Anti-Yo Antibody-mediated Paraneoplastic Cerebellar Degeneration in a Female Patient with Pleural Malignant Mesothelioma

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Paraneoplastic cerebellar degeneration is a rare non-metastatic complication of malignancies. It presents with acute or subacute onset of ataxia, dysarthria and intention tremor. Paraneoplastic cerebellar degeneration is most commonly associated with malignancies of the ovary, breast and lung. The anti-Yo (anti-Purkinje cells) antibodies that specifically damage the Purkinje cells of the cerebellum are found in the serum and cerebrospinal fluid. Anti-Yo-related paraneoplastic cerebellar degeneration is most commonly found in women with gynecological and breast cancers, but it is reported in other malignancies. Patients with paraneoplastic syndromes most often present with neurologic symptoms before an underlying cancer is detected. We report a case of anti-Yo-related paraneoplastic cerebellar degeneration associated with pleural malignant mesothelioma in a 51-year-old female patient. She presented to our department with a 2-week history after the last chemotherapy of progressive diziness related to head movement, nausea, vomiting, ataxia and unsteady gait. A western blot assay was negative for anti-Hu, anti-Ri, anti-Ma2, anti-CV2 and anti-amphiphysin paraneoplastic antibody markers but positive for anti-Yo. In conclusion, we report a case of paraneoplastic cerebellar degeneration in a patient with pleural malignant mesothelioma because of the rarity of this neurologic presentation after the diagnosis of malignant mesothelioma and of the association with anti-Yo antibodies.

Key words: mesothelioma – paraneoplastic neurologic syndrome – paraneoplastic cerebellar degeneration – anti-Yo antibody

INTRODUCTION

Paraneoplastic neurologic syndromes are rare disorders and they occur in 1–3% of all cancer patients. These syndromes are a heterogeneous group of cancer-related neurologic diseases and it may affect any part of the nervous system. These disorders caused by mechanism other than metastases, metabolic and nutritional deficits, infections, coagulopathies or anticancer treatment-related side effects (1). Paraneoplastic cerebellar degeneration (PCD) is one of these neurologic diseases and patients present with acute or subacute onset of ataxia, dysarthria and intention tremor. Although cognitive function usually preserved, mild cognitive and memory deficits can occur in ~20% of patients with paraneoplastic cerebellar syndrome. PCD presents in a patient with a known malignancy or it can precede the detection of a cancer by months to years but sometimes the diagnosis of a malignancy is made before this syndrome occurs (1–3). They will frequently have a small cell lung carcinoma, Hodgkin’s...
lymphoma or carcinoma of the breast or ovary and rarely found to be associated with other malignancies including esophagus, gastric, gastro-esophageal junction and prostate adenocarcinomas in the literature (4–10).

The presence of specific antibodies in serum samples helps to guide the identification of underlying primary malignant disease in patients with paraneoplastic neurologic disorders. Anti-Yo is one of the anti-onconeural antibodies found in PCD patients. Although PCD may occur in patients with a variety of malignancies with or without auto-antibodies, it is most commonly associated with malignancy of the ovary and breast in women seropositive for anti-Yo antibodies (4–6).

Finally, anti-Yo-related PCD is most common in patients with gynecological and breast cancer and they most often present with neurologic symptoms before an underlying cancer is detected. However, neurological symptoms in our patient were occurred after the diagnosis of mesothelioma and she had anti-Yo antibodies seropositivity. Here we report a case of PCD in patients with pleural malignant mesothelioma having high-titer anti-Yo antibodies because of an unusual clinical presentation.

