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PERIPHERAL PARANEOPLASTIC NEUROPATHY, AN UNCOMMON CLINICAL ONSET OF SIGMOID CANCER. CASE REPORT AND REVIEW OF THE LITERATURE

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A case of a 76-year-old man presenting with weakness of the lower legs and bilateral steppage gait is described. Neurological examination revealed a sensorimotor neuropathy with axonopathy and myelinic aspects. At the time of the diagnostic workup an episode of rectal bleeding occurred. Colonoscopy demonstrated an exophytic cancer of the sigmoid colon at 40 cm from the anal verge. At surgery the tumor adhered to the ileum, so a left hemicolectomy and ileo-ileal resection were performed. Tumor stage was Dukes' B, Jass III, Astler-Coller B2, T3N0M0. The patient underwent postoperative chemotherapy and was followed for the past three years. At present he is free of disease and the neuropathy has completely regressed without any dedicated therapy.

As reported in the literature the appearance of a paraneoplastic neurological syndrome (PNS) may be the first sign of a malignancy that is occult at the time of clinical presentation. The most widely supported theory about its etiology is that of an autoimmune origin. The paraneoplastic neurological syndrome is considered to be at a point of intersection between tumor immunology, autoimmune neurological disease, and basic neurobiology. Previous experience has resulted in a pathogenic model and in a definition of a group of autoantibodies related to the disease. Small cell lung cancer (SCLC) is the neoplasm most frequently associated with PNS; other malignancies include lymphomas and various hematological malignancies. Some authors reported also that the percentage of patients with a high titer of neuronal autoantibodies is small and several of the autoantibodies are present at low levels without any accompanying clinical manifestation. In a clinical retrospective study of the Mayo Clinic Group 115,081 patients were examined over the period 1984-1993 and only 58 patients (0.05%) could be defined as being affected by a paraneoplastic neurological syndrome. Only five of these patients had colon tumors. The number of patients is so small and so widely scattered among publications that no statistical analysis is possible. Probably the only possibility for early identification of such a syndrome is a high degree of suspicion. In fact, these patients are usually first admitted and studied in a neurological unit, and the diagnosis of a tumor-associated disease is a delayed event.

Key words: colorectal cancer, paraneoplastic neurological syndrome.

Introduction

The appearance of a paraneoplastic syndrome may be the first sign of a malignancy that is still occult at the time of clinical presentation. The paraneoplastic neurological syndrome (PNS) in cancer patients has an incidence of less than 1%; its pathogenesis is not completely known but there is strong evidence of an autoimmune origin[1].

We have taken the opportunity to review the literature on this topic following our experience of a case of sigmoid cancer in a patient who was previously admitted to a neurological unit for a sensorimotor neuropathy of the lower limbs of unknown origin. The patient was extensively examined but the diagnosis was confirmed only by the regression of the neurological symptoms after surgical removal of the primary tumor.

Case report

A 76-year-old man had a first episode of paresthesia in 1993, involving the extensor muscles of the left foot, which regressed spontaneously. In 1998 the patient experienced progressive weakness of the lower legs and bilateral steppage gait. EMG showed sensorimotor neuropathy with axonopathy and myelinic disease. Cerebrospinal fluid examination showed mild hyperproteinemia with normal glucose and a slight increase in IgG. The patient did not present any significant weight loss or poor nutritional status; in particular, there was no evidence of vitamin B12 deficiency. Somatosensitive motor evoked potentials demonstrated impaired conduction with bilateral peripheral nervous involvement but no involvement of the central nervous system. At the time of the diagnostic workup an episode of rectal bleeding occurred. Colonoscopy revealed an exophytic cancer of the sigmoid colon at 40 cm from the anal verge.

Preoperative examination did not show any distant metastases or suspect lymph node enlargement. Preoperative CEA was 50.1 ng/mL. At surgery the tumor adhered to the ileum so a left hemicolectomy and ileo-ileal resection were performed. Histopathological tumor stage was Dukes' B, Jass III, Astler-Coller B2,

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T3N0M0. The patient underwent postoperative chemotherapy and was followed for the past three years. At present he is free of disease and the neuropathy has completely regressed without any dedicated therapy. No other EMG was performed after surgery or chemotherapy. He is able to carry out the normal activities of everyday life and walks with the aid of a walking stick.

