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Atypical Presentation of Rheumatoid Arthritis with Erythema Nodosum Mimicking Cellulitis: A Case Report

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Abstract

Erythema nodosum (EN) is a septal panniculitis that can have several etiologies. We report a case of a 35-year-old female with recurrent fever and a painful rash on the right thigh. A skin biopsy revealed septal panniculitis and Miescher's granuloma, suggestive of EN. Since these histopathological changes are nonspecific, extensive workup was done to find out the causes of erythema nodosum, considering infectious, autoimmune, and malignant etiologies. She was found to have high rheumatoid factor and an anti-cyclic citrullinated peptide antibody, which was strongly positive and suggestive of rheumatoid arthritis. Her symptoms were resolved with steroids. It can be challenging to find out the etiology of erythema nodosum or make a diagnosis of rheumatoid arthritis when a patient presents solely with extra-articular manifestations.

Keywords: Rheumatoid Arthritis; Erythema Nodosum; Anti-Cyclic Citrullinated Peptide Antibody; Miescher's Granuloma; Steroid Therapy.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory systemic disease, among many others, including systemic lupus erythematosus that can involve multiple system organs and present with diverse clinical features [1]. As per the Global Burden of Diseases, Injuries, and Risk Factors 2017 study, the age-standardized point prevalence of RA was 246.6 (95% UI 222.4 to 270.8) [2]. Similarly, it is also one of the major contributors to global disability [3]. Rheumatoid arthritis develops as a result of genetic predispositions, environmental triggers, and immunological factors, which together lead to synovial immunological response, inflammation, and joint damage [4]. Typically RA manifests with involvement of multiple joints but can also have atypical or extra-articular involvement including skin (rheumatoid nodules), heart, lungs (interstitial lung disease), cardiac (pericardial effusion), anemia, Felty syndrome, amyloidosis, carpal tunnel syndrome, scleritis, and many others.

These extra-articular manifestations are seen in 17.8-40.9% of the patients with RA [5]. It can have various cutaneous lesions ranging from rheumatoid nodules to vasculitis and dermatitis [6]. Cutaneous lesions are common but mostly present with symmetric arthritis [7]. Erythema nodosum (EN) is a septal panniculitis that results from a reactive process to various etiologies, such as inflammation, infections, neoplasms, and medications. Very few cases of EN have been reported in patients with RA. Streptococcal infection, primary tuberculosis, sarcoidosis, Behçet's disease, medication, inflammatory bowel disease, non-Hodgkin lymphoma, and pregnancy were reported as common causes of EN but no etiology was identified in several cases [8-14]. EN presents as painful and erythematous nodules in the subcutaneous tissue usually seen on the shins. Histologically, it reveals septal panniculitis without vasculitis with early lesions showing lymphohistiocytic infiltrate along with neutrophils and eosinophils in the septae and surrounding adipose tissue [14]. Miescher's radial granuloma is characteristic of EN, consisting of small histiocytes surrounding a central cleft [15].

Case Presentation

We present a case of a 35-year-old Hispanic female with no significant past medical history who presented to the emergency room with complaints of recurrent episodes of fever, swelling, rash, and pain in her right thigh that had been going on for almost 2 months. She presented to the hospital for similar problems three times, when she was empirically treated for cellulitis each time with IV antibiotics initially during the hospital stay and was discharged on oral antibiotics. The blood culture was negative during each visit. She continued to have these symptoms persistently and again presented for the fourth time with fever, swelling, and pain in the upper inner aspect of her right thigh. These symptoms were associated with dizziness and a painful nodular rash on both thighs and shins. She denied taking any medications, having a family history of autoimmune diseases or cancer, or having a personal history of smoking, alcohol, or illicit drug use. Upon initial assessment, she was tachycardic with a pulse rate of 120 per minute, a blood pressure of 95/57 mm of Hg, a temperature of 38.5 degrees Celsius, a respiratory rate of 20 breaths per minute, and a pulse oximetry reading of 98% on room air. She had also lost 5 pounds in the last 3 months. Clinical examination showed significant induration, mild tenderness, and redness in the medial aspect of the right thigh. There were multiple nodular lesions on both legs that were tender on palpation (see figure 1). Both ankles had slight swelling, tenderness to touch, and a limited range of motion.

