



**A 5-YEAR RETROSPECTIVE STUDY OF THE CLINICAL  
CHARACTERISTICS AND HISTOPATHOLOGICAL  
FEATURES OF ERYTHEMA NODOSUM IN ADULT  
PATIENTS AT A TERTIARY CARE CENTRE  
IN BANGKOK, THAILAND**

**BY  
ANYAMON CHINGTANASAN**

**A THESIS SUBMITTED IN PARTIAL FULFILLMENT  
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Thesis entitled

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### Abstract

Erythema nodosum is the most common type of panniculitis. While previous studies suggest histopathological features can distinguish its types, no data exists for the Institute of Dermatology, Thailand. This study investigates the clinical and histopathological features of 42 adult patients diagnosed with erythema nodosum confirmed by skin biopsies, using electronic medical records from 2017 to 2022. Logistic regression analysis was conducted to compare primary and secondary erythema nodosum.

The study found that the pretibial area was the most common lesion site (64.3%). Most cases (81%) had bilateral limb involvement. A majority (76.2%) were idiopathic. Among secondary erythema nodosum cases, 11.9% had underlying infections, with 9.5% of these cases diagnosed with tuberculosis. No significant differences in histopathologic features were observed between the types. Mixed septal and lobular panniculitis was present in 88.1% of cases, likely due to late-stage biopsies. To improve statistical significance, expanding the sample size over a longer period is recommended.

(Total 42 pages)

Keywords: panniculitis, erythema nodosum, idiopathic, clinical characteristics, histopathological features

Student's Signature ..... Thesis Advisor's Signature .....

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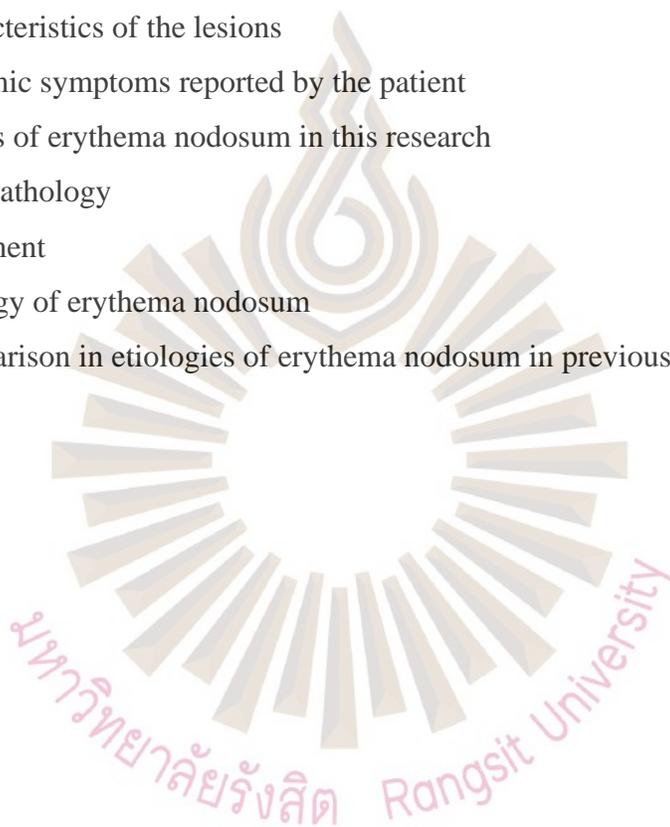
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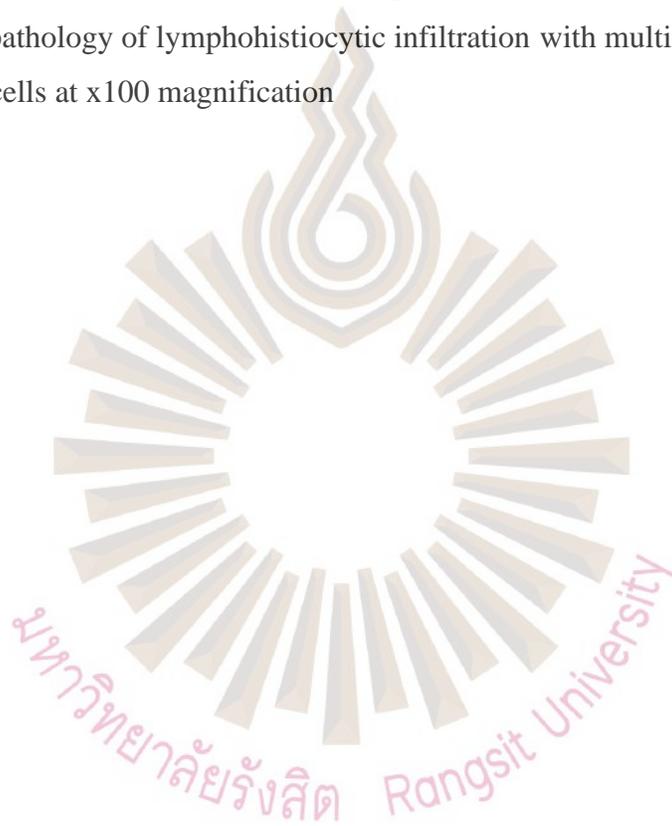
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# Chapter 1

## Introduction

### 1.1 Background and Significance of the Problem

Erythema nodosum is the most well-known type of panniculitis, presenting as poorly demarcated, tender, subcutaneous erythematous nodules that usually do not ulcerate. While these nodules most commonly affect the pretibial region, they can also appear on the thighs, arms, and trunk. The typical clinical characteristic features help in differentiate erythema nodosum from other form of panniculitis. The histopathologic feature is characterized by septal panniculitis with an absence of vasculitis. Neutrophils predominantly infiltrate the fat septum in the early stage of the disease, followed by granulomatous inflammation and multinucleated giant cells in the later stages. Recent studies have found that some specific histopathological features can indicate the type of erythema nodosum.

This study aims to examine the clinical characteristics and histopathological features of erythema nodosum, highlighting awareness and understanding of commonly encountered etiologies. Understanding the clinical characteristic and histopathological features not only aids in effective management but also represents a significant step in reducing the associated morbidity with this dermatologic condition.

### 1.2 Research Objectives

1.2.1 To study the histopathological features and clinical characteristics of patients diagnosed with erythema nodosum in the Institute of Dermatology between 2017 to 2022

1.2.2 To study the prevalence and the most common secondary cause of erythema nodosum in the Institute of Dermatology.

### **1.3 Research Questions/ Assumptions**

Can histopathological features be used as indicators to differentiate between primary and secondary erythema nodosum?

### **1.4 Research Framework**

Erythema nodosum is the most common type of subcutaneous fat inflammation, also known as panniculitis. It is characterized by distinct clinical features, including erythematous to purplish subcutaneous nodules without ulceration, typically located on the anterior aspect of the lower legs. These features aid in the differential diagnosis of this dermatologic condition among other forms of panniculitis. The pathophysiology of erythema nodosum involves a type IV hypersensitivity reaction of the immune system, leading to increased neutrophil levels that produce reactive oxygen intermediates, resulting in inflammation. Previous studies have suggested that some histopathological features could indicate the type of erythema nodosum, assisting in effectively identifying cause of the disease and prompt management.

The research proposal aims to study the clinical characteristics and histopathological features in adult patients confirmed with erythema nodosum visited the Institute of Dermatology between the year 2017-2022. The research framework is designed to explore factors that might have some correlation with the disease, including sex, age, geography, characteristics of the lesion, other systemic signs, laboratory investigations, underlying diseases, histopathology, and management.

