Prevalence of Syndecan-1 (CD138) Expression in Different Kinds of Human Tumors and Normal Tissues

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Syndecan-1 (CD138) is a transmembrane proteoglycan known to be expressed in various normal and malignant tissues. It is of interest because of a possible prognostic role of differential expression in tumors and its role as a target for indatuximab, a monoclonal antibody coupled with a cytotoxic agent. To comprehensively analyze CD138 in normal and neoplastic tissues, we used tissue microarrays (TMAs) for analyzing immunohistochemically detectable CD138 expression in 2,518 tissue samples from 85 different tumor entities and 76 different normal tissue types. The data showed that CD138 expression is abundant in tumors. At least an occasional weak CD138 immunostaining could be detected in 71 of 82 (87%) different tumor types, and 58 entities (71%) had at least one tumor with a strong positivity. In normal tissues, a particularly strong expression was found in normal squamous epithelium of various organs, goblet and columnar cells of the gastrointestinal tract, and in hepatocytes. The highly standardized analysis of most human cancer types resulted in a ranking order of tumors according to the frequency and levels of CD138 expression. CD138 immunostaining was highest in squamous cell carcinomas such as from the esophagus (100%), cervix uteri (79.5%), lung (85.7%), vagina (89.7%) or vulva (73.3%), and in invasive urothelial cancer (76.2%). In adenocarcinomas, CD138 was also high in lung (82.9%) and colorectal cancer (85.3%) but often lower in pancreas (73.3%), stomach (54.2% in intestinal type), or prostate carcinomas (16.3%). CD138 expression was usually low or absent in germ cell tumors, sarcomas, endocrine tumors including thyroid cancer, and neuroendocrine tumors. In summary, the preferential expression in squamous epithelium of various sites makes these cancers prime targets for anti-CD138 treatments once these might become available. Abundant expression in many different normal tissues might pose obstacles to exploiting CD138 as a therapeutic target, however.

1. Introduction

Syndecan-1 (CD138) is one of four members of the syndecan family. It is a cell surface protein consisting of three structural domains, one of which is extracellular and binds heparin sulfates and chondroitin sulfates [1]. Syndecan-1 has relevance for cell-cell and cell-matrix interactions [1]. It is involved in the regulation of cell proliferation, migration, and the
organism of the cytoskeleton [1]. In normal tissues, CD138 is known to be expressed on plasma cells and various epithelial cell types.

CD138 expression in cancer is of potential clinical interest as specific drugs targeting CD138 are currently being evaluated in clinical trials. In a phase II trial on plasmacytoma, clinical efficacy and low side effects have been reported [2, 3]. In preclinical studies, these antibodies also showed efficacy against triple negative breast cancer and melanoma [4, 5]. If anti-CD138 therapies should prove successful, other CD138-positive cancer types might as well benefit from such treatments.

Altered CD138 expression has been described in various malignant tumors. For example, overexpression of CD138 has been reported in breast, urinary bladder, gallbladder, pancreatic, ovarian, endometrial, and prostate cancer [1]. In other cancer types, such as lung, head/neck, gastric, renal, and colorectal cancer, CD138 expression was found to be reduced as compared to adjacent normal epithelium [1]. In several of these tumor types, either reduced or increased CD138 expression was linked to unfavorable tumor phenotype and poor patient prognosis [6–9]. Previous studies on CD138 in cancer have applied various different reagents and protocols for their immunohistochemical staining. It is probably because of this that the existing literature is highly discrepant with respect to the prevalence of CD138 expression in different tumor types. For example, the range of the reported CD138 positivity ranges from 26% [10] to 100% [11] in urinary bladder cancer, from 23% [10] to 89% [12] in squamous lung cancer, from 33% [13] to 100% [14] in breast cancer, from 50.5% [15] to 87% [10] in squamous cell carcinoma of the esophagus, and from 24.7% [16] to 89.7% [17] in squamous cell carcinoma of the cervix.

Given these heterogeneous data, the existing literature does not easily allow to determine these cancer types, where CD138 plays a particularly important role. To compare the prevalence and intensity of CD138 expression between tumor entities and to identify these cancer types that might be optimal candidates for anti-CD138 drugs, we thus analyzed more than 2500 cancer tissue samples from the archives of the Institute of Pathology, University Hospital of Hamburg (Hamburg, Germany). Each TMA block contains an identical standard tissue spot (containing up to 50 different tumor from 85 different tumor types and subtypes. The results of our study identify a broad range of highly CD138-expressing tumor entities.

