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ELSEVIER

REVIEW

Approach and management of primary ectopic breast carcinoma in the axilla: Where are we? A comprehensive historical literature review

Giuseppe Visconti^{b,g,*}, Yassir Eltahir^{a,c,h}, Robert J. Van Ginkel^{a,d,i},
Joost Bart^{a,e,j}, Paul M.N. Werker^{a,f,k}

^a Department of Plastic Surgery, University Medical Centre Groningen, Groningen, the Netherlands

^b Resident in-training, Department of Plastic and Reconstructive Surgery, Catholic University of 'Sacro Cuore' – University Hospital 'A. Gemelli', Largo A. Gemelli 8, 00168 Rome, Italy

^c Consultant Plastic Surgeon, Department of Plastic and Reconstructive Surgery, University Medical Centre Groningen, PO Box 30001, 9700 RB Groningen, the Netherlands

^d Chief, Division of Surgical Oncology, Department of Surgery, University Medical Centre Groningen, PO Box 30001, 9700 RB Groningen, the Netherlands

^e Pathologist, Department of Pathology, University Medical Centre Groningen, PO Box 30001, 9700 RB Groningen, the Netherlands

^f Professor and Chief, Department of Plastic and Reconstructive Surgery, University Medical Centre Groningen, PO Box 30001, 9700 RB Groningen, the Netherlands

^g Department of Plastic and Reconstructive Surgery, Catholic University of 'Sacro Cuore', University Hospital 'A. Gemelli', Rome, Italy

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KEYWORDS

Primary ectopic breast carcinoma;
Axillary mass;
Aberrant breast cancer;
Axillary carcinoma;
Breast cancer

Summary Primary ectopic breast carcinoma is a rare disease and, at present, no specific guidelines on its diagnosis and treatment are available. The purpose of this article is to review the world literature in English on primary ectopic breast carcinoma located in the armpit and to offer guidelines for diagnosis and treatment.

Data for this review were identified by searches of MEDLINE, PubMed, The Cochrane Library, ACNP (Italian catalogue of journals) and references from relevant articles using relevant search terms and data published in the previous reviews.

* Corresponding author. via Pietro Adami 22, 00168 Rome, Italy. Tel./fax: +39 06 6456 1525.

E-mail addresses: joervisconti@hotmail.com (G. Visconti), y.eltahir@plchir.umcg.nl (Y. Eltahir), r.j.van.ginkel@chir.umcg.nl (R.J. Van Ginkel), j.bart@kliksafe.nl (J. Bart), p.m.n.werker@plchir.umcg.nl (P.M.N. Werker).

^h Tel.: +31 50 3613531; fax: +31 50 3613043.

ⁱ Tel.: +31 50 3613409; fax: +31 50 3611745.

^j Tel.: +31 50 3619524; fax: +31 50 3619107.

^k Tel.: 0031 50 3613531; fax: 0031 50 3613043.

Primary ectopic breast carcinoma of the axilla mostly affects women of over 40 (range 28–90 yrs) years of age. The most frequent histological diagnosis is invasive ductal carcinoma not otherwise specified (NOS) (72%). Because of its rareness, in most cases, the diagnosis is delayed for on average 40.5 months. This disease is rare, but a high level of suspicion for carcinoma is mandatory when confronted with a tumour in this area.

Once diagnosed, patients should undergo staging, and prognostic and adjuvant treatment procedures identical to orthotopic breast carcinoma guidelines. There are some limitations for the staging. Loco-regional treatment, on indication, combined with endocrine therapy and/or chemotherapy seems the treatment of choice.

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Recently, we were confronted with a patient with a primary ectopic breast carcinoma (PEBC) in the axilla.¹ This is a rare disease and because of this, diagnosis and treatment are delayed. Breast tissue originates from a differentiation of an ectodermal thickening, the milk line or galactic band, which develops in the first 5 weeks of gestation and runs from the axilla to the groin bilaterally. Its incomplete embryonic regression will result in the formation of ectopic supernumerary and/or aberrant breasts along this line. Besides, ectopic breast tissue (EBT) formation has also been found outside the galactic band, that is, in the face, posterior neck, chest, midback, buttock, vulva, flank, hip, posterior and/or lateral thigh, shoulder and upper extremities.² For the purpose of this article, we will use the term 'ectopic breast tissue' (EBT) for breast tissue found elsewhere than at the pectoralis site, without specifying whether supernumerary or aberrant breast.

