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A CASE OF BONE INVOLVEMENT IN HAIRY CELL LEUKEMIA SUCCESSFULLY TREATED WITH RADIATION THERAPY

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We report the case of a 63-year-old man with a clearly established diagnosis of hairy cell leukemia, treated with multiple lines of chemotherapy, who complained of localized pain in the left humerus. Radiological findings showed a dystrophic-blastic area within the humeral head. Fine-needle biopsy confirmed the hypothesis of bone involvement of hairy cell

leukemia. The patient underwent radiotherapy at a dose of 25 Gy, obtaining a complete clinical response with resolution of pain and a partial recovery of the normal radiological structure of the humerus after 2 months. In addition to the case report, we present a short review of the literature focusing on the role of radiotherapy in this subset of patients.

Key words: bone, hairy cell leukemia, radiotherapy.

Introduction

Hairy cell leukemia (HCL) was first described in the medical literature at Ohio State University in 1958 by Bouroncle *et al.*¹ It is a rare, B-cell lymphoproliferative malignancy, occurring predominantly in men and accounting for 2% of all leukemias².

HCL has a fairly indolent course, commonly presenting with pancytopenia, bone marrow infiltration, splenomegaly, but mostly without evidence of significant lymphadenopathy. Cytopenias are often severe, particularly anemia and leukopenia, and usually lead to the initiation of therapy, causing a high risk of infection. Splenomegaly, which is usually massive, may trigger the diagnostic workup³.

Several other uncommon complications have been described in patients affected by hairy cell leukemia, such as meningitis and nerve compression⁴, pleural effusion and ascites⁵ and immunological disorders⁶. Among them, skeletal involvement is a clinically relevant finding for the patient. Localized persisting pain is the leading symptom in the majority of cases. Radiation therapy (RT) has been shown to be effective⁷.

In this paper we present a patient with a destructive bone lesion of HCL involving the left humeral head, which was treated with RT. In addition, we briefly review the available literature on this subject.

Case report

In 1996, a 54-year-old male carpenter was admitted to the emergency department of our hospital because of prolonged, severe fatigue. He had a clinical history of antibiotic-resolved syphilis and ulcerative peptic disease. He reported weight loss of about 7 kg during the

last 60 days and a flu-like episode in the previous month. Laboratory examinations were performed showing the following results: cell blood count (CBC): RBC: $2.23 \times 10^{12}/L$; Hb 7.8 g/dL; MCV: 96 fl; MCH: 34.8 pg; WBC: $0.96 \times 10^9/L$; ANC: $0.24 \times 10^9/L$; lymphocytes: $620 \times 10^9/L$; monocytes: $110 \times 10^9/L$; eosinophils: $20 \times 10^9/L$; basophils: $10 \times 10^9/L$; platelets: $20 \times 10^9/L$; ESR: 67 mm/h; total bilirubin: 1.4 mg/dL; indirect bilirubin: 1 mg/dL.

Bone marrow aspiration failed; bone marrow biopsy showed diffuse interstitial infiltration by CD20+ and DBA44+ lymphocytes, with clear cytoplasm showing a typical HCL pattern. Ultrasonography showed splenomegaly with spleen diameters of 8 and 17 cm. No enlarged lymph nodes were detected at any site. Treatment with interferon alpha-2b was started at the standard dose of $2 \times 10^6/m^2$ IU 3 times a week by subcutaneous injection for 12 months, resulting in normalization of blood parameters lasting for 2 years. In May 1998, disease recurrence was documented and the interferon alpha treatment was resumed until October 2000. This resulted in normalization of CBC with marked reduction of bone marrow HCL involvement to less than 20%. A second relapse occurred in May 2001. At this time, the patient was given cladribine (2CdA) 0.09 mg/kg/day, but treatment was interrupted after 1 week because of paroxysmal atrial flutter. In December 2002, treatment with rituximab was started, with once-weekly infusions at $375 \text{ mg}/m^2/\text{week}$ for 4 weeks, followed by splenectomy a few months later. In December 2003 the patient complained of left arm pain radiating to the ipsilateral shoulder. Plain X-ray film showed a dystrophic-blastic area in the humeral head and metaphyseal region, without cortical discontinuity. CT and MRI demonstrated a solid mass within the humeral head (5

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cm diameter) and 2 satellite lacunar lesions located on the humerus surgical neck (Figure 1). Bone scintigraphy with $^{99}\text{Tc-MDP}$ was positive only at that level. Fine-needle biopsy was performed, with a histological finding of hairy cells within the humerus. Examination of the biopsy specimen showed diffuse infiltration of trabecular bone by monomorphic neoplastic elements with oval or indented nuclei and abundant pale cytoplasm. These cells were strongly immunoreactive for CD20 and tartrate-resistant acid phosphatase and showed weak-moderate positivity for CD76 (DBA44) (Figure 2). After performing a complete restaging procedure, we observed no other evidence of disease at the time of bone involvement.

