Rare axillary cancer of unknown primary originating from the breast of a 64-year-old male patient: A case report and literature review

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Abstract. Cancers of unknown primary (CUPs) are a heterogeneous group of tumors characterized by a difficult diagnosis. The primitive tumor remains unknown, whereas metastases are the most common manifestation. Occult male breast cancers are very rare types of CUPs. The present study describes the case of a 64-year-old man affected by a CUP of presumed mammary origin. The aim of the article and the present review was to focus on their management. To the best of our knowledge, only thirteen cases have been reported in the literature. Because no specific guidelines are available, various approaches have been applied, influencing the treatment and the prognosis of patients with CUP.

Introduction

The cancers of unknown primary (commonly named CUPs) are a heterogeneous group of tumors characterized by a difficult diagnosis, because the primary site remains occult after extensive work-up (1). The CUPs represent about 3-5% of all cancer diagnosis and the most common manifestations are metastases in the lymph nodes, lung, liver, or bone (2). In 75-85% of the cases, the metastases are disseminated (3). Considering its enigmatic features, it was discussed about the validity of CUP as a distinct cancer entity supporting the hypothesis that the diagnosis of CUP could be erroneous because the work-up may be incomplete or the syndrome may be correlated to relapses of precedent cancers (4).

Therefore, International Guidelines tried to clarify the diagnostic management (5), highlighting the importance of patients' clinical and familiar history, and on risk factors such as cancer predisposition and occupational activity. A complete physical examination should be performed with accuracy for respiratory and abdominal systems which are the most common sites of primary cancers, according to the data reported in the follow-up and autopsy of CUPs' patients, without neglecting the clinical presentation that could drive the primary tumor research (6). The initial diagnostic work-up should include basic blood analyses and relevant tumor markers. A computerized tomography (CT) of chest, abdomen and pelvis is recommended by ESMO guidelines (7) and Positron emission tomography (PET) imaging is frequently additionally employed in CUP to identify unrecognized malignant lesions (8). Only after that an extensive work-up has been performed without the detection of a primitive cancer, the possibility of CUP syndrome should be considered. The pathogenesis is controversial, but CUP condition may be created by an early metastatic dissemination, whereas the primary tumor has receded or is too small to be detected (9). The CUPs of possible breast origin represent a complex topic. ESMO Clinical Practice Guidelines recommended mammography and eventual magnetic resonance image (MRI) of the breast only for the women suspected of CUP, considering the wide spreading of breast cancer in the female sex. Breast investigation is not required routinely for men because male breast cancer (BC) is rare, representing approximately 1% of cancers that occur in males (10). Therefore, CUPs of male BC origin are rarely considered for the diagnosis and very few cases are reported in literature. Their management represents an unclear topic, characterized by an extreme variety of treatments and prognosis.

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Case report

A 64 year-old male patient was admitted at the General Surgery Division of a Teaching Hospital (Luigi Vanvitelli University of Campania, Naples, Italy) for an axillary swelling with severe pain to the arm and forearm. His past medical history excluded other co-morbidities or cancer anamnesis. He was regular smoker (15 cigarettes a day for 40 years). His familiar medical history included breast cancer of one sister and ovarian cancer of the other sister. Physical examination revealed a left swelling in axilla, by the size of 2 cm, with irritated and reddened skin above. Swelling was painful and without mobility along surface and deep planes. No other signs in other districts were showed during the physical examination.

He was admitted in November 2020 and during the hospitalization (he was submitted to an axillary ultrasound (US) that revealed increased volume and thickness of many axillary lymph nodes, one of these with 2 cm of diameter and tender aspect. Magnetic Resonance Imaging (MRI) confirmed the presence of multiples oval and round homogeneous shape nodules, similar to lymph nodes, with low signal on T1 and T2. No breast lesion was identified (Fig. 1). Ultrasound guided fine needle aspiration biopsy (FNAB) was performed on the largest lymph node. Definitive pathology showed malignant cells with atypical elements like epithelioma, with clear cytoplasm, chromatin clearing nucleus and evident nucleolus. In the attempt to recognize the primary localization, a screening Total Body CT was performed and showed repetitive lung nodes and confirmed the presence of multiples axillary nodes. The largest was estimated of 4x2.3 cm in diameter. Positron emission tomography with computerized tomography (PET-CT) exam was performed in an external diagnostic center because it was not available in the hospital. The examination completed the diagnostic process, confirming the presence of numerous axillary and lung lymph nodes with elevated metabolic activity and evidencing already left thorax subcutaneous thickening and two bone lesions on D6.

