Research Article

Diagnosis and Clinical Management of Neuroendocrine Tumor of the Breast: Report of Six Cases and Systematic Review of Existing Literature

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Abstract

Introduction: Neuroendocrine neoplasms of the breast (bNETs) are considered a rare disease, even if in WHO data they represent about 2-5% of all breast cancer. The last WHO classification includes: well-differentiated neuroendocrine tumor (bNET), neuroendocrine carcinoma (NEC) and invasive carcinoma with neuroendocrine differentiation. The current knowledge on clinical management of bNETs is poor and patients are usually treated according to non-endocrine tumor components guidelines.

Materials and Methods: We presented our experience of six cases of bNETs. Moreover, we conducted a systematic review of published data on diagnosis, treatment and outcome of this kind of tumors.

Results: bNENS usually presented as palpable breast masses, classically appearing as irregular hypoechoic lesions at US examination and as hyperdense masses at mammography. Usually pre-operative tumor biopsy is not able to recognize the neuroendocrine components and the final diagnosis is performed only on definitive histopathological assessment. The most frequent subtype seems to be neuroendocrine carcinoma and synaptophysin is positive in most specimens. Treatment strategies, including surgical treatment, radiotherapy and medical treatment are nowadays based on current non-endocrine breast cancer guidelines, independently from neuroendocrine components, even if some studies have proposed the use of somatostatin analogues for bNET and cisplatin-etoposide for NEC. Prognosis of all bNETs, especially of poorly differentiated neoplasia, seems worse compared to non-neuroendocrine breast cancer and stage and morphology seem the best predictor of tumor outcome.

Conclusions: We provide an algorithm for clinical management of bNETs, basing on available data. More studies are necessary for confirming the best treatment strategy for these patients, in order to improve clinical outcome.

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Introduction

The first description of a neuroendocrine tumor (NET) of the breast dates back to 1963: an invasive breast cancer morphologically similar to intestinal carcinoids [1]. World Health Organization (WHO) recognized neuroendocrine tumors of the breast as a separate entity of breast cancer only in 2003, defining them as primary neuroendocrine carcinomas exhibiting morphological features of gastrointestinal and pulmonary NETs in which more than 50% of the cells expresses neuroendocrine markers (chromogranin A and synaptophysin) [2]. In 2012 the cut-off of 50% of the cells expressing neuroendocrine markers was eliminated and bNENS were divided in groups according to morphology: well-differentiated (carcinoid-like) neuroendocrine tumor (bNET), poorly differentiated neuroendocrine carcinoma (NEC) small-cell neuroendocrine carcinoma (SCNC) and invasive carcinoma with neuroendocrine differentiation (ICNE) [3]. According to WHO data, bNETs represent about 2.5% of all breast cancer [4]. In data from SEER database bNENS represent less than 0.1% of total invasive carcinomas of the breast [5]. Probably these frequencies may underestimate the real
incidence of bNENs: retrospective studies on breast tumor specimens showed high incidence of neuroendocrine cells with positive neuroendocrine markers [6, 7]. Nowadays, the impact of neuroendocrine differentiation of breast cancer on diagnosis, treatment and outcome is still unclear. Because of the low incidence of this kind of neoplasia, no clinical trials or guidelines are available on this topic. The aim of this systematic review is to summarize clinical presentation, diagnosis, treatment and outcomes of all available cases in Literature, adding our personal experience of six cases.

Materials and Methods

I Article Identification

We searched PubMed, Embase, Google Scholar and Cochrane databases for English language studies on neuroendocrine tumor of the breast. Search terms used were: “neuroendocrine tumor” AND breast, “neuroendocrine tumour” AND breast, “neuroendocrine cancer” AND breast; “neuroendocrine carcinoma” AND breast.

II Eligibility Criteria

We included English-language studies on humans with any of the following design: randomized clinical trials, prospective non-randomized trials, retrospective studies, case reports and case series. We selected cases classified by the pathologist as neuroendocrine breast tumor, according to WHO classification used at time of publication (2003 or 2012). For article published before 2003, we included cases defined as breast neuroendocrine tumors or carcinoids by the Authors. We included in the systematic reviews only articles with data on at least one of the following topics: clinical presentation, treatments and outcomes of neuroendocrine tumors of the breast. Last search date was February 2019.

III Article Selection

Each study was screened by abstract and title and potentially eligible studies were further assessed in detail by retrieving full-length articles. Each full-length article was independently reviewed by two separate Authors following inclusion criteria. Two authors independently extracted data from the articles that met the inclusion criteria. A standardized form was used to extract the following information: year of publication, type of study, number of patients included, age at diagnosis, sex, familiarity for breast tumors, other known risk factors for breast cancer, clinical presentation, palpability, diagnostic procedures (ultrasound, mammography, MRI, CT, PET, fine needle aspiration and biopsy), treatment strategy (surgery, medical treatment, radiotherapy), histopathological examination including immunohistochemistry, stadiation and outcomes.

Results

I Case Series

We present six cases of bNENs diagnosed in Humanitas Research Hospital of Milan from 2012 to 2018. All patients provided written informed consent to case publication. All cases were females, mean age 64.2 ± 13.7. All patients presented with breast lumps (in one case painful). When performed, breast ultrasound (US) always showed a mass (in three cases hypoechoic mass) and mammography showed 4 spiculated and 1 regular margin hyperdense lesion of 0.8-2.7 cm of maximum diameter. Breast magnetic resonance imaging (MRI) was not performed in all cases due to lack of indication. Biopsy showed in all cases infiltrating breast carcinoma but only in one case succeeded in identifying neuroendocrine differentiation. All patients underwent surgical intervention. Surgery on tumor mass was in 4 cases breast conservative surgery (BCS) and in 2 cases total mastectomy; axillary surgery consisted of 3 lymphadenectomies and 3 sentinel lymph node biopsies. Radiotherapy was performed in the 4 cases of BCS. Definitive histopathological evaluation confirmed in all cases the neuroendocrine differentiation: 2 bNET, 2 breast NEC and 2 ICNE. In our case series synaptophysin has been the most important neuroendocrine marker, been positive in 6/6 cases. Chromogranin was positive in 1/3 cases while NSE was never evaluated. 5/6 (83.3%) cases showed positivity for both oestrogen and progesterone receptors. Ki67 ranged from 10 to 90%.

