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CASE REPORT

Case Report of a Relapse of Mantle Cell Lymphoma on Patient with Chronic Infection with Covid-19

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ABSTRACT:

Background: Mantle cell lymphoma (MCL) is a distinct subtype of Non-Hodgkin Lymphoma (NHL), it affects 5 to 8% of NHL, it is a clinically heterogeneous disease occurring within a heterogeneous patient population. The median age at time of diagnosis is over 65 years old. The incidence increased with age, and also affects man more than women with ratio of 3 to 1. Overall survivor is different according to subtype of lymphoma. Most patients present at advanced stage, and 30% present in leukemic phase.

Case report: We report a case of 60-year-old women with relapsed mantle cell lymphoma. The patient had no medical past history. The diagnosis of mantle cell lymphoma was made in 2019 revealed by anemic syndrome, the morphological and histological study of lymph node and bone marrow biopsy confirmed the mantle cell lymphoma with expression of CD19+, CD20+, CD5+, CD23-, Cyclin D1+, and KI 67 at 60%. The PET Scan showed FDG-avid disease, the laboratory studies remarques for high level of LDH, elevated B2 microglobulin. The patient underwent R-DHAP regimen (Rituximab, Aracytine, Cisplatin, prednisone) and achieved complete remission after 2 curses, the PET Scan was negative, and the bone marrow biopsy was normal, the collect of hematopoietic stem cell was performed, and the patients received 2 other courses of RDHAP regimen. She does not benefit from autologous hematopoietic stem cell transplant (HSCT) because of severe infection of COVID19. In reality, patient had a server pneumoniae with chronic fever, she was admitted for intravenous antibiotics, all biological exam showed a high level of C- reactive protein, and high level of d-dimers, but no sign of relapse was found. The patient still febrile during 6 months. Autologous hematopoietic stem cell transplant was not realized, but she received maintenance treatment with Rituximab. One year later, the patient developed a mass under the knee with deep deterioration of general condition, relapse was suspected, the surgical biopsy was performed and histological study confirmed the relapse of mantle cell lymphoma. The aim of this case report is to describe the difficulties to manage mantle cell lymphoma associated to covid 19 infection and report the consequences of therapeutic decision.

Conclusion: Not all mantle cell lymphoma is the same, it is crucial to identify patients appropriate for aggressive treatment, autologous hematopoietic stem cell transplant improves event free survival with unclear benefit in all patients, maintenance Rituximab improves overall survivor. Minimal residual disease may guide future therapeutic decisions and help physicians manage these patients. Our patient does not receive autologous hematopoietic stem cell transplant and suffers from chronic Covid19 infection. This association is complicated for the physician and the difficulties of access to targeted therapy in our country limits the therapeutic proposals for patients in relapse.

Key words: mantle cell lymphoma, chemotherapy, immunotherapy, covid 19 infection

Introduction:

Mantle cell lymphoma (MCL) is a rare and heterogenous lymphoma, occurring 5 to 8% of Non-Hodgkin Lymphoma (NHL), it's characterized by involvement of the lymph nodes, spleen, blood and bone marrow. 1 It affects elderly patients, the incidence increased with age, and also affects man more than women with ratio of 3 to 1. [2,3]

The epidemiological risk factors linked to the disease are not completely identified, the data suggesting hereditary and exogenous triggers linked to the development of this malignancy. [4,5] Overall survivor is different according to subtype of MCL. Most patients present at advanced stage, and 30% present in leukemic phase. In the last few years, major advances in our understanding of the pathobiology, prognostication, and therapeutic options in mantle cell lymphoma have taken place. The therapeutic options in MCL are constantly evolving, with dramatic responses from nonchemotherapeutic agents (Ibrutinib, Acalabrutinib, and Venetoclax).

Mantle cell lymphoma remains incurable and challenging disease, through this case report we will discuss different aspects of MCL like disease transformation, impact of positron emission tomography-computerized tomography imaging, and optimal management of patients who progress after first line treatment.

