Histopathological aspects of neutrophilic dermatoses: Investigation of 38 cases and review of the literature

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ABSTRACT

Introduction: Neutrophilic dermatosis (ND) is a heterogeneous group of diseases with various etiologies and clinical presentations. NDs may clinically present as papule, vesiculopustule, plaque, and nodule of the skin, but they all share the common feature of neutrophilic predominance in the skin. Histological examination of patients with suspected ND is a key step for making the proper diagnosis.

Patients and Methods: The aim of this article was to investigate histopathological aspects of different NDs. We obtained our data from medical records of patients at Razi dermatology hospital, between 2012 and 2014. Thirty-eight biopsy records coded under the term of any ND, including Sweet's syndrome (SS), pyoderma gangrenosum (PG), skin lesions of Behcet's disease, neutrophilic drug eruption, amicrobial pustulosis of the folds, pustular vasculitis of the hands, and undetermined ND were recruited in our study. The specimens were evaluated regarding inflammatory reaction pattern, epidermal/adnexal changes, and dermal changes.

Results: Most common NDs in our study were PG (42.1%) followed by SS (21.1%). The most common pattern of inflammatory reaction was superficial perivascular and interstitial dermal inflammation in 44.7% of the patients. Exocytosis of neutrophils into epidermis, hair follicle, and eccrine gland was seen in 71%, 18.5%, and 28.9% of the specimens, respectively. Ulceration was only seen in ten PG specimens. Dermal fibrosis and vascular proliferation were reported in all PG patients.

Conclusion: The prevalence of some histopathological findings in different types of ND was significantly different. These features seem helpful in distinguishing between different NDs.

Key words: Behcet's disease, histopathology, neutrophilic dermatosis, pyoderma gangrenosum, Sweet's syndrome

INTRODUCTION

Neutrophilic dermatosis (ND) is a heterogeneous group of skin diseases with various etiologies and clinical presentations. All diseases classified under the group of ND share the common feature of neutrophilic predominance in dermis. Various skin lesions such as papule, vesiculopustule, plaque, and nodule may be seen in these diseases. NDs are categorized according to the clinical presentation and underlying etiology.

The pathogenesis of NDs remains inclusive; however, some theories have been suggested. An alternation in the function of the immune system has been most...
commonly proposed\(^3\) as evidenced by the dramatic response of these disorders to the administration of systemic corticosteroids. T-cell cytokines including interleukin-1 and immune complexes possibly play a role in the pathophysiology of ND.\(^4,6\)

Considering the heterogeneous presentation of NDs, the histopathological evaluation of skin lesions seems to be crucial for making the correct diagnosis. Well-defined NDs include Sweet’s syndrome (SS), pyoderma gangrenosum (PG), some lesions of Behcet’s disease, and amicrobial pustulosis of folds.\(^7\) SS and PG are the most prevalent diseases in this group. SS was first introduced by Sweet in 1964.\(^8\) Classic forms of SS are characterized by fever and abrupt onset of papule, plaque, or nodules, usually on the upper extremity, face, and neck and typically associated with fever and peripheral blood neutrophilia. Histopathological evaluation shows neutrophilic infiltration which is mainly found in the upper dermis. The involvement of other organs is not uncommon.\(^9\) PG is an inflammatory neutrophilic disease with both systemic and skin involvement.\(^10\) PG is thought to be a neutrophilic dyscrasia caused by the exaggerated release of cytokines as a result of immune reaction.\(^11\) The release of anti-matrix metalloproteinase and tumor necrosis factor alpha can trigger ulceration of the primary lesion of PG.\(^12\) Similar lesion to SS and PG and pathergy test-related lesion in Behcet’s disease are also categorized as ND.\(^7,13\)

Due to the heterogeneity of disorders in ND group, careful evaluation and diagnosis is of great importance. Identifying characteristic histopathologic findings is valuable for diagnosing the underlying disease properly. Our study was designated to investigate the histopathological aspects of NDs in patients and help classify and diagnose different NDs more efficiently.

**PATIENTS AND METHODS**

This was a cross-sectional retrospective study. We obtained our data from the medical records of patients at the Dermatopathology Department of Razi Dermatology Hospital, Tehran, between 2012 and 2014. All biopsy records of patients coded under the term of any ND, including SS, PG, skin lesions of Behcet’s disease, neutrophilic drug eruption, amicrobial pustulosis of the folds, pustular vasculitis of the hands, and undetermined ND were recruited in our study. Table 1 summarizes the patients’ clinical information and demographic data.

The paraffin-embedded standard hematoxylin and eosin-stained biopsies of patients were evaluated regarding inflammatory reaction pattern, epidermal/adnexal changes, and dermal changes.

