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BRIEF REPORT

# Insulinoma-associated protein 1 (INSM1) expression in breast carcinomas with neuroendocrine morphologies: application and future prospective

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## Abstract

Herein, we describe the first cases of neuroendocrine (NE) phenotype mammary carcinomas in which the NE nature of the tumors was confirmed only by insulinoma-associated protein 1 (INSM1), without expressions of traditional "gold standard" NE indicators. This is also the first analysis to use INSM1, a promising antibody with high sensitivity and specificity, in the field of breast oncology. Three patients were, respectively, 42-, 58-, and 64-year-old Japanese women with breast tumors showing characteristic NE morphologies. Immunohistochemically, these malignancies revealed diffuse nuclear expressions of INSM1, whereas chromogranin A and synaptophysin did not show distinct NE features in their cytoplasm. Based on the identification of INSM1 as well as our present immunohistochemical results, the frequency of detecting NE differentiation in systemic neoplasms, including breast NE phenotype cancers, is anticipated to increase such that, ultimately, our observations might contribute to the development of novel treatments including molecular targeted drugs for these tumor entities.

**Keywords** Breast · Immunohistochemistry · INSM1 · Neuroendocrine neoplasms · Neuroendocrine tumors

## Introduction

Insulinoma-associated protein 1 (INSM1) is a zinc-finger transcriptional repressor initially isolated from a human insulinoma phagemid cDNA library [1]. INSM1 was recently demonstrated to be a better diagnostic and prognostic indicator for small cell pulmonary carcinoma than the traditional 'gold-standard' neuroendocrine (NE) markers: chromogranin A and synaptophysin [2]. Herein, for the first time, we present three cases with NE phenotype mammary neoplasms in which the NE nature of the tumors was confirmed solely by INSM1.

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## Methods and results

Three patients were, respectively, 42-, 58-, and 64-year-old Japanese women with breast tumors showing characteristic NE morphologies, i.e., solid growth of polygonal, fusiform, or plasmacytoid cells with finely granular cytoplasm and nuclei, a peripheral palisading arrangement, and a well-developed vascular network (Fig. 1a, e, i). The clinical information and histopathological features are presented in Table 1. On immunohistochemical examinations, these malignancies showed diffuse nuclear expressions of INSM1 (mouse monoclonal, clone A-8: sc-271408, dilution 1:100; Santa Cruz Biotechnology, Inc., Dallas, TX) (Fig. 1b, f, j), whereas chromogranin A [three sources: 1) mouse monoclonal, clone LK2H10; Roche Diagnostics, Mannheim, Germany, 2) rabbit polyclonal, dilution 1:500; Dako, Copenhagen, Denmark (Fig. 1c, g, k), and 3) rabbit polyclonal, 412751; Nichirei Bioscience Inc., Tokyo, Japan] and synaptophysin [two sources: 1) rabbit polyclonal, dilution 1:50; Dako, and 2) mouse monoclonal, clone 27G12: 413831; Nichirei (Fig. 1d, h, l)] staining did not correspond to distinct NE features in the neoplastic cytoplasm, despite appropriate positive and negative controls having been provided for these NE-stained

**Table 1** Clinicopathological characteristics of three cases with neuroendocrine phenotype breast neoplasms

| Case no | Sex/ age | Site | Presentation | Invasive size (lesion size) | Histological grading | Estrogen receptor | Progesterone receptor | HER2 | Ki67 (MIB-1) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | F/42 | R/UO | Palpable mass | 2.8 cm | Histological grade 2 | 95% | 90% | 1+ | 37% |
| 2 | F/58 | R/UI | Detected by screening mammography | 2.5 cm | Histological grade 2 | 90% | 60% | 1+ | 32% |
| 3 | F/64 | L/UO | Bloody nipple discharge | 0 (4.2) cm | Low grade (Van Nuys) | 100% | 100% | 1+ | 18% |

*F* female, *R* right breast, *UO* upper outer, *UI* upper inner, *L* left breast