The incidence of EBT is 0.2–6%, being higher in Asians than in Caucasians.^{3–5} The axilla is most frequently involved (70%) and the glandular tissue is located in the subcutaneous tissue and deep dermis. This condition has also been associated with urological malformations.²

The amount of EBT can vary from a small dimension to the normal breast size.³ Its presence may cause pain, restriction of arm movement whenever located in the axilla, cosmetic problems and anxiety. Symptoms such as swelling, tenderness and, sometimes, secretion often appear during puberty, pregnancy or lactation.⁶

In this tissue, the same physiologic and pathologic changes as seen in eutopic breast tissue may occur, including carcinoma formation.^{6–9}

The purpose of this article is to comprehensively review the literature to take stock of the knowledge on EBT and PEBC and to offer guidelines for diagnosis and treatment.

Methods of literature search

A comprehensive literature review on PEBC of the axilla published in English was performed, from 1861 to 2009. Data for this review were primarily identified by searches using MEDLINE, PubMed and The Cochrane Library. Besides, the ACNP (Italian catalogue of journals) was searched as well as references from relevant articles and data published in the previous reviews (Table 1). The search terms used were 'ectopic breast tissue', 'aberrant breast tissue', 'axillary breast tissue', 'ectopic breast cancer', 'aberrant breast cancer', 'accessory breast cancer', 'ectopic breast

carcinoma', 'aberrant breast carcinoma', 'axillary breast carcinoma', 'axillary breast cancer', 'primary ectopic breast carcinoma', 'axillary mass', 'axillary tumour' and 'axillary neoplasm'.

All articles were scrutinised for number of cases, patient's age at diagnosis, risk factors for breast carcinoma, duration of delay in diagnosis and initial misdiagnosis, histology and site of the neoplasm, lymph node involvement and extra lymphatic metastasis, immune histological features, treatment and follow-up such as local recurrence, metastasis, outcome and end of follow-up (Table 2).

A total of 89 papers on EBT could be identified. Among these, 24 were included in our review because they reported malignancies in EBT of the axilla. As such, a total of 170 cases of axillary PEBC have been reported in these articles prior to our case (Tables 1 and 2).

It was not possible to identify each variable for every patient.

All articles found regarding PEBC were case reports and historical reviews. No systematic reviews or clinical trials were available. This limits the ability to draw strong conclusions on the characteristics of this tumour and its behaviour, and therefore, no specific protocols for the diagnosis and management of PEBC are available.

Demographic data

The true incidence of PEBC is not clear. It has always been reported as a rare disease. Some authors estimated the incidence of this malignancy based on their experience in relation to EBT (3.8% according to deCholnoky)¹² or to breast cancer (BC) (0.3% according to Chiari).¹³ The limited number of cases and the different methods of evaluation make these figures of limited value.

Reviews on PEBC have assumed an increased rate of malignant changes in EBT when compared with eutopic breast tissue.¹⁴ At present, this cannot be confirmed.

PEBC shows a lower female sex prevalence than BC. According to our review, 6 of 171 cases were male (two cases reported by Marshall et al.¹⁴ and four cases by Nakao et al.¹⁵). Thus, the male-to-female ratio is 0.035 for PEBC compared with the 0.01 value for BC.¹⁶

PEBC seems to affect people at a younger age compared with BC. We found that this malignancy, as well as BC, mainly affects people over 40 years old. In younger patients PEBC is rarely found. The youngest case reported was at 28

Table 1 In this flow diagram it is showed the methods used in the selection of papers included in the review*Methods of literature search : flow diagram.*

Table 2 We review the world literature on axillary ectopic breast carcinoma from 1861 to 2008. The report of the cases was performed in reference to : patient's age, risk factors for breast carcinoma, months of delayed diagnosis and the initial mis-diagnosis, histology and site of the neoplasm, lymph node and extra lymphatic metastasis, immunohistologic features, treatment and follow-up. It was not possible to provide all the information for each patient to the lack of clinical information found. To our knowledge we report the 171st case of ectopic breast carcinoma in axilla.

