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LETTER TO THE EDITOR

Combination of adalimumab with lower dose of methylprednisolone in Erdheim-Chester disease with systemic involvement

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To the Editor,

Erdheim-Chester disease (ECD) is a rare systemic non-Langerhans histiocytosis characterized by diffused infiltration of CD68-positive and CD1α/S100-negative lipid-laden histiocytes in multiple organs or tissues [1]. This disease has been reported in approximately 550 cases since its initial description in 1930 [2]. ECD frequently affects long bone and joint, which results in bone pain due to bilateral osteosclerosis. It can also involve lung, retroperitoneum, and occasionally central nervous system (CNS), cardiovascular system, kidney, and skin. ECD causes a spectrum of disorders ranging from asymptomatic bone lesions to multisystemic, life-threatening manifestations [3,4]. Due to its rare occurrence, no well established diagnosis or treatment guidelines have been built for ECD up to now. The current therapeutic strategies for ECD vary from steroid to autologous hematopoietic stem cell transplantation, depending on the extent and distribution of the lesions. However, the current regimens often cause incomplete and/or transient responses and frequent toxicity.

Emerging evidence revealed a disturbance of local and systemic cytokine network in ECD patients, which may potentially contribute to the disease process by orchestrating recruitment, retention, and activation of histiocytes and inflammatory cells [5,6]. Moreover, most of the cytokines accumulated in ECD lesions are known to be regulated by TNF-α [7]. These data raise the rationale for the treatment of ECD patients with anti-TNF-α agents. Adalimumab (ADA) is a fully humanized anti-TNF-α monoclonal antibody that has been reported to be safe and effective in psoriasis, Crohn's disease, and rheumatoid arthritis [8]. We herein report the effect of ADA in treating a case of ECD with cardiovascular and CNS involvement, which may represent a novel therapeutic option for ECD.

Case presentation

A 60-year-old woman was initially presented with numerous itchy skin rashes on her chest and back as well as multiple painless subcutaneous soft tissues mass on her armpits, breasts, and abdomen. At the same time, she had repeated fever (ranging from 37.3 to 38.9 °C) of unknown etiology, and bilateral lower limb edema. In April 2012, she underwent a surgical operation to remove the abdomen mass (5 cm × 10 cm). The histological examination suggested a dominant spindle-cell lesion and an inflammatory myofibroblastic tumor. She was then admitted to our facility for further management two months later due to the recurrent abdomen mass within the resected area.

Abdominal ultrasound and computed tomography (CT) scan demonstrated hydronephrosis, mild involvement of the thorax, lungs (thickening interlobular septa), abdomen, pelvis, bilateral perirenal, and periaortic soft tissue (Figure 1(A)). Plain radiography of lower limbs showed multiple sclerotic and lytic lesions over the metaphyseal regions of humeri, femur, and tibia (Figure 1(B)). Echocardiography showed moderate myocardial ischemia and pericardial effusions. Brain magnetic resonance imaging (MRI) revealed multiple hyperintense lesions especially in the bilateral cerebral hemispheres (Figure 1(C)). A 99 mTc-MDP bone scintigraphy revealed intense, symmetrical osteoblastic activity along long bones (Figure 1(D)). The 18F-FDG positron emission tomography (PET)/CT revealed multiple intense focal uptakes throughout the whole body, including the brain, cardiovascular system, kidneys, and skeletons (Figure 1(E)). Histological examination of the initial surgical specimen and subsequent biopsies of armpit and breast masses of the patient showed lipid-laden foamy histiocytic aggregates (Supplement Figure 1(a,b)). Immunohistochemical staining showed that the infiltrated foamy cells were CD68- and CD163-positive (Supplement Figure 1(c,d)). All macrophage were totally negative for Langerhan's cell marker CD1α (Supplement Figure 1(e)) and S100 (Supplement Figure 1(f)). Therefore, the patient was diagnosed as ECD based on the above radiological and histological features.

