A case of bone lesion in a patient with relapsed chronic lymphocytic leukemia and review of the literature

Francesca Bacchiarri[1], Alessandro Gozzetti[1], Nicola Mondanelli[1], Stefano Lazzi[1], and Monica Bocchia[1]

[1]University of Siena

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Abstract

Skeletal involvement in CLL is very rare. We present a case of ileum bone lesion during in a patient receiving 5th line of therapy. Despite radiotherapy and salvage therapies, subsequent bone lesions led to a fatal outcome. Further studies on the mechanism by which bone disease develops are currently needed.

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Francesca Bacchiarri[1], Alessandro Gozzetti[1], Nicola Mondanelli[2], Stefano Lazzi[3], Monica Bocchia[1]

[1] University of Siena, Department of Hematology, Siena, Italy

[2] University of Siena, Department of Orthopedic Surgery, Siena, Italy

[3] University of Siena, Anatomic Pathology department, Siena, Italy

Corresponding author: Francesca Bacchiarri, MD

Email: francesca.bacchiarri@hotmail.it

Address: University of Siena, Viale Bracci 16, 53100- Siena, Italy

Phone: +39 0577586798

Fax: +39 0577586185

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ABSTRACT

Skeletal involvement in CLL is very rare. We present a case of ileum bone lesion during in a patient receiving 5th line of therapy. Despite radiotherapy and salvage therapies, subsequent bone lesions led to a fatal outcome. Further studies on the mechanism by which bone disease develops are currently needed.

KEY CLINICAL MESSAGE

The mechanism by which bone lesions develop in CLL is unclear, further studies are needed in this regard, with the aim of developing more effective therapies. This case aims to review the literature, the modality of presentation and pathogenesis.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world, with a predominance in the elderly and an increasing incidence with age.[1] Characterized by heterogeneous clinical course, CLL has predominantly a B-cell origin, with a clonal expansion of mature CD5+ CD23+ B-lymphocytes that accumulate in the bone marrow and infiltrate lymphoid tissues such as the spleen and lymph nodes.[2]

Treatment has changed over the last 30 years from chemotherapy, to chemo-immunotherapy and lately to novel agents (i.e. BTK inhibitors and BCL-2 inhibitor).[3-5]

Rarely, patients can experience a skeletal progression, variously associated with hypercalcemia, as reported by some authors. Herein we present a case of skeletal progression in a patient with a 10-year history of CLL with del17p and unmutated IGHV, receiving venetoclax as 5th line of therapy.

CASE PRESENTATION

The patient was diagnosed with CLL in 2009: he presented with a mild lymphocytosis, diffuse lymphadenopathies (laterocervical and axillary lymph nodes of maximum diameter 2 cm), splenomegaly and left testicular swelling. Bone marrow aspiration was positive for CLL (CD5+ CD19+ CD23+ CD20+ CD38+); fluorescence *in situ* hybridization (FISH) analysis showed chromosome 17p delection (20% of nucleated cells), and unmutated IGHV. The patient underwent left orchiectomy, that confirmed CLL diagnosis. After 4 cycles of chemotherapy with fludarabine and alemtuzumab, he obtained a partial remission of the disease. Patient underwent maintenance therapy with rituximab until October, 2012. In December 2012, due to a disease relapse with anemia, splenomegaly and lymphadenopathy, 2nd line therapy with rituximab and bendamustine was started. After 4 cycles, patient was in stable disease, therefore a therapy with alemtuzumab and cyclophosphamide was administered from April to September 2013.

