Anti-Yo-Associated Paraneoplastic Cerebellar Degeneration in a Man with Adenocarcinoma of the Gastroesophageal Junction

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Key Words
Paraneoplastic syndrome · Esophageal cancer · Metastasis · Cerebellar degeneration · Anti-Yo

Abstract
Anti-Yo-associated paraneoplastic cerebellar degeneration is a cancer-related syndrome affecting the nervous system. This syndrome occurs almost exclusively in middle-aged women with gynecological cancers and it is rarely found in patients with other types of cancer or in males. In this report we describe a male patient adenocarcinoma of the gastroesophageal junction and PCD with anti-Yo antibodies. To our knowledge, this is only the third report of PCD with positive anti-Yo antibodies in an esophageal tumor and the first report in a tumor of the gastroesophageal junction.

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Introduction
Paraneoplastic cerebellar degeneration (PCD) is a well-characterized cancer-related syndrome of the nervous system. In most patients, PCD presents with subacute, progressive pancerebellar dysfunction including truncal and gait ataxia, dysarthria and nystagmus that are caused by the (functional) loss of Purkinje cells in the cerebellum. Several antineuronal antibodies such as anti-Hu, anti-Yo and anti-Tr are found in the sera of patients with PCD depending on the underlying tumor [1]. Anti-Yo-associated

PCD occurs almost exclusively in middle-aged women with gynecological cancers and breast cancer. It is rarely found in patients with other types of cancer or in males [1–3].

In this report we describe a male patient with adenocarcinoma of the gastroesophageal junction and PCD with circulating anti-Yo antibodies and expression of Yo antigen by the tumor. To our knowledge, this is only the third report of PCD with positive anti-Yo antibodies in an esophageal tumor and the first report in a tumor of the gastroesophageal junction [4, 5]. This case shows an unusual presentation of esophageal cancer. In addition, it aims to bring into perspective the potentially different management of the tumor in these patients.

Case Report
A 57-year-old white male presented to a local hospital (Talma Sionsberg, Dokkum, The Netherlands) with a 2-month history of progressive dysphagia and weight loss. The patient was unable to eat solid food and, at the time of presentation, he had lost 20 kg of weight. In addition, the patient had a 1-week history of walking difficulties, clumsiness of both hands, problems in writing, vertigo and double vision when gazing right.

Neurological examination revealed truncal and gait ataxia in the absence of Romberg’s sign, brisk tendon reflexes and slight dysmetria of both legs, without weakness or sensory loss. The remainder of the physical examination was unremarkable.

Routine laboratory analyses were normal except for slightly decreased hemoglobin levels. Endoscopy revealed the presence of an esophageal tumor arising at 37–44 cm from the incisors. Histological examination showed a moderately differentiated adenocarcinoma of the esophagus. Abdominal and thoracic computed tomography (CT) were performed to address the extension of the primary process. No signs of other primary tumors or liver-lung metastases were seen. Under suspicion of brain metastasis, cranial magnetic resonance imaging (MRI) and CT scan were performed. Both studies revealed no cerebellar metastasis, atrophy or signal change. Under suspicion of a Wernicke encephalopathy, due to eating difficulty and thus inadequate thiamine intake, an intramuscular injection of thiamine was given with no beneficial effect for the patient.

A paraneoplastic neurologic syndrome was suspected and the patient’s serum was analyzed for the presence of antineuronal antibodies. Anti-Hu, anti-Ri, anti-Tr, and anti-amphiphysin antibodies were negative. However, a high titer of anti-Yo antibody was detected. The patient was diagnosed with a PCD most likely caused by adenocarcinoma of the esophagus. He was transferred to a tertiary referral hospital (Academic Medical Center, Amsterdam) to treat his esophageal cancer.

Preoperative work-up with endosonography did not show invasion of the tumor into the surrounding tissues, and two suspicious lymph nodes were seen in the proximity of the tumor.
(T3N1Mx). External sonography of abdomen and neck, chest radiograph, CT and positron emission tomography showed no evidence of distant dissemination. Surgical therapy for the tumor was indicated. Meanwhile, during the diagnosis and management-decision period (approx. 2 weeks), the patient's cerebellar symptoms worsened. At the time of surgery he was wheelchair-bound and his dysarthria had worsened. His cognitive function remained preserved. Due to the condition of the patient and the absence of lymph node metastasis in the upper mediastinum, a transhiatal esophagectomy with lymphadenectomy was performed. Histopathological examination revealed a T3N1M0 poorly differentiated adenocarcinoma of the gastroesophageal junction (type II) with substantial growth into the esophagus and stomach. The resection and dissection planes were free of tumor. Of 19 resected lymph nodes, 6 showed metastatic adenocarcinoma. Five of them were localized close to the primary tumor and 1 lymph node was localized close to the origin of the left gastric artery. Tumor tissue was positive for Yo antigen (fig. 1).

Two weeks after surgery the patient was totally bedridden with unrest and progressive dysarthria. A course of intravenous immunoglobulin (0.4 g/kg for 5 days) and a trial of prednisolone were given without success. After admission in the hospital, the patient was referred to a rehabilitation center for 2 months. At last follow-up, 2 years post-surgery, the patient did not have evidence of recurrent disease, the patient's dysarthria and swallowing had improved slightly but his general neurological condition had remained unchanged. He was still bedridden, and non-ambulatory.

