Myeloperoxidase positive histiocytes in subacute necrotizing lymphadenitis express both CD11c and CD163

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Myeloperoxidase positive histiocytes in subacute necrotizing lymphadenitis express both CD11c and CD163

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Seon Jung Jang

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ABSTRACT

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Immunophenotype analysis of lesional histiocytes in subacute necrotizing lymphadenitis (SNL) has revealed several unexpected findings. Histiocytes express myeloperoxidase (MPO), and immature dendritic cells occupy a significant proportion of the lesional cells in SNL. However, whether MPO-expressing lesional histiocytes of SNL also express immunophenotypic markers of immature dendritic cells has not been determined.

The immunophenotypes of lesional histiocytes is analysed in paraffin-embedded tissue sections from 26 patients with SNL using a panel of dendritic cell and macrophage markers. It is performed double immunohistochemical staining to confirm coexpression of several markers.

CD11c-expressing histiocytes represented a major component of lesional cells (averaging 50.1% of the lesional area), surpassing CD163-positive histiocytes (averaging 32.0% of the lesional area). Double immunohistochemical staining confirmed that a significant proportion of CD11c-expressing histiocytes also coexpressed MPO as well as CD163. CD123-positive plasmacytoid dendritic cells (averaging 3.2% of the lesional

area) were minor lesional cells, and fascin-positive mature dendritic cells were not present in the lesions.

Those results demonstrate that the main lesional cells in SNL are histiocytes expressing myeloid dendritic cell and macrophage markers as well as MPO, indicating phenotypic plasticity and functional versatility of histiocyte lineage cells.

Key words: myeloid dendritic cell, myeloperoxidase, subacute necrotizing lymphadenitis, plasmacytoid dendritic cell, histiocyte

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I. INTRODUCTION

Subacute necrotizing lymphadenitis (SNL) is a self-limiting lymphadenitis of unknown cause independently described by Kikuchi[1] and by Fujimoto and colleagues[2] for the first time in 1972. Zonal necroses with numerous apoptotic bodies occur in the T zones of lymph nodes, and, characteristically, neither neutrophils nor plasma cells are present.

Histiocytes have been known as the main lesional cells of SNL, imparting the synonym of "histiocytic necrotizing lymphadenitis" to this condition.[3,4] Lesional histiocytes of SNL have several morphological and phenotypic variations[5], and many of them have been reported to express myeloperoxidase (MPO) in their cytoplasm.[6] MPO is normally present only in the cytoplasm of granulocytes and the presence of MPO-expressing histiocytes is peculiar to SNL and lupus erythematosus lymphadenitis.[6]

Plasmacytoid dendritic cells (PDCs) and myeloid dendritic cells (MDCs) are precursor dendritic cells that recognize different antigens and induce different

types of immune responses.[7-9] PDCs demonstrate CD68+, CD123+, CD303+, CD304+, HLA-DR+, CD11c-, CD13-, CD14-, CD33-, and fascin- phenotypes while MDCs demonstrate CD1c+, CD11c+, CD13+, CD33+, CD68+, CD304+, HLA-DR+, CD14-, CD123-, CD303-, CD123-, and fascin- phenotypes. PDCs produce large amounts of interferon-α (IFN-α) following ligand stimulation and mature into antigen-presenting DCs after IFN-α production. MDCs become mature antigen-presenting cells that can secrete Th-1 or Th-2 cytokines after ligand stimulation.[7-11] Although several studies analyzing lesional cells of SNL suggested a possible role of dendritic cells in SNL, this issue is not completely resolved. SNL has been reported as a prototype of lymphadenopathy with PDC proliferation.[12-14] However, a recent study demonstrated a paucity of PDCs among lesional histiocytes in SNL, while other studies identified infiltration of fairly large numbers of PDCs and MDCs in SNL lesions.[6, 12-16]

The heterogeneity and versatility of histiocyte lineage cells is well known and analyses of subtypes of lesional histiocytes using paraffin-embedded tissue sections of SNL are now possible using newly developed antibodies that work on routine sections. To the best of our knowledge, we are the first to investigate the possibility that MPO-expressing lesional histiocytes of SNL also express immunophenotypic markers of dendritic cells.