Since she exhibited features of systemic inflammatory response syndrome (SIRS), initially thought to be secondary to cellulitis, she was started on broad-spectrum antibiotics. She had experienced two spikes of fever in the first two days of admission. Despite not having leukocytosis and her recurrent admission for similar symptoms with no response to antibiotics, further workup was done. A skin biopsy was done, which showed septal panniculitis, and histiocytic collection demonstrating intercellular clefting, suggestive of Miescher granuloma (see histopathological Figures 2-4). No evidence of vasculitis or atypia was found, and the spirochete stain was negative. AFB (Acid Fast Bacilli) stain failed to highlight acid-fast bacilli and fungal hyphae, respectively. Acknowledging histologic changes are nonspecific, extensive workup was done for erythema nodosum, considering infectious, autoimmune, and malignant etiologies. Serologies for bacterial, mycobacterial, hepatitis profile, HIV, and fungal infections, including Aspergillus, Histoplasma, and Coccidioides, were sent, all of which returned negative. Antibody panel evaluations for autoimmune conditions revealed negative results for ANA, c-ANCA, p-ANCA, SSA, SSB, anti-double-stranded DNA, and anti-Smith antibodies. Anti-streptolysin O antibody screens, C3-C4 levels, and total complement were also within normal ranges. Computed tomography of the chest did not show hilar or mediastinal lymphadenopathy. The transthoracic echocardiogram showed no evidence of vegetation. Colonoscopy with a random biopsy of the colonic mucosa revealed normal mucosa with no signs of inflammation, polyps, masses, or ulcers. However, the rheumatoid factor was elevated at 128 and the cyclic citrullinated peptide (CCP) antibody test revealed a strongly positive result of 80. These findings were suggestive of rheumatoid arthritis. Given the diagnosis of erythema nodosum secondary to rheumatoid arthritis, the patient was started on prednisone at a dose of 1 mg per kg for the first 7 days. Following the initiation of steroids, her symptoms improved with the resolution of fever and tachycardia in 48-72 hours. Further investigations were conducted to assess the systemic involvement of rheumatoid diseases. The bilateral ankle and hand x-rays showed no signs of fractures, dislocations, or soft tissue inflammation. Prednisone was then planned to be tapered by 10 mg per week, consecutively. After gradual improvement and absence of other systemic signs and symptoms, the patient was discharged home with a tapering dose of steroid and trimethoprim/sulfamethoxazole for Pneumocystis jirovecii pneumonia prophylaxis. The patient followed rheumatology on an outpatient basis with improvement in rash and was started on maintenance prednisone 20 mg once a day.

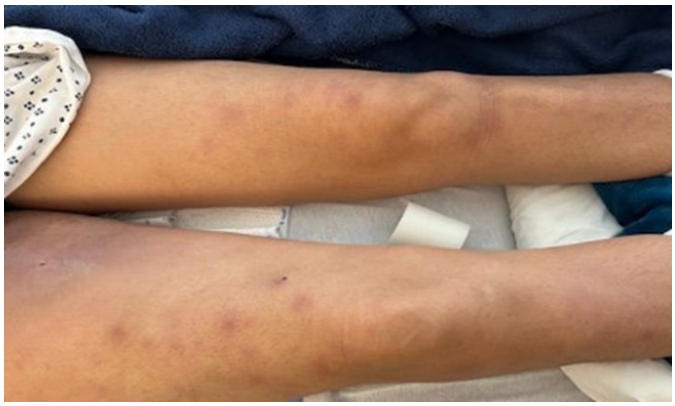

Figure 1: Erythema nodosum of bilateral thigh.

