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Case Report

A Case of CCR4-Positive, Localized Primary ATLL of the Bone

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Abstract

A 73-year old man visited our Hospital with the knee pain. X-ray showed an osteolytic lesion. A biopsy revealed the large atypical lymphocytes. Southern blotting revealed the HTLV-1 proviral DNA integration. PET-CT revealed no abnormalities other than the multiple bone lesions. There was no evidence of infiltration into the peripheral blood, bone marrow or central nervous system. He was diagnosed as a localized primary ATLL of the bone. he was started on CHOP, mLSG15,lenalidomide and mogamulizumab. He developed resistance to these treatments. He was detected as having hypercalcemia. Localized primary ATLL of the bone with multiple bone lesions carry a poor prognosis.

Keywords: Adult T-cell leukemia/lymphoma; Primary lymphoma of the bone; CCR4; Chemotherapy; Lenalidomide; Mogamulizumab

Introduction

Primary bone lymphoma (PBL) is a rare type of lymphoma, and most cases of PBL can be classified under diffuse large B-cell lymphoma (DLBCL) [1,2]. Since the tumor is localized to the bone in many cases, the prognosis is generally considered to be good [1,3,4]. However, until now, only 9 cases of localized primary adult T-cell leukemia/lymphoma (ATLL) of the bone (defined as cases where the lesions are limited to the bone; cases with extraosseous lesions in addition to the bone lesions are not classified as cases of primary ATLL), so that the precise characteristics of this disease remain unknown [1,5-9]. Since localized primary ATLL of the bone is classified as acute type, a poor prognosis would be expected [10,11], and allogeneic transplantation is considered as the standard treatment [10,12]. The prognosis has been reported to be especially poor in patients with multiple bone lesions [1,5,7,9], while being relatively good in patients with a solitary bone lesion [6,7]. Therefore, the eligibility criteria for allogeneic transplantation should be carefully considered in patients with solitary bone lesions. In this paper, we present a case of localized primary ATLL of the bone, along with an overview of the mechanism, prognosis, and treatment strategies, and a review of the literature.

Case

A 73-year old man. He had a past history of benign prostatic hyperplasia, which had been treated by prostatectomy. His family history was unremarkable. A plain X-ray of the left leg showed an osteolytic lesion in the left tibia (Figure 1a). Bone scintigraphy revealed abnormal accumulation at the same site (Figure 1b). Serological test for anti-human T-cell leukemia virus type 1 (HTLV-1) antibody was positive, and the serum soluble interleukin-2 receptor (IL-2 R) level was elevated to 21,100 U/mL. Southern blotting of the peripheral blood were not done, however, there were no atypical cells in the peripheral blood. The laboratory findings are shown in (Table 1). Serum parathyroid hormone-related peptide (PTHrP) was within normal range. A biopsy was performed at the site of the lesion in the left tibia. Hematoxylin-eosin (HE) staining revealed proliferating large atypical lymphocytes with irregularities

