

Hand Osteolysis in Patients with Adult T-Cell Leukemia-Lymphoma: Radiographic Characteristics

Shigeru Ehara,¹ Kei Takahashi,² Jun Nishida,³ Masataka Uetani,⁴
Kenjirou Ohashi^{5,*} and Takatoshi Aoki⁶

¹Department of Radiology, Iwate Medical University School of Medicine, Morioka, Iwate, Japan

²Iwate Medical University School of Liberal Arts, Morioka, Iwate, Japan

³Department of Orthopedic Surgery, Iwate Medical University School of Medicine, Morioka, Iwate, Japan

⁴Department of Radiology, Nagasaki University School of Medicine, Nagasaki, Nagasaki, Japan

⁵Department of Radiology, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan

⁶Department of Radiology, University of Occupational and Environmental Health School of Medicine, Kitakyushu, Fukuoka, Japan

Adult T-cell leukemia-lymphoma (ATLL) is caused by human T-cell lymphotropic virus I (HTLV-I) infection. Among ATLL cases, 70% of patients present with leukemia and the remaining patients present with lymphoma. Hand osteolysis in the patients with ATLL is considered as paraneoplastic syndrome and caused by parathyroid hormone-related peptide (PTHrP) released from tumor cells. Radiographic features are similar to hyperparathyroidism, but the distribution of osteolysis in hands appears to be slightly different with the authors' experiences. The objective of this study was to identify radiographic characteristics of hand osteolysis associated with ATLL. We included six ATLL patients (5 men and 1 woman; age range, 45-71 years). All the patients presented with acute leukemia, and three were associated with hypercalcemia and pain in various locations including hands. Patterns of osteolysis on hand radiographs were evaluated and recorded independently by three musculoskeletal radiologists. We analyzed the distribution of the bone resorption in the ray distribution of the hand, finger predilection, and the difference between the ulnar and radial sides. The bone resorption was characterized by frequent involvement of the distal and proximal phalanges, predilection of ring fingers and prominent involvement on the ulnar side, compared with frequent involvement of proximal and middle phalanges, index and middle fingers, and on the radial side in the bone resorption of typical hyperparathyroidism. Such distribution may be a characteristic feature of hand osteolysis in patients with ATLL. The present findings are helpful for physicians to differentiate PTHrP-mediated osteolysis in ATLL from parathyroid hormone-mediated hyperparathyroidism.

Keywords: adult T-cell leukemia-lymphoma; hyperparathyroidism; osteolysis; parathyroid hormone-related peptide; radiography

Tohoku J. Exp. Med., 2015 May, 236 (1), 63-69. © 2015 Tohoku University Medical Press

Introduction

Adult T-cell leukemia-lymphoma (ATLL) is caused by human T-cell lymphotropic virus I (HTLV-I) infection. This human retrovirus is transmitted by sexual contact, breast-feeding, and contamination with infected blood. A high prevalence of carriers is reported in Japan (particularly on its southeastern Pacific coast), sub-Saharan Africa, northeastern South Africa, and the Caribbean islands. The annual incidence among carriers is known to be low, and it is 1.5/1,000 (men) and 0.5/1,000 (woman), and the cumulative life-long risk of ATLL is 2.5% (Yamaguchi 1994;

Yamaguchi and Watanabe 2002; Qayyum and Choi 2014).

Among ATLL cases, 70% of patients present with leukemia and about 20%-30% present with lymphoma. There are 4 clinical types: smoldering, chronic, lymphomatous, and acute. Clinical features include lymphadenopathy (60%), hepatomegaly (26%), splenomegaly (22%), skin lesions (39%), and hypercalcemia (32%). Bone changes are seen in patients with acute type (Yamaguchi 1994; Yamaguchi and Watanabe 2002; Qayyum and Choi 2014).

In acute ATLL, bone resorption is uncommon, but was reported in several case reports (Ohuchida et al. 1985; Aoki et al. 1987; Austin et al. 1987; Kessar et al. 1996). Bone

Received January 6, 2015; revised and accepted April 20, 2015. Published online May 15, 2015; doi: 10.1620/tjem.236.63.

