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CONTROVERSIES IN DERMATOLOGY

Is Bone Marrow Biopsy Always Indicated in Patients With Primary Cutaneous Marginal Zone B-Cell Lymphoma?☆

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Abstract Bone marrow involvement at the time of diagnosis is uncommon in patients with primary cutaneous marginal zone B-cell lymphoma (PCMZL). Moreover, in these patients such involvement is rarely found in isolation on diagnosis. Typically the few patients with PCMZL who have early bone marrow involvement also present secondary nodal or visceral involvement, which is detected by other staging studies (usually computed tomography). In recent years, this has given rise to some debate about whether a bone marrow biopsy should be routinely performed in patients diagnosed with PCMZL in view of the good prognosis and low incidence of bone marrow infiltration and/or extracutaneous involvement in this type of lymphoma.

PALABRAS CLAVE
Linfoma primario cutáneo de células B de la zona marginal;
Biopsia de médula ósea;
Afectación extracutánea

¿Está siempre indicada la biopsia de médula ósea en los pacientes con linfoma primario cutáneo de células B de la zona marginal?

Resumen En los pacientes con linfoma primario cutáneo de células B de la zona marginal (LPCBZM), la afectación de la médula ósea en el momento del diagnóstico es poco frecuente. Además, es raro en estos pacientes detectar afectación de la médula ósea al diagnóstico de forma aislada. Los pocos casos de LPCBZM y afectación inicial de la médula ósea habitualmente presentan también afectación secundaria nodal o visceral que son detectadas con otras pruebas de estadificación (normalmente con la TAC). Por dicho motivo, en los últimos años ha sido tema de controversia si debe realizarse la biopsia de médula ósea al diagnóstico de forma sistemática en todos los casos de LPCBZM dado el buen pronóstico y la baja incidencia de infiltración medular y/o afectación extracutánea por parte de este tipo de linfoma.

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Introduction

Primary cutaneous marginal zone B-cell lymphoma (MZL), or extranodal MZL of the mucosa-associated lymphoid tissue (MALT) type, is an indolent B-cell lymphoma that first manifests on the skin with no extracutaneous involvement at the time of diagnosis. It is one of the main subtypes of cutaneous B-cell lymphoma.[1,2] Clinically, primary cutaneous MZL presents as isolated or multiple infiltrated plaques or nodules that are often found on the trunk or proximal part of the extremities (Fig. 1). These lymphomas affect middle-aged patients and tend to be somewhat more frequent in men. Although this tumor has an indolent course and is usually confined to the skin, relapses are common at the initial sites, distant sites, or both. In very rare cases, extracutaneous involvement is seen at diagnosis or during the course of the disease; other MALT sites (digestive tract, salivary glands, thyroid, breast, lung, and orbit), lymph nodes, or bone marrow may be affected. Nevertheless, prognosis is generally excellent, with a 5-year survival rate close to 100%.[3–7]

Staging of Primary Cutaneous MZL

In order to rule out potential systemic disease, the initial workup in suspected primary cutaneous MZL should include a clinical history and meticulous physical examination (detection of B symptoms, complete skin inspection, and palpation of lymph nodes and viscera). The staging study should include a laboratory workup with peripheral blood smear (formula and count), standard biochemical profile with levels of lactate dehydrogenase and β_2-microglobulin, and serological tests for hepatitis C virus, human herpesvirus 8, cytomegalovirus, Epstein-Barr virus, and *Borrelia burgdorferi*. A computed tomography scan of the thorax, abdomen, and pelvis should be performed. Pioneering studies in this field also proposed systematic inclusion of bone marrow biopsy in the initial staging.[6]

Bone Marrow Biopsy

Bone marrow biopsy is an invasive diagnostic technique in which a small fragment of bone containing a small amount of bone marrow is extracted with a needle. The procedure is generally performed by hematologists, who usually take the sample from the iliac crest. Although local anesthesia is applied, the procedure is uncomfortable and may occasionally be painful. In some cases, the physician has to exert strong pressure when inserting the needle, and the patient may momentarily feel pain when the needle crosses the bone. The patient may also feel discomfort or pain in the general area, although this usually eases within a few hours with the help of ordinary analgesics. Other side effects include hematoma or bleeding at the puncture site and risk of local or bone infection, which is very unusual today given that the procedure is performed under aseptic conditions. Histologically, extranodal MZL does not have a specific pattern of infiltration, and nodular, interstitial, paratrabecular, diffuse, or sinusoidal patterns can be observed. The fact that a median of 5% of the medullary space is infiltrated by extranodal MZL sometimes creates a diagnostic challenge for the pathologist.[8–10]

Figure 1 Isolated nodule on the arm of a patient with primary cutaneous marginal zone B-cell lymphoma.

Unlike splenic and nodal MZL, which tend to infiltrate bone marrow in 67% to 100% and 30% to 40% of cases, respectively, extranodal MZL infiltrates bone marrow much less commonly (in around 10% of cases).[8]

Primary Cutaneous MZL and Bone Marrow Involvement at Diagnosis

Bone marrow involvement is uncommon at the time of diagnosis of primary cutaneous MZL. Moreover, in patients with this lymphoma, bone marrow is rarely the only tissue affected at diagnosis, and in the few cases in which early bone marrow involvement is found, patients usually also have secondary nodal or visceral disease, which is detected using other staging studies (usually computed tomography). Therefore, the need for bone marrow biopsy at diagnosis in all cases of suspected primary cutaneous MZL has lately come under debate. In a consensus proposal from the Cutaneous Lymphoma Task Force of the European Organization for Research and Treatment of Cancer (EORTC) and the International Society of Cutaneous Lymphomas, Kim et al.[11] proposed a new TNM classification for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome. The report also listed recommended tests for initial staging of these lymphomas (Table 1). Of note, the proposal considers bone marrow biopsy essential in cases of lymphoma with a risk of extracutaneous dissemination and intermediate or aggressive behavior according to the World Health Organization (WHO)-EORTC classification (Table 2) (natural killer lymphoma; $CD8^+$ T-cell lymphoma; γ/δ T-cell lymphoma; and diffuse large B-cell lymphoma, leg type). In contrast, in slow-growing lymphomas, including primary cutaneous MZL, primary cutaneous follicle center lymphoma (FCL), and $CD30^+$ T-cell anaplastic lymphoma, bone marrow biopsy is considered an option, unless the results of other staging tests are positive. After an exhaustive review of the literature, we found that very few articles[12–15] specifically address bone marrow involvement at diagnosis in primary cutaneous MZL and that even fewer address the issue of whether bone marrow biopsy should be performed routinely in cases of primary cutaneous MZL. We found confirmation of the low frequency of early bone marrow