Am J Surg Pathol Volume 42, Number 11, November 2018

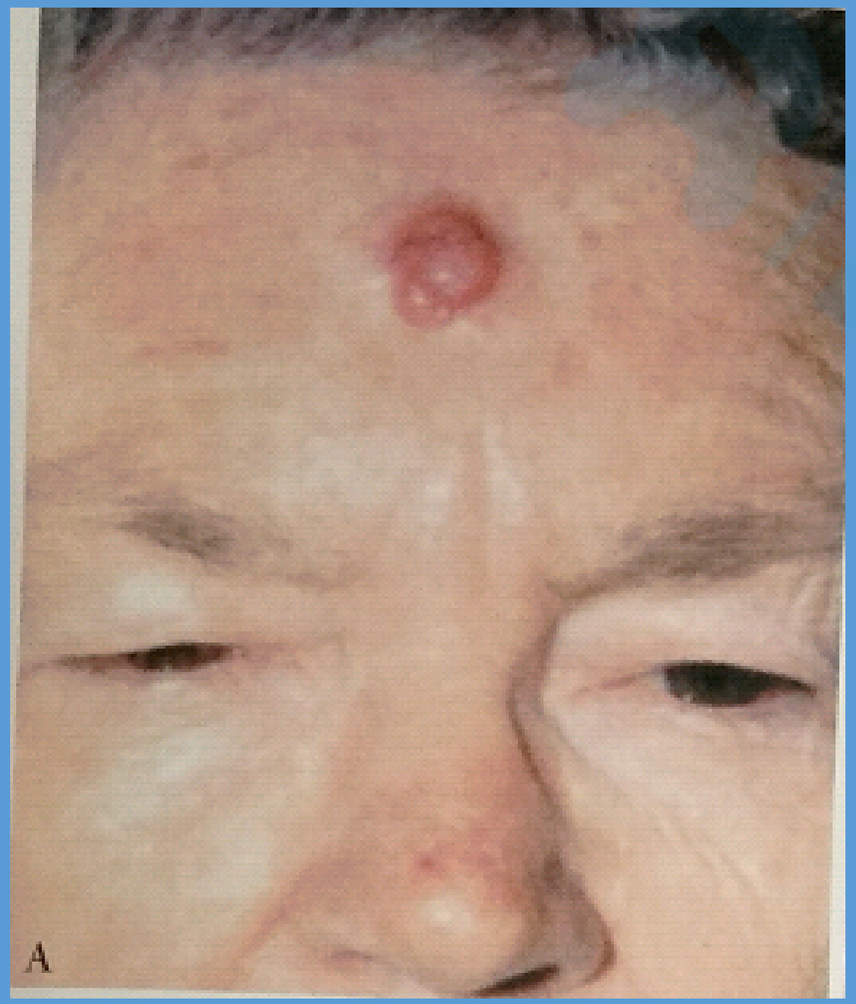
INSM1 Is More Sensitive and Interpretable than Conventional Immunohistochemical Stains Used to Diagnose Merkel Cell Carcinoma

