

MILLER FISHER SYNDROME AND CUTANEOUS T-CELL LYMPHOMA

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ABSTRACT

The association between Miller Fisher syndrome (MFS) and non-Hodgkin lymphoma is re-reported in a few cases in the current literature. We report a case of a patient known with Mycosis fungoides – cutaneous T cell lymphoma (CTCL) that developed, after 6 years of illness, a variant of Guillain Barré syndrome – Miller Fisher syndrome. The diagnosis was established based on clinical features and positive antiganglioside antibodies (anti GQ1b and anti GT1a antibodies). The neurological involvement in cutaneous T cell lymphoma has been seldom reported and the mechanism is not completely elucidated.

Keywords: Miller Fisher syndrome (MFS), cutaneous T cell lymphoma (CTCL), Mycosis fungoides, anti-ganglioside antibodies

INTRODUCTION

Mycosis fungoides is a non-Hodgkin's, peripheral T-cell lymphoma of the skin with a wide spectrum of potential clinical manifestations (1). Some histological findings are important and a lymphocytic infiltrate in the superficial dermis might be observed, with lymphocytes migrating among epidermal keratinocytes (epidermotropism) (1-3). Miller Fisher syndrome is a variant of Guillain-Barré syndrome characterized by ataxia, areflexia and ophthalmoplegia; the anti-GQ1b antibodies allows a greater diagnostic certainty (4).

Four cases of lymphoma-associated "atypical" Miller Fisher syndrome were retrieved from the literature (5). The autoimmunity due to oncoantigen may induce misdirected immune targets against epitopes presented in the peripheral nervous system (6,7). This mechanism may be involved in the case described above with cutaneous T-cell lymphoma (*Mycosis fungoides*) and Miller Fisher syndrome.

CASE REPORT

A 68 year old patient came in the emergency department for intermittent double vision, liquids

swallowing problems, dysphonia, weakness and paraesthesias in hand and feet, started one week prior to the presentation.

His past medical history included cutaneous T-cell lymphoma – stage IA *Mycosis fungoides* diagnosed in 2012 based on the following criteria:

1. a 10 year history of multiple pruriginous erythematous plaques on calves and right arm;
2. a cutaneous biopsy (January 2012) revealed epidermic hyperplasia with long dermic papillae; superficial derm lymphoid infiltrate, especially on basal layer, without Pautrier microabscess (pagetoid reticulosis); the lymphoid infiltrate is based on small lymphocytes associated with isolated big cells with irregular nuclear outline;
3. the immunohistochemistry (ICH): positive CD3, CD5, CD4 – diffuse in the major part of the lymphoid population; positive CD20 in rare lymphocytes; positive CD8 in rare lymphocytes with a CD4/CD8 report in the favor of CD4; positive CD30, Ki67 in rare big cells;

The toraco-abdominal CT scan and medullary puncture excluded lymphadenopathies, visceral or medullary involvement.

The patient was diagnosed with IA cutaneous T-cell non-Hodgkin lymphoma / *Mycosis fungoides*

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(table 1, table 2) and he was treated with topical treatment. In 2013 the histopathological and the immunochemistry reexaminations were performed so that a more accurate diagnosis will be made. The cutaneous fragment had a lymphoid proliferation in superficial dermis, with small, medium size and irregular nuclei; the overlying epidermis had sharp epidermal crests, spongiosis and exocytosis with polymorphonuclear leucocytes and vesicles in superficial layers. The immunohistochemistry results were: CD3, CD5, CD4-positive in tumoral lymphoid population, CD20-negative in lymphoid population, positive in reactive B cells, CD8-difficult to interpret, Ki67<10%. Based on clinical, pathologic and molecular feature, the diagnosis of mycosis fungoides was given.

TABLE 1. Original Mycosis fungoides Cooperative Group TNM classification of cutaneous T-cell lymphoma (CTCL) (8)

Classification	Description
T: Skin	T0 Clinically and/or histopathologically suspicious lesions
	T1 Limited plaques, papules, or eczematous patches covering 10% of the skin surface
	T2 Generalized plaques, papules, or erythematous patches covering 10% or more of the skin surface
	T3 Tumors, one or more
	T4 Generalized erythroderma

Classification	Description
N: Lymph nodes	N0 No clinically abnormal peripheral lymph nodes; pathology negative for CTCL
	N1 Clinically abnormal peripheral lymph nodes; pathology negative for CTCL
	N2 No clinically abnormal peripheral lymph nodes; pathology positive for CTCL
	N3 Clinically abnormal peripheral lymph nodes; pathology positive for CTCL
B: Peripheral blood	B0 Atypical circulating cells not present (5%)
	B1 Atypical circulating cells present (5%); record total white blood count and total lymphocyte counts, and number of atypical cells/100 lymphocytes
M: Visceral organs	M0 No visceral organ involvement
	M1 Visceral involvement (must have pathology confirmation and organ involved should be specified)

He was admitted in the Neurology department on may 2018 for the symptoms previously described. On admission in our clinic, his vital signs were normal.