We classified the histopathologic features of specimens with neutrophilic dermal infiltration into the following three groups: Superficial perivascular, superficial perivascular/interstitial, and superficial and deep perivascular/interstitial. Categorization of the inflammatory cell type including lymphocyte, histiocyte, lymphocyte, eosinophil, and plasma cell was considered for the non-neutrophilic infiltrations. We investigated the presence of ulceration and exocytosis of neutrophil to epidermis, hair follicle, and eccrine glands. Vascular changes including vasculopathy, vasculitis, fibrosis, vascular proliferation, and leukocytoclasis were noted. Panniculitis was categorized as septal or mixed septal/lobular. In addition, the presence of collagen degeneration, dermal edema, and dermal abscess was documented.

The data were collected and computerized. Descriptive statistics and percentage frequencies were calculated and analyzed with SPSS 22 (IBM SPSS Statistics V22.0).

**RESULTS**

Thirty-eight patients with various types of ND were enrolled in our study. The most common diagnosis was PG (42.1%) followed by SS (21.1%). Seven patients (18.4%) had ND due to underlying Behcet’s disease. Four patients (10.5%) were diagnosed with neutrophilic drug eruption. Least common diseases were pustular vasculitis of the hands, amicrobial pustulosis of the folds, and undetermined ND [Figure 1].

![Figure 1: Prevalence of different types of neutrophilic dermatosis in 38 cases in Razi Hospital](image-url)
Table 1: Clinical data and associated conditions of 38 patients with neutrophilic dermatosis in Razi hospital

| Number | Gender/age | Clinical presentation       | Site                                      | Associated conditions             | Diagnosis        |
|--------|------------|----------------------------|------------------------------------------|----------------------------------|------------------|
| 1      | Male/38    | Solitary ulcer             | Scalp                                    | Trauma                           | PG               |
| 2      | Female/28  | Multiple ulcers            | Hands                                    | Folliculitis                      | PG               |
| 3      | Male/56    | Solitary large ulcer       | Trunk                                    | Cribiform scar in left chest      | PG [Figure 2]    |
| 4      | Female/52  | Multiple ulcers            | Trunk (anterior and posterior)            |                                  | PG               |
| 5      | Female/70  | Solitary ulcerative nodule | Ankle                                    | Rheumatoid arthritis             | PG               |
| 6      | Female/75  | Solitary ulcer             | Leg                                      |                                  | PG               |
| 7      | Male/34    | Multiple indurated plaques and nodules | Ankle                                  |                                  | PG               |
| 8      | Male/48    | Solitary ulcer             | Chest                                    | Scar                              | PG               |
| 9      | Female/32  | Solitary ulcer             | Arm                                      |                                  | PG               |
| 10     | Female/77  | Solitary ulcer             | Ankle                                    |                                  | PG               |
| 11     | Female/16  | Multiple punch-out ulcers  | Lower limbs                              |                                  | PG               |
| 12     | Female/33  | Multiple punch-out ulcers  | Buttock                                  | Epilepsy + drug                   | PG               |
| 13     | Male/27    | Multiple ulcers            | Lower limbs                              | Behcet’s disease + drug           | PG               |
| 14     | Male/66    | Multiple ulcers + fingertip necrosis | Lower limbs                              |                                  | PG               |
| 15     | Female/43  | Multiple painful ulcers with erosion and crust | Face, trunk, extremity |                                  | PG [Figure 3]    |
| 16     | Female/45  | Solitary ulcer             | Lower limb                               |                                  | PG               |
| 17     | Male/23    | Erythematous patches and pustules | Groat and kneek                     |                                  | SS               |
| 18     | Male/66    | Painful erythematous plaques | Back                                    | Acute leukemia                    | SS [Figure 4]    |
| 19     | Female/70  | Pruritic erythematous plaques | Trunk and hands                          |                                  | SS               |
| 20     | Male/51    | Erythematous papules and plaques (some annular) | Hands                                  |                                  | SS               |
| 21     | Female/36  | Pruritic erythematous plaques | Hands                                   |                                  | SS               |
| 22     | Female/37  | Pruritic erythematous bullae with pitting edema and ecchymosis | Upper and lower limbs | Respiratory infection | SS               |
| 23     | Female/50  | Painful erythematous lesions | Hands and legs                          |                                  | SS               |
| 24     | Male/32    | Pruritic erythematous plaques | Hands                                    |                                  | SS               |
| 25     | Female/20  | Pustular lesions and folliculitis     | Forearm (pustular lesion)               | Oral and genital aphthus, pathergy+ | BD               |
| 26     | Male/30    | Well-defined ulcer          | Lower lip (ulcer)                       | Oral and genital aphthus, pathergy+ | BD               |
| 27     | Female/35  | Folliculitis-like lesions   | Axilla (acneiform lesion)                | Oral and genital aphthous, pathergy−aBD | BD               |
| 28     | Male/28    | Pustular and nodulocystic lesions + perianal furuncle and fistula | Face (cutaneous nodular lesion) | Hypercoagulopathy                | NDE              |
| 29     | Male/22    | Pustular lesions            | Back (pustular lesion)                   | Oral aphthous                      | BD               |
| 30     | Male/45    | Erythematous papules and pustules               | Extremity (pustular lesion)             | Oral aphthous, pathergy+           | BD               |
| 31     | Female/43  | Painful plaques and pustules         | Forearm and buttok (pustular lesion)     | Oral aphthous                      | BD               |
| 32     | Female/37  | Urticarial plaques with scale | Forearms                                 | Hypercoagulopathy                | NDE              |
| 33     | Female/37  | Erythematous macules and plaques | Back                                    | Depression + drug                 | NDE [Figure 6]   |
| 34     | Female/37  | Petechia and purpura        | Lower limb                              | Infertility + drug                | NDE               |
| 35     | Male/63    | Erythematous purpurc plaques | Lower limb                              | Drug (allopurinol)                | NDE               |
| 36     | Male/38    | Pyoderma-like lesions       | Axilla                                  | Drug (Dapson)                     | APF               |
| 37     | Male/57    | Pruritic bullous lesions with impetigo and crust | Trunk and extremity | Diabetes + open heart surgery     | PVH               |
| 38     | Male/36    | Papules and pustules of the folds | Trunk                                   |                                  | UND               |