汇报人：黎郁平
指导老师：徐红

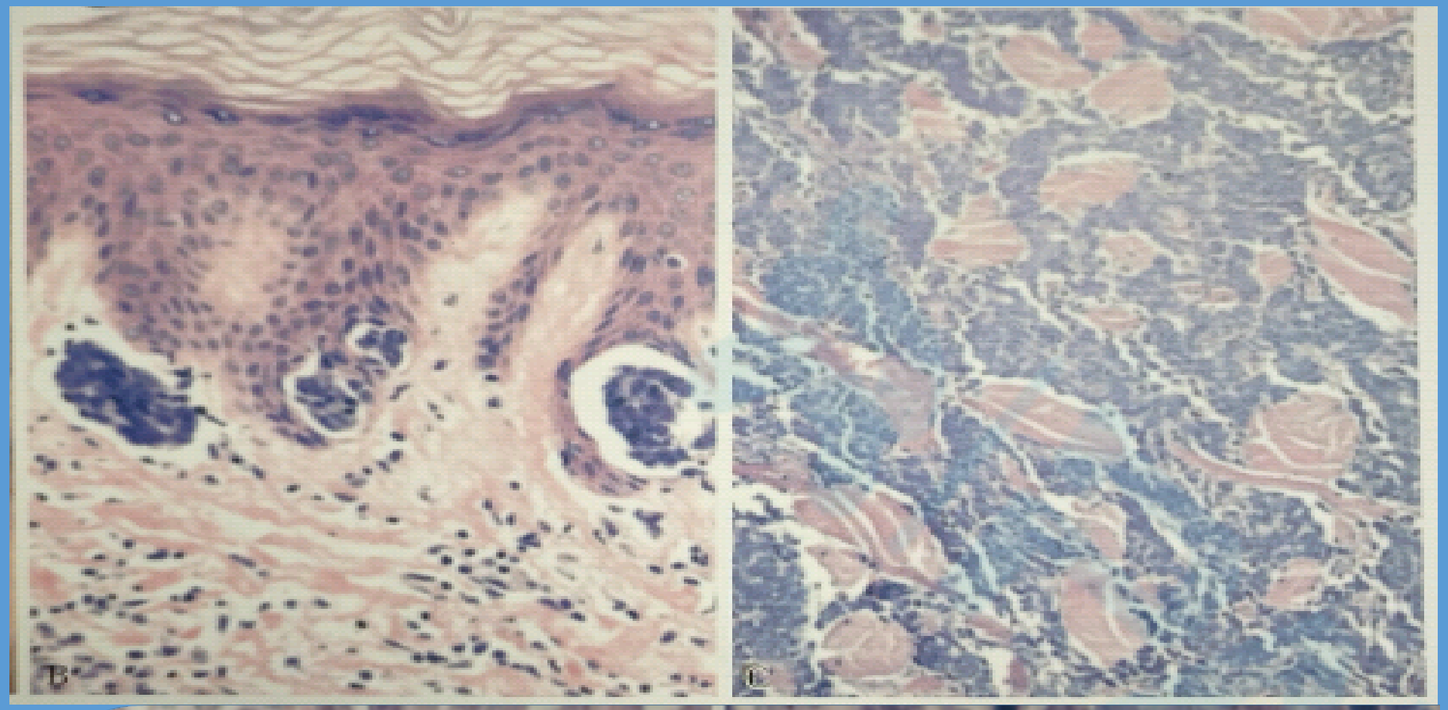
背景：

- Merkel细胞癌(MCC)是一种少见的呈上皮和神经内分泌分化的原发性皮肤肿瘤。
- ICD-O代码：8247/3。
- 发病人群及发病率：好发于老年人，男性比女性常见。近年来由于免疫抑制剂的使用和自身免疫缺陷性疾病的增加，使得MCC发病率有所增加。
- 发病部位：日光照射部位皮肤(常位于头颈部及四肢) 。
- 预后：Merkel细胞癌局部复发率、区域淋巴结转移率以及最终发生的血管和淋巴道转移率都很高。