of the nuclear contours, and some apoptotic bodies (Figure 3a and b). Immunohistochemistry revealed positive staining for CD3, 4 and 5, and CCR4 proteins (Figure 3c-j), and negative staining for CD7, 8, 20, 30 and 56 and T-cell restricted intracellular antigen (TIA) (Figure 3k-v). Southern blotting performed on the bone biopsy specimen also showed a positive result for HTLV-1 DNA monoclonal integration (Figure 2a). Based on the above findings, the patient was diagnosed as having ATLL of the bone. Southern blotting performed on a bone marrow specimen showed negative results for HTLV-1 DNA monoclonal integration (Figure 2b). Positron emission tomography□computed tomography (PET-CT) showed multiple areas of abnormal accumulation in various bone regions, but no abnormal accumulation in any organs other than the bones (Figure 4a). Based on the above findings and the classification criteria, the patient was diagnosed as having localized primary ATLL of the bone, acute type [10,11]. CHOP therapy (vincristine, cyclophosphamide, doxorubicin, and prednisolone) was started in July, Year X-1 (Figure 5). Taking into account the age and wishes of the patient, allogeneic transplantation was withheld. As the patient reported recurrent bone pain throughout the body, bone scintigraphy was performed after 3 cycles of treatment. The results showed worsened accumulation in the left tibia and new accumulation in the left ankle joint, ribs on both sides and both the ilia (Figure 1c). Therefore, he was diagnosed as having progressive disease (PD) [13] and switched to mLSG15 therapy (vincristine, cyclophosphamide, doxorubicin and prednisolone; doxorubicin, ranimustine and prednisolone; vincristine, etoposide, carboplatin and prednisolone). After the end of the first treatment cycle, PET-CT was performed, which showed disappearance of the abnormal accumulations seen prior to the start of the mLSG15 therapy, but new accumulations in the left humerus and right tibia. Based on the findings, PD was diagnosed again (red arrow in Figure 4b) [13]. Grade 4 leukopenia and neutropenia were also detected. In addition, the patient had grade 3 anorexia and generalized malaise (Common Terminology Criteria for Adverse Events (CTCAE) version 5.0) [14]. He refused further treatment and was scheduled for follow-up observation. However, in December, Year X-1, he again presented with relapse of the bone pain throughout the body, and was started on treatment with lenalidomide. The treatment proved ineffective and was switched to mogamulizumab in January, Year X. He received 6 doses, but the bone pain throughout the body only worsened. In February, Year X, blood examination revealed an increase in the serum calcium (Ca) level (corrected Ca: 16.5 mg/dL). Mogamulizumab was discontinued and replaced with only symptomatic treatment, including a bisphosphonate, PSL, morphine, etc. As of March, Year X, his performance status (PS) is 4.

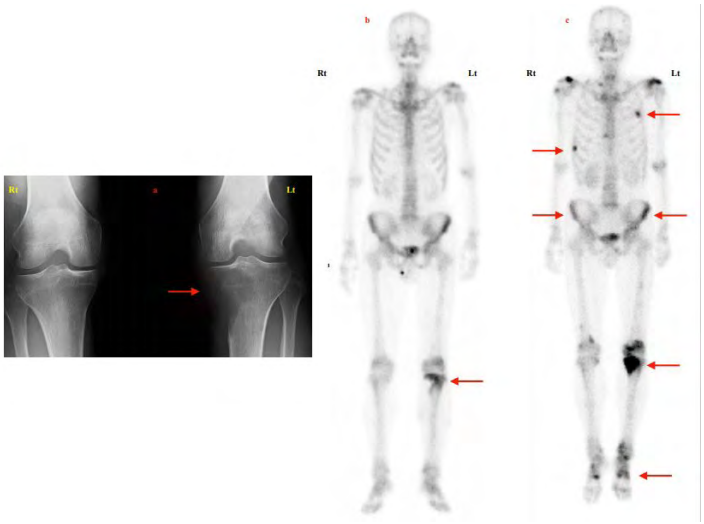

Figure 1: Bone images a. (X-P before treatment): Detection of an osteolytic lesion in the left tibia. (indicated by the red arrow.) b. (Bone scintigraphy before treatment): Detection of abnormal accumulation in the left tibia. (indicated by the red arrow.) c. (Bone scintigraphy after end of 3 cycles of CHOP therapy): Worsened accumulation in the left tibia and new accumulation in the left ankle joint, both ribs and both ilium. (indicated by the red arrow.)

