Journal of Medicinal and Chemical Sciences 6 (2023) 2824-2831

Journal of Medicinal and Chemical Sciences

Journal homepage: http://www.jmchemsci.com/

Case Report

Erythema Nodosum: A Manifestation of Trichomoniasis and Vulvovaginal Candidiasis

Alvian Arifin Saiboo[1], Dwi Murtiastutik[1]*, Sawitri[1], Rahmadewi[2], Damayanti[1], Linda Astari[1], Willy Sandhika[2], Putri Halla Shavira[1]

[1]Faculty of Medicine, Airlangga University, Dr. Soetomo General Hospital, Surabaya, Indonesia
[2]Associate Professor Department of Anatomical Pathology, Faculty of Medicine, Airlangga University, Dr. Soetomo General Hospital, Surabaya, Indonesia

ARTICLE INFO

Article history

Receive: 2023-06-15
Received in revised: 2023-07-12
Accepted: 2023-07-17
Manuscript ID: JMCS-2306-2114
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Fatima Ramezani
Editor who approved publication:
Dr. Ali Delpisheh

DOI:10.26655/JMCHEMSCI.2023.11.27

KEYWORDS

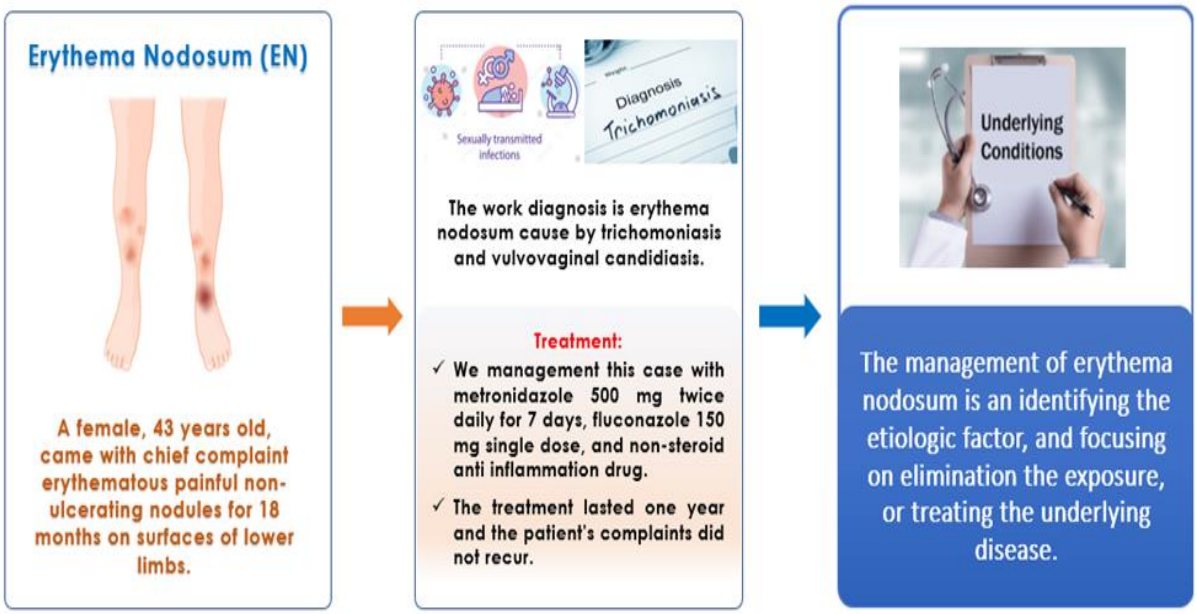
Erythema nodosum
Trichomoniasis
Vulvovaginal candidiasis
Diseases

