A 5-Year Retrospective Study of the Prevalence and Etiology of Erythema Nodosum at the Institute of Dermatology, Bangkok, Thailand

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Abstract

Erythema nodosum is the most common type of panniculitis. It can be classified as either idiopathic or secondary, predicated on the presence of underlying causes. Secondary erythema nodosum can result from a variety of triggers. However, there is no data on this condition at the Institute of Dermatology, Thailand. This study investigates the prevalence, most common causes, clinical characteristics, and histopathological features of patients diagnosed with erythema nodosum at the Institute of Dermatology. Medical records were analysed from 42 patients diagnosed with erythema nodosum by skin biopsies at the Institute of Dermatology between 2017 and 2022. Electronic medical records, including demographic data, clinical characteristics, laboratory investigations, systemic symptoms, underlying diseases, histopathological features, and treatment modalities, were reviewed. Logistic regression analysis was conducted to compare between primary and secondary erythema nodosum conditions.

The prevalence of erythema nodosum at our tertiary care center was 12 cases per 100,000 individuals, with a male-to-female ratio of 1:10. An analysis revealed that the majority, 76.2%, were idiopathic. Further analysis of the secondary erythema nodosum cases revealed that 11.9% had underlying infections, with tuberculosis diagnosed in 9.5% of the cases. Histopathological analysis revealed no significant differences between idiopathic and secondary erythema nodosum. Treatment modalities predominantly included indomethacin (83.3%) and colchicine (88.1%).

Our study found that idiopathic factors were predominantly responsible for the cases observed. Among cases of secondary erythema nodosum, tuberculosis emerged as the leading cause.

Keywords*: *Panniculitis, Erythema Nodosum, Etiology, Idiopathic, Prevalence, Tuberculosis

1. Introduction

Erythema nodosum is the most well-known type of panniculitis, manifesting as poorly demarcated erythematous nodules with tenderness, frequently located on the extensor surface of both legs (Pérez-Garza, Chavez-Alvarez, Ocampo-Candiani, & Gomez-Flores, 2021; Porges et al., 2018, Schwartz, & Nervi, 2007). Erythema nodosum is classified as idiopathic or primary erythema nodosum, meaning there are no concomitant diseases or suspected culprits for the disease. In contrast, secondary erythema nodosum occurs due to various causes, such as infection, drugs, malignancy, or inflammatory diseases (Kugathasan et al., 2003). Although the exact cause of the disease remains unknown, the main pathology results from a delayed-type hypersensitivity immune response triggered by factors like bacteria, viruses, or chemical substances

(Pérez-Garza et al., 2021). In the past, a considerable number of cases fell into the category of idiopathic, where the cause remains unknown. However, as technology and medication evolved, hidden causes were identified, leading to an ever-expanding knowledge of this disease.

Various factors, including geography, race, and socioeconomic status, influence the prevalence and nature of erythema nodosum (Pérez-Garza et al., 2021; Puavilai et al., 1995). Over the decades, changes in the percentage of primary and secondary erythema nodosum have been observed. Given the outdated nature of previous studies, it is crucial to investigate the current prevalence of both primary and secondary erythema nodosum.

This study examines the most common causes of secondary erythema nodosum, highlighting awareness and understanding of commonly encountered etiologies. Understanding the underlying causes not only aids in effective management, but also represents a significant step in reducing the associated morbidity of patients with this dermatologic condition.

2. Objectives

1) To study the most common secondary causes of erythema nodosum at the Institute of Dermatology between the years 2017 and 2022.

2) To study the prevalence, clinical characteristics, histopathologic features, and etiology of patients diagnosed with erythema nodosum at the Institute of Dermatology.

3. Materials and Methods

3.1 Population and Samples

Population - Men and women over the age of 18 diagnosed with erythema nodosum confirmed by skin biopsy as septal panniculitis without vasculitis.

Samples – Data of all patients who visited the Institute of Dermatology during the past five years (2017 -2022).

3.2 Research Instruments

Electronic medical records of patients diagnosed with erythema nodosum at 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 individual patients aged 18 years or older who were confirmed with erythema nodosum through clinical and histopathological assessment via skin biopsy. Exclusion criteria were patients lacking a histopathologic report or those without documented clinical characteristics in the outpatient department.

The collected data encompasses 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 profile. 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.

The retrospective study protocol, identified by study code IRB/IEC 010/2566, has been approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of the Institute of Dermatology, Bangkok, Thailand, ensuring adherence to ethical guidelines and standards.

3.4 Data Analysis

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

Logistic regression analysis was conducted to compare two groups-primary and secondary erythema nodosum, and the testing utilized variables including clinical signs and symptoms, laboratory results, and histopathologic features.

This section should provide enough detail to allow suitably skilled investigators to fully replicate the study. Protocols for new methods should be included, but well-established protocols may simply be referenced.

4. Results and Discussion

4.1 Results

Of the 360,426 patients visiting the Outpatient Department of the Institute of Dermatology over the relevant time range, only 42 met the inclusion criteria. The prevalence of the disease at the Institute of Dermatology was 12 cases per 100,000 in the population.

