Parivash Rahimizadeh[1], Mehrdad Farrokhnia[2], and Saman Mohammadi[1]

[1]Kerman University of Medical Sciences Faculty of Medicine
[2]Kerman University of Medical Sciences

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Title page

Familial Erythema Nodosum Secondary to Streptococcal Infection: A Case Report

Parivash Rahimizadeh*[1], Mehrdad Farokhnia[2], Saman Mohammadi[1]

1) Dermatology Research Center, Kerman University of Medical Sciences, Kerman Iran, Dermatologist.

2) Infectious and Tropical Research Center, Kerman University of Medical Sciences, Kerman Iran, Infectious Disease Specialist.

***Corresponding Author:** Parivash Rahimizadeh, Dermatology Research Center, Kerman University of Medical Sciences, Kerman Iran.

E-mail: rahimizadehp70@gmail.com

Abstract

This case report presents a rare familial cluster of erythema nodosum (EN) secondary to streptococcal infection in a 33-year-old Iranian woman and her two children, aged 13 and 8 years. EN is a form of panniculitis characterized by tender, erythematous nodules predominantly located on the lower extremities. Although various triggers have been identified, including infections, drugs, and systemic diseases, familial cases of EN are infrequently reported. All three patients presented with painful, erythematous nodules on the pretibial aspects of their lower legs, preceded by respiratory symptoms. Laboratory investigations revealed elevated antistreptolysin O (ASO) titers, leukocytosis, and increased inflammatory markers, supporting the diagnosis of EN associated with streptococcal infection. The temporal relationship between the onset of respiratory symptoms and the development of EN in all three family members suggests a shared environmental exposure to the streptococcal pathogen. This case highlights the importance of considering familial predisposition and common environmental exposures in the etiology of EN. Furthermore, it emphasizes the value of a comprehensive clinical evaluation and targeted laboratory tests in establishing the diagnosis and identifying the underlying cause. Prompt recognition and appropriate management of EN are crucial for optimal patient outcomes and the prevention of potential complications. The familial occurrence of EN underscores the need for further research to elucidate the genetic and environmental factors contributing to the development of this rare condition and to improve our understanding of its pathogenesis and management.

Key words: Erythema nodosum, Familial, Streptococcus, Genetic, Extremities

Key clinical message

This case report presents a rare familial cluster of erythema nodosum precipitated by streptococcal infection. The temporal association between prodromal respiratory symptoms and subsequent cutaneous manifestations in the mother and her children suggests a shared environmental exposure. Expeditious identification of the etiology and initiation of appropriate management are paramount for optimal patient outcomes.

Introduction

Erythema nodosum (EN) is a form of panniculitis, marked by inflammation of subcutaneous fat tissue (1). Clinically, it presents as tender, erythematous nodules, predominantly located on the anterior aspects of the lower extremities. EN frequently coexists with various systemic diseases, infections, and medication reactions, and less commonly, it has a genetic predisposition (2). Familial (EN) denotes a subset of this condition, where a significant hereditary component is evident, implying a substantial role of genetic factors in its pathogenesis (3).

EN primarily affects young adults, with a higher incidence observed in females. The precise prevalence of familial cases remains undocumented due to their rarity (4). Nonetheless, it is imperative to consider a family history in the diagnostic evaluation and management of recurrent or chronic EN cases (5).

The etiology of EN is complex and not fully understood, though it is recognized as a hypersensitivity reaction to various antigens. These antigens can be exogenous, including bacterial, viral, or fungal infections, or endogenous, related to systemic conditions such as sarcoidosis, inflammatory bowel disease, and malignancies. In familial cases, a genetic predisposition is suggested, although specific genetic markers have not been conclusively identified (1).

The clinical hallmark of EN is the acute onset of painful, erythematous nodules, ranging from 1 to 5 cm in diameter (6). These nodules often develop a bruise-like appearance as they resolve. They are most located on the shins but can appear on other areas of the body. Associated systemic symptoms include fever, malaise, and arthralgia. Diagnosis of EN is primarily clinical, based on the distinctive appearance and distribution of the nodules (7).

Management of EN focuses on treating the underlying cause if identified. General supportive measures include bed rest, leg elevation, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for pain and inflammation. In more severe cases, potassium iodide and corticosteroids may be considered (8).

The prognosis for EN is generally favorable, with most lesions resolving spontaneously within 3 to 6 weeks. However, chronic or recurrent EN, especially in familial cases, may necessitate ongoing management and monitoring for potential underlying systemic diseases (2).

