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Primary Cutaneous Adnexal Carcinoma of the Axilla: A Diagnostic Dilemma and Review of Literature

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Abstract

Primary cutaneous adnexal carcinomas are rare and often difficult to diagnose. This is particularly challenging when occurring in the axilla as they histologically resemble breast carcinoma and this is the lymphatic region to which breast cancer most commonly spreads. Management of this cancer both in the curative and palliative setting remains uncertain due to the paucity of data.

This clinical case highlights these challenges and demonstrates an unusual pattern of distant metastatic spread. This case and review of the available published data both demonstrate the possible aggressive nature of primary cutaneous adnexal carcinoma, highlights the histological prognostic factors which impact disease free and overall survival. We discuss the roles of prophylactic regional nodal clearance, adjuvant chemotherapy and radiotherapy. The best palliative treatment options in the metastatic setting are not known and we outline our experience and reflect on those within the published data.

Mini Abstract

This case and literature review highlights the prognostic factors which impact disease free and overall survival. We discuss the roles of prophylactic regional nodal clearance, adjuvant and palliative treatments.

Abbreviations

PCAC:Primary Cutaneous Adnexal Carcinoma; CK7: Cyto Keratin 7; EMA: Epithelial Membrane Antigen; CK20: Cyto Keratin 20; PSA: Prostate Specific Antigen; PETCT: Positron Emission Tomography; MRI: Magnetic Resonance Imaging; HER2: Human Epithelial Receptor 2; SLNB: Sentinel Node Biopsy; PORT: Post-Operative Radio Therapy; ECT: Electro Chemo Therapy; ER: Oestrogen Receptor Protein; PR: Progesterone Receptor Protein

Introduction

Primary Cutaneous Adnexal Carcinomas (PCAC) are rare neoplasms with more aggressive behaviour than other non-melanoma skin cancers with relative resistance to chemotherapy [1]. Delays in diagnosis may occur due to challenges differentiating these cancers from breast cancer or secondary metastatic carcinoma [2]. In an attempt to further understand the diagnosis and the optimal treatment strategy of this cancer we have reported on clinical experience gained from this case and a review of the literature.

Case Presentation

A 59 year old Caucasian male, with no significant medical history and a WHO performance status of 0, presented with a 5cm firm mass in the right axilla. The initial incisional biopsy demonstrated a diffuse pattern carcinoma. The morphology and immuno profile raised the possibility of metastasis from a primary breast carcinoma, particularly lobular carcinoma or an upper gastrointestinal and pancreato biliary tract primary as it was positive for CK7, EMA and BerEP4 but negative for CK20.

A triple breast cancer assessment, PSA, testicular ultrasound and tumour markers showed normal findings. PETCT demonstrated a right axillary lesion with equivocal uptake in the surrounding lymph nodes and a suspicious lesion in the left proximal femur; which had reassuringly benign appearance on sequential MRIs. The PETCT showed a suspected sigmoid lesion but a colonoscopy was normal. In the absence of a demonstrable primary tumour elsewhere, a diffuse variant of primary cutaneous adnexal (apocrine) carcinoma was considered.

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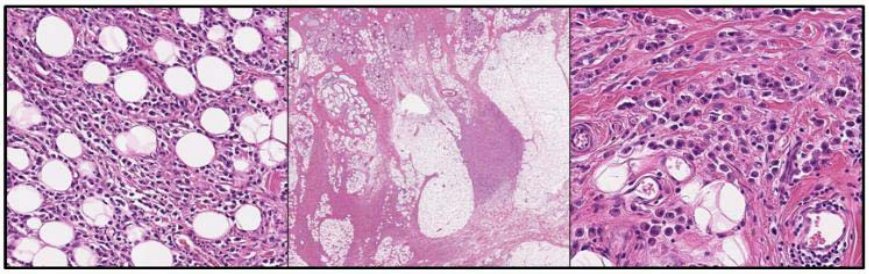

Figure 1: Diffusely invasive carcinoma, positive for CK7, EMA, E-cadherin and BerEP4 but negative for CK20.

