Mycosis Fungoides: Case report of progression successfully treated with liposomal doxorubicin

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Abstract

Mycosis fungoides is the most common primary cutaneous T-cell lymphoma. It is a non-Hodgkin lymphoma that begins in the skin and is characterized by a slow clinical evolution of three stages: macules, plaques and tumors. The advanced stage includes lymph node, visceral, or blood involvement, and requires skin-directed therapy associated with systemic medications. The case of a 49-year-old female patient with a diagnosis of mycosis fungoides in the malar region since July 2019 is presented, initially treated between November 2019 and March 2020 with 3 cycles of the CHOP chemotherapy regimen - cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin) and prednisone without achieving any clinical response. Subsequently without follow-up or treatment. In February 2023, progression of the disease was documented due to worsening of the lesion in the malar region and involvement of the glutes and back, additionally with cervical lymphadenopathy but without bone marrow involvement. She is considered a candidate for liposomal doxorubicin, with which she has completed 5 cycles to date with excellent clinical response. Current reassessment studies using positron emission tomography show complete tumor response. A bone marrow transplant is the therapeutic option that is being considered at the moment.

Keywords: Case report; Mycosis fungoides; Progression; Chemotherapy; Liposomal doxorubicin; Transplant

1. Introduction

Primary cutaneous lymphomas are a heterogeneous group of malignant lymphoproliferative processes that initially manifest in the skin [1]. After gastrointestinal MALT (mucosa-associated lymphoid tissue) lymphomas, they constitute the second most common group of non-Hodgkin’s lymphomas of extranodal location [2]. Mycosis fungoides is the most common subtype of cutaneous T-cell lymphoma [3], being responsible for almost 50% of cases, with an annual incidence of 0.3 to 0.5 new cases per 100,000 habitants. It is twice as common in males and also in black people, with a median age between 55 and 60 years, but children and adolescents can also be affected. Clinically, it typically presents with macules, plaques and erythematous skin tumors [4]. These stages can coexist and individual stages can be omitted. Lesions can be localized or generalized, and in the classic presentation they typically occur in areas protected from the sun [5]. Mycosis fungoides is a heterogeneous disease and skin lesions are often polymorphic, making clinical diagnosis particularly difficult. It can mimic a wide range of dermatological diseases and the differential diagnosis includes more than 50 different clinical entities [6, 7]. The World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC) define three subtypes of mycosis fungoides: folliculotropic, pagetoid reticulosis, and granulomatous loose skin [8]. The etiology of the disease is largely unknown. Infectious agents, ultraviolet radiation and occupational exposure are being discussed as possible triggers [9, 10, 11, 12, 13]. Current data also indicate that skin colonization with Staphylococcus aureus in patients with mycosis fungoides (a common complication) may actually promote disease progression through positive selection of CD4+ tumor cells by staphylococcal alpha-toxin [14].
Diagnosis, staging and also subsequent treatment planning are based on a careful clinical history, meticulously documented examination of skin lesions, histological investigations (including immunological phenotype and, if applicable, clonality testing), laboratory investigations (including flow cytometry) and/or molecular testing of blood or bone marrow, as well as diagnostic imaging [15]. The histopathological study of the initial macules shows an infiltrate in the superficial dermis formed by small cerebriform lymphocytes that are frequently distributed following the epidermal basal layer (epidermotropism) without spongiform changes. The progression of the lesions to plaques gives rise to a denser band infiltrate in the papillary dermis, and to a more intense epidermotropism (intraepidermal Pautrier microabscesses). Tumor lesions are characterized by dense monomorphic infiltrates of atypical, nodular or diffuse lymphocytes, affecting the entire thickness of the dermis [16].

With respect to treatment, topical therapies include corticosteroids, nitrogen mustard, carbustine, and bexarotene. In general, topical corticosteroids and nitrogen mustard are the preferred initial treatment for early-stage patients [17]. Carmustine can be absorbed systemically, resulting in hematologic toxicities including leukopenia, thrombocytopenia, and anemia [18]. Therefore, topical carbustine is generally not recommended for patients with widespread skin involvement. Topical bexarotene has been shown to be an effective and generally well-tolerated treatment [19]. Phototherapy is the standard therapy for patients with early-stage mycosis fungoides whose disease is not controlled with topical therapies. It is administered as narrow-band ultraviolet B (NB-UVB) or psoralen plus ultraviolet-A radiation (PUVA) photochemotherapy [17]. Extracorporeal photopheresis (ECP) is an immunomodulatory leukapheresis procedure used in the treatment of mycosis fungoides and Sézary Syndrome, a different entity but closely related to mycosis fungoides with which it shares clinical, pathological and evolutionary characteristics [20, 21]. In extracorporeal photopheresis, the peripheral blood is exposed to methoxsalen (a photosensitizing agent) and UVA radiation in an extracorporeal circuit. This procedure induces apoptosis in malignant lymphocytes [22]. Another therapeutic option is radiotherapy. Tumor cells in mycosis fungoides are very sensitive to radiotherapy. Therefore, in patients with localized tumor lesions it may result in disease control. For patients with widespread disease that does not respond to skin-directed therapies alone, systemic therapies are considered as monotherapy or in combination with skin-directed therapies. There are immunopreservative treatments (retinoids, methotrexate or etoposide in low doses) or immunostimulant therapies (interferon). In cases resistant to such therapies, other targeted therapies with antibodies or antibody-drug conjugates (Mogamulizumab, Brentuximab, Alemtuzumab) or chemotherapy (gemcitabine, liposomal doxorubicin, CHOP therapy - cyclophosphamide, hydroxyauronurubicin, vincristine sulfate (Oncovin) and prednisone) can be used. [17]. Finally we have hematopoietic stem cell transplantation, mainly the allogeneic for the treatment of mycosis fungoides/sézary syndrome in advanced stage, which may offer a possibility of cure with a long-lasting complete remission [23].