ABSTRACT

Background: Erythema nodosum (EN) is the most common form of septal panniculitis resulting from a hypersensitivity reaction in response to numerous antigens or triggers.
Case: A 43-year-old female presented with a chief complaint of erythematous painful non-ulcerating nodules on the lower limbs for 18 months. This was preceded by a painful, erythematous rash consisting of a few subcutaneous nodules on both limbs. A dermatological examination of the tibia region revealed multiple tender erythematous and hyperpigmented nodules. A biopsy and serology test were performed to rule out differential diagnoses. Based on the data, the working diagnosis is erythema nodosum caused by trichomoniasis and vulvovaginal candidiasis. We managed this case with metronidazole 500 mg twice daily for seven days, fluconazole 150 mg as a single dose, and non-steroidal anti-inflammatory drugs. One week after receiving treatment, her pain complaint disappeared, but the hyperpigmented macules still persisted, although they had decreased. One year after treatment, the patient's complaints did not recur.
Discussion: EN may be associated with a wide variety of disease processes, and its observation should be followed by finding the underlying etiology. The clinical presentation includes symmetrical, tender, erythematous, warm nodules, and raised plaques usually located on the shins, ankles, and knees. The lesions show spontaneous regression without ulceration, scarring, or atrophy, and recurrent episodes are uncommon. The EN diagnosis is based on clinical presentation and histopathological findings.
Conclusion: The management of erythema nodosum involves identifying the etiologic factor and focusing on eliminating exposure or treating the underlying diseases.

* Corresponding author: Dwi Murtiastutik
✉ E-mail: dwimurtiastutik@yahoo.co.id

GRAPHICAL ABSTRACT



Introduction

Erythema nodosum is the most common clinicopathological variant of panniculitis. The process is a skin reaction that can be associated with various conditions, including infection, sarcoidosis, rheumatologic disease, inflammatory bowel disease, medications, autoimmune disorders, pregnancy, and malignancy. Histopathologically, erythema nodosum is a stereotypical example of septal panniculitis, usually without vasculitis. The composition of the inflammatory infiltrate in the septa varies depending on the lesion age. Treatment of erythema nodosum should be directed to the underlying underlying condition, if identified. As the most frequent type of septal panniculitis, erythema nodosum (EN) results from a hypersensitivity reaction in response to various antigens and triggers. The characteristic feature of this condition is the presence of inflammatory nodules [1]. Clinically, erythema nodosum is characterized by painful, erythematous subcutaneous nodules, typically found in the pretibial regions of the body [2, 3].

The estimated global frequency of erythema nodosum is 1-5 per 100,000 people. Although it can occur at any age, women are three to five times more likely to be affected compared to men, with a ratio of 3-5:1. Idiopathic EN is the most common cause of the disease worldwide, accounting for 55 percent of cases. Reactive skin infections, including bacterial, viral, fungal, and protozoal infections, can also lead to erythema nodosum [4].

In cases of erythema nodosum, a comprehensive diagnostic assessment is necessary to exclude all potential causes, particularly focal infections. Erythema nodosum associated with trichomonas infection is extremely rare, with no documented cases reported [5]. We present a case of erythema nodosum in a woman who had previously undetectable underlying causes, which were found to be trichomoniasis and vulvovaginal candidiasis [6]. The patient exhibited erythema nodosum and vaginal discharge, likely resulting from vulvovaginal candidiasis and *Trichomonas vaginalis* infection.

Case

A 43-year-old married female from Papua presented to our outpatient clinic with a recurrent history of erythematous painful non-ulcerating nodules on the lower limbs for 18 months.

These nodules were preceded by a painful, erythematous rash with a few nodules on both limbs. She had sought medical advice on multiple occasions and received symptomatic treatment Six months ago, she was prescribed oral methylprednisolone for her complaints. The patient denied experiencing any other symptoms, such as fever, fatigue, malaise, weight loss, dysuria, or cough. She also denied having vaginal discharge, toothache, sore throat, or ear disorders. There was no significant past medical history. She denied any history of red spots turning into ulcers or leaving atrophic scars. There was no history of numbness in the hands and feet, previous leprosy, or a family history of leprosy.

