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Original Contribution

# A new immunohistochemical marker, insulinoma-associated protein 1 (INSM1), for Merkel cell carcinoma: Evaluation of 24 cases☆

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ABSTRACT

Merkel cell carcinoma (MCC) is an uncommon primary neuroendocrine carcinoma of the skin. Nowadays, pathologists are required to perform immunohistochemistry to demonstrate neuroendocrine and epithelial differentiation for diagnosis of MCC. Insulinoma-associated protein 1 (INSM1) is a zinc-finger transcription factor expressed in tissues undergoing terminal neuroendocrine differentiation, and INSM1 immunohistochemistry is a well-validated nuclear marker of neuroendocrine differentiation. We evaluated 24 cases of MCC for the expression of INSM1 and compared it with frequently used neuroendocrine markers, Chromogranin A, Synaptophysin, and CD56. INSM1 was positive in all cases, and its expression was stronger, more extensive, clean and homogeneous compared to other markers. As a consequence, INSM1 can be used to serve as a solitary marker for neuroendocrine differentiation due to high sensitivity and specificity in MCC cases.

## 1. Introduction

Neuroendocrine carcinoma of the skin, also called as Merkel cell carcinoma (MCC), is a rare but extremely aggressive tumor [1]. The most common sites affected are head and neck (50%), and extremities (40%) of older adults. Primary tumors of the trunk (10%) are uncommon [2]. The clinical presentation is non-specific and variable, but mostly encountered as an erythematous or violaceous nodule on sun-exposed areas [1]. Recurrences, nodal and distant metastases are common, and the overall five-year survival rates are approximately 51% for local disease, 35% for nodal disease, and 14% for metastatic disease [3]. The incidence of MCC has steadily increased over the past thirty years due to increase in number of immunosuppressed population that encompasses patients infected with the human immunodeficiency virus and solid organ transplant recipients [1].

MCC, which was originally called as trabecular carcinoma [4] due to its frequent architectural pattern, is a tumor composed of small blue round cells. Therefore, the spectrum of differential diagnosis is wide. It must be distinguished from melanoma, nodular hematopoietic tumors, basal cell carcinoma, atypical variants of squamous cell carcinoma, and metastatic neuroendocrine neoplasms. Nowadays, pathologists are required to perform immunohistochemistry to demonstrate neuroendocrine and epithelial differentiation for diagnosis of MCC. Neuroendocrine differentiation has been traditionally confirmed with one or more immunohistochemical markers, including chromogranin A (CHR), synaptophysin (SYN), CD56, or neuron-specific enolase, and epithelial differentiation with expression of cytokeratin 20 (CK20), AE1/AE3, or CAM5.2 [1].

Insulinoma-associated protein 1 (INSM1), encoded by the gene INSM1, is a zinc-finger transcriptional factor expressed in tissues undergoing terminal neuroendocrine differentiation. It is originally isolated from pancreatic insulinoma and glucagonoma samples. INSM1 functions as a transcriptional repressor that regulates entry into the cell cycle, binds to cyclin D1, directly arrests proceeding, and mediates the