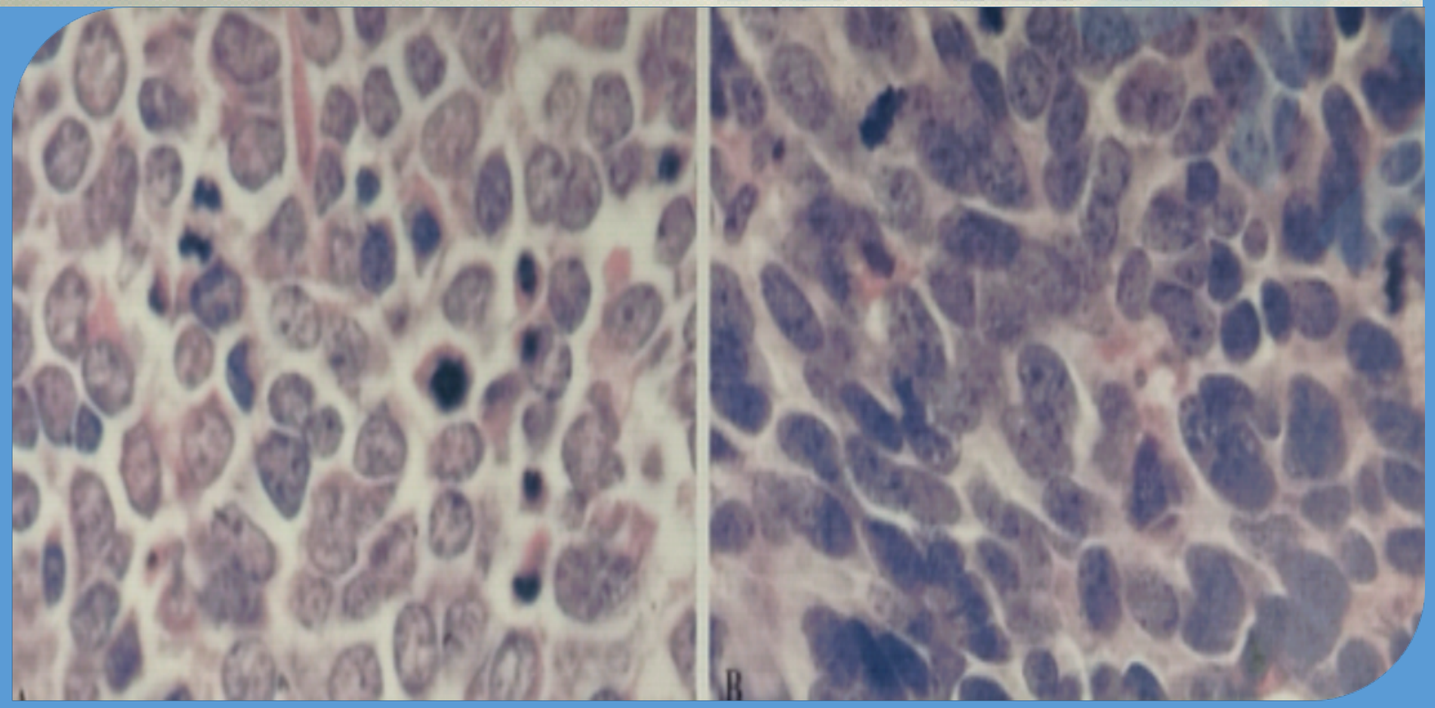
背景：



大多数肿瘤为孤立性病变，表现为无痛性、半球形结节或硬结样斑块，为红色、紫色或肉色，有时形成溃疡。一般在数周或数月内快速生长，大多数病变直径小于2cm。

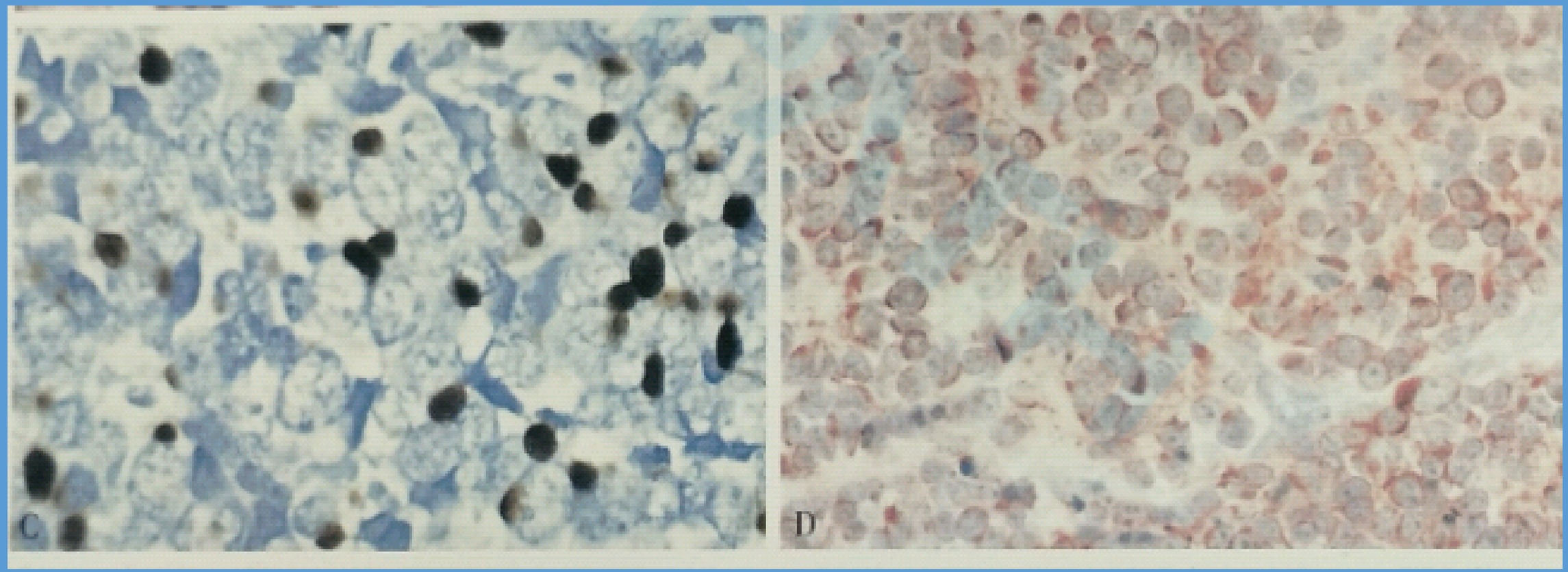


肿瘤细胞呈梁状、片状或巢状分布。



细胞大小一致、核呈圆形或卵圆形、胞浆很少，染色质细腻，核仁一般不明显。

肿瘤细胞表达低分子量CK、EMA和上皮标记BER-EP4，神经内分泌标记Syn、CgA、NES，生长抑素、降钙素、胃泌素等，CK20是Merkel细胞癌的敏感而相对特异的标记。



背景：

MCC有2个病因不同的亚型：

Merkel细胞多瘤病毒（MCPyV）阳性亚型：可以通过商业上可用的抗体诊断。

Merkel细胞多瘤病毒（MCPyV）阴性亚型：占MCC的20%，呈现胞嘧啶＞苏氨酸转变的UV模式，形态学上常和鳞癌并存。

两个亚群均显示Rb失调，并通过不同的机制灭活P53突变，MCPyV阴性亚型的疾病进展和死亡率风险更高。

胰岛素瘤相关蛋白1 (INSM1):

- 是一类转录调节蛋白，由锌指转录因子和促激素结构域组成。INSM1在胚胎发生过程中作为转录抑制因子，它调节细胞进入细胞周期并促进终末内分泌和神经内分泌分化。它主要负责突触素和嗜铬素的转录。
- 作为免疫组化染色，它在胰腺神经内分泌肿瘤、胸部、妇科及头颈部起源的神经内分泌肿瘤的诊断中显示出良好的应用前景。
- INSM1不能区分内分泌和神经内分泌肿瘤。
- 然而，根据其在其他器官中的表现，作者研究了它在鉴别MCC与皮肤肿瘤中的作用，以及它在检测MCC前哨淋巴结微转移中的作用。

材料和方法

- 作者对过去15年文献的全面回顾，选取56例标本(47例皮肤原发性MCC和9例MCC淋巴结转移)，其中2例为MCC合并鳞状细胞癌。
- 作者另外选取了50例皮肤肿瘤活检对照包括15例(BCC)、10例(PdCC)、 5例（SCCIS）、 5例皮肤(BCL)、 10例(MM)和5例(SN)及28例转移到淋巴结的非MCC肿瘤包括4例转移(PdCC)，8例转移性腺癌，3例转移(MM)，8例原发(LCL),2例转移性肺小细胞癌和1例转移性小肠类癌作为对照。

材料和方法：

- 本研究中所用到的免疫组化抗体有:INSM1（A-8)、Syn、CHR(CgA)、CK20。
- 设定了免疫组化的评判标准：肿瘤细胞的染色百分率以四分位数计（0，＜25%，25%~50%，50%~75%，＞75%），染色强度按（弱，中，强）。

