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Acute motor axonal neuropathy associated with anal carcinoma: Paraneoplastic neurological syndrome or coincidence?

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ABSTRACT

Aim: Assessment of the association of an acute motor axonal neuropathy with a squamous cell anal carcinoma.
Background: Paraneoplastic neurologic syndromes are not a direct consequence of neither primary tumor nor its metastasis. They often parallel the course of the malignancy but may be the presenting sign of an occult cancer. Sometimes it is very difficult to distinguish if it is a paraneoplastic syndrome or just a coincidence.
Materials and methods: We report a 60-year-old man that presented with an acute motor deficit of the four limbs. Clinical examination found a pure and severe motor deficit in the four limbs. No sensory abnormality was found and all motor nerves were unexcitable. Electromyography suggested the diagnosis of acute motor axonal neuropathy (AMAN). Four months after developing the AMAN, blood in the stool revealed anal carcinoma. The patient was treated with concurrent chemoradiotherapy. Radiation was given to the tumor and to the pelvis, including inguinal nodes, over a five-week period plus fluorouracil and mitomycin. We investigated the presence of antiganglioside antibodies as studies suggest that carcinomas can express antigens shared with Schwann cells.
Results: Anti-GM1 IgG antibodies were detected by an enzyme-linked immunosorbent assay method. Other antibodies, including antinuclear nucleoprotein antibody (anti-Hu), anti-Tr, anti-Ri, anti-CV2, anti-amphiphysin and anti-Yo, were negative. Clinical improvement of the motor state was observed at the fourth week of oncologic treatment.
Conclusion: The presence of anti-GM1 IgG antibodies and the clinical improvement of the motor state after concurrent chemoradiotherapy lead us to believe there is an association between anal carcinoma and this severe impairment.

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1. Background

Paraneoplastic syndromes occur in about 1% of all active cancers.[1] The clinical course of these syndromes sometimes correlates with the underlying malignancy, which may suggest an ascertain paraneoplastic etiology. However, in some other cases both the paraneoplastic syndrome and the tumor follow independent courses. In either situation it is essential to consider their potential existence for they may indicate the first sign of a malignant process. This will contribute to their early detection in a curable stage and their use as clinical tumor markers of early recurrences in treated patients. Squamous cell carcinoma is not a common histological type associated with paraneoplastic neurologic syndromes (PNS). Few cases are described in the literature.[2,3] These disorders often appear to have an autoimmune pathogenesis, as suggested by the presence of autoantibodies directed against both neurons and cancer cells.[4] We present the case of one patient with an acute motor neuropathy associated with squamous cell anal carcinoma. The association described here has not been reported before.

2. Case report

A 60-year-old man was admitted to the hospital for an acute motor deficit of the four limbs. Clinical examination found a pure and severe motor deficit in the four limbs. No sensory abnormality was found. Deep tendon reflexes were abolished. Electromyography suggested the diagnosis of acute motor axonal neuropathy (AMAN). All motor nerves were unexcitable (Fig. 1), except for the right ulnar nerve (Fig. 2), which evoked a compound muscle action potential reduced in amplitude and conducted at 34.5 m/s with F wave latencies not delayed. Sensitive nerve conductions were normal. Needle electromyography showed severe acute diffuse denervation. The patient was treated with intravenous inmunoglobulin. Despite the treatment, the patient continued to have profound ascending muscle weakness, eventually involving the bulbar and facial muscles. Due to respiratory distress and respiratory muscle weakness, the patient required mechanical ventilation. Five sessions with plasma exchanges were performed without any signs of improvement. The patient continued to stay in the Intensive Care Unit. Once the patient was able to sustain spontaneous breathing, he was taken to the Neurology Department. Four months after developing the AMAN, blood in the stool revealed anal carcinoma. The anoscopy and biopsy showed an anal squamous cell carcinoma. The tumor was classified as stage 3 (Fig. 3).

Routine laboratory data showed no abnormalities. Human papillomavirus DNA type determination was positive. Campylobacter jejuni, cytomegalovirus and Epstein-Barr virus serology were negative. CEA were normal. Cerebrospinal fluid analysis did not show any abnormalities. Anti-GM1 IgG antibodies were detected by an enzyme-linked immunosorbent assay method. Other antibodies, including antinuclear nucleoprotein antibody (anti-Hu), anti-Tr, anti-Ri, anti-CV2, anti-amphiphysin and anti-Yo, were negative. We analyzed the antibodies in serum by indirect immunofluorescence. The case was discussed in the multidisciplinary Gastrointestinal Tumor Board of our Center and the recommendation was to treat anal carcinoma by delivering concurrent chemoradiotherapy in order to achieve an adequate loco-regional control

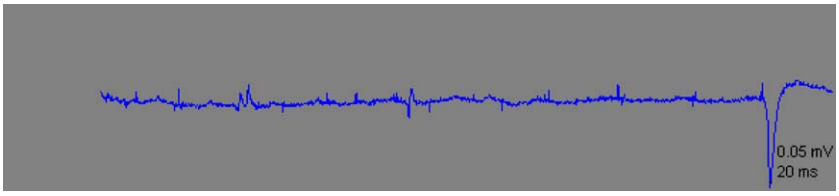

Fig. 1 – Spontaneous activity in denervated anterior tibialis muscle.