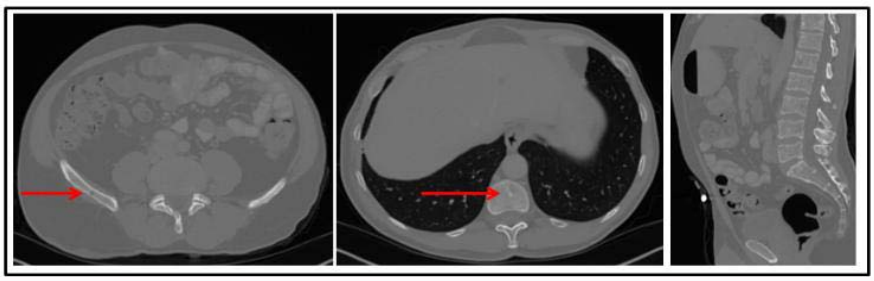

Figure 2: CT scan showing subtle, widespread sclerotic bone changes.

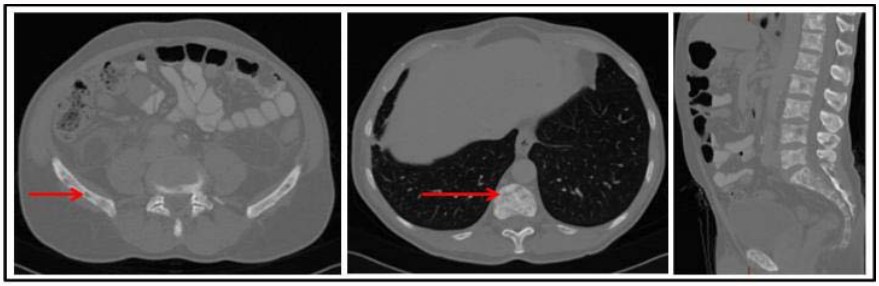

Figure 3: CT scan showing diffuse sclerotic bony changes.

Histology of the subsequent axillary node dissection confirmed a diffusely invasive carcinoma with features in keeping with a primary cutaneous adnexal carcinoma. Further immunohistochemistry performed showed positive E-cadherin and therefore inconsistent with a primary lobular breast carcinoma. Hormone receptors and HER2 were negative (Figure 1). Eighteen out of 26 lymph nodes were positive for metastatic carcinoma, including the apical node, with focal extra capsular spread and a positive resection margin. He received adjuvant radiotherapy 50 Gy in 25 fractions over 5 weeks to the right axilla.

A post-treatment CT scan at 6 months unexpectedly showed subtle multiple mixed sclerotic and lytic skeletal metastases with no evidence of locally recurrent tumour or soft tissue metastases (Figure 2). This unusual clinical pattern prompted investigation for a synchronous primary malignancy. PSA was normal and a CT guided bone biopsy was non-diagnostic. The patient began to experience global symptoms of weight loss, lethargy, reduced exercise tolerance and mild lumbar pain. A repeat CT scan showed progression of the sclerotic bone lesions with diffuse replacement throughout the skeleton by an infiltrative process, raising the possibility of a haematological malignancy (Figure 3). A myeloma screen was clear and a bone marrow trephine finally confirmed metastatic cutaneous adnexal carcinoma. He was commenced on palliative carboplatin and capecitabine chemotherapy, receiving a reduced dose of carboplatin (AUC 4) for the first cycle due to anaemia suggesting likely bone marrow infiltration. The first cycle was tolerated well so carboplatin was increased to AUC 5 for subsequent cycles. The restaging CT, following cycle 3, showed stable bone disease but an enlarging pleural effusion and increased size in the abnormal tissue surrounding the right adrenal gland. The patient gained clinical improvements in performance status and exercise tolerance therefore he went on to completed 6 cycles of chemotherapy.

One month later he was admitted with symptomatic large pleural effusions, ascites and acute renal failure. Cytology from pleural fluid confirmed metastatic adnexal carcinoma. Large pleural effusions and bilateral hydronephrosis secondary to peritoneal thickening were seen on imaging. Bilateral urinary stents were inserted, with improvement in his renal function and the aim of commencing taxane based second line chemotherapy. Oral capecitabine chemotherapy was arranged to commence as an interim measure but was never started due to progressive deterioration and death.

