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CASE REPORT

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

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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.

KEYWORDS

chronic lymphocytic leukemia, hypercalcemia, osteolysis

1 | 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 74-year-old male patient with a 10-year history of CLL with del17p and unmutated IGHV, receiving venetoclax as 5th line of therapy.

2 | CASE PRESENTATION

The patient was diagnosed with CLL in 2009: He presented with a performance status (PS) 1, mild lymphocytosis (WBC 9×10^9/L, lymphocytes count 5300×10^9/L, Hb 13 g/dL, and platelets 145×10^9/L), 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 deletion (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 hemolytic 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 (PS = 2). Laboratory findings showed no lymphocytosis with WBC 2.3 × 10^9/L (lymphocyte count 15%), Hb 11.4 g/dL, and platelets 137 × 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.

3 | 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., hemolytic 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 (Richter'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

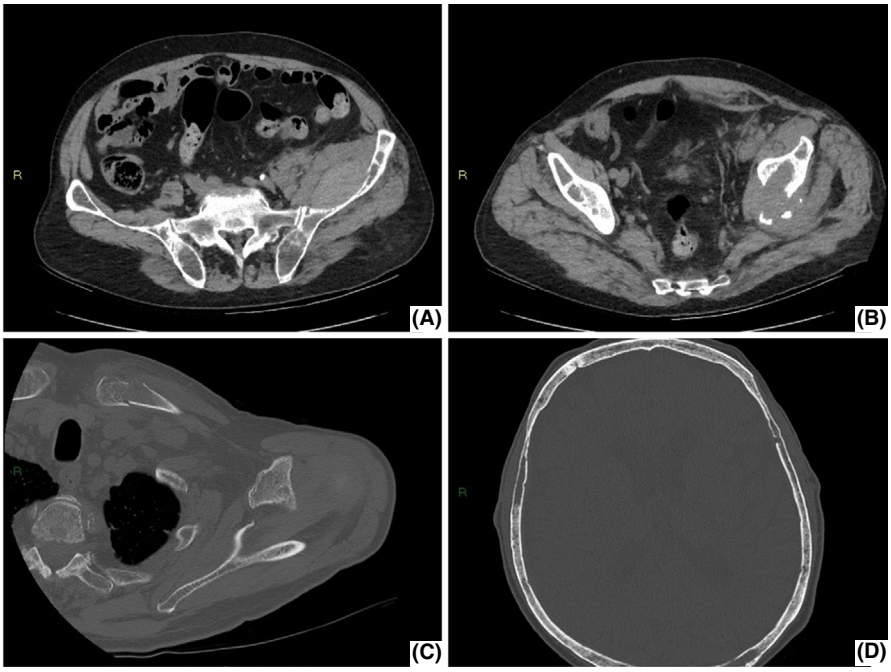

FIGURE 1 CT scan showing left ilium involvement and bone fracture (A and B), subsequently due to disease progression a left clavicule (C) and multiple cranial bone lesions (D)