After the diagnosis, the patient was initially treated with cyclophosphamide (CTX) (0.4 g/week) combined with deescalating dose of methylprednisolone (MP) from 40 to

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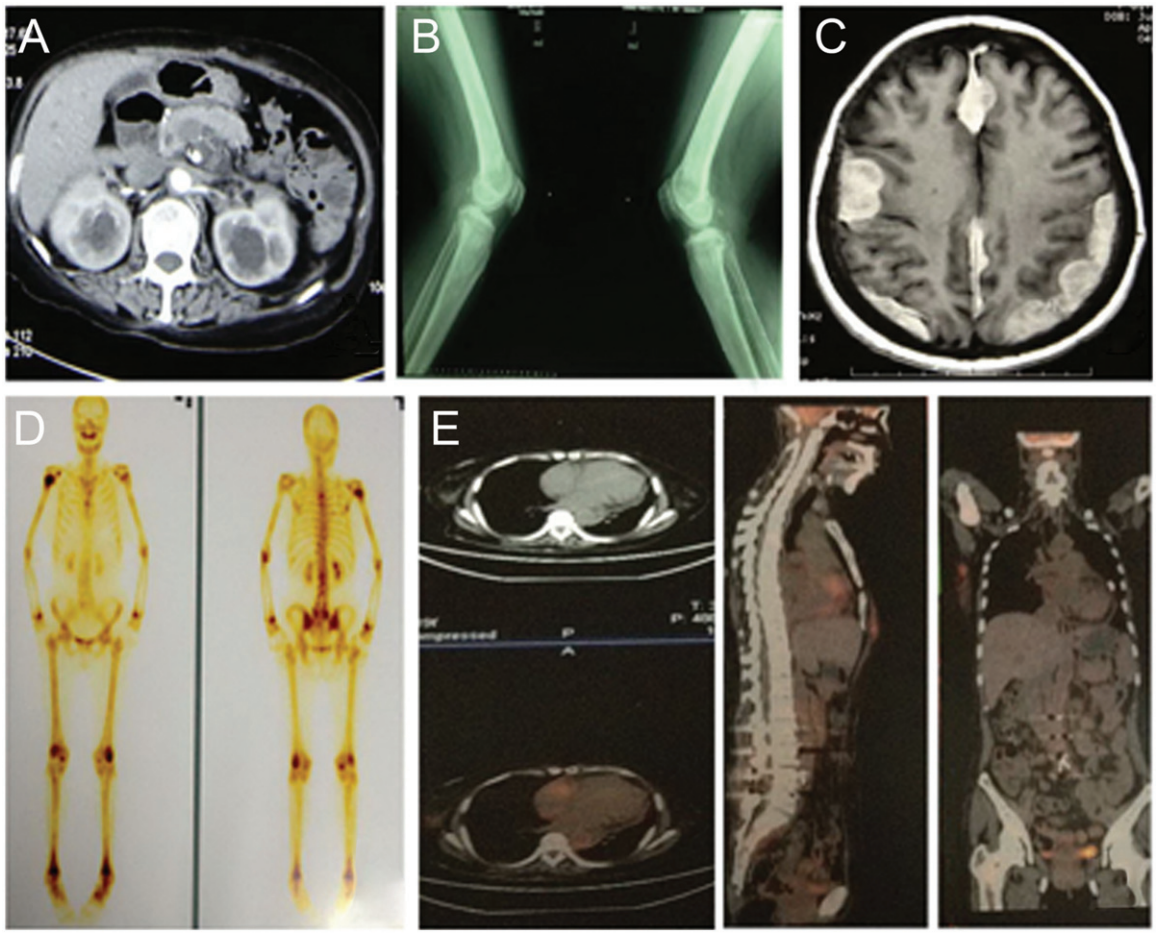

Figure 1. Initial radiographic examination of the patient before treatment. (A) Abdominal computed axial tomography scan of patient. (B) Plain x-ray of lower limbs in the patient. (C) Brain MRI with gadolinium enhancement. (D) A 99 mTc-MDP bone scintigraphy of planar whole body scan in anterior and posterior views. (E) 18F-FDG PET/CT examination showed multiple intense focal uptakes throughout the whole body with cardiac involvement.

16 mg/day for 10 days and the treatment was continued for three months. Three months later, the patient had apparently decreased skin rashes and subcutaneous soft tissue masses, and had moderate relief on fever and asthenia. However, PET/CT revealed that the brain lesions, pericardial effusion, cardiac and abdominal aorta lesions were progressed. She manifested symptoms of heart failure [New York Heart Association (NYHA) functional class II; American Heart Association (AHA) stage C]. CTX was discontinued after three months' treatment due to worsened symptoms and adverse effects, including myelosuppression and digestive tract reactions. According to previously reported therapeutic strategies, interferon-alpha (IFN-α) was administrated. However, it was discontinued because of high fever and severe gastrointestinal symptoms in the patient one month following the injections. Based on the cytokine profiles (Supplement Table 1), ADA (40 mg/2 weeks) in combination with low dose MP (8 mg/day) were used. After three months, the patient had significant improvement in excessive sweating, appetite, asthenia, and edema. Symptoms of heart failure were progressively improved, and the patient achieved NYHA class I and AHA stage B, without increased skin rashes and masses. Additionally, C-reactive protein (CRP), serum TNF-α, and IL-6 levels were substantially decreased during the period of this treatment (Figure 2(A,B)). Repeated PET-CT showed that

