A Case of Osteoarthropathy Due to Erdheim-Chester Disease with Overlapping Langerhans’ Cell Infiltration

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Abstract

Histiocytosis sometimes involves the joints, and is one of the important differential diagnoses of osteoarthropathy. A 31-year-old man presented with recurrent fever and bilateral knee arthritis two years prior to admission. He also showed the hypopituitary mass lesion and partial hypopituitarism. X-ray studies showed both osteosclerotic and osteolytic lesions near the large joints. Histological findings of bone biopsy revealed foamy macrophage infiltration, which were CD68+CD1a−S100−, and Erdheim-Chester disease was diagnosed. In addition, CD68+CD1a+ Langerhans’ cells also aggregated in the same lesions, and we thought this case was a rare variant of Erdheim-Chester disease with overlapping histiocytic invasion.

Key words: Erdheim-Chester disease, histiocytosis, Langerhans’ cell, osteoarthropathy

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Introduction

Histiocytosis includes heterogeneous conditions, and is classified based on its origin, Langerhans’ cell histiocytosis (LCH) or non-Langerhans’ cell histiocytosis. Erdheim-Chester disease (ECD) is categorized with non-Langerhans’ cell histiocytosis, and is histologically characterized by accumulation of lipid-laden foamy macrophages (1). These foamy macrophages are positive for CD68, but negative for CD1a or S100. In contrast, LCH is a disease of the dendritic cell lineages, positive for CD1a and S100 (2). Both histiocytic disorders show bone and joint lesions. Typically, ECD shows symmetrical osteosclerotic lesions in long bones, while LCH bone lesions are mainly osteolytic patterns (3). Few ECD cases have been reported in which Langerhans’ cells infiltrated the same sites or other sites of ECD lesions (4-6). We describe a new case of osteoarthropathy due to infiltration of both non-Langerhans’ cells and Langerhans’ cells in the same lesion, that was considered as a rare variant of ECD. In this report, we also analyzed the bone metabolism status of ECD by measuring bone resorption and formation markers, and demonstrated that osteolysis was dominant in this case. Since zoledronic acid could improve this unbalance, it could be considered as an important therapeutic option for osteoarthropathy due to ECD.

Case Report

A 31-year-old man was admitted to our hospital because of fever and joint pain. He presented recurrent fever and bilateral knee pain for two years before admission. Although he visited a local hospital, a diagnosis could not be made. One year before admission, gynecomastia, loss of axillary hair and loss of sexual desire developed. Polydipsia and polyuria also appeared. Since fever and joint pain grew worse several weeks before admission, he was hospitalized in our department.

On admission, his blood pressure was 137/79 mmHg, pulse rate was 117 beats per minute, and body temperature was 39.1°C. Marked swelling and tenderness were observed in bilateral knees. He showed gynecomastia, and loss of axillary hair. The results of laboratory tests were rather normal, except for an increased serum C-reactive protein level (2.36 mg/dL) and low specific gravity of urine (1.004). Serum titers of rheumatoid factor, anti-cyclic citrullinated peptide antibody, and anti-nuclear antibody were under the detectable levels. Increased bone resorption was suspected by

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the increased levels of urinary deoxypyridinoline (14.1 nmol/mmol/Cr) and N-terminal telopeptides (121.6 nmol-BCE/mmol/Cr), but the bone formation markers, including serum bone-specific alkaline phosphatase and osteocalcin, remained within the normal range. Endocrinal studies revealed partial hypopituitarism with extremely low gonadotropins, sex hormones, and vasopressin.

Radiographs of knee joints showed several osteolytic and partially osteosclerotic lesions (Fig. 1A). Similar findings were also observed in his proximal and distal tibia. Magnetic resonance imaging (MRI) of the knee revealed destruction of the anterior femoral and tibial cortex with the contrast enhancement, suggesting that there was bone necrosis and cell infiltration (Fig. 1B). Technetium-$^{99m}$ bone scintigraphy showed bilateral and symmetrical increased uptake in the systemic bones, especially in the distal femurs and proximal and distal tibias (Fig. 1C). MRI of the brain showed a pituitary mass lesion.