During the general physical examination, the patient's body weight was 72.7 kg, height was 155 cm, body mass index (BMI) was 30.2, blood pressure was 135/86 mmHg, pulse was 83 beats per minute, respiratory rate was 18 breaths per minute, and temperature was 36 °C. No signs of jaundice, cyanosis, or dyspnea were observed on the patient's face or neck. Thoracic examination revealed a normal heart, lungs, abdomen, liver, and spleen. There was no edema in the upper and lower limbs, and both limbs felt warm to the touch when palpated. The lymph nodes in the cervical, axillary, inguinal, and vaginal regions were not enlarged.

A dermatological examination (Figure 1) of the tibia region on both sides revealed multiple tender nodules with varying sizes of 1.5-2 cm x 0.5-1 cm. The color of the lesions was erythematous and hyperpigmented. There were no erosions, pus, ulcers, or signs of bleeding (Figure 1).

We suspect that this patient has erythema nodosum leprosum. However, the diagnosis has not been confirmed. Additional examinations are needed to confirm the diagnosis and exclude other differential diagnoses. In this case, we performed a biopsy to confirm the diagnosis and conducted a serology test for anti-PGL 1 to rule out leprosy as a possible differential diagnosis. A punch biopsy was performed on the red lesion of the leg, and the biopsy tissue was placed in 10% formalin as the transport medium. Venous blood serum was collected for the serology test for anti-PGL1.

The results of the serology test for anti-PGL-1 showed IgM = 0 u/ml with a cutoff of IgM = 605 u/ml, and IgG = 181 u/ml with a cutoff of IgG = 630 u/ml. The biopsy results showed mild acanthosis on the epidermal layer, a cluster of histiocytes and epithelioid cells forming granulomas with extensive tissue necrosis and infiltration on the dermal layer, and infiltration of inflammatory lymphocytes in the septa of the subcutaneous fat tissue. Acid-fast bacilli germs were not visible in the WF staining. The conclusion of biopsy examination was consistent with erythema nodosum.

Based on the patient's history, physical examination, and supporting examinations, the working diagnosis is erythema nodosum. Since there are many triggering factors for erythema nodosum, additional examinations were planned to identify the main cause in this case. The planned diagnoses include an anti-streptolysin O (ASO) titer examination for possible streptococcal infection, chest X-ray examination for possible pulmonary disease and tuberculosis infection, consultation with the ENT department for throat culture examination, urinalysis for urinary tract infections, and vaginal swab examination for vaginal infections.

The result of the ASO titer examination was negative. The chest X-ray examination showed no abnormalities in the heart and lungs. The consultation response from the ENT Department indicated no signs of infection, so there was no indication of a throat culture. The urinalysis examination of the urine sediment showed the presence of *Trichomonas vaginalis*. The vaginal swab examination using Gram staining showed positive results for blastospores and pseudo-hyphae, and wet staining showed positive results for blastospores and pseudo-hyphae.

Based on the above data, one of the possible causes of erythema nodosum, in this case, is an infection caused by *Trichomonas vaginalis*, which could also be associated with vulvovaginal candidiasis (VVC). Therefore, we diagnosed the patient with erythema nodosum caused by trichomoniasis and vulvovaginal candidiasis.