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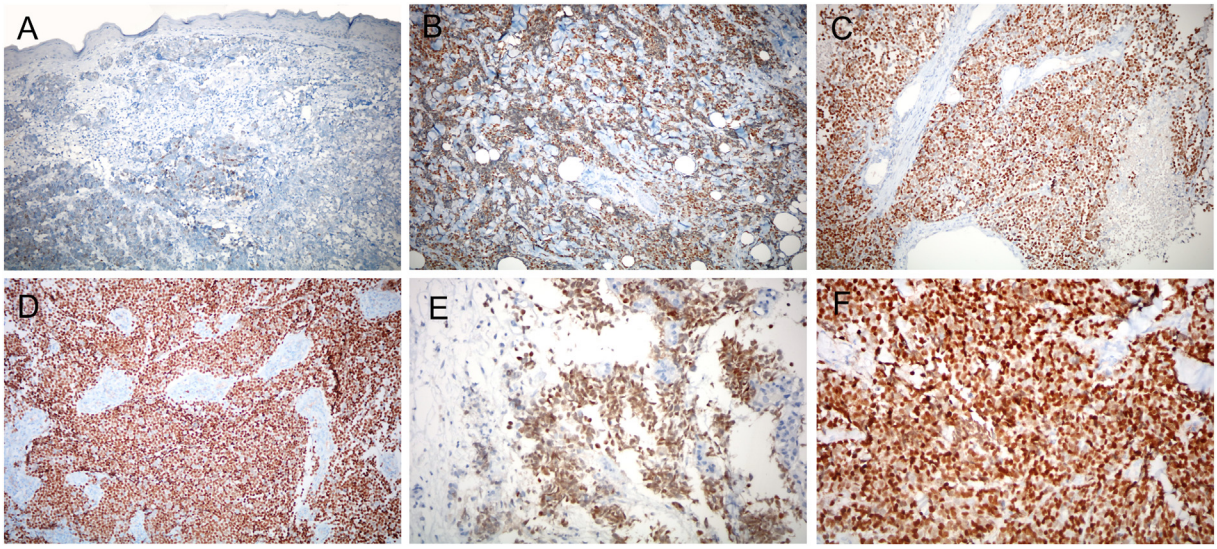


**Fig. 1.** Criteria for the assessment of immunohistochemical expression. The extent of staining of INSM1 are shown in A (< 25% of the cells, score 1), B (25–50% of the cells, score 2), C (50–75% of the cells, score 3), and D (75–100% of the cells, score 4). Staining intensity was evaluated as moderate (E, INSM1; score 2), and strong (F, INSM1; score 3). The images are at ×100 magnification (A, B, C, D) and ×200 magnification (E, F).

**Table 1**
Clinicopathological findings of the cases in this study.

| Case | Age (years) | Sex | Tumor site | Tumor size (greatest dimension) | Maximum tumor thickness | Subcutaneous invasion of tumor | Lymphovascular invasion |
|---|---|---|---|---|---|---|---|
| 1 | 80 | F | Sacral region | 2 cm | 24 mm | Present | No |
| 2 | 58 | F | Left elbow | 0.9 cm | 10 mm | Present | No |
| 3 | 87 | F | Right cheek | 1.8 cm | 14 mm | Present | No |
| 4 | 73 | M | Right arm | 3.8 cm | 22 mm | Present | No |
| 5 | 51 | M | Gluteal region | 6 cm | 30 mm | Present | No |
| 6 | 54 | M | Lumbar region | 3 cm | 25 mm | Present | Present |
| 7 | 65 | F | Left thigh | 1.4 cm | 20 mm | Present | No |
| 8 | 64 | F | Face | 3 cm | 25 mm | Present | Present |
| 9 | 52 | F | Left forearm | 4.5 cm | 25 mm | Present | Present |
| 10 | 75 | M | Right lateral nose | 1.3 cm | 8 mm | No | Present |
| 11 | 80 | M | Right frontal region | 2.5 cm | 21 mm | Present | Present |
| 12 | 62 | F | Right arm | 4.2 cm | 19 mm | Present | No |
| 13 | 49 | F | Right leg | Not known[a] | Not known[a] | Present | No |
| 14 | 70 | M | Above the upper lip | 3 cm | 20 mm | No | No |
| 15 | 69 | M | Right arm | 6 cm | 35 mm | Present | Present |
| 16 | 80 | M | Gluteal region | Not known[a] | Not known[a] | Present | No |
| 17 | 73 | F | Right thigh | 4.2 cm | 31 mm | Present | No |
| 18 | 79 | M | Gluteal region | Not known[a] | Not known[a] | No | No |
| 19 | 44 | F | Right arm | 10.5 cm | 42 mm | Present | No |
| 20 | 66 | M | Gluteal region | 5.2 cm | 29 mm | Present | No |
| 21 | 75 | M | Gluteal region | Not known[a] | Not known[a] | No | Present |
| 22 | 70 | F | Left upper eyelid | 0.8 cm | 5 mm | No | Present |
| 23 | 76 | F | Left leg | 0.6 cm | 4 mm | Present | No |
| 24 | 78 | F | Left upper eyelid | 0.8 cm | 4 mm | Present | Present |

[a] Incisional biopsy performed.

transcriptional effects, so functionally links regulation of the cell cycle to differentiation. INSM1 is essentially responsible for the transcription of SYN and CHR [5-7].