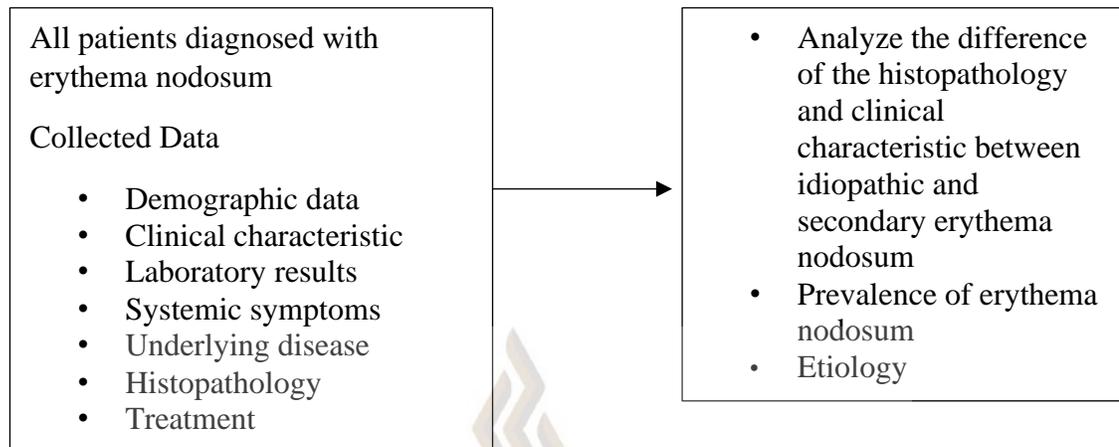


Figure 1.1 Research framework

Source: Researcher

## 1.5 Definition of terms

**Panniculitis** – inflammation of the subcutaneous tissue

**Erythema nodosum** – the eruption of bilateral tender erythematous subcutaneous nodules diagnosed by histopathology which represents septal panniculitis

**Idiopathic** – unknown cause or known to occur without any causes

**Clinical characteristics**- features of the patient's condition noted by the clinical observation

**Histopathological features** – the character shown in microscopic examination of the tissue taken by skin biopsy

## **Chapter 2**

### **Literature Review**

#### **2.1 Introduction and prevalence of erythema nodosum**

Erythema nodosum is the most common clinical form of panniculitis, which is defined as the inflammation of the subcutaneous tissue. The incidence and prevalence of erythema nodosum vary in different location according to triggering factors such as ethnicity, race, and geographic area.

The disease has the potential to impact people at any stage of life, but it is most frequently seen in individuals during their thirties and forties (Ozbagcivan, Akarsu, Avci, Inci, & Fetil, 2017). The global prevalence of this condition stands at approximately one to five cases per 100,000 people. In adults, it is more commonly found in women, with a male-to-female ratio of 1:5 to 1:6 (Ozbagcivan et al., 2017; Porges et al., 2018), whereas the ratio is 1:1 in children (Limtong, Suchonwanit, Chanprapaph, & Rutnin, 2021).

#### **2.2 Etiology**

##### **2.2.1 Etiology of erythema nodosum in the past century**

Etiology factors represent the variability in race, geographic region, technology, and lifestyle of the population in the area. Erythema nodosum is classified as idiopathic or primary erythema nodosum, meaning there are no concomitant diseases or no suspected culprits for the disease. In contrast, secondary erythema nodosum occurs due to

various causes such as infection, drugs, malignancy, or inflammatory diseases. In the past, most cases of erythema nodosum are defined as idiopathic. However, nowadays, with the healthcare system becoming more accessible, hidden causes are being identified, leading to an ever-expanding understanding of this disease.

In Thailand, a study conducted at Ramathibodi Hospital from 1982 to 1992 involved 100 biopsy-proven erythema nodosum patients aged 6 to 72, with a mean age of 31 years. The study found that 72% of total patients had idiopathic erythema nodosum, while 28% had secondary erythema nodosum. The most common cause of secondary erythema nodosum was *Mycobacterium tuberculosis* infection, affecting 12% of all patients. The results show that tuberculosis was the endemic disease during that period. Antibiotic-associated erythema nodosum ranked second at 7% among all patients. The study explained that skin reactions might appear 4 days to up to 3 weeks after drug administration. Streptococcal infection, evidenced by an increased titer of anti-streptolysin-O, ranked third in the secondary subgroup, followed by Bechet disease, which was considered the cause for up to 3 persons (Puavilai, Sakuntabhai, Sriprachaya-Anunt, Rajatanavin, & Charuwichitratana, 1995).

Following this, a study from Ramathibodi Hospital conducted from January 1990 to December 2000 collected data on 154 patients diagnosed with erythema nodosum by clinical and histological means. Patients ranged from 10 to 72 years old. Idiopathic erythema nodosum remained the most common, representing 71.6%, while secondary erythema nodosum accounted for 28.4%. *Mycobacterium tuberculosis* infection ranked first in the secondary group at 12.3%. The second most common cause was upper respiratory tract infection at 3.9%, followed by Bechet's disease. Other causes included systemic lupus erythematosus, drugs, pregnancy, and malignancy (Tantisirin & Puavilai, 2003).

The most recent study from Ramathibodi Hospital, conducted from January 2008 to September 2018, involved 169 patients with biopsy-proven erythema nodosum

attending the Ramathibodi skin clinic. The mean age of the patients was 40.6 +/- 17.3 years old. Idiopathic erythema nodosum was the most common, accounting for 62.7% of all patients. This study differed slightly from earlier ones by listing drugs along with tuberculosis as the most common cause of the secondary group, with an equal percentage of 23.8% for secondary erythema nodosum and 8.9% for all patients. Hematologic malignancy played a significant role in the past decade, affecting 14.3% of the secondary group, followed by Bechet's disease at 7.9%. Streptococcal infection, pseudomonas infection, and pregnancy had the same ranking, affecting 6.3% of all patients in the secondary group (Limtong et al., 2021).

According to all these studies from Ramathibodi Hospital, from 1982 to 2021, the percentage of idiopathic erythema nodosum decreased from 72% to 71.6% in 2003 and down to 62.7% in 2021. In other words, the percentage of secondary erythema nodosum rose from 28% to 28.4% in 2003 and to 37.3% in 2021. These changes are apparently due to the development of laboratory techniques and technology for identifying evidence of secondary causes. Moreover, the decreasing tuberculosis ratio is attributed to the decline in the rate of infected individuals. Thus, the increasing number of cases affected by drugs could possibly be due to the growing usage of medications.

Beyond studies conducted in Thailand, another example of research on the etiology of erythema nodosum is a study conducted in Turkey. This study examined the data of 88 patients diagnosed with erythema nodosum who presented at their clinic between 2013 and 2019, with patients' ages ranging from 17 to 76 years and a mean age of 41.91 +/- 13.07 years. In contrast to Thailand, where most cases were idiopathic, in Turkey, the number of cases with underlying diseases was significantly greater than primary erythema nodosum, accounting for 69.3% of all cases. Idiopathic erythema nodosum constituted 30.7% of all cases. Additionally, the most common etiological factors in Turkey were not tuberculosis, as observed in Thailand. Instead, upper respiratory tract infection ranked first in this group at 29.5% of all cases, followed by Bechet's disease at 22.7% of all cases (Singer & Özekinci, 2021).

