Alemtuzumab in refractory Sézary syndrome*

Carmen María Alcántara Reifs[1]
Gloria María Garnacho-Saucedo[1]
Alberto González-Menchen[1]
Rafael Salido-Vallejo[1]
Sofía De la Corte-Sánchez[1]
Antonio Vélez García-Nieto[1]

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Abstract: Sézary syndrome is a primary cutaneous T-cell lymphoma characterized by the triad of erythroderma, lymphadenopathy and circulating atypical cells. The emergence of new molecular targets has enabled the development of drugs such as alemtuzumab, an anti-CD52 monoclonal antibody, which has shown promising results in the treatment of this entity. We report the case of a 70-year-old male with refractory Sézary syndrome in whom treatment with alemtuzumab achieved an 80% skin lesion clearance with complete haematologic and radiologic response. The treatment was discontinued after 4 months due to adverse effects, with the patient showing a sustained response without disease progression after 13 months of follow-up.
Keywords: Antibodies, monoclonal, humanized; Lymphoma, T-Cell, cutaneous; Sézary syndrome; Treatment outcome

INTRODUCTION

Sézary syndrome (SS) is a rare entity constituting less than 5% of all primary cutaneous T-cell lymphomas (CTCLs). Its description is a clinical triad composed of erythroderma, generalized lymphadenopathy, and the presence of Sézary cells in peripheral blood. There is insufficient information to establish a prognostic index for Sézary syndrome, although it is known that the high count of Sézary cells, loss of T-cell markers and chromosomal alterations in circulating T lymphocytes are independently associated with poor prognosis.[1,2] It is a difficult-to-treat entity, which often becomes refractory to chemotherapy agents. We report the case of a patient with SS, with a favourable and maintained response to alemtuzumab.

CASE REPORT

A 70-year-old male, with hypertension and chronic obstructive pulmonary disease, and no other relevant history, was referred from another centre due to 2 years of erythroderma with intense pruritus. He was refractory to topical and oral corticosteroid therapy. On examination, the patient presented a shiny, bright red erythroderma, slightly indurated to palpation (Figure 1). Bilateral axillary and inguinal lymph nodes were palpable. Analytical studies showed a basophilia of 14.1% and a slightly elevated LDH (253 IU/l), while other values were within the normal range. A skin biopsy revealed parakeratosis and dense lymphocytic infiltrate in the papillary dermis, prone to epidermotropism (Figure 2). The immunohistochemical analysis was positive for CD2, CD3, CD4 and CD5; and negative for CD7 and CD8 (Figure 3). The presence of numerous enlarged lymph nodes in the cervical, axillary and inguinal regions was confirmed by the CT. The study of peripheral blood showed a Sézary cell count of 1031/mm^3. The axillary lymph node biopsy revealed paracortical infiltration due to Sézary syndrome. The Sézary syndrome diagnosis was performed according to the EORTC criteria. Treatment with PUVA therapy, interferon alpha, bexarotene and extracorporeal photopheresis was started, sequentially and in combination, although unsuccessful. The patient exhibited clinical and radiological signs of disease progression, with enlarged lymph nodes and pruritus, which had become uncontrollable. New analytical studies have reported 56.8% LUC (large unstained cell) and 26% basophilia. Adopting a multidisciplinary approach, and after signing the informed consent, the decision was

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[1] Hospital Universitario Reina Sofía – Córdoba, Spain.

