CASE REPORT

Diffuse Large B-cell Lymphoma of Stomach Presenting with Paraneoplastic Cerebellar Degeneration Syndrome

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ABSTRACT
Paraneoplastic syndromes are most often diagnosed in the setting of a known malignancy. It is not uncommon for a paraneoplastic disorder to develop before a cancer is identified. While syndrome of cerebellar degeneration has been identified as a paraneoplastic manifestation of Hodgkin's lymphoma, thymoma, lung and breast cancer, ovarian and testicular tumors, melanoma, renal cell carcinoma, follicular lymphoma and adenocarcinoma of stomach, its association with non-Hodgkin's lymphoma and particularly diffuse large B-cell lymphoma has not been established previously. This case report describes the primary presentation with signs of paraneoplastic cerebellar degeneration as the only manifestation of an underlying diffuse large B-cell lymphoma making it the first of its kind to be formally reported. Furthermore, it also includes the identification of associated paraneoplastic antibodies for this particular syndrome.


INTRODUCTION
Paraneoplastic syndromes are most often diagnosed in the setting of a known malignancy. It is not uncommon for a paraneoplastic disorder to develop before a cancer is identified. The clinical syndrome and identification of certain paraneoplastic antibodies may suggest a specific underlying tumor and direct investigations. While syndrome of cerebellar degeneration has been identified as a paraneoplastic manifestation of Hodgkin's lymphoma, thymoma, lung and breast cancer, ovarian and testicular tumors, melanoma, renal cell carcinoma, follicular lymphoma and adenocarcinoma of stomach, its association with non-Hodgkin's lymphoma and particularly diffuse large B-cell lymphoma has not been established previously.

We present the case of a man who developed paraneoplastic cerebellar degeneration associated with anti-Tr and mGluR1 antibodies and diffuse large B-cell lymphoma of stomach. This case further expands the clinical spectrum of malignancies associated with cerebellar degeneration and its associated antibodies.

CASE REPORT
A 57 years old gentleman, who came to the outpatient department of KRL Hospital with complaints of epigastric pain, dyspepsia, weight loss > 10% and generalized weakness for the last 6 months. He had shaky hands, was unable to hold on to things firmly (e.g. a cup of tea) for the past 4 months and had trouble while walking. He had no other systemic symptoms, was non-alcoholic, had no addictions and worked as an office clerk with no occupational hazards identified.

On examination, he was pale. His cardiovascular, respiratory and gastrointestinal examination was unremarkable. On neurological examination, he had scanning speech, bilateral horizontal nystagmus, bilateral past-pointing, bilateral dysdiadochokinesia, dysmetria and intention tremors, bilateral positive heel shin test and a broad based gait. He was unable to perform tandem walk and had ataxia with tendency to fall towards his right side.

His investigations revealed hemoglobin of 98 g/L (with normocytic normochromic anemia), hematocrit of 33% and an ESR of 115 mm in the first hour. His renal and hepatic functions, serum electrolytes, chest X-ray, reticulocyte count, peripheral smear, ultrasound abdomen and coagulation profile were all normal. Magnetic Resonance Imaging (MRI) of brain yielded normal study. A contrast enhanced Computed Tomography (CT) abdomen was done in search of occult malignancy that showed 1.6 cm intramural thickening at lesser curvature of stomach with extension into distal esophagus along with enlarged peri gastric and retro caval lymph nodes; all on one side of the diaphragm. He underwent an upper GI endoscopy which revealed a necrotizing ulcerative fungating mass at the lesser curvature of stomach measuring 5 x 3 cm² in size (Figure 1A and 1B). Upon biopsy, the lesion showed B-cell lymphoma (hematoxylin and eosin stain; 40X) (Figure 1C). On immunohistochemistry, molecular markers were positive for CD-20 and Ki-67 activity was 40%, hence, the diagnosis of diffuse large B-cell
lymphoma was made. His CT chest, CT pelvis, bone scan and bone marrow biopsy were all normal. On Ann Arbor staging with Cotswold modification, the lymphoma was graded as Stage II E (B) denoting involvement of two separate regions on one side of the diaphragm, extranodal extension and systemic symptoms respectively.