Case report

This case report describes a familial cluster involving a 33-year-old Iranian woman and her two children, a 13-year-old daughter and an 8-year-old son, who presented with similar clinical manifestations.

The mother was admitted to our medical facility, presenting with a 3-week history of persistent fever and arthralgia affecting both ankles and knees. Additionally, she exhibited symmetrical, multiple, round, light pink, tender erythematous nodules with indistinct borders over the pretibial skin (Figure 1). The patient reported a preceding episode of respiratory symptoms, including cough, pharyngitis, fever, and lymphadenopathy, occurring 4 weeks prior to the onset of the skin lesions. Notably, there was no history of recent medication use, travel, COVID-19 vaccination, or exposure to individuals with infectious illnesses prior to the onset of symptoms.

One week after the mother's respiratory symptoms began, her two children developed similar respiratory manifestations, including cough, pharyngitis, and fever. The daughter presented to our medical facility with a 3-day history of erythematous, tender nodules on her lower extremities. Physical examination revealed multiple, symmetric, erythematous, tender nodules measuring roughly 1.5 cm in diameter on the pretibial aspects of both lower legs. The lesions were similar in appearance to those observed in her mother's case. No evidence of motor deficits or sensory abnormalities was noted, and distal pulses were palpable and symmetric. The patient reported mild discomfort during the examination of her ankles and knees. Systemic examinations were unremarkable, with no signs of mucous membrane involvement or lymphadenopathy.

The son presented with a 4-day history of similar erythematous, tender nodules on his lower extremities. Physical examination findings were comparable to those of his mother and sister, with multiple, symmetric, erythematous, tender nodules measuring approximately 1 cm in diameter on the pretibial aspects of both

lower legs. No motor deficits, sensory abnormalities, or impairment of distal pulses were noted. The patient reported mild discomfort during the examination of his ankles and knees. Systemic examinations were unremarkable, with no evidence of mucous membrane involvement or lymphadenopathy.

Laboratory investigations were conducted for all three patients, including complete blood counts, renal and hepatic function tests, antistreptolysin O (ASO) titers, erythrocyte sedimentation rates (ESR), and C-reactive protein (CRP) levels. The mother's white blood cell count was elevated at 11,000 cells/μL, consistent with leukocytosis. Her ASO titer was significantly increased at 333 IU/mL, suggestive of a recent streptococcal infection. The daughter's white blood cell count was mildly elevated at 9,500 cells/μL, and her initial ASO titer was significantly elevated at 1067.6 IU/mL. A repeat test yielded a result of 327 IU/mL, still above the normal upper limit. The son's initial ASO titer was within the normal range at 31.2 IU/mL; however, due to persistent symptoms, a repeat test was performed, revealing an elevated value of 100 IU/mL. All three patients had mildly elevated ESR and CRP levels, indicating the presence of underlying inflammation. Renal and hepatic function tests were within normal limits for all patients.

Imaging studies, including chest radiographs, were performed for all three patients and showed no abnormalities. Polymerase chain reaction (PCR) tests for COVID-19 were also conducted, and the results were negative.

The constellation of clinical findings, including the characteristic erythematous nodules on the lower extremities and the preceding respiratory symptoms, along with the laboratory abnormalities, particularly the elevated ASO titers and inflammatory markers, strongly support the diagnosis of EN secondary to a recent streptococcal infection in this familial cluster. The temporal relationship between the mother's and her children's respiratory symptoms and subsequent development of erythematous nodules suggests a shared environmental exposure to the streptococcal pathogen.

Method

Upon presentation of the patients with tender, erythematous nodules on the lower extremities, a comprehensive differential diagnosis was considered. The differential diagnosis for EN includes infectious causes (e.g., streptococcal infections, tuberculosis, Yersinia, Mycoplasma, Chlamydia, Histoplasma, Coccidioides, and HIV), inflammatory conditions (e.g., sarcoidosis, inflammatory bowel disease, and Behçet's disease), malignancies (e.g., lymphoma, leukemia, and solid tumors), medications (e.g., oral contraceptives, sulfonamides, and certain antibiotics), and other causes (e.g., pregnancy, Sweet's syndrome, and idiopathic EN).

A thorough clinical evaluation and targeted laboratory investigations were conducted to establish the diagnosis and identify the underlying cause of EN in this familial cluster. Physical examination included a detailed assessment of the skin lesions, their distribution, size, color, and tenderness, as well as a comprehensive systemic examination to detect any associated signs or symptoms. Laboratory tests included a complete blood count to evaluate for leukocytosis, ASO titers to detect recent streptococcal infection, ESR and CRP levels to assess underlying inflammation, and renal and hepatic function tests to rule out systemic involvement. Imaging studies, such as chest radiographs, were performed to screen for pulmonary involvement or associated conditions, and PCR tests for COVID-19 were conducted to exclude this as a potential cause. Although not performed in this case, a deep incisional or excisional biopsy of the nodules may be considered to confirm the diagnosis of EN and exclude other nodular lesions.