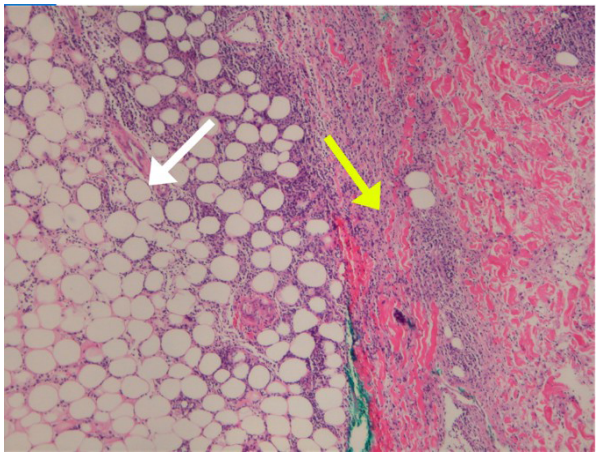

Figure 2: Histopathological images showing panniculitis (white arrow) and histiocytic infiltrates (yellow infiltrates).

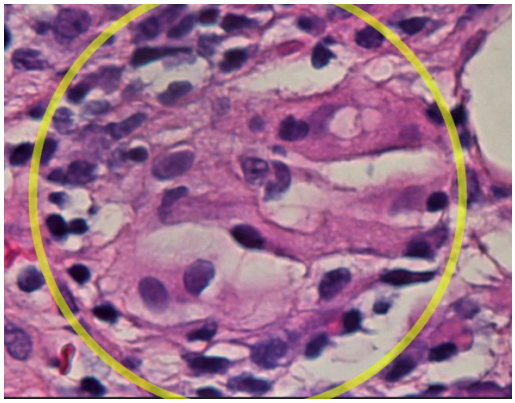

Figure 3: Magnified histopathological images of Meishner granuloma (yellow circle).

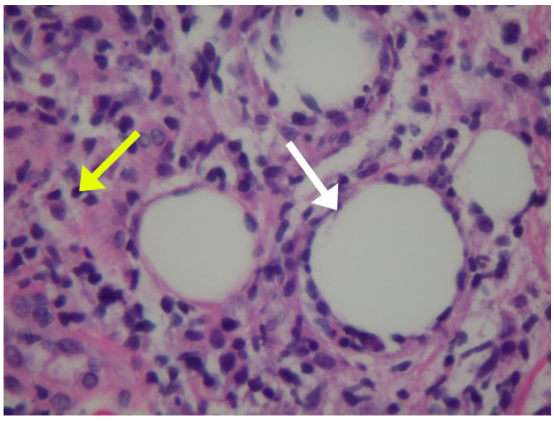

Figure 4: Magnified histopathological images of panniculitis (white arrow) and histiocytes (yellow arrow).

Discussion

Erythema nodosum (EN) can be caused by various etiologies among which bacterial infections, inflammatory conditions, or malignancies are common. Streptococcal infection and sarcoidosis are known to cause this [8-14]. It is imperative to perform a thorough patient assessment, including history, physical examination, and laboratory evaluation to reveal the etiology, as EN can be yet another manifesting symptom of an underlying disease process. EN can be identified as tender and erythematous skin lesions especially nodules located commonly on the pretibial surface of lower extremities. It can also be present elsewhere in the extremities. These nodules can coalesce to form a plaque, as seen in our case. It can be diagnosed with a skin biopsy which reveals septal panniculitis without vasculitis [14]. Our case presents a patient who initially had a fever and a rash on her right thigh for 2 months, which did not improve despite being treated with antibiotics on several occasions until she was treated with steroids. The initial diagnosis of cellulitis was reasonable given the fever, rash, and tachycardia. Cellulitis usually presents with skin redness, warmth, subcutaneous induration, and systemic features including fever and chills. Not only cellulitis, but other forms of soft tissue infection have similar presentations. Since cellulitis can occasionally lead to complications like abscess, necrotizing fasciitis, sepsis, or osteomyelitis, it is important to diagnose it early, which is mainly based on clinical features [16]. Although specific microorganisms cannot be isolated in most of the cases of cellulitis, it has been found that Streptococcus pyogenes and Staphylococcus aureus are the most common culprit bacteria [17]. As discussed earlier, EN can also occur secondary to streptococcal bacterial infection but in our case, failure to improve despite several courses of antibiotics and recurrent fever does not support

