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A case report of Erdheim-Chester disease—clinically characterized by recurrent fever, multiple bone destruction, and antinuclear antibodies

Zhong-en Gao [a,1], Jing-jing Li [a,1], Kang Sheng [a,**], Rui Liu [a], Feng Fan [b], La-mei Zhou [c], Hao Zhang [d], Dong-lin Hao [a,*]

[a] Department of Rheumatism, Suzhou TCM Hospital Affiliated to Nanjing University of Chinese Medicine, Suzhou, 215009, China
[b] Department of Pathology, Suzhou Municipal Hospital Affiliated to Nanjing Medical University, Suzhou, 215000, China
[c] Department of Rheumatism, Wuxi TCM Hospital Affiliated to Nanjing University of Chinese Medicine, Wuxi, 214000, China
[d] Anhui University of Chinese Medicine, Hefei, 230012, Anhui, China

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ABSTRACT

Background: Erdheim-Chester disease is a form of histiocytosis. It is an extremely rare illness. Since its discovery, hundreds of cases of this disease have been identified across the globe. Pathologically, the condition is characterized by proliferation of lipid-rich foam-like tissue cells, which is especially prevalent in bones. Approximately 50% of patients develop infiltration into organs other than the bones.

Case description: A patient with fever and bone pain is described in this case report. After visiting multiple hospitals and departments, undergoning battery of investigations, and ruling out other diseases, the patient was pathologically diagnosed with Erdheim-Chester disease after a biopsy of the associated bone destruction. The condition improved with symptomatic therapy.

Conclusion: Numerous clinical symptoms make non-Langerhans cell histiocytosis challenging to diagnose and requires pathological diagnosis. Patients with unexplained multiple bone destruction must be alert against this disease from a clinical standpoint.

1. Introduction

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis (NLCH), which is characterized by xanthoma-like or xanthogranuloma-like infiltration in tissues [1]. This disease has numerous clinical manifestations and can occur in almost any organ system. The most common manifestations are lesions in the bone, skin, retroperitoneum, heart, orbit, lung, and nervous system [2,3]. The condition is difficult to diagnose clinically and requires pathological diagnosis. A confirmed case of ECD is reported and analyzed in this case report after reviewing the relevant literature.

* Corresponding author. Department of Rheumatism, Suzhou TCM Hospital Affiliated to Nanjing University of Chinese Medicine, Suzhou, No.18, Yangsu Road, 215009,China.
** Corresponding author. Department of Rheumatism, Suzhou TCM Hospital Affiliated to Nanjing University of Chinese Medicine, Suzhou, No.18, Yangsu Road, 215009, China.
E-mail addresses: gaozhognengreui@outlook.com (Z.-e. Gao), jabgshengdr@outlook.com (K. Sheng), haodldrrhe@outlook.com (D.-l. Hao).
[1] These authors contributed equally to this study.

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2. Case data

A 71-year-old female patient complained of recurrent fever with cough, chest tightness, and multiple bone pain for 6 months. In November 2020, without obivious cause, the patient developed a fever and cough, followed by gradual chest tightness and discomfort, which exacerbated after exercise. She had pain in the left rib and waist, as well as fatigue, night sweats, thirst, and loss of appetite. The patient's previous examinations across hospitals were shown as below:

Blood tests: WBC(White Blood Cell, WBC):29.47 $\times 10^9$/L(3.5–9.5 $\times 10^9$/L) , N(Neutrophils, N):25.02 $\times 10^9$/L(1.8–6.310^9/L), HB (Hemoglobin, HB):98g/L(115–150 g/L), PLT(Platelet, PLT): 693 $\times 10^9$/L(125-350 $\times 10^9$/L), ESR(Erythrocyte sedimentation rate, ESR) 92 mm/H(0–20 mm/H), CRP(C reactive protein, CRP) 171 mg/L(0–5 mg/L); Biochemistry: albumin 22.5 g/L(40–55 g/L), normal liver and kidney function, immunoglobulin IgM 0.9 g/L(0.46–3.04 g/L), IgA 2.09 g/L(0.82–4.53 g/L), immunoglobulin G 10.90 g/L (7.51–15.6 g/L), normal complement C3 and C4, urine Bence Jones protein (−), blood β2-microglobulin 1.99 mg/L(0–8 mg/L), serum-free Kappa-light chain 819.00 mg/dL(598–1329 mg/dL), and Lambda-light chain 507.00 mg/dL(280–665 mg/dL).

The patient had parathyroid function. No abnormality was found in the blood, sputum culture, or other microbiological examinations. ANCA (−) ANA (±) 1: 100, *anti*-SSA(+).