The management of EN in this familial cluster focused on providing supportive care to alleviate symptoms, as the patients were referred to the doctor after the optimal window for initiating antibiotic therapy had passed. Due to the late presentation, the golden time for antibiotic initiation had ended, precluding the use of antibiotics to treat the underlying streptococcal infection. Supportive measures included rest, leg elevation to reduce swelling and discomfort, nonsteroidal anti-inflammatory drugs (NSAIDs) to manage pain and inflammation, and cool compresses applied to the affected areas to provide symptomatic relief. Close follow-up was ensured to assess the response to these supportive measures, monitor for potential complications, and evaluate for any underlying systemic diseases, particularly in the setting of familial EN. Although antibiotics are typically the mainstay of treatment for EN secondary to streptococcal infection, the delayed presentation

in this case necessitated a focus on symptom management and supportive care.

Conclusion and results

In conclusion, this case report highlights the importance of recognizing EN as a potential manifestation of streptococcal infection and emphasizes the value of a thorough clinical history, physical examination, and targeted laboratory investigations in establishing the diagnosis. The familial occurrence of EN in this case suggests a possible genetic predisposition or shared environmental exposure to the triggering pathogen. Prompt identification and appropriate management of the underlying cause are crucial for the optimal treatment of EN and the prevention of potential complications. Further research is needed to elucidate the genetic and environmental factors contributing to the development of familial EN and to improve our understanding of this rare condition.

Discussion

This case report presents a rare familial cluster of EN secondary to streptococcal infection, involving a mother and her two children. EN is the most common form of panniculitis, characterized by tender, erythematous nodules predominantly located on the anterior aspects of the lower extremities (9, 10).Although the exact pathogenesis of EN remains unclear, it is considered a delayed hypersensitivity reaction to various antigenic stimuli, including infections, drugs, systemic illnesses, and malignancies (3, 11).

The clinical presentation of EN in this familial cluster is consistent with the typical features described in the literature, including the acute onset of painful, erythematous nodules on the lower extremities (6, 12). The presence of associated systemic symptoms, such as fever and arthralgia, is also commonly reported in EN (13). The diagnosis of EN is primarily based on the characteristic clinical findings, although a deep incisional or excisional biopsy may be performed to confirm the diagnosis and exclude other nodular lesions (3, 6).

Compared to the previous case report of EN, this familial cluster presents a unique perspective on the potential genetic predisposition and shared environmental factors contributing to the development of the condition (14, 15). Familial EN is a rare subset of the disease, and its exact prevalence remains unknown (16).The occurrence of EN in multiple family members within a short time frame, as seen in this case, strongly suggests a common triggering factor, such as streptococcal infection (2).

The temporal relationship between the onset of respiratory symptoms and the subsequent development of EN in all three family members supports the role of streptococcal infection as the underlying cause. Streptococcal pharyngitis is the most common identifiable cause of EN (9, 17),and the elevated antistreptolysin O (ASO) titers in the patients further support this etiology (2, 18).

The familial occurrence of EN in this case highlights the importance of considering a family history in the diagnostic evaluation and management of the condition (19). Genetic factors may play a role in the susceptibility to EN, as suggested by the presence of human leukocyte antigen (HLA) alleles in some familial cases [6,16]. However, the specific genetic markers associated with familial EN remain to be elucidated (9, 15).

In addition to genetic predisposition, shared environmental exposures may contribute to the development of EN in family members (20). The proximity of family members and the potential for transmission of infectious agents, such as streptococcal bacteria, may explain the clustering of EN cases within families (2, 20).

The management of EN primarily focuses on identifying and treating the underlying cause, if present (9, 12). Supportive measures, such as rest, leg elevation, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or potassium iodide, can help alleviate symptoms (9, 21). In severe or refractory cases, systemic corticosteroids may be considered (21). Furthermore, patients should be monitored for potential complications or associated systemic diseases, particularly in the setting of chronic or recurrent EN (22, 23).

Key clinical message

This case report presents a rare familial cluster of erythema nodosum precipitated by streptococcal infection.

