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Lower motor neuron syndrome in a patient with HER2-positive metastatic breast cancer: A case report and review of the literature

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ABSTRACT

Paraneoplastic neurological syndromes are very rare and often associated to breast, ovarian and small cells lung cancers. Paraneoplastic motor neuron diseases (MNDs) are even rarer, and frequently described in patients with breast cancer. We presented the first case of patient affected by HER2-positive breast tumor and possible paraneoplastic lower motor neuron disease. In literature, few cases are reported but no one highlights the tumor receptors' profile. Instead, HER2-positive breast cancers are prone to be related to anti-Yo-associated paraneoplastic cerebellar disorders. Anti-onconeural antibodies positivity can be rarely found, confirming that paraneoplastic MND have no specific biomarkers. The presence of CSF oligoclonal bands (OBs) suggests the presence of immune-mediated mechanism, in absence of other possible OBs causes.

1. Introduction

Motor neuron disease (MND) is usually due to a neurodegenerative process, that involves upper (UMN) and/or lower motor neuron (LMN). MND has been reported in association with several tumors including breast cancer (BC) [1,2] but it is not considered a classical paraneoplastic neurological syndrome (PNS) [3]. Epidermal growth factor receptor 2 (ErbB2, HER2, c-erbB2 or Her2/neu), a member of the ErbB receptor tyrosine kinase family, is one of the most commonly used molecular markers for BC. HER2 amplification/over-expression is seen in up to 30% of patients with BC [4] and less frequently in patients with gastric cancer. Furthermore, HER2 seems to be associated with the occurrence of anti–Yo positive paraneoplastic cerebellar degeneration (PCD) [5] and, in a single case, with anti-Hu positive limbic encephalitis [6].

We report the first case of paraneoplastic MND associated with HER2-positive BC.

2. Case report

We describe a case of a 44-year-old Caucasian woman with a diagnosis of left breast tumor resulting an infiltrating, moderately differentiated, lobular carcinoma (ILC)(hormone–receptors positive, ki67: 50%, c–erb B2 immunohistochemistry score: 3+, stage IIIC, T3N3M0). A neoadjuvant chemotherapy with anthracyclines, taxane and anti-HER2 agent (trastuzumab) was performed with complete response. She subsequently performed a left mastectomy with axillary node dissection and a hormonal therapy.

During the adjuvant treatment, the patient developed progressive weakness with a distal–proximal gradient in upper and lower limbs, followed by diffuse severe muscular atrophy. Neurological examination showed symmetrically reduced reflexes in the four limbs. Electromyography revealed spontaneous activity in all examined muscles (bilateral tibial anterior, vastus lateralis, first dorsal interosseus, biceps) associated with chronic alterations of motor units. Brain mag-

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netic resonance imaging showed two metastatic subcentimetric lesions in the right cerebellar hemisphere and left frontal region with no edema. Cerebrospinal fluid (CSF) analysis revealed no cells, normal proteins level and unique-to-CSF numerous oligoclonal bands (OB). CSF PCR for Herpes and West Nile were negative. Serum and CSF were tested for the presence of typical onconeural antibodies with indirect immunofluorescence on rat cerebellum (Euroimmun, Lubeck) and with line blot (Ravo), and resulted negative. In order to assess the presence of unidentified anti-neuronal antibodies, an additional screening with IHC on lightly fixed whole rat brain was performed, but this provided no additional information. A final diagnosis of possible non-classical paraneoplastic syndrome was made.

The patient underwent a brain stereotactic radiotherapy (30 Gy on the cerebellar lesion and 24 Gy on the frontal lesion), and a chemotherapy with capecitabine and lapatinib was started but interrupted after two cycle for gastro-intestinal toxicity.

Neurological syndrome was inexorably progressive and fatal due to respiratory muscles involvement within few months. An empiric therapeutic approach with high doses of steroids was ineffective.

3. Discussion

PNSs are rare, and paraneoplastic MND represents the rarest form with estimated frequency of 2% [7]. BC is commonly associated with UMN degeneration, but few cases with LMN degeneration are reported [1,2] without mention of the HER2 – profile [1,2,8]. HER2-positive BC seems to have a marked tropism for the nervous system and an association with anti–Yo antibody-positive PCD [5]. Murphy et al. [9] reported a case series of 56 patients with PNS and BC, in which only 6 patients were HER2-positive but HER2-status was unknown in 23 patients. Among that series, only one patient developed paraneoplastic MND. The existence of a paraneoplastic MND is controversial [8], and establishing a clear link between tumor and neurological syndrome can be challenging. According to the PNS Euronetwork [7], our patient fulfilled the diagnostic criteria of possible non-classical PNS due to the atypical syndrome, and the absence of onconeural antibodies. The lack of response to immunotherapy is not surprising, considering the progression of the underlying cancer. The presence of OB in CSF outlines a condition of local immune responses and neuroinflammation, possibly related to PNS rather than degenerative MND [10]. Furthermore, our patient was younger compared to the average age of onset for degenerative MND. Recently, Mélé et collaborators have published a case series of oncological patients affected by MND and they underlined that paraneoplastic MND often presents as subacute LMN syndrome, and with inflammatory CSF pattern as we found in our patient [11].

4. Conclusion

In conclusion, HER2-positive tumors are prone to develop paraneoplastic MND. Paraneoplastic MND should be considered in patients presenting with rapidly progressive neurological symptoms and the presence of oligoclonal bands in CSF. The young age at MND onset could be an additional ‘red flag’ pointing towards a paraneoplastic aetiology, even if it’s not impossible for degenerative MND to occur at younger age.

Conflicts of interest

No conflict of interest to declare.

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