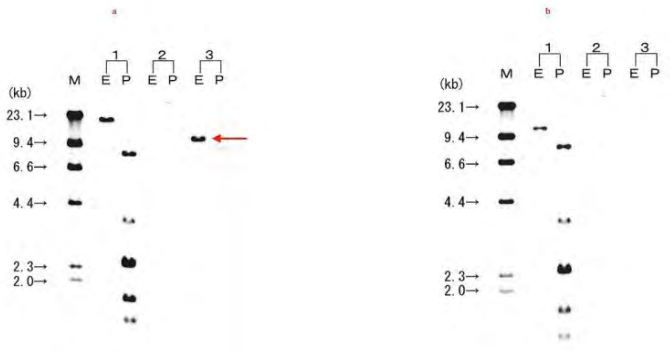

Figure 2: HTLV-1 DNA proviral integration by southern blotting 1: Positive controls, 2: Negative controls, 3: Patient specimens. a: Positive in the biopsy of the left tibia (indicated by the red arrow.) b: Negative with bone marrow blood.

CBC		Biochemistry		Tumor Marker		Immuno-Serological findings		HTLV-I DNA Southern blotting	
WBC	8,400/μL	T.P	7.1 g/dL	sIL-2R	21,100 U/mL	HTVL-I	Ab positive	Bone specimen	positive
Band	2.0%	Alb	4.1 g/dL	CEA	1.4 ng/mL	IgG	1362 mg/dL	Peripheral blood	not done
Ly	14.0%	BUN	17 mg/dL	CA19-9	6.2 ng/mL	IgA	381 mg/dL	Bone marrow	negative
Mono	4.0%	Cr	0.73 mg/dL	PSA	1.390 ng/mL	IgM	72 mg/dL		
Eo	0.5%	T-Bil	0.9 mg/dL			ANA	<40 times		
Ba	0.5%	AST	20 IU/L						
RBC	410 ×10⁴ /μL	ALT	17 IU/L						
Hb	14.0 g/dL	LDH	196 IU/L						
Hct	44.1%	ALP	234 IU/L						
MCV	107.6 fL	AMY	61 IU/L						
MCH	34.1 pg	γ—GTP	15 IU/L						
Plt	30.8×10⁴/μL	T-CHO	236 mg/dL						
Reti	6.0%	BS	99 mg/dL						
Urine	Normal	CRP	0.1 mg/dL						
		Hormone							
		PTHrP	1.0 pmol/L						

Abbreviations: WBC: White Blood Cells; Band: Band Cell; Ly: Lymphocyte; Mono: Monocyte; Eo: Esinophil; Ba: Basophil; RBC: Red Blood Cell; Hb: Haemoglobin; Hct: Hematocrit; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Haemoglobin; Plt: Platelet; T.P: Total Protein; Alb: Albumin; BUN: Blood Urea Nitrogen; Cr: Creatinine; T-BIL: Total-Bilirubin; AST: Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase; ALP: Alkaline Phosphatase; AMY: Amylase; γ-GTP: γ-Guanosine Triphosphate; T-CHO: Total Cholesterol; BS: Blood Sugar; CRP: C-Reactive Protein; PTHrP: Parathyroid Hormone-related Peptide; sIL-2R: Soluble Interleukin-2 Receptor; CEA: Carcinoembryonic Antigen; CA19-9: Carbohydrate Antigen 19-9; PSA: Public Service Announcement; HTLV-1 Ab: Human T-Cell Leukaemia Virus Type 1 Antibody; IgG: Immunoglobulin G; IgA: Immunoglobulin A; IgM: Immunoglobulin M; ANA: Antinuclear Antibody

Table 1: Laboratory findings when examined at Department of Hematology.

