Abstract. The case of a 31-year-old woman with progressive cerebellar degeneration preceding by several months the diagnosis and treatment of breast cancer initially and pseudomyxoma peritonei (PMP) with evidence of causative association with the latter is presented. Despite various chemotherapeutic and surgical manipulations, the patient did not substantially improve and succumbed 20 months following initial diagnosis of the neurological disorder. Interestingly, neurological symptoms partially regressed transiently only after surgical debulking of the PMP and not after the remission of breast cancer after various chemotherapeutic regimens suggesting an etiological relationship of the former and the cerebellar degeneration. Early recognition and appropriate therapy of this rare complication of PMP is imperative as it may be crucial for the outcome.

Paraneoplastic neurological syndromes (PNS) are rare immune-mediated syndromes occurring in less than 1% of patients with breast cancer (1, 2). Their pathogenesis is not well understood and their clinical presentation and course vary. However, specific autoantibodies targeting onconeural antigens, such as anti-Hu, anti-Ri and anti-Yo may be identified in the serum and cerebrospinal fluid (CSF) in some patients (3-5). These syndromes may precede diagnosis of cancer by months or years, therefore their diagnosis could be challenging and is usually performed in two steps. The exclusion of more common causes of neurological dysfunction and a high degree of clinical suspicion are both required and depend on the knowledge of the association of neurological symptoms and specific tumor types.

Pseudomyxoma peritonei (PMP) is a rare disease commonly diagnosed incidentally at laparotomy and characterized by disseminated mucinous ascites and peritoneal implants. The etiology of the disease remains unclear: it usually involves the appendix (6), while other sites include the ovaries and the pancreas (7); however, most cases of cystic ovarian mucinous tumors associated with PMP are associated with metastases from an appendiceal tumor (7). Radical surgical debulking and appendicectomy remain the cornerstones of treatment, although the optimal management of the disease remains controversial. Intraoperative and intraperitoneal chemotherapy have also been attempted and the clinical outcome varies widely among the benign and the malignant forms and between the different treatment modalities.

Case Report

A 31-year old nulliparous woman without significant medical history developed progressive lower extremity weakness and gait ataxia. No family history for neoplastic or neurological disease and no hormonal therapy in the past were reported. She had been an occasional, social smoker (~1 pack/week). Over a period of four months, her symptoms progressed until she was having difficulty walking unassisted. CSF analyses revealed oligoclonal bands and CNS magnetic resonance imaging (MRI) did not point to a diagnosis. She was then seen by a neurologist, who after a full work up for possible common neurological disorders, proposed that the onset of a demyelinating disease was probable. The patient subsequently received a course of intravenous high dose steroids and immunoglobulin without symptomatic improvement.

Correspondence to: A. Ardavanis, St. Savvas Anticancer Hospital, 171 Alexandras Avenue, 115 22 Athens, Greece. Tel: +30 6944421525 (mobile), Fax: +30 2106409508, e-mail: ardavanis@yahoo.com

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Three months later, following self examination, a large invasive ductal carcinoma of the left breast (maximum diameter: 8 cm, grade III, estrogen and progesterone receptor negative, and c-erB2 positive) was diagnosed after open biopsy. Three cycles of neoadjuvant epirubicin and paclitaxel (both drugs given under the standard conventional dosing) were then administered without evidence of remission. Subsequently, two different programs of trastuzumab-based therapy (trastuzumab docetaxel and trastuzumab carboplatin paclitaxel), were attempted during 6 months, leading to a minor clinical and mammographical response while neurological symptoms persisted. Yet anti-Hu, anti-Ri, and anti-Yo antibodies were negative as were multiple CSF analyses. However, an abdominal distention, probably present but underestimated a few months before, led to the diagnosis of ascites, as well as multiple, bilateral ovarian cysts. Laparoscopic biopsy revealed multiple peritoneal metastases consisting of highly differentiated mucinous, adenoid carcinoma cells; serum tumor markers were not diagnostic. The patient was then started on bevacizumab and trastuzumab-based therapy, considered as suffering a concurrent colon and breast cancer. She received two courses of a bevacizumab/oxaliplatin/trastuzumab/capecitabine combination, but therapy was discontinued due to bilateral ureteral obstruction. Thereafter bilateral pigtails were implanted and further progressive disease in the abdomen and the breast was evident clinically and by CT scans. The neurological symptoms were still present and slightly worsening.

