

Cutaneous Paraneoplastic Syndrome of Breast Cancer : About 2 Cases

Hadidane Manel¹, Slimane M², Chemlali Molka³, HENCHIRI Houda⁴, Ben Hassouna Jamel⁵, Rahal Khaled⁶

Oncology Surgical Departement, Salah Azaiz Institute, Tunis, Tunisia

Abstract: *Paraneoplastic syndromes are rare disorders that are triggered by an altered immune system response to a neoplasm. They are defined as clinical syndromes involving nonmetastatic systemic effects that accompany malignant disease. Paraneoplastic dermatoses are heterogeneous group of clinical manifestations that often appear benign. They represent the 2nd most common paraneoplastic site (the 1st endocrine syndromes). They commonly precede or follow visceral cancer. Recognition may result in earlier diagnosis and better prognosis. We report two cases of paraneoplastic dermatosis that are rarely associated with breast cancer.*

Keywords: cutaneous, paraneoplastic, syndrome, breast, cancer

1. Introduction

Paraneoplastic syndromes are rare disorders that are triggered by an altered immune system response to a neoplasm. They are defined as clinical syndromes involving nonmetastatic systemic effects that accompany malignant disease [1-2-3]. Paraneoplastic syndromes arise from tumor secretion of hormones, peptides, cytokines or from immune cross-reactivity between malignant and normal tissues. They may affect diverse organ systems, most notably the endocrine, neurologic, dermatologic, rheumatologic, and hematologic systems. It is estimated that paraneoplastic syndromes affect up to 8% of patients with cancer. The most commonly associated malignancies include small cell lung cancer, breast cancer, gynecologic tumors, and hematologic malignancies. Paraneoplastic dermatoses are heterogeneous group of clinical manifestations that often appear benign. They represent the 2nd most common paraneoplastic site (the 1st endocrine syndromes). They commonly precede or follow visceral cancer. Recognition may result in earlier diagnosis and better prognosis. In fact the skin may exhibit the first clinical evidence of a systemic disease and may provide the first clues to a diagnosis in up to 1% of internal malignancies [4]. Since cutaneous paraneoplastic syndromes commonly precede or follow visceral cancer, their recognition may result in earlier diagnosis and better prognosis for the patient [5-6]. Breast cancer is associated with paraneoplastic manifestations from many systems. The most common skin paraneoplastic manifestations of breast cancer are acanthosis nigricans, erythromelalgia, thrombotic thrombocytopenic purpura, acrokeratosis paraneoplastica, paraneoplastic hypertrichosis lanuginosa acquisita, dermatomyositis, systemic sclerosis, and scleroderma [7-8]. We present here two cases of cutaneous paraneoplastic syndrome that are rarely associated with breast cancer.

2. Case 1 :

First case is a 61-year-old woman, with history of hypertension. She consulted for a squamous nipple lesion of the left breast evolving since three months. The clinical breast examination revealed a squamous lesion in the left nipple evoking Paget disease (Figure 1)

The rest of the breast and lymph nodes were normal. Otherwise, a necrosis of the second, fourth, fifth, of the right fingertips, and of the second, and third fingertips of the left hand was objectified by the physical exam (Figure 2). Thumbs were spared.

The clinical presentation was compatible with Raynaud's phenomenon. Mammography showed suspicious microcalcifications disseminated to all the breast, concentrating in the external-upper quadrant of the left breast, that was classified ACR5 (American College of Radiology). Ultrasound imaging was not realized. Biopsy concluded at high grade of intra ductal carcinoma. Doppler ultrasound imaging of the fingers was normal. Considering all clinical, radiological and history findings, paraneoplastic Raynaud syndrome of in situ breast carcinoma was suggested. A left mastectomy with homolateral axillary node picking was realized. Definitive histopathology exam concluded at predominant intra-ductal carcinoma with a component of invasive ductal grade II SBR (Scraf Bloom Richardson) carcinoma, associated to nipple Paget disease. Nodes were negative. After surgery, the cutaneous finger lesions had remarkably decreased with impressive clinical improvement of Raynaud syndrome. That certified definitely the diagnosis of paraneoplastic Raynaud syndrome. Up to now, the patient continues to hold rather well without any recurrence neither of breast cancer nor of Raynaud's phenomenon.