In this study, we examined our case series of Merkel cell carcinoma for the expression of INSM1 to demonstrate neuroendocrine differentiation, and compared INSM1 staining with frequently used neuroendocrine markers, CHR, SYN, and CD56.

## 2. Materials and methods

### 2.1. Sample selection

The study was approved by the review board of our institution. Formalin-fixed paraffin-embedded tissue samples of 24 primary cutaneous neuroendocrine tumors were retrospectively selected from the cases diagnosed in the Departments of Pathology of eight institutions between the years 2002–2018. The medical documents were investigated to verify that all lesions originated primarily from the skin. Furthermore, diagnoses were confirmed on the basis of morphological and immunohistochemical findings according to the criteria published [8]. Clinical data including the tumor site and tumor size were collected from the medical records. 24 neoplasms that could be confused with MCC selected as a control group including 5 melanomas, 7 basal cell carcinomas, 2 squamous cell carcinoma, 3 sebaceous carcinomas, 2 mycosis fungoides (tumor stage), 3 B cell lymphomas, 2 leukemia cutis.

### 2.2. Immunohistochemistry

Immunohistochemical reactions were performed on paraffin tissue sections using an automated immunohistochemical stainer (Ventana

**Table 2**
The extent (ratio of positively stained cells) and intensity of staining for the immunohistochemical markers.

| | INSM1 | Synaptophysin | Chromogranin A | CD56 |
|---|---|---|---|---|
| Extensity | | | | |
| Score 4 (> 75% of the cells) | 21 | 20 | 17 | 8 |
| Score 3 (51–75% of the cells) | 2 | 1 | 2 | 3 |
| Score 2 (26–50% of the cells) | 1 | 1 | 2 | 5 |
| Score 1 (1–25% of the cells) | 0 | 1 | 1 | 3 |
| Score 0 (0% of the cells) | 0 | 1 | 2 | 5 |
| Intensity | | | | |
| Score 3 (strong) | 16 | 11 | 14 | 5 |
| Score 2 (moderate) | 6 | 10 | 7 | 7 |
| Score 1 (weak) | 2 | 2 | 1 | 7 |
| Score 0 (none) | 0 | 1 | 2 | 5 |
| Sensitivity of the markers for the detection of MCC | 100% | 96% | 92% | 79% |

BenchMark ULTRA, Ventana Medical Systems, Inc., Tucson, AZ), according to the manufacturer's protocol. Detection was enabled using the Ventana ultraVIEW DAB Detection kit (Ventana Medical Systems, Inc.). The 4-μm-tissue sections were deparaffinized using the EZ Prep solution (Ventana Medical Systems, Inc.). Heat-induced antigen retrieval was done using the Cell Conditioning 1 solution (Ventana Medical Systems, Inc.) at 98 °C for 60 min. Endogenous peroxidase activity was blocked by treatment with the ultraVIEW inhibitor (Ventana Medical Systems, Inc.) in 3% H2O2 for 4 min at 37 °C. Slides were incubated with the following primary antibodies for 56 min at 37 °C: INSM1 [A8] (1:100 dilution, Santa Cruz Biotechnology, Dallas, TX, USA); Synaptophysin [SP11] (1:20 dilution, Thermo Fisher Scientific, Waltham, MA, USA); ready-to-use Chromogranin A [LK2H10] (Ventana Medical Systems, Tucson, AZ, USA); ready-to-use CD56 [123C3] (CellMarque/Sigma-Aldrich, St. Louis, MO, USA). Slides were incubated with a secondary antibody of ultra-VIEW HRP Multimer (< 50 μg/mL; Ventana Medical Systems, Inc.) at 37 °C for 8 min and a diaminobenzidine + H2O2 substrate for 8 min, which was followed by counterstaining with hematoxylin and bluing reagent at 37 °C, for 16 and 4 min, respectively. Slides were mounted using a xylene-based mounting media.

