International Journal of Surgery 12 (2014) S35–S39

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Review

Acinic cell carcinoma of the breast: Review of the literature

G. Limite [a], R. Di Micco [a,*], E. Esposito [a], V. Sollazzo [a], M. Cervotti [a], G. Pettinato [b], V. Varone [b], G. Benassai [a], B. Amato [a], V. Pilone [c], G. Luglio [a], A. Vitiello [a], A. Hasani [a], F. Liccardo [a], P. Forestieri [a]

[a] Department of Clinical Medicine and Surgery, Breast Unit, University of Naples Federico II, Italy
[b] Department of Advanced Biomedical Sciences, University of Naples Federico II, Italy
[c] Department of Medicine and Surgery, University of Salerno, Italy

ARTICLE INFO

Article history:
Received 23 March 2014
Accepted 3 May 2014
Available online 22 May 2014

Keywords:
Acinic cell carcinoma
Breast cancer
Eosinophilic cytoplasmic granules

ABSTRACT

Introduction: The breast and salivary gland tissue share embryologic and thus pathological similarities. Acinic cell carcinoma (ACC) is a typical tumor in salivary glands, but rarely arises in breast too. We reviewed 38 cases of mammary ACC reported in literature and our case, the first ACC born within a fibroadenoma.

Materials and methods: Data were collected by a research for the key words *acinic cell carcinoma breast* on Pubmed in March 2014, including a case treated in our department. All reviewed cases were compared for clinical approach and histological pattern.

Results: To date 23 articles presenting cases of ACC of the breast are reported in literature. We included in our review 38 cases previously described and one new case. The histological pattern was predominantly solid with a microglandular structure. All the tumor cells were cytologically characterized by monotonous round cells with a finely granular, weakly eosinophilic, or clearly vacuolated cytoplasm. The most of the cells were intensely stained with anti-lysozime, anti-amylase, anti-α1-chimotripsin, anti-EMA and anti-S100 protein antisera. Immunohistochemistry was also performed to point out: estrogen receptor (ER), progesterone receptor (PR), androgen receptors (AR), human epidermal growth factor receptor 2 overexpression (HER2/neu), E-cadherin (E-cad), cytokeratin-7 (CK7), gross cystic disease fluid protein 15 (GCDFP15), smooth muscle actin (SMA).

Conclusion: ACC of the breast is a rare tumor, showing similarities with the salivary gland counterpart, above all in terms of good prognosis, and differences from the ordinary invasive breast carcinoma. Further investigations are needed to elucidate the true histogenesis and the correct treatment.

1. Background

The breast and salivary gland tissues share embryologic similarities. They are both tubuloacinar exocrine glands with similar histological features and consequently, some types of neoplasms may originate indistinctively in either tissue. Tumors arising in the breast gland and the salivary glands show similar morphological features, but they differ in incidence and clinical behavior depending on whether they are primary in breast or salivary glands [1].

Since the first case of ACC of the breast was described by Roncaroli et al. [2] in 1996, several cases have been reported in literature. The most of articles written about ACC are case reports, sometimes associated to partial review. We have found 38 cases described in international literature. This review discusses clinical and pathological features of ACC described in literature. One case of ACC of the breast has been treated in our department.

2. Materials and methods

Data were collected by a research for the key words *acinic cell carcinoma breast* on Pubmed in March 2014, including a case treated in our department. All studies we found were analyzed to include case reports of ACC of the breast, whose diagnosis had been confirmed by immunohistochemical findings, excluding misdiagnosis retrospectively confuted and the same cases described in partial review of the literature. We reported in Tables 1 and 2 clinical and pathological features of ACC described in the

* Corresponding author. Department of Clinical Medicine and Surgery, Breast Unit, University of Naples Federico II, Via S. Pansini 5, 80131 Naples, Italy.
E-mail address: rosadimicco@alice.it (R. Di Micco).

http://dx.doi.org/10.1016/j.ijsu.2014.05.004
1743-9191/

Table 1
Clinical characteristics of acinic cell carcinomas of the breast reported in literature.

