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Original research

Neuroendocrine differentiation in breast carcinoma with osteoclast-like giant cells. Report of a case and review of the literature

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ABSTRACT

Osteoclast-like giant cells (OGCs) may occur in several types of breast carcinomas (BS). Neuroendocrine differentiation may be present in BS but, associated with OGCs, neuroendocrine differentiation has been rarely reported. A case of invasive ductal carcinoma with OGCs and neuroendocrine differentiation diagnosed by fine needle cytology (FNC) is described. A 72-year-old woman with a nodular lesion of the right breast underwent to fine-needle cytology (FNC) The smears showed a dissociated cell population of monomorphous, mononucleated atypical cells with interspersed multinucleated giant cells osteoclast-like. The mononuclear cell component showed plasmacytoid features and frequent vacuoles of secretion. Immunostaining (IHC) performed on cell block sections showed oestrogen receptor positivity in the mononucleated cells and OGCs positivity for LCA and CD68. Histologically the tumour showed cell nests or cords separated by thin fibrovascular septa. The neoplastic cells were monomorphic, with round-oval nuclei, granular chromatin and evident nucleoli. The cytoplasm was indistinct and eosinophilic, finely granular, often containing eosinophilic globules that were positive at the PAS and mucicarmine stainings. Numerous non-neoplastic OGCs were also detected in the interstitial septa. The ICH showed positivity of the tumoral cells for E-Cadherin, oestrogen and progesterone receptors and c-ErbB2 negativity. Mitotic index was inconspicuous with a low Ki67 positivity rate (<10%). OCGs were CD68 and LCA positive. IHC also showed strong positivity for the chromogranin and synaptophysin. A diagnosis of invasive ductal BC with OGCs and neuroendocrine differentiation was performed. The expression of chromogranin and synaptophysin was then retrospectively assessed on CB sections too. The identification of OGCs component on breast FNA samples is not difficult, depending on a good sampling only. On contrary, the neuroendocrine differentiation still represents still a challenge in breast FNC.

1. Introduction

Breast carcinomas (BS) with osteoclast-like giant cells (OGCs) represents about 0.5–1.2% of all the BS [1]. OGCs have been identified in several BS subtypes as invasive and in situ ductal carcinoma, invasive lobular, mucinous, papillary–tubular and metaplastic carcinoma [2]. As for BC with neuroendocrine differentiation, their association with OGCs, has been reported, in very few cases [3–5].

Osteoclast giant cells are characterized by the histiocytic lineage, and are morphologically and immunophenotypically different from multinucleated stromal giant cells and neoplastic multinucleated cells [6]. Furthermore, the neoplastic mononucleated cells and stromal multinucleated cells show a dichotomous staining pattern suggesting that the OGCs are not tumour derived, but represent a second, presumably reactive, cell population [1]. Conversely, the neuroendocrine differentiation is observed in the neoplastic component only. Fine needle cytology (FNA) is an established procedure in the diagnosis of palpable and impalpable lesions of different organs [7–11]; Herein, we describe a case of a histologically confirmed invasive ductal carcinoma with OGCs and

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neuroendocrine differentiation diagnosed by FNA. This report highlights how cytological diagnosis of breast carcinoma with OGCs may not represent a diagnostic problem, conversely neuroendocrine differentiation can be a challenge on cytological sample.

