Successful Treatment of Erdheim-Chester Disease with Multisystemic Involvement in a 4-year-old Child by Interferon-α and Corticosteroid

Jung Won Hwang, M.D.1, Chang Hoon An, M.D.1, Min Kyung Lee, R.N.1 and Pyoung Han Hwang, M.D.1,2

1Department of Pediatrics, Chonbuk National University Medical School, 2Research Institute of Clinical Medicine of Chonbuk National University-Biomedical Research Institute of Chonbuk National University Hospital, Jeonju, Korea

Erdheim-Chester disease (ECD) is a rare form of proliferative non-Langerhans cell histiocytosis that involves multiple organs and is associated with a high mortality. The prognosis of ECD is variable, and it mainly depends on the involved anatomic sites. The treatment modalities have not been standardized, but interferon-α (IFN-α) has been reported to be effective in the management of ECD. ECD usually affects middle aged individuals with a slight male predominance but is extremely rare in children. We present an uncommon case of a 4-year-boy diagnosed with ECD who was treated with IFN-α and corticosteroid. He remained disease-free for 3 years after the completion of treatment.

Introduction

Erdheim-Chester Disease (ECD) is a rare multisystemic non-Langerhans cell histiocytosis of unknown origin that occurs mostly in adults and rarely in children. Clinical features range from focal asymptomatic processes to fatal multisystemic conditions, depending on the location and extent of disease. The primary site of histiocytic infiltration is the bone; the bony lesion displays the characteristics of bilateral symmetric sclerosis of the metaphyseal regions of the long bones [1].

Other extra-skeletal lesions can be found in the pituitary, eye orbit, heart, lung, retroperitoneum, and central nervous system. Its diverse presentations depend on the involved organ: exophthalmos, diabetes insipidus, xanthelasma, interstitial lung disease, adrenal enlargement, and retroperitoneal fibrosis [2].
Treatment options for ECD include corticosteroids, chemotherapy, radiotherapy, surgery, and immunotherapy, but overall prognosis remains dull as these treatments do not improve the survival of ECD patients. The high mortality rate associated with ECD is thus a critical issue. Although alternative treatments have been shown to be effective recently, IFN-α is still the first line therapy for ECD with variable efficacy and limited tolerance [3]. Herein, we report a case of ECD in a 4-year-old boy with the involvement of the central nervous system, lung, and bone. The boy was treated with IFN-α and prednisolone, and he has remained disease-free 3 years after the completion of treatment.

**Case Report**

A 4-year-old boy was referred to our hospital for right hemifacial palsy of 1 week duration and intermittent right arm pain. After admission, he presented with productive cough, and according to the chest X-ray, there was haziness at the right upper lung field. Laboratory results, including white blood cell count and C-reactive protein, were within normal limits.

Diffuse reticular opacities and parahilar haziness were observed in the right lung on chest X-ray (Fig. 1A). In addition, chest computed tomography (CT) clearly demonstrated interlobular septal thickening and peribronchovascular thickening with centrilobular nodular opacities and some ground-glass opacities in the right lung (Fig. 1C), as well as multiple bone lesions of both humeri.

Radiographs revealed well-defined osteolytic lesions with a diameter of less than 1 cm and osteosclerosis of the proximal metaphyses of both humeri, with greater severity on the right (Fig. 2A). Osteosclerosis and cortical thickening with osteolytic lesions were observed in the right clavicle and right ribs. Moreover, both proximal metaphyseal lesions and distal metaphyseal lesions were present in both femurs (Fig. 2C). However, these lesions did not show any uptakes on the bone scan.

Temporal MR imaging revealed an extra-axial mass of 1.0×0.9 cm, in the right cerebellopontine angle that extended to the right internal auditory canal which was hypointense on T1- and T2-weighted MR images and heterogeneously enhanced (Fig. 3). The right facial nerve was superiorly displaced by the mass without significant thickening or enhancement.

Biopsy of the right humeral bone and subsequent immunohistochemical staining showed positive CD68, neg-
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Fig. 2. Well-defined osteolytic lesions (arrows) and osteosclerosis are observed in the proximal metadiaphyses of the bilateral humeri before treatment (A), and osteosclerosis with osteolytic lesions are improved after treatment with IFN-alpha (B). Symmetrical osteosclerosis with osteolytic lesions (arrows) are also seen in the proximal and distal metaphyses of the bilateral femurs before treatment (C), and bony lesions are improved after treatment with IFN-alpha (D).

ative CD1a and nonspecific positive reaction to S-100 protein; based on which he was presumptively diagnosed with Langerhans cell histiocytosis (LCH). Chemotherapy was initiated with prednisolone, vinblastine, and etoposide based upon the LCH-II treatment protocol for 4 weeks, but he did not show any significant improvement; he developed blurred vision and seizure and, based on non-convulsive status epilepticus pattern of electroencephalography (EEG), was treated with antiepileptic drugs. Brain magnetic resonance imaging (MRI) after a 2-month follow-up showed diffuse brain atrophy and bilateral optic nerve atrophy.