On the other hand, over the past few years, our lives have been deeply impacted by the Sars-Cov2 pandemic. The management of patients with haematological malignancies was not easy. In fact, this unprecedented situation makes therapeutic decision very complicated and it was a real challenge for each patient to decide the appropriate regimen according to risk factor. Infected patients experienced major disruptions in their care pathway with significant consequences for some of them. The aim of this case is to report a delicate situation of a patient treated for a mantle cell lymphoma and massively infected by Covid 19 with persistent fever for several months which impacted our therapeutic strategy.

Case report:

We report a case of 60-year-old women with no medical past history neither comorbid condition. She presented (in 2019) with 4-month history of anemic syndrome, with cervical lymph nodes associated with fatigue, weight loss, and night sweats.

Clinical assessment found 2 lymph nodes, the first was about a left submaxillary adenopathy measuring 2 cm, the second one concerned left axillary adenopathy of 1 cm without inflammation signs. The rest of the physical examination was unremarkable.

The laboratory studies remarques the presence of moderate anemia with hemoglobin level at 9 g/dl, high level of LDH (1500 mg), elevated B2 microglobulin.

A computed tomography scan of the neck, chest, abdomen, and pelvis revealed multiples enlarged lymph nodes. The biopsy of one of them showed infiltration by small to medium-sized lymphoid cells with irregular nuclear contours and prominent nucleoli. The Immunohistochemistry study of biopsy confirmed the diagnosis of the mantle cell lymphoma with expression of CD19+, CD20+, CD5+, CD23-, Cyclin D1+, KI67= 60%.

The Patient underwent a bone marrow biopsy, which was positive for involvement by lymphoma. The patient underwent a full staging workup including positron emission tomography (PET) that showed FDG-avid disease with multiple confluent hypermetabolic nodules with an SUV of 15, and left axillary lymph node with an SUV of 9.7. Complete biological assessment including blood count, renal and liver functions, serum electrolytes, were performed.

She was staged as stage IVB based on the lymph node and bone marrow involvement with elevated level of LDH.

The patient was started on combination chemotherapy with R-DHAP regimen (Rituximab, Aracytine, Cisplatin, and Prednisone) and achieved complete remission after 2 curses, the PET Scan was negative, and the bone marrow biopsy was normal. The collect of hematopoietic stem cell was performed, and the patients received 2 other courses of R-DHAP regimen. She does not benefit from autologous hematopoietic stem cell transplant (HSCT) because of severe infection of COVID19.

In reality, patient had a server pneumoniae with chronic fever, she was admitted for intravenous antibiotics. Biological exam showed a high level of C reactive protein, and high level of d-dimers, but no sign of relapse was found. The patient still febrile during 9 months, with sever pneumoniae which was resistant to many classes of antibiotics. The chest CT scan showed diffuse interstitial lung involvement. HSCT was not realized, but she received maintenance treatment with Rituximab.

The patient remained in complete remission for 1 year but unfortunately developed a relapse in the form of a new mass under the knee with deep deterioration of general condition. The surgical biopsy was performed and histological study confirmed the relapse of MCL. Figure 1,2.