APF: Amicrobial pustulosis of the folds, BD: Behcet’s disease, NDE: Neutrophilic drug eruption, PG: Pyoderma gangrenosum, PVH: Pustular vasculitis of the hands, SS: Sweet syndrome, UND: Undetermined neutrophilic dermatosis

Demographic and clinical data with associated conditions are summarized in Table 1 and Figures 2-6. The histopathological findings in our study were described under three sections: Inflammatory reaction pattern, epidermal/adnexal changes, and dermal changes [Figure 7].

**Inflammatory reaction pattern**

Patterns of inflammatory reaction included superficial perivascular and interstitial dermal inflammation in 17 patients (44.7%) and also superficial and deep perivascular/interstitial inflammation in 15 patients (39.5%). However, six patients (15.8%) merely showed superficial perivascular inflammation.

The density of neutrophilic infiltration was mild/moderate in 24 specimens and severe in 14 cases. Severe neutrophilic density was mostly seen in PG, followed by Behcet’s disease and SS. Lymphocytes were the most common cells to cause non-neutrophilic
infiltration in our patients (42.1%). Histiocyte and plasma cell infiltration was seen only in PG [Table 2].

**Epidermal and adnexal changes**

Neutrophilic epidermotropism or exocytosis of neutrophils into epidermis was seen in 27 (71%) cases. This resulted in epidermal abscess formation in 10 patients (26.3%). Neutrophilic folliculotropism or exocytosis of neutrophils into hair follicles was observed in 7 (18.5%) patients. However, follicular abscess was reported only in two patients (5.25%). Eleven specimens (28.9%) showed neutrophilic eccrinotropism or exocytosis of neutrophils into the eccrine glands. Ulceration was seen in ten specimens (26.3%), and all the biopsies that showed ulceration were diagnosed with PG \( P < 0.001 \) [Table 3].
Dermal changes

Dermal changes are illustrated in Table 4. Vasculopathy and vasculitis were observed in 16 (42.1%) and 19 (50%) cases, respectively. Among those with vasculitis, nine cases were diagnosed with PG. Five (26.3%) and 3 (15.8%) patients were associated with Behcet’s disease and SS, respectively. The remaining two were cases of neutrophilic drug eruption and pustular vasculitis of the hands. Signs of fibrosis and vascular proliferation were seen in all patients who were diagnosed with PG. None of the patients with other diagnosis had this feature ($P < 0.0001$) [Figure 7].

Leukocytoclasia was observed in 22 (57.9%) biopsy specimens in our study. Leukocytoclasia was severe in seven patients. Progression of dermal inflammation into deep layers caused panniculitis in 9 (23.7%) patients. Superficial dermal edema was observed in twenty (52.6%) specimens. Dermal abscess was reported only in two patients (5.3%), of which both were diagnosed by PG.