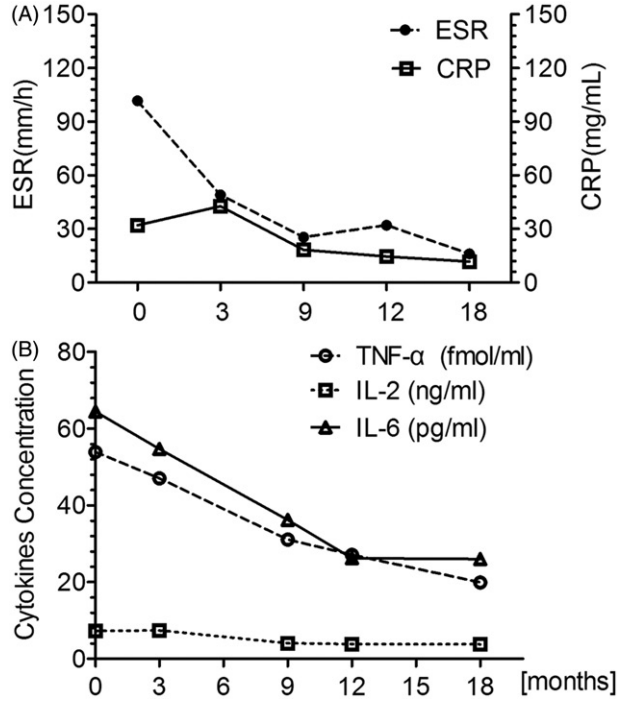

Figure 2. ELISA analysis of serum pro-inflammatory factors. (A) Serum ESR and CRP and (B) cytokines (IL-2, IL-6, and TNF-α) levels.