Patient remained asymptomatic until June 2014, when massive splenomegaly, anemia and lymphocytosis were again found. A therapy with BTK inhibitor (ibrutinib) was started. For an episode of autoimmune haemolytic anemia he required corticosteroids therapy. Patient obtained a partial remission and continued ibrutinib until March 2018, when a therapy with BCL-2 inhibitor (venetoclax) was started for massive lymph nodes enlargement. Patient had a complete remission until August, 2019 when he was admitted to the Emergency Unit for lower limbs pain complained for about 2 months. Radiographs and CT-scan demonstrated a left iliac bone pathological fracture due to a bone lesion that also affected the soft intrapelvic tissues, occupying and replacing the iliopsoas muscle (maximum diameter of the lesion 10 cm), as shown in Figure 1. A core needle bone biopsy performed under radiographic guidance confirmed CLL diagnosis (Figure 2). Physical examination revealed no lymphadenopathy nor organomegaly. Laboratory findings showed no lymphocytosis with WBC 2.3 x 10^9/L (lymphocyte count 15%), Hb 11.4 g/dL, platelets 137 x 10^9/L. Serum total proteins were low (5.6 g/dL), without monoclonal component. Uric acid (4.3 mg/dL) and serum alkaline phosphatase (125 U/L) were normal, with elevated calcium (14.6 mg/dL), β2-microglobulin (4.9 mg/L) and serum lactate dehydrogenase (250 U/L). PTH analysis was not performed. Bone marrow aspiration showed CLL infiltrate.

The fracture was treated conservatively, and radiotherapy was administered at the dose of 30 Gy, but other lytic lesions of the contralateral acetabulum, 3rd left rib and left clavicle leading to pathological fractures occurred. The patient was subsequently treated with 1 cycle of intravenous rituximab, continuing with venetoclax plus zoledronic acid as prophylaxis. Despite the radiotherapy and intensification of immunotherapy, patient developed multiple cranial lytic lesions, involving epidural and dural tissue and left occipitotemporal leptomeningeal infiltration, and he died 3 months later.

DISCUSSION

CLL is the commonest form of leukemia, presenting often with asymptomatic peripheral lymphocytosis. The clinical course can be very heterogenous with lymphadenopathy, increased incidence of infection, autoimmune phenomena (e.g., haemolytic anemia, thrombocytopenia), and B symptoms (fever, unintentional weight loss, night sweats, and severe fatigue). Active treatment is required with advanced disease stage, evidence of disease progression (e.g., cytopenias, lymphadenopathy of 10 cm, and/or splenomegaly), and/or in the

presence of constitutional B symptoms. In case of relapse, the presentation can be identical or characterized by transformation to high-grade lymphoma (Ricther's syndrome)[6]. Macroscopic skeletal involvement is extremely rare, being more frequent in other lymphoproliferative disease and some acute leukemias. Altered bone metabolism, resorption, and demineralization can lead to an increased risk of spine and pelvic fractures in untreated patients.[7-9]

Some cases in literature have already described the presence of lytic lesions in patients affected by CLL, and one of them was previously described by our group.[10]

In 11 on 22 cases of the literature, patients had the axial skeleton or proximal long bones involved [10-21] and in rare cases fractures were localized to the skull or facial bones.[17,22,23]Multiple fractures were reported in 8 cases.[24-31]

Like this one, other cases in the literature described pathological fracture due to CLL involving the spine and vertebral compression fractures.[16,19,29,30] Of note, in 13 reports symptomatic osteolysis was the first presentation of a CLL. The cases reported in the literature are summarized in table 1. Interestingly, pathological fracture can be also the first presentation of a newly diagnosed CLL. Hypercalcemia is a frequent finding with osteolysis, and can be related to Richter's transformation, or co-occurring multiple myeloma. The pathogenesis is not well understood, and can be related to primary hyperparathyroidism,[32] increased serum immunoreactive parathormone (iPTH), or osteoclast activating factor (OAF).[33]

In a recent study[34] bone erosion was particularly evident in long bone shafts, progressively increased from Binet stage A to Binet stage C, and it was directly related to the number of RANKL + cells present in the circulating blood. Also, after denosumab administration to CLL cells *in vitro* the expression of RANK decreased and also cell proliferation, this could partially be explained by the interaction between CLL lymphocytes and stromal cells.

CONCLUSIONS

Our patient had a 10-year history of CLL, with several relapses, and eventually developed multiple osteolytic lesions associated with hypercalcemia. PTH analysis was not performed, however in an end-stage disease characterized by several skeletal lytic lesions hypercalcemia can be a common finding.

The pathogenesis of bone involvement in CLL is not completely understood, and it is associated with Richter disease in the majority of cases. Of note, in 13 cases patients developed bone metastases / presented symptomatic bone lesions as first presentation of a CLL.

