

BREAST METASTASIS OF A PANCREATIC NEUROENDOCRINE TUMOR: CASE REPORT

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ABSTRACT

The breast metastasis of the Neuro endocrine tumors are exceptional. They are often under diagnosed due to their rarity and also their histological character very close to the primary NETs of the breast, The treatment of this specific location is similar to others metastatic forms of well differentiated NET, which is very wide ranging from a simple observation to a more aggressive treatment especially for symptomatic patients. We report the observation of a 65-year-old woman, followed at the National Institute of Oncology of Rabat (Morocco) for a pancreatic NET with stable breast metastasis under systemic treatment. We will discuss the epidemiological, clinical and therapeutic characteristics.

KEYWORDS: Breast Metastasis, Neuro Endocrine Tumor, Rare Entity.**BACKGROUND**

Pancreatic Neuro-endocrine tumors (NET) are rare tumors (Estimated incidence of 1/100 000 inhabitants).^[1]

Their prognosis depends on the degree of tumor differentiation as well as their metastatic character or not. It is also important to classify these tumors as functional or non-functional, depending on the presence or not of clinical symptoms.^[2]

Although they are less aggressive with often longer overall survival rate than adenocarcinoma, Pancreatic NETs are mostly diagnosed at the metastatic setting, especially in patients with non-functional tumors.^[3]

The most frequently metastatic sites of pancreatic NET are lymph nodes, liver, spleen and bone.^[4] Breast localization is rare and described as exceptional site.

We report the observation of a 65-year-old woman, followed in our structure for a pancreatic NET with stable breast metastasis under systemic treatment.

CASE PRESENTATION

This is a 65-year-old patient, followed at the National Institute of Oncology of Rabat since 2014 for an asymptomatic, initially non functional neuroendocrine tumor of the pancreas with lymph node metastasis.

Anatomopathologic and immunohistochemical study of cervical adenopathy biopsy revealed well-differentiated neuroendocrine carcinoma with Ki 67 at 3% In front of the asymptomatic character of the disease, the surgical

indication was not retained and a simple surveillance was decided during the surveillance, the patient becomes symptomatic (flash syndrome) and treatment with Somatostatin analogues was initiated.

The quarterly CT scanner performed in juillet 2017 found a nodule of the upper quadrant of the left breast. The ultrasound and mammography showed 2 nodules classified BIRADS IV of ACR. An excisional biopsy for both nodules was done.

The anatomopathological and immunohistochemical study found a secondary localization of a well differentiated NET.

The patient received one cycle of everolimus with very poor clinical tolerance and then switched to sunitinib since January 2018 at a continuous dose of 37.5 mg / day.

The patient disease is stable after sixteen months of Sunitinib.

DISCUSSION

Because of their rarity but also their histological character very close to the primary NETs of the breast, the breast metastasis of the NETs are often under diagnosed.^[6]

The immunohistochemical study, for synaptophysin and chromogranin A, does not differentiate between breast metastasis and primary breast TNE. The determination of Ki67 is often useful to establish the diagnosis.

Several studies suggest the interest of realizing large panel of tissue-specific immunostain to distinguish primitive and secondary NETs.^[11] However, the absence of a reliable histological marker is often described as a diagnostic problem.^[6,8]

Recent studies highlight the interest of mammaglobin and GCDFP-15 as relevant tools for differentiating a primary TNE of the breast from a breast metastasis.^[9,10]

It is very important to differentiate a mammary metastasis from a primary tumor because their treatment is totally different.^[7]

The treatment of rare metastasis location of NET is similar to the other forms.

The treatment depends on the aggressivity of the disease. There are several options: simple observation, somatostatin analogues, cytotoxic chemotherapy or molecular targeted therapy.^[2]

Our patient received Lanréotide since 2016 to control the flash syndrome.

Somatostatin analogues most often allow control of clinical symptoms as well as stabilization of tumor volume.^[12] Their antiproliferative effect involves both direct and indirect mechanisms to inhibit cell growth.^[13]

The development of targeted therapies has been a major advance in the treatment of pancreatic NETs.^[14] Two drugs are now approved in the treatment of metastatic pancreatic NETs: Everolimus (mTOR inhibitor) and Sunitinib (VEGFR-TKI).

In January 2018, the disease progressed, we started treatment with Everolimus. The efficacy of this drug was demonstrated in a Phase III trial (RADIANT3) comparing everolimus plus BSC versus placebo plus BSC with a statistically significant prolongation in PFS for Everolimus plus BSC arm.^[15] But our patient does not tolerate this treatment; we switch to sunitinib which is also validated by a Phase III trial comparing sunitinib (37.5 mg / day) vs placebo in 171 patients followed for a well-differentiated pancreatic NET. The study was discontinued early but the intermediate analysis showed a significant benefit in PFS for the Sunitinib arm.^[14,16]

Chemotherapy is also a validated option. It is reserved for patients resistant to targeted therapy.

Several studies have shown the role of chemotherapy in the management of metastatic and symptomatic pancreatic NETs. The Doxorubicin-Streptozocin (STZ) combination was superior to the Fluorouracil-STZ association in terms of objective response and progression-free survival.^[17,18]

At the moment, there are no clear prognostic factors to estimate the survival of these patients with well-differentiated pancreatic NETs. However, several factors were identified as possibly related to survival.

The most used are the WHO criteria that take into account the stage, tumor size, mitotic index, distant metastasis, necrosis and age of the patient.^[19]

An analysis by Clancy *et al.* suggests that elevation of chromogranin A level and / or serum alkaline phosphatase would be associated with a worse survival prognosis.^[20]

These data suggest the interest of conducting further studies to better know and establish these prognostic factors.

CONCLUSION

Breast metastasis from pancreatic NETs are often underdiagnosed. The advent of targeted therapy has improved the prognosis of patients with metastatic pancreatic NETs. Given the difference in terms of prognosis between well-differentiated and non-differentiated pancreatic NETs, multidisciplinary management remains essential in order to propose the best therapeutic options.

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