Authors	#cases, age()	RF	Del.,mis-diagnosis()	Hyst., site ()	LymphN Inv.	Immuno-hystology	Treatment	outcome
Foerster 1861 ¹⁴	1,(?)	—	—	—	—	—	Mast + ax	—
Wolkman 1875 ¹⁴	1,(?)	—	—	—	—	—	—	—
Williams 1891 ¹⁴	1,(29)	—	—	—	Pos	—	Loc	Rec
	1,(54)	—	—	—	Pos	—	Loc + Mast + ax	—
	1,(51)	—	—	—	—	—	Loc + Mast + ax	—
	1,(49)	—	—	—	—	—	Loc + Mast	Rec
Gangolph 1891 ¹⁴	1,(45)	—	—	—	—	—	Loc	—
Kelly 1898 ¹⁴	1,(80)	—	—	—	—	—	—	—
Rouville 1902 ¹⁴	1,(45)	—	—	—	—	—	Loc	—
Deniker 1913 ¹⁴	1,(33)	—	—	DC,(-)	—	—	Mast	—
Delanoy 1929 ¹⁴	1,(62)	—	—	DC,(-)	—	—	—	—
Montemartini 1929 ¹⁴	1,(40)	—	—	—	—	—	Loc	—
Mornard 1929 ¹⁴	2,(36,62)	—	—	—	2 Neg	—	—	—
Andrews 1929 ¹⁴	1,(79)	—	—	—	Neg	—	Loc + ax	—
Razeman and Bizard 1929 ^{14,23}	28	—	—	—	—	—	4 rad	Exp (2y f-up)
							3 loc + ax	—
							10 loc + ax	Rec. (2y f-up)
							11-	Lost to f-up
Giacobbe 1930 ²³	1	—	—	—	—	—	Rad	Lost to f-up
Bianchieri 1932 ^{14,23}	1,(57)	—	—	DC,(-)	Extra n mtx (in f-up)	—	Loc + ax	Exp (2y f-up)
Patel 1932 ¹⁴	1,(32)	—	—	—	Neg	—	Loc + mast	FoD (8 m f-up)
Massabau et al. 1933 ²³	1	—	—	—	—	—	Loc + ax	—
Erdman 1934 ²³	3	—	—	—	—	—	—	Rec. (f-up?)
Matti 1936 ^{14,23}	1,(52)	—	—	—	Pos	—	Xrt + rad	Rec. (f-up?)
Picagli 1938 ¹⁴	1,(56)	—	—	—	—	—	—	Rec
Rawls 1942 ¹⁴	1,(36)	—	—	DC,(-)	Neg	—	Loc, xrt, rad	—
	1,(42)	—	—	DC,(-)	Pos	—	Loc, xrt	Rec
Copeland and Geschickter 1945 ^{14,23}	1,(60)	—	—	DC,(-)	Pos (sc)	—	Rad, xrt	Exp (f-up?)
	1,(67)	—	—	DC,(-)	Pos	—	Loc	—
	1,(55)	—	—	MeC,(-)	Pos	—	—	Rec (f-up?)
	1,(42)	—	—	DC,(-)	Pos	—	Mast	—
	1,(42)	—	—	DC,(-)	—	—	Loc, xrt	Rec (f-up?)
	1,(39)	—	—	MeC,(-)	—	—	Loc	Rec (f-up?)
	1,(46)	—	—	—	—	—	Mast + ax	—
Andreasen 1958 ¹¹	1,(40)	—	0 m	MeC,(-)	—	—	Loc + ax	—
DeCholnoky 1951 ^{14,23}	1,(44)	—	—	—	Neg	—	Mast + ax	—

