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(CASE REPORT)

Mantle cell lymphoma with skin involvement: Case report of a rare manifestation in a patient with initial diagnosis of chronic lymphocytic leukemia

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Abstract

Mantle cell lymphoma is a rare subtype of B-cell non-Hodgkin's lymphoma, which mainly affects males. It has a variable clinical presentation, with a course ranging from indolent cases that do not require treatment for years to very aggressive cases. Skin involvement is a rare event. Although most patients have disease in stage III or IV at diagnosis, they generally present with good functional status. In immunohistochemistry, CD5 is commonly expressed, a feature it shares with chronic lymphocytic leukemia. Cyclin D1 and SOX11 expression are present in almost all cases. Treatment depends on multiple factors such as age, frailty, comorbidities, disease stage, symptoms and morphological characteristics. We present the case of a male patient initially diagnosed with chronic lymphocytic leukemia who was started on treatment with ibrutinib. A biopsy of the right earlobe was subsequently performed, which documented secondary skin involvement due to a classic histological variant of mantle cell lymphoma. The patient was treated with chemotherapy between March and July 2022, with positron emission tomography at the end of the proposed cycles with complete metabolic response, so maintenance treatment with rituximab was performed and subsequently consolidated with an autologous bone marrow transplant. To date, the patient is in remission of the disease.

Keywords: Mantle cell lymphoma; Chronic lymphocytic leukemia; Immunohistochemistry; Chemotherapy; Transplantation

1 Introduction

Mantle cell lymphoma (MCL) is a rare subtype of B-cell non-Hodgkin lymphomas and accounts for approximately 3% to 10% of all non-Hodgkin lymphomas. The average age of patients at diagnosis is between 60 and 70 years, with a higher incidence in males, reaching 70% of all cases [1,2]. The development of the disease is the result of a complex pathogenic interaction between cellular and microenvironmental processes. The genetic hallmark of MCL and considered the main oncogenic event in the pathogenesis is the chromosomal translocation t(11;14) (q13;q32), which leads to overexpression of cyclin D1 and deregulation of the cell cycle in the G1-S phase transition, stimulating uncontrolled cell proliferation [3]. In almost all cases, tumor cells overexpress cyclin D1, SOX11 (a transcription factor that is not normally expressed in B cells and that influences the expression of several genes involved in cell survival) and Bcl-2 (an anti-apoptosis protein). There is also expression of CD5, a characteristic shared with chronic lymphocytic leukemia that can cause confusion when establishing the diagnosis. Cytological subtypes include classical mantle cell lymphoma, blastoid subtype, and pleomorphic subtype [1]. In the 2022 update of the ICC/WHO (International Consensus Classification/World Health Organization) on lymphoid malignancies, MCL was subdivided into two distinct categories: A nodal one (80-90% of cases) characterized by unmutated immunoglobulin heavy chain variable region (IGHV) genes, SOX11 overexpression, and generally more aggressive clinical behavior. The non-nodal leukemic variant (10% to 20% of cases) usually shows mutated IGHV, SOX11 negativity, and presents with indolent biological behavior [4].

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In general, the disease is clinically characterized by its heterogeneous behavior with courses ranging from indolent cases that do not require treatment for years to very aggressive cases with a very limited prognosis [5]. Patients usually present lymphadenopathy in several sites, with the diagnosis being made in the majority at an advanced stage. Extranodal manifestations occur in 90% of patients, including infiltration of the bone marrow (53%-82%), blood (50%), liver (25%), and gastrointestinal tract (20%-60%). Splenomegaly is also documented in 40% of patients [6]. Despite this, most have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 (scale of 0 to 5, with higher numbers reflecting greater disability) [1]. Skin involvement is a rare event (1%), although it represents a frequently involved site in the blastoid variant. In the staging evaluation, patients who present with cutaneous involvement also have systemic disease, whereas cutaneous presentation without systemic involvement is a very rare event [7].