Another relevant study on the same issue by Tzvika Porges was conducted in Israel. This research focused on patients diagnosed with erythema nodosum who were hospitalized at their facility from 2004 to 2014. The study documented 45 patients with a mean age of 35 years. Surprisingly, idiopathic cases accounted for 9% of all cases in this study. Among the secondary erythema nodosum cases, the majority belonged to the streptococcal infection group at 16%, followed by contraceptive drug-related cases at 13%. Sarcoidosis, inflammatory bowel disease, and viral hepatitis shared the same rank at 7%. Other identified causes included vasculitis and medication (Porges et al., 2018).

Compared to studies from both Israel and Turkey where secondary erythema nodosum predominated, most cases in Thailand were defined as idiopathic. This disparity may be attributed to the accessibility to the health care system. In Thailand, the most common factor for secondary erythema nodosum was tuberculosis due to the endemic nature of the area. Conversely, in other countries, factors differed based on geographic area, race, and lifestyle.

Table 2.1 Etiology of erythema nodosum studied in Israel, Turkey, and Thailand

	<b>Thailand 2021</b>	<b>Turkey 2021</b>	<b>Israel 2018</b>	<b>Thailand 2003</b>	<b>Thailand 1995</b>
Number of years collected data	10	10	10	10	10
Sample Size	169	100	45	154	100
Idiopathic (%)	106 (62.7%)	27(30.7%)	4(9%)	111(71.6%)	72(72%)
Secondary EN	63 (37.3%)	61(69.3%)	41(91%)	43(27.9%)	28(28%)
Mycobacterium tuberculosis	15	3(3.4%)		19(12.3%)	12(12%)
Streptococcal	4	26(29.5%)	7(16%)	6(3%)	6(6%)

Table 2.1 Etiology of erythema nodosum studied in Israel, Turkey, and Thailand (Cont.)

	Thailand 2021	Turkey 2021	Israel 2018	Thailand 2003	Thailand 1995
Pseudomonas	4				
NTM infection	1			1(0.7%)	
UTI		2(2.2%)			
Viral infection	5		3(7%)		
Fungal infection	1				
Drugs	2	1(1.1%)	2(4%)	3(2%)	7(7%)
Contraceptive	13		6(13%)		
Hematologic malignancies	9(14.3%)		Malignancy all1(2%)	1(0.7%)	
Bechet Disease	5 (7.9%)	20(22.7%)		5(3.3%)	3(3%)
Pregnancy	4 (6.3%)	2(2.2%)	1(2%)	3(2%)	
Lung neoplasm	1 (1.6%)				
Sarcoidosis	1 (1.6%)	6(6.7%)	3(7%)		
IBS vasculitis			3(7%)	1(0.7%)	
			2(4%)		
Granulomatous mastitis		1(1.1%)			
SLE				3(2%)	
Reiter's Syndrome				1(0.7%)	

Source: Limtong et al., 2021; Singer & Özekinci, 2021; Porges et al., 2018; Tantisirin & Puavilai, 2003; Puavilai et al., 1995

### 2.2.2 Etiologic factor proven to cause erythema nodosum

Etiologic factors can be categorized as an infectious and non-infectious causes. Infectious causes include bacteria, virus, fungus, and parasite, while non-infectious causes encompass drugs, malignancy, inflammatory bowel disease, and miscellaneous.

#### Infectious group

##### 1) Bacteria:

The most common bacterial causes of erythema nodosum include tuberculosis and streptococcal infections, particularly streptococcal pharyngitis. In areas where tuberculosis remains endemic, the prevalence of tuberculosis as an underlying cause is notably high. Diagnostic investigations for pulmonary tuberculosis in such regions should include sputum examination for acid-fast bacilli smear, chest imaging, mycobacterial culture, tuberculin skin testing, and nucleic acid amplification testing.

In cases of streptococcal pharyngitis, skin lesions may manifest approximately 2-3 weeks after the initial infection. If a streptococcal infection is suspected, ordering a rapid antigen streptococcus test or anti-streptolysin O titers is recommended.

Other organisms are *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Mycobacterium leprae*, *Yersinia* species, *Salmonella* species, *Campylobacter jejuni*, *Mycoplasma pneumoniae*, *Bartonella* species and *Chlamydia trachomatis*.

##### 2) Virus:

Common pathogens in this group include viral hepatitis (B and C), Human Immunodeficiency Virus (HIV), Herpes Simplex Virus (HSV), Measles, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

### 3) Fungus:

Less common, diseases include coccidioidomycosis, sporotrichosis, aspergillosis, nocardiosis, histoplasmosis, blastomycosis, and dermatophytosis.

### 4) Parasite:

Parasitic infections are the least common underlying cause, with reported diseases such as amebiasis, giardiasis, toxoplasmosis, ascariasis, trichomoniasis, taeniasis, and hookworm infestation.

## Non-infectious group

### 1) Drugs

Commonly reported drugs include antibiotics (penicillin, sulfonamide), oral contraceptives, bromides, iodides, biological agents (e.g., dupilumab), and chemotherapies. Vaccines (tetanus, diphtheria, hepatitis, human papillomavirus, malaria, rabies, smallpox, typhoid, cholera, BCG) have also been associated with erythema nodosum.

### 2) Malignancy

Hematologic malignancies, particularly leukemia and lymphoma, play a significant role. Solid neoplasms, including lung, colon, cervix, liver, pancreatic, parathyroid, and carcinoid tumors have also been reported. Investigations should consider age and sex to rule out occult malignancy.

### 3) Inflammatory Bowel Disease

Inflammatory bowel disease (IBD), presenting as ulcerative colitis or Crohn's disease, is associated with erythema nodosum in 3-10% and 4-15% of cases, respectively, with a female predilection.

#### 4) Miscellaneous

Behcet's disease has been identified in patients diagnosed with erythema nodosum. Additionally, hormonal changes during pregnancy may act as a trigger for erythema nodosum, accounting for 2-6% of all cases. The acute presentation of sarcoidosis or Lofgren syndrome is characterized by erythema nodosum, hilar lymphadenopathy, and fever (Pérez-Garza, Chavez-Alvarez, Ocampo-Candiani, & Gomez-Flores, 2021).

## 2.3 Pathogenesis

### 2.3.1 Hypersensitivity reaction

Hypersensitivity reactions involve an exaggerated immune response to various antigens. The first three types (type I, type II, and type III hypersensitivity reactions) are immediate, occurring within 24 hours. Type IV hypersensitivity, or delayed-type hypersensitivity, occurs more than 12 hours after exposure, with maximal reaction time between 48 to 72 hours (Marwa & Kondamudi, 2022).

### 2.3.2 Pathogenesis of Erythema Nodosum

Erythema nodosum's pathogenesis is considered a delayed-type hypersensitivity reaction (type IV) responding to various stimuli. This reaction releases adhesion molecules, numerous inflammatory cytokines, and deposits immune complexes around subcutaneous tissue.

In the early lesion, the circulating neutrophil count increases, leading to reactive oxygen intermediate production, causing oxidative tissue damage and activating the inflammatory process. Cytokines (IL-6, IL-8, IL-12, interferon-gamma, granulocyte colony-stimulating factors, monocyte chemoattractant protein-1, tumor necrosis factor-alpha) are released in tissue and serum, activating and recruiting more neutrophils to the

tissue. Adhesion molecules (E-selectin, P-selectin, platelet endothelial cell adhesion molecule, vascular cell adhesion molecule-1, intercellular adhesion molecule-1) increase in endothelial cells in patients with erythema nodosum. Detection of circulating immune complexes in the early lesion supports the hypothesis that antibodies, complement, and antigens play important roles in the disease's pathogenesis (Pérez-Garza et al., 2021). Thus, a complex series of steps are involved in lesion development.