After definitive diagnosis, all patients performed a total body scans (¹⁸FDG PET/CT and contrast-enhanced total body CT scans) for excluding neuroendocrine neoplasm of other origin. After surgical removal, patients underwent chemotherapy or hormonal therapy according to associated non-endocrine breast tumor histotype guidelines (2 only hormone therapy, 1 chemotherapy, 3 hormone therapy associated to chemotherapy). One patient with NEC developed liver and bone metastasis after 6 months and is now alive with metastatic disease after one year of follow-up. Medium follow-up of other cases was 65 (35-120) months: 3 patients are today alive and disease free, two are alive with local recurrence. All data are summarized in Table 1A.

Figure 1: Flowchart of literature eligibility assessment process.

II Systematic Review

From the initial search we retrieved 445 articles. After screening for title and abstract we identified 140 potentially eligible articles. After full text examination a total of 117 articles were included in this systematic review (Figure 1). 102 articles were case reports on a total of 113 bNENs. Available data are summarized in Table 1B. 15 articles were retrospective studies or case series on a total number of 731 patients: data are summarized in Table 2.
Table 1A: Case series.

| Case | Age | Clin pres | US | MX | CT | PET | Bio / Cit | Nadj treat | Surgery | Adj treat | Adj RT | pTNM | Tum size | LNs | Histo-type | CrA | Syn | ER | PR | Her2 | Ki67 | FUP (mo) | Alive status |
|------|-----|-----------|----|----|----|-----|----------|------------|----------|-----------|--------|-------|--------|-----|------------|-----|-----|-----|-----|------|-----|---------|--------------|
| 1    | 66  | BL        | NA | NA | Neg | Neg | Bio      | NO         | BCS + ALND| ADR/CPA + DTX + Ana | Yes    | T2N3aM0 | 12/14  | ICNE | NA       | +  | 70%       | 60% | 0       | 10% | 120  | AWD    |
| 2    | 54  | BL        | HyBM | SBM | Neg | Neg | Bio      | NO         | Mast + SLNB | ADR/CPA + DTX + Ana | No     | T2N0M0 | 0/1    | NET  | -        | +  | 95%       | 29% | 0       | 70% | 60   | NED    |
| 3    | 43  | PBMB      | HyBM, N+ | SBM | Neg | BoMet, LMet | Bio     | Yes        | Mast + ALND | CDDP + VP-16 | Yes    | T4bN3aM1 | 9/14   | NEC   | +        | 0  | 0         | 0   | 90%     | 12  | AWD  |
| 4    | 66  | BL        | BM  | HypBM | Neg | Neg | Bio      | NO         | BCS + ALND | ADR/CPA + DTX + Ana | Yes    | T1N3aM0 | 13/15  | ICNE | NA       | +  | 80%       | 70% | 0       | 12% | 53   | AWD    |
| 5    | 78  | BL        | HyBM | SBM | Neg | Neg | Bio      | NO         | BCS + SLNB | Ana      | No     | T1cN0M0 | 0/16   | NET  | -        | +  | 95%       | 95% | 1+      | 25% | 76   | NED    |
| 6    | 78  | BL        | BM  | SBM | Neg | Neg | Bio      | NO         | BCS + SLNB | Ana      | Yes    | T1cN0M0 | 0/2    | NEC   | NA       | +  | 95%       | 95% | 0       | 20% | 70   | NED    |

**HeadingS:** NA = Not available data; Clin Pres = Clinical presentation; US = breast Ultrasound; MX = mammography; Bio = biopsy; Cit = citology; Ad treat = adjuvant treatment (chemotherapy and/or hormone therapy); Adj RT = adjuvant radiotherapy; Tum size = tumor size (centimeters); LNs = lymph nodes removed; CrA = Chromogranin A; Syn = Synaptophisin; ER = Estrogen receptor; PR = Progesterone receptor; Her2 = her2-neu receptor; FUP = follow-up (months).

**Clinical and radiological findings:** Pos = positive for malignancy; Neg = negative for malignancy; BM = Breast Mass; CM = carcinomatous mastitis; N+ = axillary adenopathy; PBMB = Painful breast mass; BL = breast lump; SR = Skin retraction, NR = nipple retraction, PLM = Paget-like Mass; BND = Bloody nipple discharge; UBM = Ulcerated Breast Mass; MBM = Multilobulated breast mass; HyBM = Hypoechoic (US) / Hypodense (MX) breast mass; Hyp = Hyperechoic (US) / Hyperdense breast mass; HeBM = Heterogeneous breast mass; SBM = Spiculated breast mass; Mic = microcalcifications, BoMet = Bone Metastases; LMet = Lung metastasis; PAMet = Perianal metastases, PiMet = Pituitary metastases; PaMet = Pancreatic metastases; PE = Pleural effusion; MMet = Multiple metastases; IBM = Isoechoic breast mass; Neg = Negative; Sus = suspicious; LMet = lung metastasis.

**Mast:** Mastectomy; BCS = Breast Conservative Surgery; SLNB = Sentinel Lymph Node Biopsy; ALND = Axillary Lymph Node Dissection.

**Chemotherapy:** ChT = chemotherapy (not defined); HoT = hormone therapy (not defined); CDDP = Cisplatin, CBL = Carboplatin, VP-16 = Etoposide, CPT-11 = Irinotecan, 5-FU = Fluorouracil, EPI = Epirubicin, CAP = Capetitabine, DTX = Docetaxel, 5'-DFUR = 50 deoxy-5-fluorouridine, Tor = Toremifene, CPA = Cyclophosphamide, EPI = Epirubicin, Tam = Tamoxifen, Let = Letrozole, S = Streptozocin, MTX = Methotrexate, Ana = Anastrazole, AI = Aromatase inhibitor, LHRH = Lenising hormone releasing hormone analogue, UFT = Uracil & Tegafur, PTX = Paclitaxel, ADR = Adriamycin (Doxorubicin), Sando = Sandostatin, Som = Somatostatin; Ever = Everolimus, Bev = Bevacizumab, Erl = Erlotinib; Palb = Palbociclib; Oct = Octreotide.

