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Case Report

Chronic erythema nodosum as a sign of tuberculosis infection

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Abstract

Introduction Erythema nodosum (EN) is a subcutaneous fat tissue inflammation (panniculitis) characterized by diffuse erythematous nodules symmetrically distributed in the anterior part of the lower extremities. EN is considered a reactive process that can be triggered by a wide variety of factors including mycobacterium (M.) tuberculosis infection.

Case A 21-year-old woman, presented in our department with a 9-month-history of painful erythematous nodules on both legs accompanied by ankle swelling and joint pain. Previous treatments with amoxicillin-clavulanic acid, steroid, and nonsteroidal anti-inflammatory drugs (NSAIDs) did not yield satisfactory results. On examination, we found multiple tender erythematous nodules symmetrically distributed on both legs. On laboratory examination, C-reactive protein and erythrocyte sedimentation rate were increased, interferon-gamma release assay (IGRA) test was found positive for M. tuberculosis infection. The patient was treated with a standard anti-tuberculosis regimen. At 3-month follow-up, all the skin lesions had disappeared. The patient did not report any recurrence after 1 year of follow-up.

Key words

Erythema nodosum, mycobacterium tuberculosis, interferon-gamma release assay, anti-tuberculosis drugs.

Introduction

Erythema nodosum (EN) is a form of subcutaneous fat tissue inflammation (panniculitis) characterized by painful subcutaneous erythematous nodules, symmetrically distributed in the anterior part of the lower limbs.[1] This condition is most often found in women aged 20-40 years.[2] Globally, the prevalence of EN in the world is around 1-5 per 100,000 people, with a female to male ratio of 4-6:1.[2,3] In general, EN can be self-limiting within a few weeks, but in certain cases can become chronic and recurrent, lasting months or even years.[4,5]

EN is considered a delayed-type hypersensitivity reaction, thought to involve deposition of immune complexes in septal venules of the subcutaneous fat, formation of reactive oxygen species due to the recruitment of neutrophils, production of tumor necrosis factor (TNF)-α, and formation of granulomas.[2] Various triggers include infectious (bacterial, viral, fungal, parasitic), non-infectious (sarcoidosis, drugs, pregnancy, malignancy, colitis, autoimmune), and idiopathic.[3]

The association of EN with tuberculosis (TB) has been widely reported especially in TB endemic areas and is thought to be a facultative tuberculid reaction associated with primary TB infection.[5] TB was found to be the second most common cause of secondary EN after post-streptococcal infection in Turkey.[6] A study in

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China reported that almost all patients with primary TB had manifestations of EN, and conversely, 20% of patients with EN had TB.[7] A study in Denmark showed a close association between EN and TB within 1 month of diagnosis.[8]

The principle of EN management is to identify and eliminate precipitating factors whenever possible.[1] In cases of suspected TB infection with or without a clear focus of infection, anti-tuberculosis therapy has been reported to yield satisfactory results.[6,9-12]

Herein, we report a case of erythema nodosum with a positive interferon-gamma release assay (IGRA) which was treated with an anti-tuberculosis drug regimen. Until now, cases of erythema nodosum due to TB infection have not been widely reported. This case report shows the importance of identifying and eliminating the triggering factors for EN, one of which is TB infection, considering that Indonesia is an endemic country.

Case report

A 21-year-old woman presented to our outpatient department with complaints of painful reddish bumps on both lower legs for 9 months. Other symptoms including recurrent leg swelling, joint pain, as well as low-grade fever were associated with the appearance of new bumps. The patient was otherwise healthy, with no history of chronic cough, weight loss, or night sweats. History of other diseases, allergies, malignancy, pregnancy, or drug consumption before the complaint was also denied. Before visiting our department the patient had undergone a series of examinations in an allergy-rheumatology clinic, with results as follows: hemoglobin 8.7 g/dL (normal value: 11.5-16.5), C-reactive protein (CRP) 23.8 mg/L (value >5.0 suggests infection or other inflammatory causes), erythrocyte sedimentation rate (ESR) 38 mm/hour (normal value: <21), increased anti-streptolysin O titer (ASTO) on 2 examinations (294 IU/mL and 449 IU/mL, normal value: 200), positive IGRA test suggests latent or active tuberculosis infection. Other tests include anti-nuclear antibody (ANA), anti-citrullinated peptide antibody (ACPA), anti-neutrophilic cytoplasmic antibody (ANCA), anti-mycoplasma antibody, pyloric helicobacter, hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (anti-HCV), and anti-syphilis antibodies were found to be negative/non-reactive. Chest X-ray showed no abnormalities. She was diagnosed with erythema nodosum by the previous doctor and received prednisolone treatment for 4 months, amoxicillin-clavulanic acid 625 mg twice daily for a month, non-steroidal anti-inflammatory drugs (NSAIDs), omeprazole, pre- and probiotics, as well as iron supplementation, but the complaint did not resolve. History of TB treatment was denied.