Stringa 1951 ¹⁴	1,(56)	—	—	DC,(-)	Neg	—	Loc	—
	1,(58)	—	—	DC,(-)	—	—	Loc	—
	1,(40)	—	—	DC,(-)	—	—	—	—
	1,(67)	—	—	DC,(-)	—	—	—	—
	1,(63)	—	—	—	—	—	—	—
Chiari 1958 ¹³	1,(40)	—	—	DC,(-)	Pos.	—	Loc + rtx	Rec (f-up?)-
	1,(63)	—	—	DC,(-)	Neg	—	Loc + Mast	—
Cogswell and Czerny 1961 ^{14,23}	1,(40)	—	—	—	Pos	—	Loc + ax + xrt	Exp (2y f-up)
Morganfeld 1964 ²³	1	—	—	—	—	—	Loc + xrt	FoD (4y f-up)
Smith and Greening 1972 ^{14,23}	1(43)	—	—	AnC,(-)	Neg.	—	Loc + ax + xrt	Exp (1y f-up)
	1(54)	—	—	DC,(-)	Pos.	—	Loc + ax + xrt	FoD (13y f-up)
	1(49)	—	—	DC/LC,(-)	Neg.	—	Loc + ax + xrt	FoD (1y f-up)
Mikuriya and Tsutomu 1978 ²⁷	1(51)	—	—	MeC,(-)	Pos.	—	Loc + ax + xrt	FoD (6 m f-up)
						—	Rad	—
Abedi et al. 1979 ^{14,23}	1	—	—	—	—	—	Rad	—
Interlandi, Minchio 1979 ^{14,23}	1	—	—	—	—	—	Loc + ax + ctx	FoD (4y f-up)
Walker and Fechner 1982	1(90)	—	---	PC,(-)	—	—	Rad	FoD (18 m f-up)
Kahn et al. 1982	3	—	—	—	---	—	Loc + ax	—
							1 rad	FoD (9y f-up)
							2 mod	—
Matsuoka et al. 1984 ²²	1(53)	—	—	DCis,(-)	Pos.	—	Loc + ax + xrt + ctx	FoD (5 m f-up)
Badejo 1984 ²³	2	—	—	—	—	—	Rad	FoD (4y f-up)
							Rad	FoD (18 m f-up)
Marino and Scarpati 1984 ²³	2	—	—	—	—	—	Loc + xrt	Rec. (f-up-)
							Loc + xrt	FoD (3y f-up)
Routiot et al. 1987 ⁴	1	No	5y,(-)	DC, (R)	1 In Pos.	ER+, PR+	Loc + ax + ctx(dxr-vind-cycl-5FU)+ TAM + xrt	FoD (10y f-up)
Siegel et al 1990 ¹⁴	1(50)	—	—	DC/LC	Pos.	—	Loc+ ax+ ctx	FoD (1y f-up)
Evans and Guyton 1993 ²³	1	—	—	LC, (L)	Neg.	ER+, PR+	Loc + ax	FoD (11y f-up)
Marshall et al 1994 ¹⁴	1(52)	No	—	LC,(R)	Neg	—	Bilateral Rad + ax	FoD (5y f-up)
				DC,(slqlb)				
Azuma et al. 1997	1(74)	—	—	DC, (L)	Extra n. mtx	—	Palliation	Exp. (10 m f-up)
Yerra et al. 1997	1(46)	No	6 m,(SC)	DC,(R)	Neg.	ER+,PR-	Loc + ax	FoD (3y f-up)
	1(59)	—	2 m,(-)	AC,(L)	Neg.	ER+,PR+ (30% of analyzed sample)	Loc + ax	FoD (9 m f-up)
Nakao et al 1997 ¹⁵	1(68)	—	—	DC, (R)	—	ER-,PR-,CEA++ GCDF15 +	Rad + ax + sub + ctx(CMF)	FoD (1y f-up)
Kawahara et al 1997 ⁵	1(42)	—	1y,(-)	DC, (L)	Neg.	—	Loc+ax	FoD(2y9 m f-up)

(continued on next page)