CASE REPORT

A 51-year-old previously healthy Caucasian women admitted to the other oncology department with a 3-month history of abdominal pain and discomfort in March 2009 and detected a high level of serum cancer antigen (CA)-125 (55 U/ml). She had no smoking history and was a housewife with no obvious direct exposure to asbestos. Her husband had no exposure to asbestos too. The computerized tomography (CT) of the abdomen and thorax showed the presence of ascites, celiac and mesenteric lymph nodes <1 cm and, left-sided pleural effusion. The liver, spleen, kidneys and reproductive organs all appeared normal. The gynecological examination, gastroscopy, colonoscopy and mammography were all negative. A subsequent whole body positron emission tomography with CT (PET/CT) showed multifocal tumoral masses with intense metabolic activity in the left-side parietal pleura and mediastinal prevascular, paracaeliac, paraaortic, paracaval and mesenteric multiple lymph nodes >1 cm with intense metabolic activity (Fig. 1A and D). Cytological evaluation of the pleural fluid showed atypical mesothelial proliferation and pathological examination of the pleural biopsy by video-assisted thoracoscopic surgery reflected malignant mesothelioma (Fig. 2A). Exploratory laparoscopy was performed and the omentum, right and left diaphragmatic areas presented with numerous superficial implants measuring from several millimeters to 1 cm in diameter. Subdiaphragmatic spaces, the liver, pancreas, stomach, bilateral ovary and spleen had no evidence of a primary or metastatic neoplasm. Pathological evaluation of the peritoneal biopsy showed malignant mesothelioma (Fig. 2B and C). Based on the radiological, thoracoscopic and laparoscopic findings, she was diagnosed with malignant mesothelioma originating from the pleura.

The patient was treated with nine cycles of carboplatin administered to target an area under the concentration–time curve of 5 mg/ml/min (AUC 5) and pemetrexed 500 mg/m² on day 1 every 3 weeks due to poor performance status. Due to disease progression with increased serum CA-125 levels, a second-line treatment was administered with three cycles of carboplatin AUC 5 and doxorubicin 60 mg/m² on day 1 every 3 weeks.

She presented to our department with 2-week history after the last chemotherapy of progressive diziness related to head movement, nausea, vomiting, ataxia and unsteady gait in April 2010. Physical examination revealed truncal and gait ataxia in the absence of Romberg’s sign, horizontal nystagmus on lateral gaze and dysmetria of all four limbs without weakness or sensory loss. Her gait was wide based and she could not tandem walk. Tests of finger to nose coordination were normal. The patient also had dysarthria with scanning speech. Her cognitive function was intact. Extremity reflexes were normal and both plantar responses were flexor. The remainder of the physical examination was unremarkable.

Laboratory studies revealed normal electrolytes and normal liver function tests. Further work-up with head CT was normal and contrasted cranial magnetic resonance imaging (MRI) showed no evidence of the cerebellar mass, metastasis or atrophy. The patient refused to undergo a lumbar puncture. PCD was suspected. Serum was then analyzed for the presence of onco-neural antibodies. A western blot assay was negative for anti-Hu, anti-Ri, anti-Ma2, anti-CV2 and anti-amphiphysin paraneoplastic antibody markers but positive for anti-Yo (Fig. 3). Our patient expressed high titres of anti-Yo antibody in the serum and this situation was reported in 88% of patients with PCD (4–6).

Chemotherapy with gemcitabine 1000 mg/m² on days 1, 8 and 15 every 4 weeks was initiated but she refused chemotherapy after the first cure treatment. The patient left the hospital to get an alternative treatment with ozone and then could not be reached again.

DISCUSSION

Here we describe a case of PCD caused by malignant mesothelioma and associated anti-Yo antibodies in a female patient. Because it was an exceptionally rare case and this case illustrates an unusual presentation of serum high-titer positive anti-Yo-related paraneoplastic syndrome with malignant mesothelioma.

PCD is the most common paraneoplastic disorders of the brain and thus far, several kinds of onconeural antibodies have been identified to be related with PCD. These antibodies are anti-Yo antibody (with cancer of the breast and ovary), anti-Hu antibody (with small cell lung carcinoma),...
Figure 1. Multifocal tumoral masses with intense metabolic activity in the left-side parietal pleura and mediastinal prevascular, paraceliac, paraaortic, paracaval and mesenteric multiple lymph nodes >1 cm with intense metabolic activity (A and B), multifocal peritoneal implants with intense metabolic activity in the abdomen (C and D).