**Histology:** SCNC = Small Cell Neuroendocrine Carcinoma, ICNE = Invasive carcinoma with neuroendocrine differentiation; NET = well-differentiated neuroendocrine tumor; NEC = poorly differentiated neuroendocrine carcinoma.

**Follow-up:** NED = No evidence of disease; AWD = Alive with disease; DOD = Died of disease; DUC = Died of Uncertain cause

†Median follow-up.
Table IB: Case reports available in literature.

| Author (year) | Preoperative diagnosis | Treatment | Tumor biology | Follow-up |
|---------------|------------------------|-----------|---------------|-----------|
| Wade [23] 1983 | UBM N+ MBM MBM Neg NO Bio | NO Mast + ALND VP-16 NO | pTNM Tum size LNs Histo-type CrA Syn ER PR Her2 Ki67 FUP (mo) Alive status | 1987 25/25 SCNC NA NA NA NA NA NA NA NA |
| Jendr [24] 1984 | NA NA NA NA NA | NA NA NA NA | TXN1M1 NA +/? NA NA NA NA NA NA 14 DOD |
| Francois [25] 1995 | BM HoBM HBM Neg NO Cit | NO Mast + ALND CPA/ADR/VP-16 Yes | T2N0M0 4 0/12 SCNC NA NA - NA NA 21 DUC |
| Chua [26] 1997 | BM NA NA NA NA Bio | NO BCS NA NO | T2N0MX 4.5 NA SCNC - + - - NA <1 NED |
| Yalcin [27] 1997 | BM BM BM BM Neg NO Bio | NO Mast + ALND NO | T2N0M0 5 0/7 NET + NA NA NA NA 18 NED |
| Fukunaga [28] 2004 | BM Neg BM Neg BM NA | NA Mast + ALND NA NA | T2N0M0 2.5 0/59 NET + + + - NA 16 NED |
| Fukunag [29] 2004 | BM BM BM BM Neg NO NA | NO Mast + ALND NO NO | T2N1M0 2.5 1/7 NEC + + - - NA 12% 72 NED |
| Samli [30] 2004 | BM BM BM BM Neg NO Bio | Yes Mast + ALND CDDP/VP-16+ 5-FU CPA/MTX/5-FU Yes | T4N1M0 4.5 10/11 SCNC + + + + NA 6 AWD |
| Yamasaki [32] 2001 | BM Neg SBM Neg Sus Cit | NO Mast + ALND CPA/MTX/5-FU NO | T2N0M0 3.5 1/0 SCNC + - - - NA 16 NED |
| Huang [33] 2001 | NA NA NA NA NA NA | NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA |
| Salme [34] 2001 | NA NA NA NA NA NA | NO BCS ChT YES | T2N0M0 4 NA NA NA NA NA NA NA | 9 NED |
| Bertui [35] 2001 | LMet Neg Neg LMet NO NA | Yes LMet resection Tam NO | TXN1M1 NA NA NEC + + + - 12 144 NED |
| Bigoti [36] 2004 | CM BM BM BM NA Neg Bio | Yes NO ChT + Som NO | T2N1M0 18 2/9 SCNC - + + + - NA 15 DOD |
| Bergman [37] 2004 | BL BM BM BM Neg Bio | NO Mast + ALND NO | T2N1M0 2.5 2/5 SCNC - - - - NA 14 NED |
| Jochems [38] 2004 | BM BM BM BM Neg NO | NO Mast + ALND Tam NO | T2N0M0 3 0/10 NEC + + + + - NA 12 NED |
| Mariscal [39] 2004 | BM, SR, N+ HyBM BM, N+ Neg Bio | Yes BCS + ALND HoT NO | T2N1M0 5.5 1/7 SCNC NA + NA NA NA 6 NED |
| Sridhar [40] 2004 | NA NA NA NA NA NA | NO BCS ChT YES | T2N1M0 2 NA NA NA NA NA NA NA | 18 NED |
| Yamamoto [41] 2004 | NA NA NA NA NA NA | NO Neo Mast + ALND NO | T2N0M0 6.5 NA NA NA NA NA NA NA | 34 NED |
| Adegbola [42] 2005 | BL NA NA NA NA Neg NO | NO BCS CDDP/VP-16+ Yes | T1N1M0 1 0 SCNC + + - NA - NA 48 NED |
| Hennessey [46] 2007 | PAMet Neg PAMet NO Bio | NO Mast + SLNB ChT/Tam NO | TXN1M1 NA NA NEC + + NA NA NA NA 14 NED |
| Kitakata [47] 2007 | BL HyBM BM BM Neg Neg | NO Mast + ALND CPA/Epi + DTX NO | T2N1M0 4.5 2/15 SCNC - + + + - NA 22 NED |
| La Rosal [48] 2007 | BL Pos Pos NO NO Cit NO Mast ChT NO | T2N1M0 2.5 NA NEC + + + + - NA 16 NED |
| Vidulich [49] 2007 | BM, N+, PE BM, N+ NA NA LMet MMet Cit. Bio | NO NO Oct/Ever, Bev/Eri NO | T4N1M1 5 NA NEC + + + + - NA 16 AWD |

