CASE REPORT

Incomplete Miller–Fisher Syndrome with Advanced Stage Burkitt Lymphoma

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Received: June 17, 2016;
Initial review: November 03, 2016;
Accepted: February 28, 2017.

Background: Lymphoma-associated incomplete Miller-Fisher syndrome is very rare. **Case Characteristics:** An 11-year-old boy who initially presented with headache, left ptosis, diplopia and weakness. Neurologic examination indicated left sided ptosis with ophthalmoplegia. **Observations:** Cerebral imaging and cerebrospinal fluid examinations were normal. Magnetic resonance imaging of the abdomen showed a mass lesion in the ileal loops. A bone marrow biopsy showed infiltration by Burkitt's lymphoma. **Message:** Burkitt lymphoma may present with incomplete Miller Fisher syndrome.

Keywords: *Leukemia, Ophthalmoplegia, Ptosis*.

Paraneoplastic neurological syndromes (PNS) are rare disorders triggered by an altered immune system response to a neoplasm. They are defined as clinical syndromes involving non-metastatic systemic effects that accompany malignant disease [1]. PNS affect less than 0.01% patients with cancer [2]. Small-cell lung cancer, breast cancer and ovarian cancer are the most frequent solid tumors associated wih PNS [3]. Hematological malignancies such as non-Hodgkin lymphoma are rarely accompanied by PNS affecting the central and peripheral nervous systems [1]. There are some reports on the association of non-Hodgkin lymphoma and PNS [2-6], but Miller-Fisher Syndrome (MFS) is extremely rare [6].

CASE REPORT

The patient was an 11-year-old boy who was hospitalized in our emergency department with complaints of headache, left ptosis, diplopia and weakness that started within the previous two days. Neurologic examination indicated unilateral left ptosis with ophthalmoplegia. Fundus examination and deep tendon reflexes were normal. Complete blood count, peripheral blood smear and serum electrolyte results were normal. Serology results for Hepatitis A, B and C; cytomegalovirus; Epstein Barr virus; parvovirus; and human immunudeficiency virus were negative. Chest *X*-ray, cranial magnetic resonance imaging (MRI), cranial magnetic resonance angiography and orbital computed tomography (CT) results were normal. Cerebrospinal fluid (CSF) results were: protein 22 mg/dL, glucose 71 mg/dL, and no malignant cells. Brucella and lyme serology results were negative. The oligoclonal band analysis was negative for multiple sclerosis. CSF paraneoplastic panel (anti-amphiphysin, anti-CV2.1, anti-Ma2/Ta, anti-RI/ANNA-2, anti-Yo/PCA-1, anti-Hu/ANNA-1, anti-RECOVERIN and anti-SOX1 antibodies) results were negative. We planned to administer one dose of 1 g/kg intravenous immunoglobulins (IVIG) in view of initial diagnosis of incomplete MFS. Only 50% of the targeted dose could be administered because patient experienced severe abdominal pain. There was no improvement in ptosis and eye movements. Physical examination showed a 3-4 cm mobile mass in the right lower abdominal quadrant. Lactate dehydrogenase was 1092 U/L and amylase was 496 U/L. An abdominal MRI revealed diffuse pancreatic involvement and a mass lesion of 7×5 cm in the ileal loops at the lower right quadrant (***Fig.* 1**). Lumbar and dorsal MRI revealed involvement in the L3-L4 and T3-T8 vertebral bodies and leptomeningeal dissemination in the spinal cord along the thoracic vertebrae. Fluorodeoxyglucose-positron emission tomography showed intense uptake foci on both humeri, the vertebral column, pelvic bones, and both femurs and proximal tibias, indicating malignant involvement. Bone marrow aspirate revealed lymphoblasts containing cytoplasmic vacuoles at a rate of 30%. A bone marrow biopsy revealed CD20, PAX5, bcl6 and CD34, and TDT-negative infiltration of Burkitt lymphoma in 30% of the bone marrow. Thus, bone marrow involvement in Burkitt lymphoma was confirmed, and a diagnostic of Burkitt leukemia was

