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Down-Regulation of Fructose-1, 6-Bisphosphatase-1 (FBP1) in High Grade Urothelial Carcinoma (UC); as a New Diagnostic Marker to Differentiate Nested Variants of Urothelial Carcinoma from Benign Entities

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Down-Regulation of Fructose-1, 6-Bisphosphatase-1 (FBP1) in High Grade Urothelial Carcinoma (UC); as a New Diagnostic Marker to Differentiate Nested Variants of Urothelial Carcinoma from Benign Entities.

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BACKGROUND:

Nested variants of urothelial carcinoma are characterized by deceptively bland histomorphology and aggressive clinical behavior. Previously, TERT promoter mutation has been described as specific molecular finding for Nested Variants of Urothelial Carcinoma (NVUC). But to date, no good reliable IHC markers have been discovered to differentiate benign mimickers of NVUC including Von Brunn's Nests (VBN) from NVUC. Recently, loss of FBP1 has been found to be associated with several high grade tumors and may be responsible for Warburg effect at molecular level (Nature, 513:251-5). Fructose-1, 6-bisphosphate is intermediate in glycolysis and its level is mainly controlled by upregulation of fructose-6-phosphate kinase and downregulation of FBP-1. Here, we would like to evaluate the potential role of FBP1 IHC stain to differentiate NVUC from benign entities.