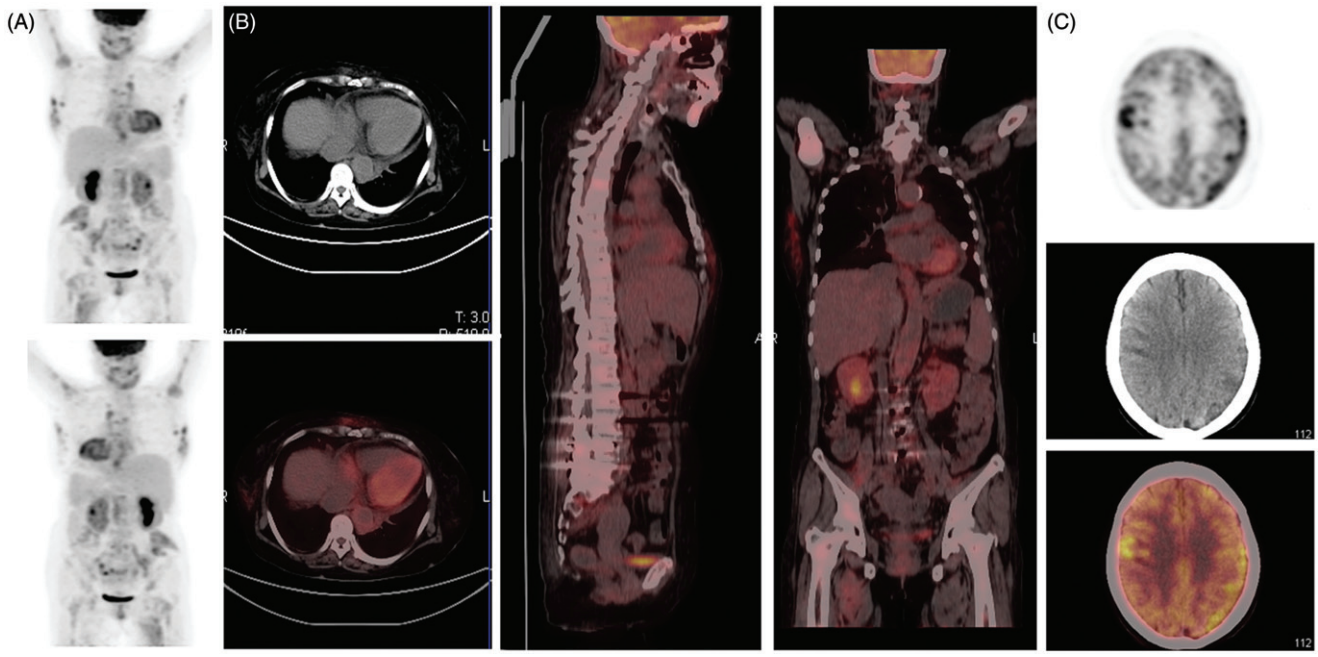

Figure 3. Evaluation of the disease activity after treatment with adalimumab for 3 months. 18F-FDG PET/CT examination of the patients in (A) three-dimensional whole body scan in anterior and posterior views; (B) cardiac system and whole body in lateral and anterior views; (C) brain.

multiple organ lesions were improved, such as bones, left hemisphere, renal, and primary soft tissue mass (Figure 3). No adverse events occurred except for mild fever and gastrointestinal symptoms. The patient's condition remained stable after 18 months of follow-up, except for the slow progression of gastrointestinal symptoms (including abdominal distension, nausea, and constipation) and hypo-immunity (chronic gastric disease with lymphocytic infiltration). Unfortunately, the patient died of progressive gastrointestinal disorders (stomach ache, inappetence, etc.) and extreme asthenia in August 2014, three years after the onset of ECD.

Discussion

This study reported the application of ADA in a rare case of ECD with repeated fever and severe cardiovascular and CNS involvements. It is estimated that the median survival of ECD patients was 32 months [3], while the mean survival time decreased to 19.2 months for patients with multisystem involvements and patients at end-stage [9]. Our data revealed that ADA substantially ameliorated the symptoms of ECD and increased median survival time of the patient.

Cytotoxic drugs, bone marrow transplantation, corticosteroids, and IFN-α were commonly used to treat ECD. Recently, the BCR-ABL/KIT inhibitor imatinib mesylate, IL-1 receptor antagonist anakinra, and TNF-neutralizing antibody infliximab were experimentally used for ECD [10–12]. However, the patients showed variable response to these treatments depending on the severity of organ involvement. In this report, the patient was initially given cytotoxic drug CTX for three months. Some complications were alleviated, while life-threatening cardiac and brain comorbidities progressed. Also, the subsequent application of IFN-α failed to rescue the adverse effects and the patient could not tolerate the recurrent high fever and severe gastrointestinal diseases. Eventually, an anti-inflammation-based treatment was used according to the serum cytokine profiles in this ECD patient. Several studies documented alterations of the cytokine network at ECD lesion sites and in serum, such as IL-2, IL-6, TNF-α, and IL-10 [13,14]. Clinical observations on a small sample demonstrated that anti-inflammation agents could be effective in the management of this disease [15].

A compelling study in ECD demonstrated that TNF-α was a master modulator of inflammation in ECD and TNF-α neutralization using infliximab may represent a promising and safe strategy for the treatment of ECD with severe cardiovascular involvement [7]. In this study, we used ADA, a fully humanized anti-TNF-α monoclonal antibody, in the treatment of ECD with systemic involvement including heart and brain. The administration of ADA combined with MP resulted in substantial improvement of symptoms in this patient. Accordingly, TNF-α, IL-2, and IL-6 plasma levels significantly decreased during anti-TNF-α therapy. Although occasional fever and some gastrointestinal symptoms remained in the patient, there were no significant adverse effects in the long-term. ADA is able to retard ECD progression in several ways, including neutralization of soluble and membrane-bound TNF-α, disruption of a TNF-regulated cytokine cascades, and possibly, the lysis of TNF-α-expressing histiocytes [14,16]. Therefore, ADA may be a more promising drug for end-stage ECD with system involvements. Moreover, it is believed that a combination of ADA with other drugs should be more effective [17].

Conclusion

ADA was efficient and safe in treating ECD with systemic involvement, which may represent an alternative option for ECD patients with cardiovascular and brain involvement. However, additional cases and further follow-up studies are needed to clearly delineate the efficacy and safety of ADA in treating ECD.

Disclosure statement

No potential conflict of interest was reported by the authors.

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