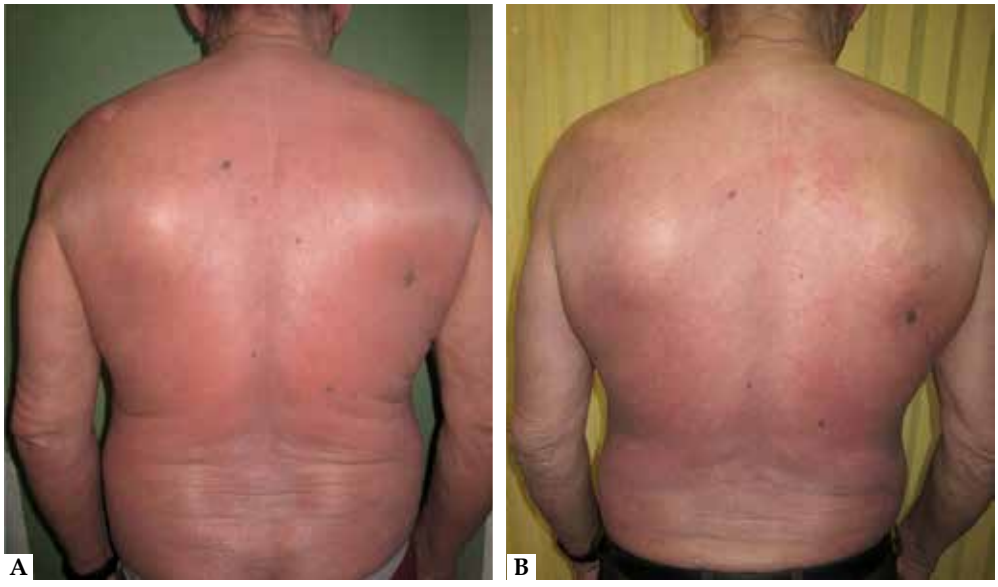

Figure 1:
Clinical images prior to treatment with alemtuzumab **(a);** and 13 months after treatment completion, sustaining an almost complete response **(b)**

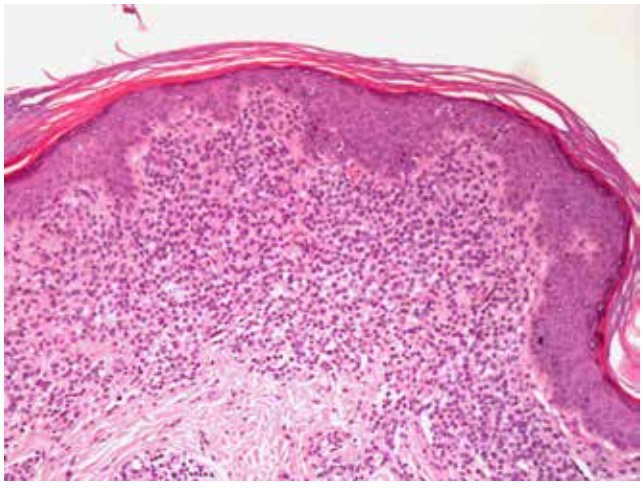

Figure 2: Parakeratotic hyperkeratosis and dense lymphocytic infiltrate in the papillary dermis, with a tendency toward epidermotropism (haematoxylin and eosin stain, 20x original magnification)**)**

taken to initiate treatment with alemtuzumab through off-label use, at doses of 30mg subcutaneously/3 times a week. Concomitantly, the patient received cotrimoxazole, famciclovir and valganciclovir as prophylactic treatment. At 3 months of treatment, the patient showed a marked improvement with 80% erythroderma clearance, pruritus cessation and a decrease in the Sézary cell count to 0. However, the treatment had to be withdrawn 4 months after starting, due to the development of severe neutropenia (leukocytes: $0.3 \times 10^3/\mu l$; neutrophils: $0.12 \times 10^3/\mu l$), grade IV heart failure and acute exacerbation of the underlying disease with bronchospasm, requiring intensive care unit admission. The patient gradually recovered with supportive treatment and G-CSF therapy. Thirteen months after medication withdrawal, there were no signs of clinical or haematological disease activity (Figure 1).

DISCUSSION

SS is a poor prognostic pCTCL, which can be refractory to the multiple regimens used in over 75% of cases.[3] The emergence of new molecular targets has allowed the use of drugs such as alemtuzumab, which has provided promising results in Phase 2 clinical trials and observational studies.[3,4,5] Alemtuzumab is a humanized, monoclonal antibody that binds to CD52, a glycosylated peptide expressed as a surface antigen by B and T lymphocytes (normal and neoplastic), monocytes, macrophages, NK cells and a granulocytes subset (< 5%), but not by hematopoietic stem cells.[3] It induces a blood depletion of these cell groups through antibody-dependent cytotoxicity, complement activation and apoptosis.[2,4] Initially approved for use in chronic lymphocytic leukaemia, its subsequent approval for multiple sclerosis has prompted its market withdrawal for hematologic use due to economic reasons.[6] Despite being classified as an orphan drug by the EMA, this drug can still be used off-label. The elevated CD52 expression on the $CD4^+$ T lymphocytes, the main circulating cell in the SS, has motivated the use of alemtuzumab in mycosis fungoides (MF) and SS.[3,7] Its efficacy is higher in patients with erythroderma, intense pruritus and those who have not received prior treatment[4,7], with response rates ranging from 70-86% of cases.[2,4,7] Masson *et al.* observed a 70% overall response rate in patients with SS after a median follow-up of 24 months. This response was sustained for 6 to 56 months in the different series.[5,7] However, the main limitation to the use of alemtuzumab is its adverse effects, particularly haematological toxicity (grade 4 cytopenias) and infectious complications (reactivation of CMV, *Pneumocystis jirovecii* infections and fungal sepsis).[3,7] In addition, post-infusion reactions may occur with fever, nausea, hypotension, rash/urticaria and fatigue, which are generally limited to the initial doses of therapy and can be minimized with corticosteroid therapy.[4] This high toxicity leads to the withdrawal of medication in 44% of cases, with a mortality rate of up to 5% that can be attributed to the drug.[7] Although the standard dose of alemtuzumab is 30mg/3 times a week in most studies, dosage regimens with lower doses