The patient underwent a lymphadenectomy of the first and second axillary levels. A drain was placed. The post-operative course was regular, and no complications occurred. A total of 3 days after admission he was discharged from the hospital with no symptoms or pain and the drain was removed the fifth postoperative day. Histological exam showed adenocarcinoma with multiples nodes, oxyphilic and apocrine aspect, sclerosis stromal and multifocal coagulative and colliquative areas into the tumor. It was described local perineural neoplastic infiltration without neoplastic embolus. Immunohistochemistry was performed automatically on BenchMark Ultra platform (Ventana Medical Systems), according to the manufacturer's instructions, as previously described (11). Immunohistochemistry (IHC) (Fig. 2) analysis was positive for cytokeratin (CK) AE1/AE3, CK7, GATA3, Gross cystic disease fluid protein (GCDFP)-15, androgen receptor (AR), human epidermal growth factor receptor 2 (HER 2), low and focal positive for mammaglobin. The lesion did not show CK20, transcriptional thyroid factor (TTF) 1, Napsin A, Estrogen Receptor (ER), Progesterone Receptor (PgR). The expression rate of proliferation marker Ki67 was 40%. The final diagnosis was moderate differentiation grade 2 (G2) apocrine carcinoma, inter-medial differentiation sec. Elston-Ellis score 7: tubules formation, nuclear pleomorphism score 2, mitosis score 3. The histological findings correlated with IHC were no sufficient to make a differential diagnosis between cutaneous annexes histogenesis and breast origin. Considering ER and mammaglobin expression, we performed Mammography and breast US searching a rare male BC, without identifying any breast lesions (Fig. 3). MRI revealed presence of focal areas on D5 and D10 (maximum diameter was 11 mm), micro nodular areas on D2, D12 and L1 and Multiples Bone lesions on pelvic region (diameter maximum of 15 mm). Dermatology visit excluded cutaneous histogenesis and the case was treated like man CUP syndrome of possible breast origin. The patients signed a written consensus and agreed the publication of his clinical case.

Discussion

CUPs are a group of neoplasms characterized by the diagnosis of metastasis in the absence of a detectable primitivity, after a complete clinical work-up (12,13). The CUPs represent about 3-5% of all cancer diagnosis with an overall age-standardized incidence ranges between 4 and 9 cases per 100.000 people annually worldwide (3). It is recognized as the fifth most common cause of cancer death (14). CUPs accounts for up to 1% of all breast cancers and the involvement of axillary is the most common presentation in these cases. It is known, in fact, that in over 50% of the cases of axillary lymphadenopathy, the primary originates from the breast (15-17). Therefore, mammography and axillary-breast US should be included in the instrumental work-up in all CUPs with axillary repetitions (18-20). Breast Magnetic Resonance Imaging (MRI) is also recommended by international guidelines because it can improve the detection of an occult primary breast cancer in a wide range of cases (from 35 to 100%) (21-23).

BC is common in women and innovative technologies for very accurate diagnosis and treatments were established (24-26) while male breast cancer is rare, and CUP of male breast origin is anecdotal. Moreover, there is no consensus in literature about a specific panel of IHC due to their rarity (27).

Using the PubMed database, a systematic review of the current literature was carried out, up to March 2023. The final article was realized in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (28). The MeSH (Medical Subject Headings) search terms used were 'breast', 'cancer of unknown primary', 'occult breast cancer'. The Authors observed that male breast cancer of unknown primary was an extremely rare neoplasm. The keywords 'male breast cancer', 'occult male breast cancer', 'male breast cancer of unknown primary' were used for the research. Several combinations of the keywords and MeSH terms were utilized, and the various terms were substituted during the search. References of the more relevant articles were manually searched. The last research was concluded on March 21, 2022.