Correspondence: Shigeru Ehara, M.D., Department of Radiology, Iwate Medical University School of Medicine, 19-1 Uchimaru, Morioka, Iwate 020-8505, Japan.

e-mail: ehara@iwate-med.ac.jp

*Present address: Department of Radiology, University of Iowa Hospitals and Clinics, Iowa City, IA, USA.

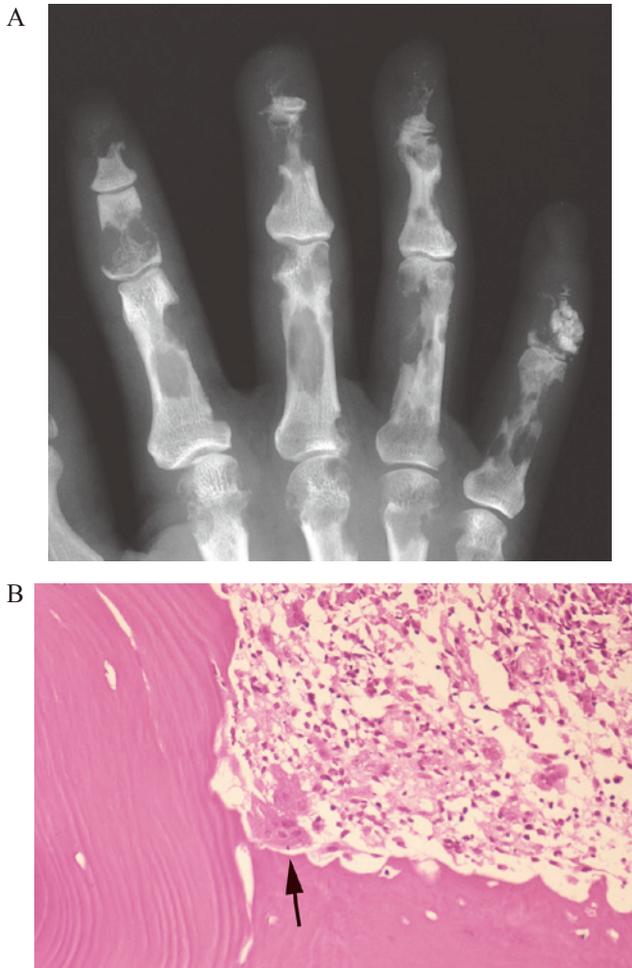


Fig. 1. Phalangeal bone resorption in ATLL.

A. Posterior-anterior radiography of the hand shows severe punched-out bone resorption (eccentric and central resorption) in the phalanges (59-year-old man). Bone density of the phalanges is relatively maintained. These findings may be confused with tumor infiltration. B. Histology of the osteolytic lesion (Hematoxylin-Eosin staining, case of Fig. 1A). Active bone resorption by osteoclast is noted (arrow). No tumor infiltration is seen. This finding is consistent with paraneoplastic bone resorption.

changes consist of two types: tumor-cell infiltration into the bone marrow and paraneoplastic syndrome with no tumor infiltration. In imaging studies, the latter phenomenon, typically seen in the hand, is characterized by a lack of bone marrow infiltration in the area of bone resorption (Fig. 1). Bone resorption and hypercalcemia are caused by the over-expression of interleukin 1 (IL-1), transforming growth factor- β (TGF- β), and parathyroid hormone-related peptide (PTHrP) (Wano et al. 1987; Niitsu et al. 1988; Motokura et al. 1989).

PTHrP has been known as a main factor of bone resorption in various malignancies (Wysolmerski and Broadus 1994), ATLL is associated with osteolysis severe enough to assess on radiography. ATLL cells produced PTHrP that could cause hypercalcemia in patients with

ATLL (Motokura et al. 1989). PTHrP mRNA was expressed in ATLL cells, and the parathyroid hormone (PTH)-like activity was detected in the pleural effusion and ascites of ATLL patients (Motokura et al. 1988). PTHrP in combination with interleukin-1 α enhanced the degree of hypercalcemia in certain circumstances (Motokura et al. 1989). PTHrP induced most osteolytic changes in ATLL patients, particularly those occurring in the peripheral skeleton, typically in hands and feet (Watanabe et al. 1990). In the case of the PTHrP-induced osteolysis, activated osteoclasts were noted in the area of bone resorption, without tumor cell invasion (Fig. 1B), as reported previously (Ohuchida et al. 1985; Aoki et al. 1987). This aberrant PTHrP secretion caused changes similar to those observed in hyperparathyroidism, including subperiosteal resorption and central punched-out lesions known as brown tumors. However, the imaging characteristics of PTHrP-mediated changes were not well described in the literature.

