A Case of Paraneoplastic Autoimmune Pancreatitis: Mini-Review of Paraneoplastic Syndromes in Breast Cancer

LAZAROS LEKAKIS, DIMITRIOS TRYFONOPOULOS, GABRIEL FAKINOS, CHRISTOS PANOPOULOS, MARIA THEOCHARI, GEORGE KOUMAKIS, STAMATINA DEMIRI and ANNA EFREMIDIS

Second Department of Medical Oncology, Agios Savvas Cancer Hospital, Athens, Greece

Abstract. *Breast cancer (BC), the most common type of cancer in women of the Western world, is often associated with paraneoplastic syndromes (PNS). Autoimmune pancreatitis is a recently recognized entity belonging to the spectrum of IgG4-related systemic diseases, which are characterized by target-organ plasmacytic infiltration and fibrosis. In this report we review PNS associated with BC and we present the first case of BC-associated autoimmune pancreatitis as well as its successful management with steroids and immunosuppressive BC-tailored chemotherapy.*

The interactions of neoplastic cells with the immune system are multifaceted and have been recognized since at least a century. The majority of carcinomas evade immune attack and create immunodeficiency through the production of cytokines (TGF-β, IL-10, *etc.*) and interaction with immunosuppressive cells (Tregs, macrophages and others). Attempts to overcome these phenomena are ongoing through immunotherapy with cytokines (IL-2, IFN-γ), vaccines (sipuleucel-T) and by blocking immunoregulatory receptors by giving ipilimumab, molecules interfering with PD-1 *etc*. Allogeneic stem cell transplantation has saved many patients in the last few decades through the graft versus malignancy effect.

Paraneoplastic syndromes (PNS) occur in approximately 5-10% of patients with malignant neoplasms and represent an aberrant reaction of the immune system towards normal tissues either through the production of auto-antibodies, or by a T-cell attack. Dysfunction of immunoregulation and cross-reactivity of the immune system towards the tumor and normal tissues participate in the pathogenesis of such reactions.

Correspondence to: Lazaros Lekakis, MD, Attending Physician, Agios Savvas Cancer Hospital, Second Department of Medical Oncology, 171 Alexandras Ave, Athens, Greece, 11522. E-mail: ljleka2@gmail.com

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Breast cancer (BC) is the commonest non-skin cancer in females and the second leading cause of cancer-related death in women of the Western world. PNS in BC have been well-described, although lower in frequency compared to other types of tumors, such as small-cell lung cancer. Both dermatomyositis and polymyositis have been associated with BC (1, 2). Mebazaa *et al*. reported an increased incidence of BC among dermatomyositis patients in Tunisia. Nine of them had a parallel improvement of dermatomyositis after treatment for BC (1). Subacute cutaneous lupus erythematosus (3), palmar fasciitis and polyarthritis syndrome (4), and cutaneous vasculitis have also been associated with BC (5). Leser-Trelat sign and acanthosis nigricans are much less frequent in BC than in gastrointestinal malignancies (6-8). Lactic acidosis (9) and Cushing syndrome (10) are extremely rare. A case of immune thrombocytopenia has been also described (11).

Neurological PNS have been better characterized. Anti-Yo positive paraneoplastic cerebellar degeneration (PCD), which is well-described in ovarian cancer not only can occur in BC, but there is a possible association with HER2 expression (12). There is also a clear association between anti-Ri -positive opsoclonus-myclonus and BC and reports of improvement of the syndrome after surgical resection of BC (13). It has to be emphasized that the presence of anti-Yo and anti-Ri syndrome can be associated with paraneoplastic neurological syndromes with different manifestations other than PCD and opsoclonus-myoclonus (14-16). Anti-glutamic acid decarboxylase (anti-GAD) antibody-positive stiff limb syndrome, accompanied a case of BC (17), which it responded to muscle relaxants and steroids. Another case of the same syndrome (18) responded to steroids and BC-specific chemotherapy. The presence of antibodies to amphiphysin has been associated with a case of transverse myelitis in a patient with BC (19). Neuropathy (anti-Hu-positive in some cases), retinopathy, encephalomyelitis, amyotrophic lateral sclerosis and atypical Lambert Eaton myasthenic syndrome have all been described (20, 21). The symptoms of sensorimotor neuropathy in a patient with BC improved with capecitabine (22). The sensitivity and specificity of onco-neural antibodies (anti-Yo, anti-Hu, anti-Ri, anti-GAD,