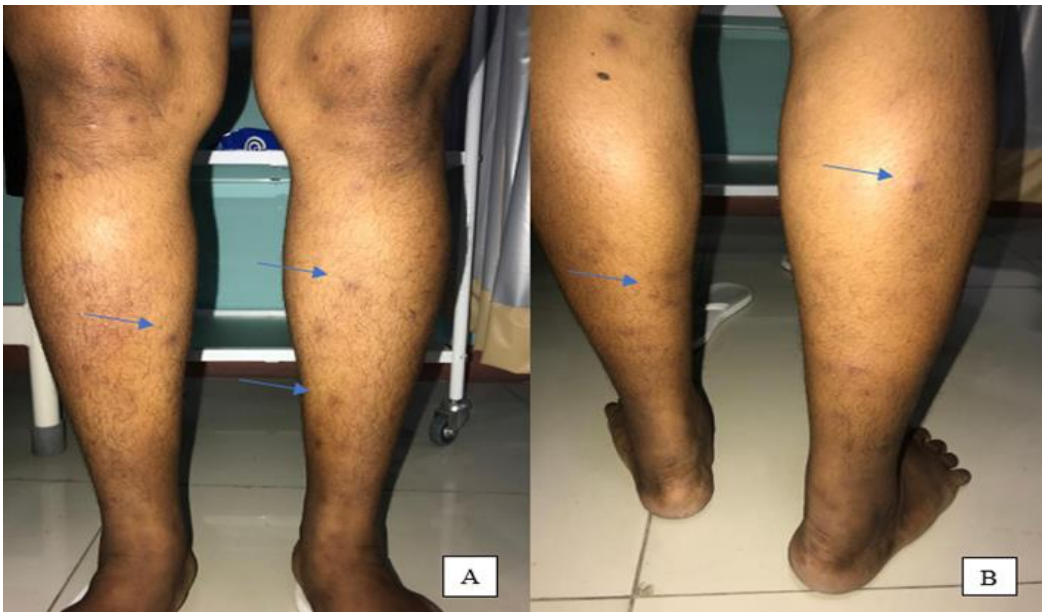


Figure 1: Dermatological examination. (A) Anterior side of the tibia and (B) Posterior side of the tibia

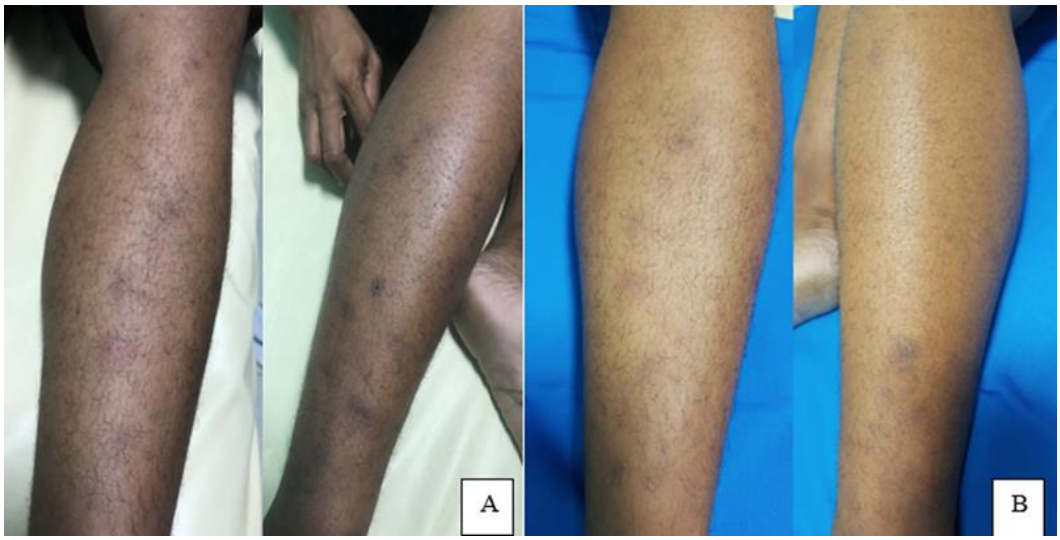


Figure 2: (A) Before treatment and (B) One week after treatment

The management plan for this case includes administering metronidazole 500 mg twice daily for 7 days to treat trichomoniasis, a single dose of fluconazole 150 mg for vulvovaginal candidiasis, and non-steroidal anti-inflammatory drugs for pain relief. One week after receiving treatment, the patient's vaginal discharge improved, and her pain complaint disappeared, although the hyperpigmented macules still persisted but decreased (Figure 2).

Results and Discussion

Erythema nodosum is the most common clinical and pathological manifestation of septal panniculitis. It is characterized by the sudden development of painful erythematous nodules and plaques on the extensor surfaces of the lower limbs. Recurrences are rare, and the lesions typically resolve on their own without scarring, necrosis, or atrophy [7, 8].