Chest CT on January 29, 2021 showed bilateral pulmonary infection, pleural effusion, and bilateral lower atelectasis(Fig. 1a). PET-CT showed systemic multiple lymphadenopathy, multiple bones with elevated glucose metabolism; pulmonary infection, pleural effusion, and atelectasis(Fig. 1b).

Pathological examination of multiple biopsy sites in different parts shows no clear malignant basis.

Pleural puncture: in the pleural effusion, a large number of neutrophils and a few mesothelial cells and histiocytes were found but no atypical cells. Mediastinal lymph node puncture biopsy by endoscopic ultrasound of bronchoscopy: hyperplasia of lymphocyte, plasma cell, and histiocyte were detected. When the above detections were combined with clinical and immunohistochemical results, the possibility of plasmacytoma could not be ruled out.

The results of clinical hematology laboratory examination were jointly used for the diagnosis. Immunohistochemistry (I21-02675): CD20 (scattered+), CD3 (scattered+), CK(−), CD68 (scattered+), CD138 (partial+), Ki-67 (+30%), Kappa(+) > Lambda(+), CD79a (partial+), CD2(−), CD10(−), CD5(−), Bcl-2(−), Bcl-6(−), MUM1 (focus+), MPO(−), VS38C (partial+), and Plasma Cell (partial +).

Puncture biopsy of right iliac bone marrow: severe bone marrow fibrosis with plasma cell proliferation, plasma cell ratio <10%. Immunohistochemistry: plasma cells CD138(+), CD38(+), CD79a(+), Kappa(+), Bcl-2 (scattered+), Ki-67 (scattered+), CD20(−), CD3(−), MPO(−), CD68(−), Lambda(−), CK(−), CD15(−), CD43(−), and Vmentin(−).

During the previous hospitalization, the patient was thought to suffer from hematological tumors, such as lymphoma, multiple myeloma, etc. But multiple myeloma was excluded because of the insufficient basis after bone marrow puncture, and there was no basis for lymphoma. Therefore, anti-infection therapy was the primary treatment during the previous hospitalization. However, the condition of the patient did not show any obvious improvement. The patient continued to suffer from fever, with the highest temperature of 39.5 °C. After intermittent use of dexamethasone, the body temperature returned to normal, but the fever recurred after more than 24 hours. Moreover, there was obvious bone pain in the bone destruction sites such as the ribs and ilium. The efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) was not good. Because the pain was unbearable, the analgesic was gradually escalated, and oral administration of OxyContin 40 mg (bi-daily) was required to relieve pain.

The abnormal ANA (+), *anti*-SSA (+), and rheumatic immune test results indicated the possibility of connective tissue disease,

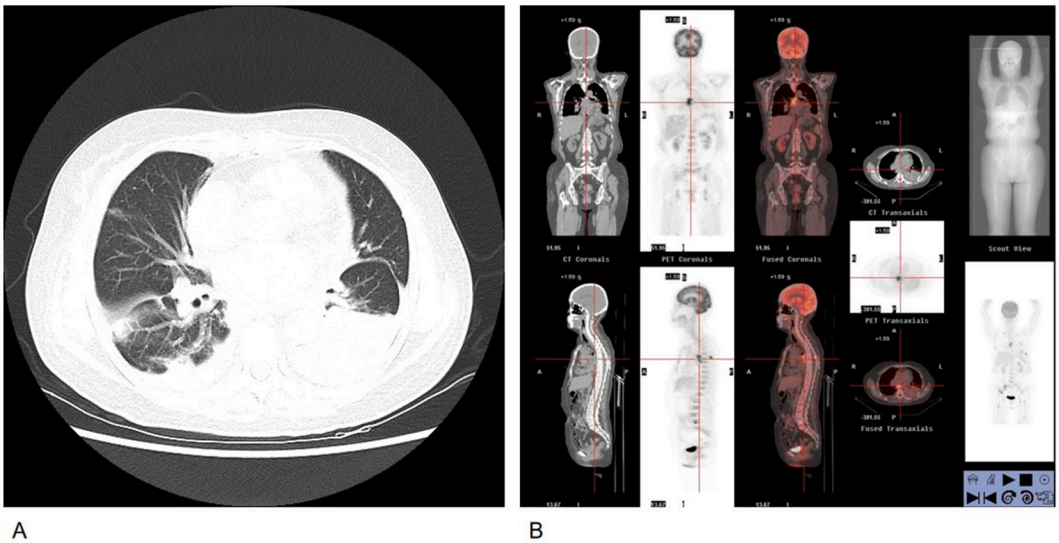

Fig. 1. Imaging examination a. Chest CT on January 29, 2021: bilateral pulmonary infection, pleural effusion, and bilateral lower atelectasis b. PET-CT: systemic multiple lymphadenopathy, multiple bones with elevated glucose metabolism; pulmonary infection, pleural effusion, and atelectasis.

hence, the patient was admitted to the rheumatism department in April 2021.