MCL is staged using either the Ann Arbor classification or the Lugano classification. When routine positron emission tomography (PET) scans are incorporated, at least 80% of patients have stage III or IV disease at diagnosis. The International Prognostic Index (IPI) predicts the outcome of MCL. The mantle cell lymphoma international prognostic index (MIPI) and the simplified MIPI have been developed specifically for this type of lymphoma [1].

A subgroup of patients does not require immediate treatment and can be observed safely ("watch and wait"). Those who present with splenomegaly, bone marrow involvement, and circulating lymphoma cells but no lymphadenopathy are usually asymptomatic and often do not require immediate treatment [8]. Patients with nodal presentation but low-volume disease and no symptoms may also be candidates for this strategy [9]. Compared with the group of patients receiving initial therapy, these patients tend to be younger and less likely to have an advanced stage of the disease, systemic symptoms and nonclassical morphological features.

Patients with MCL are frequently divided into two groups for initial therapy. One group includes patients who are young and healthy enough to be candidates for consolidated autologous bone marrow transplantation. The other group of patients are considered poor candidates for high-dose chemotherapy and autologous transplantation and are instead treated with standard chemotherapy regimens, with or without rituximab maintenance therapy [1]. The type and intensity of chemotherapy regimens used to induce remission prior to autologous bone marrow transplantation may vary. R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone) may be used, alternating with R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and cisplatin), although some physicians tend to prefer the Nordic regimen: R-maxi-CHOP (slightly higher doses of CHOP) / R-HiDAC (rituximab and cytarabine) [10]. The important thing here is to keep in mind that a report from the European Mantle Cell Lymphoma Network confirmed a better outcome after chemotherapy followed by autologous bone marrow transplantation when the initial chemotherapy regimen contained cytarabine [11,12].

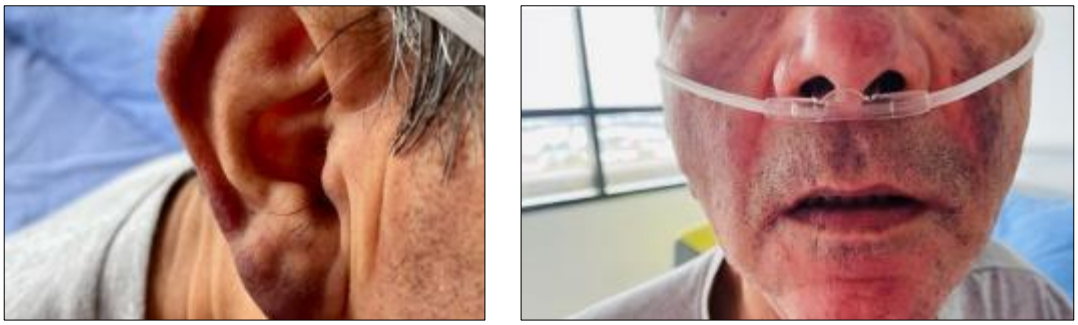
On the other hand, MCL is one of the most radiosensitive non-Hodgkin lymphomas, so it is important to consider radiotherapy in the therapeutic approach (e.g., in cases of localized relapse) [13]. However, for most patients, MCL is a systemic disease and long-term control requires systemic treatment. Several new targeted therapies are active in refractory or relapsed patients. These include lenalidomide, bortezomib, Bruton's tyrosine kinase inhibitors such as ibrutinib, and the Bcl-2 inhibitor venetoclax. These drugs are often given in combination with rituximab or another anti-CD20 antibody [14].