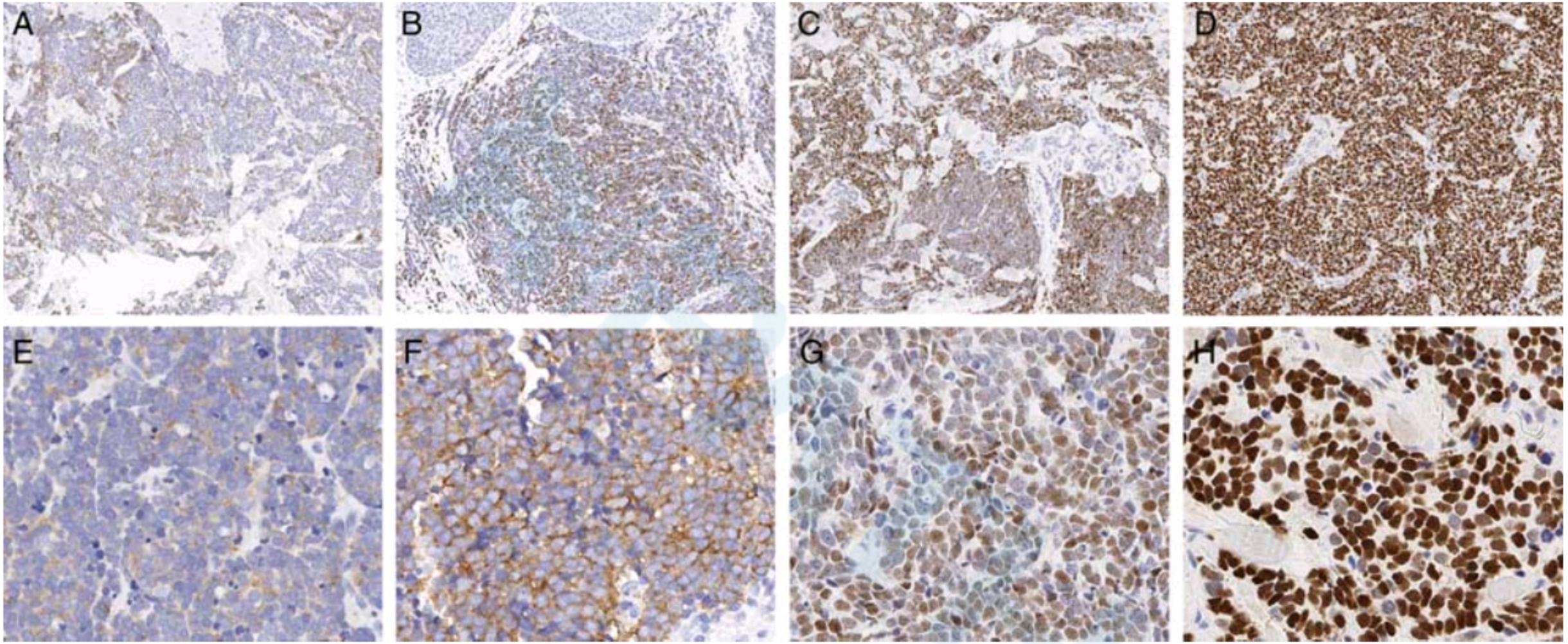


FIGURE 1. Criteria for the evaluation of lesions with immunohistochemistry. Percent of tumor cell staining was interpreted in quartiles: <25% (A, SYN), 25% to 50% (B, SYN), 50% to 75% (C, INSM1), and >75% (D, INSM1). Staining intensity was interpreted as weak (E, SYN), moderate (F, SYN and G, INSM1), and strong (H, INSM1).

TABLE 1. Comparison of INSM1 Staining in MCC and Control Cases in Skin and Lymph Node

Tissue	Neoplasm	No. Cases	
		INSM1$^+$	INSM1$^-$
Skin	Merkel cell carcinoma	47	0
Skin	Poorly differentiated squamous cell carcinoma	0	10
Skin	Diffuse large B-cell lymphoma	0	5
Skin	Sebaceous neoplasms	0	5
Skin	Basal cell carcinoma	0	15
Skin	Bowen disease	0	5
Skin	Melanoma	0	10
Lymph node	Merkel cell carcinoma	9	0
Lymph node	Poorly differentiated squamous cell carcinoma	0	4
Lymph node	Adenocarcinoma, gallbladder	0	1
Lymph node	Adenocarcinoma, esophageal	0	1
Lymph node	Adenocarcinoma, lung	0	1
Lymph node	Adenocarcinoma, lung	0	1
Lymph node	Adenocarcinoma, gastric	0	1
Lymph node	Adenocarcinoma, pancreatic	0	1
Lymph node	Adenocarcinoma, endocervical	0	1
Lymph node	Prostatic carcinoma	0	1
Lymph node	Melanoma	0	3
Lymph node	Diffuse large B-cell lymphoma	0	2
Lymph node	Follicular lymphoma	0	2
Lymph node	Classic Hodgkin lymphoma	0	1
Lymph node	Angioimmunoblastic T-cell lymphoma	0	1
Lymph node	Marginal zone lymphoma	0	1
Lymph node	Small lymphocytic lymphoma	0	1
Lymph node	Carcinoid, small bowel	1	0
Lymph node	Small cell carcinoma, lung	2	0
Lymph node	Pancreatic neuroendocrine tumor	2	0

TABLE 2. Evaluation of INSM1 Signal Strength and Robustness

	INSM1				
	None	**Weak**	**Moderate**	**Strong**	**Total**
(A) CK20					
None	0	0	0	0	0
Weak	0	0	0	0	0
Moderate	0	0	6	1	7
Strong	4	3	14	19	40
Total	4	3	20	20	47
(B) Chromogranin					
None	0	0	0	0	0
Weak	0	0	0	0	0
Moderate	6	1	0	0	7
Strong	26	8	5	1	40
Total	32	9	5	1	47
(C) Synaptophysin					
None	0	0	0	0	0
Weak	0	0	0	0	0
Moderate	0	3	2	2	7
Strong	2	11	17	10	40
Total	2	14	19	12	47

	χ^2 statistics	Raw *P*	Bonferroni *P*
(D) Summary			
CK20 (A)	18.3	3.88e−04	1.16e−03
CHR (B)	43.3	2.10e−09	6.31e−09
SYN (C)	26.5	7.37e−06	2.21e−05

(A–C) Four-way contingency table used for separate Stuart-Maxwell tests. (D) Summary of all statistical comparisons with INSM1.