After admission to our department, the related examinations that were conducted are as follows.

Blood routine: hemoglobin fluctuated at 80 g/L; the neutrophil count was 5.76 × 10^9/L; platelet count was 586 × 10^9/L; white blood cell count was 8.10 × 10^9/L; CRP was 114.10 mg/L; ESR fluctuated at 111 mm/h. ANA: very weakly positive. ENA antibody spectrum: *anti*-Ro-52 antibody was weakly positive (+); anti–SS–A antibody was weakly positive.

Chest CT: inflammatory changes in both lungs, bone destruction of bilateral ribs and part of thoracic vertebrae, possible metastasis, and pathological fracture of some ribs.

Abdominal B-ultrasound and other examinations were normal. In the preliminary diagnosis, connective tissue disease and hematologic tumors were considered as a result of the aforementioned examination, pre-examination, and multidisciplinary consultation.

The patient was then administered the glucocorticoid methylprednisolone 80 mg intravenous drip, hydroxychloroquine sulfate, cyclophosphamide, and other immunosuppression drugs; gamma globulin blocked antibodies and zoledronate sodium was administered to relieve bone pain and inhibit bone destruction, along with symptomatic support treatment. Oral administration of traditional Chinese medicine (TCM) was used to tonify kidneys, strengthen bones, nourish yin, and eliminate dampness. The condition progressively improved, the body temperature returned to normal, and the inflammatory index steadily dropped over time. The lowest CRP was 20.3 mg/L. The ESR was 60 mm/h. Hypoalbuminemia was gradually corrected. However, there was obvious bone pain. A large dose of OxyContin 60 mg (bi-daily) was administrated orally to relieve the pain.

The diagnosis is still uncertain. The inflammatory index decreased and then increased. After communicating with the patient and her family multiple times, the patient was recommended to conduct a biopsy of the bone destruction site. The patient underwent a right iliac bone biopsy. The pathological indications were shown in Fig. 2. Immunohistochemistry: Vim and CD68 of the lesions were both (+); SMA, LCA, and CD38 were scattered focal positive; Ki-67(8%+), Des(−), S100(−), CKpan(−), CD138(−), CD30(−), ALK(−), CD21(−), CD117(−), IgG(−), and IgG4(−) (see Fig. 3).

Pathologically, the bone biopsy indicated the possibility of Erdheim-Chester disease (non-Langerhans cell histiocytosis). At this point, after 8 months of disease, the diagnosis was conformed and ECD was considered. Treatment was adjusted according to the diagnosis. The steroid treatment was gradually decreased, and drugs were continued to be used to inhibit bone destruction and relieve bone pain. The interferon-α subcutaneous injection was administered once a week. OxyContin 120 mg (bi-daily) was administrated orally to relieve pain. The patient's condition improved, but there was obvious bone pain, and the inflammatory index was obviously higher. Related studies have reported that biological agents may be effective, hence, 400 mg Actemra (tocilizumab) intravenous drip was administrated once a month. After the administration, the ESR and CRP inflammatory indexes returned to normal and the bone pain reduced. OxyContin was then reduced to 30 mg (bi-daily) for maintenance.

Based on the patient's previous medical history of 8 months or more, she has visited 3 hospitals and 4 departments. Her condition began with fever, lung infection, and bone pain. In conjunction with antinuclear antibody (ANA) positivity, pathological bone destruction, lymph node enlargement, and other malignant diseases were found during the examinations. Multiple lymph node biopsies at different sites, bone marrow puncture biopsies, and other investigations did not meet the diagnostic criteria for hematological multiple myeloma. No solid tumor was found based on numerous device-based examinations. Eventually, a biopsy was performed on the partially destroyed bones and the underlying cause was identified. This offered a peak into the rarity of this disease and the difficulty in diagnosis.