The typical presentation of erythema nodosum includes the abrupt appearance of nodules and raised plaques on the lower legs. The nodules, which can reach up to 5 cm in diameter, are commonly observed on both sides of the body (Figure 3). In some cases, erythematous plaques may form when nodules merge. Lesions can also occur in other areas, such as the thighs, arms, neck, and face. Initially, the nodules are bright red and slightly raised above the skin surface. Within

a few days, they flatten and turn a vibrant crimson or purple colour. In some cases, they may have a yellow or greenish hue resembling a severe bruise ("erythema contusiformis"). The colour evolution from red to contusiform can aid in the diagnosis of erythema nodosum. The nodules resolve without scarring or ulceration. During an acute attack of erythema nodosum, common symptoms include fever (38-39 °C), fatigue, malaise, joint pain, headache, nausea, vomiting, cough, and diarrhea. Episcleral lesions and conjunctivitis may accompany the cutaneous lesions. Less commonly, lymphadenopathy, hepatomegaly, and splenomegaly may be observed. The eruption typically lasts between three and six weeks [9]. In this case, the patient presented with erythematous, painful, non-ulcerated nodules on both tibias, along with malaise and joint discomfort.

When erythema nodosum is observed, it is crucial to investigate the underlying cause, as it can be associated with various diseases. Infections, medications, cancer, and other conditions can all trigger erythema nodosum (Table 1). The condition is considered a hypersensitive reaction to a wide range of stimuli. The extensive antigenic stimuli associated with erythema nodosum suggest a cutaneous reactive process, where the skin exhibits sensitivity to different triggers. It is likely that immune complexes accumulate in and around the venules of the subcutaneous fat's connective tissue septa, leading to erythema nodosum. Patients with erythema nodosum often have elevated levels of circulating immune complexes and complement activation [10].

To determine the presence or absence of erythema nodosum, symptoms, and histological findings are evaluated. A comprehensive medical history and physical examination are essential in the initial evaluation to identify the underlying cause. The diagnostic work-up should focus on the most common causes of the disease. Specific and nonspecific symptoms, such as fever, fatigue, malaise, weight loss, organ-specific symptoms, and recent medication use, should be investigated. Diagnostic testing should be selected based on the patient's history, physical examination, and laboratory results. In the case of erythema nodosum, histopathological examination reveals septal panniculitis without vasculopathy. The subcutaneous fat's septa are infiltrated by inflammatory cells, resulting in thickening (Figure 4). Furthermore, there is infiltration of lymphocytes in the superficial and deep dermis.

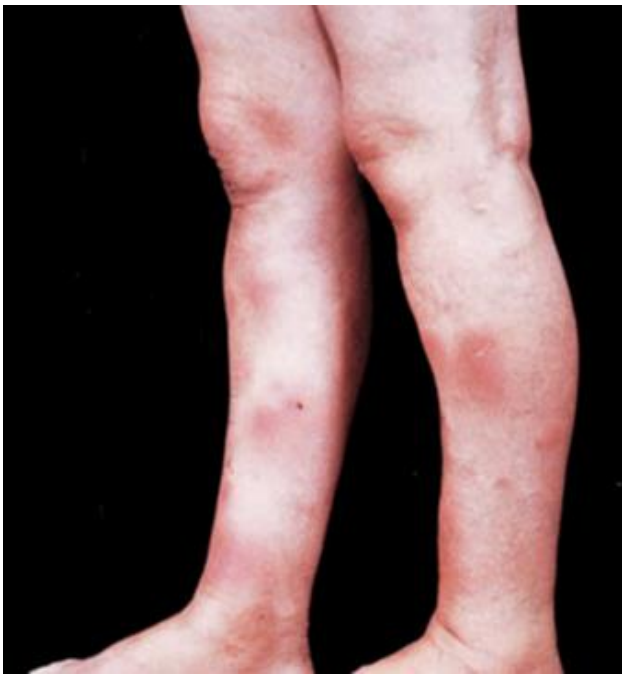


Figure 3: Clinical appearance of erythema nodosum [9]

