Triple Negative Invasive Ductal Carcinoma with NTRK Fusion

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Introduction

Neurotropic Tyrosine Kinase Receptor fusion mutations are a family of oncogenic drivers rarely seen in solid tumor oncology (<1% of cases). Although exceedingly rare in common cancer types (breast, lung), NTRK fusions are considered hallmarks of certain rare cancers such as secretory breast cancer and infantile fibrosarcoma [1]. Despite their rarity, NGS (next generation sequencing) testing is a crucial step in the workup for many solid tumors as the discovery of certain mutations confers eligibility for novel therapies. NTRK inhibitors target fusion driven signaling of the NTRK oncogene and are approved for use in all cases of NTRK fusion mutations regardless of primary tumor site [2,3]. Given the rarity of NTRK alterations, the optimal sequencing of targeted and conventional therapies is an evolving area of research. Here we describe a case of metastatic triple-negative IDC with a TRPC6-NTRK3 fusion, highlighting the value of broad molecular testing in aggressive breast cancers where targeted therapies are otherwise limited.

Case Presentation

- **Patient:** 45-year-old premenopausal female with no significant medical history.
- **Symptoms:** Lump in left breast x 7 months, progressively enlarging; pain in left arm, lower back, and pelvis.
- **History:**
  - Prior benign biopsy of breast lump in same area at age 19.
  - Mammogram 2 years prior was BIRADS 1, no evidence of malignancy.
- **Workup:**
  - Diagnostic mammogram & core biopsy *(Figure 1)* → 5.2 cm poorly differentiated invasive ductal carcinoma (IDC) with apocrine and focal micropapillary features (ER-, PR-, HER2- (0)).
  - Axillary node biopsy → metastatic carcinoma (ER-, PR-, HER2- (1+)).
- **Staging:** CT of chest/abdomen/pelvis + bone scan → metastases to spine and pelvis *(Figure 2)*.
- **Genomics (Guardant 360):** TRPC6-NTRK3 fusion; PD-L1 negative, MSS, TP53 E271 mutation.
- **Treatment:** Palliative radiation to the spine → planned NTRK targeted therapy with Larotrectinib.

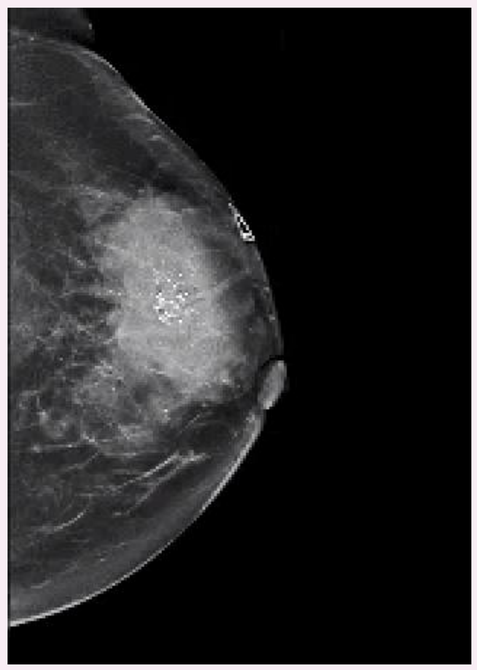

Figure 1. Left breast mammogram showing a 5 cm irregular subareolar/upper central mass with fine pleomorphic calcifications spanning ~7 cm.