3. Discussion

ECD is a form of histiocytosis. It was first described by Jakob Erdheim and William Chester as "lipid-like granulomatosis." It was also described as "lipoid granulomatosis," "cholesterol granulomatosis," multiple osteosclerotic histiocytosis, etc. In 1972, Jaffe reported this disease again and officially named it "Erdheim-Chester disease." This disease is more common in males than in females, with a male-to-female ratio of 1.5 to 1. The peak age of onset is 40–70 years old (the median age is 53 years old). The condition is characterized pathologically by lipid-rich, foam-like tissue cell proliferation, which is especially prevalent in bones. Approximately 50% of patients experience infiltration in other organs other than the bones. This is a rare disease, and from the time it was first

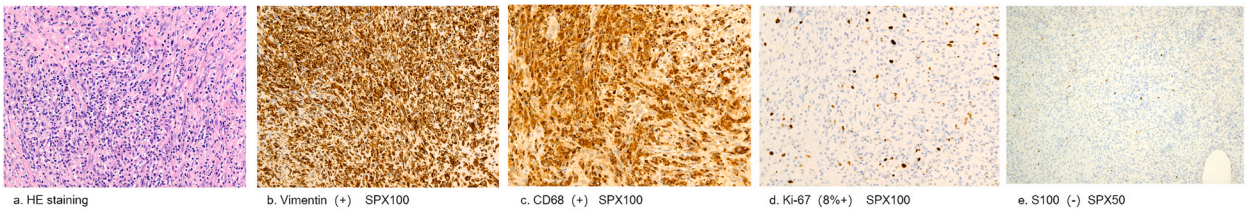

Fig. 2. a. Diffuse infiltration of histocytes can be seen in the marrow cavity, and peripheral lymphocytes and plasma cells infiltrate HEx100
b. Immunohistochemistry: Vimentin (+) (SPx100)
c. Immunohistochemistry: cells express CD68 (SPx100)
d, Immunohistochemistry: Ki67 (8%+) Ki67 value-added index reaches 8% (SPx100)
e. Immunohistochemistry: S100 (SPx50) is not expressed in tissue cells.

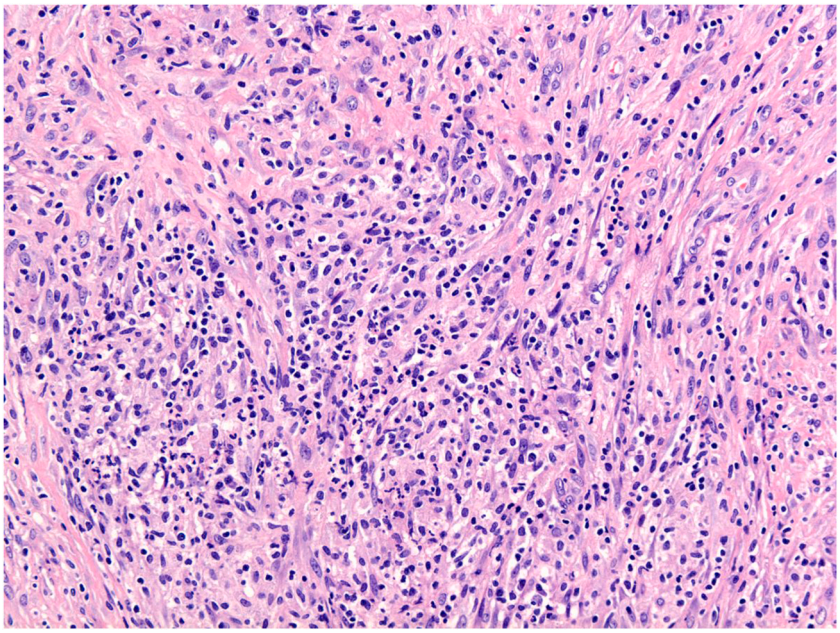

Fig. 3. HE x 100 Diffuse infiltration of tissue cells in the bone marrow cavity, with infiltration of surrounding lymphocytes and plasma cells.

discovered, approximately 700 cases of the disease have been reported worldwide [1,2].

Histiocytosis is a xanthogranulomatous disease caused by the proliferation and accumulation of reactive or neoplastic histiocytes. This kind of disease has a very complex naming and classification. At present, the most commonly used classification methods divide such diseases into four categories(Table .1). ECD belongs to class II (non-Langerhans cell histiocytosis) with multiple organ system involvements [2]. It was classified as a tumor with unclear tumor nature among the soft tissue and bone tumors by the WHO (2013) and as a histiocytic and dendritic cell tumor among the hematopoietic system tumors by the WHO (2017) [4,5].

3.1. Pathogenesis

The etiology and pathogenesis of ECD are not clear. Although WHO (2017) classified it as a tumor of histiocyte origin [5], whether ECD is a tumor proliferative disease, or a reactive proliferative disease is still a controversial issue [6]. There are two main theories. The first is that ECD is a non-clonal lesion related to abnormal Th1 immune response. Corrado and Arnaud et al. confirmed that pro-inflammatory cytokines and chemokine networks play an important role in cell recruitment and activation of ECD patients [1,7]. These inflammatory cytokines include increased levels of IFN- α(Interferon-α, IFN-α), IL-12(Interleukin, IL), monocyte chemoattractant protein-1 (Monocyte chemoattractant protein-1, MCP-1), and decreased levels of IL-4 and IL7. Among them, IFN-α is a regulatory factor, which recruits tissue cells and activates its downstream inflammatory factors, resulting in tissue injury. In addition, IL-6 plays a vital role in the pathogenesis of ECD. This is because IL-6 participates in the differentiation of osteoclasts and eventually leads to osteosclerosis.