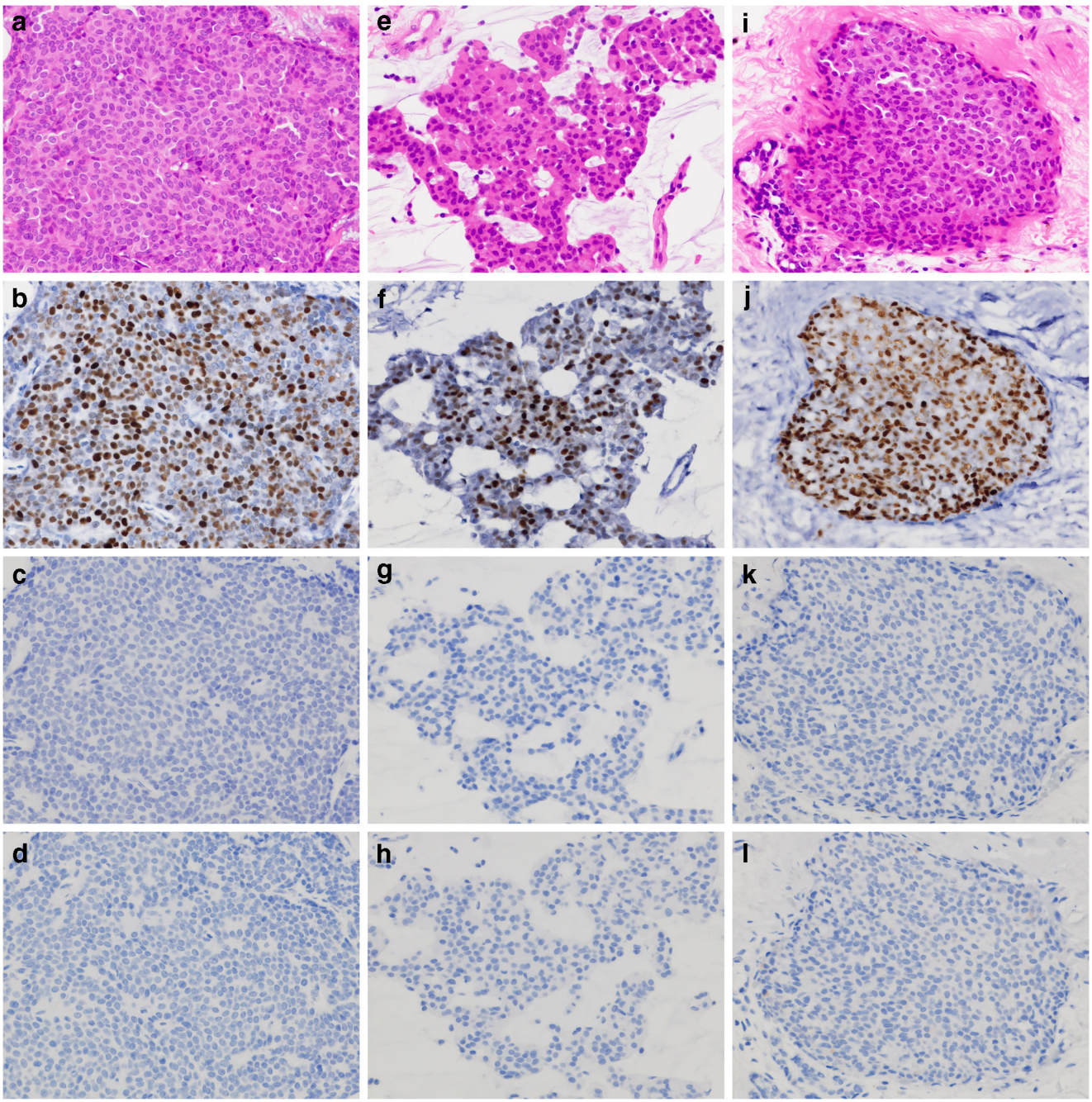


**Fig. 1** Pathological findings of mammary carcinomas with neuroendocrine morphologies accompanied by distinct immunoexpression of only insulinoma-associated protein 1 (INSM1). **a**–**d** Neuroendocrine tumor, grade 2. **e**–**h** Cellular mucinous carcinoma. **i**–**l** Neuroendocrine ductal carcinoma in situ. H&E (**a**, **e**, **i**) and immunostaining for INSM1 (**b**, **f**, **j**) or chromogranin A (**c**, **g**, **k**) or synaptophysin (**d**, **h**, **l**) (magnification × 400)

sections. In addition, we detected no INSM1-reactive cells in breast parenchyma surrounding the tumors.

## Discussion

The World Health Organization (WHO) reclassified neuroendocrine neoplasms (NENs) of the breast as an independent disease concept representing < 1% of mammary carcinomas [3, 4]. Several investigators have demonstrated that this rare condition is a distinctive type of aggressive breast carcinoma, even though most cases are positive for ER and/or PgR without HER2 gene amplification [5–7]. Furthermore, it was very recently reported, in the lung oncology field, that patients with NENs showing high-INSM1 had significantly poorer outcomes than those with low-INSM1 reactivity [2]. Based on the establishment of INSM1, a promising NE marker with high sensitivity and specificity, accompanied by our current immunohistochemical results, the frequency of detecting mammary NENs as well as carcinomas with NE differentiation, represented by type B/hypercellular mucinous carcinoma and solid papillary carcinoma, is anticipated to increase. Our observations might ultimately contribute to the development of novel treatments including molecular-targeted therapies for these tumor entities.

In the great majority of previous cases reported to be only positive for INSM1 but negative for chromogranin A, synaptophysin and CD56 (NCAM) were viewed as indicating neuroendocrine carcinoma (NEC) represented by small cell type. From this perspective as well, the actual proof that the same immuno-NE-results have been obtained, i.e. INSM1+/chromogranin A−/synaptophysin− panel, without distinct NCAM expression (data not shown) in our present study, using various NE phenotype tumors, not so-called NEC, appears to be a novel finding of great interest. It is well known that CD56 (NCAM) is generally used as an additional or supplementary NE indicator, except in specific circumstances such as the diagnosis of small cell lung carcinoma. Recently, we have demonstrated that in the field of breast oncology, NCAM is a considerably less sensitive and less specific NE marker, because the antibody expression is commonly found in normal mammary ducts and lobules without intrinsic NE cells [8]. Therefore, INSM1 can serve as an alternative as well as an innovative diagnostic tool for neoplasms potentially possessing NE features, thereby making it a potentially valuable research tool in the academic discipline of mammary diseases.

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**Authors' contributions** T. Kawasaki and K. Kaira designed the study, gathered the clinical data, histopathologically analyzed the cases, and interpreted the results. T. Kawasaki drafted the manuscript and conducted the literature search. K. Kaira reviewed the manuscript.

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## Compliance with ethical standards

The paper complies with ethical standards, informed consent has been obtained from the patient, and the paper does not contain any identifying information pertaining to the patient.

**Conflict of interest** The authors declare that they have no conflict of interest.

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