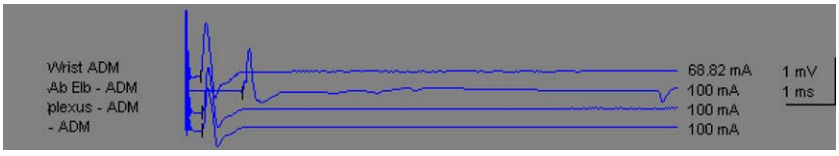

Fig. 2 – Ulnar motor nerve conduction velocity. ADM: abductor digiti minimi; Ab: abduction; Elb: elbow.

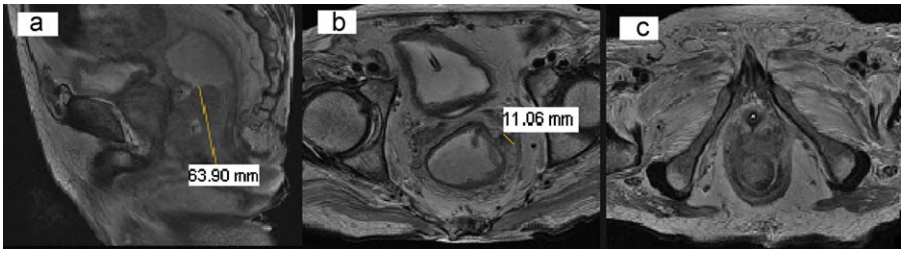

Fig. 3 – Magnetic resonance imaging scan of the pelvis showing: (a) Solid mass measuring 63 mm in length and 53 mm × 33 mm in diameter, (b) perirectal lymph node 11 mm in diameter, and (c) invasion of the internal anal sphinter.

and motor improvement. Radiation was given to the tumor and to the pelvis including inguinal nodes, in 25 fractions over a five-week period plus fluorouracil and mitomycin. The chemoradiotherapy was well tolerated. Clinical improvement of the motor state was observed at the fourth week of the oncologic treatment. Unfortunately, three days after finishing the chemoradiotherapy the patient died due to an episode of bronchoaspiration.

3. Discussion

The patient developed ascending paralysis, progressing to tetraplegia within two weeks. No history of intoxication or porphyria was apparent. The main clinical symptoms of the patient were characterized by acute motor deficit of the four extremities without sensory affectation. The motor impairment was apparent four months before the detection of anal carcinoma. We detected an autoantibody against the ganglioside in the serum of the patient. Therefore, it was possible that the patient had paraneoplastic motor neuropathy. The presence of this severe impairment and anal carcinoma are unique clinical features in this patient.

In parts of China, Japan, India, and central part of South America, the underlying abnormality is more commonly an acute motor axonal neuropathy, in which the primary autoimmune attack is directed against the axon. Patients with AMAN are more likely than other GBS patients to have IgG antiganglioside GM1 antibodies.[5] Pathologically, one can observe motor axonal degeneration with antibody mediated attacks of motor nerve and nodes of Ranvier.[6] Elevated titers of serum anti-ganglioside antibodies are characteristic of Guillain-Barré syndrome (GBS). Complement system has been shown to be involved in the anti-ganglioside antibody-mediated pathogenetic mechanisms. Some GBS patients have antibodies specific to a conformational epitope formed by two different gangliosides. Among such anti-ganglioside complex antibodies, anti-GD1a/GD1b IgG antibodies are shown to be associated with severe GBS requiring artificial ventilation. In contrast, antibodies highly specific to GD1b are associated with GBS with ataxia. Sensory ataxic neuropathy is induced by sensitization of rabbits with GD1b. An apoptotic mechanism has recently been shown to be involved in the pathogenesis of this animal model. Most of the patients with Fisher syndrome have anti-GQ1b IgG antibodies. Recent investigation on anti-ganglioside complex antibody showed that antibodies in Fisher syndrome can be subdivided into three groups; GQ1b-specific, GQ1b/GM1-specific, and GQ1b/GD1a-specific.