At that time, the patient was referred to us for further treatment. Given the inadequate local control in the breast cancer (increasing tumor size and worsening of inflammatory signs) achieved by the previous therapy, as well as the low cumulative dose of anthracycline delivered (90 mg/m² of epirubicin), 6 courses of dose-dense epirubicin/cyclophosphamide (75 mg/m² and 600 mg/m² respectively, q2 weeks) with evidence of a clinical complete response were administered. However, no change in the abdomen and the neurological symptoms was seen. Follow-up screening with CT scan of the chest, abdomen and pelvis revealed an increase in the size and number of the peritoneal implants as well as of the ovarian cysts (Figure 1). In the neurological assessment, limb and truncal ataxia (tremor, dysdiadochokinesia) compatible with cerebellar disease was firstly hypothesized, while a new MRI of the brain and spinal cord revealed severe progressive cerebellar degeneration, present but obviously underestimated since the first MRI. Diseases that feature cerebellar degeneration are presented in Table I. Serum antineuronal autoantibodies were not detectable (negative for anti-Hu, anti-Ri, anti-Yo antibodies). Moderate doses of corticosteroids (16 mg methylprednisolone daily p.o.) were then administered, without detectable response and treatment with immunoglobulin was reconsidered although never tried.

In view of a dissociated course of the entire neoplastic syndrome (complete response in the breast, progression in the abdomen), together with a progressive paraneoplastic neurological syndrome (cerebellar ataxia), we had to relate the latter with the abdominal cancer. A debulking surgery was then proposed and performed; unfortunately, complete surgical excision was not feasible and cystic lesions ≤2.5 cm were left. Surprisingly, microscopical examination showed a progressive supranuclear palsy arising from the appendix. The patient recovered rapidly from surgery and anesthesia, while ataxia improved dramatically although transiently (starting the day after surgery and lasting for a week), associated with a reappearance of abdominal distention. Yet three weeks after surgery, the cancer-bearing breast was swollen and peculiar multiple confluent cystic lesions appeared in the skin, suggesting the presence of underlying mucous or externalizing breast edema (Figure 2). Two sessions of investigational electro-chemotherapy were applied with minimal results.

The patient refused further investigation and opted for supportive care only. Therefore, treatment in that setting was restricted to palliative measures; breast lesions worsened rapidly along with enlarging abdominal masses and obstructive jaundice that appeared 6 weeks after surgery. The patient succumbed 12 weeks after surgery.

### Table I. Diseases that feature cerebellar degeneration.

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<tr>
<th>Neurological diseases</th>
<th>Acute and hemorrhagic stroke</th>
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<tr>
<td></td>
<td>Friedreich’s ataxia and other spinocerebellar ataxias</td>
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<td>Transmissiblocerebellar encephalopathies (&quot;Mad Cow Disease&quot;, Creutzfeldt-Jakob disease)</td>
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<td>Cerebellar cortical atrophy, multisystem atrophy and olivopontocerebellar degeneration</td>
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<th>Other diseases</th>
<th>Chronic alcohol abuse</th>
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<td>Endocrine diseases (that involve the thyroid or the pituitary gland)</td>
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<td>Paraneoplastic disorders</td>
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Discussion

PNS are rare neurological complications in patients with breast cancer (BC) and their prognosis remains poor; PMP is an uncommon and poorly understood disease, while the association of the two disease entities has not previously been described.