After a careful re-review of the radiologic images, it was understood that, despite the young age of the patient, the probability of LCH was low, but that of ECD high. A retrospective pathological review was performed again, which revealed some portions of intertrabecular fibrosis with foamy histiocytes (Fig. 4), and positive CD68, negative CD1a and negative S-100 protein. As a result of the high prevalence of BRAF V600E mutation in ECD, we performed Sanger sequencing of BRAF exon 15 from bone marrow DNA sample of the patient; however, BRAF V600E mutation was not detected.
Finally, the patient was treated for ECD through chemotherapy with IFN-α (3 × 10^6 units 2-3 times per week) and prednisolone (1 mg/kg/day). Chest radiographs showed a significant improvement of reticular opacities and parahilar haziness (Fig. 1B, D). However, bony lesions showed little change (Fig. 2B, D), and bone pain and other manifestations improved slowly throughout the treatment period. After 24 months of treatment, IFN-α was discontinued, and after the end of the treatment duration, no relapse was observed for 3 years.

Discussion

ECD is usually not suspected during the initial workup because systemic pediatric histiocytic diseases generally present as LCH in children. The classic triad symptoms of ECD are bone pain, diabetes insipidus, and painless bilateral exophthalmos with visual impairment [4]. The initial clinical presentation may show a broad spectrum of clinical manifestations in children. In our case, the child complained of right hemifacial palsy accompanied with right shoulder pain.

Bone involvement is the most common symptom, reported in 74% of the ECD populations [4], presenting as bilateral symmetrical osteosclerosis at the metaphyseal and diaphyseal portions of the long bones, sparing the epiphyses [1,2]. Bone pain usually manifests around the knees and ankles. Although the classical hallmark of skeletal involvement for ECD is osteosclerosis, it has previously been reported to occasionally manifest as mixed sclerotic and lytic lesions, as in our case. Osteolytic lesions may be explained by recent infiltrations of histiocytes, giant cells, and unossified fibrosis, while osteosclerosis is related to fibrosis [5].

Central nervous system (CNS) involvement was reported in 56% of the overall population and was the second most common site of ECD [1]. As multifocal involvement of CNS and orbits was a frequent manifestation, pituitary involvement, retro-orbital masses, and infiltrative axial lesions have been proposed as a neuroradiological triad strongly suggestive of ECD, when presented with a positive bone scan or
osterosclerosis of the facial sinus walls [4]. The meningeal mass is usually hypointense or isointense on T1- and T2-weighted images with homogeneous intense enhancement, and the cerebellopontine angle is a common site [6]. However, a gradual development of brain atrophy as in our case is unusual. We consider that it may be related to chemotherapy or valproic acid administration for seizure attack.

Mediastinum, heart, lungs, gastrointestinal tract, kidneys, retroperitoneum, CNS and orbits are the extra-skeletal sites that have been reported to date. The sheathing of the whole thoraco-abdominal aorta called the "coated aorta" and the perirenal fascia infiltration taking the appearance of "hairy kidneys" are highly suggestive features of ECD [4]. Orbital involvement of ECD is also a common manifestation, and presents as intraorbital masses resulting in bilateral exophthalmos and visual impairment. Optic nerve atrophy secondary to the intraorbital masses has also been reported as in our case [7].

Pulmonary and renal impairments of ECD are uncommon but often contribute to the death of patients [4]. The characteristic radiological finding is a pattern of interstitial lung disease with symmetrical smooth thickening of the interlobular septa, peribronchovascular thickening, centrilobular nodular opacities, and pleural effusion. These distinctive findings, which are different from that of LCH represented by cystic lesions and centrilobular nodules, caused us to consider ECD as an alternative diagnosis [8]. Radiological finding of pulmonary involvement often precedes clinical symptoms. Our case also showed interstitial infiltrations without specific symptoms. However, these findings can also be observed in other interstitial disorders, such as lymphangitic disorders, pulmonary edema, and idiopathic fibrosis. Bilateral symmetrical osteosclerosis of the long bones, in addition to the interstitial pulmonary infiltration, can be the most important contrasting point, and a final diagnosis should be made by histopathological findings such as diffuse infiltrates of foamy histiocytes accompanied by lymphocytes, monocytes and multinucleated giant cells of the Touton type, Touton giant cells, immunohistochemically positive for CD68, are typical of ECD and Birbeck granules, seen on electron microscopy, and positive staining for S-100 protein, is absent in ECD [8].

To date, various treatments have been attempted to achieve remission in ECD patients. However, there has not been a standard treatment method with good efficacy and improved survival, and more than half of the patients show relapse within 3 years. Since ECD is extremely rare in children, evidence regarding its treatment is limited to case reports [1].

Treatment for ECD has previously been carried out with steroids, various cytotoxic agents, and tandem autologous hematopoietic-stem-cell transplantation. Corticosteroids are the traditional first-line therapy; however, they are generally either ineffective or only transiently effective. Chemotherapy can induce transient partial responses but is often ineffective [2,9]. Recent studies suggest IFN-α is as the most efficacious agent and recommended as the first-line therapy for ECD [4,9]. Our observations suggest that this well-tolerated therapy with steroid and IFN-α (starting dose: 3 to 6×10^6 units, maintenance: 1×10^6 units 2 to 3 times per week) has a significant effect on the outcome of ECD without BRAF V600E mutation.

Several mechanisms have been proposed to explain the biological effects of IFN in ECD, such as induction of functional maturation and activation of dendritic cells, immune-mediated destruction of histiocytes and direct antiproliferative effects on histiocytes [10].

Anakinra [11] and infliximab [12] have also achieved good results and should be taken into consideration for treating ECD when IFN-α treatment fails. More recently, the BRAF-inhibitor vemurafenib has been used in ECD patients with desirable efficacy [13]. Nevertheless, its adverse effects and limited data on its long-term efficacy discourages many clinicians to use this as a first-line therapy option. Further prospective studies about new therapy using monoclonal antibodies for BRAF inhibitor and TNF-α inhibitor are needed.

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