Editorial

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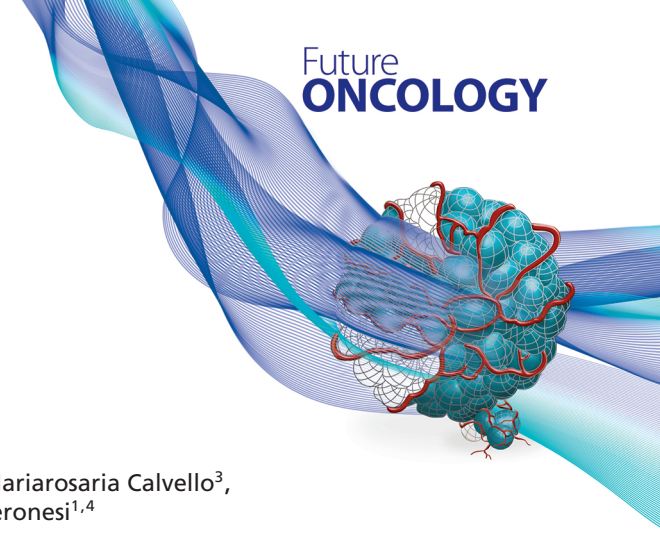

Breast cancer with rare metastatic manifestation

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"In this dissertation of metastatic appearance of pancreatic adenocarcinoma on the breast, we illustrate the vague traits of its clinical behavior, underlying how pathological support and correlation with a patient's genetic and oncological history are mandatory for a proper diagnosis, in order to avoid unnecessary surgical procedure and to provide an adequate clinical management."

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Metastases to the breast represent approximately 2% of all mammary malignancies and are characterized by poor prognosis. The most common metastatic lesion to involve the breast is metastasis from a contralateral mammary cancer [1–3]. Excluding hematologic malignancies, the rate of nonmammary metastases drops to well below 1% [1,2].

In literature, a wide variety of primitive solid cancers from many different sources has been reported: the most common include gynecologic site, in particular ovarian, skin, specially melanoma, lung and gastrointestinal tract [4–8].

Breast metastases from pancreatic adenocarcinoma are very rare, as documented in literature. Domanski *et al.* reported one case of breast metastasis as the first manifestation of a poorly differentiated pancreatic adenocarcinoma [9]. In 2001, Georgiannos *et al.* described one case of breast metastasis from pancreatic adenocarcinoma diagnosed in one woman in 1955, diagnosis resulted in an autopsy series, obtained from the Surgical and Postmortem Archives of the Royal London Hospital Histopathology Department [1]. Moreover, in a recent study, De Lair *et al.* described two cases of pancreatic metastasis among 85 patients with metastatic lesions to the breast [2].

Breast metastasis from pancreatic adenocarcinoma represents an interesting issue, due to its heterogeneous and indistinct clinical features. Immunohistochemical analysis, genetic assessment and oncological history of patient evaluated in a multidisciplinary context, are all precious tools to set up a proper diagnosis and plan a relevant management of this infrequent clinical condition.

In this dissertation of metastatic appearance of pancreatic adenocarcinoma on the breast, we illustrate the vague traits of its clinical behavior, underlying how pathological support and correlation with a patient's genetic and oncological history are mandatory for a proper diagnosis, in order to avoid unnecessary surgical procedure and to provide an adequate clinical management.

Extramammary metastases to the breast are often associated with the presence of other metastases from the primary cancer [10]. They can be detected as palpable breast masses, or on screening mammography with the integration of breast ultrasound. Breast metastases may be also incidentally identified through computed tomography (CT) imaging, or positron emission tomography (PET), commonly performed in staging and follow-up of primary extramammary neoplastic diseases. Nevertheless, their clinical and radiological features do not significantly differ from those of a primary breast malignancy, so the first appearance of a metastasis to the breast may be misinterpreted as primary breast cancer. Indeed, they have heterogeneous and not distinctive imaging hallmarks [11,12]. In this

perspective, fine needle aspiration biopsy (FNAB) plays a key role in correct diagnosis of this disease, and decisive is the support of immunohistochemistry in differentiating primary from metastatic breast lesion [4].

Pathology

Specific immunohistochemical markers have a significant part in the study of such tumors.

Cytokeratins phenotyping, in particular CK7 and CK20, which are well-characterized immune-histochemical markers, are helpful in determining the site of origin of an unknown source's metastatic tumor [13]. Both cytokeratins may be associated to pancreatic primitiveness, in line with literature reports: in their review study, Tot *et al.* reported 87% of CK7 positivity and 62% of CK20 positivity in metastatic pancreatic adenocarcinoma [14]. Moreover, Morini *et al.* underlined the significance of CK20 expression-independent factors related to prognosis for pancreatic–biliary cancer [15].