The temporal association between prodromal respiratory symptoms and subsequent cutaneous manifestations in the mother and her children suggests a shared environmental exposure. Expeditious identification of the etiology and initiation of appropriate management are paramount for optimal patient outcomes.

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Declaration

Ethics approval and consent to participate

This case report was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of the Kerman University of Medical Sciences. Written informed consent form was obtained from the adult patient and the parents of the pediatric patients for their participation in the study.

Consent for publication

Written informed consent was obtained from the adult patient and the parents of the pediatric patients for the publication of this case report and any accompanying images. A copy of the written consent (written in Persian language) is available for review by the Editor-in-Chief of this journal.

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Availability of data and materials The data used during the current study are available from the corresponding author on reasonable request.

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Competing interests The authors declare that they have no competing interests.

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Author contribution

Saman Mohammadi and Mehrdad Farokhnia conceptualized and designed the study. Saman Mohammadi and Parivash Rahimizadeh drafted the initial manuscript. Mehrdad Farokhnia critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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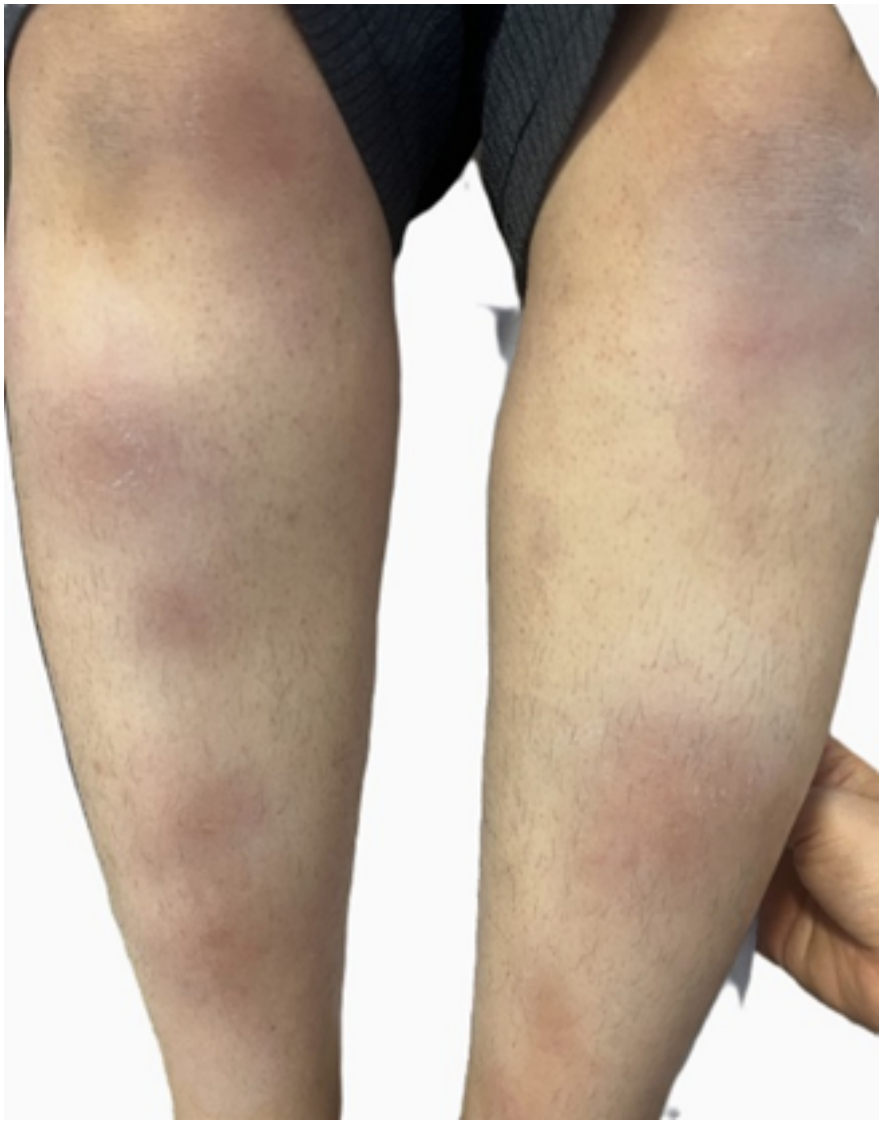
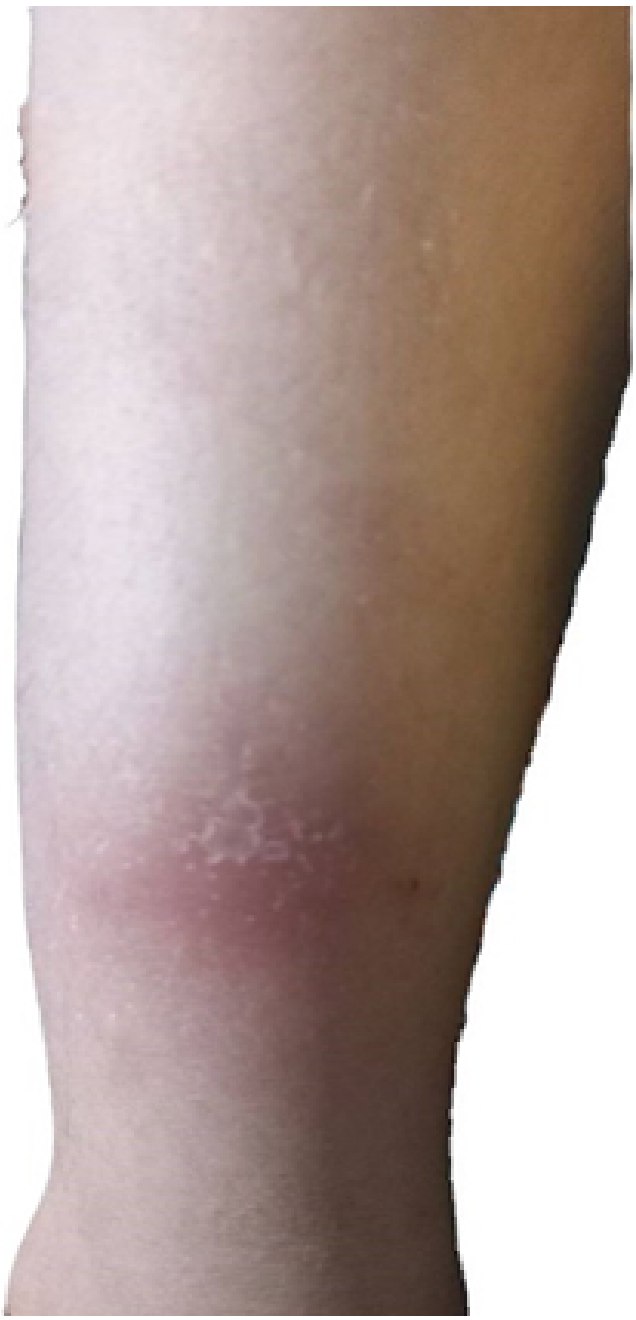
Images