2. Case presentation

49-year-old female patient with a history of obesity and prediabetes. Diagnosed with mycosis fungoides in the right malar region since July 2019, she consulted a level IV complexity institution in one of the 4 main cities in Colombia, where she was not considered a candidate for phototherapy. Subsequently, she was evaluated at another highly complex institution that has hematology, oncological dermatology, and a transplant unit. She was initially treated between November 2019 and March 2020 with 3 cycles of the CHOP chemotherapy regimen. A positron emission tomography (PET) scan was performed on 03-31-2020, reporting patchy diffuse hypermetabolism in the bone marrow in both the axial and appendicular skeleton predominantly proximal, mild hypermetabolism in both knees, left cervical lymphadenopathy of reactive character and mediastinal mass measuring 45 x 42 x 43 mm considering refractory disease. The treatment team proposed a second line but the Sars CoV2 pandemic arrived, therefore application was not possible in a Latin American country. Subsequently without follow-up or treatment until a year later when she received oral methotrexate on a regular dose but this only relieved symptoms of pruritus but without a reduction in tumor size, that is, working as a palliative treatment. The patient returns for hematology and oncological dermatology controls in January 2023. Worsening of the lesion is seen in the malar region and associated involvement in the buttocks and back. A bone marrow aspirate was performed on 01-25-2023, without demonstrating infiltration. Oncological dermatology assessed on 01-26-2023, finding soft/rubbery erythematous-violaceous tumor lesions with a soft center without crusted areas, irregular but well defined, about 8 cm in diameter, located on the right cheek, not painful but with scratch marks. Lichenified, hyperchromic dark brown plaques with scratching stigmas located on the posterior surface of the thighs and faceted papules with a linear arrangement with a tendency to converge, discreetly lichenified and with scratching stigmas located on the back. It was decided to perform two biopsies of the back and two biopsies of the tumor lesion on the right cheek. Dermatopathology report indicates that, in the clinical context, what was evaluated is compatible with mycosis fungoides in the tumor phase on the right cheek (dense atypical lymphoid infiltrate in the dermis). Methenamine Silver and Modified Zielh-Neelsen histochemistry were performed and were negative for atypical mycobacteria and fungal structures. Likewise, a short immunohistochemistry panel is added where a negative CD30 result is obtained (see figure 1).
On 02-07-2023, a new PET scan was performed, which reported hypermetabolic dermal thickening of the cheek and right malar region in relation to the known history of mycosis fungoides (see figure 2), Deauville Score 4. Mild and diffuse reactive-type metabolic activity at the level of some lymph nodes of the cervical stations, the lymphoid tissue of Waldeyer’s ring and the bone marrow. No evidence of mediastinal masses at present.

After the new staging of the disease, new histopathological confirmation and taking into account previous treatments, she was considered a candidate for liposomal doxorubicin at dose 15 mg/m2/bsa (body surface area), but the start of the treatment was delayed due to herniorrhaphy complicated by small intestine perforation that required laparotomy + enterorrhaphy + peritoneal lavage. New concept of dermatology on 05-09-2023 does not consider concomitant management with PUVA due to improvement in the majority of the lesions, a topical steroid was only formulated in some that were still elevated on the back. Because it was CD30 negative mycosis fungoides, brentuximab was not considered. On 05-18-2023 the first cycle of liposomal doxorubicin begins with excellent tolerance. In October 2023 she completed 5 cycles of liposomal doxorubicin with wonderful clinical response (see figure 3). PET scan was realized for re-evaluation, in which no areas with abnormal increase in metabolism are observed that suggest tumor pathology of moderate-high metabolic degree, the hypermetabolic nodular thickening of the soft tissues of the right malar region completely disappears, showing only slight residual dermal thickening without associated metabolic activity. Mediastinal masses are not visualized either. In summary the patient achieved metabolic complete remission. The case was presented at a medical meeting, bone marrow transplant was proposed as the only alternative for the patient.
3. Discussion

In the latest 2018 update, the WHO-EORTC considers mycosis fungoides to be the most frequent of primary cutaneous T-cell lymphomas (50%), with its 3 variants (folliculotrophic mycosis fungoides, pagetoid reticulosis and loose granulomatous skin) with presenting characteristics, different histology and prognosis, with folliculotrophic being the most common (10%) [1].