## **2.4 Clinical characteristic**

The clinical manifestation of erythema nodosum is an acute onset of tender bilateral symmetrical erythematous nodules and plaques, each measuring 1-6 cm in diameter, possibly up to 10 cm (Fig.2.4). Typically located on the extensor aspect of lower extremities or the pretibial areas, lesions may also occur on ankles, thighs, and forearms.

The prodromal phase of erythema nodosum is characterized by nonspecific systemic signs that persist for 3 to 6 days. During this phase, patients may experience fever, joint involvement such as arthritis or arthralgia, and abdominal pain (Hafsi & Badri, 2022). A study in Israel reported that 18% of patients exhibited fever, and 27% had joint involvement (Porges et al., 2018).

The subsequent stage rapidly develops over 1 to 2 days. This phase is marked by the appearance of painful, bilaterally symmetrical, small nodules on the anterior aspect of the distal part of the lower extremities, and sometimes on the thighs and forearms. These lesions are characterized by warmth and firmness. Pain may be exacerbated by orthostatism but relieved by elevating the legs. Some patients may experience ankle edema with morning stiffness or hilar adenopathy.

Erythema nodosum typically resolves spontaneously within 1-6 weeks without sequelae. Rest and symptomatic treatment can expedite the resolution, although worsening

may occur with orthostatism. Lesions may develop a polymorphic appearance, leading to necrosis, ulceration, atrophy, and scarring (Pérez-Garza et al., 2021).



Figure 2.1 Erythema nodosum on the anterior aspect of the lower extremities

Source: Pérez-Garza et al., 2021

## 2.5 Histopathology

A definitive diagnosis of erythema nodosum should be established through a skin biopsy. A deep incisional or excisional biopsy specimen provides adequate samples, facilitating a detailed visualization of the tissue (Schwartz & Nervi, 2007).

The prototypical histology of erythema nodosum reveals inflammatory cells surrounding septa of the subcutaneous fat tissue, resulting in septal thickening in early lesions. Neutrophils predominate in both the fat tissue and surrounding capillaries. Lobular panniculitis may be observed mixed with septal panniculitis, and capillary proliferations are noted, sometimes associated with hemorrhage. Early acute inflammation can feature Miescher's microgranulomas or Actinic radial granulomas, characterized by small, well-defined nodular aggregates of multiple histiocytes surrounding a central stellate cleft - a hallmark finding of erythema nodosum. Although vasculitis or small vessel inflammation is not typical in erythema nodosum, it may still be present. In late lesions,

multinucleated giant cells are observed with widened fibrotic subcutaneous septa, and neutrophils are less predominant in this stage.

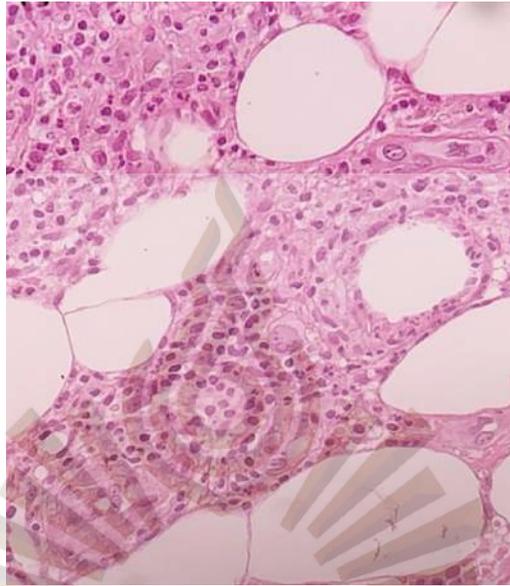


Figure 2.2 Histopathology of lymphohistiocytic infiltration with multinucleated giant cells at x100 magnification

Source: Pérez-Garza et al., 2021

A study in Turkey examined histopathologic features in 65 patients. The research reported that 58 patients, or 89.2% of all, had septal panniculitis, 6 patients, or 9.2%, had mixed panniculitis, and 1.5% had lobular panniculitis. Granuloma formation was found in 11 patients, accounting for 17%. Of these 11 patients with granuloma, 4 had sarcoidosis, 3 could not find the cause of erythema nodosum, 2 were infected with tuberculosis, 1 had Bechet disease, and 1 had upper respiratory tract infection. Histopathology was studied in 14 patients with Bechet disease. The pathology revealed typical septal panniculitis in 9 patients, mixed panniculitis in 4 patients, and lobular panniculitis in 1 patient. Among these 14 patients, 5 of them had vasculitis, with 3 patients detected with neutrophilic vasculitis and 2 with lymphocytic vasculitis (Singer & Özekinci, 2021).

According to a previous study at Ramathibodi Hospital, the results indicated that patients with focal peripheral lobular panniculitis were more likely to have secondary erythema nodosum compared to the idiopathic group. Meanwhile, patients who had eosinophils in focal peripheral lobular panniculitis were likely to have idiopathic erythema nodosum. The study found no association between acute/chronic erythema nodosum and its etiological subtype (Limtong et al., 2021).

## 2.6 Treatment and Prognosis

Erythema nodosum is a self-limiting disease with treatment modalities categorized into supportive and pharmacologic approaches. Supportive measures, such as leg elevation, bed rest, and compression bandages, are crucial for alleviating edema and pain.

Pharmacologic treatments include:

1) Nonsteroidal anti-inflammatory drugs (NSAIDs): These inhibit cyclooxygenase enzymes, reducing prostaglandin production and T-cell proliferation. Indomethacin (100-150mg daily) or naproxen (500-1000mg daily) is recommended, with caution in patients with inflammatory bowel disease (IBD) due to potential flare-ups (Pérez-Garza et al., 2021).

2) Potassium iodide: Prescribed at 300-900mg daily for 2-4 weeks in patients resistant to anti-inflammatory drugs, it helps reduce inflammation by increasing Interleukin-10 and Interleukin-35. Caution is advised in pregnancy (Pérez-Garza et al., 2021; Acosta, Haver, & Kelly, 2013).

3) Corticosteroids: Effective in reducing inflammation by decreasing the production of pro-inflammatory cytokines, corticosteroids require caution, especially with long-term systemic use. Intralesional corticosteroids can be used to treat recalcitrant nodules.

4) TNF-alpha inhibitor: Employed in patients resistant to traditional treatments, such as infliximab, with proven efficacy in pediatric Crohn's disease patients (Kugathasan et al., 2003).

5) Hydroxychloroquine: Proven effective in chronic erythema nodosum patients.

6) Colchicine: Administered at 1-2 mg daily, it is effective in erythema nodosum patients with Bechet's disease as the underlying condition (Alloway & Franks, 1995).

The prognosis for erythema nodosum is generally favorable, with spontaneous resolution within 2-8 weeks in the majority of patients and without sequelae. Recurrences, predominantly in idiopathic erythema nodosum and secondary cases with uncontrollable underlying diseases, may occur in about one-third of patients.



## **Chapter 3**

### **Research Methodology**

#### **3.1 Population and Samples**

##### **3.1.1 Population**

Men and women with age above 18 years old, diagnosed with erythema nodosum confirmed by skin biopsy as septal panniculitis without vasculitis

##### **3.1.2 Samples**

Data all patients who visited the Institute of Dermatology during the past 5 years, 2017 to 2022.