3. Case 2 :

The second case was a 44-year-old single non menopausal woman with no significant medical history. Her family history was significant for breast and gynecologic cancer in her mother and sister. Initially, she was treated for a T1 N0 M0 invasive ductal carcinoma of the right breast cancer according to TNM (Tumor Node Metastasis) stadification. It was a triple negative type, SBR III. She had a conservative surgery with three positive nodes / 19 nodes. Then she had loco regional radiotherapy followed by eight cycles of chemotherapy (4 cycles of 5 Fluoruracil, Epirubicine, Cyclophosphamide and 4 cycles of Taxoter). Two years after a regular monitoring, with unremarkable mammograms, the patient consulted for an abdomino-pelvic mass. On physical exam she had in addition to the palpable

mass, an enlarged ulcerative painful cutaneous lesion, with purple and undermined edge situated on the anterior surface of both legs that evolving rapidly since 1 month (Figure 3). The cutaneous presentation was typically correlated with pyoderma gangrenosum. The patient received anti-inflammatory and anti staphylococcus therapy for two weeks without success in her cutaneous disease. The abdominal mass was explored by MRI (magnetic resonance imaging) showing a well-limited abdomino-pelvic mass measuring 20x15x12 cm, surrounded by a thick wall. The mass was a heterogeneous hypo intense in T1 and T2, with necrosis area. The CA 15-3 (>200 U/ml) and CA 125 (carbohydrate antigen) (<600 U/ml) level were pathologic with normal level of CA 19-9. Then she underwent a laparotomy with right adnexectomy of an ovarian suspicious mass. The extemporaneous exam revealed metastatic lesion of anterior breast cancer. One month later, CA 15-3 and CA 125 level had been standardized. The cutaneous lesions had been remarkably improved after the resection of ovarian metastasis and within chemotherapy for metastatic disease. Currently, the patient is still receiving chemotherapy with good resolution of her cutaneous lesion.

4. Discussion

In the clinical setting, the paraneoplastic manifestation may precede the diagnosis of the related neoplasm, often by months or years.

In some instances, the timely diagnosis of these conditions may lead to detection of an otherwise clinically occult tumor at an early and highly treatable stage.

In other cases, confirmation of the association may require a statistical approach.

In general, the skin may be directly or indirectly involved in malignancies. Indirect involvement, as in paraneoplastic dermatosis, is caused by a variety of factors (inflammatory, proliferative or metabolic factors) related to the neoplasia, such as polypeptides, hormones, cytokines, antibodies or growth factors that act as mediators, interfering with cell communication and, consequently, with its activity. In this case, there is no presence of neoplastic cells in the skin, and this involvement is considered a dermatological paraneoplastic syndrome [9-10].

Moreover, cutaneous paraneoplastic syndromes are important clinical markers that may also precede (most commonly), occur simultaneously or after the diagnosis of a given neoplasm. More than 50 dermatoses have been correlated with underlying neoplastic processes.

The presence of cutaneous paraneoplastic syndrome is often associated with a poor prognosis.

Cutaneous paraneoplastic changes may be an important clue to the presence of an otherwise asymptomatic malignancy. Indeed, in over one third of patients, complaints related to the paraneoplastic condition precede the diagnosis of the malignancy by months or years. Sometimes, they may also be suggestive of the specific type of cancer present. The clinician must be aware of these dermatosis to rule out a

potential cancer underlying or simple benign manifestation of a systemic disease.

In general, since paraneoplastic syndromes are caused by the tumor, the cancer must precede the development of the dermatosis and the two conditions should follow a parallel course [11]. In the first case of our report, the paraneoplastic Raynaud's phenomenon appeared simultaneously with the breast cancer diagnosis and had parallel progression.

However, in the second case, the paraneoplastic dermatosis onset with the breast metastatic recurrence. Thereby, paraneoplastic syndromes may be the first indication of a new or recurrent tumor and failure to recognize their import may have significant consequence.