His autoimmune profile and colonoscopy were normal. The studies for vitamin levels, trace elements, infections including viral serology, thyroid and parathyroid functions, drugs and occupational toxicity were also unremarkable. As the MRI was normal, signs of cerebellar degeneration were explained with the clinical diagnosis of an associated paraneoplastic syndrome. The diagnosis in entirety was thus concluded as diffuse large B-cell primary lymphoma of stomach with paraneoplastic cerebellar degeneration. On antibody screening, anti-Tr and mGluR1 antibodies were positive. The patient was referred to Oncologist where treatment was started using R-CHOP regime i.e., Rituximab, Cyclophosphamide, Hydroxydaunorubicin, Oncovin (vincristine) and Prednisone. On follow-up, the patient showed significant resolution of gastrointestinal and systemic symptoms but neurological symptoms did not show any remarkable improvement.

**DISCUSSION**

Primary gastric lymphoma is a rare tumor and its frequency is less than 5% among the gastric neoplasms. Although the histological diagnosis is diverse, most of these are either diffuse large B-cell lymphomas or MALT (Mucosa Associated Lymphoid Tissue) lymphomas. Diffuse large B-cell lymphoma is the most common histologic subtype of non-Hodgkin’s lymphoma accounting for approximately 25% of NHL cases.

Patients with DLBCL typically present with a rapidly enlarging symptomatic mass, most usually nodal enlargement in the neck or abdomen. Systemic “B” symptoms (i.e., fever, weight loss, drenching night sweats) are observed in approximately 30% of patients. Incidence varies by ethnicity with Caucasian Americans having higher rates than Blacks, Asians, and American Indian or Alaska Natives, in order of decreasing incidence. Incidence increases with age; the median age at presentation is 64 years for patients as a whole, but appears to be younger for Blacks than for Caucasian Americans. Paraneoplastic neurological syndromes constitute an unusual manifestation of cancer. Paraneoplastic syndromes associated with DLBCL include paraneoplastic pemphigus, limbic encephalitis, necrotizing myelopathy and Guillain Barre syndrome.

Although the pathogenesis of paraneoplastic neurologic syndrome is incompletely understood, immunologic factors are believed to be important because antibody and T-cell responses against nervous system antigens have been described for many of these disorders. The immunologic response is directed against shared antigens that are ectopically expressed by the tumor, but otherwise exclusively expressed by the nervous system. For unknown reasons, the immune system identifies these antigens as foreign and mounts an immune attack against them. One report suggests that the immune system can mount a T-cell response to a normal protein when it is expressed in a cancer cell, suggesting that normal self antigens may be processed differently in cancer cells than in the normal cells. Antibodies can be detected in the serum and cerebrospinal fluid of many, but not all, patients with paraneoplastic syndromes and are highly suggestive of one or a restricted group of syndromes and types of tumors.

Paraneoplastic disorders are more frequent than previously considered, with an incidence that varies with the neurologic syndrome and type of tumor. The more common syndromes are Lambert-Eaton Myasthenic syndrome, which affects approximately 3% of patients with small-cell lung cancer, and myasthenia gravis, which affects 15% of all patients with thymoma. For other solid tumors, the incidence of paraneoplastic neurologic syndromes is far less than 1% in most tumors.

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uncommon for a paraneoplastic disorder to develop before a cancer is identified. The clinical syndrome and identification of certain paraneoplastic antibodies may suggest a specific underlying tumor and direct investigations.1,3 Patients with paraneoplastic cerebellar degeneration may develop signs of atrophy detectable by MRI several months after the onset of symptoms.9,10 The main concern of the clinician should be to rule out other diagnostic entities and to uncover the presence of the associated neoplasm that often remains elusive to detection. In general, the best approach to treat paraneoplastic symptoms is to discover and treat the tumor promptly, and provide supportive care for the neurologic deficits with symptomatic treatment and physical therapy. In a few cases, depending on the syndrome, if the patient is in the early stages of the neurologic disease, treatment with immunosuppression or plasmapheresis may have some effect on the paraneoplastic symptoms.7,9,10

While syndrome of cerebellar degeneration has been identified as a paraneoplastic manifestation of Hodgkin’s lymphoma, thymoma, lung and breast cancer, ovarian and testicular tumors, melanoma, renal cell carcinoma, follicular lymphoma and adenocarcinoma of stomach, its association with NHL and particularly DLBCL has not been established previously to our knowledge and we are the first one to do so. This case not only further expands the clinical spectrum of malignancies associated with paraneoplastic neurological syndromes but also identifies the associated antibodies in the clinical setting of DLBCL.

**REFERENCES**