The demographic information for 42 patients was extracted from the electronic medical records at the Institute of Dermatology. Notably, a substantial majority of the patients (90.5%) identified as female. Primary or idiopathic cases were found in 76.2%, and 12.5% were male. The overall mean age for the entire population sample was 46 years, 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 years, while secondary cases exhibited a slightly higher mean age of 50 years.

In our study, a significant majority of patients (81%) exhibited bilateral limb involvement. The pretibial area was the most common area of involvement. The majority of lesions displayed an erythematous color (71.4%), while others appeared purplish. Nodules were observed in 83.3% of cases, and tenderness was a prevalent symptom reported by 92.9% of individuals. Only one participant noted the presence of an ulcer, and a minority reported pruritus (16.7%).

Additionally, 7.1% of the patients documented a fever. Just 4.8% of the patients claimed to have malaise, and 6.3% reported joint involvement. In summary, there were no significant differences in clinical features between idiopathic and secondary erythema nodosum.

To compare the differences in histopathologies between the two groups, primary and secondary erythema nodosum, both types of erythema nodosum exhibited septal panniculitis with evidence of lobular inflammation and a small area of necrosis (88.1%). Only 11.9% of the patients had septal panniculitis alone, the classical pattern seen in erythema nodosum. The type of inflammatory cell infiltration in both groups did not appear to be different. Furthermore, 57.1% of the cases found Miescher's microgranulomas. In summary, there were no significant differences in histopathology features between idiopathic and secondary erythema nodosum.

Erythrocyte sedimentation rate (ESR) values revealed a mean of 31mm in primary erythema nodosum, with a maximum value of 47mm. In contrast, secondary erythema nodosum demonstrated a higher mean ESR of 74.3mm, reaching a maximum value of 130mm, indicating a more pronounced inflammatory response in secondary cases. Evaluation of liver enzymes demonstrated slightly elevated levels in primary erythema nodosum compared to secondary cases.

The tuberculin skin test was conducted for tuberculosis screening in 14 patients, constituting 33.3% of the group total. Of these, three patients tested positive, accounting for 7.1%. Subsequently, two of the

three underwent the QuantiFERON test for confirmation, and unsurprisingly, one of them received a positive confirmation, representing 2.4% of the total. In the case of the third patient, a history of treated tuberculous lymphadenitis existed for years. Nonetheless, the recent demise of a family member due to pulmonary tuberculosis raised concerns about her tuberculosis status. Chest radiography (CXR) and sputum acid-fast bacilli (AFB) tests were conducted, and all results returned negative. Finally, one additional patient had a clear diagnosis of pulmonary tuberculosis from their previous hospital records. Consequently, this brings the total number of tuberculosis infections diagnosed in this study to four.

A single individual had a positive result of hepatitis B surface antigen, calculated as 2.4% of all patients, and this patient was diagnosed as a hepatitis B carrier. Only one patient had the hepatitis B surface antibody positive (2.4%). This was a result of her previous hepatitis B vaccination.

In summarizing the causes of erythema nodosum, the majority of subjects (76.2%) were reported to have idiopathic erythema nodosum, where no probable 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. Another 10% had discoid lupus erythematosus (DLE). Notably, 30% of the patients 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.

For the treatment modalities, indomethacin and colchicine emerged as the most prescribed drugs, with nearly 90% of patients receiving these medications. All of the patients reported complete remission.

4.2 Discussion

In our research, the prevalence of erythema nodosum at the Institute of Dermatology was 12 cases per 100,000 individuals, significantly higher than the 1-5 cases per 100,000 individuals reported in previous studies (Ozbagcivan, et al., 2017). This difference is likely due to our Institute's status as a tertiary care center in the central region of Thailand, receiving patients from government hospitals all across the country.

In comparison to the demographic profile observed in the study conducted by Limtong et al., our research provides distinctive insights (Limtong, Suchonwanit, Chanprapaph, & Rutnin, 2021). Our sample's mean age at diagnosis was 46 ± 16 years, indicating a higher mean age compared to the study of Limtong et al. Our study also demonstrated a broader age range, spanning from 18 to 88 years. Most of our subjects were female, constituting 90.5% of all cases, similar to the 85.2% observed in the Limtong study. Furthermore, our data revealed a distribution of primary and secondary cases, with the mean age of primary cases (45 years) being lower than that of secondary cases (50 years). Notably, all male patients in our study were diagnosed with primary erythema nodosum, comprising 12.5% of all primary subjects.

For the clinical characteristics, we observed a prevalence of multiple lesions in 78.6% of cases, and the pretibial region emerged as the most common location for lesions, aligning with findings from the study of Limtong et al. (2021). In our study, 75.7% of the patients were documented as having bilateral, tender, erythematous nodules without pruritus or ulceration in both cases of idiopathic and secondary erythema nodosum. Statistical analysis did not reveal any significant differences in the characteristics between these two classifications of erythema nodosum. Our study results are consistent with the existing knowledge of erythema nodosum and align with the findings of Limtong et al. (2021).

Our study conducted comprehensive laboratory investigations of patients with erythema nodosum. Regarding white blood cell count, both primary and secondary erythema nodosum cases showed mean values of approximately 8,200 cells/uL, with distinct ranges. 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.