II. MATERIALS AND METHODS

1. Patients and tissue samples

Formalin-fixed and paraffin-embedded tissue blocks from 26 patients with SNL diagnosed between 2000 and 2008 were retrieved from the files of the Department of Pathology of Severance Hospital, Seoul, Korea. Clinical data, including age, sex, sites of biopsy, and presenting symptoms were obtained from pathology reports and electronic medical records. The protocol of this study was approved by the Institutional Review Board of the Severance Hospital (4-2011-0262).

2. Immunohistochemical staining

Immunohistochemical analyses were performed using a broad panel of antibodies (Table 1). Fascin as a mature dendritic cell marker, CD11c and CD13 as MDC markers, CD123 and CD303 as PDC markers, and CD163 as a type 2 macrophage marker were used. Sections of 4-μm thickness on silane-coated slides (Muto Pure Chemicals Co., LTD., Tokyo, Japan) were deparaffinized in xylene and dehydrated in decreasing concentrations of ethanol. After rehydration and blocking of endogenous peroxidase activity with 3% hydrogen peroxide for 10 minutes, heat-induced epitope retrieval in 0.01 M citrate buffer

(pH 6.0) was performed for 20 minutes using a pressure cooker. After cooling, samples were subjected to 20 minutes of incubation with a serum-free protein-blocking reagent (Dako, Glostrup, Denmark). Incubation with primary antibodies was conducted overnight at 4°C, and a peroxidase-labeled EnVision™ (Dako) kit was used for detection of signals. Color was developed using the DAB liquid (Dako) as the chromogen. Sections were counterstained with Mayer's hematoxylin before dehydration and cover slipping. Incubation without the primary antibody was used as a negative control, and incubation with a primary antibody to albumin was performed to detect false-positive reactions via passive absorption or endocytosis of antigens by histiocytes.[17]

Double immunohistochemical staining were performed the first round of immunostaining using a peroxidase-labeled EnVision™ (Dako) as a detection kit and DAB liquid (Dako) as the chromogen, followed by a second round using an alkaline phosphatase-labeled EnVision™ (Dako) as a detection kit and Permanent red (Dako) as chromogen.

Table 1. Antibodies used for immunohistochemical staining

Antibody	Clone	Dilution	Source	City, State Nation
CD11c	5D11	1:80	Leica Biosystems	Newcastle, United Kingdom
CD13	38C12	1:40	Novocastra Laboratories	Newcastle, United Kingdom
CD123	6H6	1:100	e-Bioscience	San Diego, CA
CD163	10D6	1:100	Leica Biosystems	Newcastle, United Kingdom
CD303	Polyclonal	1:500	Abcam	Cambridge, MA
Albumin	Polyclonal	1:200	Dako	Glostrup, Denmark
Fascin	IM20	1:200	Leica Biosystems	Newcastle, United Kingdom
Myelopero-xidase	Polyclonal	1:500	Dako	Glostrup, Denmark

3. Analysis of immunohistochemical staining

The ImageJ, open source image analysis program were used. [18] The area was calculated that occupied by cells with positive immunostaining among lesional areas rather than counting cell numbers because calculating the areas was technically more feasible.

4. Statistical analysis

The independent-sample t-test and the SPSS software version 13.0 (SPSS Inc, Chicago, IL) was used for the comparison of 2 groups. *P* values of less than 0.05 were considered to be statistically significant.

III. RESULTS

1. Clinical and pathological findings

This study included 16 women and 10 men, with a mean age of 26.9 years (range, 6 to 52 years). All patients presented with cervical lymphadenopathy, occasionally accompanied by fever and leukopenia. Using Kuo's classification system,[19] 15 cases were classified as necrotic and 11 as apoptotic. Although foam cells were intermixed in several cases, none were classified xanthomatous.

2. Immunohistochemical staining

MPO-positive cells occupied 45.7% (range, 18.8–80.2%) of the lesional areas (Table 2). Although lesional histiocytes expressing faint cytoplasmic albumin through endocytosis were present (Figure 1A), especially in the necrotic subtype of SNL, they did not exhibit a strong granular cytoplasmic staining pattern compared with MPO (Figure 1B).

