NEUROENDOCRINE DIFFERENTIATION IN INVASIVE LOBULAR BREAST CARCINOMA

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Figure 1. Ultrasonographic and elastographic aspects of the lesions (BIRADS 5): (A) elastography of first tumor; (B) 2nd tumor; (C) needle biopsy of the first tumor.

Neuroendocrine differentiation is a form of immunophenotypical metaplasia encountered in tumors lacking neuroendocrine morphological features, especially high grade carcinomas of cohesive types, including up to 18% of breast carcinomas. Neuroendocrine type is exceedingly rare encountered in discohesive lobular breast carcinomas, as few case reports indicate (1-3). In most cases, neuroendocrine differentiation occurred in less than 50% of the tumor cells.

A 63 year old female patient presented with self-identified nodules - two dense nodules located in the superior quadrants of her left breast 10 weeks earlier, less than 1 cm in largest dimension, painless, persistent, with no other symptoms. Anamnesis was unremarkable. Clinical evaluation confirmed two tumor areas of elastic consistency, with no alteration of the adjacent skin; no axillary lymph nodes were noted and the opposing breast was clinically normal.

Mammographic examination that revealed two irregularly shaped areas in each of the left superior

quadrants, suspect of malignancy, scored BIRADS 5. Ultrasonographic examination of the left breast revealed two separate solid lesions with lobulated margins, different shapes, one of them containing vessels with high resistance index, typical for a malignant condition and measuring 1.1/1.2 cm. The second nodule was paucivascular and measured 1.4/1.4 cm. The elastographic appearance of the two nodular areas and the complex lesional area in between was also suspect, showing stiff structures (Fig. 1A, B). No suspect axillary adenopathies were found.

The ultrasound-guided biopsy procedure involved the two solid nodules and the third area of stiff shadowing structures in between (Fig. 1C). Pathology of the four biopsy fragments identified an architectural disarray caused by neoplastic infiltrates disposed in trabeculae, single cell files and sheets without tubular lumina, occasionally alveolar/nested areas, containing discohesive cells with marked nuclear pleomorphism and intense mitotic activity suggestive of pleomorphic lobular carcinoma (Fig. 2). The tumoral proliferation reached Nottingham score 9, being classified as G3. Tumor emboli were not identified in lymphatic and venous structures. Perineural invasion could not be determined since nervous structures were not intercepted. The composite morphology including areas of alveolar/nested pattern required immunohistochemistry. The complete lack of E-Cadherin expression (Fig. 3) in tumor cells confirmed a discohesive carcinoma.

Immune profiling suggested a Luminal B molecular subtype with high (99%) estrogen receptors (Fig. 5); progesterone receptors were present in 60% of tumor cells, androgen receptors (AR) in 90% of tumor cells; Her2 scored 0; Ki67 in 50% of tumor cells. Diffuse GATA3 (Fig. 4) expression and hormone receptor positivity confirmed breast histogenesis and eliminated the possibility of metastases in the breast. AR expression at high intensity and in large percentage of cells possibly cancel the estrogen expression benefit since AR expression is an estrogen blockade resistance mechanism.

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Figure 2. Morphological aspect of the lesion (HE stain, 20x).

Figure 3. Absent E-Cadherin staining in tumoral cells (20x).

Figure 4. Intense diffuse GATA3 expression in tumoral cells (20x).

Figure 5. High estrogen receptor expression in tumoral cells (20x).

Figure 6. Synaptophysin expression of moderate and high intensity in cca 85% of tumoral cells (20x).

Figure 7. Negative Chromogranin A in tumoral cells (10x).

The high histological grade features (G3) and the Luminal B molecular subtype contribute further to the unusual nature of the presentation, as most reported cases are low grade (G1/G2) fitting the Luminal A molecular subtype, with no particular consequences on prognosis (2).

Other neuroendocrine markers: high intensity Synaptophysin positivity was noted in frequent tumor cells (*cca* 85%) (Fig. 6), while CD56 (not shown) and Chromogranin A were entirely negative (Fig. 7). Synaptophysin positivity in over 50% of tumor cells is unusual and imposed the extension of immunohistochemical testing to evaluate other neuroendocrine markers which turned out negative.

Multicentricity is a recognized feature of lobular carcinomas (1), similar to bilaterality and perineural invasion as escape and recurrence mechanism. The lack of tumor emboli in lymphovascular structures, correlated with absent axillary adenopathies and the reduced dimensions are counterbalanced by the high histological grade and the molecular subtype.

Neuroendocrine differentiation in breast tumors, most of them low grade in all studies, appears to have no actual influence on prognosis (3). Therefore, all these tumors are treated as conventional breast carcinomas. However, no references exist on the impact of neuroendocrine

differentiation in high grade carcinomas of the breast. Thus, the patient was referred to an oncologist for further investigation and treatment strategy.

In conclusion, the case describes an unusual presentation of breast carcinoma with multicentric invasive lobular morphology and extensive neuroendocrine differentiation in 85% of tumor cells, with high histological grade and Luminal B phenotype.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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