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| Year | Cases | Method | Treatment | Outcome |
|------|-------|--------|-----------|---------|
| 2007 | 76    | NA     | NA Mast + ALND | NA Mast + ALND |
| 2008 | 39    | BL     | HypBM NO Mast + ALND | Ctx / Hot |
| 2008 | 27    | BM     | HeBM Neg Bio | BCS + ALND |
| 2008 | 31    | BL     | HyBM Neg MMet | Mast + ALND |
| 2008 | 30    | PLM    | NA No BCS + SLNB | T2N0M0 |
| 2008 | 62    | NA     | NA Mast + ALND | NA T1N2MX |
| 2008 | 41    | NA     | NA Mast + ALND | NA T2N1MX |
| 2008 | 33    | NA     | NA Mast + ALND | NA T2N1MX |
| 2008 | 60    | BM     | MBT Neg | T2N0M0 |
| 2009 | 40    | BL, N+ | NA Mast + ALND | NA |
| 2009 | 84    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2009 | 40    | BM     | NA BM Neg | NA BCS |
| 2009 | 50    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2009 | 68    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2009 | 60    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2009 | 65    | BM     | HyBM Neg | T4N2M1 |
| 2009 | 63    | BM HyBM Neg | NA Mast + ALND | NA |
| 2009 | 41    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2009 | 81    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2009 | 48    | BoMet  | NA Mast + ALND | NA T2N0M0 |
| 2009 | 70    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2009 | 64    | BM BM  | Bl Neg | NA Mast + ALND |
| 2009 | 51    | BM BM  | Neg Bio | NA Mast + ALND |
| 2010 | 61    | NA     | NA Mast + ALND | NA |
| 2010 | 40    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2010 | 54    | BIND   | HyBM | NA Mast + ALND |
| 2010 | 65    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2010 | 53    | BM     | Neg BM | NA Mast + ALND |
| 2010 | 60    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2010 | 72    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2011 | 63    | Na     | Na Pos | Na BCS |
| 2011 | 68    | BM N+  | BL | HypBM Mast + ALND |
| 2011 | 64    | BM N+  | BN Neg | Mast + ALND |
| 2011 | 28    | BL     | BN NA Bio | Mast + ALND |
| 2011 | 43    | BM     | BM NA NA | Mast + ALND |
| 2011 | 67    | UMB    | BM BM NA | Mast + ALND |

**Overall**

| Year | Cases | Method | Treatment | Outcome |
|------|-------|--------|-----------|---------|
| 2007 | 76    | NA     | NA Mast + ALND | NA Mast + ALND |
| 2008 | 39    | BL     | HypBM NO Mast + ALND | Ctx / Hot |
| 2008 | 27    | BM     | HeBM Neg Bio | BCS + ALND |
| 2008 | 31    | BL     | HyBM Neg MMet | Mast + ALND |
| 2008 | 30    | PLM    | NA No BCS + SLNB | T2N0M0 |
| 2008 | 62    | NA     | NA Mast + ALND | NA T1N2MX |
| 2008 | 41    | NA     | NA Mast + ALND | NA T2N1MX |
| 2008 | 33    | NA     | NA Mast + ALND | NA T2N1MX |
| 2008 | 60    | BM     | MBT Neg | T2N0M0 |
| 2009 | 40    | BL, N+ | NA Mast + ALND | NA |
| 2009 | 84    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2009 | 40    | BM     | NA BM Neg | NA BCS |
| 2009 | 50    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2009 | 68    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2009 | 60    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2009 | 65    | BM     | HyBM Neg | T4N2M1 |
| 2009 | 63    | BM HyBM Neg | NA Mast + ALND | NA T2N0M0 |
| 2009 | 41    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2009 | 81    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2009 | 48    | BoMet  | NA Mast + ALND | NA T2N0M0 |
| 2009 | 70    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2009 | 64    | BM BM  | Bl Neg | NA Mast + ALND |
| 2009 | 51    | BM BM  | Neg Bio | NA Mast + ALND |
| 2010 | 61    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2010 | 40    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2010 | 54    | BIND   | HyBM | NA Mast + ALND |
| 2010 | 65    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2010 | 53    | BM     | Neg BM | NA Mast + ALND |
| 2010 | 60    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2010 | 72    | NA     | NA Mast + ALND | NA T2N0M0 |
| 2011 | 63    | Na     | Na Pos | Na BCS |
| 2011 | 68    | BM N+  | BL | HypBM Mast + ALND |
| 2011 | 64    | BM N+  | BN Neg | Mast + ALND |
| 2011 | 28    | BL     | BN NA Bio | Mast + ALND |
| 2011 | 43    | BM     | BM NA NA | Mast + ALND |
| 2011 | 67    | UMB    | BM BM NA | Mast + ALND |

**Systematic Review of Existing Literature**

- **Mast + ALND**: Mastectomy + Axillary lymph node dissection
- **BCS + ALND**: Breast conserving surgery + Axillary lymph node dissection
- **HyBM**: Hyperthyroidism
- **BM**: Breast mass
- **MB**: Metastatic breast
- **ICNE**: Incomplete carcinoma of neuroendocrine
- **NEC**: Neuroendocrine carcinoma
- **AWD**: Advanced
- **NED**: Not evaluable due to death