Discussion

Diagnostic challenge

Metastatic cutaneous adnexal carcinomas are rare and present a huge diagnostic challenge and it is often a diagnosis of exclusion. It is

Table 1: Summary of prognostic studies.

Author	No. of patients	Prognostic factors considered	Comments
El-Domeiri et al. [4]	83	Inferior prognosis associated with: ● Undifferentiated and anaplastic histology ● Lymph node metastases	42.6% of patients had lymph node metastasis; 14.7% at presentation.
Luz et al. [5]	8	● Tumour depth >7 mm ● Infiltrative margin	
Mahomed et al. [6]	21	● Ultra Violet radiation ● Chronic immunosuppression	Malignant squamous differentiation was seen in a subset of PCAC's
Oyasiji T et al. [7]	50	● Age >60 ● Nodal metastases	
Prieto-Granada [8]	103	● Age >70 years, ● Tumour dimension > 2 cm, ● Sentinel node positive lymph nodes ● Eccrine derivation, esp. porocarcinomas are high risk for nodal spread	16% of patients had nodal metastasis; 10% at presentation.
Puleo et al. [9]	65	Porocarcinomas have a high risk of regional node metastasis and local recurrence. Tumours of sebaceous and pilar origin demonstrated lower grade behavior.	Sentinel Lymph Node Biopsy (SLNB) was performed in 14 Patients and positive in 6 (43%)
Robson et al. [10]	69	Inferior prognosis associated with: ● >14 Mitoses per HPF ● Lympho vascular invasion ● tumour depth > 7 mm, ● "infiltrating' advancing margin	17% experienced local recurrence, 19% LN metastases and 11% distant metastases or death
Robson et al. [11]	24	● Grade 3 predicted poorer OS	
Shiohara et al. [12]	12	● Lympho vascular invasion correlated with lymph node metastasis Poorer OS associated with: ● Infiltrative grown pattern ● Lymph node metastasis	
Wong et al. [13]	71	No significant OS or DFS difference based on ● Tumour location, ● Histologic subtype, ● SLNB status. A subgroup analysis on the eccrine group demonstrated no OS or DFS difference between porocarcinoma vs other histology.	no survival differences were noted based on subtype

OS: Overall Survival; SLNB: Sentinel Lymph Node Biopsy; DFS: Disease Free Survival

histologically indistinguishable from metastatic breast carcinoma as it may show considerable variation of morphology and may resemble various histological types of breast carcinoma. Moreover, axilla is the most common site for apocrine carcinoma (given the high apocrine sweat gland density at this site) and is also usually the first site of metastasis for breast carcinoma. In addition, there are no specific immuno histochemical markers to distinguish between the two tumours. GATA-3 had recently been described as a specific marker for breast and urothelial tumours. However, this has also been shown to be positive in cutaneous apocrine tumours [3]. In this case, due to the lack of an identifiable primary site elsewhere and extensive involvement of local lymph nodes the tumour was interpreted as being consistent with a primary axillary adnexal carcinoma. Gastric carcinoma was a potential diagnosis on the basis of histological findings but with no gastrointestinal symptoms or radiological changes this was felt unlikely.

Management challenge

Prognostic factors: There is paucity of data on prognostic factors and treatment due to the rarity of these neoplasms. A number of case reports have stated outcomes suggesting prognostic factors (Table 1) [4-13]. One of the largest case series reported by El-Domeiri et al. [4] found that 29 of 68 patients followed up for 5 year or more, developed regional lymph node metastases; 10 of whom presented with positive lymph nodes and 19 developed lymph node spread within 9 years of diagnosis. There was a higher incidence of regional lymph node metastases in the patients with high grade histology compared to low grade; 86% versus 9%. Those with regional nodal involvement had a worse 5 year and 10 year survival rate compared to patients with no nodal spread; 29% versus 67% and 9% *vs.* 56% respectively [4]. Lymph node involvement, poorly differentiated subtype and high grade histology all appear to negatively impact prognosis and should prompt aggressive adjuvant treatment [4,7,10,14,15]. Robson et al. [10] reviewed 69 patients and found lympho vascular invasion and tumour depth >7 mm were associated with lower rates of survival [10]. Two single centre studies reported by Oyasiji T et al. [7] and Prieto-Granada et al. [8] suggested older age >60, large size (>2 cm) and eccrine differentiation were significantly associated with inferior Overall Survival (OS) [7,8].

