

Mantle cell lymphoma and systemic sclerosis

Marto G¹, Aguiar R², Barcelos A²

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ABSTRACT

Systemic sclerosis (SSc) is a rare disease with an increased incidence of cancer, but the occurrence of Non-Hodgkin lymphoma (NHL) is a very uncommon event. We report a case of a 76-year-old female admitted to the hematology clinic with long-term adenopathies and occasional gastro-intestinal symptomatology. Progressive symmetrical swelling of hands was also noticed. Colonoscopy revealed multiple polyps and histopathology was consistent with Mantle-Cell Lymphoma (MCL)-NHL. R-CHOP (rituximab, cyclophosphamide, doxorubicine, vincristine and prednisone) regimen was promptly initiated with complete response. Persistent swelling of both hands was observed, with thickening of the skin of both hands with proximal extension until the forearm. Biopsy confirmed the diagnosis of scleroderma. Symptomatic and rehabilitation treatment was initiated with mild improvement of symptoms. To our knowledge this is the first case of MCL associated with SSc.

Keywords: Mantle cell lymphoma; Systemic sclerosis; Non-Hodgkin lymphoma.

INTRODUCTION

Autoimmune-inflammatory systemic diseases, including rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, dermatomyositis and SSc have an increased incidence of solid tumors, but also lymphoproliferative disorders¹. SSc is a chronic multisystemic autoimmune disorder characterized by fibrosis and vascular abnormalities on both skin and internal organs. The increased risk of malignancy in patients with SSc has already been described², but the cause is not fully understood. Immunossuppressive agents³⁻⁵, paraneoplastic phenomena^{6,7} and chronic B-cell stimulation⁸ were linked to the biopathogenesis of cancer in SSc.

The most common malignancies noted are lung, breast and gastrointestinal cancers⁹. The occurrence of lymphoma is a rare event, with less than 50 cases reported, although a study found an increased incidence of these lymphomas associated with the disease¹⁰. Many subtypes of NHL were described but to our knowledge there has been no report of MCL.

CASE REPORT

A 76-year-old female was admitted to the hematology clinic due to recent unintended weight loss of 6 kilograms and occasional night sudoresis. She had a 4-year history of multiple adenopathies, which had recently become painful and with progressive enlargement, and occasional gastro-intestinal symptoms namely abdominal pain, diarrhea and rectorrhagia in the past 6 years. She also reported a progressive, symmetrical and mild swelling of hands and feet in the past year. Her medical history was positive for hypertension, dyslipidemia and gastritis. At examination, she presented multiple adenopathies – submandibular, cervical, supraclavicular, axillary, epitrochlear and inguinal, the greater on the left axilla, with 10 cm. No palpable masses or any organomegaly were noticed on abdominal evaluation and rectal examination showed no masses or blood. The laboratory tests revealed a normal hemogram; erythrocyte sedimentation rate of 64 mm at first hour; normal liver and renal function; lactic dehydrogenase 208 U/L (normal < 190 U/L); C-reactive protein 5.61 mg/dL; protein electrophoresis with elevation of alpha 2 and gamma globulins; β 2 microglobulin 6740 ng/mL (normal range 1100-2300 ng/mL). Colonoscopy demonstrated multiple polyps, particularly distal to the splenic angle of the colon; ileocecal valve was engorged, with a pseudopolypoid aspect, seeming affected by an expansive process. Histopathological examination showed a lymphoproliferative disease with small/medium-sized lymphoid cells, with irregular and hyperchromatic nucleus, without nucleolus and scarce cytoplasm. Immunohistochemical study of the polyps and ileocecal valve revealed positivity to CD20,

1. Serviço de Medicina Interna, Centro Hospitalar Baixo Vouga, EPE, Aveiro

2. Serviço de Reumatologia, Centro Hospitalar Baixo Vouga, EPE, Aveiro

blc2, CD43, CD79a and D1 cyclin, consistent with the diagnosis of a MCL-NHL of the colon (Figures 1 and 2). Upper gastrointestinal endoscopy showed erosive bulbitis. Toracoabdominopelvic computed tomography (CT) demonstrated multiple adenopathies: paratracheal, bilateral axilar, celiac trunk, para-aortic and intercavaoortic. The biopsy of an axillary lymph node was consistent with the same diagnosis, with a Ki67 of 50%. The flux cytometry of bone marrow showed no monoclonality of B-lymphocytes, with a normal immunologic phenotype. The diagnosis of a IIIB-staged Mipi 7.5 (high-risk) MCL-NHL was therefore established and the patient started a R-CHOP regimen (rituximab, cyclophosphamide, doxorubicine, vincristine and prednisone). After 6 cycles, she achieved a completed response. NHL-related symptoms dramatically improved, but bilateral hand swelling was still present. The patient was referred to the dermatology clinic. Physical examination revealed thickening of the skin in both hands with proximal extension up to the forearm, without skin ulcers. Histopathological analysis of a biopsy of the skin confirmed the diagnosis of scleroderma. The autoimmunity study showed a strongly positive test for antinuclear antibodies (ANA) (>1/1260 IU with a centromeric pattern) and anti-centromere antibodies (>1/640 IU) with negative anti-scl 70 antibodies. The patient was started on pentoxifylline and referred to the rheumatology clinic. In a more exhaustive inquiring, the patient confirmed she had Raynaud phenomena triggered by cold exposition on her hands and feet with 2 years duration. The sclerodactily was quite painful and caused functional limitation. Moreover, she also had recent onset of non-se-