References	Sex/age	Site	Tumor size (mm)	Node status	Surgery	Adjuvant therapy	Follow-up (months)	Recurrences/metastases
Roncaroli et al. [2] (1996)	F/42	R uoq	30	1/18	MRM + ALND	CT	60	–
Schimao et al. [3] (1998)	M/23	L	48 × 42	na	BCS + ALND	–	34	–
Damiani et al. [4] (2000)	F/35	R uoq	40	2/20	MRM + ALND	Neo-CT	12	–
	F/63	L	50	na	BCS	–	48	Local
	F/55	L	20	na	BCS	–	Lost	na
	F/64	L uiq	33	0/8	BCS + ALND	–	12	–
	F/80	R uoq	20	na	BCS	HT	12	–
Schmitt et al. [5] (2000)	F/79	na	45	0/23	MRM + ALND	RT	21	–
Coyne and Dervan [6] (2002)	F/49	R	20	2/11	MRM + ALND	Neo-CT + Ad-CT	36	liver
Elster et al. [7] (2002)	F/48	na	30	0/6	BCS + ALND	CT + RT	na	na
Hirokawa et al. [8] (2002)	F/20	R	25 × 27	0	MRM + ALND	–	6	–
	F/61	L	25	0	MRM + ALND	–	24	–
	F/59	R	10	0	MRM + ALND	–	84	–
Kahn et al. [9] (2003)	F/56	L	22	0/18	MRM + ALND	–	28	–
Peintinger et al. [10] (2004)	F/36	R	35 × 35	0/15	BCS + ALND	CT + RT	120	Lung
Kinkor et al. [11] (2005)	F/70	na	na	na	na	na	na	na
	F/40	na	na	na	na	na	na	na
Tanahashi et al. [12] (2007)	F/80	R	21 × 14	0/1	MRM + SLND	–	22	–
Reis-Filho et al. [13] (2008)	Six cases	na	na	na	na	na	na	na
Stolnicu et al. [14] (2010)	F/79	L uoq	25 × 20	10/15	MRM + ALND	–	9	–
Huo et al. [15] (2011)	F/40	R uoq	36 × 29 × 24	1/21	MRM + ALND	Neo-CT + RT + HT	12	–
	F/30	R	26	2/33	BCS + ALND	CT + RT	34-died	Bone metastases
Chang et al. [16] (2011)	F/39	na	55 × 30	1/not known	BCS + ALND	–	na	na
Choh et al. [17] (2012)	F/79	Lupper pole	27	0/1	BCS + SLND	RT	9	–
Sakuma et al. [18] (2012)	F/61	R uoq	14 × 13	0	BCS + ALND	–	14	–
Zhao et al. [19] (2013)	F/38	R uoq	30	0/23	MRM + ALND	CT	10	–
Shingu et al. [20] (2013)	F/41	L	35 × 30 × 20	0/1	BCS + SLND	CT + RT	36	–
Osako et al. [21] (2013)	F/50	na	52	0/30	MRM + ALND	–	184.8	–
	F/37	na	22	0/23	BCS + ALND	–	139.2	–
	F46	na	50	0/4	MRM + SLND	–	64.8	–
Winkler et al. [22] 2013)	F/56	R	NMLE 40 × 29	0/1	MRM + SLND	Neo-CT + HT	24	–
Ripamonti et al. [23] (2013)	F/44	L uoq	13	0/2	MRM + SLND	HT	19	–
Falleti et al. [24] (2013)	F/58	R peri-areolar	30	0/1	BCS + SLND	–	na	na
Present case	F/26	R lqu	16 × 12 × 10	0/1	BCS + SLND	–	8	–

Abbreviations: uoq: upper outer quadrant, uiq: upper inner quadrant, lqu: lower quadrant union, MRM: modified radical mastectomy, BCS: breast conserving surgery, ALNA: axillary lymph node dissection, SLNA: sentinel lymph node dissection, CT: chemotherapy, Neo-CT: neo-adjuvant chemotherapy, HT: hormone therapy, na: not available.

reviewed articles. We calculated mean values and range of: age, tumor size and follow-up. We collected data about: surgical treatment, in terms of Modified Radical Mastectomy (MRM) or Breast Conserving Surgery (BCS such as lumpectomy or quadrantectomy), axillary treatment, in terms of Axillary Lymph Node Dissection (ALND) or Sentinel Lymph Node Dissection (SLND), neo-adjuvant(Neo-CT) or adjuvant chemotherapy (CT) or hormonal therapy (HT), and radiation therapy (RT). Recurrences and metastases, in terms of onset time and location, were annotated. The more applied immunohistochemical reactivity was registered as positive or negative staining or not available, when not described by authors. All reviewed cases were compared for clinical approach and histological pattern.