**Outcome**

- **Mast + ALND**: Mastectomy + Axillary lymph node dissection
- **BCS + ALND**: Breast conserving surgery + Axillary lymph node dissection
- **HyBM**: Hyperthyroidism
- **BM**: Breast mass
- **MB**: Metastatic breast
- **ICNE**: Incomplete carcinoma of neuroendocrine
- **NEC**: Neuroendocrine carcinoma
- **AWD**: Advanced
- **NED**: Not evaluable due to death
| Navrozoglou[86] | 2011 | 73 | NO | BN | BN | NA | Neg | Bio | NO | Mast + ALND | NO | NO | T1N0M0 | 1,1 | 0/17 | NET | + | + | NA | NA | NA | NA | 48 | NED |
| Nicoletti[87] | 2011 | 40 | BM | BN | BN | Neg | NO | Bio | NO | Mast + ALND | ADRC/CPA + CBL/V-16 + Triamcinolone | NO | T2N1M0 | 3 | 1/16 | SCNC | + | + | + | - | + | 96 | NED |
| Nozoe[88] | 2011 | 57 | BL | HyBM | BM | NA | NA | NA | NO | Mast + ALND | CMF + AI | NA | NA | 3 | 0/7 | NEC | NA | + | + | - | NA | NA | NA |
| Zhang[89] | 2011 | 29 | BND | BM | BM | NO | NO | Cit | NO | BCS + SLNB | CPA/EP/5-FU + DTX + Tor | NO | T2N0M0 | 2 | 0/2 | NET | + | + | - | - | 1% | 20 | NED |
| Alkaied[90] | 2012 | 83 | Anorexia | Neg | Neg | NO | Pos | Bio | Yes | NO | Letrozole + Ana | NO | TXNM1 | NA | NA | SCNC | - | + | + | NA | NA | NA | NA | 12 | NED |
| Flessas[91] | 2012 | 59 | NO | NA | Mic | NO | NO | Bio | NO | BCS + ALND | NA | NA | T2N0M0 | 2.8 | 1/7 | ICNE | + | + | - | NA | NA | NA | NA | NA |
| Graça[92] | 2012 | 83 | BM | BM | BM | Neg | Neg | Cit | NO | BCS + SLNB | HoT | NO | T2N0M0 | 2.4 | 0/1 | NEC | NA | + | + | NA | NA | NA | NA | NA | NED |
| Menéndez[93] | 2012 | 44 | NO | NA | BM | NA | NA | NA | NO | BCS + ALND | 5-FU/EP/CPA | Yes | T2N0M0 | 2 | 1/7 | NEC | NA | + | + | - | NA | 48 | NED |
| Zhang[94] | 2012 | 68 | NO | NA | BM | NA | NA | NA | NO | BCS + SLNB | 5-FU/EP/CPA + DTX + Ana | Yes | 3.6 | NA | NEC | NA | + | + | - | NA | 24 | NED |
| Miura[94] | 2012 | 69 | NO | HyBM | BM | NA | NA | NA | NA | BCS + SLNB | 5-FU/EP/CPA | Yes | T1N0M0 | 1 | 0/1 | NEC | NA | + | + | - | NA | 8 | AWD |
| Psona[95] | 2012 | 72 | NO | NA | NA | Neg | NA | Cit, Bio | NO | BCS + SLNB | NA | NA | T1N0M0 | 1.4 | 0/1 | ICNE | + | + | + | - | 10% | 2 | NED |
| Sui[96] | 2012 | 46 | BM | HyBM | HxHyBM | Neg | NO | NA | NO | Mast + ALND | CDDP/EP/VP-16 | Yes | T3N0M0 | 6.5 | NA | NET | + | NA | NA | NA | NA | 6 | NED |
| Watrowski[97] | 2012 | 75 | PB | BM | HyBM | Neg | NA | NO | Bio | NO | Mast + ALND | Letrozole | NO | T2N0M0 | 4 | 0/7 | ICNE | + | + | + | - | NA | 20 | NED |
| Yavas[98] | 2012 | 56 | BM | HyBM | NA | NO | NO | Bio | NO | BCS + SLNB | CPA/EP/5-FU + HoT | Yes | T1N0M0 | 1.7 | 0/1 | NET | NA | + | + | - | 46% | 15 | NED |
| Abbas[99] | 2013 | 37 | BL, N+ | NA | NA | BoMet | NA | Bio | NO | Mast + ALND | 5-FU/ADR/CPA + CDDP + VP-16 | No | T3N2M1 | 7.5 | 9/19 | ICNE | + | NA | NA | NA | NA | 6 | NED |
| Angarita[100] | 2013 | 31 | BL | Neg | SBM | Neg | NO | Bio | Yes | BCS + ALND | CDDP/VP-16 + PTX | NA | T2N0M0 | 3.2 | 0/7 | ICNE | + | + | - | NA | >20% | 13 | AWD |
| Chang[101] | 2013 | 42 | BL | MBM | HyBM | NO | Neg | Cit | No | NO | NA | NA | T2N1M0 | NA | +/?- | NEC | + | + | NA | - | NA | NA | NA | NA |
| Hannon[102] | 2013 | 60 | PB | MBM | Neg | Neg | NO | Bio | NO | BCS | CBL/V-16 | NO | T1N2M0 | 1.4 | 4/11 | NEC | - | + | + | NA | - | NA | NA | NA |
| Senetla[103] | 2013 | 82 | Asthenia | BM | NA | Pimet | NO | Bio | NO | BCS + SLNB | CPA/EP/5-FU + HoT | NO | T1N0M1 | 2.3 | NA | NEC | + | + | - | 10 | NA | NA | NA |
| Yoon[8] | 2013 | 44 | BM | HyBM | HyBM | Neg | Neg | Bio | NA | Mast + ALND | CPA/AD | NA | T2N0M0 | 2 | NA | NEC | + | + | + | NA | 2 | NED |
| Cnikir[104] | 2014 | 75 | BM | BM | BM | NA | NA | Bio | NO | Mast + ALND | CDDP/VP-16 | Yes | T0N0M0 | 0 | 0/7 | SCNC | + | + | + | 5% | 30% | NED |
| Pagano[105] | 2014 | 77 | PB | SBM | SBM | NA | NA | Bio | NO | Mast + ALND | CPA/MTX/5-FU + Tamoxifen | NO | T2N0M0 | 2.3 | NA | NEC | + | + | + | - | 10% | 9% | NED |
| Suhani[106] | 2014 | 51 | BL, NR | NA | BM | Neg | NA | Bio | NO | Mast + ALND | CPA/AD/5-FU + AI | Yes | T3N1M0 | 6.5 | 1/15 | NET | NA | + | + | - | NA | 48 | NED |
| Suhani[106] | 2014 | 66 | BL | NA | NA | Neg | NA | Bio | NO | Mast + ALND | CPA/AD/5-FU + AI | Yes | T2N0M0 | 4.5 | 2/16 | NET | + | + | - | NA | 36 | NED |

*Abbreviations: ADRC, adjuvant double dose; APA, adjuvant peglated epirubicin; BCS, breast conserving surgery; CT, chemotherapy; DM, docetaxel; E, docetaxel; F, fluorouracil; II, second line; I, first line; IV, third line; MBA, tamoxifen; MC, mitotane; M, melphalan; N, cyclophosphamide; T, taxol; T, taxotere; T, tamoxifen."
| Case | Age | Sex | Hist | Size | Malignancy | Treatment | Follow-up | Status |
|------|-----|-----|------|------|------------|-----------|-----------|--------|
| 1    | 50  | BL  | NA   | NA   | Neg        | Mast + ALND | Yes       | T2N0M0  |
| 2    | 60  | BL, BND | NA   | NA   | Neg        | Mast + ALND | Yes       | T3N1M0  |
| 3    | 2015 | 34  | BL   | Neg  | HypBM     | NA         | Yes       | T2N0M0  |
| 4    | 2015 | 60  | SR   | HyBM | NA         | NO         | YES       | T3N0M0  |
| 5    | 2015 | 65  | BL   | NA   | Neg        | NO         | NA        | T3N2M0  |
| 6    | 2015 | 80  | BM   | Neg  | NO         | Yes        | NO        | T4NXM1  |
| 7    | 2016 | 60  | BL, N+ | NA   | NA         | NA         | NO        | NA      |
| 8    | 2015 | 43  | BM   | HyBM | MBM       | NO         | Yes       | T2N1M0  |
| 9    | 2016 | 53  | BL   | Neg  | MBM       | NO         | Cit       | T2N0M0  |
| 10   | 2016 | 73  | SR   | BM   | BM        | PaMet      | NA        | T2N3M1  |
| 11   | 2016 | 50  | BL   | Neg  | Neg       | NA         | NA        | NA      |
| 12   | 2016 | 42  | BL   | HyBM | HypBM, Mic| NA         | NA        | T2N1M0  |
| 13   | 2016 | 46  | PBM  | HyBM, N+ | NA   | NA         | NA        | T2N2M0  |
| 14   | 2016 | 57  | Neuralgia | NA  | NA        | NA         | NA        | NA      |
| 15   | 2017 | 47  | NO   | NA   | BM, NO    | Neg        | Bio       | NA      |
| 16   | 2017 | 67  | Neurajla | HyBM | BM, MMet  | MMet       | Bio       | NO      |
| 17   | 2017 | 57  | BL   | HyBM | BM        | NA, BoMet  | NO        | BCS     |