The most common lesional cells in the 26 cases of SNL were CD11c-expressing histiocytes. These cells occupied 50.1% (range, 26.9–77.6%) of the lesional areas (Table 2). Strong cell membrane and cytoplasmic immunoreactivity for CD11c was observed in lesional histiocytes (Figure 2A). Double staining for CD11c (DAB, brown chromogen) followed by MPO

(Permanent red, red chromogen) revealed a significant proportion of CD11c-positive histiocytes coexpressing MPO. Some CD11c-negative histiocytes expressing only MPO were also present (Figure 2B). CD13 staining was generally less intense and CD13-positive histiocytes occupied much less area compared to CD11c staining (Figure 2C). CD13-positive histiocytes occupied 13.5% (range, 1.2–54.4%) of the lesional areas (Table 2), and CD11c-positive histiocytes were statistically more prevalent than were CD13-positive histiocytes ($p < 0.001$).

CD163 staining detected on the cell membrane and cytoplasm was as intense as that for CD11c, even in necrotic areas (Figure 3A). CD163-positive histiocytes occupied 32.0% (range, 11.4–53.8%) of the lesional areas (Table 2). Statistical analysis showed that CD163-positive histiocytes occupied less lesional area than did CD11c-positive histiocytes ($p< 0.001$). Double immunostaining revealed that most CD163-positive lesional histiocytes also coexpressed CD11c (Figure 3B). Double staining for CD163 (DAB, brown chromogen) followed by MPO (Permanent red, red chromogen) also revealed that a significant proportion of CD163-positive histiocytes coexpressed MPO. However, CD163-negative histiocytes expressing only MPO were also observed and were more numerous than CD11c-negative and MPO-expressing histiocytes (Figure 3C).

CD123- and CD303-positive PDCs were not the most abundant lesional histiocytes and, in some cases, they were found as small clusters mainly at the

borders of the lesion (Figure 4A and 4B). CD123-positive cells occupied 3.2% (range, 0–10.5%) and CD303-positive cells occupied 3.5% (range, 0–11.4%) of the lesional areas (Table 2). There was no statistically significant difference between areas occupied by CD303- and CD123-positive cells (p = 0.723). Double staining for CD123 (DAB, brown chromogen) followed by CD11c (Permanent red, red chromogen) or MPO (Permanent red, red chromogen) showed no cells expressing both markers (Figure 4C and 4D).

No fascin-positive mature dendritic cells were present in the lesions, but clusters of these cells were observed in the nearby paracortex in some cases.

Table 2. Percentage of areas occupied by cells positive for CD11c, CD13, CD123, CD163, CD303, and MPO in total lesional areas

Case number	CD11c (%)	CD13 (%)	CD123 (%)	CD163 (%)	CD303 (%)	MPO (%)
1	61.6	7.4	2.2	48.0	0	59.2
2	54.3	4.7	2.0	27.4	6.0	18.8
3	37.4	8.5	0.8	45.1	0.6	30.9
4	31.4	6.0	10.5	23.8	2.9	46.6
5	38.7	2.2	3.6	34.5	3.4	30.8
6	43.6	5.0	1.6	31.2	0.4	54.6
7	26.9	7.9	1.2	11.4	9.9	24.9
8	46.0	16.4	2.9	38.4	3.9	29.7
9	35.7	13.3	2.2	29.7	5.3	29.1
10	51.6	7.7	0.4	43.6	0	54.6
11	29.6	6.6	0.9	45.7	3.4	40.3
12	49.8	17.8	2.4	26.6	1.9	35.2
13	62.4	6.9	1.7	53.8	1.5	58.8
14	42.5	29.7	0.3	21.5	0.2	80.2
15	65.7	54.4	8.8	18.9	3.3	71.3
16	66.2	48.4	3.7	35.3	01.0	67.7
17	44.1	10.8	7.7	16.4	0	64.6
18	42.2	37.6	1.7	23.2	3.9	30.5
19	60.1	2.8	8.7	25.2	7.2	45.5
20	51.3	1.6	5.1	25.3	4.3	39.3
21	50.7	1.2	3.1	39.6	11.4	41.7
22	65.7	2.4	0.9	39.6	7.8	45.9
23	77.6	6.5	2.2	30.7	4.8	22.5
24	43.5	42.0	8.5	36.6	7.8	66.4
25	74.8	1.3	0	43.1	0.5	56.9