Table 1: Etiologies of erythema nodosum [10]

Etiology			
Primary	Idiopathic		
Secondary	Infection	Bacterial	*Beta-hemolytic Streptococcus, Staphylococcus, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Mycobacterium tuberculosis, syphilis, leprosy, Chlamydia pisttaci, Bartonella henselae, Borrelia burgdorferi,* and *Cutibacterium acnes*.
		Viruses	Infectious mononucleosis, hepatitis B and C, cytomegalovirus, herpes simplex, parvovirus B19, HIV, measles, varicella, poxvirus, and COVID-19.
		Fungal	Coccidioidomycosis, blastomycosis, histoplasmosis, sporotrichosis, nocardiosis, mucormycosis, aspergilosis, and dermatophytosis.
		Parasites	Amebiasis, giardiasis, toxoplasmosis, taeniasis, ascariasis, hydatidosis, trichomoniasis, and hookworm infestation.
Systemic Diseases			Sarcoidosis, inflammatory bowel disease, celiac disease, colon diverticulosis, Behcet disease, Reiter syndrome, systemic lupus erythematous, rheumatoid arthritis, ankylosing spondylitis, Berger disease, Sweet syndrome, and chronic active hepatitis.
Drugs			Penicilin, amoxicillin, ampicillin, cephalosporin, ciprofloxacin, sulfonylureas, cotrimoxazole, streptomycin, minocycline, oral contraceptives, progesterone, carbamazepine, ACE inhibitors, ARBs, proton pump inhibitor, and Vaccines.
Malignancies			Hodgkin and non-Hodgkin lymphoma, leukemia, sarcoma, pelvic carcinoma, carcinoid tumor, renal, cervix, gastric, colo-rectal, pulmonary, hepatocellular, and pancreatic carcinoma.
Pregnancy			

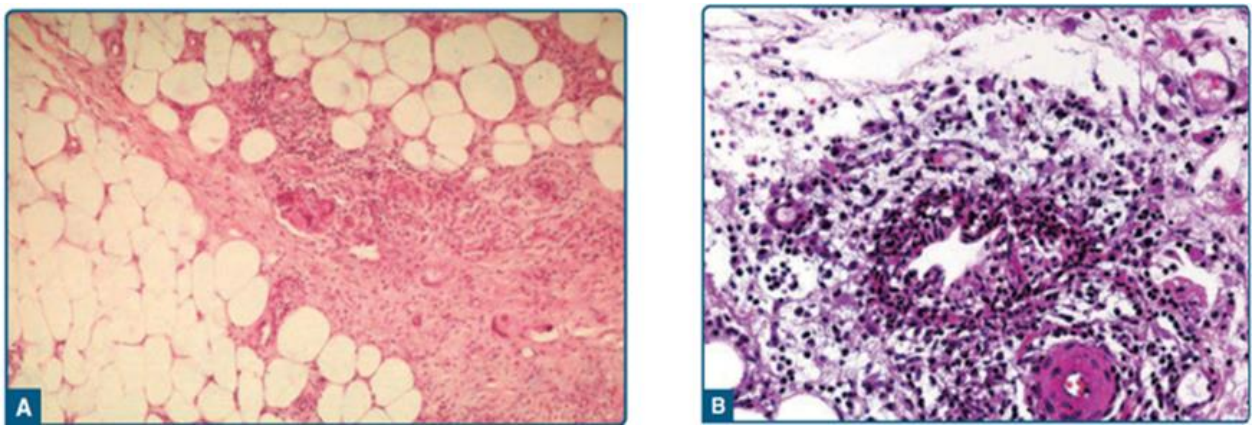


Figure 4: (A) Widened septa with inflammatory infiltrate including multinucleated giant cells and (B) High-power magnification of Miescher granuloma shows a discrete micronodular aggregate of small histiocytes around a central stellate cleft [9]

The erythematous appearance of early lesions is likely due to cutaneous inflammation and vasodilation, while the nodularity is attributed to alterations in the subcutis [11, 12]. These findings align with the clinical presentation and histopathological findings in this case, supporting the diagnosis of erythema nodosum. The epidermal layer, in this case, showed mild acanthosis, while the dermal layer exhibited a cluster of histiocytes and epithelioid cells forming granulomas with extensive tissue necrosis and infiltration. The subcutaneous fat tissue demonstrated the infiltration of inflammatory lymphocytes in the fat tissue septa. Therefore, the biopsy examination's conclusion is consistent with erythema nodosum.