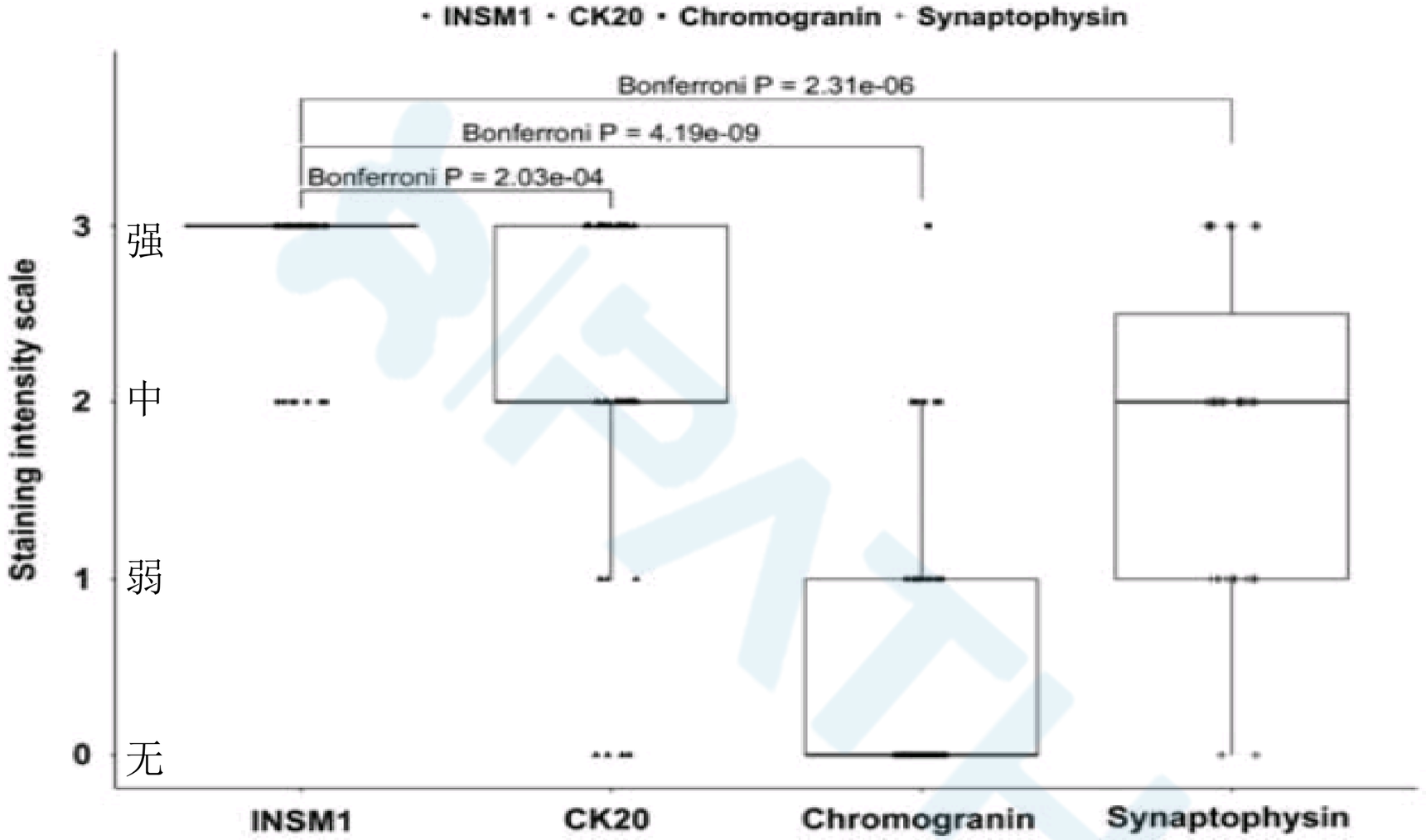


FIGURE 2. Comparison of staining intensity INSM1 with other biomarkers. Each comparison was made by a 2-sided, paired Wilcoxon test. Multiple testing was corrected by the Bonferroni method.