the diagnosis of cellulitis. Moreover, serologies for common bacterial and fungal infections were also negative. This shows the need to further investigate the cause of EN. Löfgren syndrome is an acute form of sarcoidosis where one can have erythema nodosum, fever, acute arthritis, and bilateral hilar lymphadenopathy [18]. Chest imaging of our patient did not show hilar or mediastinal adenopathy. It is also important to rule out other autoimmune conditions associated with EN including SLE. The patient denied recurrent oral ulcer, and genital ulcer, and vascular ultrasound showed the absence of thrombosis in the deep venous system of the right lower extremity making Bechet syndrome unlikely. Considering the patient had anorexia, and weight loss with gastrointestinal discomfort, a colonoscopy with random colon biopsy was also done with no signs of inflammation, polyps, masses, or ulcers, ruling out IBD. Previously RA was simply diagnosed based on the presence of symmetric arthritis but with the development of serological diagnostic tools, the American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) shifted the diagnostic criteria from late-stage features to early-stage features along with the incorporation of serological abnormality [19]. This increased the sensitivity of the diagnosis of the disease [20,21] and led to the diagnosis and treatment of the disease in its early stage which can slow the progression. Anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF) are widely used serological markers for diagnosing RA. ACPA has higher specificity and sensitivity than RF for diagnosing RA but may not correlate with disease activity [22,23]. In our patient, an X-ray image of the ankle or the hands did not show any hallmark changes of RA including marginal erosions or soft tissue swelling. However, these findings may not be present in early RA but they still can have seropositivity with ACPA [24-26]. RA can present with a wide variety of cutaneous manifestations, including rheumatoid nodules, neutrophilic dermatoses, and vasculitis as in Felty syndrome and rheumatoid vasculitis, which are usually seen in patients with severe RA [6,27]. Rheumatoid nodules are common skin lesions seen in patients with RA (14.7%-16.7% as per some studies) [28,29]. However, RA can rarely manifest with erythema nodosum. There have been only a few reported cases of EN in patients with rheumatoid arthritis [30,31]. A study of 130 patients by Karpova et al. who were referred with a diagnosis of erythema nodosum showed that 35% were secondary to infectious causes and the other 35% due to Löfgren syndrome. Around 15% (20 patients) had EN secondary to rheumatic disease, out of which 2 (1.54%) were identified to have rheumatoid arthritis [32]. Treatment of erythema nodosum is largely based on etiology. Symptomatic treatment is aimed at alleviating pain and fever with anti-inflammatory medications including NSAIDs [8]. Steroids can be helpful once infectious causes or malignancies have been excluded and a preliminary diagnosis of an inflammatory disease including rheumatoid arthritis is made.

Conclusion

This case emphasizes the necessity of a comprehensive differential diagnosis when patients present with systemic symptoms and skin lesions. It also underscores the importance of conducting an exhaustive investigation to uncover potential systemic diseases in patients diagnosed with erythema nodosum. Erythema nodosum can be attributed to autoimmune disorders, infections, neoplasms, and medications. Rheumatoid arthritis can initially manifest with extra-articular symptoms, including erythema nodosum. Although erythema nodosum is not a typical manifestation of rheumatoid arthritis, if a patient presents with erythema nodosum, a detailed examination, including for autoimmune causes, is required. If autoimmune causes are identified including RA, steroids are helpful.

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Ethical considerations: Ethical approval was not required for this study in accordance with local or national guidelines.

Conflict of Interest: No conflict of interest was declared by the authors.

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