#### **3.2 Research Instruments**

Electronic medical record of patients diagnosed with erythema nodosum in the Institute of Dermatology from 2017 to 2022.

#### **3.3 Data Collection**

Retrospective analytic study of patients diagnosed with erythema nodosum. This study focused on patients meeting specific inclusion criteria. These criteria comprised individuals of Thai nationality, aged 18 years or older, and confirmed with erythema nodosum through clinical and histopathological assessment via skin biopsy. Exclusion

criteria encompassed patients lacking a histopathologic report or those without documented clinical characteristics in the outpatient department

The collected data encompass demographic details, clinical characteristics, laboratory investigation results, systemic symptoms, underlying diseases, a review of histopathology, and treatment information. Laboratory results include assessments such as complete blood count (CBC), renal function tests, C-reactive Protein (CRP) levels, Anti-streptolysin O (ASO) levels, chest radiography, and hepatitis results. In cases where no information was available, the researcher recorded it as 'No data.' The data will be collected in a standardized form or case record form, and stored electronically for each data set.

### **3.4 Data Analysis**

The study will employ descriptive analysis to examine demographic data, clinical characteristics, histopathology, and treatment. Continuous quantitative data will be presented as mean, median, and standard deviation, while discrete data will be reported as percentages.

Logistic regression analysis was conducted to compare two groups—primary and secondary erythema nodosum—considering variables such as clinical signs and symptoms, laboratory results, and histopathologic features

## Chapter 4

### Research Results

Of the 181 patients diagnosed with erythema nodosum, 139 were excluded due to incompatible histopathologic results, resulting in 42 eligible patients for the study.

#### 4.1 Prevalence

Out of the 360,426 patients who visited the outpatient department of the Institute of Dermatology, only 42 met the inclusion and exclusion criteria. The prevalence of the disease in the Institute of Dermatology is 12 cases per 100,000 individuals in the population.

#### 4.2 Demographic Data

The demographic information for 42 patients was extracted from the electronic medical records at the Institute of Dermatology. Notably, a substantial majority of subjects (90.5%) identified as female, whereas male patients exclusively received diagnoses of primary erythema nodosum, comprising 12.5% of the total primary cases. The overall mean age for the entire cohort was 46.3, with an age range spanning from 18 to 88 years. Upon closer examination of primary and secondary cases, the mean age for primary cases was 45.1, while secondary cases exhibited a slightly higher mean age of 50.2.

Regarding residence, most patients (52.4%) lived in Bangkok, with an additional 14.3% residing in the central part of the country. The majority of patients (78.6%) were reported to have multiple lesions, and the pretibial area was the most common location for

lesions (61.9% in both primary and secondary erythema nodosum). Additionally, 61.9% of subjects experienced only the first attack. In summary, there is no statistically significant difference in demographic data and location of the lesions between primary and secondary erythema nodosum.

Table 4.1 Demographic data

Variables	n (%) (42)	Erythema nodosum		p-value
		Primary (n = 32)	Secondary (n = 10)	
Gender				0.557
Male	4 (9.5)	4 (12.5)	0 (0)	
Female	38 (90.5)	28 (87.5)	10 (100)	
Age (years)				0.707
<30	9 (21.4)	8 (25)	1 (10)	
30 - 59	24 (57.1)	17 (53.1)	7 (70)	
>60	9 (21.4)	7 (21.9)	2 (20)	
Mean + SD	46.3 + 16.6	45.1 + 16.8	50.2 + 16.4	
Min, Max	18, 88	18, 88	26, 76	
Region				0.782
Bangkok	22 (52.4)	17 (53.1)	5 (50)	
Central Thailand	6 (14.3)	4 (12.5)	2 (20)	
NA	14 (33.3)	11 (34.4)	3 (30)	
Number of lesions				0.858
1	3 (7.1)	2 (6.3)	1 (10)	
2	2 (4.8)	2 (6.3)	0 (0)	
3	2 (4.8)	1 (3.1)	1 (10)	
4	2 (4.8)	2 (6.3)	0 (0)	
>4	33 (78.6)	25 (78.1)	8 (80)	

Table 4.1 Demographic data (Cont.)

Variables	n (%) (42)	Erythema nodosum		p-value
		Primary (n = 32)	Secondary (n = 10)	
Location of lesion				0.618
Pretibial	27 (64.3)	21 (65.6)	6 (60)	
Posterior lower extremities	3 (7.1)	3 (9.4)	0 (0)	
Ankle	1 (2.4)	1 (3.1)	0 (0)	
More than one location	11 (26.2)	7 (21.9)	4 (40)	
Arm & Forearms & Posterior lower extremities	1 (2.4)	0 (0)	1 (10)	
Pre & Post tibial	5 (11.9)	4 (12.5)	1 (10)	
Pretibial & Arm & Forearms	3 (7.2)	1 (3.1)	2 (20)	
Pretibial & thighs	1 (2.4)	1 (3.1)	0 (0)	
Pretibial & Arm & Forearms & Trunk	1 (2.4)	1 (3.1)	0 (0)	
Number of attacks				0.717
1	26 (61.9)	20 (62.5)	6 (60)	
2	11 (26.2)	8 (25)	3 (30)	
3	2 (4.8)	1 (3.1)	1 (10)	
>3	3 (7.1)	3 (9.4)	0 (0)	

### 4.3 Characteristics of the lesions

In our study, the majority of patients (81%) exhibited bilateral limb involvement, as opposed to unilateral. Only a small percentage (16.7%) reported experiencing pruritus. The majority of lesions displayed an erythematous color (71.4%), while others appeared purplish. The most commonly observed characteristic was nodules, present in approximately 83.3% of cases. This was followed by a combination of nodules and

plaques, seen in 7.1% of cases. Nearly all patients (92.9%) reported experiencing tenderness. Only one participant noted the presence of an ulcer (10%). Statistical analysis indicated no significant differences in clinical characteristic of the lesions between the primary group and the secondary group.

Table 4.2 Characteristics of the lesions

Variables	n (%) (42)	Erythema nodosum		p-value
		Primary (n = 32)	Secondary (n = 10)	
Affected limb				0.626
Bilateral	34 (81)	26 (81.3)	8 (80)	
Unilateral	8 (19)	6 (18.8)	2 (20)	
Pruritus	0 (0)	0 (0)	0 (0)	0.328
Yes	7 (16.7)	4 (12.5)	3 (30)	
No	35 (83.3)	28 (87.5)	7 (70)	
Color				0.600
Erythematous	30 (71.4)	23 (71.9)	7 (70)	
Purplish	12 (28.6)	9 (28.1)	3 (30)	
Characteristic				0.235
Patch	1 (2.4)	0 (0)	1 (10)	
Plaque	2 (4.8)	1 (3.1)	1 (10)	
Nodules	35 (83.3)	28 (87.5)	7 (70)	
Nodules + Patch	1 (2.4)	1 (3.1)	0 (0)	
Nodules + Plaque	3 (7.1)	2 (6.3)	1 (10)	
Tender				0.568
Yes	39 (92.9)	30 (93.8)	9 (90)	
No	3 (7.1)	2 (6.3)	1 (10)	

Table 4.2 Characteristics of the lesions (Cont.)