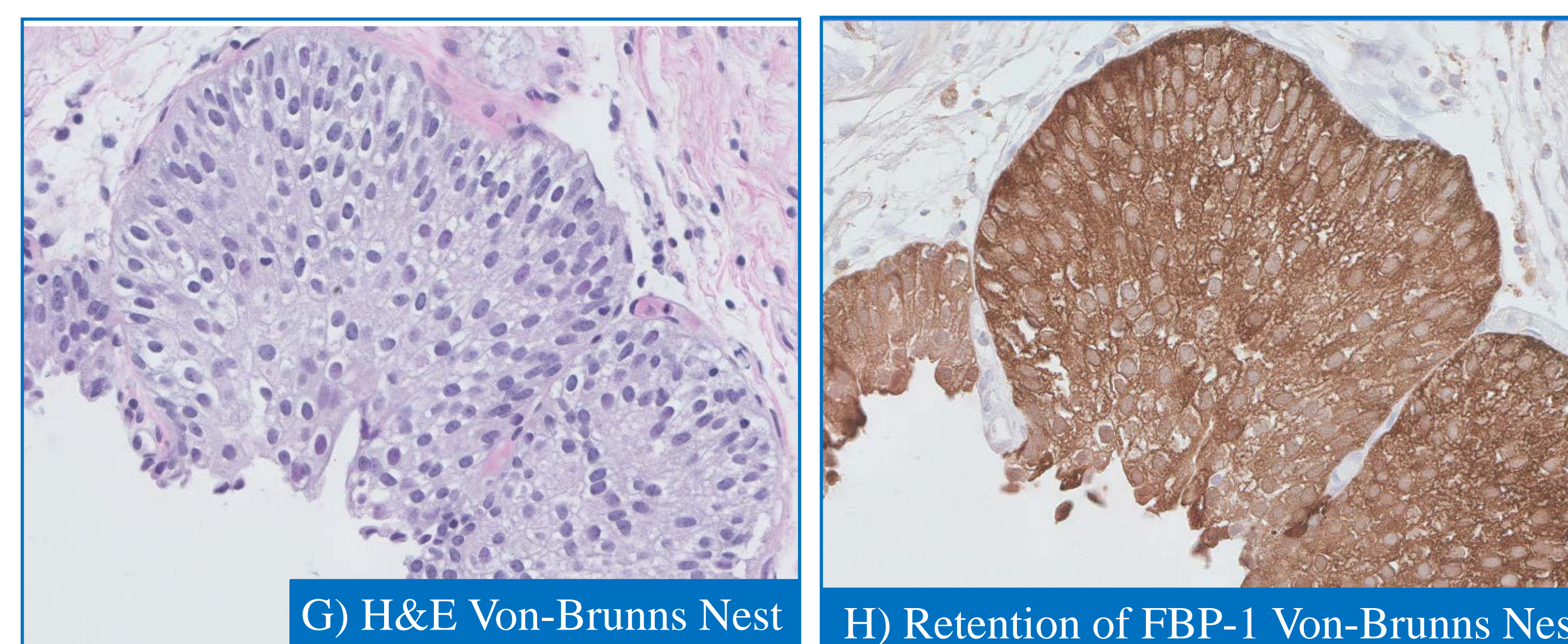
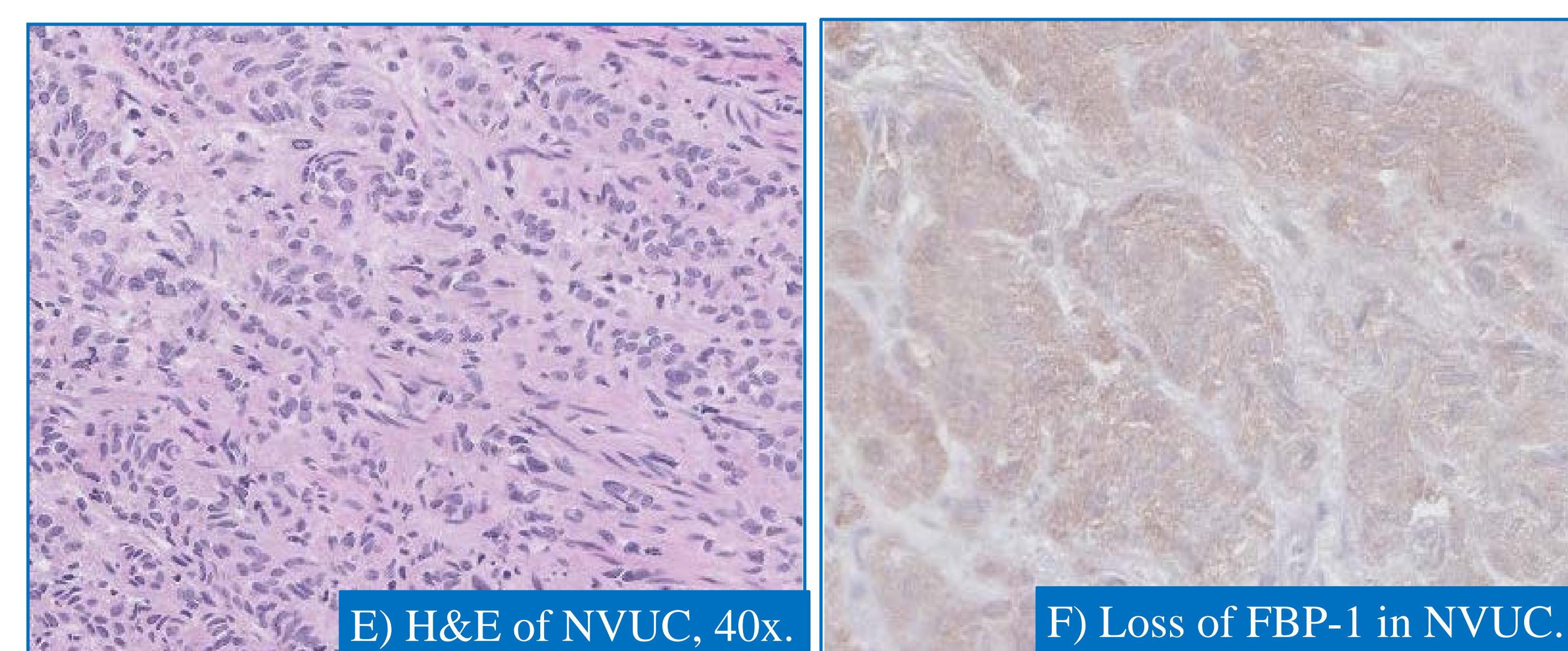