Bone erosions in patient affected by CLL can be related to an increased expression of RANK or locally released osteoclast stimulating factors.

This overview suggests that bone lesion are not rare events in CLL and further investigation is required to clarify the underlying mechanism and to find suitable therapies for this group of patients, which often presents a high morbidity and mortality.

AUTORSHIP

FB wrote the manuscript, AG followed the patient, NM performed patient's bone biopsy, SL analyzed bone biopsy, MB designed the study. All authors have contributed to, read and approved the manuscript and this submission.

ETHICS STATEMENT

relatives of the deceased patient were informed and agreed to the publication.

CONFLICT OF INTEREST

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

REFERENCES

1. Baumann T, Delgado J, Santacruz R, et al. Chronic lymphocytic leukemia in the elderly: clinico-biological features, outcomes, and proposal of a prognostic model. *Haematologica.* 2014; 99(10):1599–604
2. Chiorazzi N, Rai KR, Ferrarini M. Chronic lymphocytic leukemia.*N Engl J Med.* 2005; 352(8):804–15.
3. Zinzani PL, Lauria F, Rondelli D, et al. Fludarabine in patients with advanced and/or resistant B-chronic lymphocytic leukemia. *Eur J Haematol* . 1993;51(2):93-97.
4. Laurenti L, Innocenti I, Autore F, et al. Bendamustine in combination with rituximab for elderly patients with previously untreated B-cell chronic lymphocytic leukemia: A retrospective analysis of real-life practice in Italian hematology departments. *Leuk Res* . 2015;39(10):1066-1070.
5. Gozzetti A, Candi V, Brambilla CZ, et al. Bruton Kinase Inhibitors in Chronic Lymphocytic Leukemia. Anticancer Agents Med Chem. 2017;17(8):1040-1045.
6. Mauro FR, Galieni P, Tedeschi A, et al. Factors predicting survival in chronic lymphocytic leukemia patients developing Richter syndrome transformation into Hodgkin lymphoma. *Am J Hematol* . 2017;92(6):529-535.
7. Ducassou S, Ferlay C, Bergeron C, et al. Clinical presentation, evolution, and prognosis of precursor B-cell lymphoblastic lymphoma in trials LMT96, EORTC 58881, and EORTC 58951. *Br J Haematol* . 2011;152:441-451
8. Olszewski AJ, Gutman R, Eaton CB. Increased fracture risk in patients with untreated chronic lymphocytic leukemia (CLL): a population-based analysis. *Blood* . 2015;126:878
9. Olszewski AJ, Gutman R, Eaton CB. Increased risk of axial fractures in patients with untreated chronic lymphocytic leukemia: a population-based analysis. *Haematologica* . 2016;101:e488-e491
10. Fabbri A, Gozzetti A, Marotta G, et al. An unusual presentation of chronic B-cell lymphocytic Leukaemia. *Br J Haematol.* 2004 Jan;124(2):129
11. Abboud SL, Gordeuk V, Schacter LP, et al. Well-differentiated lymphocytic lymphoma with peripheral blood involvement, osteolytic bone lesions, and hypercalcemia. A case report and review of the literature. *Cancer* . 1985 Nov 15;56(10):2508-11.
12. Hatum G, Meshkin C, Alkhunaizi S, et al. The Risk of Misdiagnosing the Primary Site Responsible for Bone Metastases in Patients With Chronic Lymphocytic Leukemia and a Second Primary Carcinoma. *World J Oncol* . 2015;6(2):332-334
13. Katz H, Sagun S, Griswold D, et al. Solitary lytic bone metastasis: a rare presentation of small lymphocytic leukemia. *Case Rep Hematol* . 2018 Oct 30;2018:6154709.
14. Htet ZM, Gomez C, Ahsan A, et al. Multiple faces of chronic lymphocytic leukaemia: a patient with renal, cardiac and skeletal complications. *Case Rep Nephrol* . 2019 Mar 12;2019:5390235.
15. Hua J, Ide S, Ohara S, et al. Hypercalcemia and osteolytic bone lesions as the major symptoms in a chronic lymphocytic leukemia/small lymphocytic lymphoma patient: a rare case. *J Clin Exp Hematop* . 2018 Dec 13;58(4):171-174
16. Langenberg JCM, Bosman WM, Bremer J, Ritchie ED. Pathological fractures in a patient with chronic lymphatic leucaemia without disease progression. *BMJ Case Rep* . 2015; Feb 25: 2015:bcr2014208118
17. Littlewood TJ, Lydon APM, Barton CJ. Hypercalcemia and osteolytic lesions associated with chronic lymphatic leukaemia (CLL). J Clin Path 1990;43(10):877
18. Narayan H, Bandyopadhyay D, Schmidt K, *et al.* Successful treatment of a patient with chronic lymphocytic leukaemia (CLL) presenting with bony metastases with aggressive antibody and chemotherapy. *Clin Lab Haematol.* 2005; 27:405-408
19. Redmond J, Stites D, Beckstead J, et al. Chronic lymphocytic leukemia with osteolytic bone lesions, hypercalcemia, and monoclonal protein.*Am J Clin Path* 1983;79:616–620
20. 16 Yau V, Christakis M, Ismiil N, et al. Chronic lymphocytic leukemia resembling metastatic bone disease-unusual manifestation. *J Pain Symptom Manage* . 2003 Dec;26(6):1074-6.
21. Soni P, Aggarwal N, Rai A et al. Chronic lymphocytic leukemia: a rare cause of pathological fracture of the femur. *J Investig Med High Impact Case Rep* . 2017 Oct 3;5(4): 2324709617735135
22. Dunphy CH, Oza YV, Skelly ME. Previously undescribed form of B-cell chronic lymphoid leukemia