Twelve articles published from 2008 to 2020 and reporting cases of CUP of breast cancer origin were identified (27,29-39) (Table I). The mean age of the patients was 59,23 years (range 29 to 83). Three men were smokers (35,38,39) and two of them (35,38) referred a familiarity for gastric cancer: in a

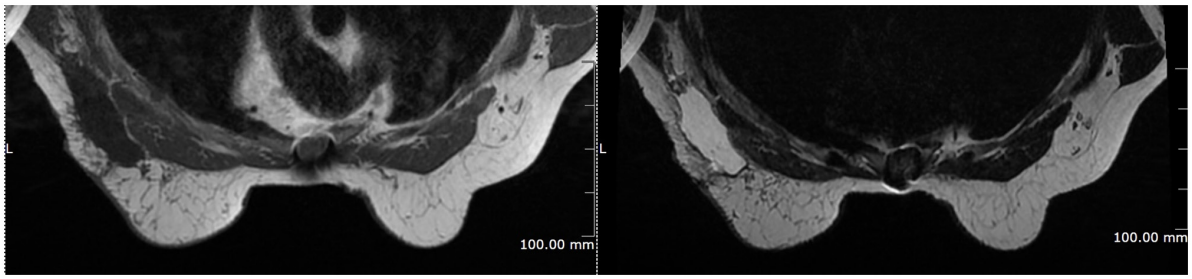

Figure 1. Bilateral breast magnetic resonance imaging. No breast lesion was identified.

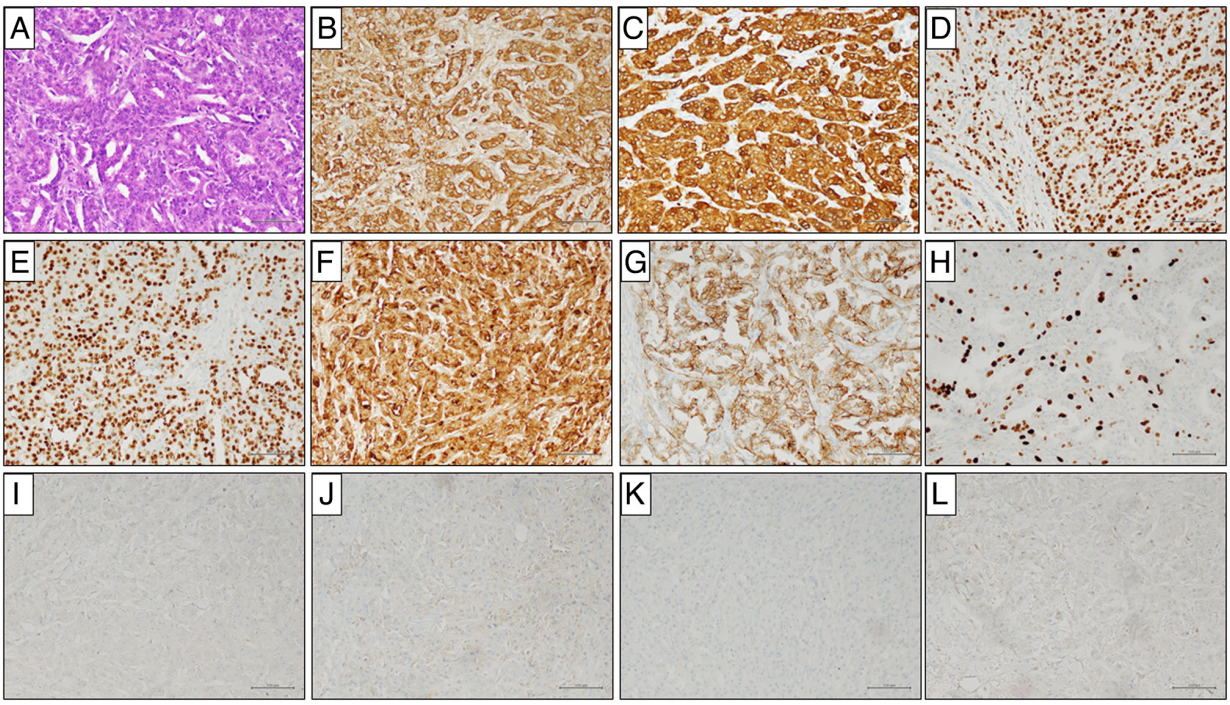

Figure 2. Histological and immunohistochemical findings. (A) Histology showing malignant epithelial neoplasm constituted by atypical cells with oxyphilic cytoplasm arranged in cribriform and glandular pattern (hematoxylin and eosin stain, original magnification 200x). By immunohistochemistry, the neoplasm expressed (B) CK AE1/AE3, (C) CK7, (D) GATA3, (E) androgen receptor, (F) GCDFP-15 and (G) HER2; (H) Ki67-positive expression was ~40%; the neoplasm did not express (I) estrogen receptor, (J) progesterone receptor, (K) TTF1 and (L) Napsin A (immunohistochemical stains, original magnification x200).

