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Teaching Case

A rare case of appendicular skeleton localization in a patient with chronic lymphocytic leukemia successfully treated with salvage radiation therapy

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Introduction

Chronic lymphocytic leukemia (CLL) is a common hematological disorder. Because of its indolent course, patients with CLL usually do not need immediate treatment and watch-and-wait is the standard of care in patients with early stage and asymptomatic CLL. Only patients with late-stage or symptomatic CLL require antileukemic therapy.[1]

A Boolean Medline advanced search of the English-language medical literature was conducted using the terms "chronic lymphocytic leukemia" AND "bone metastases" OR "bone lesions" OR "bone localization" as keywords. A total of 54 articles were identified and reviewed by 2 clinicians. Among them, 7 with therapeutic options of CLL bone metastases were selected.[2-8] Interestingly, none of the papers included ionizing radiation as a therapeutic option for this condition.

We present the case of a bony localization in a patient with CLL who was successfully treated with salvage conformal radiation therapy.

Case report

In 2011, a 66-year-old man was diagnosed with CLL, Rai stage 0, and Binet stage A. The principal characteristics

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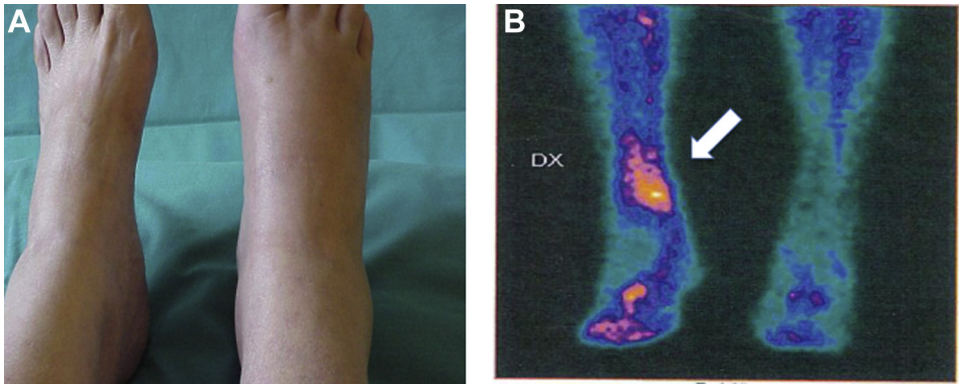

Figure 1 Distal tibial swelling (A). Bone scan with Technetium-99m-methylene diphosphonate, demonstrating early intense uptake in the distal third of right tibia (B, white arrow).

at diagnosis were hemoglobin values of 13.2 g/dL, white blood cell count of 15,800/mm^3, lymphocytes 61%, neutrophils 32%, monocytes 4%, platelets 141,000/mm^3, and normal hepatic and renal function. Flowcytometric immunophenotyping of the peripheral blood revealed a B-cell CLL and the following prognostic factors: CD38 negative, ZAP70 positive, rearrangement of the immunoglobulins mutated; and FISH: negative. Computed tomography (CT) scans of the chest/abdomen/pelvis showed the presence of multiple aortopulmonary and axillary adenopathies (maximum diameter of 2 cm), and a bone marrow biopsy showed an infiltration of CLL that was equal to 60% of the global cellularity.

The patient was observed only until January 2015, when he was hospitalized for acute anemia (hemoglobin values, 7.8 g/dl) that required supportive therapy and for pain in the right foot that was nonresponsive to common nonsteroidal anti-inflammatory drugs (visual analogue scale pain score of 8 at the time of diagnosis). It was decided to re-evaluate the disease as a whole to decide optimal management. Leukemia was staged again with instrumental and laboratory tests, which documented the presence of moderate renal insufficiency (creatine, 2.1 mg/dL), but esophagogastroduodenoscopy, colonoscopy, and Coomb's test results were negative. A bone marrow biopsy confirmed the diagnosis of CLL with bone marrow infiltration of 90%. Abdomen ultrasounds showed only moderate splenomegaly.

In February 2015, because of the persistent pain in the right foot and the appearance of swelling, a bone scan was performed, which showed a pronounced osteometabolic reaction in the distal third of the right tibia. To rule out algodystrophic syndrome, a local biopsy was performed; surprisingly, a bone localization of CLL was detected (Fig 2).

In March 2015, a total body CT scan showed 2 nodular calcifications in the right lung lobe, multiple right paratracheal, aortopulmonary window, and axillary adenopathies. The size of the prostate had also increased. A subsequent 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/CT scan showed a slight increase in metabolic activity (standardized uptake value maximum, 2.2) at the endomedullary tibial distal bone segment (Fig 3). After a multidisciplinary board, the patient was referred for a rituximab and bendamustine chemotherapy regimen with a slow recovery rate of grade 4 thrombocytopenia (23,000/mm^3).