3. Results

3.1. Technical Issues. A total of 2,518 (69%) of the 3,642 tumor tissue samples were interpretable in our TMA analysis. Reasons for analysis failure included a fraction of missing samples or samples lacking unequivocal tumor cells. A sufficient number of samples were analyzable for all 76 normal tissue types enabling a complete normal tissue evaluation.

3.2. Syndecan-1 in Normal Tissues. All positive CD138 immunostainings in normal tissues are summarized in Table 2. CD138 was abundantly expressed, mostly in various epithelial cell types. A particularly strong expression of CD138 was observed in squamous epithelial cells of various organs (Figure 1(a)), goblet cells of the gastrointestinal tract (Figure 1(b)), columnar cells in the gall bladder (Figure 1(c)), and hepatocytes (Figure 1(d)). No CD138 staining was detected in the following tissues: aorta/intima, aorta/media, heart (left ventricle), skeletal muscle, skeletal muscle/tongue, myometrium, muscular wall appendix, esophagus, stomach, ileum, colon descendens, kidney pelvis and urinary bladder, penis (glans/corpus spongiosum), ovary (stroma), fat tissue (white), spleen, thymus, ovary (corpus luteum), ovary (follicular cyst), thyroid, cerebellum, cerebrum, pituitary gland (posterior lobe), pituitary gland (anterior lobe), and bone marrow.

3.3. CD138 in Tumorous Tissues. Immunostaining was predominantly membranous but sometimes also in the...
Table 1: CD138 expression in different tumorous tissues.

