INTRODUCTION

Hormonal mediated watery diarrhea can be caused by several neuroendocrine tumors. These include carcinoid tumors, pancreatic endocrine neoplasms, and medullary cancer of the thyroid [1]. Serum release of peptides such as somatostatin, gastrin, pancreatic polypeptide, vasoactive intestinal polypeptide (VIP), and calcitonin fully explain the mechanism of diarrhea [2]. VIPomas are rare pancreatic endocrine tumors associated with a well-defined clinical syndrome characterized by watery diarrhea, hypokalemia and metabolic acidosis [3]. We are reporting the case of a VIPoma syndrome secondary to VIP secretion by inflammatory breast cancer cells and the resolution of diarrhea by anti-aromatase and tumor-oriented chemotherapy.

CASE REPORT

In February 2005, a 62-year-old woman was admitted twice to the gastro-intestinal department of our hospital for refractory diarrhea, dehydration, and hypokalemia. Stool analysis and culture were negative. Colonoscopy, gastroscopy, abdominal computed tomography (CT) scan and magnetic resonance imaging (MRI) were unremarkable.

Urinary level of 5-HIAA, and serum levels of gastrin, somatostatin and calcitonin were in the normal ranges (normal levels are • 5-HIAA: 2-6 mg/24 h • gastrin: 0-9 pg/ml • calcitonin: < 30 pg/ml). However, VIP level was as high as 419 ng/l (normal level: < 65 ng/l).
Physical examination revealed a whole redness of her right breast with deep fixed ipsilateral axillary lymph node exceeding 8 cm in diameter. Subsequent bilateral mammography revealed an ill-defined mass infiltrating the whole right breast, and the CA 15-3 level was 153 IU/ml (normal level less than 35 IU/ml).

An incisional biopsy of the breast was performed and showed a moderately differentiated invasive ductal carcinoma with dermal infiltration of all specimens. Hormonal receptor staining was highly positive and c-erb-2 was negative. Immunohistochemical stainings with chromogranin, synaptophysin and VIP were moderately positive on tumor cells suggesting neuroendocrine differentiation. (Figures 1-4)

Total body CT scan with radioactive somatostatin showed an impressive uptake in the right breast and the right axilla. Anastrozole 1 mg/day was initiated in April 2005 as primary hormonal therapy allowing the disappearance of diarrhea, the reduction of VIP to 121 ng/l and CA 15-3 to 48 IU/ml. However, a small reduction of the breast swelling and redness was noted. 

Diarrhea reappeared in December 2005, and the patient then agreed to receive pre-operative chemotherapy. Three cycles of epirubicin and cyclophosphamide were given, but the tumor and the diarrhea remained unchanged, and the VIP and CA 15-3 levels increased to 276 ng/l and 121 IU/ml, respectively. In March 2006 a second-line hormonal treatment was initiated with exemestane 25 mg/day and failed to reduce diarrhea and tumor size. Second-line chemotherapy with vinorelbine and carboplatin was chosen to prevent alopecia according to patient’s will, and was started in July 2006. The diarrhea disappeared after the third cycle and redness of the right breast was reduced. However, a deep contralateral breast nodule became palpable after the sixth cycle. Evaluation in December 2006 showed the inflammatory right breast, a median left breast mass, and bilateral axillary lymph node enlargement exceeding 8 cm in diameter, and the absence of distant metastases. VIP level was 210 ng/l and CA 15-3 132 IU/ml. Since the tumor seemed to be almost refractory to chemotherapy but always bilateral, a bilateral modified radical mastectomy and bilateral axillary resec-
tion was performed. Pathological examination revealed a bilateral moderately differentiated ductal carcinoma with completely infiltrative and capsular effraction nodes bilaterally with dermal infiltration at the right side. Margins were negative. Hormonal receptors, c-erb-2, and VIP staining were identical to the primary biopsy.

Bilateral irradiation to the chest wall, axilla and supraclavicular area was performed.

In April 2007, few days after the end of radiotherapy, severe diarrhea recurred, necessitating urgent recovery of the patient. Metastatic workup showed diffuse liver metastases and disseminated bone lesions. Salvage therapy with continuous infusion of 5-fluorouracil, docetaxel, zoledronic acid, and long-acting octreotide was initiated.

Diarrhea resolved after the second cycle and partial regression of liver metastases was obtained. However, disease progression with diarrhea, cervical lymph nodes and deep left jugular venous thrombosis occurred eight months after salvage treatment initiation, and the patient died in January 2008 from liver failure.

DISCUSSION

Neuroendocrine differentiation can be sometimes identified in breast cancer tissue [4]. Performing immunohistochemical staining for neuroendocrine markers such as chromogranin, synaptophysin, neuron-specific enolase, or VIP can detect population of tumor breast cells with neuroendocrine differentiation [5-6]. However, this intracellular hormonal content was never reported to be associated with high serum release of the enzyme or expression of related symptoms such as chronic watery diarrhea [7-9].

Recently, Al Saudi et al. reported on an 83-old-male with breast cancer and chronic diarrhea. Both pancreatic polypeptide and gastrin levels were increased. Mastectomy led to diarrhea resolution and the reduction of serum concentration of pancreatic polypeptide but not to the decrease of gastrin blood concentration. Radioactive somatostatin scintigraphy showed increased uptake by the breast tumor, and tumor cells immunostaining showed neuron-specific enolase reactivity in the cytoplasm [1]. Authors concluded that their reported case supported the diarrheagenic potentials of neuroendocrine cells originating from a malignancy outside the gut or pancreas.

Our patient represents the first reported case of VIPoma where VIP was unequivocally secreted by breast malignant cells. It is well documented in the medical literature that breast cancer expresses high densities of VIP receptors [10]. In addition, VIP receptor antagonists inhibit the growth of breast cancer cells [11]. In our patient, the positive effect of anti-aromatase and breast directed chemotherapy combinations on both tumor extension and VIPoma syndrome confirms the causal relationship between breast tumor burden and VIP secretion.

The uptake by the right breast and axilla of radioactive somatostatin and the positive immunostaining of tumor cells by neuroendocrine markers sustain our confirmation about VIP release from inflammatory breast tumor cells. We believe that the inflammatory nature of this tumor is not related to the VIP secretion of the tumor, and the dermal infiltration by inflammatory tumor cells as evident by pathology supports this view.

To our knowledge, this case represents the first reported case of inflammatory breast cancer secreting VIP and causing a clinical VIPoma syndrome.

REFERENCES