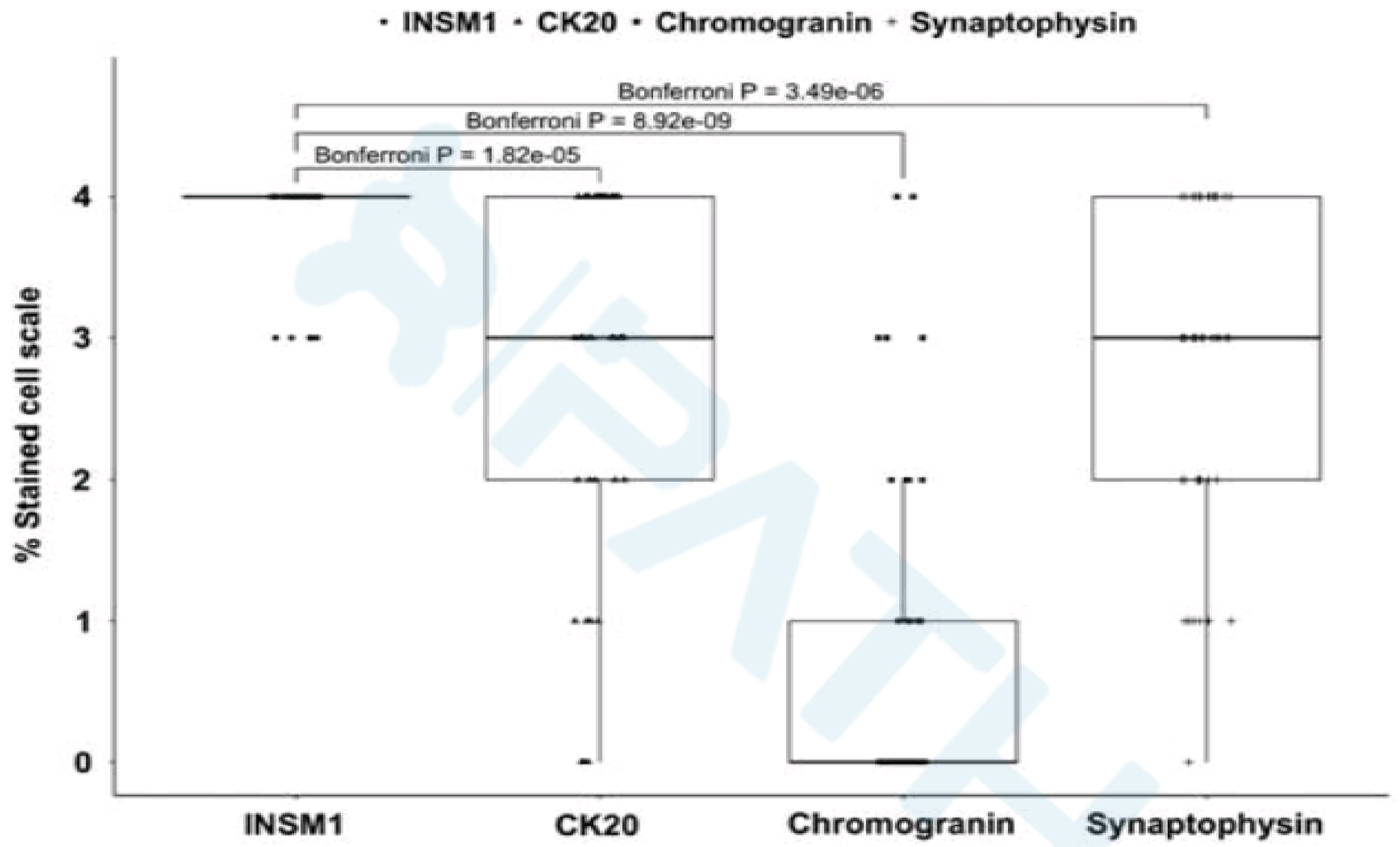


FIGURE 3. Comparison of percent stained cells of INSM1 with other biomarkers. Each comparison was made by a 2-sided, paired Wilcoxon test. Multiple testing was corrected by the Bonferroni method.