### 2.3. Evaluation of immunohistochemistry

Immunohistochemical evaluation was based on the ratio of positively stained tumor cells and the staining intensity. Positivity of the tumor cell population was recorded as 0 (when none of the cells stained), 1+ (< 25% of tumor cells stained), 2+ (26–50% of tumor cells stained), 3+ (51–75% of tumor cells stained) or 4+ (> 75% of tumor cells stained). Staining intensity was evaluated as weak (1+), moderate (2+), or strong (3+). Criteria for the assessment of immunohistochemical expression in tumor cells have been explained in detail in Fig. 1. Immunohistochemical findings were evaluated by one pathologist (C. L.).

## 3. Results

Clinical and histopathological data of the cases are summarized in Table 1. 10 of 24 lesions (42%) were located on the extremities, 7 (29%) were on the face, 7 (29%) were on the lumbosacral or gluteal region. 11 (46%) patients were male and 13 (54%) were female, ranging in age from 44 to 87 years (mean, 68 years). Tumor sizes ranged from 0.6 cm to 10.5 cm. Maximum tumor thickness ranged from 4 mm to 42 mm. Subcutaneous invasion of the tumor was detected in 19 cases. 9 cases had lymphatic invasion. All of the cases were positive for pancytokeratin and/or CK20 performed when diagnosing MCC, mostly in a perinuclear dot-like pattern.

INSM1 immunoreactivity was detected in all samples of MCC and confined to the nuclei of positive cells. Staining intensity was mostly strong, enabling easy and rapid decision of positivity and negativity. Background staining was not observed. There was neither cytoplasmic nor membranous staining. Of the 24 cases, 16 (67%) demonstrated strong nuclear staining intensity, whereas 6 (25%) showed moderate staining intensity, and 2 (8%) weak staining intensity. In 21 (88%) of 24 MCC cases, 76% to 100% of tumor cells were positive for INSM1 (score 4). Two cases (8%) were positive for INSM1 in 51% to 75% of tumor cells (score 3). Immunohistochemical positivity for INSM1 between 26% and 50% of tumor cells was seen in only one case (4%; score 2). Compared to INSM1, other immunohistochemical markers, i.e. SYN, CHR, CD56, showed immunohistochemical expression in a lower intensity and in a lesser number of tumor cells (Table 2).

In some of our Merkel cell carcinoma cases, the tumor cells were positive for SYN and CHR in addition to INSM1 (Fig. 2). In one case