On physical examination, the patient was well and alert, vital signs were within normal limits, chest examinations were normal. Dermatological examination revealed multiple erythematous nodules with diffuse borders, symmetrically distributed in the anterior part of the legs and feet. The nodules were warm and tender on palpation with mild feet edema and no ulcerations. Multiple hyperpigmented macules were also found, marking the location of resolved nodules **(Figure 1A)**.

Complete blood count, blood sugar, liver function, kidney function and urinalysis showed no abnormalities, HIV and HBsAg tests were non-reactive. On the other hand, CRP and ESR were found to be elevated, IGRA test was positive for *M. tuberculosis* infection.

The patient was diagnosed with erythema nodosum suspected due to an underlying

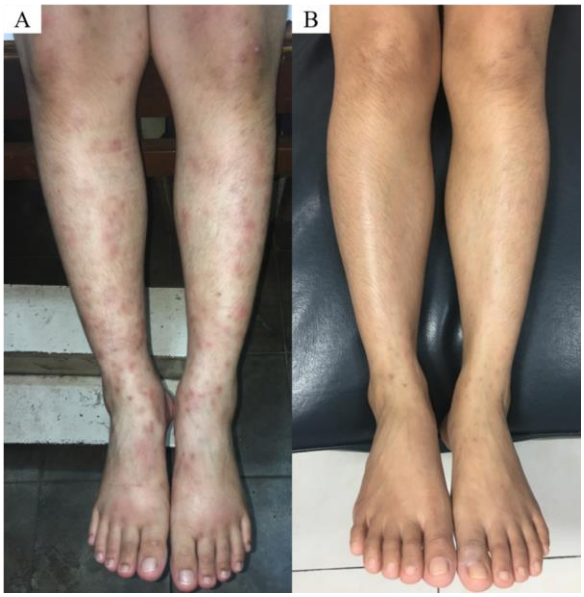

Figure 1 (A) Patient's legs before therapy. (B) 3 months after anti-tuberculosis therapy.

tuberculosis infection, and treated with four-drugs fixed-dose combinations (4FDCs) for tuberculosis (each tablet consists of 150 mg rifampicin, 75 mg isoniazid, 400 mg pyrazinamide and 275 mg ethambutol) 3 tablets daily for 2 months (intensive phase); followed by 2FDCs (each tablet consists of rifampicin 150 mg and isoniazid 150 mg), 3 times a week, 3 tablets per time, for 4 months (continuation phase). In addition, the patient was also prescribed vitamin B6 10 mg daily. NSAID was prescribed in early weeks of treatment without steroid. At 3-month follow-up, all the skin lesions had disappeared **(Figure 1B)**, only occasional joint pain was reported. The patient did not report any recurrency after 1 year of follow-up.

Discussion

The clinical findings in this case support the diagnosis of EN, which is characterized primarily by painful erythematous nodules in the anterior region of the lower limbs.[1] These nodules generally persist for up to 2 weeks and then slowly subside and new nodules may appear.[3] The appearance of nodules usually stops on its own after a few weeks to 1-2 months, but in certain circumstances it can become recurrent or chronic for more than 6 months,[4] as in this case. In EN ulcers are rare and nodules usually resolve without atrophy or scarring.[3] Systemic symptoms include fever, malaise, arthralgia with or without arthritis, may occur 1-3 weeks before the appearance of nodules.[2,3] The presence of symptoms of pain and warmth in the limb joints should be considered the possibility of reactive arthritis (Poncet's disease), i.e., aseptic polyarthritis that occurred during acute tuberculous infection,[13] but was not confirmed in this case.