However, recent studies have reported that more than half of ECD patients have BRAFV600E gene mutations, suggesting that they may be neoplastic lesions. Haroche et al. reported that 54% of ECD patients had BRAF V600E gene mutations [8]. Estrada-Veras et al. also reported that the mutation of BRAF V600E was detected in 31 (52%) of 57 ECD patients, which confirmed the high mutation rate of BRAF V600E in ECD patients [5]. Not only were BRAF V600E gene mutations found in 54% of ECD patients, but they were also found in 38% of LCH patients. This gene mutation was not found in patients with other histiocytic diseases.

3.2. Clinical features

More than 95% of cases involve bone tissue, mainly in the long bones of limbs, but also in flat bones [5]. The most frequently

Table 1
Classification of ECD.

Class I	Langerhans cell histiocytosis (LCH)
Class II	Non-Langerhans cell histiocytosis (NLCH)
Class III	Phagocytic lymphocyte tissue cells
Class IV	Malignant tumors related to histiocytic lineage, including monocytic leukemia, monocyte, and histiocytic sarcoma

affected sites other than bone were cardiovascular system, central nervous system, lung, orbit and so on [9]. Other areas that have been reported to be affected are the urinary tract, retroperitoneum, gastrointestinal tract, skin, adrenal gland, breast, thyroid, and other areas [9–11]. Patients may have systemic symptoms such as fever, weight loss, and night sweats. The clinical symptoms vary with the location of the lesion. Bone involvement most commonly manifests as bone pain; central nervous system lesions may result in neurogenic diabetes insipidus, cerebellar ataxia, hypopituitarism, optic papilledema, cerebellar syndrome, and others, while diabetes insipidus is the most common clinical manifestation of ECD central nervous system diseases [5,12]. Pulmonary lesions may cause cough, dyspnea, and others; cardiovascular system involvement may result in pericardial pain, cardiac tamponade, heart failure, myocardial infarction, and others; renal lesions may result in abdominal pain, dysuria, and renal insufficiency [1]; while gastrointestinal lesions may result in long-term diarrhea, fatigue, and weight loss [13]. Orbital lesions may have exophthalmos, diplopia, visual impairment, and other features.

3.3. Diagnosis

The gold standard for diagnosis of ECD is a combination of the clinical manifestations, typical imaging features, and the biopsy of the lesion. Diagnostic criteria include: (1) It is rare, with an average age of onset of 55–60 years, and it has also been reported in children. The most common sites of lesions were bone (>95%), cardiovascular disease, retroperitoneum (kidney), central nervous system, lung, and skin. (2) The histomorphology and immunology of the lesions were similar to those of Disseminated juvenile xanthogranulomatosis juvenile xanthogranuloma (DJXG) is characterized by hyperplastic histiocytes with foamy (lipid-containing) cytoplasm, often Touton giant cells, and fibrosis. They can be mixed with other inflammatory cells. (3) Histiocyte $CD68^{+}$, CD163+, Factor Vlla+, $CD14^{+}$, S100-, CD1a-, Langerin-. (4) X-ray showed characteristic symmetrical sclerotic changes in the metaphysis of long bones. (5) BRAF (V600E) mutation was present in most cases (>50%). In addition, a minority of cases had mutations in the gene encoding the phosphoinositide 3-kinase (PI3K) catalytic subunit p110aipa (PIK3CA) channel of the neuroblastoma RAS viral oncogene homolog (NRAS).

In pathological tissues, the typical histological features of ECD are the proliferation of lipid-rich, foam-like tissue cells, accompanied by infiltration of a small number of lymphocytes, plasma cells, and Touton giant cells, and sometimes with varying degrees of fibrosis. Immunohistochemical staining is characterized by CD68 and CD163 being positive, while CD1a and langerin are negative with S-100 (Fig. 7) rarely being positive (80% negative) [7,12,14].