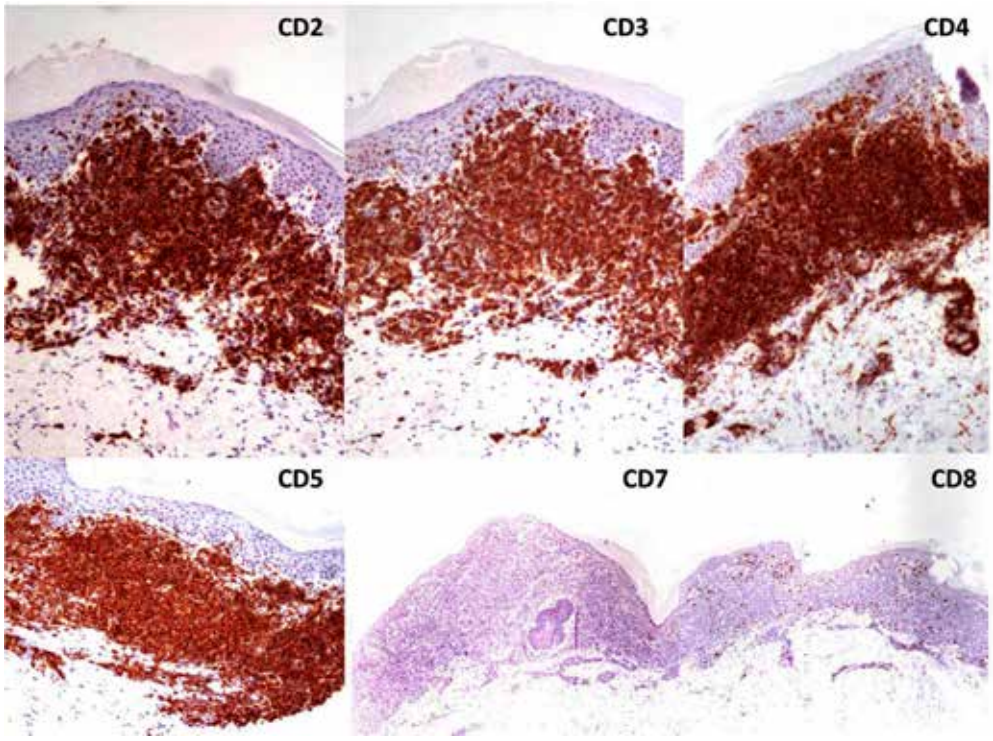

Figure 3:
Skin biopsy immunohistochemical analysis. Positive for CD2, CD3, CD4 and CD5 (10x original magnification); and negative for CD7 and CD8 (4x original magnification)

(10mg/3 times a week) revealed similar efficacy with a decreased risk of infection and haematological toxicity.[8] Alemtuzumab has proven to be a useful alternative in patients with advanced MF and SS; however, its high toxicity means that its use is reserved for cases of rapidly progressive refractory disease with lymph node or metastatic involvement.[2,3,7] Further studies are required to establish the safety and efficacy of this drug in Sézary syndrome, as well as a better characterization of the patient profile that could most benefit from its use.❑

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Mailing address:
Carmen María Alcántara Reifs
Avenida Menéndez Pidal s/n,
14004 Córdoba, Spain.
E-mail: ayla88_@hotmail.com

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