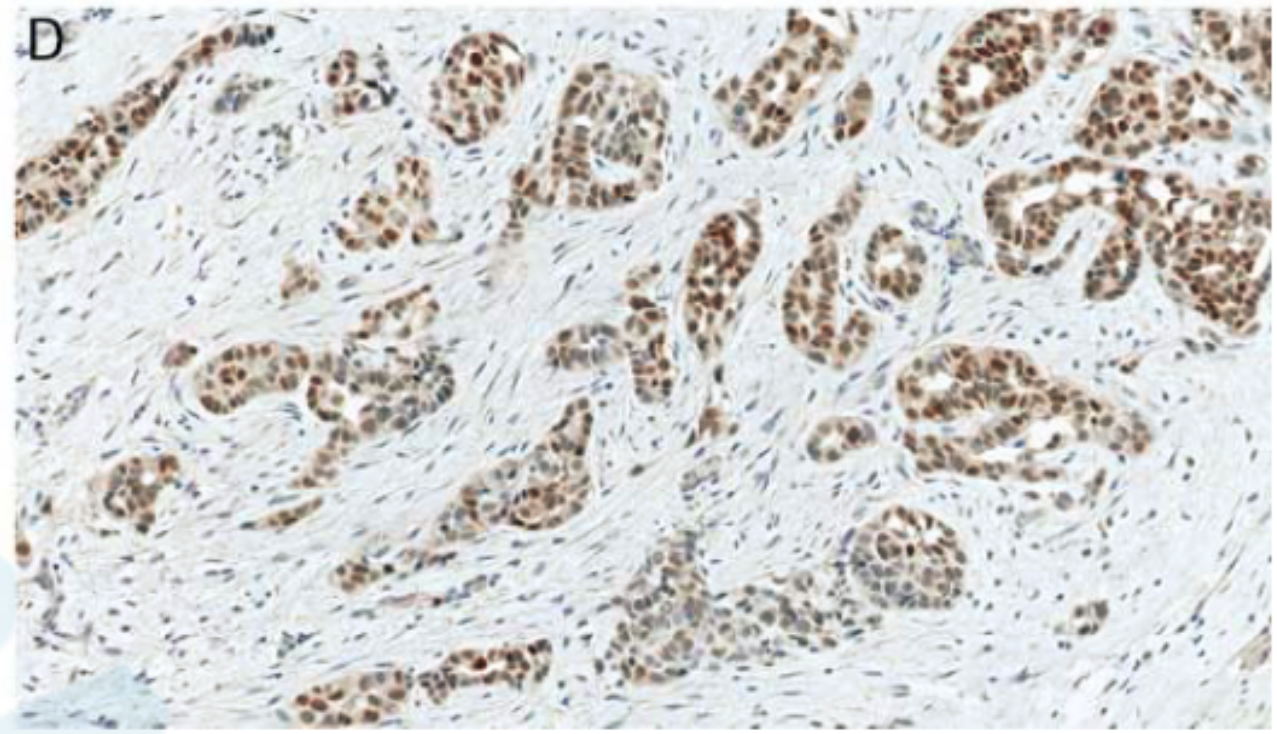


FIGURE 3. A and B, Case 4, 81-year-old man. A, Invasive malignant peritoneal mesothelioma with focal stromal hyalinization (H&E). B, Mesothelioma cells exhibit diffuse nuclear PAX8 expression. Other tumor foci showed patchy to absent nuclear PAX8.





C and D, Case 5, 70-year-old man. C, Invasive malignant peritoneal mesothelioma with stromal desmoplasia (H&E). D, Diffuse nuclear PAX8 expression in a focus of mesothelioma cells. Other tumor foci in case 5 showed complete absence of nuclear PAX8 expression.

DISCUSSION

- As PAX8 is widely accepted as a specific marker of müllerian origin, it is routinely used both to resolve the differential diagnosis of an OST versus MPM;
- This is the first study to report 5 cases of MPM with nuclear PAX8 expression, including 3 cases with diffuse nuclear PAX8;
- The difficulties stemming from PAX8 expression in mesothelial proliferations are further complicated by additional IHC overlap between MPM and OST.

- MPM could still be confidently rendered in light of diffuse positivity for WT-1, CK5/6, and calretinin, along with nuclear loss of BAP1.
- Furthermore, all cases of benign and malignant PAX8+ mesothelium in our series were negative for ER;
- Loss of nuclear BAP1 is observed in approximately one-half of pleural MM and two-thirds of MPM, but in <1% of HGSC.Furthermore, published data indicate that BAP1 expression is universally retained in benign mesothelium.

- On a technical but nonetheless important note, our study examined PAX8 expression using both monoclonal and polyclonal anti-PAX8 antibodies;

CONCLUSION

- PAX8 is not entirely specific for müllerian lesions in the differential diagnosis with peritoneal mesothelial lesions,including MPM.
- Inclusion of BAP1 in the routine IHC panel for this differential diagnosis is recommended, as loss of nuclear BAP1 is highly specific for mesothelial origin.

谢谢！