Management of primary and regional metastases: Treatment decisions rely on case studies as there are no prospective randomised trials to guide treatment. The widely recommended approach is a wide local excision of the primary site with a 1 cm to 2 cm surgical margin [2,16]. Regional lymph node dissection is indicated for clinically evident nodal involvement and for large sized or poorly differentiated localised primary tumours [2,16]. Prophylactic lymph node resection does not seem to improve disease-free survival. Puleo et al. [9] have demonstrated that porocarcinomas have a high risk of nodal involvement and distant spread [9]. However, a case series reported by Wong et al. [13] found no significant impact on overall survival of histological subtype [13]. Respecting this uncertainty, and although Sentinel Node Biopsy (SLNB) for staging requires further evaluation, it could be considered in primary tumours demonstrating lympho vascular invasion, poor differentiation or eccrine derivation, especially porocarcinomas [4,8,9,14].

The role of adjuvant radiotherapy remains unclear. Chamberlain et al suggested that predictors of high risk advanced local or regional cancer, and therefore the indications for adjuvant radiotherapy, include; large tumour size (>5 cm), positive or close resection margins and moderate to poor differentiation [16]. Relative indications for adjuvant radiotherapy include extra nodal extension or extensive

Table 2: Publications reporting adjuvant treatment.

Author	No. of patients	Intervention	Outcome	Comments
Oyasiji et al. [7]	10	1 patient received definitive CRT and 6 patients received adjuvant RT. 3 patients were treated with adjuvant chemotherapy & 1 with palliative chemotherapy with the following regimens; - Single agent cisplatin - Single agent paclitaxel - Carboplatin & paclitaxol combined - Adriamycin, citoxan and paclitaxel combination	No comment made on survival	Indications for chemotherapy: • Nodal metastasis • Positive margin • PNI • Aggressive disease with periorbital involvement Indications for RT: • Locally aggressive disease • PNI • Nodal metastasis.
Marone et al. [14]	1	Electro Chemo Therapy (ECT) with bleomycin for local recurrence	Local complete response at 5 months	Proposed ECT as adjuvant treatment after surgery.
Wang et al. [18]	9	PORT delivered to a median dose 60Gy to the primary and 50Gy to the neck: - Primary site only (n=3) - Draining lymphatics (n=2) - Both (n=4) - One patient received concurrent cisplatin	Loco regional control 100% 5 yr PFS 89%	Indications for RT • Involved LN • ECE • Positive margin • High-grade histology • Multifocal disease • Recurrent disease
Wauer at al. [19]	1	PORT to regional LN 50.4 Gy in 28 fractions	29 months DFS	
Baxi et al. [20]	14	PORT of 50 Gy or greater with generous margins (3 cm to 5 cm)	Crude local control rate of 93%	
Chintamani et al. [21]	1	Limb amputation followed by adjuvant sequential chemotherapy with 5FU and cisplatin followed by 70 Gy to the primary site and 50 Gy to the axilla	Distant metastatic disease within 6 months	
Daniel et al. [22]	1	Tamoxifen	DFS at 3 years	
Gallerani [23]	1	PORT 54 Gy with 9 Gy boost PORT to resected recurrence in a different site 60Gy		
Gonzales-Lopez et al. [24]	1	Lymphadenectomy, radiotherapy followed by sequential oral isotretionoin and tegafur	No evidence of distant metastases at 5.6 yrs.	
Seong et al. [25]	2	PORT 50 Gy in 25 fractions over 5 weeks following complete axillary nodal dissection	No local or distant recurrence	
Vucini et al. [26]	1	PORT 50 Gy in 25 fractions	Recurrence	
Waqas et al. [27]	11	PORT offered to 8 patients; median dose of 4 5Gy to the primary site (45 Gy in 10 fractions or 50 Gy in 20 fractions) One patient had palliative radiotherapy for locally advanced disease (14 Gy via Quad shot regimen) One patient with regional recurrence despite PORT 40 Gy in 10 fractions went on to receive 60 Gy in 30 fractions to the site of recurrence.	1 patient developed Local recurrence 2 patients developed distant metastases	Indications for PORT: • Close margins (n=2) • Positive margins (n=1) • High grade histology (n=3) • Multifocal disease (n=1)