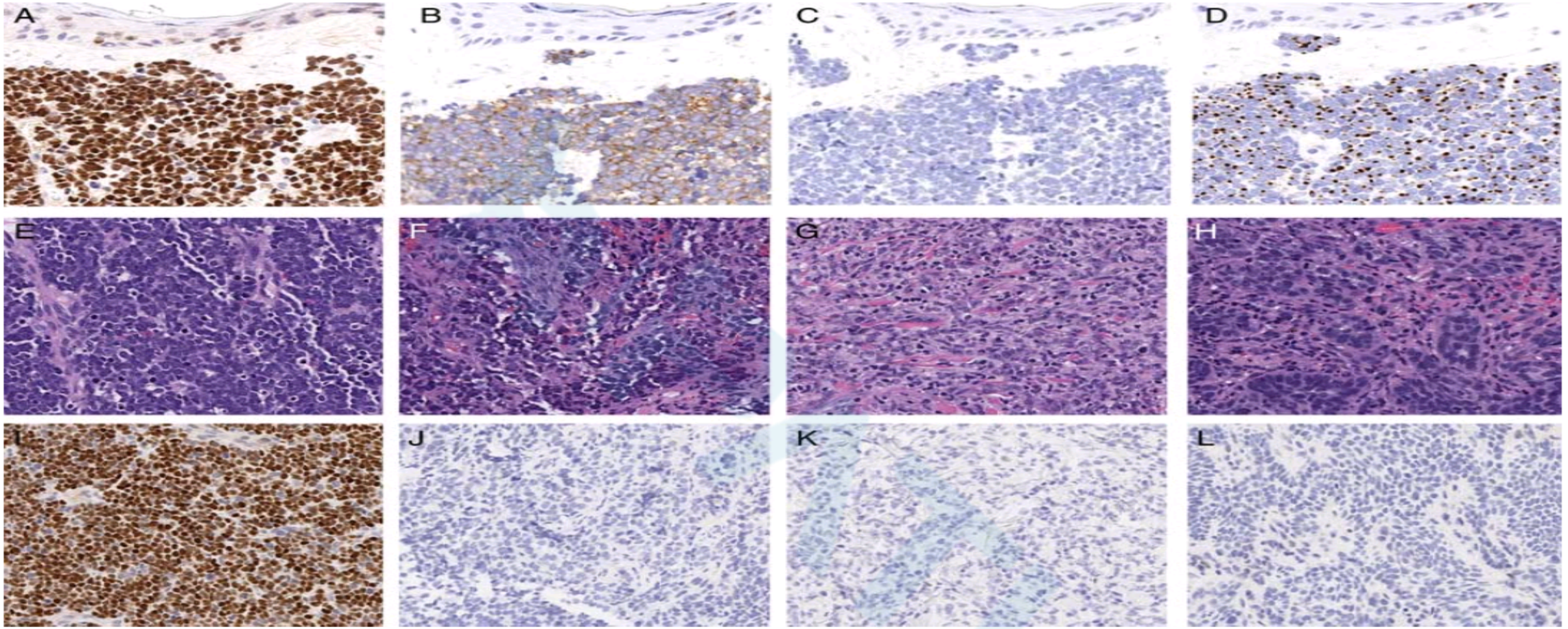


FIGURE 4. INSM1 stains the nuclei of neuroendocrine neoplasms and has a greater sensitivity than conventional markers. Immunohistochemistry in a representative case of Merkel cell carcinoma shows strong INSM1 staining in >75% of lesional nuclei (A). Synaptophysin demonstrates moderate cytoplasmic staining in a similar distribution of cells (B) and chromogranin is negative in the portion of the carcinoma present for evaluation (C). In this example, CK20 shows strong dotlike expression in >75% of lesional nuclei (D). Strong INSM1 nuclear expression can help distinguish Merkel cell carcinoma (E, H&E) from other cutaneous basaloid cutaneous neoplasms that sometimes share a striking resemblance. The differential diagnosis includes melanoma (F, H&E), diffuse large-B cell lymphoma (G, H&E), basal cell carcinoma (H, H&E), sebaceoma, sebaceous carcinoma, poorly differentiated squamous cell carcinoma, and Bowen disease. INSM1 immunohistochemistry helps distinguishes these neoplasms from one another: Merkel cell carcinoma (I), melanoma (J), diffuse large-B cell lymphoma (K), and basal cell carcinoma (L).

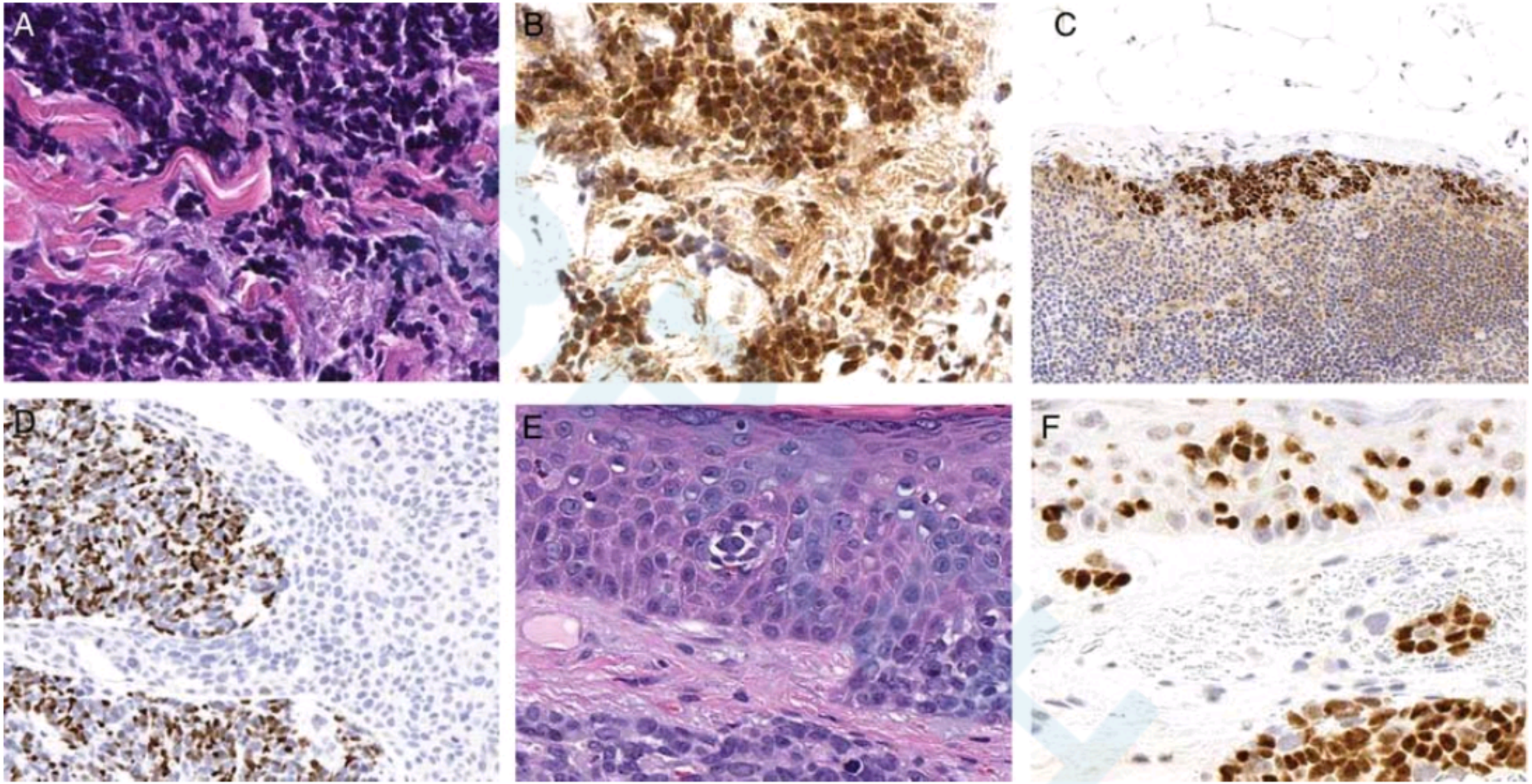


FIGURE 5. Practical applications of INSM1 immunohistochemistry. Establishing a diagnosis of neuroendocrine carcinoma (in this case Merkel cell carcinoma) on a core needle specimen obscured by crush artifact (A) is greatly aided by INSM1 immunohistochemistry (B, INSM1). INSM1 can also identify small sentinel lymph node micrometastases (C), highlight the neuroendocrine component of a cutaneous squamous and neuroendocrine carcinoma (D) and help identify Merkel cell carcinomas that exhibit unusual patterns such as intraepidermal pagetoid spread (E, H&E and F, INSM1).