2 Case presentation

A 60-year-old male patient with a history of arterial hypertension and COPD/Asthma overlap, ECOG 0, consulted at a high-complexity institution in Medellín, Colombia, in June 2021 due to a weight loss of 7 kg in 4 months, associated with a feeling of abdominal fullness, night sweats, asthenia, chills, and the appearance of cervical and inguinal lymphadenopathy. Complete blood count with severe leukocytosis (118,000/µL), with lymphocytosis of 106,650/µL and the presence of 3% blasts. A biopsy of the right cervical lymph node, bone marrow aspiration and peripheral blood flow cytometry were performed. The latter was CD5 (+), suggesting the presence of chronic lymphocytic leukemia. While the results of the lymph node biopsy were obtained, cytoreduction was started with dexamethasone 40 mg intravenously every 24 hours plus hydroxyurea 1000 mg orally every 12 hours. Staging CT scans reported adenopathy in the supraclavicular, mediastinal, retroperitoneal and inguinal areas, associated with hepatosplenomegaly and bone marrow infiltration. Outpatient treatment with ibrutinib 420 mg/day has continued since June 9, 2021.

Immunohistochemical staining of the lymph node biopsy with the following profile: CD3 (-), CD20 (+), CD5 (CD20-like positivity), PAX 5 (CD20-like), Bcl6 (weak focal positivity), Bcl2 (+), CD23 (-), CD30 (-), CD10 (-), cyclin D1 (focal nuclear positivity), Lmp1 (-), Ki67 11-20%, diffuse SOX11 (+) and diffuse MYC (+).

During treatment with ibrutinib, in September 2021, he presented severe hepatotoxicity due to elevation of transaminases 10 times the upper normal value, requiring adjustment to lower doses on October 25, 2021.



(a) (b)

Figure 1 Hyperpigmented lesions on the right ear (a) and face (b)

Despite treatment with ibrutinib, the patient presents hyperpigmented macules and patches on the face and right ear (Figure 1). Initially, a vasculitic phenomenon associated with the intake of ibrutinib was thought to be present, but given the need to rule out leukemic vasculitis, a skin biopsy was performed on the affected earlobe on October 27, 2021, with a final immunohistochemistry report in January 2022, concluding atypical lymphoid infiltrate (+) for CD20, CD5, Bcl2, Cyclin D1 and SOX11, Ki67 proliferation index of 10%, negative for CD3, CD10, Bcl6, and CD23, making a diagnosis of secondary cutaneous involvement due to a classic histological variant of mantle cell lymphoma, which, together with no improvement of hepatosplenomegaly, was considered intra-treatment progression in a patient candidate for autologous hematopoietic progenitor cell transplant. Ibrutinib was discontinued and the MCL Younger protocol was started, receiving 6 cycles of R-CHOP/R-DHAP between March and July 2022. A positron emission tomography scan was performed at the end of said chemotherapy regimen, documenting complete metabolic response, including resolution of skin lesions (Figure 2). While a date was being scheduled for the hematopoietic progenitor transplant, maintenance therapy with rituximab 1400 mg subcutaneous every 8 weeks was received. The transplant was successfully carried out at a highly complex institution in the municipality of Rionegro, Colombia on November 19, 2022. The patient is in remission of the disease to date, on maintenance therapy with rituximab, last application in May 2024.