| Entity                               | n on TMA | n analyzable | CD138 immunohistochemistry results (%) |
|--------------------------------------|----------|--------------|----------------------------------------|
|                                      |          |              | Negative | Weak | Moderate | Strong | Positive |
| Tumors of the skin                   |          |              |          |      |          |        |          |
| Pilomatrixoma                         | 35       | 30           | 63.3     | 26.7 | 10.0     | 0.0    | 36.7     |
| Basalioma                             | 48       | 41           | 2.4      | 7.3  | 73.3     | 10.0   | 97.6     |
| Epidermal nevus                       | 29       | 19           | 100.0    | 0.0  | 0.0      | 0.0    | 0.0      |
| Cutaneous squamous cell carcinoma     | 50       | 42           | 7.1      | 21.4 | 9.5      | 61.9   | 92.9     |
| Malignant melanoma                    | 48       | 39           | 97.4     | 2.6  | 0.0      | 0.0    | 2.6      |
| Merkel cell carcinoma                 | 46       | 42           | 69.0     | 21.4 | 2.4      | 7.1    | 31.0     |
|                                      |          |              |          |      |          |        |          |
| Laryngeal squamous cell carcinoma     | 50       | 44           | 15.9     | 31.8 | 11.4     | 40.9   | 84.1     |
| Oral squamous cell carcinoma          | 50       | 45           | 11.1     | 22.2 | 20.0     | 46.7   | 88.9     |
| Lung squamous cell carcinoma          | 50       | 21           | 14.3     | 14.3 | 9.5      | 61.9   | 85.7     |
| Large cell bronchial carcinoma        | 31       | 25           | 56.0     | 32.0 | 4.0      | 8.0    | 44.0     |
| Lung adenocarcinoma                   | 50       | 35           | 17.1     | 34.3 | 20.0     | 28.6   | 82.9     |
|                                      |          |              |          |      |          |        |          |
| Lung in situ pulmonary adenocarcinoma | 6        | 15           | 80.0     | 20.0 | 0.0      | 0.0    | 20.0     |
| Lung small cell carcinoma             | 20       | 5            | 20.0     | 20.0 | 40.0     | 20.0   | 80.0     |
| Malignant mesothelioma                | 48       | 35           | 97.1     | 2.9  | 0.0      | 0.0    | 2.9      |
| Parotid gland pleomorphic adenoma     | 50       | 37           | 21.6     | 10.8 | 18.9     | 48.6   | 78.4     |
| Parotid gland Warthin tumor           | 49       | 41           | 7.3      | 29.3 | 22.0     | 41.5   | 92.7     |
| Salivary gland Basal cell adenoma     | 15       | 15           | 0.0      | 33.3 | 33.3     | 33.3   | 100.0    |
| Gynecological tumors                  |          |              |          |      |          |        |          |
| Vagina squamous cell carcinoma        | 48       | 29           | 10.3     | 27.6 | 24.1     | 37.9   | 89.7     |
| Vulva squamous cell carcinoma         | 50       | 30           | 26.7     | 13.3 | 33.3     | 26.7   | 73.3     |
| Cervix squamous cell carcinoma        | 50       | 39           | 20.5     | 23.1 | 25.6     | 30.8   | 79.5     |
| Cervix adenocarcinoma                 | 50       | 41           | 85.4     | 14.6 | 0.0      | 0.0    | 14.6     |
| Endometrial carcinoma endometrioid    | 50       | 44           | 72.7     | 13.6 | 11.4     | 2.3    | 27.3     |
| Endometrial carcinoma serous          | 50       | 33           | 60.6     | 9.1  | 18.2     | 12.1   | 39.4     |
| Uterus stromal sarcoma                | 12       | 10           | 90.0     | 0.0  | 10.0     | 0.0    | 10.0     |
| Carcinosarcoma                        | 48       | 47           | 74.5     | 12.8 | 8.5      | 4.3    | 25.5     |
| Ovarian carcinoma endometrioid        | 37       | 30           | 56.7     | 16.7 | 6.7      | 20.0   | 43.3     |
| Ovarian carcinoma serous              | 50       | 39           | 79.5     | 10.3 | 7.7      | 2.6    | 20.5     |
| Ovarian carcinoma mucinous            | 26       | 21           | 33.3     | 19.0 | 0.0      | 47.6   | 66.7     |
| Brenner tumor                         | 9        | 6            | 0.0      | 0.0  | 0.0      | 0.0    | 100.0    |
| NST breast carcinoma                  | 46       | 28           | 46.4     | 17.9 | 7.1      | 28.6   | 53.6     |
| Lobular breast carcinoma              | 43       | 27           | 74.1     | 11.1 | 7.4      | 7.4    | 25.9     |
| Medullary breast carcinoma            | 15       | 11           | 72.7     | 9.1  | 9.1      | 9.1    | 27.3     |
| Tubular breast carcinoma              | 18       | 10           | 40.0     | 10.0 | 10.0     | 40.0   | 60.0     |
| Mucinous breast carcinoma             | 22       | 14           | 64.3     | 28.6 | 0.0      | 7.1    | 35.7     |
| Phyllodes breast tumor                | 50       | 18           | 5.6      | 22.2 | 38.9     | 33.3   | 94.4     |
| Gastrointestinal tumors               |          |              |          |      |          |        |          |
| Colon adenoma, low grade              | 50       | 27           | 0.0      | 3.7  | 3.7      | 92.6   | 100.0    |
| Colon adenoma, high grade             | 50       | 25           | 0.0      | 4.0  | 4.0      | 92.0   | 100.0    |
| Colon adenocarcinoma                  | 50       | 34           | 14.7     | 35.3 | 20.6     | 29.4   | 85.3     |
| Small intestine adenocarcinoma        | 10       | 4            | 75.0     | 25.0 | 0.0      | 0.0    | 25.0     |
| Stomach carcinoma diffuse type        | 50       | 24           | 45.8     | 16.7 | 8.3      | 29.2   | 54.2     |
| Stomach carcinoma intestinal type     | 50       | 28           | 21.4     | 42.9 | 14.3     | 21.4   | 78.6     |
| Esophageal adenocarcinoma             | 50       | 33           | 30.3     | 27.3 | 12.1     | 30.3   | 69.7     |
| Esophageal squamous cell carcinoma    | 49       | 33           | 0.0      | 12.1 | 9.1      | 78.8   | 100.0    |
| Anal squamous cell carcinoma          | 50       | 22           | 9.1      | 18.2 | 9.1      | 63.6   | 90.9     |
cytoplasm. Occasional stroma staining also occurred but was disregarded for this analysis. CD138 positivity was seen in 1,118 of 2,518 analyzable tumors (Table 1). CD138 immunostaining was considered weak in 330 (13%), moderate in 226 (9%), and strong in 562 tumors (22%). Representative tumor tissue spots with CD138 expression are shown in Figures 1(e) and 1(h). At least some CD138 expression could be detected in 75 of 85 (88%) of our tumor categories, including 60 (71%) categories where at least one tumor showed a strong positivity (Table 1). The tumor types where some CD138 was seen in all analyzed cases included basal cell adenoma, colon adenoma, squamous carcinoma of the esophagus, granular cell