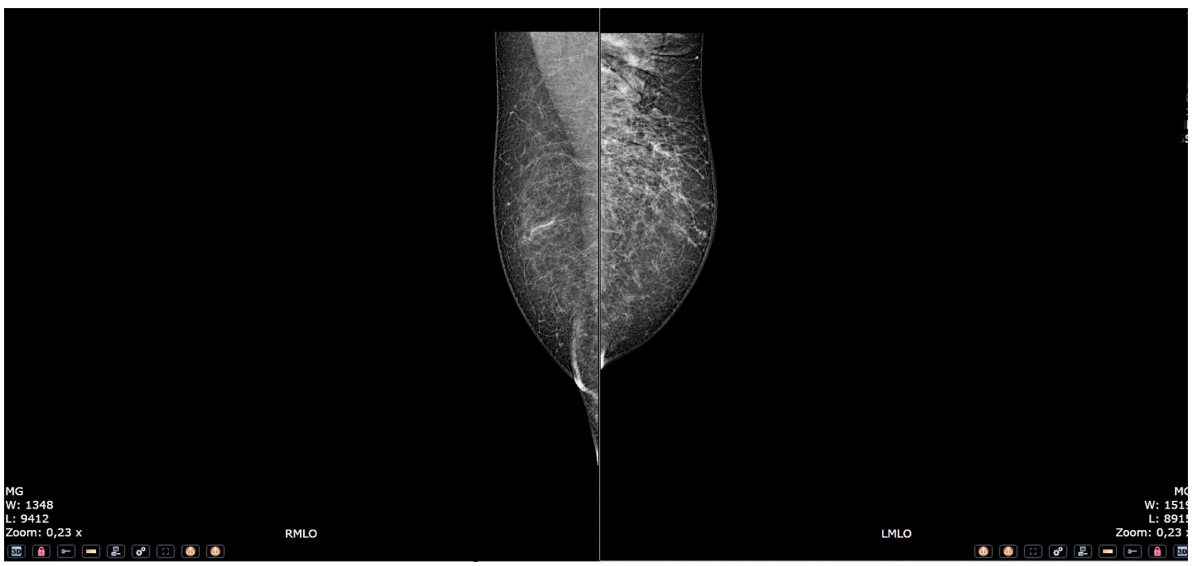

Figure 3. Bilateral mammography. No breast lesion was identified.

Table I. Reported cases of occult male breast cancers.