Since the bone pain was worsening, with impaired left arm function, the patient was referred to our radiation oncology department for clinical evaluation. After review of the radiological imaging, the whole humerus was treated with 25 Gy in 10 fractions using parallel opposed fields with 6-MV photons. Substantial pain relief was obtained a few days after the start of RT, and a complete clinical response was observed by the end of the whole treatment. Plain X-ray after 2 months showed partial recovery of the bone structure at the involved site.

Discussion

Skeletal involvement during HCL is an uncommon, but well described event. The reported incidence ranges

from 0% to 13% in different series⁸⁻¹⁰. Most patients have a previous history of HCL when developing bone lesions; in rare cases bone lesions are the initial disease manifestation leading to the diagnosis¹¹. Nevertheless, a presentation as localized skeletal involvement without abnormal peripheral blood counts, splenomegaly or bone marrow infiltration has been described¹².

Most of these lesions develop in the axial skeleton or in the proximal part of long bones¹³. Commonly involved sites are the femoral head and neck, vertebral column, pelvis, skull, tibia, humeral head and femoral diaphysis⁷. Localized, prolonged pain is the most prominent clinical feature in almost all cases. More rarely there are multiple painful sites, sometimes associated with arthralgia and joint effusion¹⁴.

Local skeletal lesions can be successfully treated with radiotherapy, achieving rapid and substantial pain relief¹⁵. Several fractionation schedules and total doses have been reported in published papers. The first report is by Rhyner *et al.*¹⁶, who described 3 cases of bone metastases of HCL. Two were irradiated, with a dose of 60 Gy in one case and of 8 Gy in a single fraction in the other. In both cases there was resolution of hip pain.

One of the largest series has been described by Lembersky *et al.*⁸ These authors reviewed the records of 267 HCL patients at the University of Chicago and identified 8 cases of skeletal complications. The latter patients were treated with radiotherapy at doses ranging from 15 Gy to 30 Gy. In all cases there was symptom improvement. In this series, bone lesions were clearly associated with a large tumor burden, with all patients examined having hypercellular marrow with at least 90% of the hematopoietic elements being hairy cells. In the paper by Quesada *et al.*¹⁵, 4 patients with bone involvement are described. Two of them were treated with radiotherapy (20-25 Gy), with marked pain relief and a complete radiological response in one case. No relationship between skeletal involvement and tumor burden was found by the authors.

The work by Demanes *et al.* reports 2 cases of HCL with bone lesions¹¹. One of these patients was treated with 60 Gy in 30 fractions. Interestingly, the patient developed aseptic necrosis of the femoral head. The authors conclude that radiation therapy in moderate doses (approximately 5000 rad in 5 weeks) is beneficial in patients with symptomatic or strategically located bone lesions.

From this short overview of the literature it seems clear that there is no general agreement on the best radiation treatment for skeletal localization of HCL in terms of dose and fractionation. If we consider the matter from a radiobiological point of view, low doses are probably sufficient to obtain complete disease control¹⁷. Leukemic clones of B-cell origin like HCL are extremely radiosensitive, with a surviving fraction after 2 Gy (SF2) in vitro of approximately 0.2-0.3. Taking into account these SF2 values, a dose of 20-25 Gy given with conventional fractionation is theoretically sufficient to reduce a clone of 10^9 cells to 1. In treating our patient,

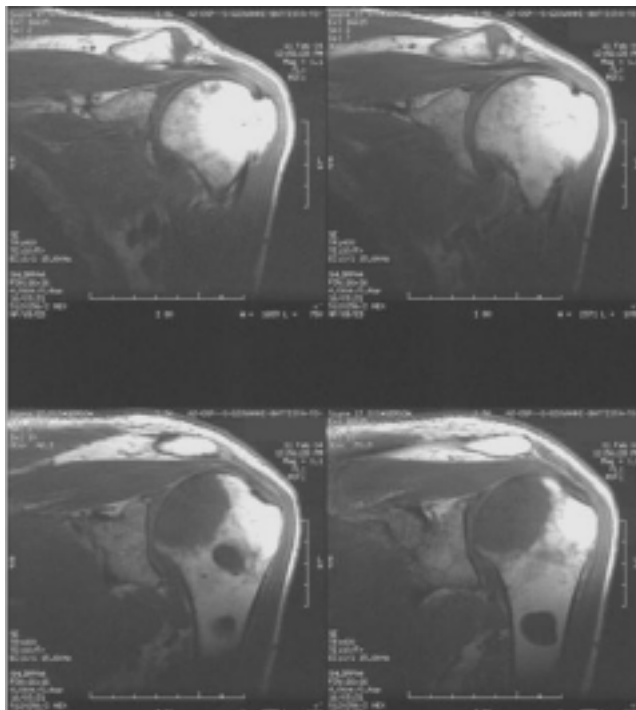


Figure 1 - Circumscribed replacement of the normal bone marrow by patchy areas of low signal intensity on both T1- and T2-weighted MRI images within left humeral head.