Research on antibodies to gangliosides and ganglioside complexes will provide a clue to develop a novel treatment of GBS.[7] Hadden et al. performed an electrophysiological and serological testing within 15 days of symptom onset on 369 patients with GBS enrolled in a trial comparing plasma exchange, intravenous immunoglobulin, and both. Antiganglioside GM1 antibodies were present in a higher proportion of patients with axonal physiology or inexcitable nerves than other patients. Pure motor GBS patients were more likely than other GBS patients to have IgG antiganglioside GM1 antibodies.[8]

PNS may indicate the first sign of a malignant process. This will contribute to the early detection of tumors and their use as clinical tumor markers. In more than 50% of cases, they precede the finding of the underlying neoplasm.[9] PNS have been linked to the production of antibodies stimulated by tumor antigen, consequently attacking neuronal antigen. Anti-Hu antibodies in small-cell lung carcinoma damage the nuclei of peripheral nervous system neurons and are associated with subacute sensory neuropathy; anti-Yo antibodies in ovarian cancers damage Purkinje cells. The presence of specific Hodgkin's Disease associated with paraneoplastic cerebellar degeneration autoantibodies against Purkinje cells, called Anti-Tr, has been reported.[10,11] De Toni et al. described two patients with progressive neuropathy and lung cancer in whom gangliosides may represent the oncoantigens. One patient had motor neuropathy, high titers of IgG1 and IgG3 to GD1a and GM1; the other presented with Miller–Fisher-like syndrome and IgG3 activity to disialo-gangliosides. In both cases, responses and stabilization of neuropathy were accomplished by tumor treatment. Ganglioside expression on neoplastic tissue may elicit autoimmune responses, which also target neural structures.[12] PNS include abnormalities in the peripheral or central nervous system, in patients with malignancy, and result from mechanisms other than metastasis, metabolic or nutritional deficits, infections, coagulopathy or side effects of chemotherapy.[13–15]

The prevalence of PNS ranges from 0.5 to 2.0% and is highest in patients with small cell lung cancer or gynecologic tumors.[16] Other tumors associated with PNS are breast cancer and Hodgkin's Lymphoma.[17] Although squamous cell carcinoma is not a common histological type associated with PNS, some cases have been described in the literature.[2,3] Central nervous system manifestations of a PNS comprise limbic encephalitis, cerebellar degeneration with dizziness, vertigo, limb and trunk ataxia, dysarthria, dysphagia, nystagmus, oscillopsia, vertigo, or diplopia, encephalomyelitis, retinal syndrome, opsoclonus, motor-neuron disease, or stiff-person syndrome.[15,18] Peripheral nervous system manifestations of a PNS comprise polyneuropathy, polymyositis/dermatomyositis, necrotizing myopathy, endocrine myopathy, neuromyotonia, myasthenia gravis, or Lambert–Eaton syndrome.[16] Generally, PNS can occur without antineuronal antibodies and antineuronal antibodies without PNS.[13] We speculate that Anti-GM1 IgG antibodies are mediated by the tumor, as studies suggest that carcinomas can express antigens shared with Schwann cells.[19,20] IgGs are readily absorbed from the nerve terminals for retrograde transport to the soma and transneuronal uptake by the neuropils in the spinal grey.[21] Prompt internalization of IgGs may cause damage and dysfunction of not only the axon but also the soma.

Despite the lack of clinical improvement of AMAN for four months, we thought it could improve if we treated the tumor. Shoulder and pelvis movements were observed the last week of the chemoradiotherapy treatment. Despite the good tolerance of the oncologic treatment, the patient died three days after finishing the treatment due to an episode of bronchoaspiration. The possibility could not completely be ruled out that the presence of the IgG antiganglioside GM1 antibody was incidental in this patient. However, the association between

the autoantibody and the tumor seems to be possible by several reasons: response and stabilization of neuropathy were accomplished by tumor treatment and the fact that there was no antecedent of infection that could explain the presence of antiganglioside antibodies produced by the mechanism of molecular mimicry between gangliosides and lipopolysaccharides of infectious pathogens.

We agree with Vallat et al.[22] that looking for the presence of an intercurrent condition, such as an underlying carcinoma, in front of acute polyneuritis should be the rule. It would help to deliver the adequate treatment in early stages for improving both the tumor control and the acute polyneuritis (pure sensitive, pure motor or sensorimotor).

Conflict of interest statement

The content has not been published or submitted for publication elsewhere and all persons listed as authors have given their approval for the submission of the paper. Authors declare not to have any financial support or relationships that may involve a conflict of interest.

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