Immunopathologia Persa
http immunopathol.com
DOI:10.34172/ipp.2025.43857

Interferon α-2b and quality of life improvements in Erdheim-Chester disease; a longitudinal case report

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Received 16 Feb. 2025
Revised: 19 May 2025
Accepted 27 Jun. 2025
ePublished 7 Jul. 2025

Keywords: Erdheim-Chester disease, Non-Langerhans-cell histiocytosis, Interferon therapy, Skin lesions, Histiocytes

Abstract

Introduction: Erdheim-Chester disease (ECD) is a form of histiocytosis and a sporadic illness with diverse clinical manifestations. Although ~500 to 550 cases have been described in the literature, increased physician awareness has driven a dramatic increase in ECD diagnoses over the last decade. ECD frequently involves multiple organ systems and has historically lacked effective therapies.

Case Presentation: A 43-year-old male who had a familial background of autoimmune disorders, exhibited widespread skin manifestations and systemic manifestations that resulted in notable social and psychological distress.

Results: Despite the administration of extensive therapy with corticosteroids, cyclosporine, and thalidomide, the individual's health status persisted in declining. Skin biopsy verified ECD diagnosis, but interferon α-2b treatment did not stop disease progression. Vemurafenib did not cause regression either. However, regular Interferon therapy and follow-ups reduced lesions by 30%-40% and improved social health and quality of life.

Conclusion: ECD should be included in the differential diagnosis of skin lesions, especially those with systemic symptoms, and regular follow-up, and consistent therapy may help manage this difficult condition.

Citation: Razavi SM, Sadati S, Tavakoli Shiraji S, Adib Sereshki MM, Ghoreyshi M. Interferon α-2b and quality of life improvements in Erdheim-Chester disease; a longitudinal case report. Immunopathol Persa. 2025;x(x):e43857. DOI:10.34172/ipp.2025.43857.

Introduction

Erdheim-Chester disease (ECD) is a rare multisystem non-Langerhans cell histiocytic proliferative condition. It peaks in the fifth to seventh decades of life, with a slightly higher male incidence (40–70 years) (1-3). Chronic uncontrolled inflammation and organ infiltration by CD68(+)/CD1a(−) non-Langerhans foamy histiocytes surrounded by fibrosis characterize this clonal illness of unclear cause (4-6). ECD symptoms are nonspecific and may differ based on the site of involvement (4,6,7). Fever, weight loss, and nocturnal sweats may be misinterpreted as tuberculosis in impoverished nations. Skeletal involvement is most common, with bone pain often first (6,8,9). The symptoms range from asymptomatic localized disease to catastrophic multisystem dysfunction. Symmetric osteosclerotic lesions of long bones in the lower extremities are the most typical manifestation. The cardiovascular, neurological, and endocrine systems may be impacted. The prognosis is bad for instances with central nervous system involvement, which can reach 50% (10). ECD prognosis varies on location and extraosseous involvement (11). Skin lesions biopsy (e.g., xanthelasma) or per-nephric fat infiltration (computerized tomography guided) can confirm the diagnosis of ECD (12). The specimens are expected to test positive for one or more cell markers: CD68, CD163, or FXIIIa. If Langerhans cell histiocytosis (LCH) is not simultaneously involved, the CD1a test results should be negative (13).

Presently, the most extensively supported initial treatment for ECD is IFN-α and PEGylated IFN-α (PEG-IFN-α) (grade C2) (5). In the most extensive trial to date, a cohort of 53 patients with ECD was observed in a prospective, nonrandomized manner. Out of these patients, 46 individuals who received treatment with IFN-α or PEG-IFN-α showed a substantial improvement in overall survival compared to those who received different medications. Furthermore, the use of IFN-α or PEG-IFN-α was identified as an independent factor that predicted increased survival in a multivariate analysis (14). The effectiveness of IFN-α varies depending on the specific organ affected and the dosage

Key point

- Erdheim-Chester disease (ECD) should be considered as a rare but probable differential diagnosis in diffused skin lesions mimicking other conditions such as psoriasis.
- It can cause a decreased quality of life and limited function for patients.
- A personalized strategy, including treatment (which was interferon therapy in our case) and follow-up, can improve this condition alongside with patient's quality of life.

schedule (14). Several alternative therapies, including kinase inhibitors (vemurafenib, and cobimetinib) (15-18), biologics (anakinra, infliximab, and tocilizumab) (19-22), and cladribine (23) are conducted as second-line treatments, can be used to treat ECD when IFN-α is not effective or not tolerated, or in cases when there are life-threatening symptoms.

Case Presentation

We report a case study of a 43-year-old Iranian male patient who first presented with diffused symmetric yellowish plaques and was initially misdiagnosed as having psoriasis (Figure 1A, 1B).

The study was done after receiving his informed consent, and the ethics committee approved the study.