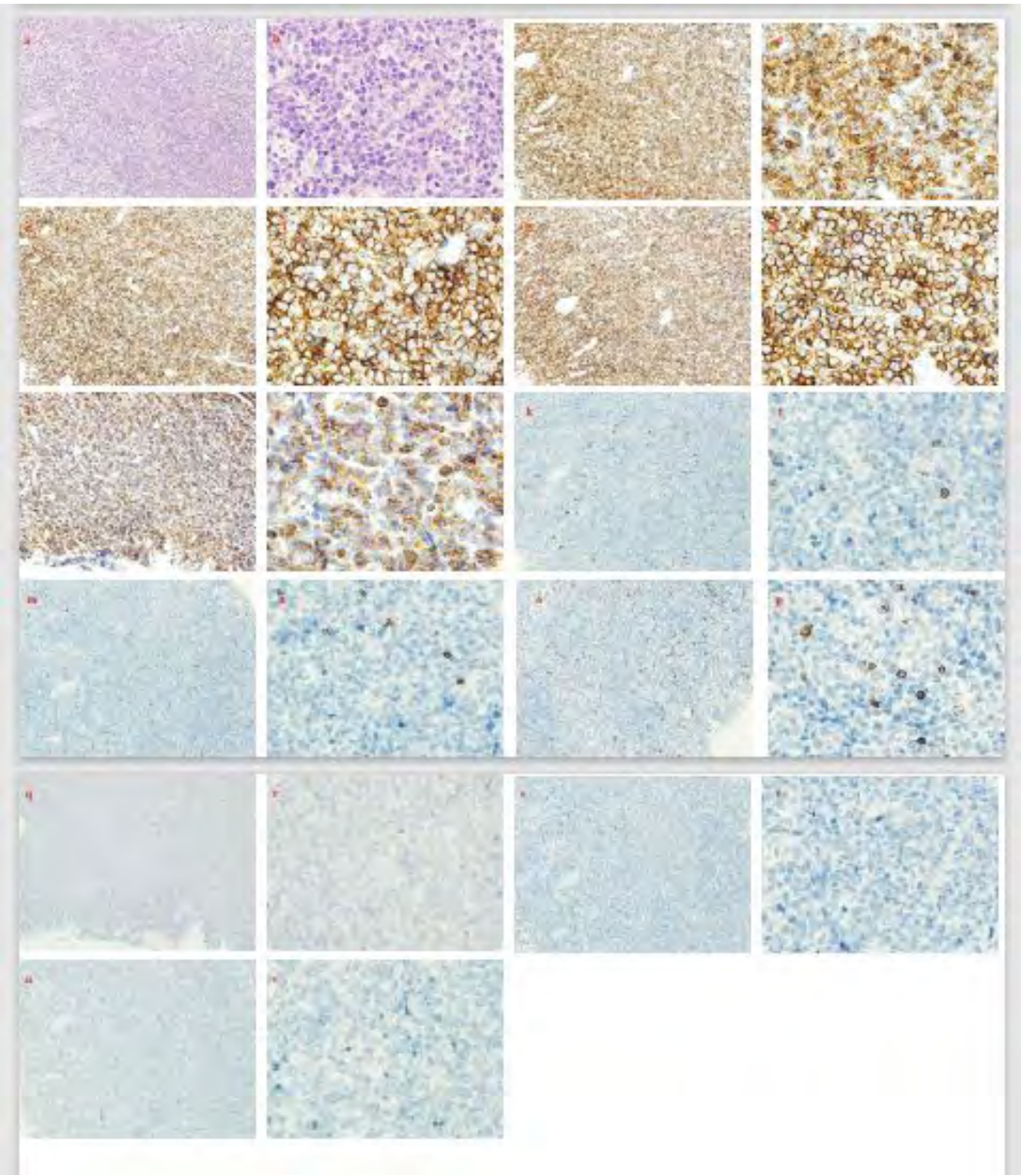

Figure 3: Bone biopsy. a (HE×100); positive, b (HE×400); positive, c (CD3×100); positive, d (CD3×400); positive, e (CD4×100); positive, f (CD4×400); positive, g (CD5×100); positive, h (CD5×400); positive, i (CCR4 protein×100); positive, j (CCR4 protein×400); positive, k (CD7×100); negative, l (CD7×400); negative, m (CD8×100); negative, n (CD8×400); negative, o (CD20×100); negative, p (CD20×400); negative, q (CD30×100); negative, r (CD30×400); negative, s (CD56×100); negative, t (CD56×400); negative, u (TIA×100); negative,v (TIA×400); negative