**Headings:** NA = Not available data; Clin Pres = Clinical presentation; US = breast Ultrasound; MX = mammography; Bio = biopsy; Cit = citology; Ad treat = adjuvant treatment (chemotherapy and/or hormone therapy); AdJ RT = adjuvant radiotherapy; Tum size = tumor size (centimeters); LNs = lymph nodes removed; CrA = Chromogranin A; Syn = Synaptophisin; ER = Estrogen receptor; PR = Progesterone receptor; Her2 = her2-neu receptor; FUP = follow-up (months)

**Clinical and radiological findings:** Pos = positive for malignancy; Neg = negative for malignancy; BM = Breast Mass; CM = carcinomatous mastitis; N+ = axillary adenopathy, PBM = Painful breast mass; BL = breast lump; SR = Skin retraction, NR = nipple retraction, PLM = Paget-like Mass; BND = Bloody nipple discharge; UBM = Ulcerated Breast Mass; MBM = Multilobulated breast mass; HyBM = Hypoechoic (US) / Hypodense breast mass, HeBM = Heterogeneous breast mass, SPM = Spiculated breast mass, Mic = microcalcifications, BoMet = Bone Metastases; LMet = Lung metastasis; PAMet = Pancreatic metastases; PE = Pleural effusion; MMet = Multiple metastases; IBM = Isoechoic breast mass Neg = Negative; Sus = suspicious; LMet = lung metastasis Mast = Mastectomy; BCS = Breast Conservative Surgery; SLNB = Sentinel Lymph Node Biopsy; ALND = Axillary Lymph Node Dissection

**Chemotherapy:** ChT = chemotherapy; HoT = hormone therapy; CDDP = Cisplatin, CBL = Carboplatin, VP-16 = Etoposide, CPT-11 = Irinotecan, 5-FU = Fluorouracil, EPI = Epirubicin, CAP = Cyclophosphamide, DTX = Docetaxel, 5'-DFUR = 50 deoxy-5-fluorouridine, Tam = Tamoxifen, LHRH = Leutinising hormone releasing hormone analogue, UFT = Uracil & Tegafur, PTX = Paclitaxel, ADR = Adriamycin (Doxorubicin), Sando = Sandostatin, Som = Somatostatin; Ever = Everolimus, Bev = Bevacizumab, Erl = Erlotinib; Palb = Palbociclib; Oct = Octreotide

**Diagnosis and Clinical Management of Neuroendocrine Tumor of the Breast: Report of Six Cases and Systematic Review of Existing Literature**
**Histology:** SCNC = Small Cell Neuroendocrine Carcinoma, ICNE = Invasive carcinoma with neuroendocrine differentiation; NET = well-differentiated neuroendocrine tumor; NEC = poorly differentiated neuroendocrine carcinoma

**Follow-Up:** NED = No evidence of disease; AWD = Alive with disease; DOD = Died of disease; DUC = Died of Uncertain cause

†Median follow-up

Table 2: Case series and retrospective studies reported in literature.