First author, year	Age, years	Risk factors	Clinical presentation	Examinations	H&E histopathological examination	Immunohistochemical staining	Surgery	Neoadjuvant therapy	Adjuvant CT	RT	Follow up	(Refs.)
Gu, 2008	72	N/A	Painless and enlarged lymph node	MX, breast and axillary US	Breast infiltrating ductal carcinoma	ER (-), PgR (-), P53 (+), PCNA (+), BCL 2 oncoprotein (+), Nm 23 (+), HER2 score 3+, MPR (+)	ALNB, mastectomy, ALND	No	No	No	After 18 months: The lesion disappeared	(36)
Gu, 2009	72	No	Painless enlarged axillary lymph node	MX, breast and axillary US	Infiltrating breast ductal carcinoma	ER (-), PgR (-), P53 (+), PCNA (+), BCL 2 oncoprotein (+), Nm 23 (+), HER2 score 3+, MPR (+)	ALNB, mastectomy	No	No	No	After 24 months: The lesion disappeared	(31)
Takeyama, 2010	58	N/A	1 cm right, non-mobile, hard axillary mass	Chest CT, MX, breast and axillary US, breast MRI, head, lung, upper and lower gastrointestinal system endoscopy	Metastatic adenocarcinoma from an unknown primary	ER 40%, PgR 30%, mammaglobulin 70-80%, HER2 (-), P53 (-)	ALNB, resection, ALND	Cisplatin, paclitaxel	Anthracycline, taxane, tamoxifen	No	N/A	(27)
Hur, 2012	59	Smoking; gastric cancer familiarity (father)	Palpable mass in right axilla	MX, breast and axillary US, breast MRI, chest CT, abdominal US, EGDS, colonoscopy AFP, CEA, PSA, CA 19-9, CA 15-3	Metastatic poor differentiated adenocarcinoma likely of breast origin	ER (+), PgR (+), HER2 (score 1+), BRST-2 (+), S-100 (-)	ALNB, skin sparing mastectomy, ALND	No	Doxorubicin, cyclophospha-mide, docetaxel, tamoxifen		After 10 years: The lesion disappeared	(35)
Hur, 2012	45	No	Palpable mass in left axilla	MX, breast and	Adenocarcinoma axillary US, breast MRI, PET, chest CT, abdominal CT, EGDS; CEA, PSA, CA 19-9, CA 15-3, Calcitonin blood test	TTF-1 (-), CK 20 (-), CEA (+), ER (+), PgR (+), HER2 (-), Ki-67 (+), EGFR (-), BRST-2 (+)	ALND	No	Doxorubicin, cyclophospha-mide, docetaxel, tamoxifen	Yes	After 24 months: The lesion disappeared	(35)
Wang, 2014	58	N/A	Left armpit painful 0.8x0.6 cm mass	Breast and axillary US, MX, PET-CT; CA-125, CEA blood test	Glandular cancer with high possibility of primary mammary tumor	After neoadjuvant CT: E-cadherin (+), P120 (+), CK7 (+), ER 90%, PgR 85%	ALNB, mastectomy	Paclitaxel, oxaliplatin with partial response; docetaxel,	Doxorubicin	Yes	After 12 months: The lesion disappeared	(32)

Table I. Continued.

First author, year	Age, years	Risk factors	Clinical presentation	Examinations	H&E histopathological examination	Immunohistochemical staining	Surgery	Neoadjuvant therapy	Adjuvant CT	RT	Follow up	(Refs.)
								lobaplatin with no response				
He, 2015	40	No	Left axillary palpable 2.2 cm nodule	Breast and axillary US, total body CT, abdominal US, thyroid US, genitourinary US, breast MRI, PET; CEA, PSA, CA 19-9, CA 15-3, Calcitonin, AFP blood test	Moderately differentiated adenocarcinoma with solid nests and cord-like arrangements of cancer cells	CK 20 (-), mammaglobin (-), TTF-1 (-), ER (-), GCDPF 15 (-), PgR (+), HER2 (score 2+)	ALNB, mastectomy, ALND	No	Trastuzumab, paclitaxel, carboplatin	No	After 9 months: Newly increased uptake on left supraclavicular region detected on PET/CT; after 3 years Stable disease	(37)
Rigakos, 2016	54	Smoking	Painful vertebral mass, right axillary mass, bone lesions	Lumbar spinal MRI, PSA, total body CT, PET-CT	Metastatic low grade carcinoma of epithelial origin origin	CK AE1/3 (+), CAM 5.2 (+), epithelial membrane antigen (+), E-cadherin (+), melan A (+), synaptophysin (+), placental alkaline phosphatase (+), NSE (+), CD (1), human melanoma black 45 (+), renal cell (-), inhibin (-), TTF-1 (-), CK5/6 (-), GCDPF 15 (-), vimentin (-), CD 117 (-), PSA (-); after Micro-RNA: ER (+), PgR (+), HER2 (+)	ALNB, ALND		Capecitabine, trastuzumab, vinorelbine, tamoxifen, letrozole		After 33 months: Stable bone disease	(39)
Zhang, 2017	84	No	Palpable 3.9 cm nodule in right axilla	Total body CT	Metastatic poor differentiated adenocarcinoma likely of breast origin	ER (-), PgR (-), PSA (-), GCDPF 15 (+), AE1/AE3 (+), CK 7 (+), CK 20 (+), HER2 (-)	Core needle biopsy, ALND	No	Paclitaxel, cyclophospha-mide	No	After 24 months: The lesion disappeared	(34)

Table I. Continued.