The low level of compliance level with this pharmacologic approach shifted the therapeutic program to

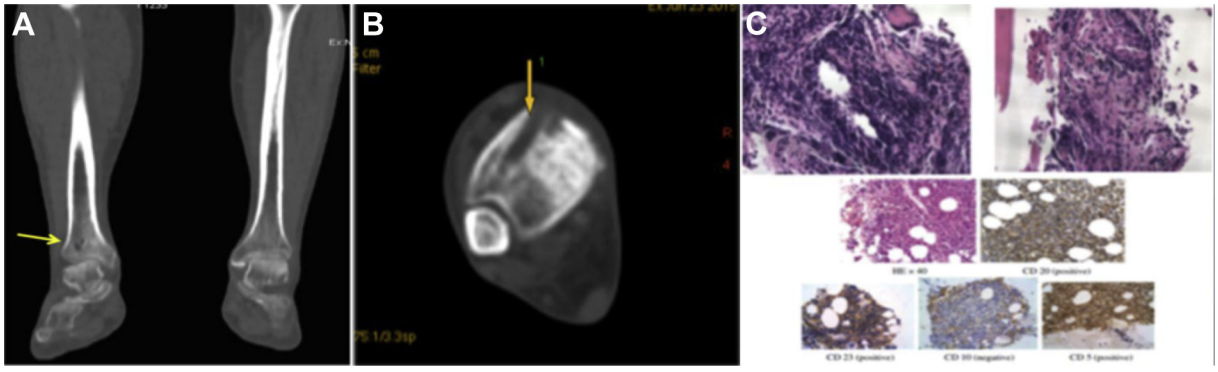

Figure 2 Right distal tibia bone biopsy (yellow arrows) with hematoxylin and eosin staining, showing monomorphic and diffuse paratrabecular proliferation of small lymphocitic elements, apparently with a normal maturation pattern. Immunophentypic analysis determining positivity for CD20, CD3 (less than 1 %), CD5, and CD23 and with a Ki-67 of approximately 5%.