The typical X-ray features are symmetrical osteosclerosis in the diaphysis or metaphysis of bilateral long bones. There is increased involvement around the knee joint, that is, the distal femur and proximal tibia. Osteolytic lesions and osteosclerosis coexist in roughly 1 to 3 cases, while simple osteolytic lesions are less than 10%. CT of the involved internal organs shows local pseudo-tumor-like lesions; CT of the involved breast and muscles shows irregular masses with unclear boundaries and uniform density. Due to its invasion of bilateral pararenal and perirenal space, “hairy kidney” is manifested. The typical CT of cardiovascular ECD shows soft tissue infiltration around the aorta, forming the “coated aorta” sign [15,16].

The manifestations in this patient are quite distinctive. For example, lung involvement is more common in other cases, but the main manifestations in this patient were bilateral pleural effusion, non-bacterial inflammation of both lungs, and left lung atelectasis.

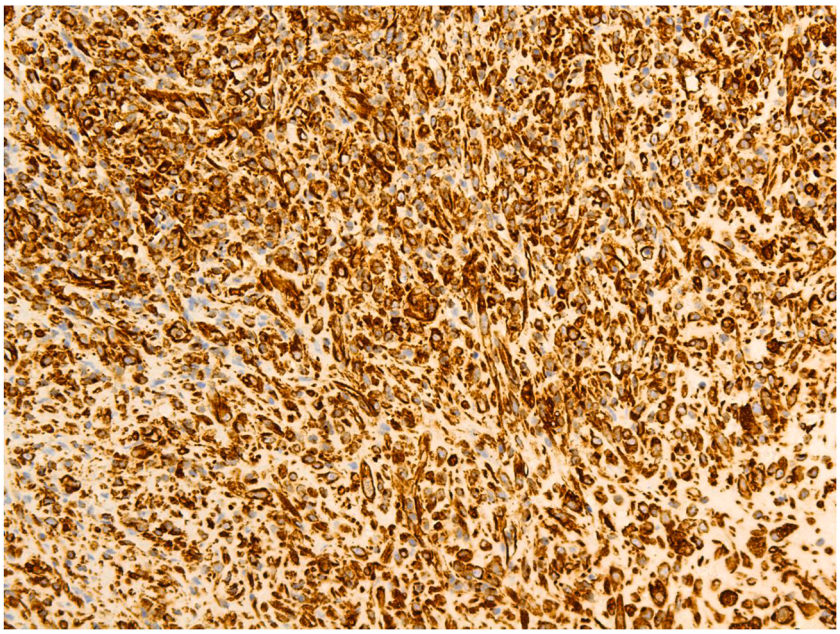

Fig. 4. Immunohistochemistry: Vimentin(+) (SP × 100).

Clinically, the bone destruction is characterized by symmetrical osteosclerosis of long bones, metaphysis, and craniofacial osteosclerosis; the radionuclide bone scan shows bilateral symmetrical radiation concentration in the metaphysis of limbs, while the main manifestations in this patient were damage to lumbar vertebrae and ribs. After multidisciplinary consultation and the exclusion of other diseases, this patient was pathologically diagnosed with ECD. Pathological examination is of vital importance for the diagnosis. Pathology of the patient: histiocytic proliferative tumor; Vim(+) and CD68(+) (Figs. 4 and 5); SMA, LCA, and CD38 were scattered focal positive; Ki-67(8%+) (Fig. 6); Des(−) and S100(−) (Fig. 7).

3.4. Differential diagnosis

Langerhans cell histiocytosis (LCH) is the most important differential diagnosis of ECD, both of which can have bone involvement. Its identification points: LCH is more common in children and adolescents, while the peak age of ECD is 40–70 years old (the median age is 53 years old). X-ray findings of LCH often show osteolytic lesions, which are common in ribs, skulls, and femurs, and generally do not involve the skin and internal organs. X-ray findings of ECD are characterized by symmetrical osteosclerosis in the bilateral long bone shaft or metaphysis, which mostly involves around the knee joint. Meanwhile, about 50% of ECD patients have involvement outside the bone, while simple osteolytic lesions are rare. A typical "coffee bean-like" nuclear groove can be seen under the microscope in LCH patients, and eosinophil infiltration is often seen in the background. Under the electron microscope, Birbeck particles are found in the cells of CD1a, langerin, and S-100, the dendritic cell markers of immunohistochemical staining LCH. ECD does not express these three markers and there are no Birbeck particles in the cells under the electron microscope.

In addition, the disease should be differentiated from Rosai-Dorfman disease (RDD), xanthoma of bone, benign fibrous histiocytoma of bone (BFH), metastatic clear cell carcinoma, and other diseases.