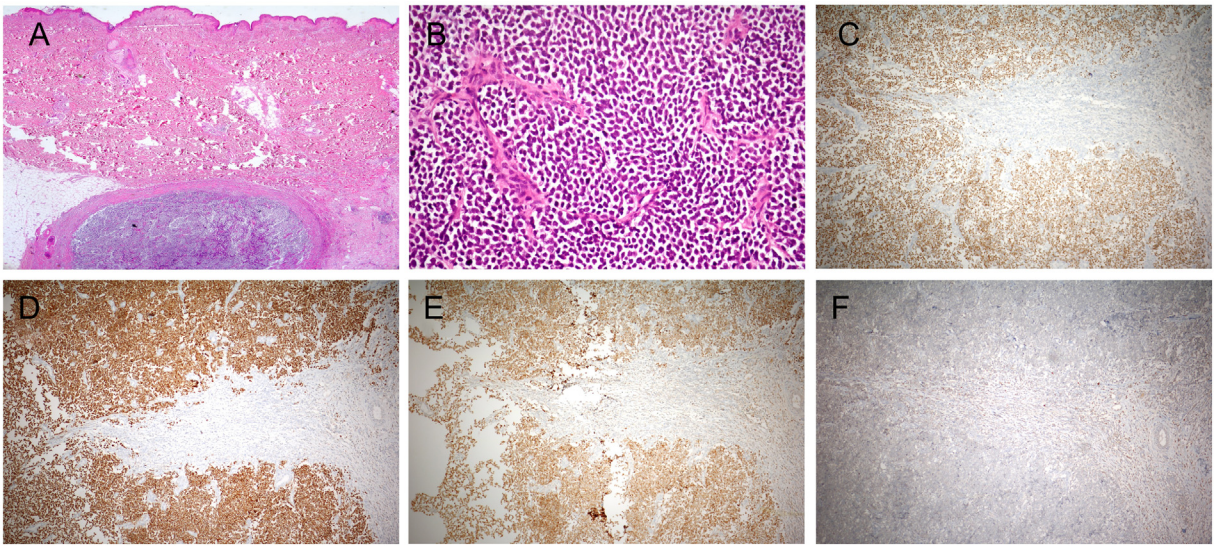


**Fig. 2.** Case 6. A - MCC with lobular growth pattern in subcutaneous tissue (HE ×20). B - Tumor cells are composed of small blue round cells (HE ×200). C, D, E - This tumor shows diffuse and strong positivity for INSM1, SYN, and CHR (C, INSM1 ×100; D, SYN ×100; E, CHR ×100). F - CD56 is negative (CD56 ×100). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

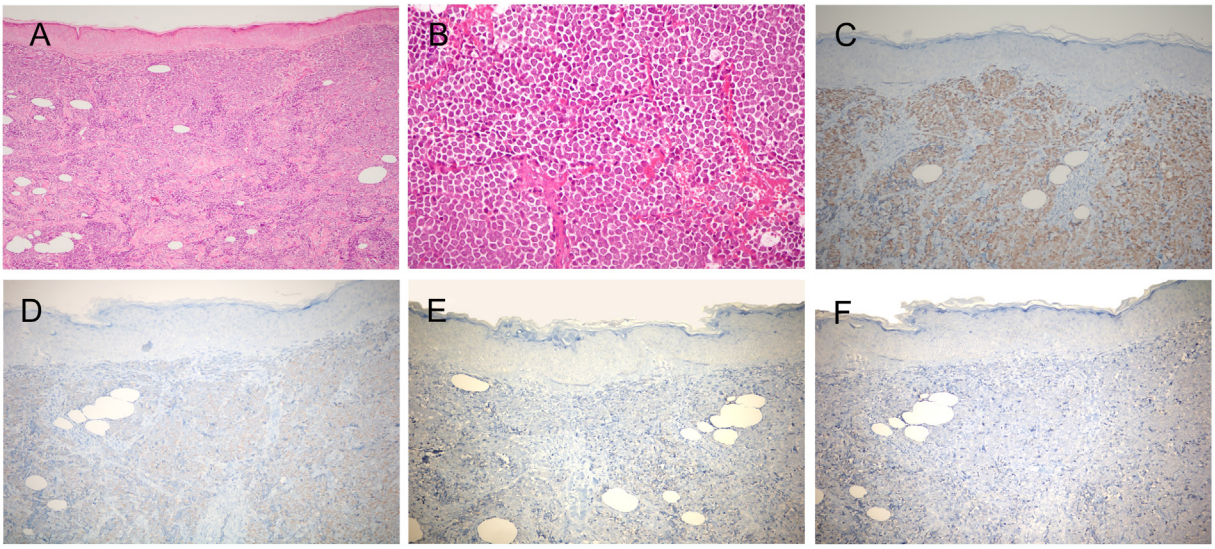


**Fig. 3.** Case 1. A - Dermal tumoral infiltration (HE ×100). B - Characteristic nuclear features of MCC (HE ×200). C - Diffuse and strong INSM1 positivity (INSM1 ×100). D - Weak staining for SYN (SYN ×100). E, F - CHR and CD56 are negative, respectively (CHR ×100, and CD56 ×100).