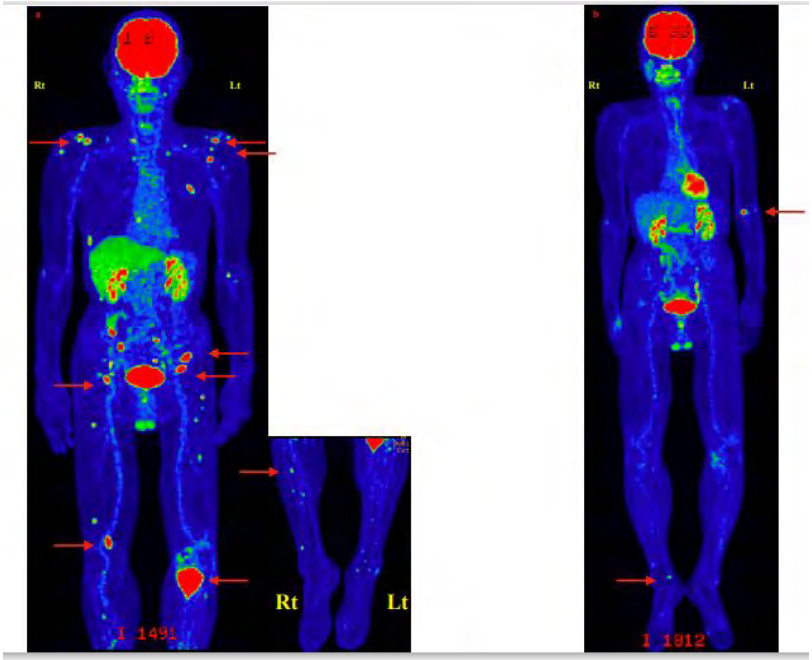

Figure 4: PET-CT findings, a. (Before treatment): Multiple abnormal accumulations in bone regions. (indicated by the red arrow.) b. (After end of the first cycle of mLSG therapy): Disappearance of the abnormal accumulation seen before the treatment, but new accumulation in the left humerus and right tibia. (indicated by the red arrow.)