Variables	n (%) (42)	Erythema nodosum		p-value
		Primary (n = 32)	Secondary (n = 10)	
Ulcer				0.238
Yes	1 (2.4)	0 (0)	1 (10)	
No	41 (97.6)	32 (100)	9 (90)	

#### 4.4 Systemic symptoms

7.1% of the patients documented fever along with the appearance of a dermatologic lesion. Just 4.8% claimed to have malaise and 6.3% reported joint involvement. One of them reported a cough and sore throat. None of them reported weight loss, lymph node enlargement, or night sweating. However, no statistical significance was detected between the two groups.

Table 4.3 Systemic symptoms reported by the patient

Variables	n (%) (42)	Erythema nodosum		p-value
		Primary (n = 32)	Secondary (n = 10)	
Systemic symptom				0.062
Yes	7 (16.7)	3 (9.4)	4 (40)	
Fever	3 (7.1)	2 (6.3)	1 (10)	
Malaise	2 (4.8)	0 (0)	2 (20)	
Joint involvement	3(7.1)	2(6.3)	1(10)	
Cough, Sore throat	1 (2.4)	1 (3.1)	0 (0)	
No	32 (76.2)	26 (81.3)	6 (60)	
NA	4 (9.5)	3 (9.4)	1 (10)	

## 4.5 Causes of erythema nodosum

In summarizing the causes of erythema nodosum, the majority of subjects (76.2%) were reported to have idiopathic erythema nodosum, where no possible cause was identified based on laboratory investigations. The remaining 23.8% were diagnosed with secondary erythema nodosum. Within the secondary group, 50% had infections, with tuberculosis accounting for 40% and hepatitis B carriers for 10%. Additionally, 10% of the secondary group had metastatic bone cancer, with no precise diagnosis noted. Another 10% had discoid lupus erythematosus (DLE). Notably, 30% of subjects attributed their erythema nodosum to drug-related causes, with 20% of these cases specifying an unknown drug, and 10% implicating the use of amoxicillin/clavulanate and clindamycin.

Table 4.4 Causes of erythema nodosum in this research

<b>Factor</b>	<b>n (%)</b> <b>(n = 42)</b>
Idiopathic	32 (76.2)
Secondary	10 (23.8)
<b>Infection</b>	<b>5 (50)</b>
Tuberculosis	4 (40)
Hepatitis B Carrier	1 (10)
<b>Malignancy</b>	<b>1 (10)</b>
Metastatic bone cancer	1 (10)
<b>Autoimmune disease</b>	<b>1 (10)</b>
DLE	1 (10)
<b>Drugs</b>	<b>3 (30)</b>
Unknown	2 (20)
Amoxicillin/Clavulanate and Clindamycin	1 (10)

## 4.6 Histopathology

Almost all patients reported inflammatory cells infiltration, with only one patient not mentioning it. To compare the difference in histopathology between the two groups, primary and secondary erythema nodosum, all types of inflammatory cells—including neutrophils, lymphocytes, eosinophils, plasma cells, and histiocytes—could be found in both groups with no statistical significance. Surprisingly, just 11.9% of subjects had septal panniculitis alone. The majority exhibited mixed septal and lobular inflammation in the fat tissue, accounting for 88.1% of cases. Also, both types of erythema nodosum can also exhibit either septal panniculitis alone or septal panniculitis with evidence of lobular inflammation and a small area of necrosis. In the case of Miescher's microgranulomas, 57.1% of cases exhibited the presence of granulomas, occurring in both primary and secondary erythema nodosum with no difference between the two types. The presence of Miescher's microgranulomas aligns with established knowledge of erythema nodosum.

Table 4.5 Histopathology

Variables	n (%) (42)	Erythema nodosum		p-value
		Primary (n = 32)	Secondary (n = 10)	
Type of cell infiltrate				0.762
Yes	41 (97.6)	31 (96.9)	10 (100)	
Neutrophils				0.433
Yes	39 (92.9)	30 (93.8)	9 (90)	
No	2 (4.8)	1 (3.1)	1 (10)	
Lymphocytes				-
Yes	41 (97.6)	31 (96.9)	10 (100)	
No	0 (0)	0 (0)	0 (0)	
Plasma cells				0.647

Table 4.5 Histopathology (Cont.)

Variables	n (%) (42)	Erythema nodosum		p-value
		Primary (n = 32)	Secondary (n = 10)	
Yes	36 (85.7)	27 (84.4)	9 (90)	
No	5 (11.9)	4 (12.5)	1 (10)	
Eosinophils				0.556
Yes	34 (81)	26 (81.3)	8 (80)	
No	7 (16.7)	5 (15.6)	2 (20)	
Histiocytes				0.567
Yes	39 (92.9)	29 (90.6)	10 (100)	
No	2 (4.8)	2 (6.3)	0 (0)	
No	0 (0)	0 (0)	0 (0)	
NA	1 (2.4)	1 (3.1)	0 (0)	
Type of Panniculitis				0.659
Septal	5 (11.9)	4 (12.5)	1 (10)	
Mixed septal and lobular	37 (88.1)	28 (87.5)	9 (90)	
Miescher's microgranulomas				0.566
Present	24 (57.1)	18 (56.3)	6 (60)	
Absent	18 (42.9)	14 (43.8)	4 (40)	

#### 4.7 Treatment

Indomethacin and colchicine emerged as the most prescribed drugs, with nearly 90% of patients receiving this medication. One-third of patients were treated with corticosteroids, while only 9.5% were treated with antibiotics, either in topical or oral form. The use of antibiotics aimed to address secondary bacterial infections and served as empirical therapy until the diagnosis of erythema nodosum was confirmed through biopsy.

Approximately 5% of subjects received potassium iodides, evenly distributed between primary and secondary cases.

Table 4.6 Treatment

Variables	n (%) (42)	Erythema nodosum		p-value
		Primary (n = 32)	Secondary (n = 10)	
Received Treatments				0.762
Yes	41 (97.6)	31 (96.9)	10 (100)	
No	0 (0)	0 (0)	0 (0)	
NA	1 (2.4)	1 (3.1)	0 (0)	
Corticosteroids				0.697
Yes	13 (31)	9 (28.1)	4 (40)	
No	29 (69)	23 (71.9)	6 (60)	
Indomethacin				0.328
Yes	35 (83.3)	28 (87.5)	7 (70)	
No	7 (16.7)	4 (12.5)	3 (30)	
Antibiotics				0.953
Yes	4 (9.5)	3 (9.4)	1 (10)	
No	38 (90.5)	29 (90.6)	9 (90)	
Colchicine				0.831
Yes	37 (88.1)	28 (87.5)	9 (90)	
No	5 (11.9)	4 (12.5)	1 (10)	
Potassium iodide				0.424
Yes	2 (4.8)	1 (3.1)	1 (10)	
No	40 (95.2)	31 (96.9)	9 (90)	

## Chapter 5

### Conclusion and Recommendation

#### 5.1 Conclusion

Erythema nodosum is the most common type of panniculitis which manifests as multiple ill-defined erythematous to purplish tender subcutaneous nodules on the pretibial area of the lower limbs. It can be classified as idiopathic or secondary erythema nodosum, depending on the underlying causes or stimuli. Secondary erythema nodosum can result from various types of stimuli. The histopathology of septal panniculitis without vasculitis is the gold standard for diagnosis.

In our research, the prevalence was 12 cases per 100,000 individuals, significantly higher than 1-5 cases per 100,000 people reported in previous studies. This difference is likely due to our institute's status as a tertiary care center in the central region of Thailand referring patients from government hospitals all over Thailand.