In contrast to the PTHrP-induced osteolysis, the pattern of bone resorption in hyperparathyroidism was well described. Meema and colleagues (1978) reported higher involvement at the radial surface than the ulnar surface of the phalanges in patients with chronic renal failure and secondary hyperparathyroidism. Sundaram et al. (1979) also reported that the earliest osteodystrophic changes in patients with chronic hemodialysis occurred in the phalangeal tuft. Resnick et al. (1981) reported frequent involvement of radial aspect of index and middle fingers and phalangeal tuft in patients with secondary hyperparathyroidism.

Our experience indicated that the pattern of bone resorption in ATLL may differ from that of hyperparathyroidism, with more prominence distally and ulnarly. The objective of this study was to elucidate the radiographic patterns of bone resorption in the hands of patients with ATLL and to compare them with the reported radiographic findings of hyperparathyroidism.

Materials and Methods

Patients

Included in this study were six ATLL patients seen in four hospitals during a 10-year period. There were five men and one woman, ranging in age from 45-71 years (median, 58 years) (Table 1). All the patients presented with acute leukemia with characteristic hematological features and positive HTLV-I antibody. Hypercalcemia was documented in three patients (one not present, and two unknown). Pain was documented in the various locations. The diagnosis was based on peripheral blood and bone marrow findings. Radiography in all cases was obtained because of pain and skin rashes. Radiographs included 12 hands from the 6 patients, with both posterior-anterior view and oblique view in 2 patients and only the posterior-anterior view in 4 patients. The diagnosis of paraneoplastic bone resorption, not tumor invasion, was confirmed in one case by biopsy (Fig. 1), and the diagnosis of the other five cases was confirmed by clinical course (Fig. 2). This study is compliant with the legislation of personal information protection, and the approval of the institutional review board was obtained from Iwate Medical University where the analysis was performed.

Table 1. Summary of patients with acute type of ATLL.

Age, gender	Clinical type	Hypercalcemia	Location of osteolytic lesions (digits*, bones**, side***)	Type of hand bone resorption****	Bones involved except hands*****
45 M	acute	+	Right: all; P, D (Mt, M); R = U Left: all; P, D (Mt, M); R < U	periosteal periosteal	skull, lumbar spine, pelvis, feet
49 M	acute	?	Right: all; P, D (Mt); R > U Left: all; P, D (Mt); R > U	periosteal (eccentric, central) periosteal (eccentric, central)	feet
57 F	acute	?	Right: four; P (M); R = U Left: all; P, D (Mt, M); R = U	eccentric (central), Fig. 2C eccentric (central)	skull, lumbar spine, pelvis, feet
59 M	acute	-	Right: all; P, D (Mt, M); R < U Left: all; P, D (Mt, M); R = U	eccentric (central) eccentric (central), Fig. 1A	lumbar spine, pelvis, femora
62 M	acute	+	Right: two; P; R = U Left: four; Mt; R < U	eccentric (periosteal, central), Fig. 2B eccentric (periosteal, central)	none
71 M	acute	+	Right: all; P, D; R = U Left: four; P, D (M); R > U	periosteal periosteal, Fig. 2A	generalized osteoporosis

*involved digits based on the majority of three observers, five: all five digits, four: all digits except thumb, two: middle and ring fingers

**dominant lesion (less common lesion) based on the majority of three observers. Mt, metacarpal; P, proximal phalanx; M, middle phalanx; D, distal phalanx.

***dominant side based on the majority of three observers, R > U: more lesions on the radial side, R < U: more lesions on the ulnar side, R = U: no significant differences.