PNI: Peri Neural Invasion; PORT: Post-Operative Radio Therapy; RT: Radio Therapy; ECE: Extra Capsular Extension; DFS: Disease Free Survival; 5FU: 5 Fluoro Uracil; OS: Overall Survival

nodal involvement (>4 lymph nodes) [7,16-19]. Post-Operative Radio Therapy (PORT) doses utilised vary as demonstrated in Table 2 [7,14,18-27]. Wang et al. reviewed 9 patients with good loco regional control of 89% progression free survival following PORT for head and neck cutaneous primary cancers with doses varying between 50 Gy to 60 Gy, 2 Gy per fraction and acceptable toxicity. One patient also received concomitant cisplatin [18]. However, in a retrospective study by Waqas et al. [27] of 8 patients who underwent PORT with median doses of 45 Gy, 3 cases experienced local or distant spread and suggests that higher doses may be required to effectively reduce risk of recurrence [27]. Oyasiji et al. [7] reported the use of primary sequential chemotherapy and radiotherapy treatment with 70 Gy to the eyebrow for a non-surgical case but no other cases have reported using definitive radiotherapy, with or without chemotherapy [7]. There remains a lack of evidence to guide the appropriate dose and schedule for adjuvant radiotherapy, however, doses of 50 Gy or greater seem to be required to effectively reduce the risk of recurrence in patients with high risk histopathological features [26].

Adjuvant chemotherapy is not routinely offered for PCAC as they are considered relatively chemo resistant [1,2,28]. The few case reports describe the use of varied adjuvant chemotherapy regimens and their sequencing; including concomitant, before or after adjuvant radiotherapy (Table 2) [7,21,24,26]. Oyasiji et al. [7] reported on 3 patients who received adjuvant chemotherapy with regimens including single agent platinum or taxane and another receiving a combination of both. Indications for adjuvant chemotherapy included nodal metastatic spread, positive margin or peri neural invasion [7]. Gonzales-Lopez et al. [24] reported a case of cutaneous PCAC with regional nodal spread who underwent surgery, adjuvant radiotherapy followed by sequential oral isotretinoin and tegafur, with no distant spread seen at 5.6 years [24]. The use of Electro Chemo Therapy (ECT) with bleomycin led to a complete response in a local recurrence within the dermis, 5 months after treatment. Based on this, Marone et al. [14] have proposed ECT as an adjuvant treatment after surgery in view of the propensity of loco regional metastases [14]. Daniel and colleagues reported the use of adjuvant tamoxifen, anti-oestrogen treatment, in a patient with Oestrogen Receptor Protein (ER) and Progesterone Receptor Protein (PR) positive on histopathology. The patient was disease free for over 3 years raising the possibility of anti-oestrogen treatments in the adjuvant setting in addition to the metastatic setting where use of anti-oestrogens is more frequently reported [22].

Table 3: Publications reporting metastatic treatments.