In comparison to the demographic profile observed in the Ramathibodi Hospital study, our research provides distinctive insights. The mean age at diagnosis in our sample was  $46.3 \pm 16.6$  years, indicating a higher age compared to the Ramathibodi Hospital study, which reported a mean age of  $40.6 \pm 17.3$  years. Our study also demonstrated a broader age range, spanning from 18 to 88 years. The majority of our subjects were female, constituting 90.5% of all cases, in contrast to the 85.2% observed in the Ramathibodi Hospital study. Furthermore, our data revealed a distribution of primary and secondary cases, with the mean age of primary cases (45.1 years) lower than secondary cases (50.2 years). Notably, all male patients in our study were diagnosed as primary cases, comprising

12.5% of all primary subjects. Comparatively, the Ramathibodi Hospital study included 169 patients with a mean age of  $40.6 \pm 17.3$  years and a female-to-male ratio of 5.8:1 (Limtong et al., 2021).

In terms of clinical characteristics, we observed a prevalence of multiple lesions in 78.6% of cases. The pretibial area was identified as the most common site of lesions, occurring in 64.3% of cases, consistent with the findings of the Ramathibodi Hospital study (Limtong et al., 2021). The second most frequently reported site involved multiple locations, accounting for approximately 26.2% of cases. Among these, the concurrent involvement of the pretibial and post-tibial regions was most prominent, affecting about half of the patients with lesions in multiple locations. Most patients, over 80%, had bilateral, tender nodules without pruritus or ulceration, in both idiopathic and secondary erythema nodosum. Additionally, 71.4% presented with erythematous color. This aligns with the established knowledge of the disease. The clinical characteristics of the rash are useful in differentiating it from other forms of panniculitis, such as erythema induratum, which commonly affects the post-tibial area and usually presents with ulceration. However, it is important to note that about 20% of cases may present as unilateral, purplish in color, or with pruritus. Approximately 10% of cases could present as nodules and plaques or with non-tender lesions. Although ulceration is very unlikely to be a feature of erythema nodosum, dermatologists should still consider it in the differential diagnosis, as lesions could present with ulcers in about 2% of cases. Statistical analysis did not reveal any significant differences in the characteristics between these two classifications of erythema nodosum. Our study results are consistent with previous knowledge of erythema nodosum and align with the findings of Limtong et al.

Our study conducted comprehensive laboratory investigations on patients with erythema nodosum. Notably, secondary cases exhibited higher ESR values, indicative of a more pronounced inflammatory response. The elevated levels of leukocytes and ESR detected in secondary cases align with findings from a previous study in Turkey (Singer & Özekinci, 2021). It is emphasized that elevated ESR levels alert to the possibility of

secondary erythema nodosum. Therefore, performing laboratory investigations of ESR levels in patients with biopsy-proven erythema nodosum could be useful in categorizing the type of erythema nodosum, thereby aiding in the management and treatment of the disease.

According to our study, 76.2% of patients in the study had idiopathic erythema nodosum, while 23.8% had secondary cases. The incidence of primary erythema nodosum is notably higher compared to the previous study, likely because our hospital is a tertiary care center. Some patients were referred for skin biopsy and then returned to their regional hospital for laboratory investigation to identify the underlying causes. Unfortunately, most of them did not provide us with the results of those laboratory tests, which possibly led to missing data.

Table 5.1 Etiology of erythema nodosum

Factor	n = 42 (%)
Idiopathic	32 (76.2)
Secondary	10 (23.8)
Tuberculosis infection	4 (9.5%)
Hepatitis B Carrier	1 (2.4%)
Metastatic bone cancer	1 (2.4%)
DLE	1 (2.4%)
Drugs	3 (7.1%)

In our study, we have identified a range of underlying medical conditions and factors that are associated with secondary erythema nodosum.

#### 1) Tuberculosis Infection

We observed that 4 out of 42 patients (9.5%) with erythema nodosum had tuberculosis infection as the underlying disease, considered to be the most common cause

in our study. Our finding of 9.5% is lower than the number reported in studies conducted at Ramathibodi Hospital at the years 1993 and 2003, which reported incidences of 12% and 12.3%, respectively. (Puavilai et al., 1995; Tantisirin & Puavilai, 2003) When comparing our study to the most recent research at Ramathibodi Hospital, the incidence of secondary erythema nodosum associated with tuberculosis is nearly at 8.9%. In contrast, when compared to reports from Israel and Turkey, our study exhibits a substantially higher incidence of tuberculosis, aligning with the characteristics typically seen in developing countries (Porges et al., 2018; Singer & Özekinci, 2021).

## 2) Drug

Interestingly, drugs are listed as the second most common cause of the disease, accounting for 7.1% of cases of erythema nodosum. Three patients in our study had a history of taking drugs before the onset of the rash. This percentage stands out significantly when compared to findings in other research studies. This observation highlights the challenge of identifying specific drug culprits in some cases of secondary erythema, a situation that has been reported in other studies as well. In 4.8% of erythema nodosum cases, the specific drug responsible for the condition was not documented in the medical records. Instead, only the history of prescriptions from a previous hospital or clinic was recorded. Some patients mentioned receiving antibiotics with an unknown name. Among these patients, 2.4% reported having taken amoxicillin/clavulanate in combination with clindamycin before the onset of the rashes.

## 3) Hepatitis B Carrier

One patient in our study had untreated hepatitis B viral infection or known as hepatitis B carrier, associated with secondary erythema nodosum. While this is an uncommon finding, it has been reported in the previous study, indicating that viral hepatitis can potentially cause the development of the erythema nodosum.

#### 4) Discoid Lupus Erythematosus (DLE)

In our research, one patient (2.4%) presented with discoid lupus erythematosus. This patient had a history of systemic lupus erythematosus (SLE) and presented with atrophic hyperpigmented papules with follicular plugging at the right external ear canal, which was later diagnosed as DLE. The exacerbation of their underlying disease was detected, and it was treated along with their dermatologic condition. While this autoimmune disease has been associated with erythema nodosum in previous reports, it remains an uncommon trigger.

#### 5) Metastatic bone Cancer

A single patient in our study had metastatic bone cancer as an underlying disease. The patient had metastatic bone cancer and had undergone orthopedic surgery in previous years. Following the operation, she lost followed up with her orthopedist. There was uncertainty regarding her metastatic history before the onset of skin lesions. While this is a less common cause, it's important to consider neoplasm as potential triggers of erythema nodosum in clinical practice.

In our study, the majority of subjects (76.2%) received a diagnosis of idiopathic erythema nodosum, consistent with the findings from Ramathibodi hospital (Limtong et al., 2021), where idiopathic cases accounted for 62.7%. However, the Turkish study (Singer & Özekinci, 2021). reported a lower percentage of idiopathic cases at 30.7% and the Israel study reported 9% (Porges et al., 2018). Among secondary cases, infections predominated in our research (50%), with tuberculosis emerging as the leading cause (40%), in line with the recent Ramathibodi study. Streptococcal infections, which were commonly found in the past, were not found to be a triggering factor of erythema nodosum in our study. Notably, our research identified subjects with metastatic bone cancer and discoid lupus erythematosus as causes of secondary erythema nodosum, contributing unique insights in this research. Additionally, drug-induced cases were more prevalent in our study (30%), with amoxicillin/clavulanate and clindamycin specified in 10% of cases, showcasing variations from the Ramathibodi study where contraceptives play a significant

role. These differences underscore the complex etiological landscape of erythema nodosum and highlight the importance of considering geographical, demographic, lifestyle, and endemic factors in understanding the diverse causes of this condition.