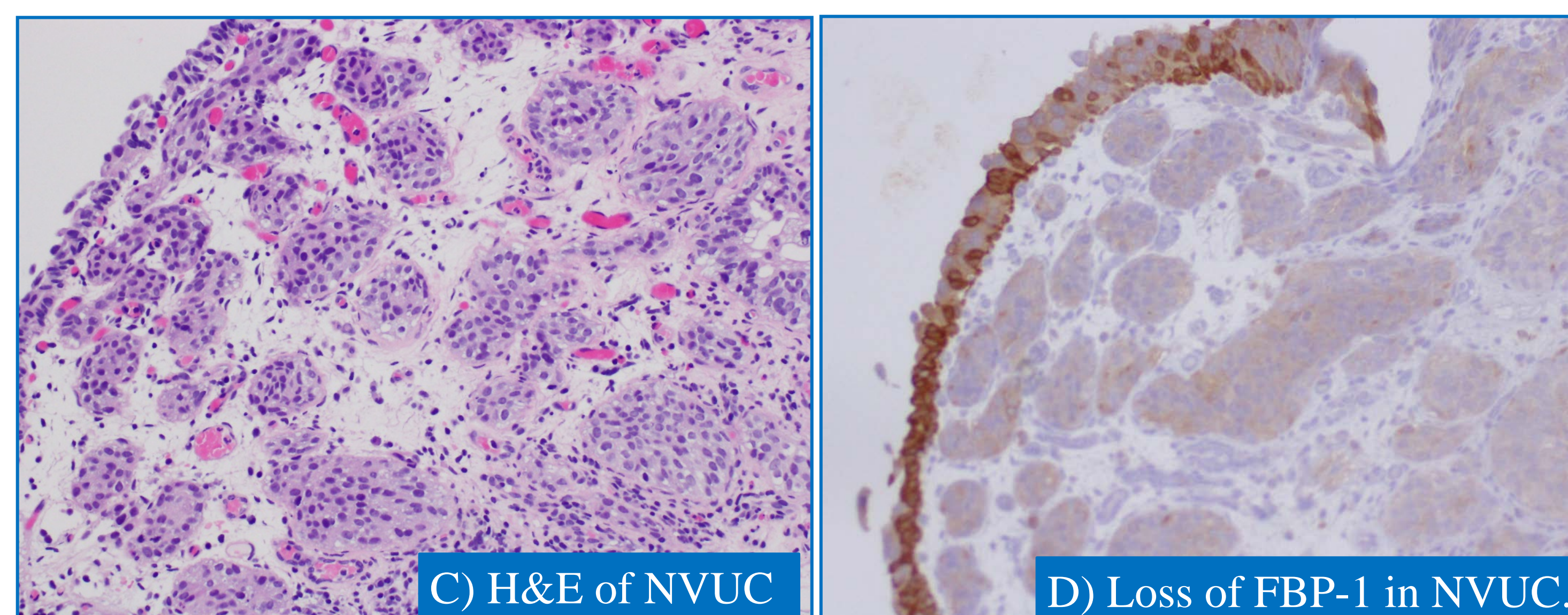
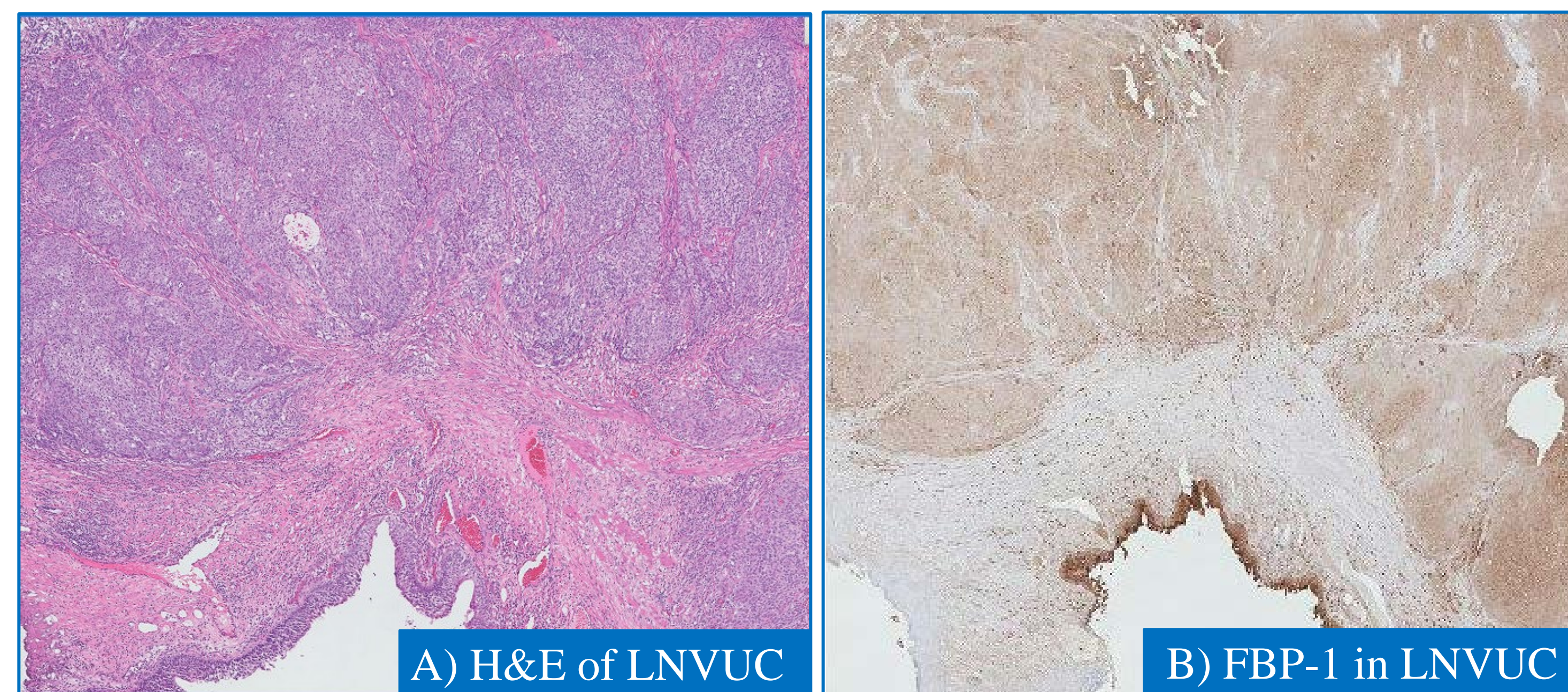
DESIGN:

Tissue microarray slides (TMA) were constructed from 141 cases of UC, including 97 high grade (HG) and 44 low-grade (LG) cases.

We also retrieved Nested (21) and Large Nested (5) variants of urothelial carcinoma from two institutes. The TMA slides and full section slides were subjected to IHC stain for FBP1 (Sigma, 1:100 dilutions). The morphology and FBP-1 staining intensity of urothelial component were carefully examined.

RESULTS:

1. Normal urothelium are strongly positive for FBP1.
2. Among 141 case of UC from TMA, 79% HG UC and 56% LG UC had decrease or loss of FBP1.



3. Decrease expression or loss of FBP-1 was noticed in 19/21 (90%) NVUC and 4/5 (80%) of LNVUC (non-neoplastic urothelium serves as an internal control).

Decrease Or loss of FBP-1 in urothelial carcinoma	79% of High grade UC	56% of LG UC
Decrease or loss of FBP-1 in NVUC	19/21 (90%) NVUC	4/5 (80%) of LNVUC

CONCLUSIONS:

- 1) Loss of FBP1 is associated with UC and especially high grade UC.
- 2) Loss of FBP-1 can be used as a diagnostic marker to differentiate NVUC from other benign entities including VBN.
- 3) Down-regulation of FBP1 may be one of the mechanisms of urothelial carcinoma to gain cancer cell proliferation and tumourigenicity. It may be potential target for novel therapy.

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