| Author   | Year | Study type | N. patients | Mean age (range) | Only breast | N+ (%) | M1 (%) | ER+ | PR+ | Her2+ | CxA+ | Syn+ | Mast | BCS | No surgery | Adj RT | Adj CHT | Adj OT | Mean FUP (range) |
|----------|------|------------|-------------|------------------|-------------|--------|--------|-----|-----|-------|------|------|------|-----|------------|-------|---------|--------|------------------|
| Papotti[122] | 1992 | CS*        | 4           | 56 (41-64)       | 25,00%      | 75,00% | 50,00% | NA  | NA  | NA    | NA   | NA   | NA   | NA  | 100,00% | 0,00%  | 0,00%   | 25,00% | 25,00% (9-44)    |
| Shin[123]   | 2000 | CS*        | 9           | 55.4 (43-70)     | 44,44%      | 55,56% | 0,00%  | 66,67% | 55,56% | 0,00%  | 44,44% | 44,44% | 33,33% | 66,67% | 0,00% | 44,44% | 77,78% | 0,00% (3-35)     |
| Zekioglu[124] | 2003 | CS**       | 12          | 65.0 (43-49)     | 91,67%      | 8,33%  | 0,00%  | 91,67% | 91,67% | 16,67% | 41,67% | 91,67% | 50,00% | 50,00% | 0,00% | NA       | NA    | NA     | 24,1 (1-54)      |
| Bonet[125]  | 2008 | CS**       | 7           | 61,3 (35-88)     | 57,14%      | 42,86% | NA     | 100,00% | 100,00% | 14,29% | 0%     | 100%  | 71,43% | 14,29% | 14,29% | 28,57% | 28,57% | 100,00% | 51,64 (2-7-115,5) |
| Tian[126]   | 2011 | Ret***     | 74          | 61 (29-82)       | 52,70%      | 41,89% | 8,11%  | 95,00% | 80,00% | 9,00%  | NA    | NA    | 40,54% | 57,81% | 17,27% | NA       | NA    | NA     | 46,92 (0-260)    |
| Kanat[127]  | 2011 | CS**       | 7           | 43,8 (29-56)     | 14,29%      | 85,71% | 28,57% | 28,57% | 28,57% | 0,00%  | 57,14% | 100%  | 85,71% | 14,29% | 0,00%  | 71,43% | 85,71% | 28,57% | 22,40 (9-48)    |
| Kawasaki[128] | 2011 | Ret**      | 27          | 47,8 (28-74)     | 95,83%      | 4,17%  | 0,00%  | 100,00% | 100,00% | 54,17% | NA    | NA    | 37,50% | 62,50% | 0,00%  | NA       | NA    | NA     | 83,7 (64-101)    |
| Zhang[129]  | 2013 | Ret**      | 107         | 65 (25-95)       | NA          | NA     | NA     | 94,39% | 85,05% | 2,80%  | NA    | NA    | NA    | NA    | NA     | NA     | NA     | NA     | 27,4 (3-134)    |
| Wu[130]     | 2012 | Ret**      | 13          | 55,4 (36-78)     | 92,31%      | 7,69%  | 7,69%  | 100,00% | 100,00% | 0,00%  | 69,23% | 30,77% | 100,00% | 0,00%  | 0,00%  | NA       | NA    | 100,00% | 67,5 (41-89)    |
| Rovera[131] | 2013 | Ret**      | 96          | 70,1 (40-94)     | NA          | NA     | NA     | NA     | 90,00% | 75,00% | 1,04%  | NA    | NA    | 30,21% | 31,25% | 36,46% | 48,00% | 5,00%  | 75,00% | 88,4 (4-242)    |
| Zhu[132]    | 2013 | Ret**      | 22          | 52,5 (29-77)     | NA          | NA     | NA     | NA     | 90,91% | 95,00% | 25,00% | 95,00% | 14,29% | 68,18% | 31,82% | 0,00%  | 0,00%  | 63,64% | 90,91% | 64,5 (4-89)     |
| Charfi[133] | 2013 | Ret***     | 15          | 62,3 (37-78)     | 73,33%      | 26,67% | 0,00%  | 80,00% | 93,33% | 0,00%  | 73,33% | 6,67%  | 80,00% | 20,00% | 0,00%  | 86,67% | 46,67% | 60,00% | 40,14 (3-125)   |
| Cloyd[134]  | 2014 | Ret***     | 284         | NA              | 43,40%      | 36,20% | 20,40% | 46,5%  | 35,6%  | NA     | NA    | NA    | 35,20% | 36,60% | 27,80% | 41,50% | NA       | NA    | NA     | 38,6 (21-76)    |
| Jeon[135]   | 2014 | Ret***     | 11          | 54,7 (29-79)     | NA          | NA     | NA     | NA     | 100,00% | 100,00% | 0,00%  | 54,55% | 0,00%  | 36,36% | 63,64% | 0,00%  | NA       | NA    | NA     | 38,6 (21-76)    |
| Reina[136]  | 2017 | Ret***     | 43          | 66 (NA)         | 55,8%       | 39,53% | 9,3%   | 97,70% | 86,10% | 4,70%  | 69,80% | 0,00%  | 58,20% | 39,60% | 2,27%  | 74,40% | 34,09% | 75,00% | NA     | 30,2 (21-44)    |

**Headings:** Ret = retrospective; CS = Case Series;
*Previous to 2003 criteria, ** According to 2003 criteria, *** According to WHO 2012 criteria

†Median follow-up
Clinical Characteristics

From the analysis of 113 reported cases (Table 1), the most frequent clinical presentation was breast mass, which was present in 37 cases (in 7 cases also associated to axillary adenopathy and in 5 cases painful) followed by breast lump in 22 patients (of which 3 associated to axillary adenopathy, 2 to bloody nipple discharge, 1 to nipple retraction) and symptoms due to metastatic diffusion (1 jaundice, 1 haematuria, 1 bone pain, 1 respiratory symptoms, 1 perianal pain, 2 neuralgia). Less frequent clinical presentations were: isolated bloody nipple discharge (3 cases), only skin retraction (2 cases), anorexia (2 cases), locally advance disease in 3 cases (2 ulcerated breast masses, 1 carcinomatous mastitis, 1 Paget like mass). In 33 cases clinical presentation was not reported. Tumor was palpable in 58/77 cases (75%).

Radiological Findings

Radiological findings of bNENs were often similar to other breast cancer histotype, like ductal or lobular breast tumors. From available data, sonography was performed in 61 cases. In 11 cases US failed to detect breast lesions. In the other cases tumor appeared as irregular hypoechoic lesion. Data on mammographic finding was present in 61 cases and tumor always appeared as hyperdense mass. Notably, tumor was detected in all cases in which US and mammography were both performed. Only in 14 cases reported data on breast MRI: tumors were detectable in all cases in which US and mammography were performed. Only in 14 cases reported data on breast MRI: tumors were detected in 11 cases and not detected in 3 cases. Notably, tumor was detected in 14 cases in which US and mammography were both performed.

Histopathological Assessment

According to morphology, NEC was the most common histotype (36 cases), followed by bNET (20 cases), SCNC (20 cases), ICNE (10 cases). In 27 cases morphology was not described. Estrogen receptors were positive in 60/85 cases, progesterone receptors were positive in 50/53 cases, HER2 were positive in 18/53 cases. Considering neuroendocrine markers, chromogranin was positive in 62/75 cases (83%), synaptophysin was positive in 70/78 cases (90%). Considering data from case series and retrospective study (Table 2) chromogranin was positive in 41.67%- 95% of specimen, synaptophysin in 0%-100%.

Treatment

Most of the patients received surgical treatment (97/108 cases). The most frequent type of surgical intervention was total mastectomy, performed in 54/97 cases, followed by breast conservative surgery, in 43/97 cases. These data are concordant with retrospective studies and large case series available, in which mastectomy was performed in 30.21-100% of patients, breast conservative in 0-66.67% and no surgical treatment in 0-36.46% of patients. Considering case reports, radiotherapy was performed in 37/84 cases (44%), similarly to data from retrospective studies and large case series in which radiotherapy rate range from 25 to 86.67%.