In most cases, basic laboratory screening tests are helpful for identifying the underlying cause of erythema nodosum. These tests may include a complete blood count, sedimentation rate, anti-streptolysin-O (ASO) titer, urinalysis, throat culture, intradermal tuberculin test, and chest radiograph. In this particular case, the patient underwent tests such as ASO titer, urine analysis, throat culture, vaginal swab, and chest X-ray to identify potential triggers. The urinalysis and vaginal swab examination revealed the presence of trichomoniasis and vulvovaginal candidiasis, which could contribute to the development of erythema nodosum.

The management of erythema nodosum focuses on identifying and treating the underlying cause [3]. Supportive care is also important. In most cases, the condition resolves on its own, but close monitoring is recommended. Bed rest with elevation of the lower extremities and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly recommended.

In this case, trichomoniasis was identified as the primary etiological factor for erythema nodosum. Trichomoniasis is typically diagnosed through microscopic inspection [6]. Wet mount preparations are useful for observing fresh specimens under the microscope, where the flagella of Trichomonas can be clearly seen in motion [11]. The treatment options for trichomoniasis, as recommended by the CDC's 2015 STD treatment guidelines, include metronidazole, tinidazole, or a seven-day course of metronidazole 500 mg taken twice a day for a single infection [12]. In addition, vulvovaginal candidiasis was identified as a contributing factor. Several tests can be performed to rule out other potential causes of vaginal discharge and infection, particularly gonococcal and chlamydial diseases. Microscopists can observe yeast budding, hyphae, or pseudo-hyphae when using potassium hydroxide. Anti-fungal medications are prescribed for severe candida vulvovaginitis, and a single dose of fluconazole (150 mg) can be administered orally or intravaginally in a single-day or three-day regimen [13].

Based on the above data, the management of erythema nodosum, in this case, involved treating the underlying etiological factors and providing supportive care. The patient received a single dose of fluconazole 150 mg for vulvovaginal candidiasis treatment, metronidazole 500 mg twice daily for one week for trichomoniasis treatment, nonsteroidal anti-inflammatory drugs for symptomatic relief, and bed rest as part of supportive care. One week after treatment, a follow-up assessment showed the significant improvement in the patient's condition. During the one-year follow-up period, the patient did not experience any recurring complaints.

Conclusion

Erythema nodosum (EN) is the most common form of septal panniculitis characterized by tender, erythematous, warm nodules, and elevated plaques symmetrically appearing on the shins, ankles, and knees. Diagnosis is based on clinical presentation and histopathology. The EN management focuses on identifying and addressing the underlying causes, aiming to reduce exposure or treat the associated disorders. The prognosis for EN is generally favorable, with the condition resolving on its own in most cases without specific treatment for the underlying condition.

Disclosure Statement

No potential conflict of interest was reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Orcid

Alvian Arifin Saiboo
https://orcid.org/0009-0001-1014-8696
Dwi Murtiastutik
https://orcid.org/0000-0002-5486-5291
Sawitri
https://orcid.org/0000-0002-0978-1339

Damayanti
https://orcid.org/0000-0003-2388-6740
Linda Astari
https://orcid.org/0000-0002-2939-1493
Willy Sandhika
https://orcid.org/0000-0002-8499-1600
Putri Halla Shavira
https://orcid.org/0009-0009-3235-9580