| Entity                                         | n on TMA | n analyzable | Negative % | Weak % | Moderate % | Strong % | Positive % |
|------------------------------------------------|----------|--------------|------------|--------|------------|----------|-------------|
| Cholangiocarcinoma                            | 50       | 23           | 60.9       | 17.4   | 8.7        | 13.0     | 39.1        |
| Hepatocellular carcinoma                      | 50       | 44           | 2.3        | 15.9   | 9.1        | 72.7     | 97.7        |
| Pancreatic ductal adenocarcinoma               | 50       | 30           | 26.7       | 36.7   | 16.7       | 20.0     | 73.3        |
| Pancreas/papilla adenocarcinoma                | 30       | 17           | 29.4       | 17.6   | 11.8       | 41.2     | 70.6        |
| Pancreatic neuroendocrine tumor                | 49       | 28           | 82.1       | 3.6    | 3.6        | 10.7     | 17.9        |
| Gastrointestinal stroma tumor (GIST)           | 50       | 37           | 100.0      | 0.0    | 0.0        | 0.0      | 0.0         |
| Urothelial carcinoma pTa                       | 50       | 41           | 12.2       | 2.4    | 4.9        | 80.5     | 87.8        |
| Urothelial carcinoma T2-4                      | 50       | 42           | 23.8       | 4.8    | 16.7       | 54.8     | 76.2        |
| Small cell urothelial carcinoma                | 18       | 18           | 100.0      | 0.0    | 0.0        | 0.0      | 0.0         |
| Clear cell renal cell carcinoma                | 50       | 46           | 45.7       | 13.0   | 17.4       | 23.9     | 54.3        |
| Papillary renal cell carcinoma                 | 50       | 44           | 59.1       | 22.7   | 6.8        | 11.4     | 40.9        |
| Chromophobe renal cell carcinoma               | 50       | 42           | 81.0       | 9.5    | 9.5        | 0.0      | 19.0        |
| Renal oncocytoma                               | 50       | 44           | 38.6       | 27.3   | 20.5       | 13.6     | 61.4        |
| Prostate carcinoma                             | 49       | 43           | 83.7       | 4.7    | 4.7        | 7.0      | 16.3        |
| Small cell prostate carcinoma                  | 17       | 11           | 54.5       | 27.3   | 9.1        | 9.1      | 45.5        |
| Seminoma                                       | 50       | 47           | 100.0      | 0.0    | 0.0        | 0.0      | 0.0         |
| Embryonic carcinoma (testis)                   | 50       | 39           | 97.4       | 2.6    | 0.0        | 0.0      | 2.6         |
| Yolk sac tumor                                 | 50       | 25           | 92.0       | 4.0    | 4.0        | 0.0      | 8.0         |
| Teratoma                                       | 50       | 23           | 17.4       | 4.3    | 8.7        | 69.6     | 82.6        |
| Thyroid adenoma                                | 50       | 45           | 80.0       | 13.3   | 2.2        | 4.4      | 20.0        |
| Papillary thyroid carcinoma                    | 50       | 36           | 63.9       | 8.3    | 13.9       | 13.9     | 36.1        |
| Follicular thyroid carcinoma                   | 49       | 44           | 77.3       | 9.1    | 6.8        | 6.8      | 22.7        |
| Medullary thyroid carcinoma                    | 50       | 29           | 82.8       | 3.4    | 0.0        | 13.8     | 17.2        |
| Anaplastic thyroid carcinoma                   | 26       | 19           | 89.5       | 5.3    | 0.0        | 5.3      | 10.5        |
| Adrenal adenoma                                | 50       | 48           | 72.9       | 10.4   | 6.3        | 10.4     | 27.1        |
| Adrenal carcinoma                              | 26       | 14           | 35.7       | 21.4   | 14.3       | 28.6     | 64.3        |
| Pheochromocytoma                               | 50       | 32           | 100.0      | 0.0    | 0.0        | 0.0      | 0.0         |
| Neuroendocrine tumor (NET)                     | 50       | 27           | 81.5       | 7.4    | 7.4        | 3.7      | 18.5        |
| Hodgkin lymphoma                               | 45       | 43           | 100.0      | 0.0    | 0.0        | 0.0      | 0.0         |
| Non-Hodgkin lymphoma                           | 48       | 42           | 97.6       | 2.4    | 0.0        | 0.0      | 2.4         |
| Thymoma                                        | 29       | 24           | 70.8       | 16.7   | 8.3        | 4.2      | 29.2        |
| Giant cell-long sheath tumor                   | 45       | 41           | 97.6       | 2.4    | 0.0        | 0.0      | 2.4         |
| Granular cell tumor                            | 30       | 24           | 0.0        | 12.5   | 25.0       | 62.5     | 100.0       |
| Leiomyoma                                      | 50       | 41           | 100.0      | 0.0    | 0.0        | 0.0      | 0.0         |
| Leiomyosarcoma                                 | 49       | 46           | 93.5       | 0.0    | 6.5        | 0.0      | 6.5         |
| Liposarcoma                                    | 49       | 34           | 97.1       | 2.9    | 0.0        | 0.0      | 2.9         |
| Angiosarcoma                                   | 32       | 22           | 90.9       | 4.5    | 4.5        | 0.0      | 9.1         |
| Osteosarcoma                                   | 25       | 17           | 88.2       | 5.9    | 5.9        | 0.0      | 11.8        |
| Chondrosarcoma                                 | 25       | 8            | 87.5       | 0.0    | 12.5       | 0.0      | 12.5        |
tumor, and ovarian Brenner tumor. A particularly significant CD138 expression was also detected in anal carcinoma (90.9%), squamous carcinoma of the skin (92.9%), hepatocellular carcinoma (97.7%), phyllodes carcinoma of the breast (94.4%), and in Warthin tumor of the parotis (92.7%). Tumor types with a particularly low or absent CD138 immunostaining included testicular germ cell tumors, several sarcomas, melanoma, malignant mesothelioma, and small cell urinary bladder carcinoma.