Liver enzyme levels were slightly elevated in primary cases compared to secondary ones, and thyroid function tests yielded negative results in both groups. Urine analysis and stool examinations in a subset of patients indicated the absence of urinary and gastrointestinal tract infections. Tuberculosis screening via the tuberculin skin test revealed positive results in 7.1% of patients, with subsequent confirmation utilizing the QuantiFERON test. Anti-streptolysin O titer results were negative in the assessed subset.

Hepatitis B surface antigen was positive in 2.4% of the patients, designating them as carriers, while another 2.4% had hepatitis B surface antibody due to a previous vaccination. No patients tested positive for hepatitis B core antigen, hepatitis C virus antibody, hepatitis A virus antibody, or anti-HIV.

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

In our study, most subjects (76.2%) received a diagnosis of idiopathic erythema nodosum, consistent with the findings from Limtong, where idiopathic cases accounted for 62.7% (Limtong, et al., 2021). However, Singer reported a lower percentage of idiopathic cases at 30.7%, and Porges reported only 9% (Singer, & Ozekinci, 2021; 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 study of Limtong et al. (2021), see Table 1.

Table 1 shows the etiologies of erythema nodosum in this study and others

	Limtong *et al.*, Thailand 2021	**Singer & Özekinci Turkey 2021**	**Porges *et al.*, Israel 2018**	**Tantisirin *et al.*, Thailand 2003**	**Puavilai *et al.*, Thailand 1995**	**Our study**
Number of years of collected data	10	10	10	10	10	5
Sample Size	169	100	45	154	100	42
Idiopathic (%)	106 (62.7%)	27 (30.7%)	4 (9%)	111 (71.6%)	72 (72%)	32 (76.2%)
Secondary (%)	63 (37.3%)	61 (69.3%)	41 (91%)	43 (27.9%)	28 (28%)	10 (23.8%)
Mycobacterium tuberculosis	15 (23.8%)	3 (3.4%)		19 (12.3%)	12 (12%)	4 (40%)
Streptococcal	4 (6.3%)	26 (29.5%)	7 (16%)	6 (3%)	6 (6%)	
Pseudomonas	4 (6.3%)					
NTM infection	1 (1.6%)			1 (0.7%)		
UTI		2 (2.2%)				
Viral infection	5 (7.9%)		3 (7%)			1 (10%)
Fungal	1 (1.6%)					
Drugs	2 (3.2%)	1 (1.1%)	2 (4%)	3 (2%)	7 (7%)	3 (3%)
Contraceptive	13 (20.6%)		6 (13%)			
Hematologic malignancies	9 (14.3%)		Malignancy all (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 (1.6%)					1 (1%)
Sarcoidosis	1 (1.6%)	6 (6.7%)	3 (7%)			
IBS			3 (7%)	1 (0.7%)		
vasculitis			2 (4%)			
Granulomatous mastitis		1 (1.1%)				

Streptococcal infections, which were commonly found in the past, were not found to be a triggering factor for erythema nodosum. Notably, our research identified subjects with metastatic bone cancer and

discoid lupus erythematosus as causes of secondary erythema nodosum, contributing unique insights to this research. Additionally, drug-induced cases were more prevalent in our study (30%), with amoxicillin/clavulanate or clindamycin specified in 10% of cases, showcasing variations from the study of Limtong, where contraceptives played a significant role (Limtong et al., 2021). 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.

Our study found no significant differences in the histopathological features between idiopathic and secondary erythema nodosum. Septal panniculitis remains the gold standard for diagnosing the disease. 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 are exhibited in 88.1% of cases. Septal and lobular panniculitis may be described through a 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 suggesting that focal peripheral lobular panniculitis may indicate secondary erythema nodosum (Limtong, et al., 2021). The detection of Miescher's microgranulomas is in accordance with the established understanding of erythema nodosum. Four different types of 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 kind of erythema nodosum. This differs from the Limtong study that suggested the presence of eosinophils in focal lobular panniculitis favors an idiopathic erythema nodosum diagnosis (Limtong et al., 2021). Note that the analysis in our study found no statistically significant differences.

Our study has limitations, including a study design in a retrospective manner with 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. First, consider expanding the sample size by collecting data over a longer period of time to create more group diversity. This may improve the inherent limitations of a compact sample size. Second, we recommend a prospective study design. By incorporating these recommendations into future research, we may improve the statistical validity of our results, leading to a more comprehensive understanding of erythema nodosum.

5. Conclusion

In conclusion, our findings revealed a higher prevalence of erythema nodosum in our patient group compared to previous studies, which can likely be attributed to our institution's status as a tertiary care center specializing in dermatology and serving the central (most populous) region of Thailand. Also, we observed a higher incidence of secondary erythema nodosum associated with tuberculosis compared to worldwide studies, likely due to an endemic incidence of Tuberculosis in Thailand. Finally, there was no significant difference in histopathology features between idiopathic and secondary erythema nodosum, but elevated ESR levels should raise awareness of the possibility of secondary erythema nodosum.

6. Acknowledgements

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