3.5. Treatment and prognosis

At present, there is no unified standard for the treatment of ECD. The treatment mainly includes the intervention of the cytokine/chemical factor network. IFN-α or polyethylene glycol IFN-α is the initial option for treatment. Others, such as Anakinra and infliximab, could also be used. The most common treatment is interferon-α. It is speculated that this treatment can affect mature and active dendritic cells, destroy tissue cells, or inhibit their expansion ability through immunomodulation, which can significantly reduce the infiltration of foam cells into tissues and relieve the pain in patients. It has been proved that it can prolong the overall survival of patients.

As per recent studies, more than half of ECD patients have BRAF V600E mutations, thus it is critical to further study the role of this pathway in ECD and LCH as this can provide new opportunities for targeted therapy. Vemurafenib (Zelboraf), a BRAF inhibitor, has been used in the treatment of patients with ECD and has achieved certain efficacy. In the research of Haroche et al. [8], 8 patients with systemic ECD were treated with the BRAF inhibitor vemurafenib. After 6–16 months of follow-up, all patients showed improvement in general symptoms and sustained response to vemurafenib, which indicates that vemurafenib has an objective and sustained curative effect in the treatment of ECD patients with BRAF V600E mutation. In recent years, with the growth in development of biological

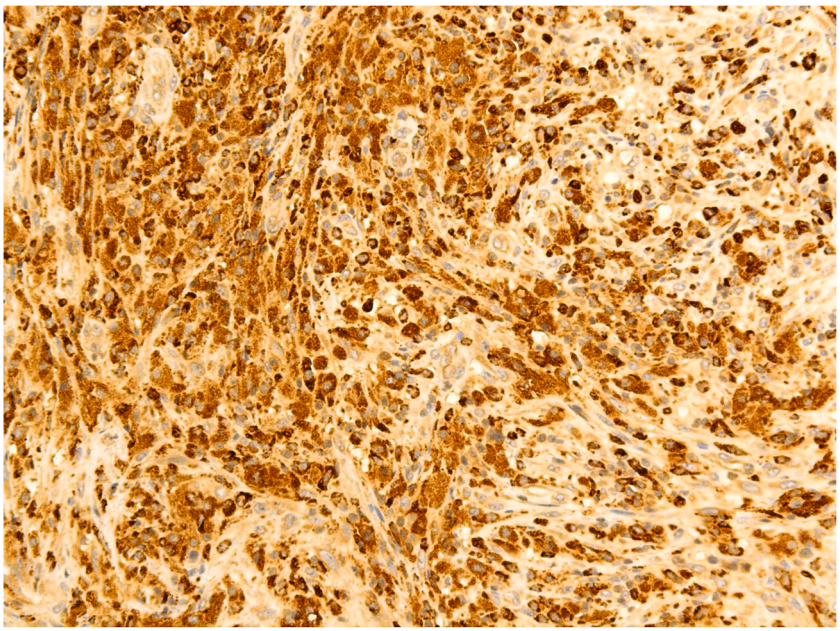

Fig. 5. Immunohistochemistry: Tissue cells expressing CD68 (SP × 100).

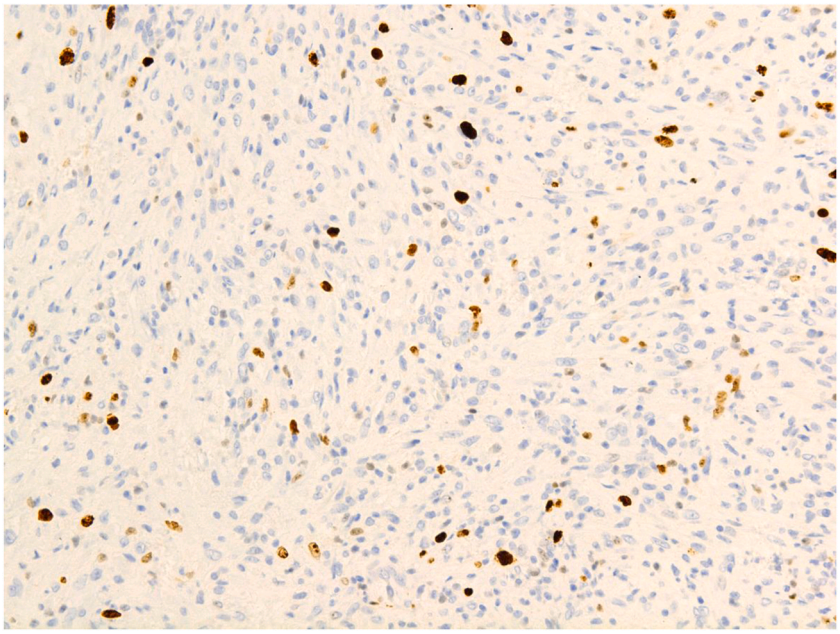

Fig. 6. Immunohistochemistry: Ki67(8%+) Ki67 proliferation index reaches 8% (SP × 100).