lective dysphagia. She denied dyspnoea, cough, digital ulcers or any other symptoms. Physical examination revealed tight, shiny and atrophic skin over the face and fingers and face telangiectasias. There was no calcinosis. Nifedipine was added and physiotherapy was started. The patient didn't tolerate nifedipine due to dizziness and headache, but the hand pain relieved with physiotherapy. Chest high resolution CT didn't revealed pulmonary fibrosis. Lung function tests (DLCO, spirometry, vital capacity) were inconclusive due to lack of collaboration. Transthoracic echocardiography revealed mild left ventricular hypertrophy, preserved systolic function, impaired relaxing diastolic pattern and an estimated pulmonary systolic arterial pressure of 41 mmHg. The patient refused any further investigation. After three years of follow-up, the patient is stable, with sustained remission of the lymphoma and no new symptoms related to systemic sclerosis.

DISCUSSION

MCL was known like as an indolent variant of mature B-cell NHL¹¹, but it often behaves as an aggressive form, requiring treatment at presentation. MCL was previously referred to as mantle zone lymphoma, centrocytic lymphoma, intermediate lymphocytic lymphoma or lymphocytic lymphoma of intermediate differentiation¹². Incidence increases with age, with a median age of 68 years at diagnosis. Approximately 75 percent of affected individuals are male and IT is more common in caucasians than in afro-americans¹³. The

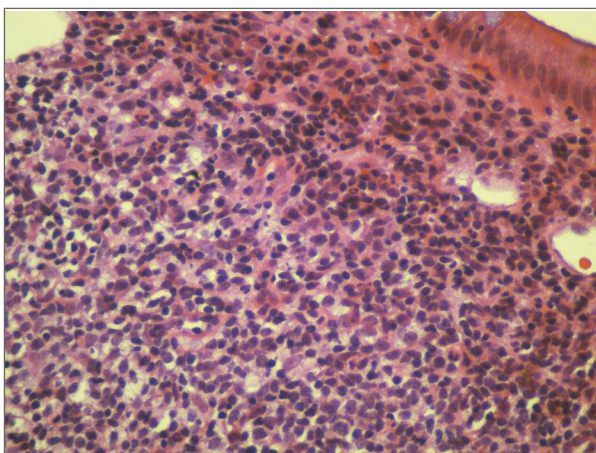


FIGURE 1. H & E (400x): Biopsy of colon showing diffuse proliferation of small/medium-sized lymphoid cells

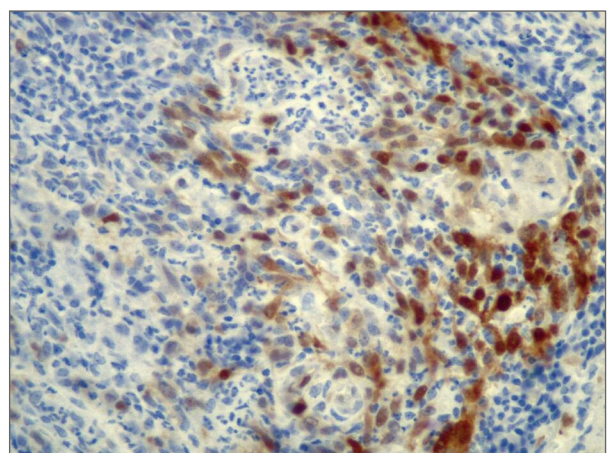


FIGURE 2. H & CyclinD1 (400x): Biopsy of colon showing intense reactivity for CyclinD1