Table 2 (continued)

Authors	#cases, age()	RF	Del.,mis-diagnosis()	Hyst., site ()	LymphN Inv.	Immuno-hystology	Treatment	outcome
	1(62)	—	—	DC, (R)	Neg.	—	Loc+ax	FoD(1y6 m f-up)
	55 ^a (31-84) of whom 4 men	—	—	3DCis	Neg.	—	26 Mod/Rad+ax,	28 FoD of whom
				35DC	12Neg	—	5TG+ax,24Loc+ax,	5 with axillary lymph nodes involment f-up(1 m to 13y)
					14Pos, 9-	—	2Loc	
				10-	—	—		
				1MeCis	—	—		
				3MeC	3Pos	—		
				1AnC	Pos	—		
				2Nlis	1Neg, 1-	—		
				2MC	1Pos,1Ng	—		
Cheong JH et al. 1999	1(70)	—	10 m,(-)	DC,(L)	Neg.	—	Loc+ax +xrt+TAM	FoD (6 m f-up)
	1(73)	BC	2 m,(-)	MC,(L)	Neg.	—	Loc + QU + ax	FoD(11,4y f-up)
	1(35)	—	—	DC, (R)	Neg.	—	Loc + ax	—
	1(47)		4y,(-)	DC,(L)	Neg.	—	Loc + ax + xrt + ctx	—
	1(75)	No	—	DC, (L)	Neg.	ER-, PR-	Rad + ctx(CMF) + TAM	FoD (18 m f-up)
	1(62)	No	—	LC, (R)	Neg.	ER+,PR+	Loc + ax + xrt +	FoD (7y f-up)
	1(69)	No	—	DC, (L)	10 ln Pos.	ER+,PR-	TAMLoc + ax + xrt + ctx + TAM	FoD (8y f-up)
Shin et al. 2001 ⁸	1(46)	fam	8y,(-)	LC, (R)	Pos.	ER-,PR-. Her2/neu -	Loc + ax + ctx(AC)	—
Amsler et al. 2002 ⁹	1(62)	—	4y,(-)	LC, (L)	—	—	Loc + ax + xrt + TAM	FoD (f-up-)
Giron et al. 2004	1(65)	No	2,5y,(-)	LC, (L)	Neg.	ER+, PR+	Loc + ax + xrt + TAM	FoD (6 m f-up)
Vignal 2005 ¹⁸	1(47)	No	?,(H)	DC, (L)	Neg.	ER+,PR+	Loc + ax + xrt	—
Avilés Izquierdo et al. 2005 ⁷	1(43)	No	1y,(-)	DC, (L)	1 ln Pos.	ER+, PR+	Loc + ax + xrt + ctx (CMF) + TAM	FoD (2y f-up)
Bakker et al. 2005	1 (53)	No	?	DC, (L)	Neg	ER+, Pr+Her2/neu -	Loc+ aNSB + xrt + TAM	FoD (1y f-up)
Tjalma and Senten 2006 ³	1(51)	-	-, (SC)	DC, (L)	Neg.	ER+, PR+	Loc+ax+TAM	FoD(4y3 m f-up)
Gutermuth et al. 2006 ⁶	1(54)	E ₂ - E ₃ t	1y,(Ab)	DC, (R)	2 ln Pos.	ER+, PR+ CEA-, Her2/neu-	Loc + ax + TAM	FoD (3y f-up)
Welch et al 2007 ²⁴	1(56)	famE ₂ t	2y,(H)	DC,L	14 ln Pos	ER+, Her2/neu-, PR(5% of analyzed sample)	Loc + QU (slq) +ax + ctx(TAC) + (xrt + AI planned)	In treatment
Teke et al. 2008	1 (52)	No	6 m,(?)	DC, (R)	Neg.	ER+, Pr+Her2/neu +	Loc + ax + xrt + TAM	FoD (5y f-up)
Visconti et al. 2008	1(61)	fam	20y,(M)	DC,(L)	3 ln Pos	ER+, PR+, Her2/neu-, GCDP/15-	Loc + ax + xrt + AI	FoD (22 m f-up)

RF: (Risk Factors): Fam (familiarity for breast carcinoma), BC (previous/concomitant eutopic breast cancer), E₂t (estradiol therapy).