with IgA expression/secretion and lytic bone lesions. *Am J Hematol* . 1997 Aug;55(4):208-11.
23. Wright GW, Wiesenfeld D, Seymour JF. Bilateral fracture of the mandible in chronic lymphocytic leukaemia. Case report. *Aust Dent J* . 1997;42:20-24
24. Aiwaladhi S, Baddoura FK, Haumesser JC, et al. Hypercalcemia and Osteolytic Bone Lesions in B-Cell Chronic Lymphocytic Leukemia: A Case Report. *Clinical Leukemia* , Vol. 1, No. 1, 57-60, 2006
25. Alanoglu G, Dagdas S, Aki Z. Hypercalcemia and multiple pathological fractures in chronic lymphocytic leukaemia: a case report. *Turk J of Haematol.* 2003*;* vol. 20, no. 3, pp. 167–170
26. Greenfield HM, Hunt R, Lee LK, Jowitt SN. B-cell chronic lymphocytic leukaemia with extensive lytic lesions. *Eur J Haematol* 2006: 76: 356–357
27. Mian M, Cerù S, Billio A, et al. Osteolytic bone lesions as a rare sign of progression of chronic lymphocytic leukemia without evidence of Richter syndrome. *Leukemia & Lymphoma* , May 2012; 53(5): 993–995
28. Rossi JF, Bataille R, Chappard D, et al. B cell malignancies presenting with unusual bone involvement and mimicking multiple myeloma. Study of nine cases.*Am J Med.* 1987 Jul;83(1):10-6
29. McMillan P, Mundy G, Mayer P. Hypercalcemia and osteolytic bone lesions in chronic lymphocytic leukaemia. *Br Med J* 1980; 281:1107
30. Van de Casteele M, Verhoef GEG, Demuynck H, et al. Hypercalcemia, monoclonal protein, and osteolytic bone lesions in chronic lymphocytic leukemia. *Ann Hematol* 1994;69:79-80
31. Fain O, Selmi A, Dosquet C, et al. Hypercalcemia in B-cell chronic lymphocytic leukemia. *Br J Haematol* 1994;87: 856-8.
32. Laugen RH, Carey RM, Wills RW, Hess CE. Hypercalcemia associated with chronic lymphocytic leukemia. *Arch Intern Med.* 1979; 1339:1307
33. Mundy GR, Raisz LG, Cooper R, et al. Evidence for the secretion of an osteoclast stimulating factor in myeloma. *N Engl J Med* 290:867, 1974
34. Marini C, Bruno S, Fiz F, et al. Functional Activation of Osteoclast Commitment in Chronic Lymphocytic Leukaemia: a Possible Role for RANK/RANKL Pathway. *SCIENTIFIC RePOrTs* , 7: *14159.*

Figure legends

Figure 1. CT-scan showing left ilium involvement and bone fracture (a and b), subsequently due to disease progression a left clavicule (c) and multiple cranial bone lesions (d).