****dominant pattern of bone resorption (less common pattern), resorption of phalangeal tuft is present in all the cases.

*****direct tumor invasion could not be excluded in bones other than hands and feet.

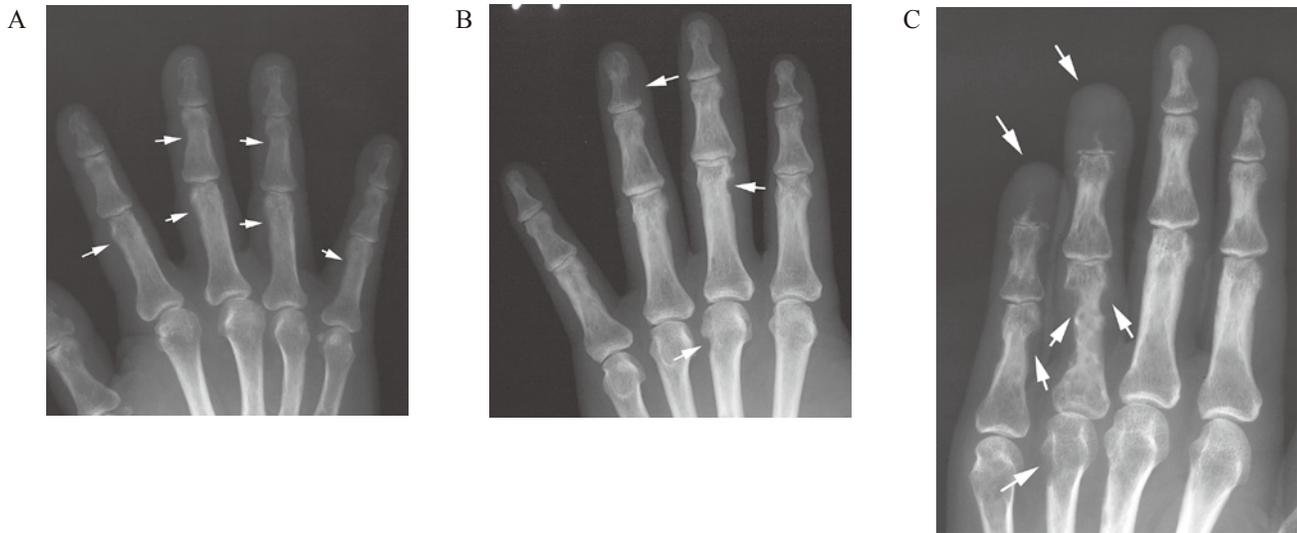


Fig. 2. Patterns in the bone resorption.

A. Posterior-anterior radiography of mild subperiosteal bone resorption (arrows). This finding is similar to hyperparathyroidism (71-year-old man). B. Localized eccentric bone resorption (arrows) (62-year-old man). This finding is not typical for hyperparathyroidism. C. Severe eccentric bone resorption, prominent in the ring and little fingers (57-year-old woman). Resorption of the phalangeal tuft is also severe (arrows), atypical for hyperparathyroidism.

Methods

The hand radiographs were evaluated and recorded independently by three musculoskeletal radiologists, each having more than 10 years of experience. The observers knew the diagnosis, but did not know the other observers' evaluations. Patterns of bone resorption in the proximal and middle phalanges of the metacarpals included subperiosteal resorption (resorption of the cortical surface), eccentric bone resorption (resorption of more than one cortical thickness) and central bone resorption (epicenter of resorption in the bone marrow,

brown tumor). The radial and ulnar sides were graded separately.

Inter-observer agreement: The index of agreement among the three raters was assessed using the Fleiss' kappa test at 5 levels (distal radius, distal ulna, metacarpal, proximal phalanx and middle phalanx) in each of the 5 digits. The statistical significance of observed agreements was determined.

Ray distribution: Ray (longitudinal) distribution was evaluated

at the wrist (distal radius and ulna), carpus, metacarpals, and phalanges (proximal, middle, and distal phalanges). For each of the three observers, differences in the rate of positive findings between these locations were assessed using Friedman's test, with a statistical significance of $p < 0.05$. The significance of individual differences was then evaluated by using Bonferroni's multiple comparisons test.