The clinical examination revealed pruriginous hyperpigmented patches and plaques, petechiae on anterior and posterior trunk, tights and calves, right axillary erythematous area, erytemato-scuamous area with keratin crusts on anterior left thigh and right calf (Figure 1).



FIGURE 1. Panel A: Left thigh erythemato-scuamous plaque. Panel B: Anterior erythematous patches on right calf. Panel C: Scuamous hyperkeratotic plaque on the right heel. Panel D-E: Hyperpigmented areas on anterior and lateral trunk.

TABLE 2. The staging system designed by the Committee on Staging and Classification of cutaneous T-cell lymphomas and published by Bunn and Lamberg in 1979 (9)

IA	T1N0M0
IB	T2N0M0
IIA	T1–2N1M0
IIB	T3N0–1M0
IIIA	T4N0M0
IIIB	T4N1M0
IVA	T1–4N2–3M0
IVB	T1–4N0–3M1

No lymphadenopathy or organomegaly could be detected.

The neurologic examination revealed normal cognitive function; the cranial nerve examination revealed bilateral ophthalmoplegia (grade I-II left ptosis, normal pupillary reactions, limited lateral gaze in left eye on abduction, intermittent horizontal diplopia), bulbar nerve palsies (dysphonia and dysphagia for liquids and solids, diminished superior gag reflexes and weakness when the patient opened his mouth to show the palate elevation); coordination was impaired in upper and lower limbs: he had dysmetria bilaterally (more obvious on right) on finger-to-nose testing and heel-to-shin testing; the plantar responses were left Babinski sign and right flexion; Muscle stretch reflexes revealed decreased reflexes in lower limbs; Sensory examination revealed decreased sensation of pin-prick, light touch and vibration in distal feet.

TABLE 3. Laboratory data

Variable	Value	Reference Range Adults
WBC count	7.3*10 ³ /mmc	4-9*10 ³ /mmc
RBC count	4.42*10 ³ /mmc	4-4.5*10 ³ /mmc
Platelet count	290*10 ³ /mmc	150-400*10 ³ /mmc
Mean corpuscular volume	95 fL	80-100 fL
Hemoglobin	13.5 g/dl	12-16 g/dl
CHEM	32.4 g/dl	32-36 g/dl
ESR	10 mm/1 h	<20 mm/h
Creatinin	0.78 mg/dl	0.5-1.2 mg/dl
Alkaline phosphatase	45 U/l	42-98 U/l
AST	16 U/l	0-31 U/l
ALP	31 U/l	0-34 U/l
Gamma Glutamyl Transferase	10 U/l	0-38 U/l
Lactic dehydrogenase	344 U/l	120-246 U/l
Total Bilirubin	2.13 mg/dl	0.05 -1.2 mg/dl
Fibrinogen	319 mg/dl	180-350 mg/dl

INVESTIGATIONS AND DIFFERENTIAL DIAGNOSIS

The laboratory data revealed a normal cell blood count, increased lactic dehydrogenase and increased total bilirubin (Table 3).

The cerebral MRI excluded secondary lesions associated with Non-Hodgkin Lymphoma like meningeal infiltration of malignant cells (these are rarely cited in the literature). To exclude a paraneoplastic syndrome there were performed anti-neuronal antibodies (Amphiphysin, CV2, PNMA2, Ri, Yo, Hu, Recoverin, SOX1, Titin) – with a negative result.

A lumbar puncture was proposed, but the patient refused it.

We suspected a Lambert-Eaton syndrome evolving in the non-Hodgkin lymphoma. The electrodiagnostic tests confirmed an axonal sensitive polyneuropathy. The anti-calcium channel antibodies type N and PQ were negative.