Paraneoplastic neurological syndromes associated with breast cancer are rare and usually occur several months or years before tumor diagnosis (1, 2). They include cerebellar degeneration, sensory and motor neuropathy, limbic encephalitis, opsoclonus myoclonus ataxia (POMA), Lambert-Eaton myasthenic syndrome (LEMS) and stiff-man syndrome. The majority of these syndromes have a subacute, progressive course. The primary tumor is often occult and the neurological dysfunction typically precedes the detection of neoplastic disease (3). The pathogenesis of PNS is not completely understood and it has been postulated that specific antibodies expressed in tumors may cross-react with nervous system cells. However, while a subset of patients presenting with PNS have no identifiable antibodies in their serum, in some cases the anti-neuronal antibodies anti-Hu, anti-Ri, anti-Yo and anti-Ma have been detected in serum or CSF. In a previous survey of patients with breast-cancer related PNS autoantibodies could be found in only 36% of patients, no identifiable antibodies were found in 32% of patients and unknown antibodies in 16% of patients. The status of the paraneoplastic antibodies was not reported in 16% of patients (1). It is believed that an immune attack is mounted involving a cytotoxic T-cell response (2, 3).

No established protocol for the treatment of PNS exist. Treatment of the underlying tumor and suppression of the immune response by corticosteroids, immunoglobulin or other agents have been used without encouraging results (8, 9). Further investigation of the role of immunotherapy is required, while treatment of the underlying disease has so far been the most effective approach (8, 9).

PMP remains an enigmatic, often fatal disease, characterized by gelatinous ascites and multifocal peritoneal epithelial implants secreting copious globules of extracellular mucin. This results in a “jelly belly” macroscopic appearance. PMP is a term used to describe a wide range of neoplasms varying from benign or borderline malignant to malignant. The condition has mostly been linked to appendiceal mucinous neoplasms, however, there has been insufficient attention to the classification, histological characteristics and differential diagnostics of these neoplasms. Definitive diagnosis requires the presence of i) mucinous neoplastic cells/epithelium and ii) mucinous ascites/diffuse intraabdominal mucin. Histological analyses must also identify viable epithelial glandular cells within the mucin pools. PMP is often asymptomatic until very late in its course. Presenting symptoms include abdominal pain and distention. Occasionally a palpable abdominal mass may be present. PMP can be confused with loculated ascites and ovarian carcinoma.

Extensive surgical cytoreduction, sometimes accompanied by appendicectomy as well as bilateral salpingo-oophorectomy in females, combined with adjuvant chemotherapy remain the cornerstones of treatment. The measurement of the tumor marker CA 19-9 is useful in evaluating therapy and predicting disease recurrence (10).
Although administration of selected chemotherapy agents (mitomycin-C, 5-fluorouracil and leucovorin) into the peritoneal cavity offers direct delivery of high concentrations of the drug, a major concern has been the non-uniform drug distribution. Therefore, following debulking surgery the use of heated intraoperative intraperitoneal chemotherapy has been proposed to improve drug penetration and distribution (11). Recent research has linked MUC2 enzyme overexpression with proliferation of pseudomyxoma tumor cells pointing to possible new drug treatments (12).

Conclusion

We have reported a case of paraneoplastic cerebellar degeneration without detectable onconeural antibodies, apparently attributed to PMP with concurrent breast cancer. The neurological syndrome was not detected early, although it seemed to have a typical clinical presentation; the same is true for its probable causative factor, the PMP, while the course of breast cancer seemed to be independent, although a peculiar myxomatous appearance of the breast was present during the late phase of the disease (an occult histology similar to that of the abdomen?). The synchronous manifestation of these two neoplastic entities is very interesting as it has not been previously described. Given the young age of the patient, a specific genetic disorder might be the underlying cause although further study was not feasible due to refusal of the patient and relatives.

A different, better outcome of the patient in the case of earlier detection and successful treatment of the PMP cannot be excluded, although the concomitant breast cancer does not allow such a statement. However, the need for early suspicion, diagnosis and appropriate intervention in PMP should be emphasized, while more investigation into the etiology and treatment of severe disability-inducing paraneoplastic disorders is warranted.

References


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