Raynaud's phenomenon associated with malignancies is a rarely reported clinical entity. An important review identified only 33 cases of paraneoplastic Raynaud's syndrome in the medical literature [12]. The underlying malignancies among patients with paraneoplastic Raynaud's phenomenon can be highly varied, including carcinomas of the lung, breast, ovary, testes, skin and thyroid. Sarcomas and haematological malignancies too have been associated [13-14]. The first case of secondary Raynaud's phenomenon associated with breast cancer in the absence of an underlying rheumatic condition was reported by David Allen in 2010 [15].

Pyoderma gangrenosum is a rare clinical entity of poorly understood pathogenesis, characterized by rapidly progressing skin necrosis. In around half of cases, pyoderma gangrenosum is associated with various underlying specific conditions, most frequently rheumatoid arthritis, inflammatory bowel disease or myeloproliferative disorders. There have been few reports on the association of pyoderma gangrenosum with solid malignancies including breast cancer [16-17]. Additionally, a few cases of pyoderma gangrenosum of the breast precipitated by breast surgery were reported [16-18]. The most common location of pyoderma gangrenosum is the legs but the disease may also involve other regions, particularly at the site of even minor trauma or surgery [18]. One case report of recurrent pyoderma gangrenosum that was precipitated by breast cancer was published in 2014 by Rinata Duchnowska [19].

Because of their protean manifestations, paraneoplastic syndromes should be managed by a coordinated team of physicians, including medical oncologists, surgeons, radiation oncologists, endocrinologists, hematologists, neurologists, and dermatologists.

Since they often cause considerable morbidity, effective treatment of paraneoplastic dermatosis can improve patient quality of life, enhance the delivery of cancer therapy, and prolong survival. Treatments include addressing the underlying malignancy, immunosuppression (for neurologic, dermatologic, and rheumatologic paraneoplastic syndromes), and correction of electrolyte and hormonal derangements (for endocrine paraneoplastic syndromes).

Most of paraneoplastic dermatoses disappear when the primary tumour is removed and reappear in the case of recurrence or metastases of the cancer. Due to association

with serious underlying conditions, rapid development and potentially serious consequences, Raynaud's phenomenon and pyoderma gangrenosum necessitates especially prompt and thorough diagnosis, including the search for coexisting disease.

5. Conclusion

Early recognition of these cutaneous hallmarks offers an opportunity for early diagnosis, treatment of the internal malignancy and monitoring for tumor recurrence.

A sudden onset of any dermatosis should raise suspicions of its character being paraneoplastic.

Paraneoplastic dermatosis if not addressed can adversely affect quality of life.

Like all other paraneoplastic symptomatology, paraneoplastic dermatosis can be expected to abate after treatment against the underlying malignancy is initiated. In addition to eradication of the underlying malignancy, treatment of these syndrome may acquire immunotherapy and anti inflammatory therapy. A regular follow up of both underlying malignancy and associated paraneoplastic dermatosis is mandatory to make the diagnosis of a potential recurrence in time for an adequate treatment.

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Written consent for publication was obtained from the patient.

7. Conflict of Interest Statement

The authors have no competing interests.

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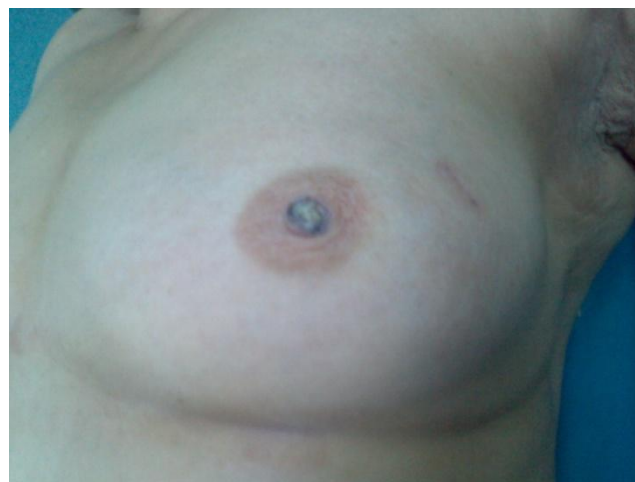


Figure 1: Squamous lesion of the left nipple



Figure 2 : Necrosis of fingertips



Figure 3 : ulceration of the anterior surface of both legs