First author, year	Age, years	Risk factors	Clinical presentation	Examinations	H&E histopathological examination	Immunohistochemical staining	Surgery	Neoadjuvant therapy	Adjuvant CT	RT	Follow up	(Refs.)
Kuninaka, 2017	67	N/A	3 cm left anterior chest wall tumor	CT	Metastatic adenocarcinoma from an unknown primary	ER (+), PgR (<1%), HER2 score 3+, CK 7 (+), CK 20 (-), GCDPF 15 (+)	ALNB	No	Trastuzumab	No	After 18 months: The lesion disappeared	(29)
Xu, 2017	29	Smoking, gastric cancer familiarity (mother)	Left axillary palpable 4.3x2.3 cm nodule	Chest CT, PET-CT, breast and axillary US, MX (rejected); CEA, PSA, CA 19-9, CA 15-3, CA 72-4, NSE, Cyfra 21-1, Calcitonin, AFP blood test	Infiltrating ductal carcinoma	CK 5/6 (+), CK 7 (+), CDX-2 (+), P63 (+), TTF-1 (+), synaptophysin (+), chromogranin A (+), S 100 (+), GCDPF 15 (-), HER2 (score 2+), FISH (-), ER (-), PgR (-), EMA (+), GATA-3 (-), CK 20 (-), mammaglobin (-)	ALND	No	Adriamycin, docetaxel	Yes	After 9 months: The lesion disappeared	(38)
Wang, 2018	49	N/A	Painless 4x3 cm side mass in left axilla	US PET-TC, MX (rejected)	Metastatic adenocarcinoma from an unknown primary	ER (+), PgR (+), GCDPF 15 (+), HER2 (-), CK 7 (-), CK 20 (-), TTF-1 (+)	ALNB, mastectomy (rejected), ALNB	No	Paclitaxel, phosphamide, pharmorubicin, tamoxifen	Yes	After 4 years: The lesion disappeared	(33)
Sood, 2020	83	N/A	10x6 cm right axillary mass	Mammography	Metastatic adenocarcinoma from an unknown primary	ER (+), PgR (+), GCDPF 15 (+), androgen receptor (+), E-cadherin (+), calponin (-), P53 (-), HER2 (-), NSE (+), synaptophysin (+)	ALNB, ALND	No	Yes	No	N/A	(30)

MX, mammography; US, ultrasound; ALNB, axillary lymph node biopsy; ALND, axillary lymph node dissection; H&E, hematoxylin and eosin; CT, chemotherapy; RT, radiotherapy; ER, estrogen receptors; PgR, progesterone receptors; P, protein ; PCNA, proliferating cell nuclear antigen; BCL, B-cell lymphoma 2; Nm 23, non metastasis 23; HER2, human epidermal growth factor receptor 2; MPR, mannose phosphate receptor; MRI, magnetic resonance imaging; EGDS, esopahgo-gastro-duodenoscopy; TTF-1, thyroid transcription factor-1; CK, creatine kinase; CEA, carcino-embryonic antigen; BRST-2, Gross Cystic Disease Fluid Protein 15; PSA, prostate specific antigen; CA, carbohydrate antigen; PET, positron emission tomography; CAM 5.2, cell adhesion molecule; NSE, neuronal specific enolase; CD, cluster of differentiation; GCDPF, anti-human gross cystic disease fluid protein; AFP, α fetal protein; FISH, fluorescent *in situ* hybridization; EMA, anti-endomysium protein; N/A, not available.

case the father, and in the other the mother was affected. In 12 cases reported the first presentation was an axillary mass; in one case the tumor was located on the anterior chest wall (29) while in another case, a vertebral painful lesion was diagnosed in the same moment of the axillary nodule (39). Seven men was affected by comorbidities: four of them showed dermatologic disease such as eczema, reddish skin, dermatomyositis, and erythema (27,29,34-35). A patient had a benign thyroid nodule (35), one presented gynecomastia (37), and another found out a renal cystic (39).