EN can generally be diagnosed clinically, and a biopsy is rarely needed except in obscure cases.[2,3] Investigations are performed to help determine the etiology of EN, including infectious (bacterial, viral, fungal, parasitic) or non-infectious (sarcoidosis), drugs, pregnancy, malignancy, colitis), and if not known, it is classified as idiopathic EN.[3] In this case, EN was suspected to be caused by infectious agent, based on the history of increased ASTO titer and a positive IGRA test result. ASTO is a blood test to measure the level of antibodies to streptolysin O produced by group A Streptococcus bacteria, while IGRA is a blood test that can quantitatively measure interferon-γ synthesis due to TB infection, both are infectious agents often associated with EN.[1,2,4,5] In this case, the patient had a history of treatment with amoxicillin-clavulanic acid, corticosteroids, and NSAIDs. Amoxicillin-clavulanic acid is a beta-lactam antibiotic with a beta-lactamase inhibitor that can be used in various bacterial infections, including streptococcal infections, which are often the cause of EN. However, there was no significant improvement reported. The fact that the patient had a positive IGRA result but never received treatment for TB, raised our suspicion for the possibility of TB as the trigger for EN

reaction in this case. Chest X-ray showed no abnormalities in the lungs, thus latent TB or active extrapulmonary TB infection was suspected.

The differential diagnosis of EN including erythema nodosum leprosum (ENL) reaction, erythema induratum Bazin (EIB), and several types of cutaneous vasculitis.[3,4] ENL is a type 2 leprosy reaction which also manifests on the skin as painful erythematous nodules, however unlike regular EN, ENL needs to have a positive history of leprosy, the lesions are not limited to the lower limbs, and peripheral nerve abnormalities can be found.[4] EIB or nodular vasculitis is another type of panniculitis with clinical manifestations of painful violaseus nodules in the lower limbs similar to EN, the difference is the location of the lesion. EIB more dominant in the posterior (calf) and ulcers often form.[3,4] Small vessel vasculitis such as Henoch-Schonlein purpura (HSP) and leukocytoclastic vasculitis usually manifests as palpable purpura. In moderate vascular vasculitis such as cutaneous polyarteritis nodosa, in addition to subcutaneous nodules, livedo reticularis may also appear and if left untreated can become ulcers and gangrene. Behçet's disease may be accompanied by erythematous nodules similar to EN, but are not confined to the limbs and involve oral, ocular, genital and other organ systems.[4]

The principle of treating EN is to eliminate precipitating factors whenever possible. Symptomatic therapy includes rest, leg elevation and compression, and also administration of drugs such as NSAIDs, potassium iodide or colchicine.[2-4] In several case reports[6,9-11] and cases of EN with a positive tuberculin test or IGRA that we have treated (unpublished), the administration of anti-tuberculosis drug regimen gave satisfactory results. Controversy remains about whether TB-associated EN without an identifiable focus of infection should be treated as active TB or given preventive monotherapy for latent TB. Referring to the definition from the Indonesian Ministry of Health, latent TB is TB with a positive tuberculin test or IGRA without general and/ or specific symptoms and radiology, while active TB is TB with general and/ or specific symptoms and radiology,[14] thus this case was considered as an active TB. The active TB treatment regimen is divided into 2 phases, namely the intensive phase (rifampicin 8-12 mg/ kgBW/ day, isoniazid 4-6 mg/ kgBW/ day, pyrazinamide 20-30 mg/ kgBW/ day, and ethambutol 15-20 mg/ kgBW/ day) for 2 months, followed by a continuation phase (rifampicin and isoniazid, 8-12 mg/ kgBW/ day each) 3 times per week for 4-7 months for extrapulmonary TB intensive for 2 months and continued phase for at least 4 months according to clinical response. Vitamin B6 (pyridoxine) 10 mg/ day is also given concurrently with TB treatment to prevent isoniazid-associated peripheral neuropathy.[14]

In this case, the prognosis of the patient is excellent. EN does not cause death and most cases of EN with a positive tuberculin test or IGRA who are successfully treated with FDC for tuberculosis do not report recurrence after treatment, but arthralgia can persist for up to 2 years.[2,3]

Conclusion

We reported a case of EN which was caused by *M. tuberculosis* infection. EN is generally a self-limiting disease but in certain cases it can become chronic and refractory. Identification and adequate treatment of the precipitating factors of EN are essential to achieve satisfactory outcome. In TB endemic countries, the possibility of underlying TB infection needs to be considered in the diagnosis of EN. In this case report, the diagnosis of EN due to TB

infection was based on the history of symptoms, physical signs, and a positive IGRA examination. The patient was treated with the standard anti-tuberculosis regimen with satisfactory results.

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