4. Discussion

The results of this study provide a comprehensive overview on Syndecan-1 expression in human tumors. The data show that—across all organs of origin—squamous cell (and urothelial) carcinomas are particularly prone to express Syndecan-1, often at high levels. Even though adenocarcinomas derived from the colon and the lung are also high expressers, CD138 immunostaining appears to be generally less intense and less frequent in adenocarcinomas. This is best visible in organs where both adenocarcinomas and squamous cell carcinomas occur as in the uterine cervix and in the esophagus. The squamous cell predominance of CD138 expression even becomes apparent in cancers with identical pathogenesis such as cervical cancer, oral cancer, or squamous cell carcinoma of the anus, which are often human papilloma virus associated. Clinically important cancer types with low to intermediate frequencies and levels of CD138 expression include cancers of the kidney and of the endometrium while low frequencies of positivity were found in prostate cancer, endocrine tumors including thyroid cancer, and neuroendocrine tumors as well as germ cell cancers. Despite some outliers, our data are largely consistent with the literature. Several other investigators had earlier described
particularly high levels of CD138 expression in squamous cell cancer [17, 19, 20].

The standardized assessment of 85 different tumor types and subtypes enabled us to define a ranking order with respect to the level of CD138 expression in cancer. We believe these data are particularly helpful for these tumor types for which previous data had been partially discrepant. The study also provided information on a number of relevant tumor types for which CD138 data were lacking so far. These for example include squamous cell carcinoma of the vulva.
and the anal canal, adenocarcinoma of the esophagus, seminoma, embryonal carcinoma and yolk sac tumor of the testis, small cell bladder cancer, neuroendocrine tumors of the pancreas, pheochromocytoma, thymoma, gastrointestinal stroma tumor (GIST), angiosarcoma, and leiomyosarcoma. Moreover, subtype-specific data were obtained for several tumor types, for which previous analyses were performed on tumor cohorts with less detailed information on tumor morphology such as urothelial carcinoma, breast, endometrium, and ovarian cancers. These data thus represent another example of the suitability of TMAs composed of samples of many different tumor types and normal tissues for comprehensively characterizing a biomarker or antibody (demonstration of our data compared to previous studies is shown in Figure 2) [6–13, 15–17, 19–60].