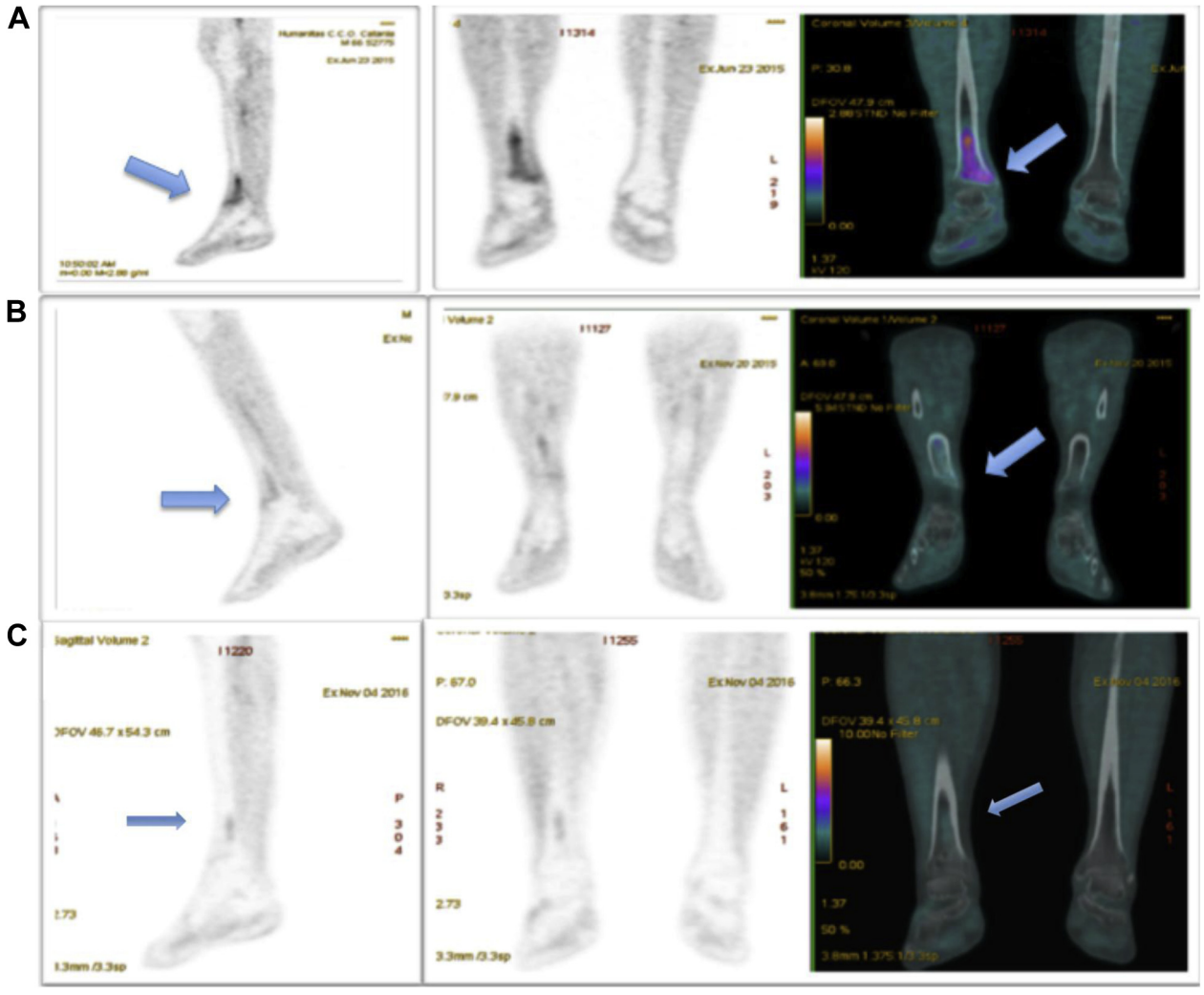

Figure 3 Positron emission tomography/computed tomography scan with 18F-fluorodeoxyglucose shows, at time of diagnostic workup, hypermetabolic glucose activity (standardized uptake value maximum, 2.2) at the level of the endomedullary compartment of the right distal tibia (A, blue arrows). Complete metabolic answer after salvage radiation therapy with an indolent lymphoma dose range of 24 Gy (B, blue arrows) at 3 months and 17 months (C, blue arrows).

salvage radiation therapy. Although choosing the radiation therapy dose was challenging because of a lack of data in the literature, a dose of 24 Gy in 12 fractions with a clinical target volume drawn on the PET/CT hypermetabolic area and a 2-cm isotropic expansion aimed at creating the planning target volume was erogated,[9] starting with the assumption that leukemic neoplastic and indolent non-Hodgkin lymphoma cells have similar radiobiologic features. A re-evaluation PET/CT scan at 3 months and 17 months after the end of radiation therapy demonstrated the full metabolic response of the lesion (Fig 3). The patient also showed a very good hemotologic compensation and clinical response in terms of pain control and leg swelling (visual analogue scale pain score 0-2 at the subsequent follow-up examinations without use of antalgic drugs), which did not require any form of maintenance therapy while continuing with a conservative observation strategy.

Discussion

Bone involvement of CLL is a rare complication that usually derives from Richter's transformation and occurs in approximately 3% of patients with CLL.[8] The lack of evidence for this rare condition became clear after a search of the English-language literature produced only sporadic case reports. Unlike the few reports we found in the English-language literature,[2-8] our patient did not show any sign of hypercalcemia and the anatomical features of the bone lesion were typical not of a pure osteolytic lesion, but of an endomedullary permeative lesion with periostium flogistic involvement. It is also a peculiar event because its distal appendicular skeleton location is a rare eventuality that is described mainly at the axial level.

As described by Narayan et al[7] in their case report, chemotherapy with or without radiation therapy

consolidation appears to be the most reasonable option for these patients, considering the similarity to other lymphoproliferative disorders such as lymphoma or multiple myeloma. Chemotherapy also underlines the need for systemic control of possible undetectable disease. This line of reasoning is undoubtedly justified, but in selected patients without systemic signs such as hypercalcemia and low burden of neoplastic diffusion on morpho-functional imaging (eg, 18F-FDG PET/CT as in our case), a local treatment with a lower toxicity charge may be considered a good option. It is intriguing to presume a different biologic phenotype,[10] and consequently different growth pathways, between 18F-FDG avid bone lesions and other classic sites of leukemic disease in which the glucose metabolism measured with PET scan is normal.

To a certain extent, the bone leukemic spot in our patient should be considered an independent pathology that is more similar to a form of indolent lymphoma[8] with excellent radiobiologic features in order to obtain significant responses with the typical radiation doses around 24 Gy. In selected cases with clinical behaviors that determine a predominant locoregional invasiveness, this could give us the opportunity to obtain a good symptomatic remission that prolongs the period of freedom from more toxic systemic management strategies. We are aware that ours is a speculative approach to a very complex matter, but considering the extreme rarity of this clinical presentation, we seriously doubt it will be possible to obtain an evidence-based resolution.

Acknowledgements

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