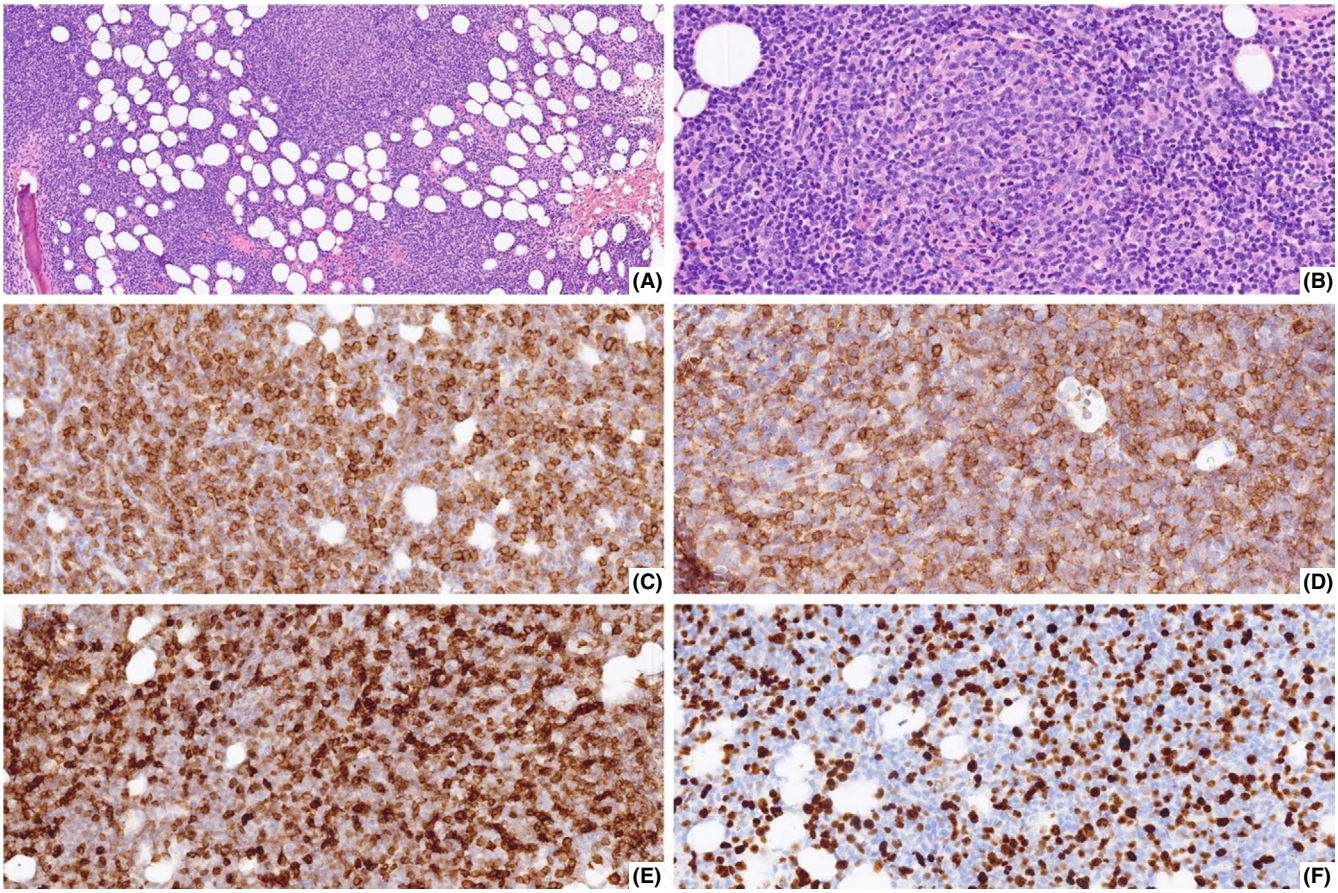

FIGURE 2 Hematoxylin and eosin stain of bone biopsy showing at 2× (A) and 20× (B) lymphoid infiltrate characterized by small size cells. Immunohistochemical staining (20×) was positive for CD20 (C), CD5 (D), and CD23 (E), and Ki67 was expressed at 30%–40% (F)

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.

4 | 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.

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)/ Lym	Hb (g/dL)	Plt (10^9/L)	M protein	Bone lesions	Hypercalcemia	Treatment	Prognosis
Laungen (1979)	69/M	IIIC/Y	352/99%	8.6	76	NA	−	+	CVP	7 M, dead
McMillian (1980)	73/F	NA/y	2.8/78%	9.3	NA	NA	+	+	Chlor	3 W Alive
Redmon (1983)	65/M	NA/Y	68.3/90%	11	22	K (U)	+	+	NA	NA
Abboud (1985)	70/M	NA/Y	19.2/61%	12.9	N	NA	+	+	RT, Chlor + PDN	1, 5 y dead
Rossi (1987)	74/M	Rai II/Y	80/88	NA	NA	NA	+	+	NA	NA
Rossi (1987)	72/F	Binet C/N	95/80%	12	40	−	−	+	−	15 y, dead
Littlewood (1990)	72/M	NA/N	14.8/61%	9.1	14.2	−	+	+	Chlor + PDN	3 W Dead
Littlewood (1990)	70/F	Binet C/N	NA/NA	NA	NA	−	+	+	NA	10 M Dead
Fain (1994)	56/M	Binet C/N	98.1/90%	9	78	NA	+	+	CHOP	1 M, Dead
Wright (1997)	72/F	NA/N	9.1/4.45	12.2	624	−	+	−	surgery	1y, dead
Dunphy (1997)	72/M	Binet C/Y	26.4/86%	8.2	85	IgA k	+	−	Chlor + PDN, VAD	NA, dead
Alanoglu (2003)	74/M	Rai I/Y	154	11	283	−	+	+	CVP	dead
Yau (2003)	66/F	I/Y	16.2/0.6	14.9	177	NA	+	−	RT, CVP	Dead?
Fabbri (2004)	63/M	Binet C/Y	43.5/78%	10.8	196	NA	+	NA	RT, FC	dead
Narayan (2005)	83/M	NA/N	NA/40X10^9/L	10.1	21.3	NA	+	+	CHOP	6 M CR
Ailawadhi (2006)	57/M	Binet C/N	117/98%	8.1	139	IgM k	+	+	−	3d, dead
Greenfield (2006)	81/M	Binet A/N	NA/NA	NA	NA	IgG k	+	−	NA	NA
Mian (2011)	60/M	NA/N	3.52/57%	12.7	6.2	−	+	−	CHOP	2 M Dead
Hatoum (2015)	61/M	NA/N	NA	NA	NA	NA	+	−	RT	Alive
Langenberg (2015)	59/F	NA/N	NA/NA	NA	NA	NA	+	NA	FCR	Alive
Koutroumpaki (2016)	70/M	Rai III/Y	10.9/93.6%	9.1	18.9	−	−	+	BR	Alive
Soni (2017)	85/F	Binet C/Y	107/NA	10.2	149	NA	+	−	−	alive
Hua (2018)	40/F	Rai III/Y	6.5/65%	7	12.4	k	+	+	FCR/BR	2 Y Dead
Htet (2018)	55/F	IA/N	L = 56.5	NA	NA	IgG λ	+	−	BR	NA
Katz (2018)	76/F	0A/Y	4.4/0.66	13.7	178	NA	+	NA	−	Alive
Present case	74/M	IVC	2.3/15%	11.4	137	NO	+	+	Venetoclax + R	2 M dead

Note: Adapted from Hua et al.[15]

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

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 is 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.

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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.

AUTHOR CONTRIBUTIONS

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

CONSENT

Written informed consent was obtained from the relatives of deceased patient to publish this report in accordance with the journal's patient consent policy.

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