DISCUSSION

To the best of our knowledge, the current study is among few to describe the histological features of Table 2: Patterns of dermal changes in 38 patients of neutrophilic dermatosis in Razi hospital

| Type of ND (n) | Leukocytoclastic vasculitis (%) | Panniculitis | Collagen degeneration (%) | Dermal edema (%) | Dermal abscess (%) |
|---------------|--------------------------------|--------------|---------------------------|------------------|-------------------|
| PG (16)       | 5 (66)                         | 6 (37.5)     | 5 (31)                    | 2 (13)           |
| SS (8)        | 4 (50)                         | 2 (25)       | 5 (63)                    | 0                |
| BD (7)        | 4 (75)                         | 0            | 0                         | 0                |
| NDE (4)       | 3 (75)                         | 1 (25)       | 0                         | 0                |
| APF (1)       | 1 (100)                        | 0            | 0                         | 0                |
| PVH (1)       | 1 (100)                        | 0            | 0                         | 0                |
| UND (1)       | 0                              | 0            | 0                         | 0                |
| Total (38)    | 22 (58)                        | 8 (21)       | 20 (53)                   | 2 (5)            |

APF: Amicrobial pustulosis of the folds, BD: Behcet’s disease, PG: Pyoderma gangrenosum, PVH: Pustular vasculitis of hand, ND: Neutrophilic dermatosis, NDE: Neutrophilic drug eruption, SS: Sweet syndrome, UND: Undetermined neutrophilic dermatosis
various NDs in a considerable number of patients. NDs are heterogeneous both in clinical presentation and underlying etiology, so histological evaluation is necessary for an exact diagnosis. The most common types of NDs in our study were PG and SS.

Since the first description of SS by Dr. Sweet, hundreds of cases have been reported in literature. Skin biopsy is usually necessary in the diagnosis of SS. Histopathological findings of SS include diffuse dermal neutrophilic infiltration with variable degrees of dermal edema. Dermal infiltration of neutrophils can be diffuse and pan-dermal or perivascular with the occasional involvement of follicles and eccrine glands. Superficial dermal edema is a common finding in SS. In our study, mild/moderate and severe neutrophilic infiltrations were seen in five and three patients, respectively, out of the eight cases with SS. Involvement of follicles or eccrine glands was not observed in any of the patients with SS.

Historically, it was believed that no true vasculitis should be seen when the diagnosis of SS is suggested, but several observations showed that true vasculitis can be encountered in SS. Our findings revealed that three out of eight patients with SS had signs of vasculitis with fibrinoid necrosis. The current study confirmed that existence of vasculitis cannot rule out the diagnosis of SS.

PG was the most frequently diagnosed ND in our patients. Regardless of the underlying etiology of PG, fibrosis and vascular proliferation and ulceration were seen in all cases. No other diagnosis was associated with these features. Histopathological findings of PG tend to be different according to the type of PG, duration of the lesion, and site of biopsy. As it has been illustrated in the earlier studies, the primary lesions of PG can be similar to SS. Our study confirmed that many features such as heavy dermal infiltration, leukocytoclasis, and vasculopathy are prominent in both SS and PG. However, vascular proliferation and fibrosis can be pathognomonic of PG. Dermal edema was found occasionally in PG specimens. Abscess formation was seen in only two specimens, both of which were diagnosed with PG. In our study, more than half of the patients with PG showed vasculitis. This finding was compatible with previous studies that mention a variable degree of vascular damage in PG such as focal vasculitis in well-developed lesions.

Panniculitis was the feature most commonly encountered in patients with SS and PG in our study. Although panniculitis is observed frequently in ND, it should be differentiated from neutrophilic panniculitis, a condition also referred to as subcutaneous SS.

In our study, vasculitis was observed in more than half of the patients with Behcet’s disease. Leukocytoclasis along with dermal edema was the other prominent feature. However, the other characteristics of ND such as epidermotropism and adnexal involvement were not frequently observed in this type of ND. It has been proposed that the earlier lesions of Behcet’s disease show neutrophilic vascular reaction while the older lesions have perivascular lymphocytic infiltration. The type of non-neutrophilic infiltrate in Behcet’s disease cases in our study was lymphocyte and histiocyte in five out of seven patients.

CONCLUSION

Histological examination of patients with suspected neutrophilic dermatoses is a key step for proper diagnosis of the underlying etiology. This finally results in timely diagnosis and eventually better management of ND patients. Identifying the histopathological features of each type of ND is necessary to reach this goal. Our study revealed some histopathological findings that are helpful in distinguishing between NDs. Ulceration, dermal fibrosis, and vascular proliferation were most commonly seen in PG.

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Conflicts of interest

There are no conflicts of interest.

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