Table 5.2 Comparison in etiologies of erythema nodosum in previous studies

	<b>Our study</b>	<b>Thailand 2021</b>	<b>Turkey 2021</b>	<b>Israel 2018</b>	<b>Thailand 2005</b>	<b>Thailand 1993</b>
Number of years collected data	5	10	10	10	10	10
Sample Size	42	169	100	45	154	100
Idiopathic (%)	32 (76.2)	106 (62.7%)	27(30.7%)	4(9%)	111(71.6%)	72(72%)
Secondary (%)	10 (23.8)	63 (37.3%)	61(69.3%)	41(91%)	43(27.9%)	28(28%)
<i>Mycobacterium tuberculosis</i>	4 (40%)	15 (23.8%)	3(3.4%)		19(12.3%)	12(12%)
<i>Streptococcal</i>		4 (6.3%)	26(29.5%)	7(16%)	6(3.%)	6(6%)
<i>Pseudomonas</i>		4 (6.3%)				
NTM infection		1 (1.6%)			1(0.7%)	
UTI			2(2.2%)			
Viral infection	1 (10%)	5 (7.9%)		3(7%)		
Fungal infection		1 (1.6%)				
Drugs	3 (3%)	2 (3.2%)	1(1.1%)	2(4%)	3(2%)	7(7%)
Contraceptive		13 (20.6%)		6(13%)		

Table 5.2 Comparison in etiologies of erythema nodosum in previous studies (Cont.)

	<b>Our study</b>	<b>Thailand 2021</b>	<b>Turkey 2021</b>	<b>Israel 2018</b>	<b>Thailand 2005</b>	<b>Thailand 1993</b>
Hematologic malignancies		9(14.3%)		Malignancy all1(2%)	1(0.7%)	
Bechet Disease		5 (7.9%)	20(22.7%)		5(3.3%)	3(3%)
Pregnancy		4 (6.3%)	2(2.2%)	1(2%)	3(2%)	
Solid neoplasm	1 (1%)	1 (1.6%)				
Sarcoidosis		1 (1.6%)	6(6.7%)	3(7%)		
IBS				3(7%)	1(0.7%)	
Vasculitis				2(4%)		
Granulomatous mastitis			1(1.1%)			
Lupus	1(1%)				3(2%)	
Erythematous						
Reiter's Syndrome					1(0.7%)	

Source: Limtong et al., 2021; Singer & Özekinci, 2021; Porges et al., 2018; Tantisirin & Puavilai, 2003; Puavilai et al., 1995

For histopathological findings, our study found no significant differences in histopathological features between idiopathic and secondary erythema nodosum in term of type of panniculitis, the presence of Miescher's microgranulomas and the type of inflammatory cells infiltration.

Septal panniculitis remains the gold standard for diagnosing the disease which surprisingly presented in 11.9% of our patients' histopathology. In addition to inflammation of the fat septa, both idiopathic and secondary erythema nodosum may exhibit lobular inflammation of subcutaneous fat with focal small necrosis, without

indicating a specific subtype. In our study, the most common histopathological features are mixed septal and lobular panniculitis which exhibit in 88.1% of cases. The presence of septal and lobular panniculitis may be described through the skin biopsy taken from late-stage lesions. Furthermore, the presence of septal panniculitis alone, without lobular panniculitis, does not provide information about the type of erythema nodosum. This contrasts with previous research that suggested the presence of focal peripheral lobular panniculitis may be indicative of secondary erythema nodosum (Limtong et al., 2021). However, the statistical analysis of our study shows no statistically significant.

The detection of Miescher's microgranulomas in more than half of our patients aligns with the established understanding of erythema nodosum. However, the presence of typical Miescher's microgranulomas does not distinguish between specific types of the disease, as they may occur in both primary and secondary erythema nodosum.

Four different types of inflammatory cells (neutrophils, lymphocytes, eosinophils and histiocytes) were observed in the skin biopsies of both groups. The presence of each type of cell does not provide an indication of the specific type of erythema nodosum. This differs from the previous study that suggested the presence of eosinophils in focal lobular panniculitis favors an idiopathic erythema nodosum diagnosis (Limtong et al., 2021).

In conclusion, our research studied the 5-year prevalence, etiology, clinical characteristics, histopathology, and treatment of erythema nodosum at the Institute of Dermatology and has provided knowledge of this dermatologic disease. Our findings revealed a higher prevalence of erythema nodosum in our patients compared to previous studies, likely attributed to our institution's status as a tertiary care center serving the central region of Thailand. Also, we observed a clinical characteristics as bilateral, tender, erythematous nodules without pruritus or ulceration located on pretibial area concurring with the established knowledge of the disease. In terms of histology, our findings revealed that the majority of cases exhibited a combination of septal and lobular panniculitis with evidence of focal necrosis, which contrasts with the gold standard for diagnosis of the

disease. This discrepancy may be due to biopsies being taken in the later stages of the disease. Finally, elevated ESR levels should raise awareness of the possibility of secondary erythema nodosum due to the pronounced inflammatory response.

## 5.2 Recommendation

This study has limitations, including a study design in a retrospective manner with a limited sample size and data availability constraints, which may affect the data collection and results. To improve the statistical significance of our research findings, we suggest two key strategies for future research. Firstly, consider expanding the sample size by collecting data over a longer period to create more extensive diversity. This may improve the limitations of compact sample size. Secondly, we recommend a change in our data collection approach. Instead of referring patients back to their primary hospital for laboratory investigation, consider conducting these tests at our hospital. This would reduce the risk of data loss due to patient incomplete follow-up. By incorporating the mentioned recommendations into future research, we may improve the statistical validity of our results, leading to a more comprehensive understanding of erythema nodosum.

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**Appendix**

**Case Record Form**

มหาวิทยาลัยรังสิต Rangsit University

**Case Record Form**

Participant ID .....

**Demographic Data**

Gender  Male  Female

Age \_\_\_\_\_ years

Region  Bangkok  Central  the North  
 South  Northeastern  No data

Number of lesion \_\_\_\_\_

Location of lesion  Pretibial  Pretibial+other  Arm+Forearms  
 Posterior Lower extremities  Face and Neck  
 Trunk  Others

Number of Attacks \_\_\_\_\_

**Characteristics**

Unilateral  Bilateral  
 Pruritus  No Pruritus  
 Erythematous  Purplish  Nodules  
 Patch  Plaque  
 Tender  Not tender  
 Ulcer  No ulcer

**Systemic Symptoms**

Fever  Yes  No  No data  
Malaise  Yes  No  No data  
Weight Loss  Yes  No  No data  
Lymphadenopathy  Yes  No  No data  
Joint Involvement  Yes  No  No data  
Night sweating  Yes  No  No data  
Others \_\_\_\_\_

**Laboratory Investigation Result**

Leukocytes \_\_\_\_\_  No data  
CRP \_\_\_\_\_  No data  
ESR \_\_\_\_\_  No data  
ASO \_\_\_\_\_  No data  
Culture \_\_\_\_\_  No data  
Hepatitis profile \_\_\_\_\_  No data  
Biopsy \_\_\_\_\_  No data  
CXR \_\_\_\_\_  No data  
UA \_\_\_\_\_  No data  
UPT \_\_\_\_\_  No data  
Tuberculin skin test \_\_\_\_\_  No data  
Others \_\_\_\_\_



## Biography

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