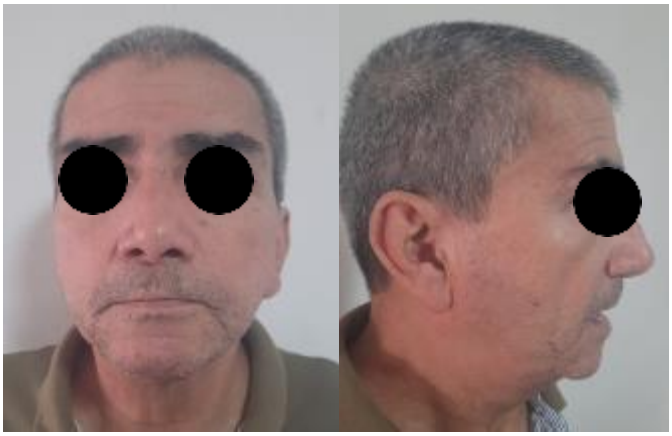


Figure 2 100% resolution of skin lesions, July 2024

3 Discussion

Mantle cell lymphoma cases have a distinctive immunophenotype, positive for CD5, B-cell markers, cyclin D1, and SOX11, and negative for CD10, CD23, CD200, and LEF1. This unique immunophenotype helps distinguish it from other small mature B-cell neoplasms, especially another CD5(+) low-grade B-cell lymphoma, chronic lymphocytic leukemia; the latter shows uniform expression of CD23 and CD200 and is negative for cyclin D1 and SOX11. Distinguishing between the two entities is critical because both treatment and prognosis are significantly different. Although this classic description of MCL applies to approximately 80% of all cases, MCL is a heterogeneous neoplasm and about 20% of cases have variable clinicopathologic, immunophenotypic, cytogenetic, and molecular features. Some cases have been

reported to express one of the markers not usually expressed in MCL, including CD10, CD23, BCL-6, LEF1, or CD200, and others may lack CD5 or SOX11 expression [15].

Our patient is male and is within the average age at diagnosis, both situations where it is more common to find MCL. After the initial peripheral blood flow cytometry, it was determined that he had stage IV chronic lymphocytic leukemia, for which ibrutinib was started. He presented hepatotoxicity that required discontinuation of therapy, and due to skin involvement, a new biopsy was taken, which documented mantle cell lymphoma, an entity in which there is expression of CD5, a characteristic shared with chronic lymphocytic leukemia.

Cutaneous involvement in MCL usually represents a relapse or progression. Skin involvement in this lymphoma is extremely rare, accounting for only 2% to 6% of all cases [16], with most occurring due to secondary cutaneous dissemination from generalized disease, and even rarer is cutaneous presentation without systemic disease [17]. Differential diagnosis includes skin toxicity as one of the most common non-hematologic side effects of ibrutinib, which may occur in 13-27% of patients and includes rashes ranging from asymptomatic ecchymosis and nonpalpable petechial rash to palpable purpura resembling leukocytoclastic vasculitis. The main dermatopathologic differential diagnosis is leukemic vasculitis, a specific form of vasculitis mediated by leukemic blast cells rather than reactive inflammatory cells [18].

After several months of treatment with ibrutinib, our patient underwent a CT scan in February 2022, where countless lymphadenopathy persisted in the neck, anterior, middle and posterior mediastinum, accompanied by retroperitoneal and inguinal lymphadenopathy, adjacent to the iliac vessels, with hepato- and splenomegaly. In addition, there was an increase in the density of the mesentery with associated mesenteric lymphadenopathy and nodules on both chest walls. Taking into account the patient's profile, the therapeutic plan was completely changed with curative intent. High-intensity chemotherapy was started, obtaining a complete metabolic response, and treatment was consolidated with a bone marrow transplant, achieving a cure for the disease.

4 Conclusion

Mantle cell lymphoma is a hematological neoplasm of the non-Hodgkin B-cell lymphoma type. It is generally seen in the male population and it is very rare to see cutaneous manifestations. In this review, we report the case of a patient initially diagnosed with chronic lymphocytic leukemia who begins treatment with ibrutinib and during the course of treatment begins with skin lesions, in which the dermatopathological study is essential to establish the origin and take action. After a new biopsy, it was concluded that the skin involvement was secondary to mantle cell lymphoma. There are fewer than 50 cases reported in the literature, hence the importance of our case. It should be noted that this skin involvement almost always appears mainly in cases with systemic disease, which show invasive clinical progression and poor prognosis due to a high recurrence rate, and in this scenario systemic chemotherapy is the standard treatment. It is important not to ignore the cutaneous manifestations of hematological malignancies, which, as in this case, contributed to the diagnosis. Although ibrutinib is also used in mantle cell lymphoma, the patient's functional status and the progression of the disease allowed for consideration of a more aggressive therapy, with which an adequate response with remission of the lymphoma was finally achieved. It is always suggested to individualize each patient to determine the best possible therapy.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Written informed consent was obtained from the patient for publication.

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