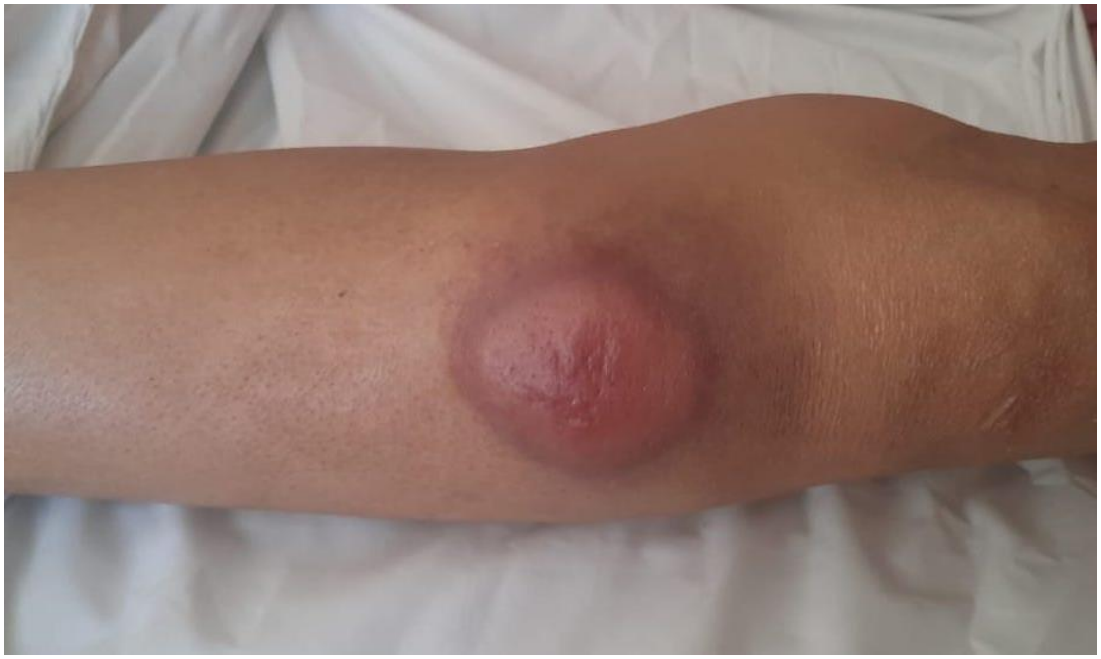

Figure 1: The mass under the knee

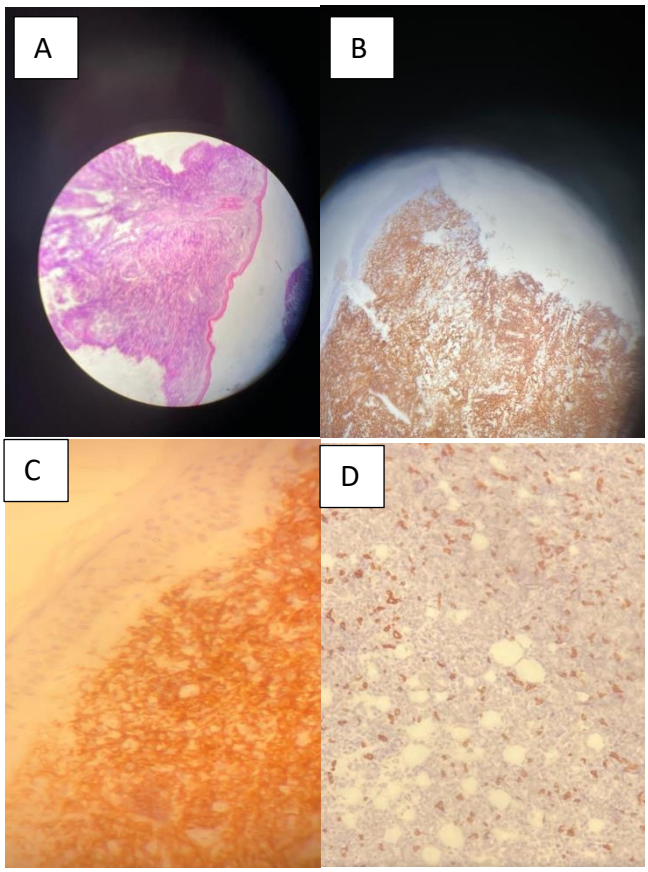

Figure 2:
A: Cellular infiltrate of high density at the level of the farm along its entire height HÈ (GX40)
B: Diffuse expression of CD 20 (Gx40)
C: Diffuse expression of CD5 (GX100)
D: Expression of CD 3 by reactive lymphocyte (GX40)

The patient could not have target therapy with Ibrutinib, so she received salvage chemotherapy with R-BENDAMUSTIN regimen, and achieved partial remission after 2 courses. However, she eventually developed progressive disease and passed away 2 years after the initial diagnosis.

Discussion:

Mantle cell lymphoma is a type of non-Hodgkin's lymphoma that typically arises from the outer edge, or mantle zone of the lymph nodes. It's usually presents in older patients, with the median age at time of diagnosis at 65 years old, and it affects men more often than women, but our case is about a woman.