anti-amphiphysin) are not perfect. Furthermore, anti-tumor T-cell reactivity without detectable antibodies is an important documented mechanism of PNS and has been associated with high IFN-γ concentration in the tumor microenvironment (23).

Autoimmune pancreatitis (AIP) (24, 25) was first described in 1995 and is associated with increased levels of IgG4 (26). High levels of IgG4 are also seen in sclerosing cholangitis and several other diseases characterized by plasmatocytic infiltration and fibrosis, so that the term 'IgG4-related systemic disease' has been coined. The spectrum of this syndrome includes pancreatitis, cholangitis, retroperitoneal fibrosis, prostatitis, tubulointerstitial nephritis, sialadenitis (Miculicz disease), fibrosing thyroiditis (Riedel), interstitial pneumonitis, Castleman-like lymphadenopathy and pseudotumor of the breast (27). Recently a novel antibody against plasminogen binding peptide of *Helicobacter pylori* (anti-PBP) has shown high specificity for the diagnosis of AIP (28) and has reinforced the hypothesis that *H. pylori* predisposes for the development of AIP. AIP responds dramatically to prednisone (40 mg a day, for 4 weeks, with an 8 week subsequent gradual tapering). Higher doses of steroids, anti-metabolites (mercaptopurine, azathioprine, mycophenolate mofetil) and rituximab have all been used in the treatment of IgG4-related diseases (29).

AIP as a PNS has been reported only once in a patient with myelodysplastic syndrome (30), who also developed vasculitis and pericarditis. In this case, pancreatitis was recurrent with flares corresponding to primary disease activity and was being controlled with corticosteroids and chemotherapy.

Case Report

Our patient is a 38-year-old woman who underwent a modified radical mastectomy, in 2002, for a stage IIIA, T1cN2M0, multifocal, grade II, ER^+, PR^+, HER2-negative ductal invasive breast adenocarcinoma. She had undergone neoadjuvant therapy with four cycles of epirubicin-cyclophosphamide followed by four cycles of paclitaxel. She underwent postoperative radiation therapy followed by three years of adjuvant goserelin and tamoxifen. Three years after diagnosis, she developed bone metastasis for which she underwent radiation to the lower thoracic spine and later she was put back on goserelin in combination with letrozole. Fifty-six months later she was presented with pleural effusion, rib and adrenal metastases as well as mediastinal lymphadenopathy. Pleural biopsy confirmed $ER^+PR^-HER2^-$ breast adenocarcinoma. She was treated with four cycles of bevacizumab-paclitaxel with very good partial response, followed by maintenance with anastrozole-goserelin-zoledronic acid.

A year after the development of the non-osseous metastasis, she was presented with severe abdominal pain to a different hospital and during her hospitalization, she was diagnosed with acute pancreatitis. She was transferred to our hospital for continuation of her care.

Multiple attempts of bowel rest, followed by gradual re-feeding were complicated by flares of abdominal pain and elevation of amylase. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) showed changes compatible with chronic pancreatitis, fluid in the lesser omental sac, main pancreatic duct dilation, gas dilation of the transverse colon and peripancreatic fat stranding (Figure 1). Endoscopic Retrograde Cholangio-Pancreatography (ERCP) did not reveal an underlying cause for pancreatitis. She did not consume ethanol, she did not have a family history of pancreatitis, nor was she found to have cholelithiasis, hyperlipidemia or hypercalcemia. No masses were found close to or inside the pancreas by CT and MRI.