Del. (Delayed diagnosis), misdiagnosis: SC(sebaceous cyst), Ab (abscess), H(hydradenitis), M (many).

Hist. (Histology): DC(ductal carcinoma), LC (lobular carcinoma), MC (mucoïd carcinoma), AC (adenocarcinoma), AnC (anaplastic carcinoma), PC (papillary carcinoma), MeC (medullary carcinoma), MeCis (medullary carcinoma in situ), Nlis (non invasive in situ).

Site: L (left axilla), R (right axilla), slqlb (superior lateral quadrant of left breast), Lymph N. inv. (Lymph nodes involvement): Neg. (Negative), Pos. (Positive), Extra n. Mtx (extra nodal metastasis), #ln (number of lymph node), # without ln (number of cases with positive or negative lymph node involvement), sc (subclavicular lymph nodes).

Treatment: Rad (radical mastectomy), Mod (modified mastectomy), Loc (wide local excision), Mast (unspecified mastectomy), QU (quadrantectomy), slq (superior lateral quadrant), ax (axillary lymphadenectomy), aNSB (axillary node sentinel biopsy xrt (radiotherapy), ctx (chemotherapy), TAM (tamoxifen), CMF (cyclophosphamide, methotrexate, 5FU), vind (vinorelbine), 5FU (5-fluorouracil), cycl (cyclophosphamide), dxr (doxorubicin), TAC (adriamycin, cyclophosphamide, docetaxel), AI (aromatase inhibitor).

Follow-up: FoD (free of disease), f-up (follow-up), Exp. (expired), Rec. (recurrence of disease).

^a the total number of patient reported is 57, but two cases have been already analyzed in detail (Mikuriya et al, Matsuoka et al).

years of age and the oldest was 90 years of age. However, PEBC shows a 50% peak of incidence between 40 and 45 years of age (Figure 1) and a median age at diagnosis of 51 years of age, approximately 10 years less than BC.¹⁶ This difference is even higher if one includes the delay in diagnosis for PEBC.

It is not clear if PEBC has a race-prevalence as for BC.¹⁶ Asians have a higher incidence of EBT, but it is unknown if they carry a higher risk of developing PEBC.

There is a general belief that the risk factors for BC apply also to ectopic tissue. Indeed, in our case, there was a familial predisposition for BC and a history of radiation.

Clinical presentation and examination

From our review, it may be deduced that the clinical picture of an axillary PEBC is constant. The patient normally consults the physician for the presence of an axillary mass with the following features: persistent unilateral growing subcutaneous/dermic nodule previously misdiagnosed, irregular, firm and not tender, red and painless, without any local symptoms associated. In most cases, the general condition of the patient is good. Some patients may show clinical signs of supernumerary breast such as partial/complete areola and/or nipple at the site of the axillary mass.

In the presence of these features, the contralateral axilla and both breasts should be clinically examined as well as the supraclavicular fossae and bilateral laterocervical nodes.

Diagnosis

The diagnosis of PEBC is not always thought of and is, therefore, often delayed. We found that the delay until diagnosis was missing in most old articles and clear in only 16 cases, including our case¹ From the available data, the calculated delay was 40.5 months on average

Figure 1 The dispersion graph describes the age of the patients when they presented with the neoplasm. The patients under 40 years old are rarely interested. The majority are over 40 years old. The group age between 40 and 45 years old is the most interested. 50% of the patients are between 40 and 55 years old.

(range 0 months–20 years). Andreasen's report¹¹ is probably the only case in which the diagnosis was suspected preoperatively.

Axillary PEBC should be included in the differential diagnosis of any axillary mass. We propose a diagnostic algorithm on the signs and symptoms that may aid in the diagnostic process (Table 3).