3. Results

We included in our review 23 articles from 1996 to 2013, presenting at least one case report of ACC of the breast [2–24]. In three of these studies a review of the literature was associated, referring to one [24], five [20], eight [19] and ten [20] previous reports. We collected a total of 39 patients, affected by ACC of the breast. Only one patient was a man [3]. Two cases described by Kinkor et al. [11] in Czech are not fully analyzed, while six cases considered by Reis-Filho et al. [13] have only been studied for the presence of *t* (12; 15) ETV6-NTRK3 translocation, so neither clinical or pathological data are reported. The clinicopathological features of 39 cases of primary acinic cell carcinoma of the breast are presented in Tables 1 and 2. The age of all patients, whose data are available, ranged from 20 to 80 years (mean age: 51 years). Tumor size ranged from 10 to 55 mm in the greatest axis (mean value: 30.5 mm). All 39 patients, whose clinical features are reported in Table 1 were treated surgically, 16 with MRM and 15 with BCS such as lumpectomy or quadrantectomy. Axilla was treated in 29 cases. In 21 patients ALND, in 8 patients SLND was performed. The node status was reported in 22 cases, in 7 cases at least one node was positive for metastases. In 4 cases neo-adjuvant chemotherapy was performed prior to surgery. In 10 patients adjuvant therapy was reported: seven of them had CT, other four HT. In 6 cases radiation therapy (RT) followed surgery (Table 1). Follow-up was available in 26 patients and the longest follow-up period was 184.8 months (range: 6–184.8 months). Recurrence occurred in one patient after lumpectomy. Three patients reported metastases: one occurring in the liver, one in the lung and one in bone after 12, 96 and 34 months after surgery, respectively. Apart from one patient who developed liver metastases, and died of disease three years after diagnosis, none of the other patients with follow-up has died of disease.

The histopathological features of the same 39 cases of ACC are reported in Table 2. The histological pattern was predominantly solid with a microglandular structure, in four cases a cystic or/and papillary components were associated [8,11,21]. All the tumor cells were cytologically closely similar to each other, characterized by monotonous round cells with a finely granular, weakly eosinophilic, or clearly vacuolated cytoplasm. The coarse bright granules were electron-dense and consistent with zymogen granules, sized from 0.08 to 0.9 μm. Mitochondria and granular endoplasmic reticulum were abundant.

Immunohistochemistry was performed using some common antibodies, but not always the same in each study. 26 cases were

Table 2
Immunohistochemical characteristics of acinic cell carcinomas of the breast reported in literature.

References	Sex/age	LYS	AMY	α_1-ACT	S-100	EMA	ER	PR	AR	Her2	E-cad	Ck 7	GCD FP15	SMA
Roncaroli et al. [2] (1996)	F/42	+	na	+	+	+	−	−	−	na	na	na	na	−
Schimao et al. [3] (1998)	M/23	+	+	+	+	+	+	na	na	na	na	na	na	na
Damiani et al. [4] (2000)	F/35	+	+	+	+	+	−	−	−	na	na	na	na	−
	F/63	+	+	+	+	+	−	−	−	na	na	na	+	−
	F/55	+	+	+	+	+	−	−	−	na	na	na	na	−
	F/64	+	+	+	+	+	−	−	−	na	na	na	+	−
	F/80	+	+	+	+	+	−	−	−	na	na	na	na	−
Schmitt et al. [5] (2000)	F/79	+	na	na	−	+	−	−	na	−	na	na	na	−
Coyne and Dervan [6] (2002)	F/49	+	na	+	+	na	na	na	na	na	na	na	na	na
Elster et al. [7] (2002)	F/48	+	na	na	+	+	−	−	na	−	na	na	na	−
Hirokawa et al. [8] (2002)	F/20	+	+	+	+	na	−	na	na	na	na	na	−	na
	F/61	+	+	+	+	na	+	na	na	na	na	na	+	na
	F/59	+	+	+	+	na	+	na	na	na	na	na	+	na
Kahn et al. [9] (2003)	F/56	+	na	na	+	+	na	na	na	na	na	na	na	na
Peintinger et al. [10] (2004)	F/36	+	na	+	+	+	−	−	−	na	na	na	na	na
Kinkor et al. [11] (2005)	F/70	+	na	na	na	na	na	na	na	na	na	na	na	na
	F/40	+	na	na	na	na	na	na	na	na	na	na	na	na
Tanahashi et al. [12] (2007)	F/80	−	+	na	−	na	−	−	na	−	na	+	−	na
Reis-Filho et al. [13] (2008)	6 cases	na	na	na	na	na	na	na	na	na	na	na	na	na
Stolnicu et al. [14] (2010)	F/79	+	na	na	na	na	−	+	+	−	+	na	+	na
Huo et al. [15] (2011)	F/50	na	na	na	+	+	+	−	na	−	na	na	na	−
	F/30	na	na	na	+	na	−	−	na	−	na	na	na	na
Chang et al. [16] (2011)	F/39	+	na	+	+	+	−	−	na	−	+	+	−	−
Choh et al. [17] (2012)	F/79	na	na	na	na	na	na	na	na	na	na	na	na	na
Sakuma et al. [18] (2012)	F/61	na	+	+	−	+	+	+	na	−	na	na	na	na
Zhao et al. [19] (2013)	F/38	+	n	−	+	+	−	−	na	−	na	na	+	na
Shingu et al. [20] (2013)	F/41	+	−	+	+	+	−	−	na	−	na	na	na	na
Osako et al. [21] (2013)	F/50	+	+	na	+	na	−	−	na	−	na	na	na	na
	F/37	+	+	na	+	na	−	−	na	−	na	na	na	na
	F46	+	+	na	+	na	−	−	na	−	na	na	na	na
Winkler et al. [22] 2013)	F/56	na	na	na	na	na	−	−	na	−	na	na	na	na
Ripamonti et al. [23] (2013)	F/44	na	na	+	+	+	−	−	−	na	na	na	−	−
Falleti et al. [24] (2013)	F/58	+	+	+	+	+	−	+	−	−	−	−	+	−
Present case	F/26	+	+	+	+	na	−	−	na	na	+	+	na	−