Figure 2. Hematoxylin and Eosin stain of bone biopsy showing at 2x (a) and 20x (b) lymphoid infiltrate characterized by small size cells. Immunohistochemical staining (20x) was positive for CD20 (c), CD5 (d), CD23 (e) and Ki67 (f).

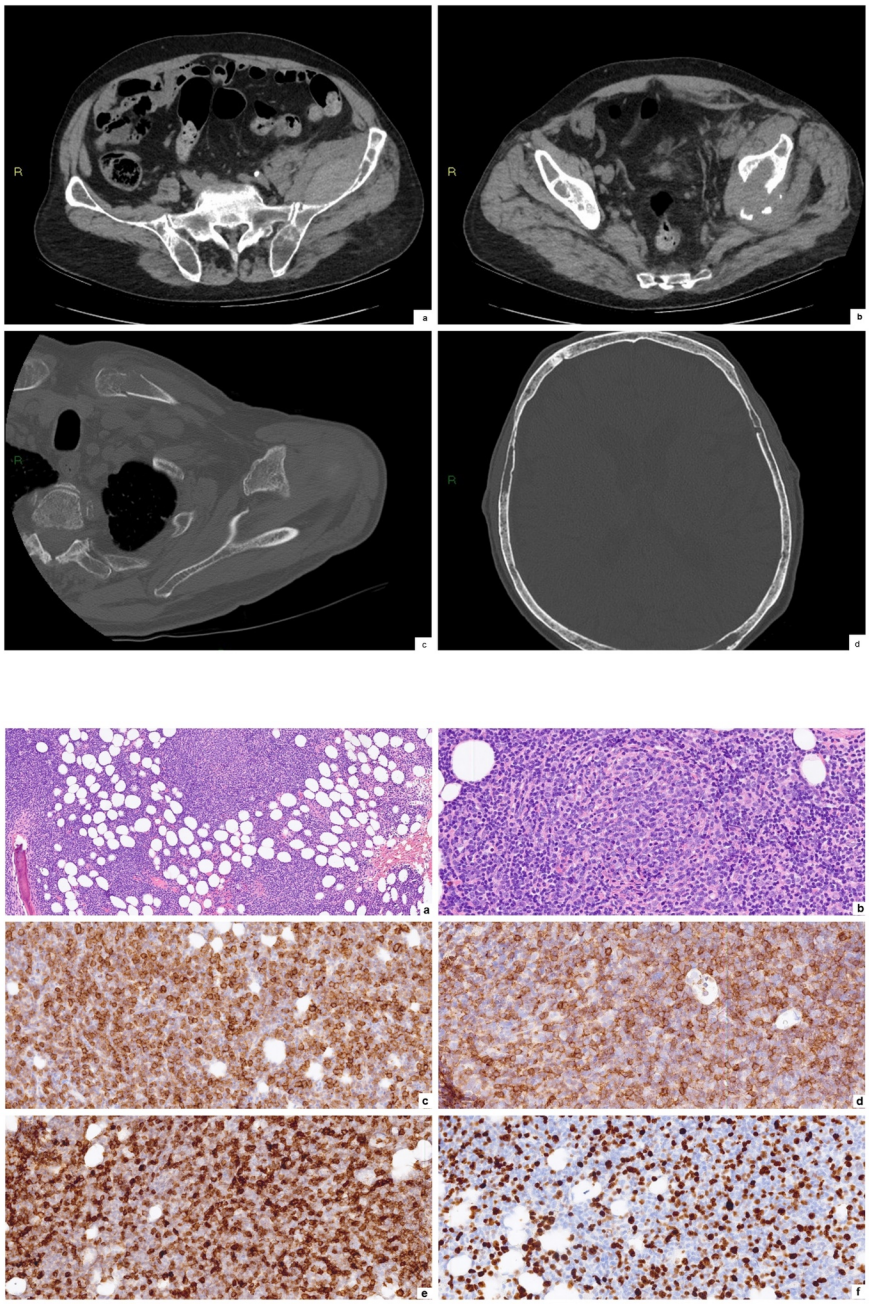

Table 1. Overview of previously reported cases of CLL compromised by osteolytic bone lesions and/or hypercalcemia