The presence of a subcutaneous mass along the milk line with the clinical features described above should provoke a high suspicion for PEBC, and this disease should be ruled out first.^{3,9} To this end, following history and physical examination, ultrasound is the first additional step.¹⁷ The presence of a hypo-echoic, not well-defined heterogeneous mass (differential diagnosis: sebaceous cyst), without signs of inflammation such as in hydradenitis, is suspicious.¹⁸ Mammography may add further information, for the evaluation of the axillae (microcalcifications) and for both breasts.¹⁹

In case of a suspicious lesion, fine-needle aspiration biopsy (FNAB)/core biopsy of the axillary lump should be performed to harvest cells/tissue for histologic diagnosis.²⁰ If a PEBC in the axilla is diagnosed, the regular work-up guidelines for BC should be followed.²¹ The contralateral axilla should be examined in detail as should be the eutopic breasts. A contrast-enhanced computed tomography (CT) scan and/or magnetic resonance imaging (MRI) might be useful in defining the dimension and the extension of the tumour before surgery.

Histopathology

The most frequent histological diagnosis was invasive ductal carcinoma not otherwise specified (NOS) (72%), which is quite similar to that in eutopic breast, where this type of tumour is found in 40–75% of cases.¹⁰ Invasive lobular carcinoma and medullary carcinoma represent the next frequent histotypes, with a total of 12% of the cases. Other histotypes form the remaining 16%.

However, when histopathology indicates an axillary carcinoma, it can be difficult to differentiate between a carcinoma of adnexal origin, a breast-like or apocrine carcinoma, a metastatic BC and a PEBC.

Several pathologic and immunohistologic features can help clarify this matter: (1) Histologic pattern of a primary breast carcinoma in situ. (2) Presence of normal breast tissue surrounding the tumour, areola and/or nipple. (3) Specific immunohistology for BC such as ER (oestrogen receptor) and PR (progesterone receptor), and common breast markers such as gross cystic disease fluid protein (GCDFFP)-15. Although Her 2/Neu, CEA and glandular keratins can be expressed in BC, they do not discriminate between a PEBC and a skin adnexal tumour, because they are not specific for the breast. Their expression in other lesions, especially skin adnexal tumours is either not well known or is not different from breast cancer. (4) No malignant lesions in the eutopic breast tissue.^{6,8}

In the diagnosis of PEBC in the armpit, axillary node metastasis should be excluded. Histopathologically, metastases tend to be multiple and exhibit expansive growth.

Lymphatic spread

In BC, homolateral axillary and internal mammary nodes are considered possible sites of lymphatic metastasis. The lymphatic spread of axillary PEBC is most likely only towards the homolateral axillary nodes and from there towards the supraclavicular nodes because this is the normal lymphatic drainage of the subcutaneous and cutaneous tissues of the armpit. In addition, indeed, in the literature, we found that, when present, nodes' dissemination involved only the homolateral axillary nodes and, in one case, the ipsilateral supraclavicular nodes.

Therefore, we believe that involvement of the internal mammary lymph nodes should be looked upon as distant metastases (M1) rather than N1 or N2 disease.

Staging

After diagnosis of a PEBC has been made, staging is performed, and this depends on tumour size and lymph node status, combined with clinical symptoms. The role of sentinel node biopsy (SNB) for PEBC of the axilla is not clear. The general trend has been to perform axillary clearance in all patients. We found only one case, which underwent R0 local excision and SNB (found negative) plus radiation and endocrine therapy. The Free of Disease (FoD) period reported for this patient is only 1 year.²²

Additional staging may include chest X-ray, abdomen and cervical ultrasound, abdomen and thoracic CT scan, breast MRI, brain MRI and bone metastasis detection with 99mTc-disodium oxidronate (HDP) scintigraphy, according to the BC guidelines.

Prognosis

The prognosis of PEBC may be considered similar to an equivalent BC, although some authors concurred that it could have a higher rate of lymph node involvement.^{4–6,8,14,23,24}

In many reported cases, at diagnosis, there was no lymph node involvement and there was a long-term interval FoD after the treatment. So far, even though the axillary lymph nodes and lymphatic vessels are close to an axillary PEBC, no higher rate of lymph node metastases has been demonstrated than in BC. In our case, no distant metastasis was found, notwithstanding a 20 years' diagnostic delay.