References

[1]. Leung A.K.C., Leong K.F., Lam J.M., Erythema nodosum, *World Journal of Pediatrics*, 2018, **14**:548 [Crossref], [Google Scholar], [Publisher]
[2]. Rizvi Z., Iqbal T., Javed A., Rizvi A., Erythema nodosum: A consequence of tuberculosis, *Cureus*, 2019, **11**:e4724 [Crossref], [Google Scholar], [Publisher]
[3]. Listiawan M.Y., Prakoeswa C.R.S., Agusni I., Comparison of TLR2/1, NF-ÐºB p105/50, NF-ÐºB p65, and TNF-Î± expressions in the macrophages between multibacillary leprosy patients with and without erythema nodosum leprosum signifying innate immune system activity, *Bali Medical Journal*, 2019, **8**:347 [Crossref], [Google Scholar], [Publisher]
[4]. Baruah C., Joseph T., Mitra S., Erythema Nodosum: An Unusual Chronic Presentation Secondary to Latent Tuberculosis, *Assam Journal of Internal Medicine*, 2021, **11**:37 [Google Scholar], [Publisher]
[5]. Darmaputra I.G.N., Herwanto N., Rusyati L.M., Riawan W., Endaryanto A., Prakoeswa C.R.S., Distribution of iNOS expressions and TNF neutrofil cells as well as PGE2 and S100 Schwann cell dermal nerves in the erythema nodosum leprosum patients, *Bali Medical Journal*, 2018, **7**:262 [Google Scholar], [Publisher]
[6]. Karna N.L.P.R.V., Concurrent infections of Trichomoniasis and nongonococcal cervicitis in a menopausal woman: a case report, *Bali Medical Journal*, 2020, **9**:318 [Google Scholar], [Publisher]
[7]. Szczęch J., Matławska M., Rutka M., Reich A., Clinical Presentation of Erythema Nodosum, *Post N Med*, 2018, **31**:25 [Crossref], [Google Scholar], [Publisher]
[8]. Hassan A., Alsaihati A., Al Shammari M., Sharroufna M., Alaithan H., Aljubran S., Erythema Nodosum: A Manifestation of Salmonella Infection, *Case Reports in Gastroenterology*, 2019, **13**: 456 [Crossref], [Google Scholar], [Publisher]
[9]. Mukherjee T., Basu A., Disseminated histoplasmosis presenting as a case of erythema nodosum and hemophagocytic lymphohistiocytosis, *Medical journal, Armed Forces India*, 2015, **71:**S598 [Crossref], [Publisher]
[10]. Pérez-Garza D.M., Chavez-Alvarez S., Ocampo-Candiani J., Gomez-Flores M., Erythema Nodosum: A Practical Approach and Diagnostic Algorithm, *American Journal of Clinical Dermatology*, 2021, **22**:367 [Crossref], [Google Scholar], [Publisher]
[11]. Al-Mamoori, Z.Z., Alhisnawi A.A., Yousif J.J., Prediction of Trichomoniasis in Women Complaining Vaginal Discharge by Different Methods and Determine Some Immunological Markers, *Plant Archives*, 2020, **20**:3653 [Crossref], [Google Scholar], [Publisher]
[12]. Schumann J.A., Plasner S., Trichomoniasis. In: StatPearls., Treasure Island (FL): StatPearls Publishing, 2023 [Publisher]
[13]. Jeanmonod R., Jeanmonod D., Vaginal Candidiasis, In: StatPearl. Treasure Island (FL): StatPearls Publishing; 2023 [Publisher]

HOW TO CITE THIS ARTICLE
Alvian Arifin Saiboo, Dwi Murtiastutik, Sawitri, Rahmadewi, Damayanti, Linda Astari, Willy Sandhika, Putri Halla Shavira. Erythema Nodosum: A Manifestation of Trichomoniasis and Vulvovaginal Candidiasis. *J. Med. Chem. Sci.*, 2023, 6(11) 2824-2831.
DOI: https://doi.org/10.26655/JMCHEMSCI.2023.11.27
URL: https://www.jmchemsci.com/article_175873.html