Finger predilection: Finger predilection (thumb, index, middle, ring, and little finger) was assessed using Friedman's non-parametric test. The statistical significance of differences between the observers was also evaluated. The average rate was assessed using Friedman's test, and the differences in the rates among the 5 digits were considered statistically significant for $p < 0.05$. The significance of differences was evaluated using Bonferroni's multiple comparisons test.

Side differences: ulnar vs. radial sides: We compared the bone resorption on the ulnar or the radial side at 3 levels (metacarpals, proximal phalanx, and middle phalanx) and the difference between the ulnar and the radial side of the each digit. Differences among the 3 observers were evaluated and the significance was determined using the Chi-square test ($p < 0.05$).

Results

Clinical data

Bone lesions of the patients were summarized in Table 1. Predominant patterns were periosteal resorption in three cases (Fig. 2A), and eccentric bone resorption in three cases (Fig. 2B and C). Resorption of the phalangeal tuft existed in all the cases.

Inter-observer agreement

At the metacarpal, the agreement between observers for the ulnar and middle sides was not statistically significant, with $p < 0.05$ in the thumb. The agreement for the radial side in the little finger was also not significant ($p < 0.05$). At other locations, the levels of agreement were better than moderate, $\kappa > 0.4$.

Ray distribution

Differences in the rate of positive findings among the 7 locations were statistically significant for all 3 observers. The positive rate at the distal phalanx was significantly higher than that of all other locations (Fig. 3). Except for the distal phalanx, the observed positive rate at the proximal phalanx was the highest among the metacarpal bone, proximal phalanx, and middle phalanx for all 3 observers, although the differences were not statistically significant between 2 of these 3 levels.

Finger predilection

The positive rate of the ring finger was higher than that of the other fingers, although not all the rate differences were statistically significant (Fig. 4). As assessed using Friedman's non-parametric test, the differences in the positive rates among the 5 fingers were statistically significant for observers 1 and 3 but not significant for observer 2 ($p < 0.05$). The positive rate in the thumb was significantly less than the rates of the middle and ring fingers ($p < 0.05$), but this difference may be related to the small sample size.

Side differences: ulnar vs. radial sides

Difference in level: More positive findings were observed 1) on the ulnar side than the radial side of the metacarpal and 2) on the radial side than the ulnar side of the proximal and middle phalanges (Fig. 5A). However, the differences in the positive rate between the 2 sides were not statistically significant for any of the 3 levels ($p < 0.05$).

Difference in finger: The observed rates at the ulnar side involvement were slightly less than those at radial side of the index and little fingers (Fig. 5B). For the ring finger, the observed rate of the ulnar side involvement was clearly higher than the radial side. However, the difference in the positive rate between the ulnar and radial sides was not statistically significant for any of the fingers.

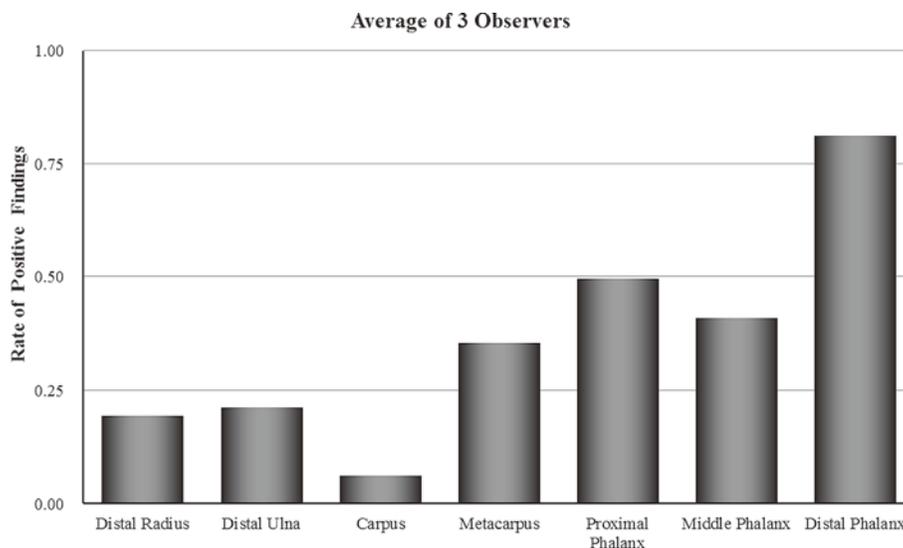


Fig. 3. Ray distribution.