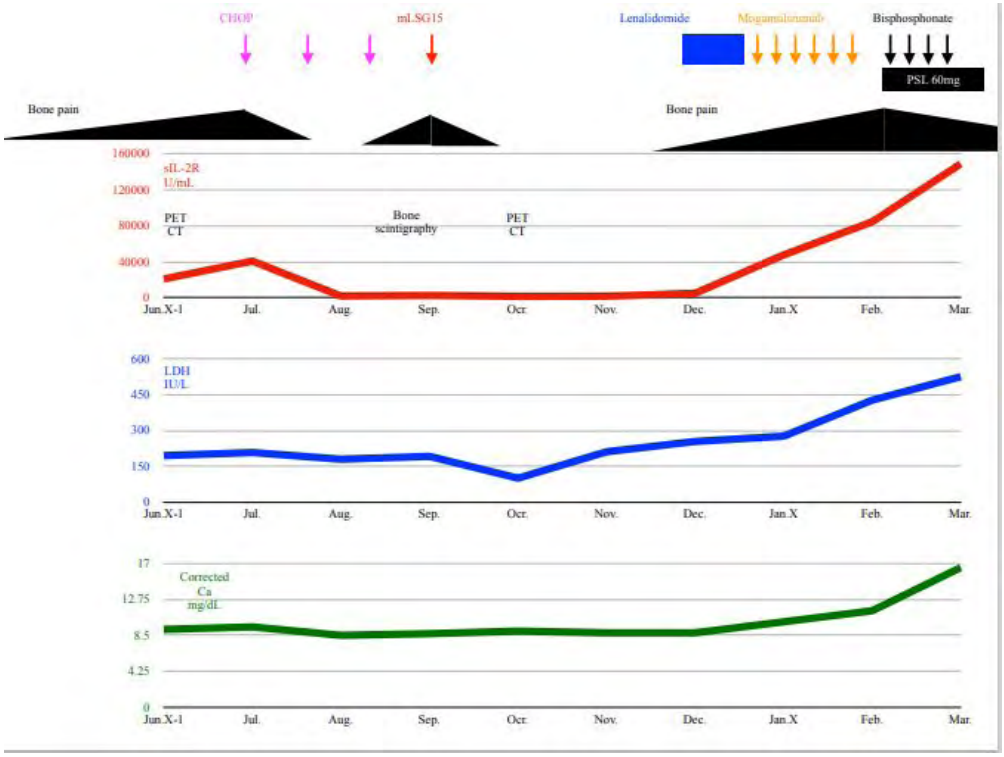

Figure 5: Clinical course.

Discussion

We encountered a case of localized primary ATLL of the bone (with multiple bone lesions) which showed transient response, but eventually resistance, to chemotherapy; lenalidomide, and mogamulizumab were also transiently effective, with subsequent development of treatment resistance.

As the mechanism of development of the bone lesions in ATLL, it is known that ATLL cells accelerate bone resorption by producing PTH rP1) and also activate osteoclasts through increasing receptor activator of nuclear factor- kappa B ligand (RANKL) activity [15]. It has been reported that, in cases of localized primary ATLL of the bone, ATLL cells produce MIP-1 and induce the RANKL-RANKL interaction, leading to osteoclast activation [1,5]. However, factors that determine whether a patient develops solitary or multiple lesions remain unknown. Therefore, the possibility of simply observing the process of tumor development could not be ruled out.

There are only 9 case reports of localized primary ATLL of the bone, including the present case (Table 2). The treatments vary, and there is no established treatment. Allogeneic transplantation was not performed in any of the cases. Of the 9 reported patients, 3 were alive and 6 had died as of the time of writing of this paper. The median survival duration was poor, being 9 months (range, 7 to 39 months). However, 2 patients with solitary lesions (Case 4 and Case 6) survived for relatively long periods of time. On the other hand, of the remaining 7 patients with multiple lesions, 6 died (only the case reported herein remains alive, but it looks unlikely that he will survive for long). In addition, patients with multiple lesions are considered to have a poor prognosis, with shorter survival times. Thus, since the prognosis differs depending on whether the lesion is solitary or multiple, the treatment strategy needs to be devised separately for patients with solitary and multiple lesions.

Prognostic indices for ATLL include the prognostic index for acute- and lymphoma-type ATL (ATL-PI) and the Japan Clinical Oncology Group prognostic index (JCOG-PI). However, these indices do not take into account factors associated with bone lesions [16,17]. In addition, there are reports suggesting that CCR4-positive ATLL has a particularly poor prognosis [18,19], but the significance of CCR4 positivity in localized primary ATLL of the bone remains unknown. No information is available on the CCR4 protein expression status for 8 of the 9 cases, that is, in any of the reported cases, except the patient reported herein [1,5-9]. It would be desirable to identify factors related to bone lesions that would be predictive of the outcomes in the future.

Since the clinical subtype of ATLL is determined by a process of elimination [10], localized primary ATLL of the bone is classified as the acute type [11]. In principle, allogeneic transplantation is considered as the standard treatment for the acute types [10,12]. However, since patients with solitary lesions survive for relatively long periods of time, the eligibility for allogeneic transplantation needs to be carefully examined for patients with solitary bone lesions. It may be reasonable to follow up patients with solitary bone lesions after chemotherapy (mLSG15 therapy and mogamulizumab) [20] or chemotherapy combined with radiation, [6] and examine the eligibility of these patients for allogeneic transplantation on a case-by-case basis. However, since allogeneic transplantation is considered as the only potentially curative treatment [12,13,21], it has been suggested that treatment without allogeneic transplantation may be challenging [1]. Careful follow-up of the patients is necessary. Since the prognosis is considered to be poor in patients with multiple bone lesions, allogeneic transplantation should be considered [12,13,21]. In addition, since these patients are reported to be at a higher risk of central nervous system infiltration [1], it is essential to take measures to prevent central nervous system infiltration [1].