majority of patients present with advanced stage disease. The primary presentation is often lymphadenopathy (75%), with the remaining presenting initially with extranodal disease¹⁴. MCL can involve any region of the gastrointestinal tract, with a colic involvement of 90 percent of cases, usually with polyps found in colon and small bowel¹⁵, as we found in our case. Histologically, the pattern may be diffuse, nodular, mantle zone, or a combination of the three and tumor cells are usually small to medium-sized B lymphocytes with irregular nuclei, typically CD5+ and CD23-, with nuclear staining cyclin D1 present in more than 90 percent of cases. The majority of MCL cases are believed to derive from naïve pre-germinal centre B cells of the mantle zone, and a minority from marginal zone or peripheral blood memory B cells. All patients with MCL demonstrate increased cell division and replication. Overexpression of the cyclin D1 gene is present in most cases¹⁶, while a minority is thought to overexpress other cell cycle mediators, like cyclin D2 and D3. Most patients will require treatment of MCL at the moment of diagnosis, but there is a small subset of patients with a more indolent course who won't. Chemoimmunotherapy remains the main treatment modality. R-CHOP and R-CVP (cyclophosphamide, vincristine, prednisone plus rituximab) are the preferred treatments. Intensive chemoimmunotherapy R-Hyper-CVAD (rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) and off-label BR (bendamustine and rituximab) are alternative treatments, occasionally employed. The course and prognosis of MCL are variable, with median overall survival between three to four years. MIPI (Mantle Cell Lymphoma International Prognostic Index), IPI (International Prognostic Index) and FLIPI (Follicular Lymphoma International Prognostic Index) are examples of prognosis indexes that were developed in the last years, with evidence showing that FLIPI gathers better prognostic information¹⁷. Recently, Ki-67 staining, a cellular marker of proliferation was associated with a worse prognosis¹⁸.

The prevalence of malignant neoplasia in SSc is estimated between 3.6% to 10.7% and identified risk factors for malignancy are old age, female gender and diffuse skin involvement². Malignancy in SSc may coincide with the diagnosis or may be a consequence of treatment for it or another condition.

Lung and breast cancer remain the most frequently reported types of malignancy, followed by gastrointestinal cancers². There is a close relationship between scleroderma-related abnormalities of esophageal motility, the development of Barrett metaplasia and the sub-

sequent development of adenocarcinoma of the esophagus^{19,20}. There is no clear explanations at the moment for the frequency of lymphomas and hematological malignancies in patients with SSc. It has been suggested that it may be incidental or secondary to an emergence of a malignant clone from a pool of polyclonal chronically stimulated B-cells²¹, deficiency of T and NK cells²¹⁻²³, or common genetic background that predisposes to both disorders, like the HLA-DR5 haplotype²⁴.

Recently, a systematic review of all cases of NHL reported in association with SSc was published by Vettori et al²⁵. The T-cells NHL were angioimmunoblastic and diffuse large cell subtypes. Subtypes of NHL were all of the B-cell type and included chronic lymphocytic leukemia¹⁰, mucosa-associated lymphoid tissue-type (MALT)^{26,27}, *Helicobacter pylori* associated MALT²⁸, small lymphocytic follicular¹⁰, diffuse large cell^{29,8}, Pinkus variant of skin and muscle³⁰ and intermediate lymphocytic³¹. More recently, was described a case report of a small lymphocytic lymphoma in a patient with CREST syndrome was described³².

Raynaud's phenomenon and scleroderma-like syndrome may occasionally be a paraneoplastic rheumatic disease³³. While several studies³⁴ have demonstrated an increased frequency of lung, esophageal and breast cancer in patients with scleroderma, there are only a few observations of scleroderma-like syndrome preceding the manifestation of cancer. Very little is known about potential mechanisms underlying this connection³⁵.

Several mechanisms could explain the relationship between malignancy and scleroderma. For example: multiple chemotherapeutic agents have been implicated as potential causes of scleroderma-like disease or severe Raynaud's phenomena³⁶, radiation therapy may cause localized scleroderma in patients without a prior history of connective tissue disease³⁷.

In the other hand, lymphoproliferative diseases are one of the most common group of disorders associated with autoimmune disturbances³⁸. The presence of ANA in patients with NHL isn't an uncommon phenomena since in the past, a significant incidence of ANA was demonstrated before any treatment in NHL patients. Specifically, ANA directed against mitotic-associated or mitotic apparatus proteins have been found in the sera of patients with MCL³⁹. Nevertheless, its significance or prognostic importance isn't established.

In this particular case, the patient had a close temporal relationship between cancer diagnosis and systemic sclerosis clinical onset, which raises the possibility that the presence of one disease may be implicated

in the subsequent development of the second or may influence the behaviour of the second pathology.

To our knowledge, this is the first case report of MCL associated with SSc. Older age and female gender were known risk factors present in our case. Our patient didn't seek medical care until severe symptomatology related to lymphoma developed. We postulate that a humoral or cell mediated immune process initiated by the lymphoma was responsible for the development of SSc in our patient.

In conclusion, patients with SSc probably need close vigilance for symptoms suggestive of malignancy. At the same time, the clinicians should further investigate concomitant symptoms not related with LNH (such as Raynaud phenomena) and/or their treatment, particularly if persistent after complete remission of the disease.

CORRESPONDENCE TO

Gonçalo Marto
Rua dos Arcos, nº 10
2660-130 Santo Antão do Tojal
Portugal
E-mail: marto.goncalo@gmail.com

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