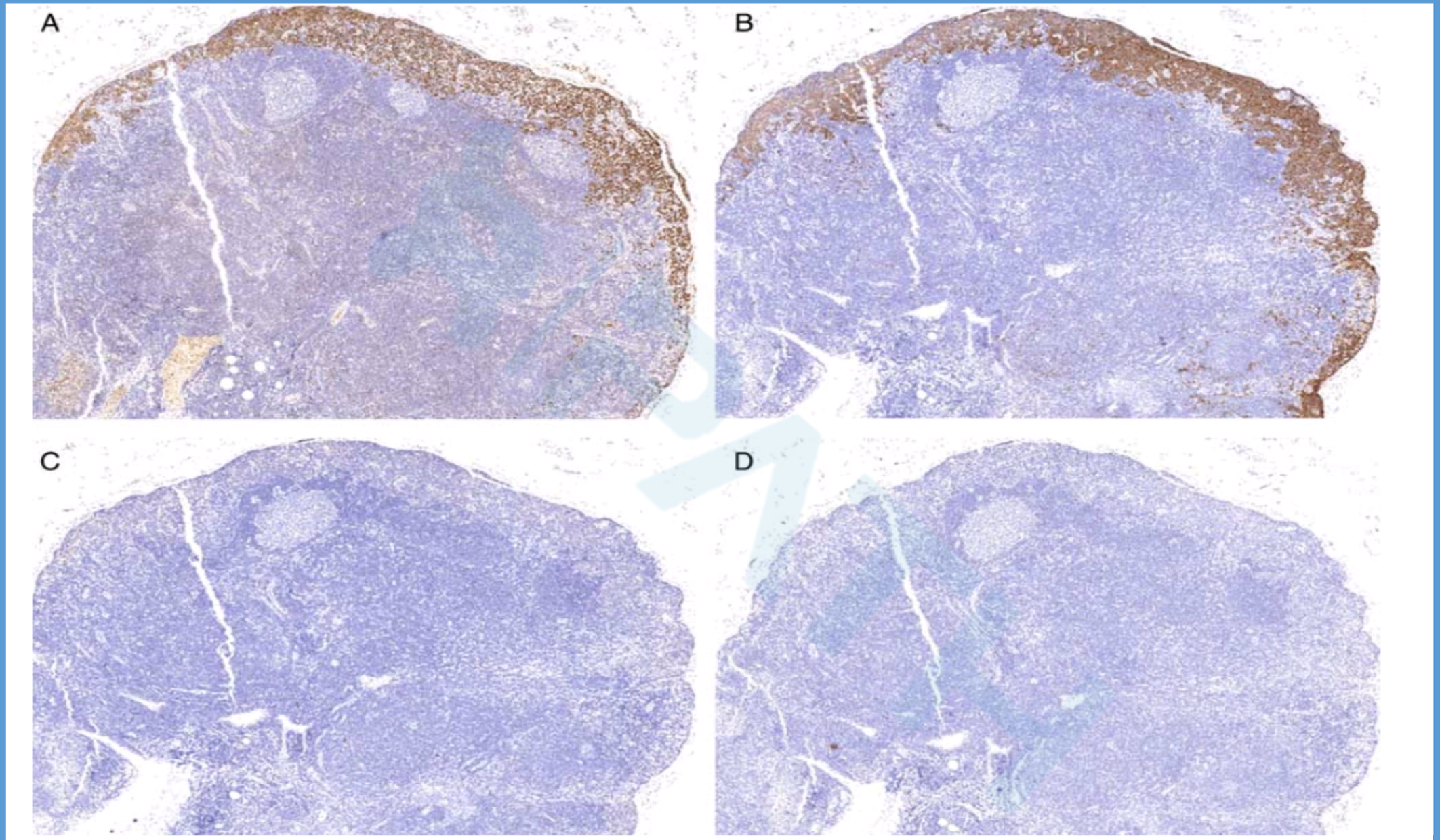


FIGURE 6. Comparison of conventional markers in identifying metastatic Merkel cell carcinoma in a sentinel lymph node. INSM1 (A), CK20 (B), synaptophysin (C), and chromogranin (D).

讨论：

INSM1在MCC中100%表达，通常呈弥漫强阳性，因其清晰的核着色，更易显示出常规切片中很容易忽略的淋巴结受累的微小病灶，淋巴血管侵犯、表皮内派杰样扩散。

讨论：

在我们的队列病例中，INSM1对MCC的敏感性比Syn、Cga和CK20单独或联合使用时更高，其均匀的表达及清晰的核染色更有利于MCC和原发性皮肤肿瘤之间的鉴别。然而,它不能区分MCC和由皮肤外来源的转移性神经内分泌癌。

总结：

综上所述，INSM1的核表达在神经内分泌肿瘤具有广泛的应用前景。在与CK20、Syn、CgA常规标记物相比，对MCC的诊断敏感性更高，染色强度更强，更有助于检测被挤压变形的核芯针活检标本，前哨淋巴结、表皮内受累和淋巴血管浸润情况。

再次强调的是INSM1在皮肤外来源的内分泌和神经内分泌癌转移灶中也表达，因此，它不能区分MCC和此类转移肿瘤。

Thank you !

謝謝！