Average of the 3 observers. Involvement of distal and proximal phalanges is common.

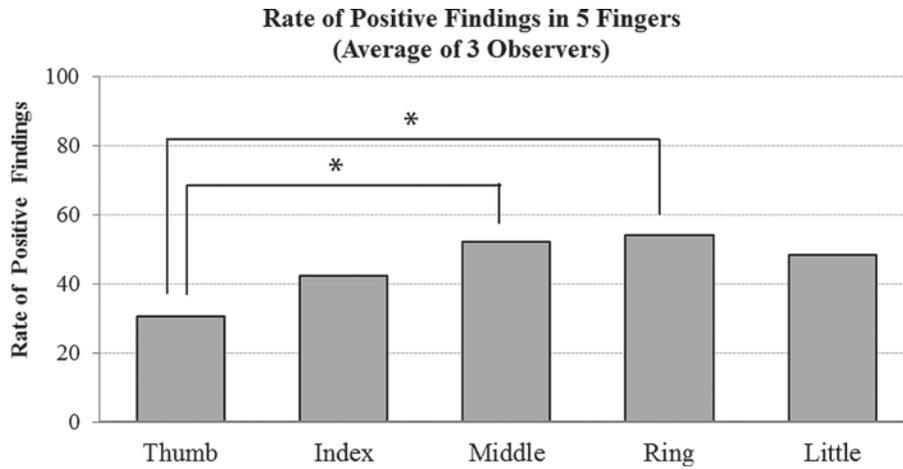


Fig. 4. Finger predilection. Average of the 3 Observers (*significantly different rate, $p < 0.05$). Involvement of ring finger is the most common, although not significant when compared with the adjacent fingers.