A bone biopsy of the distal femur was performed. Hematoxylin-Eosin staining revealed sheets of lipid-rich foamy macrophages along with scattered Touton giant cells, lymphocytes, plasma cells and varying amounts of reactive fibrous tissue (Fig. 2A). Immunohistochemistry staining revealed that these foamy cells were positive for CD68, but negative for CD1a or S100, which were consistent with ECD (Fig. 2A). In addition, several aggregations of CD1a-positive Langerhans’ cells were also observed among the foamy macrophages (Fig. 2B). Based on the clinical features and morphologic characteristics, we considered that ECD was the main disorder rather than LCH. Therefore, we started to treat him with interferon alfa, at a dose of $3 \times 10^6$ IU subcutaneously three times a week, and zoledronic acid (4 mg/body) (7, 8). For diabetes insipidus, desmopressin spray was started to control polyuria. His condition remains generally well after three months of the therapies.

**Discussion**

ECD is a rare form of non-Langerhans’ cell histiocytosis, and to date about 350 cases of ECD have been described in the medical literature. Bone and joint pain is the most common feature of ECD, and extraskeletal lesions develop in half of the patients. Extraskeletal manifestations include central nervous system, cardiovascular system, retroperitoneal infiltration, interstitial lung disease, and exophthalmos (1). The clinical courses of ECD depend on the involved organs, and in particular involvement of the central nervous system and cardiovascular system results in a poor progno-

Figure 1. A: Roentgenograph of the right knee. B: Gadolinium-enhanced T1-weighted magnetic resonance imaging of the knee. Scattered enhanced masses are indicated by arrows. C: Technetium-$^{99m}$ bone scintigraphy.
sis (9, 10). Treatment strategy of ECD is still controversial, and there is no established treatment of ECD. Recently, interferon alfa-2a was reported as a promising reagent, and these reports showed regression of radiographic lesions and improvement of clinical manifestations with interferon alfa (2, 7).

We diagnosed the present case as ECD, based on the clinical and histological features, but infiltration of Langerhans’ cells were also observed, that was a rare finding in ECD. Nevertheless, a few reports have discussed about osteoarthropathy due to ECD which represented the overlapping infiltration of Langerhans’ cells in the same or other sites (4-6). Interestingly, some common features were observed in these cases: (a) The age was in early adulthood (from 27 to 43-year old), compared to typical ECD (average age 53 years old) (2). (b) Osteoarthritis developed symmetrically in large joints. (c) Radiographs showed both osteosclerotic and osteolytic lesions in the long bones, while 5-8% of ECD cases also showed a similar pattern (1). Therefore, the cases of osteoarthropathy due to ECD with the overlapping infiltration of Langerhans’ cells might be a distinct variant of ECD. However, clinical manifestation, laboratory data, and MRI findings do not show any characteristic finding of this variant form of ECD, and more reports are necessary for determining this point. The causes of Langerhans’ cell aggregation remain unclear, but foamy macrophages in ECD lesions express several chemokines, including CCL19 and CCL21, which could attract dendritic cells (11). The chemotaxis of Langerhans’ cells could be one of the cases of mixed histiocytosis.

In this case, we measured the bone resorption and formation markers. In ECD lesions, interleukin-6 (IL-6), tumor necrosis factor (TNF)-α and receptor activator of NFκB ligand (RANKL) expression are increased in macrophagic cells (11). These molecules promote differentiation and activation of osteoclasts. Indeed, the bone resorption markers, urinary deoxypyridinoline and N-terminal telopeptides, were markedly increased in our ECD case, while the bone formation markers remained normal. Srikulmontree, et al. reported that zoledronic acid was effective for the treatment of skeletal ECD (8). In ECD cases, this unbalance of bone metabolism could play a role in the pathogenesis of osteoarthropathy, and may be considered as a therapeutic target.

In conclusion, ECD cases with overlapping infiltration of Langerhans’ cells are considered as a rare variant of ECD, which possesses some common clinical features, and we have to regard ECD as one of the important candidates for differential diagnosis of inflammatory osteoarthropathy. We also propose that the unbalance of bone metabolism might play an important role in the pathogenesis of osteoarthropathy due to ECD, and zoledronic acid could be a good therapeutic option for osteoarthropathy due to ECD.

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