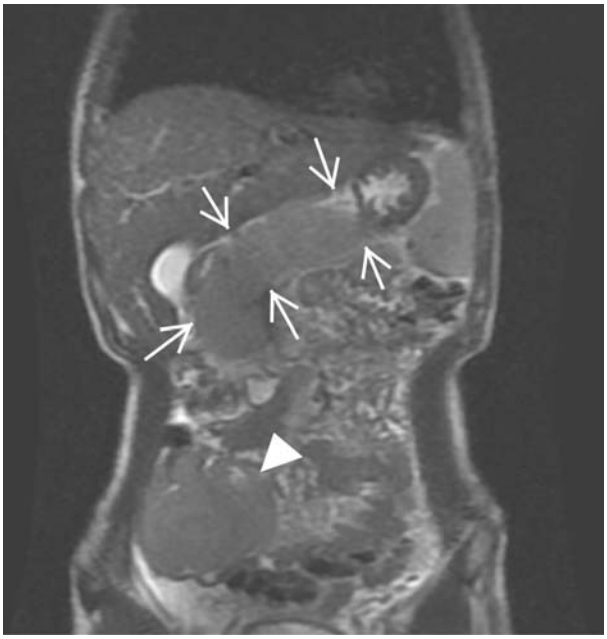

FIG. 1 *Axial abdominal magnetic resonance imaging showing diffuse pancreatic involvement (arrows) and a mass lesion in the ileal loops (arrowhead).*

made. Chemotherapy was started and the patient's symptoms resolved completely after two cycles of chemotherapy (***Fig.* 1b**).

DISCUSSION

MFS is typically characterized by a triad of ataxia, areflexia and ophthalmoplegia, which is considered to be a variant of Guillain Barré Syndrome. The annual incidence of MFS is 0.09 cases/100.000 population [7]. Diplopia is the most common initial symptom in MFS, and it arises because of acute onset of external ophthalmoplegia. Most patients with MFS exhibit bilateral, relatively symmetrical ophthalmoplegia, but the condition can also be unilateral [7]. Although most published reviews define MFS strictly as an acute monophasic illness featuring the clinical triad of ataxia, areflexia and ophthalmoplegia, it can present with only one or two of these features [8]. In our patient, sudden onset ptosis and ophthalmoplegia were consistent with this syndrome.

The differential diagnosis of MFS includes myasthenia gravis, botulism, brainstem stroke, infective conditions (listeriosis, tuberculosis, brucellosis, Lyme disease, herpes simplex virus, Epstein–Barr virus), autoimmune (multiple sclerosis, sarcoidosis, Behçet's disease, systemic lupus erythematosus), malignancy (lymphoma, paraneoplastic syndrome), and basal meningitis [9]. In our patient, extensive diagnostic work-up excluded all other conditions. Several pathogenetic mechanisms of neuropathy associated with lymphoma have been suggested. These include direct invasion of lymphoma cells, metabolic and infectious processes, vascular impairment, and immunological mechanisms as in paraneoplastic neuropathy [10]. MFS in the form of multiple cranial neuropathy, ataxia and areflexia has been reported in patients with B-cell lymphoma [3]. Association of Burkitt lymphoma with GBS and multiple cranial neuropathy is also reported, but in these patients, symptoms could be explained by nerve invasion by the tumor [4,5]. There is an earlier report of in a patient of Burkitt lymphoma who presented with renal and hepatic involvement [6]. In this patient, increased levels of protein, but no antibodies, were found in the CSF [6]. It is not possible to detect antibodies in all patients with paraneoplastic syndrome. As our patient neither had leptomeningeal involvement level nor the imaging examinations could explain the cranial nerve involvement, the possibility of a paraneoplastic syndrome was more likely. Lack of improvement with IVIG and complete resolution after chemotherapy also supported a diagnosis of PNS secondary to malignancy.

In conclusion, children may rarely present with symptoms of PNS secondary to malignancy. In children diagnosed with incomplete MFS, hematological malignancies should be suspected.

Contributors: ÖZC, DKY, BÖ: reviewed the literature and wrote the paper; DKY, ÖZC, YC: collected the data; ÞS: assessed the radiologic finding.
Funding: None; *Competing interest*: None stated.

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