Case	Age (years)	Sex	Clinical symptoms	Bone lesions	Hyper calcemia	CNS invasion
1	41	F	Fever, Backache	Multiple	+	+
2	65	M	Right coxodynia	Right femur Lumbar vertebra	-	+
3	77	M	Chest pain Multiple bone pain	Multiple	-	n.a
4	57	M	Right knee pain	Right Tibia	n.a	n.a
5	40	F	Right hip joint pain	Multiple	n.a	n.a
6	32	M	Right fore arm pain	Skeletal	-	n.a
7	35	M	right clavicle and right ankle joint pain	Multiple	-	n.a
8	53	M	Lumbago	Multiple	+	n.a

9	73	M	Left knee pain	Multiple	-	-

Therapy	Best response	Final response	Outcome	OS (months)	Cause of death	Reference
mLSG15 ESHAP	Response	PD	Death	7	CNS invasion	[1]
mLSG15 IT	Response	PD	Death	10	CNS invasion	[1]
CY,DOX,VCR,PSL,bisph osphonate	Bone pain completely disappeared	Bone pain completely disappeared	Survival	9	-	[5]
Rx/amputation/CHOP/ MIT/VP-16/PSL	CR	CR	Survival	22	-	[6]
Chemotherapy	n.a	n.a	Death	8	Respiratory Failure	[7]
Chemotherapy	Bone lesion disappeared	Bone lesion disappeared	Death	24	Respiratory Failure	[7
Rx/VEPA/CVEPP	Response	PD	Death	39	MOF	[8]
Chemotherapy	n.a	n.a	Death	6	Candidiasis Pneumonia	[9]
CHOP/mLSG15/IT Lenalidomide Mogamulizumab Bisphosphonate	PD	PD	Survival	9	-	This case

Abbreviations: F, Female; M: Male; +: Positive; -: Negative; CNS: Central Nervous System; n.a: Not Available;m: Modified;

LSG15: vincristine+cyclophosphamide+doxorubicin+prednisolone+doxorubicin+ranimustine+prednisolone+vincristine+etoposide+carboplatin+prednisolone;

ESHAP: etoposide+cytarabine+cisplatin+methylprednisolone; IT: Intrathecal Injection; CY: Cyclophosphamide;

DOX: Doxorubicin; VCR: Vincristine; PSL: Prednisolone; Rx: Radiation Therapy;

CHOP: cyclophosphamide+doxorubicin+vincristine+prednisolone; MIT: Mitoxantrone; VP-16: etoposide;

VEPA: vincristine+cyclophosphamide+doxorubicin+prednisolone;

CVEPP: cytarabine+vincristine+cyclophosphamide+prednisolone+pepleomycin; CR: Complete Response;

PD: Progressive Disease; OS: Overall Survival; MOF: Multiple Organ Failure

Table 2: Reports of localized primary ATLL of bone.

There is a report [22] suggesting the effectiveness of denosumab for the bone lesions of ATLL and of the direct antitumor activity of bisphosphonates against ATLL [22]. However, neither drug has yet been approved for this indication in Japan, and their approval in the future is awaited. (In Japan, bisphosphonate is approved for the treatment of hypercalcemia in patients with malignant tumors). In the patient reported herein, a bisphosphonate was administered after the patient was detected as having hypercalcemia, but no clear effect of the drug could be observed.

In conclusion, it would be desirable to elucidate the mechanism of onset of localized primary ATLL of the bone, the differences in the mechanisms between the development of solitary and multiple lesions, the prognostic factors, and the treatment strategies. Towards this end, it is necessary to accumulate and analyze cases in the future.

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