Although speculative, this may be explained by the fact that the forming of metastases is related to biologic properties of the tumour rather than to the anatomic properties of the localisation.

Due to the diagnostic delay, as in our case, tumours might have grown for a longer time, resulting in higher tumour stage and possibly higher lymph node stage, requiring more extensive surgery, potentially leading to worse outcome, or to morbidity due to systemic therapy or to limited survival.

The diagnostic delay of these malignancies may lead to an apparent poorer prognosis than for BC.²⁴

Table 3 Diagnostic flow-diagram on signs and symptoms for unilateral axillary mass

Treatment

No specific treatment protocol is available in the literature for axillary PEBC and, furthermore, there is no consensus on whether to excise the EBT prophylactically, to prevent the malignancy.^{25,26} Treatment and follow-up details were provided for only 52 cases. In 12 of the reported cases (23%), a local recurrence of the neoplasm occurred following excision, 11 of which dated from the time era between 1891 and 1958. Since 1984, no local recurrence has been reported, apart from our case.

Six patients died of metastatic disease before publication (12%), five of them within 2 years after the diagnosis. All these cases had had involvement of their axillary nodes. Among these, two presented with extra-nodal growth and one case showed metastasis to the infraclavicular lymph nodes.

A total of 34 (65%) patients were found FoD at the time of publication. Based on the follow-up period reported, we divided these cases into three groups: shorter than 5 years (25 patients), between 5 and 10 years (five patients) and longer than 10 years (four patients).

In the 5–10 years FoD group, loco-regional surgery (R0 local excision, axillary lymphadenectomy) plus radiotherapy and endocrine therapy had been successful in three cases, including a patient with 10 positive nodes. Radical mastectomy had been performed on the other two cases, one of which had negative nodes. In the ≥ 10 years FoD group, all cases underwent loco-regional surgery, two with and two without postoperative radiation treatment. Only one case received endocrine therapy.

So far, in early days, the surgical approach of this tumour was more aggressive, justified by the limited knowledge of the biological behaviour of BC and by the paucity of adjuvant treatments available: surgeons performed either a local tumourectomy or an ipsilateral prophylactic mastectomy for axillary PEBC. Since 2001, the loco-regional approach only (local excision, axillary clearance and radiation) is preferred (Table 2).

Adjuvant treatments that had been found to be effective for BC were successfully applied to PEBC as well. In fact, in seven of the nine cases reported with a follow-up of longer than 5 years, two of whom were N+, loco-regional surgery plus radiotherapy, followed by endocrine therapy and/or chemotherapy on indication, was successful until more than 10 years' follow-up.

Again, the therapeutic approach used in most of the cases was inspired by the BC treatment guidelines. Hormonal therapy, when appropriate, was an integral part of the treatment, as well.

From our review, it is conceivable that loco-regional surgery (R0 local excision and axillary lymphadenectomy) plus radiation, followed by hormonal and/or chemotherapy on indication, is effective for patients staged I, II and IIIA–B, according to the American Joint Committee on Cancer (AJCC) stage groupings for BC, when N₁₋₂ is determined by ipsilateral axillary nodes metastasis.

A careful follow-up is essential because of the limited knowledge of this tumour.

Mastectomy, both radical and modified, is no longer performed if the breast is free of any malignant lesion,

because it was found that the loco-regional approach, when possible, allows for the same therapeutic result, with a more acceptable aesthetic outcome.

PEBC is a rare disease. In the presence of any axillary lump, this neoplasm should be the first to be excluded. Once diagnosed, these patients should undergo staging and treatment according to BC guidelines, with some limitations for the staging. As for now, radical excision and axillary lymphadenectomy with or without reconstruction of the defect plus adjuvant radiotherapy combined, on indication, with endocrine therapy and/or chemotherapy, may result in long-term tumour-free survival for patients staged I, II and IIIA–B.

Conflict of interest

All the authors disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work.

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