Medical therapy was suggested in 79% of patients (73/92). Hormone therapy was indicated in 18/92 (19%), chemotherapy alone 36/92 (39%) and a combination of these two treatments were indicated in 38/92 cases (41%). Somatostatin analogue, the most used drugs in neuroendocrine tumors of other origin, was used only in three cases.

Outcome

Data on tumor outcome are available only for 91 patients: 18 patients were alive with active disease, 8 were dead of disease, 1 dead of uncertain causes and 63 were alive with no evidence of disease with a mean follow-up of 24.01 ± 29.8 months.

Discussion

bNENs are rare entities and no guidelines are available for the management of this kind of neoplasia. According to our systematic review, the most frequent clinical presentation is palpable breast mass, sometimes associated to axillary adenopathy or bloody nipple discharge. bNENs appears as hypervascular and irregular hypoechoic lesions at US examination and as hyperdense masses at mammography [8]. The detection rate of these two instrumental evaluations is high, even if is not possible to clearly differentiate this kind of tumor from another breast cancer histotype [9]. When performed, breast MRI shows irregular masses, usually hyperintense in T2-weighted sequences [8]. Before establishing treatment strategies, as recommended in all suspicious breast lesions, tumor biopsy should be performed, even if it is not always able to recognize a breast neuroendocrine tumor, which is often detected only by definitive histopathological assessment [10].

The contemporary presence of neuroendocrine cells with ductal carcinoma is usually considered a sign of the breast origin of the neuroendocrine lesions, even if a total body examination is mandatory for excluding neuroendocrine neoplasm of other origin [11]. Recommended imaging techniques are total body CT or PET/CT scan: 66Gallium PET/CT in case of well-differentiated neuroendocrine tumors or 18FDG PET/CT in case of poorly differentiated NEN (NEC, ICNE, SCNC) as commonly performed in other neuroendocrine neoplasia [12]. Considering available data, the most frequent subtype is NEC. Most all cases were positive for synaptophysin staining, followed by chromogranin; hormone receptors and Her2 expressions were heterogeneous but luminal type (estrogen and progesterone receptors positive and HER2 negative) was the most common, as previously published [13]. This finding is in accordance with the hypothesis that bNENs develop from breast stem cells which divides into neuroendocrine and epithelial cells [14].

Surgical treatment strategies are nowadays based on tumor size and lymph node status basing on current breast cancer guidelines, independently of neuroendocrine component. Likewise, radiotherapy is usually performed after BCS [10, 15]. Medical therapy depends on immunohistochemical analysis: in case of strong hormone receptors positivity, hormonal therapy is usually indicated [10]. In hormone-negative tumors, chemotherapy regimen, based on anthracyclines and or taxanes, is often used [10]. The possibility of using a cisplatin and etoposide regimen in breast NEC, as indicated for small cell carcinomas of other origin, has been evaluated only in small studies [16]. Specific treatment for well-differentiated neuroendocrine component is not routinely used. Only in 3 on 113 cases somatostatin analogues have been used as adjuvant therapy. Even if somatostatin analogues are considered first line therapy in the treatment of neuroendocrine tumors of other origin according to ENETS guidelines, this kind of drug is not approved for bNET, probably because of the paucity of data. Interestingly,
somatostatin receptors have been found in non-neuroendocrine breast tumors with high estrogen and progesterone receptor expression and low HER2 [17-20]. Moreover, somatostatin analogues are able to reduce breast cancer cells proliferation especially in case of low estrogen levels, providing the rationale for contemporary administration of hormonal therapy and somatostatin analogue therapy [21, 22]. In Figure 2, we propose a diagnostic and therapeutic algorithm for bNENs.

Finally, if the prognosis of all bNENs is different compared to non-neuroendocrine breast cancer is still debated. From the published cases, only 8 patients on a total of 91 deceased for the disease. When available, histotype of these neoplasms was NEC/SCNC. In the other 4 cases, tumor histology was not reported but tumor stage was advanced, implying that tumor stage and histology could be the main predictors of poor outcome. Data from the SEER database, comparing 142 breast NEC and non-neuroendocrine breast tumors, demonstrated a shorter overall survival and disease-specific survival of breast NEC and in a multivariate analysis neuroendocrine differentiation was an independent determinant of poorer prognosis [5]. Similarly, Bogina et al. have demonstrated a worse prognosis in 55 breast NEC patients compared to 115 matched non-neuroendocrine breast tumors patients [7].

**Conclusions**

bNENs are rare tumors, usually identified only during definitive histopathological examinations of surgical specimen. bNENs are nowadays treated similarly to non-neuroendocrine breast cancer, but they are very heterogeneous and not well understood. Similarly, to NEN of other origin, we should probably distinguish between well differentiated tumors, NET, and poorly differentiated tumors, NEC/small cells carcinomas regarding treatment and prognosis. Specific trials on adjuvant therapy, for example with somatostatin analogues for well differentiated form, bNET, or classical chemotherapy with cisplatin and etoposide in NEC and SCNC are necessary for establishing the best treatment strategy for these patients and improving clinical outcome.

**Abbreviations**

**NET:** neuroendocrine tumor  
**bNENs:** breast neuroendocrine neoplasia  
**NEC:** neuroendocrine carcinoma  
**ICNE:** invasive breast tumor with endocrine differentiation  
**WHO:** World Health Organization  
**US:** ultrasound  
**MRI:** magnetic resonance imaging  
**BCS:** breast conservative surgery  

**Consent for Publication**

All patients provided written informed consent to case publication.

**Conflicts of Interests**

The Authors have no conflicts of interest for this Paper. All authors disclose any financial and personal relationships with other people or organizations in the writing of this Paper.

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Dr. Federico Frusone and Dr. Giulia Puliani cowrote this paper. Dr. Federico Frusone collected information of the case series from the database of Humanitas Research Hospital of Milan. Dr. Andrea Sagona,
Dr. Emilia Marrazzo and Dr. Erika Barbieri helped analysing the results of the case series. Dr. Giulia Puliani and Dr. Federico Frusone performed literature research and analysed the results. Dr. Alessandro De Luca helped analysing these results. Dr. Wolfgang Gatzemeier, Dr. Alberto Bottini and Dr. Corrado Tinti reviewed the manuscript. All the authors read and approved the final manuscript.

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