Despite the fact that the other immunoglobulin classes were in the low normal range, the levels of IgG4 were elevated (251 mg/dl). A diagnosis of AIP was made and prednisone at 1mg/kg was started, with rapid improvement of pain and normalization of amylase levels. Staging of BC showed pleural effusion, small lung and liver metastases, as well as bone metastasis with pathological fracture of the left femoral head which was causing significant pain and inability to walk. Attempts to lower the prednisone dose were associated with mild exacerbation of pancreatitis, and it was decided that chemotherapy would be given. One cycle of intravenous cyclophosphamide was followed by three cycles of doxorubicin-cyclophosphamide (AC). No relapse of pancreatitis was observed after the first cycle of AC and she underwent a successful operation for fixation of her pathological hip fracture. The patient was mobilized and with intensive physical therapy, she was able to eat and walk without pain while she regained some of her lost weight. She then underwent a fourth cycle of AC, and the restaging of BC surprisingly showed a complete remission. She received 15 mg of prednisone/day and she had had an excellent performance status for seven months after the first pancreatitis episode until she developed leptomeningeal carcinomatosis and brain metastasis with *cauda equina* syndrome and leg weakness. She underwent three cycles of high-dose methotrexate (3.5 g/m^2) with leucovorin rescue, along with oral capecitabine and intrathecal thiotepa and had clearance of the leptomeningeal carcinomatosis (cerebrospinal fluid was twice negative for carcinoma cells), with symptomatic improvement and partial response of the brain metastasis. The patient was started on tamoxifen at 20 mg twice a day and has been only mildly symptomatic with residual leg weakness and mild low back pain.

Conclusion

To our knowledge, this is the first case of AIP as a PNS associated with a solid tumor to have been reported in the literature. The patient did not have an alternative etiology, the MRI showed changes compatible with chronic pancreatitis, probably related to fibrotic changes which are common in AIP, and she had high levels of IgG4. Furthermore, she

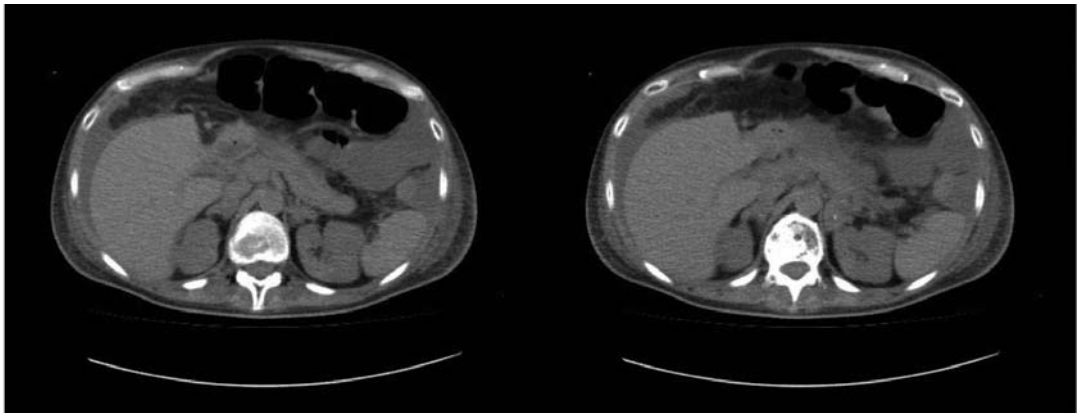

Figure 1. *Computed tomographic findings of dilatation of the main pancreatic duct, peripancreatic fat stranding, and transverse colon dilatation with air during a pancreatitis bout in the patient.*

responded quickly to prednisone but had mild flares until the administration of chemotherapy for BC, which produced a complete remission. Despite the relapse in the CNS, this was successfully treated with aggressive chemotherapy and the patient currently enjoys a good quality of life without relapse of AIP. She is also about to get consultat with a Clinical Geneticist for consideration of *BRCA* testing.

Conflict of Interest

None of the Authors have any conflict of interest to report.

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