Abbreviations: LYS: lysozyme, AMY: amylase, α_1-ACT: α_1 anti-chimotrypsin/trypsin, S-100: S-100 protein, EMA: epithelial membrane antigen, ER: estrogen receptor, PR: progesterone receptor, AR: androgen receptor, Her2:, human epidermal growth factor receptor 2, E-cad: E-cadherin, Ck 7: cytokeratin 7, SMA: smooth muscle actin, na: not available.

positive for lysozyme (LYS), only one was negative. 15 cases were intensely stained with anti-amylase (AMY), only one not. 18 cases showed positivity for α1-antichimotripsin/tripsin (α1-ACT), only one not. S-100 protein was found in 25 cases, but three cases were not stained. Epithelial membrane antigen (EMA) was present in 18 cases, negative in no one studied. 5 cases resulted positive for estrogen receptor (ER), 3 for progesterone receptor (PR), only one case showed positivity for androgen receptors (AR), 3 tumors showed positive immunoreactivity for E-cadherin, other 3 for Cytokeratin-7 (CK7). 4 previous reports showed focal positivity for gross cystic disease fluid protein 15 (GCDFP15). Human epidermal growth factor receptor 2 overexpression (HER2/neu) and smooth muscle actin (SMA), when studied, were absent.

4. Discussion

ACC is a rare histological type of malignant epithelial neoplasms characterized by widespread acinar cell-like differentiation. The typical location are major and minor salivary glands, but ACC has been occasionally reported in other organs, such as stomach, lung, pancreas, liver, retroperitoneum, lacrimal glands and breast [2,25–33]. ACC is listed in the 2003 World Health Organization (WHO) classification of tumors of the breast as invasive breast carcinoma. Salivary gland-like tumors represent approximately 2% of primary breast carcinomas. These lesions of the breast can be subdivided into two main groups: tumors with diffuse or scanty myoepithelial differentiation, the last ones include: ACC, oncocytic carcinoma and mucoepidermoid carcinoma. ACC of the breast is similar to its salivary gland counterpart at the morphological, immunohistochemical and ultrastructural aspects. Anyway some differences should be noted: salivary ACC are circumscribed, with pushing borders, solid and cystic areas, while breast ACC are less circumscribed and infiltrating [1,34].

The ACC of the breast was first described in 1996 by Roncaroli et al. [2], and since then, several such cases have been reported. Hitherto we have found 38 cases of ACC described in literature [3–24] and one has been diagnosed in our department. Over time the diagnosis have been more and more defined, so that 6 cases of these were diagnosed as ACC retrospectively. Hirokawa et al. [8] demonstrated features of acinar cell differentiation in three secretory carcinoma of the breast, suggesting that a considerable number of ACC might have been overlooked. Osako T. et al. [21] reviewed a series of 19 cases diagnosed initially as secretory carcinoma using a panel of four markers (ETV6 rearrangement, amylase, α-lactalbumin and adipophilin) for distinguishing secretory carcinoma, ACC, cystic hypersecretory carcinoma and invasive ductal carcinoma, so that three amylase positive tumors (negative for other markers) were reclassified as ACC.