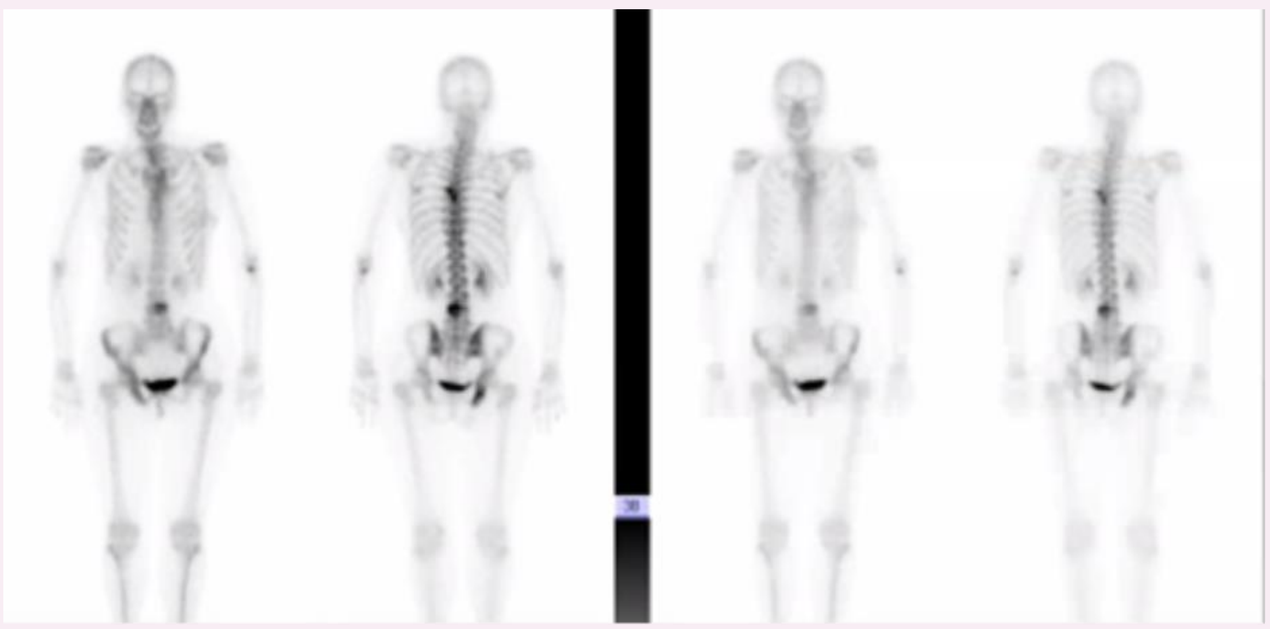

Figure 2. Whole-body bone scintigraphy showing abnormal uptake of radiotracer in the thoracic (T5-T7) and lumbar (L3) vertebrae and right iliac bone, consistent with metastatic disease. Additional uptake in the shoulders and pelvis likely represents degenerative changes.

Discussion

Mechanism:
- NTRK fusions arise from chromosomal rearrangements involving NTRK1 (1q23.1), NTRK2 (9q21.33), and NTRK3 (15q25.3), encoding for the tropomyosin receptor kinases TRKA, TRKB, and TRKC, respectively.
- Result is constitutive tyrosine kinase activity → aberrant activation of PI3K-AKT, PLC, and MAPK pathways (drivers of oncogenesis)

Prevalence of NTRK fusions:
- Hallmark in rare cancers (infantile fibrosarcoma, secretory breast cancer, MASC, congenital mesoblastic nephroma) [1].
- Secretory breast cancer: > 95% harbor ETV6-NTRK3 fusion [4].
- Invasive ductal carcinoma of the breast (non-secretory): < 1% of cases have NTRK fusion.
- Despite rarity, NTRK testing should be considered, especially in cases of advanced disease with limited treatment options [5].

Targeted therapy considerations:
- NTRK inhibitors (Larotrectinib, Entrectinib): target TRK A/B/C; approved as a tumor agnostic therapy based on high efficacy across multiple tumor types.
- Overall response rates (ORR): 60-75%, though outcomes vary by histology.
- Adverse effects: weight gain (up to 20% of body weight in 20-30% of patients), ↑ LFTs, myalgias, constipation, and dizziness [2,3].

Relevance of this case:
- TRPC6-NTRK3 fusion in triple-negative IDC emphasizes the need for broad molecular testing.
- Comprehensive genomic profiling can reveal rare but actionable targets that broaden treatment options in aggressive cancers.

References

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