After three months of topical corticosteroids, cyclosporine, and thalidomide, his condition worsened, across with nodular lesions, requiring a dermatologist visit. The cutaneous manifestations, concomitant with intense myalgia, disturbances in sleep patterns, hemoptysis, weight increase, occupational impairment due to depression, and challenges in social interactions, affected his entire physique. Furthermore, the patient manifested a familial predisposition to rheumatoid arthritis and Behçet's syndrome in his siblings. The physical examination indicated hepatomegaly and laboratory findings showed proteinuria (urine protein; 2+) elevated C-reactive protein (CRP; >20 mg/L), and erythrocyte sedimentation rate (ESR; 30 mm/h). The findings from the complete blood count, urea and electrolytes, lipid profile, hepatic function, and antinuclear antibody panels indicated values that fell within the established healthy ranges. The level of antinuclear antibodies (ANA) was measured at 0.5.

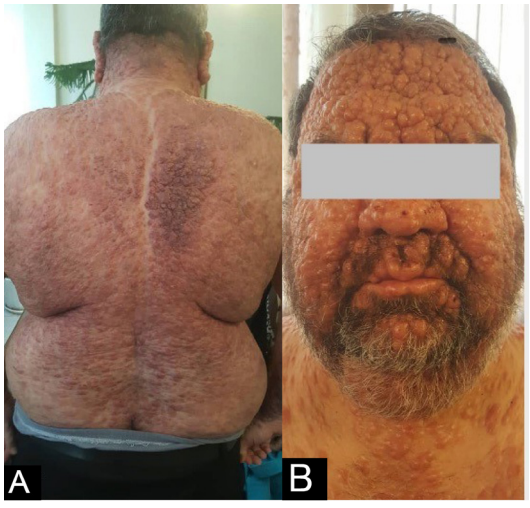

Figure 1. Skin lesion distribution before treatment.

The punch biopsy of the skin lesions on the right shoulder and abdomen revealed a widespread nodular presence of histocytes. These histocytes had vesicular nuclei, irregular nuclear borders, and a cytoplasm that ranged from clear to pale eosinophilic. They were arranged in sheets and mixed with lymphocytes, and their presence extended into the deeper layers of the skin and subcutaneous fat. The overlying epidermis is atrophic with affected rete ridges and invasion of histiocytes into the epidermis (Figure 2, A-C).

Immunohistochemistry in lesional cells showed the following staining profile: strongly positive CD68 and non-specific staining for S-100 only. HMB-45, CD1a, and langerin were all negative. The LCA staining exhibited favorable outcomes within the inflammatory cells, while the Ki67 staining demonstrated a nuclear positivity ranging from 20% to 25%. Consequently, these findings led to the identification of ECD as the primary etiology of the patient's manifestations.

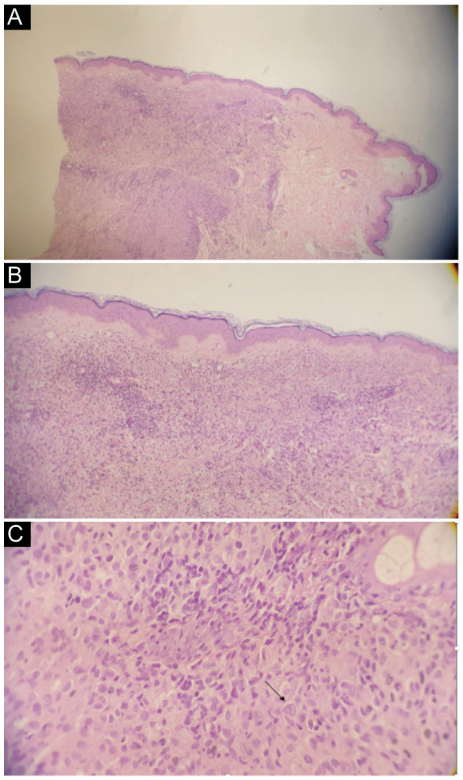

Figure 2. A) low power examination shows dense dermal infiltration by cells with abundant clear. B) intermediate power shows infiltration by Langerhans cells: 12-15 microns in diameter with abundant, pale eosinophilic cytoplasm (x20). C) Langerhans cell histiocytosis with abundant, pale eosinophilic cytoplasm, irregular and elongated nuclei, and prominent nuclear groove (black arrows) (x40).

Despite encountering challenges during the initial therapy and observing no favorable reaction to Interferon α-2b and Zelboraf, a remarkable enhancement was evident upon consistent reintroduction of Interferon treatment. As a result, there was a 30%-40% reduction in the size of the lesions and notable improvements in the patient's social well-being and overall quality of life. The patient is undergoing Interferon therapy and is presently in a stable condition (Figure 3).