According to reviewed articles, diagnostic tools could not be compared among the 39 cases analyzed, first because from 1996 a lot of things have changed in the management of breast cancer, such as the spreading of ultrasound and then of MRI, or microhistological biopsy. Nevertheless even if the presence of acinic cell at the fine needle cytology could suggest the serous acinar differentiation, the imaging could confound the diagnosis showing a well-defined mass or even a common infiltrating lesion, easily associated to a common ductal invasive carcinoma [12,16,18]. Maybe a micro-biopsy could led to a definitive diagnosis

preoperatively, because only immunohistochemistry is diriment in ACC. As regards the therapeutic course the comparison among articles written along an eighteen years-period is difficult. The approach seems to be regulated on the basis of the clinical staging as for an invasive breast cancer is, but the impact on prognosis is not so clear. The only case with local recurrence was treated by BCS without any adjuvant therapy [4]. Nevertheless two cases developing liver and metastases had been treated radically with adjuvant CT and neo-CT [6] or RT [10], respectively. Another case treated conservatively showed bone metastases, but after 34 months. No information about further treatment of these metastatic cases have been reported [35]. According to these data it is not possible to trace a way to follow. Although metastases and recurrences exist, their rates is so low that the prognosis of the breast acinic cell carcinoma can be considered good.

The most difficult aspects of diagnosis of ACC are the rarity of this pathology, the best-known behavior of ACC localized in salivary glands, the differential diagnosis with secretory carcinoma of the breast, the dilemma between good prognosis and common infiltrating microglandular pattern. The differential diagnosis with microglandular adenosis and granular cell carcinomas (apocrine carcinomas, oncocytomas and neuroendocrine carcinomas) is based on morphological, immunohistochemical and ultrastructural features [4].

Four cases of ACC arose in a background of Microglandular Adenosis (MGA) [9,10,15,24]. According to the literature the relationships between ACC, microglandular adenosis and microglandular adenosis-associated lesions remains unclear. MGA is a well-known benign breast lesion that has been reported in association with breast cancer in up to 27% of cases [36,37]. Previous reports have shown that the pathogenesis of ACC is related to MGA. Even if coarse bright eosinophilic cytoplasmic granules are present both in MGA-associated lesions and ACC, each of these lesions show a typical feature. Microglandular carcinoma show chondroid metaplasia, absent in ACC. Similar to carcinoma arising in MGA, ACC has a microglandular pattern, cytoplasmic granules and diffuse immunoreactivity for S-100 protein. However, ACC is also positive for EMA, lysozyme, amylase and α1-antichymotripsin. While the glands in typical and atypical MGA are surrounded by basal lamina, the neoplastic glands in ACC are not so [4,8,9,13,37].

These last features best link ACC to invasive ductal carcinoma. The cases described by Kinkor [11] and Winkler [22] showed breast invasive carcinoma with serous acinar differentiation, simulating ACC. The association of acinic cells to intraductal low-grade component [11,14], sharing ACC morphological and immunohistochemical characteristics, could suggest the origin of this tumor from a pre-invasive lesion.

With regard to the immunohistochemical findings (Table 2), the most of the cells in almost all tumors were intensely stained with anti-lysozyme, anti-amylase, anti-α1-chimotripsin, anti-EMA and anti-S100 protein antisera. Amylase, lysozyme and α1-chimotripsin were components of salivary gland acinar cells and the first two enzymes are virtually absent in ordinary breast cancer. A common "triple negativity" for ER, PR and Her2/neu should suggest the possibility of a breast cancer a quite different from ordinary, such as salivary gland-like tumors [34].

The cases reviewed showed sometimes uncommon negativity for lysozyme, for amylase, for S-100 [5,12,18,20]. Otherwise in some cases strange positivity for ER, PR or AR could confound the diagnosis. Positivity to GCDFP15 could suggest an apocrine differentiation associated to ACC. Interestingly Zhao et al. [19] found a positivity for neuron-specific enolase (NSE) in their case of breast ACC, thus giving space to differential diagnosis with neuroendocrine tumors, where chromogranin and synaptophysin stain were positive too.