Figure 2. Atypical, infiltrative epithelial cell groups (H–E × 200): (A) in the pleura, (B) in the peritoneum and (C) mesothelin positivity in neoplastic cells (anti-mesothelin × 400), peritoneum and (D) cytokeratine 5/6 positivity in neoplastic cells (anti-cytokeratine 5/6 × 400), in the peritoneum.
anti-Ri (with breast cancer) and anti-Tr antibody (with Hodgkin’s disease) (4). Although the pathogenic mechanism(s) of PCD is still not understood, the anti-Yo antibodies have reactivity against Purkinje cells of the cerebellum and brainstem neurons. All those of paraneoplastic syndromes are believed to be caused by an autoimmune reaction against antigen or antigens over-expressed by tumor cells and neurons. In addition to antibody-mediated immune response, cytotoxic T-cell responses appear to play an important role in the pathogenetic mechanism (3, 4).

PCD with the anti-Yo antibody is typically associated with gynecological malignancies and breast cancer in >85% of all cases and this syndrome occurs exclusively in women (1–4). Only very occasionally has anti-Yo-related PCD been reported in other malignancies including prostate adenocarcinoma, esophageal adenocarcinoma, gastric adenocarcinoma, parotid adenocarcinoma and adenocarcinoma of unknown origin (5, 7–10). However, anti-Yo-associated PCD in patients with malignant mesothelioma has so far never been reported persuasively in the English literature.

In our patient, the pathology specimens were re-evaluated by immunohistochemical work-up because of anti-Yo-associated PCD more frequently seen in ovary and breast cancers. The specimen was fixed in 10% buffered formalin, paraffin embedded and 4 mm sections were cut and stained with hematoxylin and eosin (H&E). Histochemical examination included periodic acid-Schiff with and without diastase pretreatment. Light microscopy revealed a diffuse epithelioid type of malignant mesothelioma of the pleura and peritoneum. Figure 1 shows the typical histological apperance of malignant mesothelioma with focal cellular stratification, cellular buds and hobnail-type cells (H&E) in pleura and peritoneum, respectively. The tumor was characterized by a papillary and solid pattern. The cells exhibited severe atypicality and moderate mitotic rate. The stroma was typically hyalinized and papillae with hyalinized cores were a striking finding. Psammoma bodies were not present. The cells were negative for carcinoembriogenic antigen, CA-125, cytokeratine 7, cytokeratin 20 and vimentin. Although immunostaining was negative for calretinin, the tumor cells show strong cytoplasmic reactivity for cytokeratin 5/6 and mesothelin (Fig. 2C and D).

The differentiation between mesothelioma and adenocarcinoma based on the morphology alone can be a diagnostic challange. Immunohistochemical staining may be very helpful in the differential diagnosis between pleural malignant mesothelioma and primary lung adenocarcinoma, and between peritoneal malignant mesothelioma and ovarian adenocarcinoma or primary peritoneal serous carcinoma. Although malignant mesotheliomas are usually positive for one or more of immunostains, these antibodies generally show low frequencies of reactivity in adenocarcinomas. Cytokeratin 5/6 is one of these antibodies and it appears to be one of the most sensitive and specific positive immunohistochemical markers for the differential diagnosis of epitheloid malignant mesothelioma. Calretinin has been studied extensively in mesothelioma of the pleura with some disparate values, although many studies have reported positive staining in 80% to 100% of pleural malignant mesotheliomas. Similar results of positivity for calretinin have been declared in malignant mesothelioma of peritoneum. However, mesothelin was positive in 65% of peritoneal malignant mesothelioma and was not considered helpful for the differential diagnosis between malignant mesothelioma of the peritoneum and peritoneal serous carcinomas (11). In conclusion, pathological evaluation was performed using microscopic features and results of immunohistochemical stainings, and the patient was diagnosed with pleural malignant mesothelioma.

Mesothelioma is a highly lethal and an insidious malignacy arising from the mesothelial surfaces of the pleural and peritoneal cavities, the tunica vaginalis or the pericardium (12). Eighty percent of all cases are pleural in origin and the peritoneum is the second most frequent site of origin of mesothelioma (12). The predominant cause of malignant mesothelioma is inhalational exposure to asbestos and industrial pollutants, with ~70% of cases of malignant mesothelioma being associated with documented asbestos exposure.

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**Figure 3.** A western blot assay was negative for anti-Hu, anti-Ri, anti-Ma2, anti-CV2 and anti-amphiphysin paraneoplastic antibody markers but positive for anti-Yo.
In contrast, two case series of peritoneal diffuse malignant mesotheliomas in women found no association of the malignancy with a history of asbestosis. In our case also, neither the patient nor her husband had any history of direct asbestos exposure (12).