As our patient presented, the most common symptom is swilling of the lymph nodes, particularly in the neck, armpits. Other symptoms may be present like fatigue, weight loss or night sweats and fever and our patient reported all those symptoms. [2,3]

The exact pathogenesis of MCL is not fully understood, but it involves several known genetic and molecular abnormalities, which have been shown to contribute to the genesis of lymphoma. Mantle cell lymphoma pathogenesis is largely mediated by aberrant cell cycle regulation, DNA damage response, molecular and genomic alterations, B cell antigen receptor (BCR) signaling, and inter- actions with the lymphoid tissue microenvironment. A combination of these factors forms the basis of MCL cell growth. The Cyclin D1 takes an important place on lymphoma development, the Cyclin D1 overexpression is a key event in MCL pathogenesis in the naïve pregerminal-center B cells, and it is largely associated with a translocation t [11;14] (q13; q32). [6,7]

Mantle cell lymphoma cells also exhibit other genetic abnormalities, including mutations in the tumor suppressor gene p53 and the DNA damage response pathway genes ATM and/or TP53. These mutations can lead to further genomic instability and contribute to the aggressive behavior of MCL. [8]

Currently, practiced prognostic factors is based on the MIPI risk score (Mantle Celle Lymphoma International Prognostic Index) and simplified MIPI score including: performance status, age, LDH levels > upper limit of normal, and white blood cell count. This score divides the patients into low-, intermediate-, and high-risk categories. [9]

For our patient, the mantle cell lymphoma was diagnosed by lymph node and bone marrow biopsy with expression of cyclin D1 by tumoral cell, she was scored as high risk by MIPI risk score (6.6 point) and treated by R-DHAP regimen. Complete remission was confirmed by the PET scan and the negativity of the bone marrow biopsy performed after chemotherapy, but the intensification was not performed because of the covid 19 infection. The fever persists for a long time and biological markers like C-reactive protein and D-dimers still high for a long time. The therapeutic strategy was deeply impacted for our patient and the real challenge was to obtain apyrexia. In fact, covid 19 infection causes immunodepression which represents a real threat for patients with cancer and it has been documented for several cancers worldwide that covid 19 infections is responsible for higher mortality rate. [10] This immunosuppression is all the more serious when it occurs in patients treated for hematological malignancy especially lymphoma; this can be explained by the fact that the malignant transformation in lymphoma affects immunocompetent cells themselves and/or can be secondary to cancer treatments targeting the immune system. [11,12]

For our patient, autologous stem cell transplantation was deferred because covid 19 infection and the failure to use of several classes of antibiotics. The persistence of the pulmonary lesions and the fever made the therapeutic decision delicate. Despite the certainty that this patient had received insufficient treatment, the pandemic disrupted the reasoning and the risk-benefit balance was not balanced. The relapse was aggressive with many localizations, the patient could not get Ibrutinib. Consequently R-Bendamustin was proposed with short response and the patient dies. Despite the data reported in the literature on the effectiveness of targeted therapy in mantle cell lymphoma, access to this therapy remains very limited in our country.

Effectively, several studies have focused on mutational dynamics and clonal evolution on Bruton's tyrosine kinase (BTK) inhibitors (Ibrutinib, Acalabrutinib) and/or Bcl2 antagonists (Venetoclax) have demonstrated the prognostic impact of somatic mutations in TP53, BIRC3, CDKN2A, MAP3K14, NOTCH2, NSD2, and SMARCA4 genes. [13, 14] In therapy, the long-term follow-up of chemo-immunotherapy studies has proven the possibility of obtaining lasting remissions in certain patients; however, the accessibility of those treatment is still very limited on out-come countries.

Conclusion

Overall, the prognosis for mantle cell lymphoma is generally poor, with a median survival time of around 4 to 5 years. However, new treatments including targeted therapies have shown promise in improving outcomes for some patients. Unfortunately, access to these drugs is not always easy in our context.

on the other hand, through this case we highlight the difficulties encountered during the covid 19 pandemic in making therapeutic decisions. in fact, the covid 19 pandemic has disrupted treatment decisions in patients but reminded that infectious complications are among the most important causes of adverse outcomes in patients with hematological malignancies.

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