Huo et al. [15] reported three cases of breast carcinomas presenting prominent coarse eosinophilic cytoplasmic granules reminiscent of those in intestinal Paneth cells, but only two cases showed areas of acinic carcinoma-like features. They conclude that prominent coarse eosinophilic granules are a rare and nonspecific feature in breast epithelium.

A recent study by Ripamonti et al. [23] described the first case of ACC of the breast occurring in a BRCA 1 mutation carrier, according to previous studies, they suggest the notion that rare histological types of breast, such as malignant phylloides tumor, atypical medullary carcinoma and metaplastic breast carcinomas can occur in patients with BRCA 1 mutations.

The history of neo-CT in 4 of the cases reviewed gives origin to the question of the relationship between granules and therapy. In the first reported case information regarding the granules in pretreatment tumor was not available [4]. In a more recent study the cytoplasmic granularity was greatly reduced after neo-CT [6], in other studies represented the predominant component of the residual tumor suggesting a granular cell resistance or therapy induced granularity [4,22].

Our case present the third youngest patient among the cases reviewed and is the only one describing an association with a fibroadenoma. Nevertheless we could not establish if its true origin is in or out from the fibroadenoma. Some cases of ACC of the breast lack a fibrous capsule, but could infiltrate or not the surrounding breast tissue. In correspondence of the less differentiated component, our case showed an extensive infiltration of the sclerotic stroma forming the fibroadenoma. No true fibrous capsule was formed, but only a thin collagen stripe surrounding more differentiated acinic cells was evident. Other cases contained intraductal carcinoma with comedotype necrosis [2,16], but not our case. Immunohistochemical features are similar to other reported cases, it showed a common absence of hormonal receptor and myoepithelial differentiation. Nevertheless an uncommon positivity for pan-cytokeratin, cytokeratin 7, E-cadherin and focally for vimentin was observed.

These results suggest that further investigations are required to elucidate the histogenesis of mammary ACC, thus the guidelines for diagnosis and treatment. This review is the first to collect 23 articles and present 39 cases of ACC; only case reports, eventually combined to a partial review, have been published previously. The limits of this review are linked to the limited sources, because all data have been collected on websites; to the data not fully comparable, because of the lack of complete clinical features; to the dissimilarity in diagnostic and immunohistochemical testing applied.

5. Conclusions

ACC of the breast is a rare tumor, similar to its salivary gland counterpart regarding the morphological, immunohistochemical and ultrastructural aspects, but it not always shares the same benign behavior. The constant negativity for hormone receptor signs a great difference from the ordinary breast carcinoma, so perhaps different therapeutic strategies should be proposed. We reviewed 39 cases of ACC sharing typical pathologic characteristics, but no accordance in clinical management was found. We added an interesting case of mammary ACC for the concomitant presence of a fibroadenoma, forming a unique lesion. By comparison we note several similarities with previously described tumors, but we suggested no adjuvant therapy and the prognosis seems to be good. Further studies are needed to better understand the origin and the correct treatment of the ACC arising in the breast.

Funding

All authors have no source of funding.

Ethical approval

Ethical approval was requested and obtained from the University of Naples Federico II ethical committee.

Conflicts of interest

All Authors have no conflict of interests.

Author contribution

Limite Gennaro: Participated substantially in conception, design, and execution of the study and in the analysis of data, reviewing the manuscript.

Di Micco Rosa: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Esposito Emanuela: Participated substantially in the analysis and interpretation of data, reviewing the manuscript.

Sollazzo Viviana: Participated substantially in the analysis and interpretation of data.

Cervotti Maria: Participated substantially in the analysis and interpretation of data.

Pettinato Guido: Participated substantially in analysis and interpretation of pathologic and immunohistochemical data; he also contributed to edit figures.

Varone Valeria: Participated substantially in analysis and interpretation of pathologic and immunohistochemical data; she also contributed to edit figures.

Benassai Giacomo: Participated substantially in the analysis and interpretation of data.

Amato Bruno: Participated substantially in reviewing the manuscript.

Pilone Vincenzo: Participated substantially in the analysis and interpretation of data.

Luglio Gaetano: Participated substantially in reviewing the manuscript.

Vitiello Antonio: Participated substantially in the analysis and interpretation of data.

Hasani Ariola: Participated substantially in reviewing the manuscript.

Liccardo Filomena: Participated substantially in the analysis and interpretation of data.

Forestieri Pietro: Participated substantially in reviewing the manuscript.

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