Despite mammography is considered the gold standard for the breast cancer diagnosis, in four cases it was not recommended by the surgeons (29,34,37,39) and in another two studies the patient rejected it (32,38). US was performed in 9 out of 13 cases (27,31-33,35-38), while breast MRI was planned for only 4 patients (27,35,37). A complete work-up with the association of US, mammography and breast MRI has been realized in only three case reports (27-35). Therefore, it is possible to assume that more accurate and diagnostic process would be desirable to define a diagnosis of CUP. In fact, a patient underwent to an incomplete diagnostic work-up is not suitable to receive this kind of diagnosis. In the present case, despite the complete preoperative diagnostic work-up with mammography, US, MRI, Total Body CT and 18 FDG PET-CT was not possible to clearly identify a primary origin conuring a 'real' CUP. The clinical suspicious was driven only by the familiarity for breast and ovarian cancers of the sisters, and for the IHC on the resected specimen. Moreover, the diagnostic trouble appears even more relevant considering that even after the definitive pathology was not possible to certainly distinguish between the breast and the cutaneous annexes histogenesis. Only the dermatological counselling, after an accurate clinical examination was able to exclude the cutaneous annexes origin.

The most important method for the individuation and characterization of the breast origin of a CUP was the immunochemistry (IHC) performed on the biopsied specimen, pointing out the preeminence of the surgical approach. Only Zhang *et al* (34) obtained the diagnosis performing an IHC analysis on a core needle biopsy. Noteworthy, the necessity of the surgery in the diagnostic process reduces the opportunities for the neoadjuvant approach and this fact could negatively influence the prognosis. The conventional histological diagnosis with eosin and hematoxylin (H&E) staining was able to reach the diagnosis only in 5 cases on 13 (38,5%) (31,32,34-36); three patients was affected by infiltrating ductal carcinoma (31,32,36), while for the other two case the diagnosis was less accurate (34-35). Considering the c-erbB-2 mutation, three tumors were Her2 positive with score 3+ (29,31,36); some authors reported a positive determination for Her2 with lower score while He *et al* (37), referred about a Her2 positivity with score 2+ but the florescent *in situ* hybridization (FISH) test was not reported. Wang *et al* (33) had not mentioned Her2 verify and Rigakos *et al* (39) had not detailed the Her2 positivity. Lack of the FISH analysis and Her2 determination has precluded any possible adjuvant treatment with Trastuzumab. Luminal forms were the most diagnosed (6 out of 13 cases, 46.2%) (27,29,33,35,37,39). Only one patient was candidate to neoadjuvant treatment (27), after an incisional biopsy. Taxane drugs were indicated for 7 patients on 13 (27,33-35,37,38). Only four patients underwent to irradiation during the neoadjuvant phase (32,33,35,38). Two studies did not reported data about the follow up (27,30). The other papers referred that the patients were alive until the last follow up. The mean period of observation was 22,4 months (range 9-48).

Rigakos *et al* (39) performed the microRNA Rosetta Cancer Origin test to find out the primitivity after the failure of PET-TC, Total body CT and MRI. Many studies have demonstrated that microRNA profiling may be useful for the CUPs' work up, with agreement to final diagnosis for microRNA testing ranging from 84 to 92% (40-42). MicroRNAs are small, non-coding RNAs of 17-25 nucleotides involved in a regulatory function in protein translation and expression. Since their discovery, they are becoming important as cancer biomarker. However, it is not clear if this technique was necessary in the diagnostic process, because it was performed before the axillary surgery and the HIC test.

Despite CUP of male BC origin is very rare, this review highlighted the heterogeneity of the diagnostic methods and the therapeutic strategies. In any suspicious cases of CUP, a strict and accurate diagnostic work-up appears mandatory to exclude any possible primary origin of the tumor. This aspect seems even more important since the scarce experience with this pathology and the absence of guidelines could influence the treatment and the prognosis of the CUP patients. Larger comparative studies about the diagnostic methods and therapeutic approach are needed to address this issue.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

SP was responsible for collecting clinical, imaging and pathological data of the patient, and was responsible for the conception, design, content and writing of the manuscript. FF, FI, MLV, GC, FMM and LB collected data. CG, RR, ST, LD and FSL contributed to the conception and revisions of the manuscript. RA contributed to the writing of the manuscript, the conception of the study and the collection of pathological images. All authors agreed on the journal to which the article has been submitted and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript. SP and CG confirm the authenticity of the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

Competing interests

The authors declare that they have no competing interests.

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