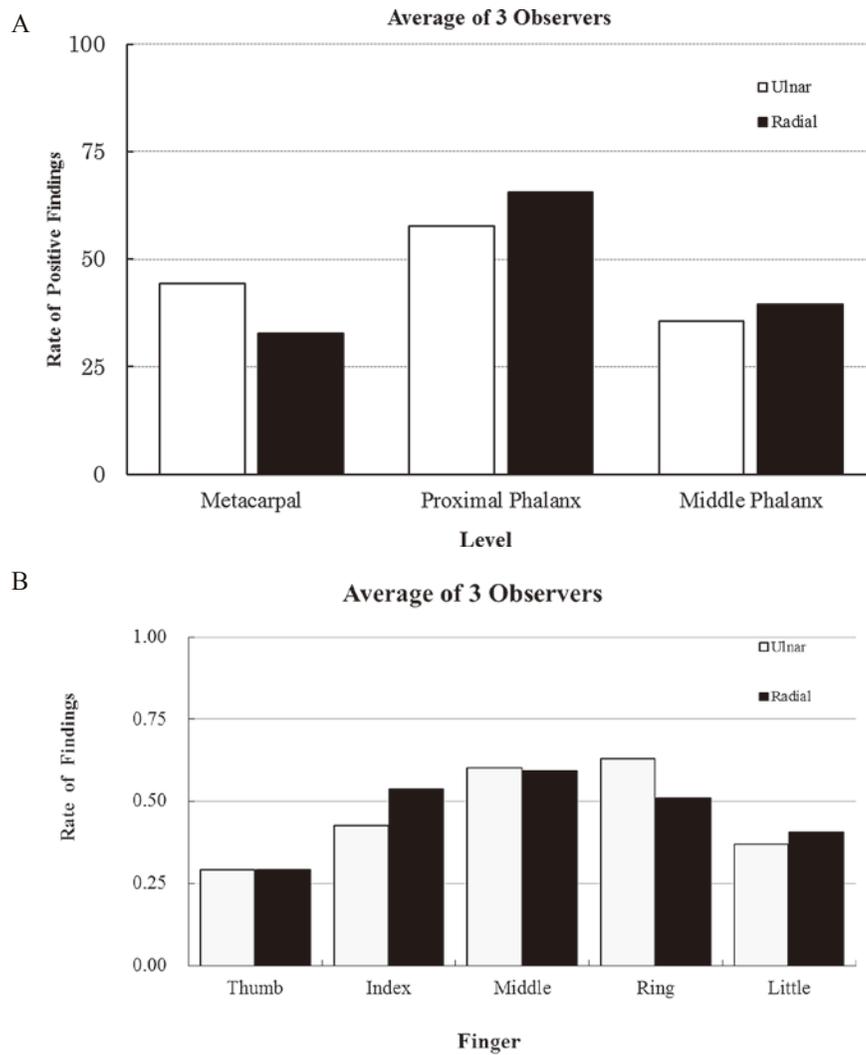


Fig. 5. Side differences: ulnar vs. radial sides. A. Difference in the 3 tubular bones. Average of the 3 observers. There is no side difference at metacarpals or phalanges. B. Differences between radial vs. ulnar sides of the finger. Average of the 3 observers. Ulnar side involvement is evidently more common in the ring finger, although statistically not significant.

Discussion

ATLL is a concern of public health in the endemic region, and prompt and appropriate diagnosis is important. Although overall imaging findings in ATLL are non-specific, osteolysis as a paraneoplastic syndrome is a relatively characteristic feature. Paraneoplastic osteolysis due to PTHrP produced by ATLL cells was described in 1980s (Ohuchida et al. 1985; Aoki et al. 1987; Austin et al. 1987; Kessar et al. 1996), but most such reports were only in case reports, and the patterns of osteolysis have not been well characterized. PTHrP-induced osteolysis seems to be a relatively common phenomenon in overall malignancies, but cases with severe osteolysis suitable for imaging analysis are rare and mainly seen in ATLL. Correlation with the clinical findings and hormonal activity may be a subject of investigation in the future.

In our study, the dominant radiographic pattern of hand osteolysis was either periosteal or eccentric, and eccentric osteolytic changes on radiography in ATLL patients were slightly different from the well-described hyperparathyroidism (Fig. 2). Such well-defined osteolytic changes could be easily confused with direct tumor infiltration. In addition, periosteal bone resorption may be similar to that of hyperparathyroidism, but the distribution may be somewhat different. Based on this study, the characteristics of PTHrP-related hand osteolysis are summarized as follows:

1. Distal phalangeal involvement was occasionally prominent, presenting as acro-osteolysis.
2. Although such bone changes may be similar to hyperparathyroidism, frequent changes on the ulnar aspect, particularly in the ring finger, may be characteristic of ATLL, and they differ from those associated with hyperparathyroidism.

The mechanism of such differences in imaging presentation is not certain. Minor differences between PTH and PTHrP may possibly affect the local differences in bone metabolism. In general, clinical presentations of paraneoplastic syndromes are often atypical, and are somewhat different from more “physiologic” hyperparathyroidism. Clinical significance in imaging findings exists in early recognition of paraneoplastic syndrome, not direct tumor invasion, and it contributes to precise tumor staging.

There are several limitations in this study. First, the small number of patients included in our cohort results in inadequate power for analysis. The scarcity of patients with this condition makes it difficult to accumulate an adequate number of cases for statistical analysis. Second, histological confirmation excluding direct tumor infiltration was not obtained, but the clinical course and imaging features are those of paraneoplastic syndrome. Third, no direct correlation between PTHrP value and osteolysis was assessed because of the retrospective nature of the study. Fourth, analysis of the carpus and distal phalanges are somewhat different from tubular bones including metacarpals and

other phalanges. In addition, analysis of the thumb may be somewhat difficult with regular posteroanterior and oblique radiographs.

In conclusion, the frequent involvement of the ring finger possibly on the ulnar side is a feature of PTHrP-related paraneoplastic osteolysis in ATLL patients, which may differ from the typical pattern of hyperparathyroidism. Prominent distal phalangeal involvement representing acro-osteolysis is also a prominent feature.