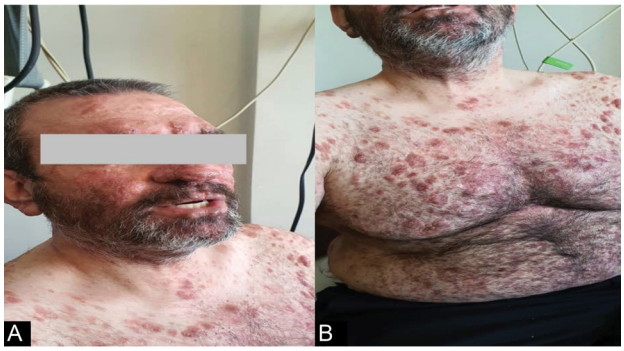

Figure 3. Distribution of skin lesions after treatment.

Discussion

Erdheim-Chester disease is an uncommon form of non-Langerhans cell histiocytosis characterized by the invasion of tissues by foamy histiocytes with a xanthogranulomatous appearance. Although recent case reports about this disease have been reported in Iran, no case of generalized skin involvement of ECD in Iran has been mentioned in the literature (24). Our case is a 43-year-old Iranian male patient who presented diagnostic and therapeutic challenges typical of this rare condition.

In this case, the skin was the major site of clinical alteration characterized by widespread involvement of head and neck, chest, abdomen and extremities.

The patient's widespread yellowish nodules and systemic manifestations initially misinterpreted as psoriasis, necessitated a comprehensive evaluation that led to a skin biopsy and the precise diagnosis of ECD.

The observation of autoimmune conditions, such as rheumatoid arthritis and Behçet's syndrome, in the patient's familial background, implies a possible genetic susceptibility or shared pathogenic mechanisms, warranting further scrutiny. The involvement of multiple organs, including hepatic enlargement, abnormal protein levels in urine, elevated inflammatory markers (CRP and ESR), and normal ANA levels, added intricacy to the clinical presentation (25).

The histopathological analysis showed a diffuse and nodular infiltrate of histiocytes, which tested positive for CD68 and non-specific for S-100 while testing negative for Langerhans cell markers (HMB-45, CD1a, and langerin). This confirmed the diagnosis of ECD (26). The substantial nuclear positivity of Ki67 (20-25%) indicates a high rate of cell proliferation, which suggests the presence of active illness (27).

Previously, ECD was seen as a condition with a bleak outlook due to the absence of effective therapy, resulting in a 60% mortality rate within 3 years after diagnosis. Patients with extraskeletal involvement have a more unfavorable prognosis (6).

The ROPEG-IFN-α 2b, a modified form of IFN-α, has been created specifically for patients suffering from myeloproliferative neoplasms. This medication possesses a prolonged elimination half-life, which allows for less frequent administration and presents a reduced risk of harmful effects (28,29). Its efficacy and toxicities have not yet been reported in ECD patients.

The initial absence of a reaction to IFN-α and vemurafenib, which are both established therapies for ECD, was worrisome. Though, the significant enhancement observed with persistent administration of Interferon therapy highlights the crucial role of adhering to treatment and maintaining frequent follow-up. The observed 30%-40% reduction in lesions and enhancements in social health and quality of life align with the advantages of prolonged immunomodulatory treatment documented in scientific literature (25). This instance adds to the increasing amount of evidence that supports the necessity of customized medication in ECD, when standard treatment procedures may not be efficacious. Furthermore, it emphasizes the potential of consistent and prolonged administration of IFN-α as a means of treating ECD, even in cases where early treatment attempts have been unsuccessful (30).

Conclusion

This case illustrates the diagnostic and therapeutic complexities of ECD, the importance of considering ECD in the differential diagnosis of dermatological and systemic symptoms, and the challenges in finding effective treatment regimens. Additionally, this case report emphasizes the need for personalized treatment plans and the potential benefits of long-term, consistent therapy, especially improvements in quality of life and life expectancy. Further research is needed to understand the pathogenesis of ECD better and to optimize therapeutic strategies for this rare and enigmatic condition.

Authors' contribution

Conceptualization: Seyed Mohsen Razavi.
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Project administration: Mohammad Mahdi Adib Sereshki.
Resources: Seyed Mohsen Razavi.
Software: Sina Sadati.
Supervision: Seyed Mohsen Razavi.
Validation: Seyed Mohsen Razavi.
Visualization: Sina Sadati.
Writing–original draft: Sina Sadati.

Writing–review & editing: Sahar Tavakoli Shiraji, Mohammad Mahdi Adib Sereshki, Maryam Ghoreyshi.

Conflicts of interest

The authors declare no conflict of interest.

Ethical issues

This case report was conducted in accordance with the World Medical Association Declaration of Helsinki. The patient has given written informed consent for publication of this case report. Ethical issues (including plagiarism, data fabrication, and double publication) have been thoroughly addressed.

Data availability statement

The original contributions generated for the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Funding/Support

The authors declared that this study received no financial support.

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