Discussion

The appearance of PNS may be the first sign of a malignancy that is occult at the time of clinical presentation. Commonly the affected subjects, like our patient, are referred and investigated for a neurological disorder and the identification of the disease as a paraneoplastic disorder is delayed. This delay is partly due to the small number of cases reported in the literature. As a consequence, no statistical evaluation is available on these patients, and colon tumor origin in particular is so uncommon that these patients are usually classified into a general gastrointestinal group.

As regards the etiology of these diseases, the most widely supported theory is that of an autoimmune origin[2-7]. PNS is considered to be at a point of intersection between tumor immunology, autoimmune neurological disease, and basic neurobiology[2]. The first evidence was reported by Posner and coworkers[3-6], who identified high antibody titers in the serum and spinal fluid of patients with PNS. These antibodies recognize antigens of normal nervous tissue as foreign antigens ("oncoantigens") every time they are produced ectopically by the tumor tissue. In a recent publication Darnell proposed a classification of paraneoplastic neurological disorders and perfomed a correlation between the categories of onconeural antigens, their functions, and the associated syndromes[2]. In another paper Dropcho illustrated the mechanism: the tumor cells express antigens that are identical or related to molecules normally expressed by neurons, an autoimmune response arises against these "neural" tumor antigens ("onconeural antigens"), and the autoimmune response "spills over" [7]. A comprehensive overview of the most extensively studied oncoantigens is also presented in this publication in relation to the respective primary tumors and the most frequently associated neurological syndromes. Small cell lung cancer (SCLC) is the neoplasm most frequently associated with PNS[8-10]. Other malignancies include Hodgkin's and non-Hodgkin's lymphomas and various hematological malignancies.

In a recent review Inuzuka reported on a nationwide survey in Japan in which the highest incidences of each PNS, the most frequently associated tumors, the related clinical forms, as well as the antibodies and the target antigens of each PNS were presented[9]. However, the percentage of patients with a high neuronal autoantibody titer was small and several of the autoantibodies were present at low levels without any accompanying clinical manifestation. Furthermore, a considerable proportion of patients with a PNS either lack any demonstrable antineuronal antibodies or have atypical antibodies that may not be detected with commercially available assays. In view of these observations it seems reasonable to define PNS as a disease characterized by a high titer of specific antibodies, or a disease where it is possible to identify a tumor and where the course of the neurological disease is related to the evolution of the primary tumor (clinical definition)[8].

Furthermore, it should be remembered that peripheral neuropathy is a well-known consequence of the severe weight loss that usually occurs in cancer patients and is defined as a terminal event. In a clinical retrospective study of the Mayo Clinic Group[11] on peroneal neuropathy and footdrop of paraneoplastic origin, 115,081 patients were examined over the period 1984-1993. After a careful selection only 58 patients remained in the study (0.05%) and only five patients had a colon tumor. The authors applied the following clinical exclusion criteria: an alternative neuromuscular diagnosis including focal or multiple lumbosacral radiculopathies, generalized peripheral neuropathy, sciatic neuropathy, lumbosacral plexopathy, absence of a neurological evaluation or of an electromyography examination, no history or future development of systemic malignant disease. A further reason for exclusion was a clearly defined cause unrelated to malignancies such as blunt trauma or other traumatic injury. The authors defined the neuropathy as severe, moderately severe and mild. The symptoms developed before the diagnosis in eight patients, with the earliest onset occurring 12 months before diagnosis. With regard to outcome the results were classified as resolved, improved, no change and worsened. In 22.4% the neuropathy resolved completely and in 25.5% partially. Unfortunately also in this study the number of patients was too small for statistical analysis.

In conclusion, the only possible way to ensure the early identification of a paraneoplastic neurological syndrome is probably a high degree of suspicion. Usually these patients are admitted to a neurological unit because the neurological disorder may precede the first symptoms of the tumor by many years and the discovery of a link between the two disorders if often retrospective, based on clinical features. Unfortunately, due to the limited number of patients no statistical analysis is possible. Probably in the future a meta-analysis of the available cases will provide suggestions for the definition of a protocol for early detection[12].

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