2. Case report

A 72-year-old woman presenting with a 2-month-old right breast lump was referred to our hospital. Clinical examination revealed a nodular lesion in the upper inner quadrant of the right breast without axillary lymphadenopathy. Mammography showed a dense circumscribed opacity of 17 mm of diameter. The patient underwent US-guided FNA of the nodular lesion using a 23G needle without aspiration. A cytopathologist ensured the proper smearing technique and on-site adequacy assessment; one smear smears was immediately Diff Quik stained and on-site evaluated (ROSE) as previously described [12–16]; another one was alcohol-fixed and Papanicolaou stained. The cellularity was deemed to be satisfactory at ROSE and one additional pass was performed to obtain tissue material for ancillary studies. The material obtained from second pass was suspended in 5 ml of buffered formalin and used for immunocytochemical (ICC) on cell-block (CB). Diff Quik and Papanicolaou stained smears showed a high cellularity represented by dissociated cellular population of monomorphic, medium-sized mononucleated atypical cells with interspersed multinucleated giant cells osteoclast-like (Fig. 1a). The mononuclear atypical cell component shows frequently plasmacytoid features and a more than occasional vacuole of secretion, sometimes eosinophilic, with the presence of true "signet-ring cells" (Fig. 1b). ICH was then performed on CB sections as previously reported [6–9] showing expression of oestrogen receptor in the mononucleated cells (Fig. 2a); OGCs showed positivity for LCA (Fig. 2b) and CD68. On the basis of this morphological and phenotypical findings a cytological diagnosis of "dissociated" breast carcinoma [17] with OGCs was performed. The patient underwent to quadrantectomy with axillary lymph nodes remotion. A well-circumscribed firm nodule of 15 × 13 mm, with pushing margins, whitish with hemorrhagic red-brown areas was found. Histologically, the tumour was composed of cellular nests, cords or islands separated by thin fibrovascular septa. The neoplastic cells were monomorphic, with round–oval nuclei, granular chromatin and moderately prominent nucleoli; the cytoplasm was indistinct, and eosinophilic finely granular, often containing an eosinophilic globule. In large areas of the tumour the globules were contained in a clear vacuole displacing the nucleus to the periphery, showing a "signet-ring cells" feature. These globules were positive for PAS and mucicarmine stainings. Numerous non-neoplastic OGCs were also detected wrapping the tumour nests, mainly in the interstitial septa where haemorrhage and haemosiderin pigment was also present. The IHC showed positivity of neoplastic cells for E-Cadherin, oestrogen receptor and progesterone receptor and negativity for c-ErbB2. Mitotic index was inconspicuous with a low Ki67 (%). OCGs were CD68 and LCA positive. The presence of some cytoarchitectural features such as cellular monomorphism with low-grade nuclear atypia, eosinophilic granular cytoplasm and "picked fence" arrangement of the cells at the periphery of the groups suggested a neuroendocrine differentiation. The IHC was positive for the neuroendocrine markers chromogranin and synaptophysin confirming the histological suggestion. Therefore a diagnosis of invasive ductal carcinoma with OGCs and neuroendocrine differentiation was performed. We the retrospectively tested, on CB sections, the expression of neuroendocrine markers chromogranin and synaptophysin; the cellular population showed positivity for both markers (Fig. 2c,d).

3. Discussion

Carcinoma with OGCs and carcinoma with neuroendocrine differentiation represent two unusual variants of breast cancer, which are respectively about 1% and 2–5% of breast carcinomas [1]. In all histological types in which the OGCs are present, these cells are generally dispersed mainly in the stroma. This latter appears hypervascularised, with numerous fibroblasts and haemorrhagic extravasations. The stroma also contains lymphocytes admixed with mononucleated and binucleated histiocytes, often containing haemosiderin. The presence of OGCs is probably due to the production of chemotactic factors produced by cancer cells responsible for the migration of monocytes in the breast cancer stroma and the subsequent transformation of cells in OGCs. As for the neuroendocrine differentiation, in breast carcinoma it can be assessed if neuroendocrine markers are express in more than 50% of the neoplastic cells. The first breast carcinomas with neuroendocrine differentiation aspects were described by Feyrter and Hartmann [18] and subsequently by Cubilla and Woodruff [19]. These authors described a tumour with carcinoid aspects using silver precipitates staining and electron microscopy. Currently, neuroendocrine differentiation in a breast cancer can be detected by IHC with the use of Chromogranin A and B and Synaptophysin; being neuron-Specific Enolase (NSE) not routinely used because of its low specificity. Both the neuroendocrine and OGCs variants are mammographically represented as well-circumscribed lesions that may be misdiagnosed as benign; therefore a preoperative diagnosis by core o fine needle biopsy combined with ancillary technique [13–16] is

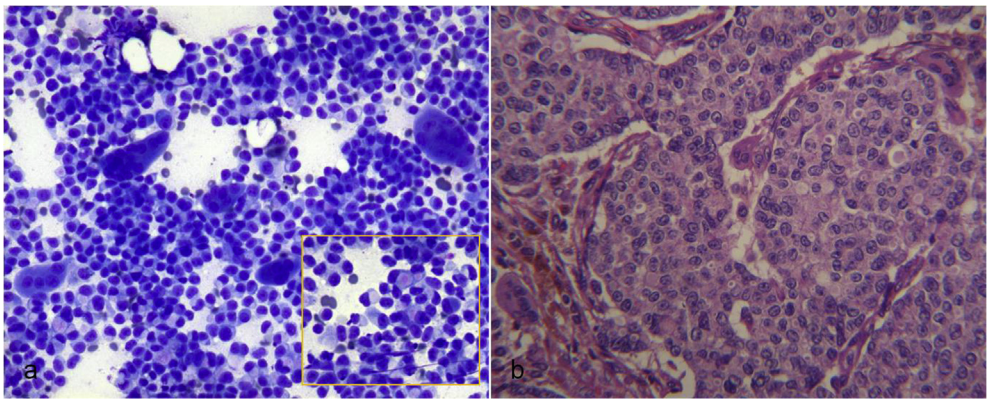

Fig. 1. a) dissociated neoplastic mononucleated cell population mixed osteoclast-like giant cells (MGG, 106×); b) Histological features of the tumour showing monomorphous appearance, wide cytoplasmas and cytoplasmic globules. Note the osteoclast-like giant cells (HH 430×).