Another hypothesis was CANOMAD syndrome (Chronic Ataxic Neuropathy Ophthalmoplegia M-protein Agglutination Disialosyl antibodies syndrome). The seric protein electrophoresis revealed the absence of monoclonal IgG/ IgA/ IgM/ kappa, lambda chains; the direct Coombs test was negative.

The anti-ganglioside (Ig G/Ig M) antibodies were positive for anti-GQ1B and anti-GT1A (Table 4). These autoantibodies are associated with Miller Fisher syndrome – sensitivity > 90%, specificity > 90%.

The patient had an excellent response to corticosteroids. He was directed to oncology for reexamination and disease staging.

TABLE 4. The anti-ganglioside antibodies

Anti-ganglioside antibodies (Ig G/ Ig M)	
Anti-GM1, Anti-GM2, Anti-GM3, Anti-GM4	Negative
Anti-GD1a	Negative
Anti-GD1b	Negative
Anti-GD2, Anti-GD3	Negative
Anti- GT1a	Positive
Anti- GT1b	Negative
Anti-GQ1b	Positive

DISCUSSIONS

There are 4 cases in the literature with the association between Miller Fisher syndrome and lym-

phoma: 1 – Mixed cellularity Hodgkin lymphoma (10), 2 – Burkitt’s lymphoma (11), 3 – B-cell chronic lymphocytic leukemia (12), 4 – diffuse large B-cell lymphoma (13). The temporal correlations were: in the first case the MFS appearance was in the second relapse of the lymphoma (10); in the second case the MFS was in the same time with the discovery of the lymphoma in a renal transplant recipient on anti-rejection therapy (11); in the third case the onset of MFS was during chemotherapy in a chronic lymphocytic leukemia (12); in the fourth case the evaluation of a recurrent MFS detected lymphoma (13). The first case was associated with an elevated serum anti-GQ1b antibody titre (useful supportive evidence for MFS) and 3 patients showed only elevated protein concentrations. The electrodiagnostic tests were interpreted as: axonal sensory polyneuropathy (10); axonal sensorimotor polyneuropathy (11,12), sensorimotor demyelinating polyradiculoneuropathy (13). The responses to treatment were different: 1st, 3rd, 4th patient responded to immunomodulating therapy; the 2nd patient was unresponsive to immunomodulating therapy but had an improvement to systemic therapy for lymphoma. The 4th patient showed neurological improvement to a combined systemic/intrathecal chemotherapy regimen (13). This fact was interpreted as evidence of a “paraneoplastic” pathogenesis (the production of a specific antibody against an antigen of malignant cells that cross-reacts with an antigen of normal neurological tissue) (5).

The malignant cells in *Mycosis fungoides* are able to reside in the skin through complicated immune mechanisms. These cells express E-selectin and migrate along endothelial cells. Chemokine receptors from T cells (chemokine receptor 4) recognize chemokines from epidermis (chemokine ligand 17) and bound to the luminal side of endothelial cells. The next step is the extravasation into dermis; the lymphoma cells are clustering

around Langerhans cells, forming Pautrier’s microabscesses (1).

The autoimmune mechanisms in non-Hodgkin lymphoma could be represented by oncoantigens inducing misdirected immune targets against epitopes from peripheral nervous system (14). The axonal neuropathy may be also secondary to an epineurial and endoneurial infiltration by malignant cells.

Due to the fact that patients had a neurological improvement after systemic chemotherapy, we reinforce the idea that specific antibodies against antigens of the malignant cells cross-react with parts of neuronal components (13).

In our case, we noticed a significant improvement of the neurologic symptoms after corticosteroids. This recovery of these symptoms after the therapy suggests an immune-mediated mechanism of the disease that may be assumed with a breakdown of the blood-nerve barrier and immune mediated inflammation (15).

CONCLUSIONS

Patients with non-Hodgkin’s lymphoma may develop inflammatory, autoimmune conditions such as brachial plexopathy, Guillain–Barré syndrome, CIDP (16) or Miller Fisher syndrome, like in our case. There are many theories about the pathogenesis of the peripheral nervous system and lymphoma: invasion of tumoral cells, metabolic processes, vascular impairment, immunologic mechanisms including paraneoplastic neuropathy (17,18).

In our case, the neurologic complication occurred in the remission of the lymphoma and we detailed above a probable immune mediated mechanism. In this case, the improvement after corticosteroids sustains the immunologic involvement.

Future perspectives are directed to the identification of the cellular mechanisms and the use of molecular antagonists in therapies.

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