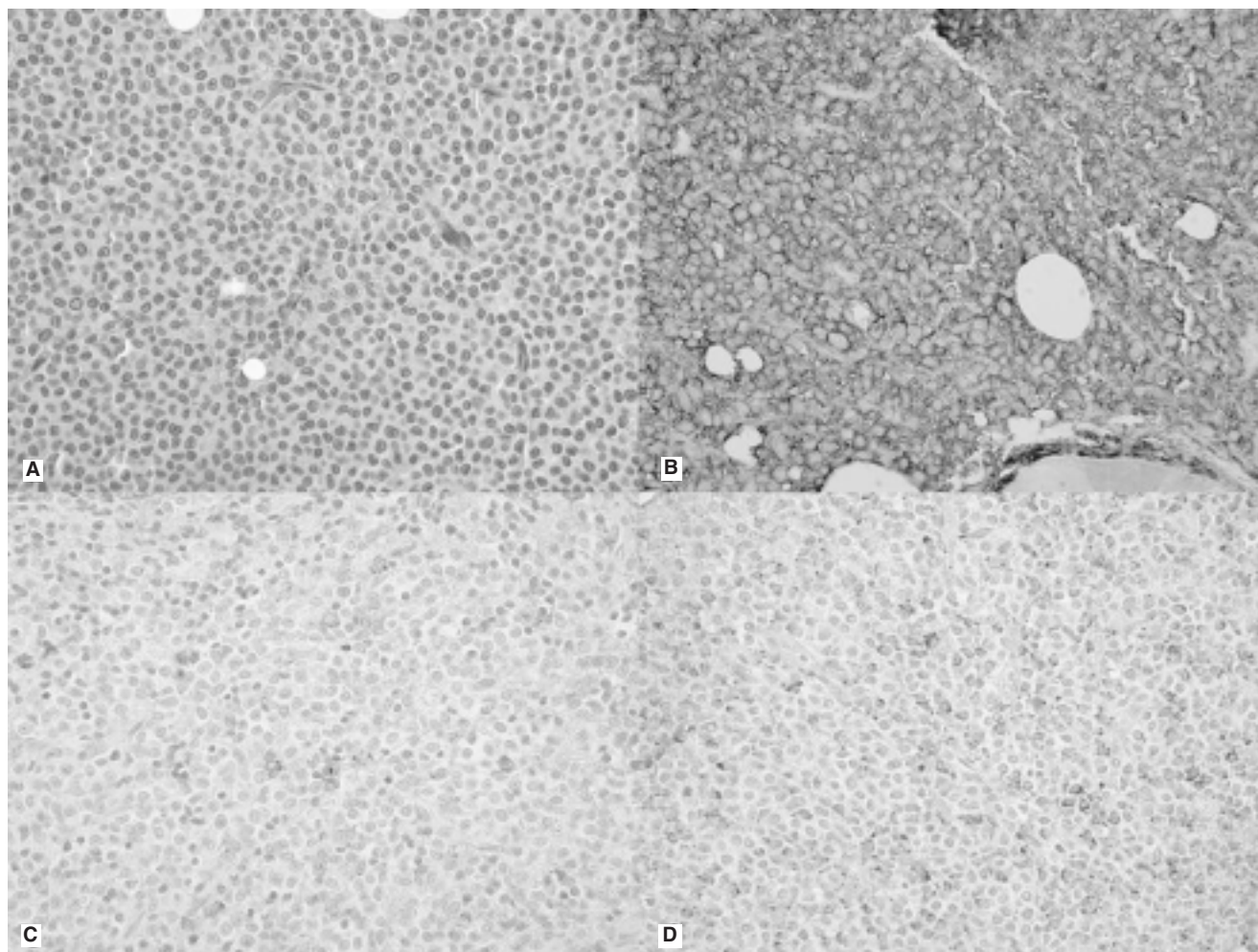


Figure 2 - Hematoxylin and eosin-stained section (original magnification x400) showing infiltration of trabecular bone by neoplastic cells with oval-indent nuclei and abundant cytoplasm. A) Immunohistochemistry showed positivity for B) CD20, C) CD76 and D) tartrate-resistant acid phosphatase (original magnification x400).

we chose a slightly more aggressive fractionation schedule because of the rapid disease progression with extensive humeral involvement and difficult pain control. Low toxicity is expected with this kind of treatment, allowing fractionation to be adapted to the patient's characteristics. In conclusion, since skeletal in-

volvement seems not to affect prognosis and since systemic disease can be well controlled with drugs (interferon alpha, pentostatin, cladribine), it is worth treating this kind of patient with eradicating intent (in terms of adequate dose), but with attention to the issue of normal tissue preservation.

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