Acknowledgments

This work has been partly supported by the National Cancer Center Research and Development Fund (Japan).

Conflict of Interest

The authors declare no conflict of interest.

References

- Aoki, J., Yamamoto, I., Hino, M., Torizuka, K., Uchiyama, T. & Uchino, H. (1987) Case report 429. *Skeletal Radiol.*, **16**, 412-415.
- Austin, C.B., Young, J.W., Park, H.J., Needleman, B.W., Handwerker, B.S. & Rosenbaum, R.C. (1987) Massive acroosteolysis in adult T-cell leukemia/lymphoma. *Radiology*, **164**, 787-789.
- Kessar, P., Raftery, M.J. & Blakeney, C.G. (1996) Case report: multiple lytic lesions in HTLV1 associated ATLL in the absence of lymphadenopathy and peripheral blood changes. *Clin. Radiol.*, **51**, 299-301.
- Meema, H.E., Meema, S. & Oreopoulos, D.G. (1978) Periosteal resorption of finger phalanges: radial versus ulnar surfaces. *J. Can. Assoc. Radiol.*, **29**, 175-178.
- Motokura, T., Fukumoto, S., Matsumoto, T., Takahashi, S., Fujita, A., Yamashita, T., Igarashi, T. & Ogata, E. (1989) Parathyroid hormone-related protein in adult T-cell leukemia-lymphoma. *Ann. Intern. Med.*, **111**, 484-488.
- Motokura, T., Fukumoto, S., Takahashi, S., Watanabe, T., Matsumoto, T., Igarashi, T. & Ogata, E. (1988) Expression of parathyroid hormone-related protein in a human T cell lymphotropic virus type I-infected T cell line. *Biochem. Biophys. Res. Commun.*, **154**, 1182-1188.
- Niitsu, Y., Urushizaki, Y., Koshida, Y., Terui, K., Mahara, K., Kohgo, Y. & Urushizaki, I. (1988) Expression of TGF-beta gene in adult T cell leukemia. *Blood*, **71**, 263-266.
- Ohuchida, T., Nishitani, H., Kamikawaji, N., Niho, Y., Ooiwa, T. & Matsuura, K. (1985) “Adult T-cell leukemia/lymphoma” with bone demineralization. *Skeletal Radiol.*, **14**, 194-197.
- Qayyum, S. & Choi, J.K. (2014) Adult T-cell leukemia/lymphoma. *Arch. Pathol. Lab. Med.*, **138**, 282-286.
- Resnick, D., Deftos, L.J. & Parthemore, J.G. (1981) Renal osteodystrophy: magnification radiography of target sites of absorption. *AJR Am. J. Roentgenol.*, **136**, 711-714.
- Sundaram, M., Joyce, P.F., Shields, J.B., Riaz, M.A. & Sagar, S. (1979) Terminal phalangeal tufts: earliest site of renal osteodystrophy findings in hemodialysis patients. *AJR Am. J. Roentgenol.*, **133**, 25-29.
- Wano, Y., Hattori, T., Matsuoka, M., Takatsuki, K., Chua, A.O., Gubler, U. & Greene, W.C. (1987) Interleukin 1 gene expression in adult T cell leukemia. *J. Clin. Invest.*, **80**, 911-916.
- Watanabe, T., Yamaguchi, K., Takatsuki, K., Osame, M. & Yoshida, M. (1990) Constitutive expression of parathyroid hormone-related protein gene in human T cell leukemia virus type 1 (HTLV-1) carriers and adult T cell leukemia patients that can be trans-activated by HTLV-1 tax gene. *J. Exp. Med.*, **172**, 759-765.

Wysolmerski, J.J. & Broadus, A.E. (1994) Hypercalcemia of malignancy: the central role of parathyroid hormone-related protein. *Annu. Rev. Med.*, **45**, 189-200.

Yamaguchi, K. (1994) Human T-lymphotrophic virus type I in

Japan. *Lancet*, **343**, 213-216.

Yamaguchi, K. & Watanabe, T. (2002) Human T lymphotropic virus type-I and adult T-cell leukemia in Japan. *Int. J. Hematol.*, **76** Suppl 2, 240-245.