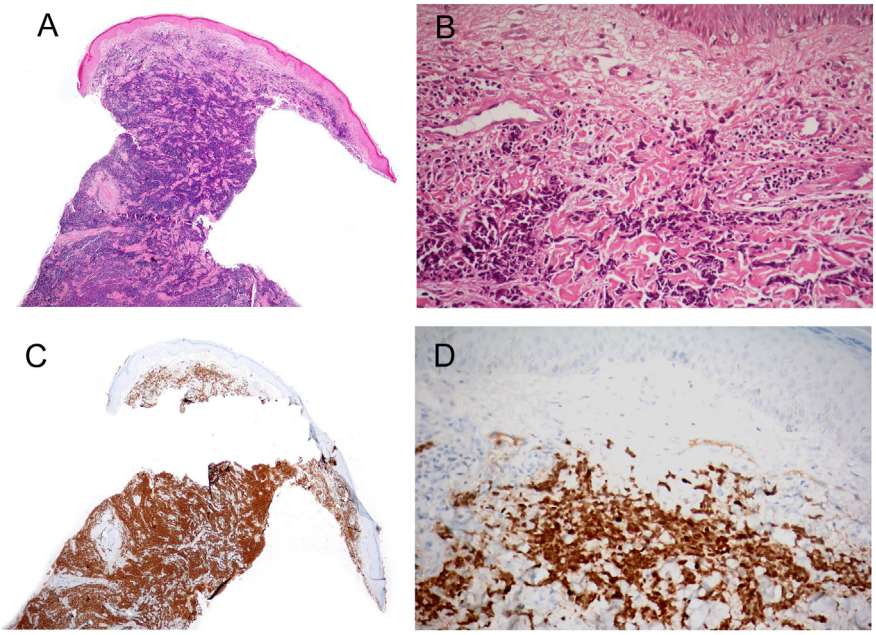


**Fig. 4.** Case 3. A, B - Skin punch biopsy shows extensive crush artifact leading to difficulty of assessment (A, HE ×40; B, HE ×200). C, D - INSM1 is helpful for establishing the diagnosis of MCC (C, INSM1 ×40; D, INSM1 ×200).

**Table 3**
Immunohistochemical expressions of INSM1 and other neuroendocrine markers in MCC in the previous studies.

| | INSM1 | SYN | CHR | CD56 |
|---|---|---|---|---|
| Visscher et al. [13] | NI | 6/21 (28%) | 11/21 (52%) | NI |
| Bobos et al. [14] | NI | 10/13 (77%) | 13/13 (100%) | 9/13 (69%) |
| Fukuhara et al. [12] | NI | 19/20 (95%) | 16/20 (80%) | NI |
| Rosenbaum et al. [11] | 6/6 (100%) | NI | NI | NI |
| Fujino et al. [21] | 7/7 (100%) | 5/7 (71%) | 7/7 (100%) | 5/7 (71%) |
| Panse et al. [18] | NI | NI | NI | 15/17 (88%) |
| Rush et al. [9] | 14/15 (93%) | 7/8 (88%) | 6/7 (86%) | NI |
| Lilo et al. [10] | 47/47 (100%) | 43/47 (91%) | 15/47 (%32) | NI |
| Present study | 24/24 (100%) | 23/24 (96%) | 22/24 (92%) | 20/24 (83%) |

NI: not investigated.

showing weak expression for SYN, INSM1 staining was diffuse and strong while the other neuroendocrine markers were negative (Fig. 3). INSM1 staining in the tissue samples with crush artifact was very clean (Fig. 4).

The percentage of positively stained cells and the intensity of staining for all of the immunohistochemical markers studied have been summarized in Table 2. The sensitivities of the immunohistochemical markers for the detection of MCC, as a neuroendocrine marker, were 100% for INSM1, 96% for SYN, 92% for CHR, and 79% for CD56.

INSM1 expression was not detected in any of the control cases of cutaneous neoplasms mimicking MCC including melanoma, basal cell carcinoma, squamous cell carcinoma, sebaceous carcinoma, mycosis fungoides, B cell lymphoma, and leukemia cutis. INSM1 was not expressed in any of the non-neoplastic cutaneous cells including squamous epithelial cells, melanocytes, adnexal cells, fat cells, muscle cells, endothelial cells, fibroblasts, and lymphoid cells. Only resident Merkel cells located at the epidermis or hair follicles were stained with INSM1.

## 4. Discussion

The critical finding of this study is that INSM1 is a more sensitive marker than SYN, CHR and CD56 for the detection of MCC. Expression of INSM1 was detected in all of the cases. The staining was strong and diffuse. Furthermore, nuclear staining of INSM1 was clean and homogenous, making an easier distinction between MCC and other cutaneous neoplasms mimicking MCC. On the contrary, SYN, CHR and CD56 were expressed in lesser number of tumor cells than INSM1, and staining intensity was also usually weaker (Table 2). INSM1 appears superior to other conventional neuroendocrine markers.