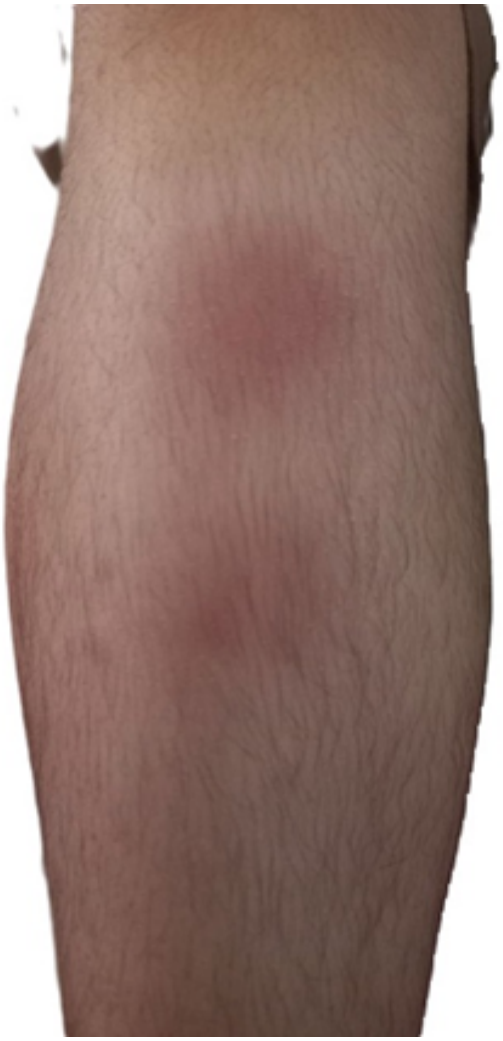


Figure 1. Clinical photograph showing multiple symmetrical, round, light pink, tender erythematous nodules with indistinct borders over the pretibial skin. The images demonstrate the familial occurrence of erythema nodosum in this case, with the first picture (left) depicting the lesions in the mother, the second picture (center) showing the son's presentation, and the third picture (right) illustrating the daughter's cutaneous findings.

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