The clinical presentation of mycosis fungoides can be patches, plaques or tumors. Our patient had an erythematous-violaceous tumor of 8 cm diameter in face and other corporal regions, lichenified, hyperchromic dark brown plaques with scratching and papules. Lesions in patches or plaques have preferences in non-photoexposed areas and can become with different pigmentation (hypopigmentation or hyperpigmentation). They generally progress slowly from patches to thicker plaques and eventually to tumors, apparently this could be related to the progressive density of malignant T cells.

The mean age at the time of diagnosis is 55 years, relatively similar to that of our patient who was almost 50 years old, although it can occur at earlier or later stages of life [24]. The patient also presented pruritus, hyperpigmentation and lesions in different stages. In mycosis fungoides the histopathology is characterized by infiltrates of malignant T cells. These are small to medium in size and characteristically have irregular cerebriform nuclei. The diagnosis is not easy and clinical characteristics and histopathology findings must be taken into account, making biopsy a very important element in the approach. And in recent years the PET scan with FDG 18, as a good staging tool. One study included 135 patients with T-cell lymphoma, documenting involvement in 122 (90%), of which 55 (45%) had cutaneous involvement, 95 (78%) had lymphadenopathy, and 54 (44%) had extranodal disease [25]. For adequate staging of the disease, we propose the revised ISCL/EORTC classification for mycosis fungoides/Sézary syndrome. In early stages, topical corticosteroids, nitrogen mustard, carmustine, local or total body radiotherapy, topical bexarotene, and phototherapy are available for treatment. Systemic or monoclonal antibody chemotherapy, oral retinoids, recombinant interferon alpha, and fusion toxins may be used alone or in combination.

Our patient was managed with systemic chemotherapy (biweekly liposomal doxorubicin) with a favorable response after 2 previous unsuccessful lines of treatment. Several patients may experience relapses, or even be refractory, as in our case, but many others also experience prolonged periods of disease control. Treatment depends on the stage. In the patch or plaque stage they have a better prognosis, and in some cases it can even be left on a watch and wait or given topical therapies. As the combination of chemotherapy with radiotherapy, although it may respond more quickly, may cause more toxicity without impact on long-term survival. There is a wide range of topical therapies (steroids, ultraviolet A and B, nitrogen mustard, topical carmustine and local radiotherapy), early systemic therapy (oral retinoids, bexarotene and methotrexate), interferon and extracorporeal photopheresis. In these cases, the participation of dermatologists and radiotherapists is required.

In recent years, the concept of a risk-adapted approach has been discussed, but in general individualized decisions are made according to age, functionality, tumor burden, previous treatments, rate of disease progression, biological
response modifiers (bexarotene, interferon), histone deacetylase inhibitors (romidepsin) monoclonal antibodies (mogamulizumab, brentuximab) and conventional chemotherapy agents. With the latter, a good response can be achieved but with only months of duration and multiple adverse effects, which is why liposomal doxorubicin is most often chosen as a second-line treatment [26]. A study that included 13 French dermatology centers verified the effectiveness of liposomal doxorubicin. 25 patients between 18 and 75 years of age with a diagnosis of mycosis fungoides or Sézary syndrome from stage II to IV who had received at least 2 lines of treatment including topical, localized or chemotherapy after verification of cell counts, cardiac and hepatic function and dose less than 300 mg/m² at the end of treatment, the response rate was 56% (14/25, 5 complete and 9 partial responses) with median survival of 43.7 months [27]. On some occasions, maintenance therapy with this agent has been discussed, but serious studies are lacking. Considering that experience with high-dose chemotherapy and autologous stem cell transplantation has demonstrated transient responses, more durable remissions have been observed with allogeneic transplantation given the graft versus lymphoma immune response. Allogeneic hematopoietic stem cell transplantation is an option with potential for cure in this entity. In a study of 113 patients from the European Society for Blood and Marrow Transplantation (EBMT) between 1997 and December 2010, 68% (77 patients) had an estimated 5-year overall survival and progression-free survival of 38% and 26%, respectively, concluding that a third of patients could be effectively rescued [28].

4. Conclusion
The diagnosis, staging, risk classification and treatment of mycosis fungoides requires multidisciplinary management. Although adequate responses are achieved, most are of low durability, adding to the toxicity, which is why it must be individualized and according to the availability of the options in each region. In the ideal scenario, we could have access to clinical trials that are not very feasible in Latin America. We recommend the usefulness of PET scan in the staging of T-cell lymphomas, as it helps to make better decisions. Taking into account the multiple treatments available and the short responses, the toxicity of the treatments and the high relapse rates, allogeneic transplantation should be considered as a therapeutic strategy. In selected cases, liposomal doxorubicin could be considered as a beneficial action in terms of activity and toxicity in advanced stages that have received other lines of treatment, in monotherapy or in combination with other agents or therapies, but even more studies are needed.

Compliance with ethical standards

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Disclosure of Conflict of interests
The authors declare no potential conflicts of interest.

Statement of Informed consent
Written informed consent was obtained from the patient for publication.

References