There are few reports of INSM1 expression in MCC. During the preparation of this manuscript, a total of 75 cases have been studied in four reports in which the INSM1 expression has been investigated in Merkel cell carcinoma to date in our best knowledge (Table 3) [9-11]. All cases were positive for INSM1 except one case. In this unexpected case in the study of Rush et al., CK20 and CHR were also negative just as INSM1, and the diagnosis was dependent on focal positivity for SYN [9]. In previous reports, the sensitivities of other immunomarkers for the detection of MCC were 28% to 95% for SYN, 32% to 100% for CHR, and 69 to 88% for CD56 [12-18].

Consistent with prior works and this study, INSM1 was not expressed in any epidermal, adnexal or dermal cell except resident Merkel cells found in epidermis and hair follicle [11,19]. Besides, there was no staining with INSM1 in any tumor within the differential diagnosis of MCC including basal cell carcinoma, basaloid squamous cell carcinoma, Bowen disease, sebaceous neoplasms, melanoma, and hematolymphoid neoplasms [9-11,19].

In some cases of MCC, the diagnosis is performed on a small biopsy sample such as punch or core needle biopsy. These small tissues may present a challenge in the differential diagnosis resulting from crush artifacts, and/or little amount of tumor cells. INSM1 staining in crushed samples is clear with a clean background [10]. It might be more appropriate to use a nuclear stain like INSM1 rather than cytoplasmic conventional markers, i.e. SYN, CHR, and CD56. Furthermore, the staining intensity and percentage of cells staining with SYN, CHR, and CD56 demonstrated considerable heterogeneity in the present study as well as the others [10,20]. This variability could be partially responsible for misdiagnosing in small biopsy samples. Certainly, none of these stains can distinguish MCC from extracutaneous (metastatic) neuroendocrine carcinomas, as they are general neuroendocrine markers.

In the diagnosis of neuroendocrine and endocrine tumors of extracutaneous organs, INSM1 is also a highly sensitive and specific pan-neuroendocrine marker. In a large series, INSM1 expression was not detected in any adult non-neoplastic, non-neuroendocrine tissue, and was detectable in 88.3% of 129 neuroendocrine neoplasms [11]. Only one breast carcinoma in 27 neoplasms without neuroendocrine component exhibited INSM1 immunoreactivity [11]. In another study, INSM1 demonstrated an overall sensitivity of 96.4% in neuroendocrine tumors of the thoracic cavity, and focal staining was noted in only 3.3% of adenocarcinomas and 4.2% of squamous cell carcinomas among 156 non-neuroendocrine carcinomas of the lung. The authors suggested that these low-level stainings probably indicate focal neuroendocrine differentiation [20]. Fujino et al. showed that INSM1 was expressed in 98% of 102 neuroendocrine tumors (NETs) including gastrointestinal, lung, thyroid, and pancreas NETs. Five NETs which were negative for SYN, CHR and CD56, showed INSM1 expression in their series, and they suggested that very early phase of neuroendocrine differentiation can be detected using the INSM1 marker [21]. Furthermore, INSM1 was detected in 95% of high-grade neuroendocrine carcinoma of uterine cervix [22], 92.3% of prostate [23], 99% of all types of head and neck neuroendocrine tumors [24]. Also, INSM1 is useful to detect neuroendocrine lung tumors in cytopathology cell blocks with great sensitivity and high specificity [25]. Expression of INSM1 has been reported in some small round cell tumors, including neuroblastoma, extraskeletal myxoid chondrosarcoma and Ewing family tumors reflecting their neuroendocrine differentiation [26,27]. These tumors have, however, specific clinical and immunohistochemical findings that could easily differentiate them from MCC.

In conclusion, INSM1 is adequately sensitive and specific to serve as a single marker for neuroendocrine differentiation in MCC cases, and ensures several specific benefits when compared to other traditional markers. INSM1 is a nuclear protein, and exhibits a very clear nuclear expression, which is less susceptible to potential non-specific staining and difficulties in evaluation that could occur in cytoplasmic neuroendocrine markers such as SYN, CHR and CD56.

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