Author	No. of patient	Intervention	Outcome
El-Domeiri et al. [4]	4	5-Fluorouracil (5Fu), doxorubicin and cyclophosphamide	No response
Shiohara et al. [12]	4-12	Cisplatin and 5FU (n=3) Oral tegafu-uracil (n=2)	No clinical response
		Palliative radiotherapy; 30-50Gy to cutaneous or bone metastasis	Short term Good local and pain control
Wauer et al. [19]	1	Surgery and PORT 40 Gy in 20 fractions to oligometastatasis	12 months DFS
Gallerani et al. [23]	1	Cisplatin 3 weekly combined with weekly cetuximab, 2 cycles	Progressive Disease
		Second line 7# weekly docetaxel	Short term stable disease
		Whole brain EBRT 30 Gy	No clinical benefit
Batistella et al. [29]	2	Sunitinib	8monthsstable disease 10 monthsstable disease
Aaribi et al. [31]	1	3 cycles of cisplatin and 5FU	PD (increase in metastases)
		Second line docetaxel	Complete response at time of report
Barzi et al. [32]	1	Isotretinoin and IFN alpha	10month stable disease
de Bree et al. [33]	1	Topical 5FU and intra-arterial chemotherapy with docetaxel	Complete response of multiple regional skin mets up to 2 years
Goldstein et al. [34]	1	Tamoxifen	Complete response 7m
Gutermuth et al. [35]	1	Combination of interferon-alpha (IFN-alpha) 9 million units subcutaneously three times per week and paclitaxel 100 mg/m (2) weekly	Long-term stable disease (local recurrence and regional lymph node metastasis)
Mezger et al. [36]	2	Adriamycin, cyclophosphamide, vincristine and bleomycin	Complete response for 2 years
Piedbois et al. [37]	1	Doxorubicin, mitomycin C, vincristine and cisplatin, 4 cycles	Complete response 16 m and OS 50 m
Plunkett et al. [38]	1	Epirubicin	Progressive disease
		Second line docetaxel	Limited response
		EBRT to bone metastases	Limited response
Tlemcani et al. [40]	1	Paclitaxel and carboplatin (200 mg/m^2) (AUC6) 21 day cycles	Complete response for 16months

PNI: Peri Neural Invasion; PORT: Post-Operative Radio Therapy; EBRT: External Beam Radio Therapy; DFS: Disease Free Survival; ER: Endocrine Receptor; 5FU: 5 Fluoro Uracil; OS: Overall Survival

Management of distant metastases: Our patient developed metastatic spread a short period after completing adjuvant radiotherapy suggesting early haematological spread. Systemic dissemination remains rare, particularly the diffuse pattern of bony spread we observed [29,30]. This prompted investigations into a concurrent primary before confirming PCAC metastatic spread and commencement of palliative chemotherapy.

Chemotherapy is most commonly used in the metastatic setting with a small number of case publications reporting responses to both single agent and combination chemotherapy (Table 3) [4,12,19,23,29,31-40]. Mezger et al. [36] reported outcomes for 2 patients who received a combination regimen with doxorubicin, cyclophosphamide, vincristine and bleomycin with a complete response for 2 years in one patient and a partial response for 4 months in the other patient. However this regimen carried high levels of toxicity [36]. Piedbois et al. [37] reported a complete remission for 16 month and survival prolongation for a patient who received 4 cycles of combination regimen of doxorubicin, mitomycin C, vincristine and cisplatin [37]. Whereas El-Domeiri [4] reports no response to chemotherapy in 4 paediatric cases treated with 5-Fluorouracil (5Fu), doxorubicin and cyclophosphamide [4]. Shiohara et al. [12] also reported no clinical response to cisplatin and 5FU combination for 3 patients and oral tegafu-uracil for 2 patients with metastatic PCAC [12].

Targeted treatment with sunitinib, oral tyrosine kinase inhibitor, have been reported in one study of 2 patients with metastatic adnexal carcinoma, with evidence of disease control lasting at least 10 months [16,29].

In our case the patient progressed through first line platinum and was planned to receive second line chemotherapy with Taxanes. There is very limited evidence for second line options. Two cases have been published reporting good response to second line docetaxel having shown resistance to first line chemotherapy including single agent epirubicin and cisplatin and 5FU, respectively with tolerable side effects [31,38].

Role of maintenance chemotherapy: PCAC frequently express ER and PR which may offer a justification for endocrine treatment including tamoxifen [10]. Goldstein et al. [34] reported a case of complete response at 7 months following the use of tamoxifen in a patient with metastatic PCAC [34]. Shidhar et al. [39] reported 2 cases with sustained partial response to tamoxifen in a patient with ER positive metastatic eccrine tumour but no response in an ER negative patient [39]. These cases raise the potential for anti-oestrogen treatment options in apocrine carcinomas that express endocrine receptors.

Conclusion

These are rare cancers which often represent a diagnostic dilemma to pathology experts and often an unavoidable delay to definitive treatment. As treatment options are limited early diagnosis and treatment is important. With apparent relative resistance to chemotherapy agents to guide treatment in locally advanced and metastatic cases further information is required about targeted treatments for this population of patients.

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