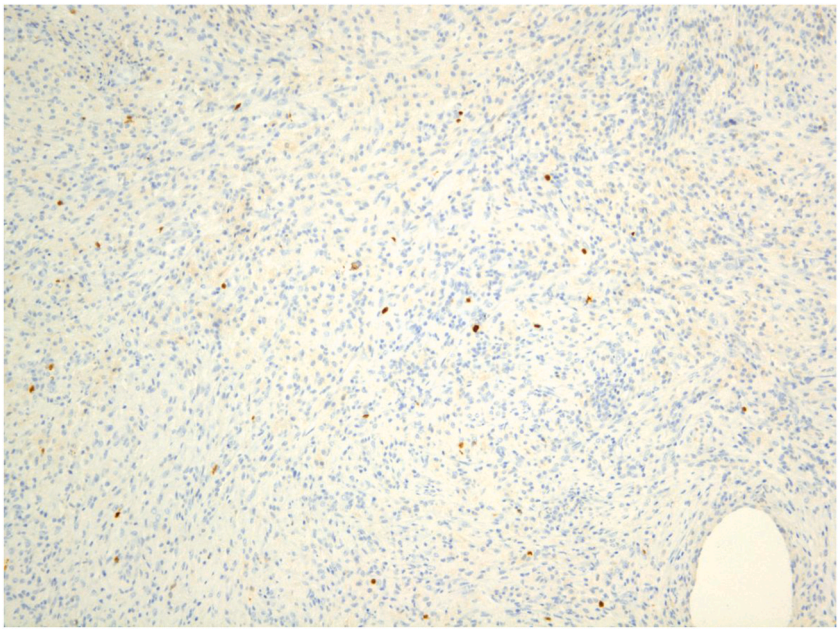

Fig. 7. Immunohistochemistry: S100(-) S100 is not expressed in tissue cells (SP × 50).

agents, it has also been reported that infliximab, a TNF-a inhibitor, significantly improved cardiac involvement in two ECD patients [17]. In addition, it has been reported that IL-6 can be a central mediator in the pathogenesis of ECD, so the IL-6 inhibitor Actemra is effective in ECD [18]. The patient in this case report was treated with TNF-a, a biological agent for two months, but the inflammatory indexes did not improve significantly. One month after the treatment with Actemra, an IL-6 inhibitor, ESR, CRP, and other inflammatory indexes could be reduced to the normal level.

The poor prognosis of ECD is mainly due to the lack of knowledge about ECD or the low rate of accurate diagnosis, which leads to the fact that most patients are in the late stage of the disease when they are successfully diagnosed, and their 3-year survival rate is only about 50% [16]. Another factor related to prognosis is the degree of internal organ involvement, for instance, the central nervous system, cardiovascular system, digestive system, lung, and kidney are independent prognostic risk factors [13,15,16,19,20]. In

addition, Toya et al. confirmed that age >60 is also a factor that makes for poor prognosis [19]. The effect of ECD treatment is not good, and there are no reports of self-remission cases. Recently, a study by Zhang et al. in China confirmed the feasibility of surgical treatment for ECD patients [21]; in the 9 cases that were studied, the pain was relieved and the risk of pathological fracture in the lesion was avoided after surgical treatment and follow-up for 3–24 months. Therefore, Zhang et al. proposed that surgical treatment can be performed for ECD patients with good conditions, mild illness, and slow disease progression.

4. Conclusion

After more than 8 months of diagnosis and treatment, the patient was found to present with a fever and pulmonary infection. Various investigations excluded blood- and tumor-related malignant diseases, and finally, a biopsy of a part of the destroyed bone revealed a diagnosis of ECD. The patient was administered anti-infection, anti-immunity treatments, and other treatments. After the confirmed diagnosis, the patient received standardized therapy with interferon-α and Intermittent therapy with tocilizumab, an IL-6 inhibitor. The symptoms were finally relieved. Follow-ups revealed that the pain had subsidized, the bone destruction did not progress further, and she was able to take care of herself normally. However, because this disease is rare clinically, the diagnosis rate is low, and there are very few patients who can be treated in a standardized manner. Most patients have poor prognoses. At present, interferon is still the primary mode of treatment. Vemurafenib (Zelboraf), a BRAF inhibitor, can also be considered for patients with BRAF V600E mutations.

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Ethics approval and consent to participate

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Nanjing University of Traditional Chinese Medicine(2020 No.084). A written informed consent was obtained from all participants.

Consent for publication

Consent for publication was obtained from every individual whose data are included in this manuscript.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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