What we know about the paraneoplastic syndromes occurring in patients with malignant mesotheliomas is limited to case reports. Most common ones are hematological disorders such as thrombocytosis, leukocytosis/granulocytosis, thrombosis, membranous glomerulonephritis, dermatomyositis, hypertrophic osteoarthropathy, esophageal achalasia and syndrome of inappropriate anti-diuretic hormone secretion (13–15). The association between anti-Yo-mediated PCD and malignant mesothelioma has not been reported in the English literature. However, a case of subacute cerebellar degeneration with pleural malignant mesothelioma has been reported by Tassinari et al. (16) in Italian. The comparison of our case with that reported by Tassinari et al. is shown in Table 1.

Patients with PCD typically present with nausea, vomiting and dizziness, frequently beginning acutely, and followed several days later by diplopia, dysarthria, gait instability, both truncal and appendicular ataxia, oscillopsia and dysphagia. Neurological symptoms typically continued to exacerbate for weeks to months before stabilizing. Our patient presented with progressive dizziness related to head movement, nausea, vomiting, ataxia and unsteady gait within 2 weeks (3–6).

Clinical history, examination, neuroimaging and laboratory testing help to differentiate PCD from other conditions (3). MRI and CT are usually normal early in the course of PCD and they are not helpful for positive diagnosis of this syndrome but are important to exclude metastatic, demyelinating and ischaemic or haemoragastic cerebrovascular diseases. Sometimes MRI can show cerebellar atrophy in advanced cases (4, 5). In our patient, contrasted MRI and CT of brain revealed no pathologic findings. Treatment of the underlying malignancy is considered essential for neurologic stabilization; improvement in clinical symptoms is less likely but may occur (4–6).

In conclusion, we report a case of PCD in a patient with pleural malignant mesothelioma because of the rarity of this neurologic presentation after the diagnosis of malignant mesothelioma and of the association with anti-Yo antibodies.

Conflict of interest statement
None declared.

Table 1. Comparison of the demographic, clinical and treatment features of our case and other case in current literature

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
<th>Previous case (Tassinari et al.) (16)</th>
<th>Our case (Tanriverdi et al., 2012)</th>
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<tr>
<td>Age (year)</td>
<td>64</td>
<td>51</td>
</tr>
<tr>
<td>Gender</td>
<td>Unknown</td>
<td>Female</td>
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<tr>
<td>Localization of primary tumor</td>
<td>Pleura</td>
<td>Pleura</td>
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<td>Presence of operation</td>
<td>Inoperable</td>
<td>Inoperable</td>
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<tr>
<td>Neurologic symptoms</td>
<td>Gait disorders and difficulty in reference to the articulation of the words</td>
<td>Progressive diziness related to head movement, nausea, vomiting, ataxia and unsteady gait</td>
</tr>
<tr>
<td>Neurologic findings</td>
<td>Ataxia, disartria</td>
<td>Ataxia, disartria</td>
</tr>
<tr>
<td>Onset of neurologic symptoms</td>
<td>After the diagnosis of mesothelioma</td>
<td>After the diagnosis of mesothelioma</td>
</tr>
<tr>
<td>Radiological findings by MRI</td>
<td>Cerebellar atrophy</td>
<td>Normal imaging</td>
</tr>
<tr>
<td>Previously treatment</td>
<td>Mitoxantrone × 8 cycles; intrapleural cisplatin-cytosine; arabinoside × 3 cycles</td>
<td>Carboplatin-pemetrexete × 9; cycles; carboplatin–doxorubicin × 3 cycles</td>
</tr>
<tr>
<td>Anti-Yo antibodies</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Other onco-neural antibodies</td>
<td>Unknown</td>
<td>Sero-negative for anti-Hu, anti-Ri, anti-Ma2, anti-CV2 and anti-amphiphysin</td>
</tr>
<tr>
<td>Treatment of PCD</td>
<td>High-dose corticosteroids immunoglobulin</td>
<td>Refused for new chemotherapy</td>
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<td>Clinical differentiation</td>
<td>Localized disease in the chest</td>
<td>Peritoneal involvement</td>
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References