Furthermore, CDX2 immunohistochemistry is a considerable used tool even if – in literature – its role in metastatic pancreatic adenocarcinoma is not clearly known. CDX2 is a typical homeobox domain containing transcription factor involved in intestinal development by regulating the proliferation and differentiation of intestinal cells [16]. Werling *et al.* and Barbareschi *et al.* both reported CDX2 expression in a percentage of pancreatobiliary adenocarcinoma [17,18], even if, as specified by Xiao *et al.*, with an expression pattern heterogeneous and less strong then in colon cancer [19]. These studies also underlined the correlation between CDX2 expression and worst survival in pancreatic adenocarcinoma.

Finally, a further valuable immunomarker in differentiating primary breast cancer from other carcinomas is immunohistochemical analysis of Gata-3 expression: it is widely considered a marker for breast carcinoma, in particular, associated to luminal subtype, presenting high specificity and sensitivity in ER-positive and Her2-positive subtypes [20,21]. The lack of its expression should significantly strengthen the diagnostic hypothesis of nonmammary primitiveness.

Germline PALB2 mutations

A patient's genetic history may represent an accessory mean in diagnosis of pancreatic metastasis to the breast. Pancreatic adenocarcinoma, according to several studies, is the third most common cancer associated with *BRCA* mutations, in particular *BRCA2* [22]. Moreover, recently the relevance of identification of germline *PALB2* mutations in pancreatic cancer has been more deeply investigated in the literature [23–26].

The role of germline *PALB2* mutations in non-*BRCA1*/*BRCA2* hereditary breast cancer is widely studied. *PALB2* is a recently discovered moderate-risk breast cancer susceptibility gene [27,28]. The *PALB2* gene product functions as a tumor suppressor and interacts closely with both *BRCA1* and *BRCA2* during double-strand DNA repair. *PALB2* acts as a bond protein between *BRCA1* and *BRCA2* to form a '*BRCA* complex' that is implicated in homologous recombination [28–30].

In breast cancer patients, germline mutations of *PALB2* are rare, varying from 0.1 to 2.7% depending on the population [28,31]. In a recent paper, Li *et al.* reported a relationship between *PALB2* expression and a specific breast cancer clinical behavior: high-level expression of *PALB2* at immunohistochemical analysis in the breast cancer tissue results in significant correlation with poor prognosis, rapid progression to advanced stage and aggressive phenotype [29].

PALB2 germline mutations have also recently been shown to be associated with an increased risk of familial pancreatic cancer [27], and appear to be more prevalent in those patients with a family history of pancreatic cancer. It seemed that *PALB2* mutations occur with a prevalence of 2.1% in a population of *BRCA1*/*2*-negative breast cancer patients specifically selected for a personal and/or family history of pancreatic cancer [27].

Although the majority of pancreatic adenocarcinoma cases appear to be sporadic, about 5–10% occurs in inherited cancer predisposition syndrome [25]. Shindo *et al.* showed that the prevalence of germline mutations of *PALB2* is about 0.2% in patients affected by apparently sporadic pancreatic cancer [26], proving that *PALB2* is one of the main genes involved in pancreatic cancer predisposition, while the most common mutated gene is *BRCA2*, whose protein product is a binding partner for *PALB2* protein [26].

Further studies are necessary to define the prevalence of *PALB2* mutations and their clinical utility for those individuals affected with both breast and/or pancreatic cancers.

The advantage of pancreatic cancer screening in patients at increased risk of developing pancreatic cancer, such as those who carry a *BRCA2* or *PALB2* mutation, is uncertain [27].

Conclusion

Breast metastases from extramammary tumors are infrequent, particularly the nonhematologic types. They affect preferentially the fifth–sixth decades, with primary malignancies originating from skin, lung, ovary and gastrointestinal tract [2]. In particular, breast metastases from pancreatic adenocarcinoma are quite uncommon; a few cases are reported in the literature [1,2,9]. Pancreatic ductal adenocarcinoma most commonly metastasizes to lymph nodes, liver, lung and peritoneal cavity, while rarely to the bone, brain, myocardium, umbilicus and esophagus [32].

Radiological instruments, as reported in literature, do not offer correct and diriment means to resolve it [6,33], because of the absence of pathognomonic imaging signs of breast metastasis. Decisive in its management are pathological acquisitions, supported by immunohistochemistry and contextualized in the oncological history of the patient. Genetic counseling could be helpful to investigate the possibility of a specific germline mutation, making further elements useful in breast metastasis management, even if its clinical significance is still an object of scientific studies [34].

A careful clinical history is essential, with special attention to the simultaneous or previous diagnosis of extramammary malignancy, combined to a radiological and pathological examination. In particular, contribution of immunohistochemistry is decisive to differentiate these lesions from primary breast cancers. All these aspects, discussed in a multidisciplinary assessment, are all crucial to ensure accurate diagnosis, avoid useless surgery and define correct systemic treatment.

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