Ref.	Age/ Sex	Stage/new diagnosis	WBC (10^9/L)/Ly(%)	Hb (g/dL)	Plt (10^9/L)	M protein	Bone lesions	Hypercalcemia	Treatment
Laungen,1976	69/M	IIIC/Y	352/99%	8.6	76	NA	-	+	CVP

Ref.	Age/ Sex	Stage/new diagnosis	WBC (10^9/L)/Ly%	Hb (g/dL)	Plt (10^9/L)	M protein	Bone lesions	Hypercalcemia	Treatment
McMillian,1978	78/F	NA/y	2.8/78%	9.3	NA	NA	+	+	Chlor
Redmon,1985	65/M	NA/Y	68.3/90%	11	22	K (U)	+	+	NA
Abboud,1985	70/M	NA/Y	19.2/61%	12.9	N	NA	+	+	RT,Chlor+P
Rossi,1987	74/M	Rai II/Y	80/88	NA	NA	NA	+	+	NA
Rossi,1987	72/F	Binet C/N	95/80%	12	40	-	-	+	-
Littlewood,1990	79/M	NA/N	14.8/61%	9.1	14.2	-	+	+	Chlor+PDN
Littlewood,1990	70/F	Binet C/N	NA/NA	NA	NA	-	+	+	NA
Fain,1994	56/M	Binet C/N	98.1/90%	9	78	NA	+	+	CHOP
Wright,1997	72/F	NA/N	9.1/4.45	12.2	624	-	+	-	surgery
Dunphy,1997	72/M	Binet C/Y	26.4/86%	8.2	85	IgA k	+	-	Chlor+PDN VAD
Alanoglu,2003	74/M	Rai I/Y	154	11	283	-	+	+	CVP
Yau,2003	66/F	I/Y	16.2/0.6	14.9	177	NA	+	-	RT, CVP
Fabbri,2004	63/M	Binet C/Y	43.5/78%	10.8	196	NA	+	NA	RT,FC
Narayan,2008	83/M	NA/N	NA/40X10^9/L	10.1	21.3	NA	+	+	CHOP
Ailawadhi,2007	56/M	Binet C/N	117/98%	8.1	139	IgM k	+	+	-
Greenfield,2008	81/M	Binet A/N	NA/NA	NA	NA	IgG k	+	-	NA
Mian,2011	60/M	NA/N	3.52/57%	12.7	6.2	-	+	-	CHOP
Hatoum,2015	61/M	NA/N	NA	NA	NA	NA	+	-	RT
Langenberg,2015	39/F	NA/N	NA/NA	NA	NA	NA	+	NA	FCR
Koutroumpakis,2016	70/M	Rai III/Y	10.9/93.6%	9.1	18.9	-	-	+	BR
Soni,2017	85/F	Binet C/Y	107/NA	10.2	149	NA	+	-	-
Hua,2018	40/F	Rai III/Y	6.5/65%	7	12.4	k	+	+	FCR/BR
Htet,2018	55/F	IA/N	L=56.5	NA	NA	IgG λ	+	-	BR
Katz,2018	76/F	0A/Y	4.4/0,66	13.7	178	NA	+	NA	-
Present case	74/M	IVC	2.3/15%	11.4	137	NO	+	+	Venetoclax+

Adapted from Hua et al.[15]

Abbreviations: WBC, white blood cell; Lym, lymphocyte; Hb, hemoglobin; Plt, platelet; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CVP, cylophosphamide, vincristine, prednisone, Chlor, chlorambucil; FCR, fludarabine, cyclophosphamide, rituximab; ; FC, fludarabine, cyclophosphamide; FR, fludarabine, rituximab; BR, bendamustine, rituximab; PDN, prednisolone; CR, complete remission; NA; not available, N normal; PDN prednisone; RT, radiotherapy; VAD (Vincristine, Adriamycin, Dexametasone).