Immunological Studies

The patient's serum stained Purkinje cell cytoplasm on rat frozen cerebellar sections by indirect immunofluorescence [6]. Anti-Yo antibodies were confirmed by Western blotting using CDR62 recombinant protein [1]. To detect expression of Yo antigens by the patient's tumor, we purified and biotinylated IgG from the plasma of another patient with anti-Yo antibodies and from plasma of an anti-Yo-negative control patient using previously described methods [7]. Frozen sections were fixed for 10 min in acetone and washed in phosphate-buffered saline (PBS). Later, the sections were treated at room temperature with 0.3% hydrogen peroxide for 10 min and incubated with 10% normal human serum for 10 min to suppress aspecific binding. After removal of excess serum, the sections were incubated for 2 h with the indicated amounts of biotinylated anti-Yo or control IgG, diluted in PBS containing 10% normal human serum. Sections were then labeled with streptavidin-biotin-peroxidase complex and diaminobenzidine. It was shown that tumor cells were reactive with anti-Yo IgG (fig. 1a) but not with control IgG (fig. 1b), indicating that the primary tumor produced anti-Yo antibodies.

Discussion

Anti-Yo-positive PCD is usually associated with ovarian, uterine, adnexial and breast cancer and rarely with other tumors [1–3]. To the best of our knowledge, only 7 male patients with anti-Yo-associated PCD have been described so far [4, 5, 8–12]. Including our patient, 5 had an underlying gastrointestinal adenocarcinoma (3 esophageal [4, 5] and 2 gastric [9, 12]). The other 3 had adenocarcinoma of the parotid gland [8], lung [11] or of unknown origin [10].

In breast and gynecological cancers, anti-Yo-positive PCD is closely associated with aberrant expression of the Yo antigens by the tumor [7]. In 6 of 8 male patients with anti-Yo-positive PCD, the associated adenocarcinoma was examined for expression of the Yo antigens by immunohistochemistry. In all 6 cases, including ours, the tumor expressed the Yo antigens [4, 9–12]. Normally, the Yo antigen is only expressed in the cytoplasm of cerebellar Purkinje cells [13]. Most likely, the aberrant expression of Yo antigens by the tumor induces an immune response that subsequently reacts with the same or similar antigens in the cerebellum [14].

The median survival of patients with anti-Yo-positive PCD varies between 13 and 22 months [1, 3]. One study indicates [1] that patients with PCD due to anti-Yo antibodies die primarily from neurological causes (67%) while another study found that

**Fig. 1.** Frozen sections of the patient's tumor were incubated with biotinylated anti-Yo IgG (13 μg/ml) or control IgG (12 μg/ml). Tumor cells are reactive with anti-Yo IgG from another anti-Yo-positive patient (a) but not with control IgG (b). Dilution in both samples was 1:100 and the magnification was 40x.
tumor progression was the main cause of death (55%) in these patients [3]. Several studies show that patients with PCD receiving antitumor treatment (in combination with or without immunosuppressive therapy) live longer [1–3]. However, treatment has no effect on functional outcome. Neurological improvement is mostly anecdotal and transient since most patients show rapid deterioration even after receiving treatment [1–3]. Functional outcome is worst in PCD patients with anti-Yo antibodies, with 80–94% of the patients becoming non-ambulatory during the course of the disease [1, 3].

In the case of patients presenting with a carcinoma of the esophagus and cerebellar symptoms, metastases should first be excluded by MRI. If the MRI is negative, a paraneoplastic etiology should be considered and serum should be examined for antineuronal antibodies [15]. In the few cases reported, including ours, surgery was performed in order to give the patient a higher chance of survival with reasonable quality of life. However, because of the poor prognosis of patients with anti-Yo-associated PCD, even after complete removal/cure of the cancer, the indication of a surgical procedure with high morbidity and mortality can be debated. In our case, surgery was substantially delayed because of logistic reasons, allowing neurological deterioration to progress. If we take into account that the cancer is the most likely source of production of the Yo antigen and therefore the cause of the clinical syndrome, we believe that the tumor should be removed as soon as possible. Immediate surgery to remove the tumor upon confirmation of PCD with anti-Yo antibodies would probably be most beneficial for the patient. Further research into new and effective therapies targeting the neurological deterioration is warranted to give patients with anti-Yo-associated PCD a better chance for survival and/or a better quality of life.

References


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Splenic Abscesses Caused by a Reptile-Associated Salmonella Infection

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Salmonella infection · Splenic abscess · Surgery, splenic abscess

Abstract
Salmonella infections are not very uncommon. The source generally has to be looked for in food. The syndrome concerns mostly gastro-enteritis. We present a 17-year-old girl with sepsis caused by splenic abscesses which was successfully treated with splenectomy and antibiotics. After analysis (blood and surgical specimen samples), she appeared to be infected with Salmonella type Telek ewir, a rare variant that is associated with exotic animal species, mainly reptiles. The same variant was cultivated from the faeces of the reptile pets that were held in the patients’ home. We describe a case with a not often recognized source and an unusual course of Salmonella infection. Exotic pets can be a source of Salmonella infections with a catastrophic course of the disease even in healthy people.

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