Various earlier studies have suggested a link to poor patient outcome for either increased or decreased Syndecan-1 levels [1]. CD138 protein can have tumor suppressor and tumor-promoting functions which depend on the tumor [61]. Our tumor cohort was devoid of any tumor...
stage or clinical outcome information. Indirect evidence for a variable role of differential CD138 expression for tumor progression comes from the comparison of related tumor subtypes, however. For example, the lower expression levels of CD138 in colorectal adenocarcinoma and in invasive urothelial carcinoma (pT2–4) as compared to colon adenomas and noninvasive bladder tumors (pTa) argues for a loss of CD138 paralleling tumor progression in these tumors. The lower expression of CD138 in chromophobe renal carcinoma as compared to its benign counterpart oncocytoma may also be viewed as an argument for CD138 downregulation being linked to tumor aggressiveness in these kidney cancers derived from the distal nephron tubulus. However, higher levels of CD138 expression in the cortical adrenal carcinoma than in the adrenal adenoma suggest that increased CD138 levels may accompany progression in these tumors.

CD138 is a membrane protein and as such a potential target for antibody therapeutics. There are efforts to develop a suitable therapy for CD138-positive cancers. CD138 was shown to be overexpressed on the surface of multiple myeloma cells which is used in a preclinical study for an antitumor therapy with indatuximab, a monoclonal antibody coupled with a cytotoxic agent, which is currently evaluated in preclinical studies on plasmacytoma [3] and triple-negative breast cancers in combination with other drugs [4]. Based on our data, squamous cell carcinomas, irrespective of their site of origin, emerge as further possible candidates for anti-CD138 therapy once such a treatment should prove to be efficient and become available. The abundant expression of CD138 in various normal tissues including squamous epithelium from various different organs identifies various sites where potential side effects of these therapies might emerge.

CD138 expression analysis is currently used in routine diagnostic pathology to distinguish and quantitate plasma cells, for example, in the bone marrow and in endometrial biopsies where the presence of plasma cells indicates chronic endometritis. Apart from two possible exceptions, our data provide little evidence for Syndecan-1 expression analysis providing diagnostic clues in difficult diagnostic situations. The low expression in mesothelium as compared to the high prevalence of strong expression in pulmonary adenocarcinoma suggests that Syndecan-1 could be potentially added to the long list of antibodies that help to distinguish these tumor entities. A low frequency of Syndecan-1 expression (10%) has recently also been described for peritoneal mesothelioma [62]. Moreover, CD138 was markedly higher in hepatocellular carcinoma as compared to cholangiocellular carcinoma of the liver. However, other antibodies as, for example, arginase or BSEP are better separators of these tumor entities [63–65].

It is a limitation of this study that immunohistochemistry approaches, especially when using bright-field visualization, are not optimal for protein quantification. Importantly, the lack of immunostaining does not exclude a biologically relevant CD138 expression in “negative” normal or neoplastic cells. Every protocol defines a detection threshold below of which tissues are considered negative. Above this detection limit, the staining intensity enables a certain quantification of proteins but this is limited by a maximum intensity staining which cannot become discernably stronger in case of even higher protein expression levels. Moreover, occasional stromal staining had been disregarded in our study, although others and us have shown that there is evidence for a clinically relevant role of CD138 expression in the tumor-associated stroma [23, 57, 66]. However, stroma staining is infrequent and would require larger sample numbers per cancer type for a meaningful analysis.

In summary, this study provides a comprehensive overview on CD138 expression in human tumors. The preferential expression in squamous cell carcinomas of various sites makes these cancers prime targets for anti-CD138 treatments once these might become available. Abundant expression in many different normal tissues might pose obstacles to exploiting CD138 as a therapeutic target, however.

Data Availability

The immunohistochemistry data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors’ Contributions

JI, DP, C H-M, GS, RS, CM, and C M-K conceived and designed the study, analyzed the data, and drafted the manuscript. SW, CF, and SK performed most of the key immunohistochemical analyses. GS, SK, and RS were involved in the original conception of the study. TC, FB, FJ, and C H-M provided the data. WW, VC, AL, AH, DH, GS, SK, and KM participated in tissue processing, pathological diagnosis, and immunohistochemical analysis. DD, AB, CG, AM, GS, and RS provided the materials, clinical follow-up data, and technical assistance. All authors have read and approved the manuscript.

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