26	50.2	1.5	0.4	18.6	0.3	41.8
Average	50.1	13.5	3.2	32.0	3.5	45.7

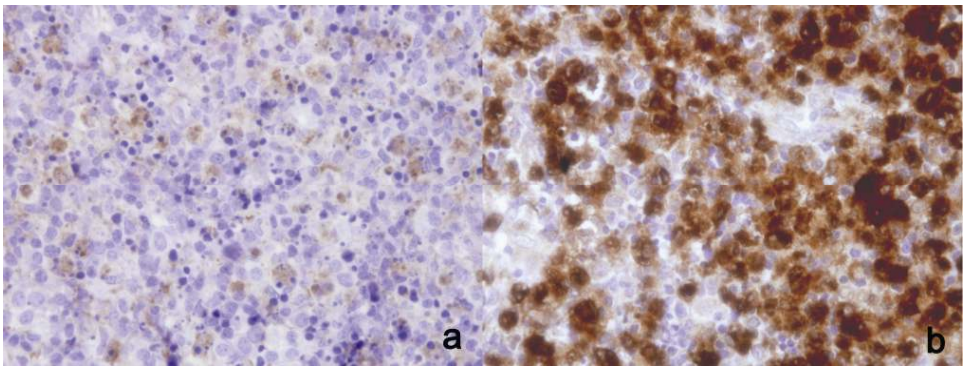

Figure 1. Immunohistochemical staining of subacute necrotizing lymphadenitis (SNL) shows (A) some lesional histiocytes expressing cytoplasmic faint staining for albumin through endocytosis (×400), and (B) many lesional histiocytes strongly expressing cytoplasmic MPO (×400).

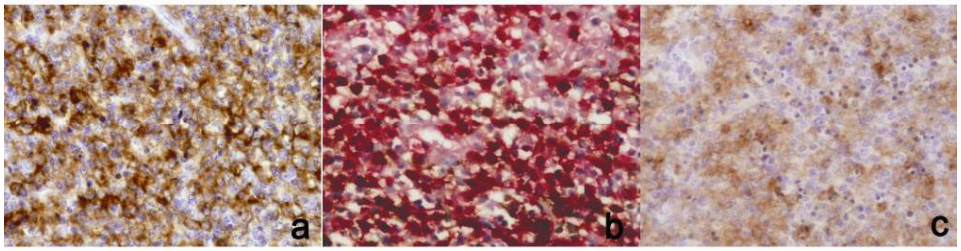

Figure 2. (A) Immunohistochemical staining of SNL demonstrates that most lesional histiocytes express strong cell membrane and cytoplasmic staining patterns for CD11c (×400). (B) Double immunohistochemical staining for CD11c (DAB, brown chromogen) and MPO (Permanent red, red chromogen) shows double-positive histiocytes and some CD11c-negative and MPO-positive histiocytes, shown by the red cytoplasmic signals (×400). (C) Some lesional histiocytes of SNL expressing cell membrane and cytoplasmic staining patterns for CD13 are present (×400).

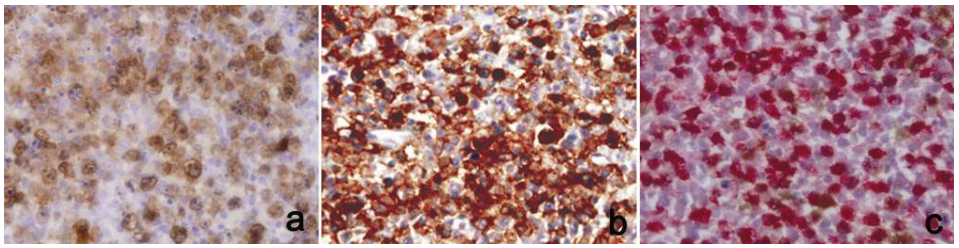

Figure 3. (A) Immunohistochemical staining of SNL shows many lesional histiocytes expressing strong cell membrane and cytoplasmic positivity for CD163 (×400). (B) Double immunohistochemical staining for CD11c (DAB, brown chromogen) followed by CD163 (Permanent red, red chromogen) shows no lesional histiocytes expressing only CD163, shown by the red cytoplasmic signals (×400). (C) Double immunohistochemical staining for CD163 (DAB, brown chromogen) followed by MPO (Permanent red, red chromogen) shows many double-positive histiocytes and some CD163-negative and MPO-positive histiocytes, indicated by the red cytoplasmic signals (×400).

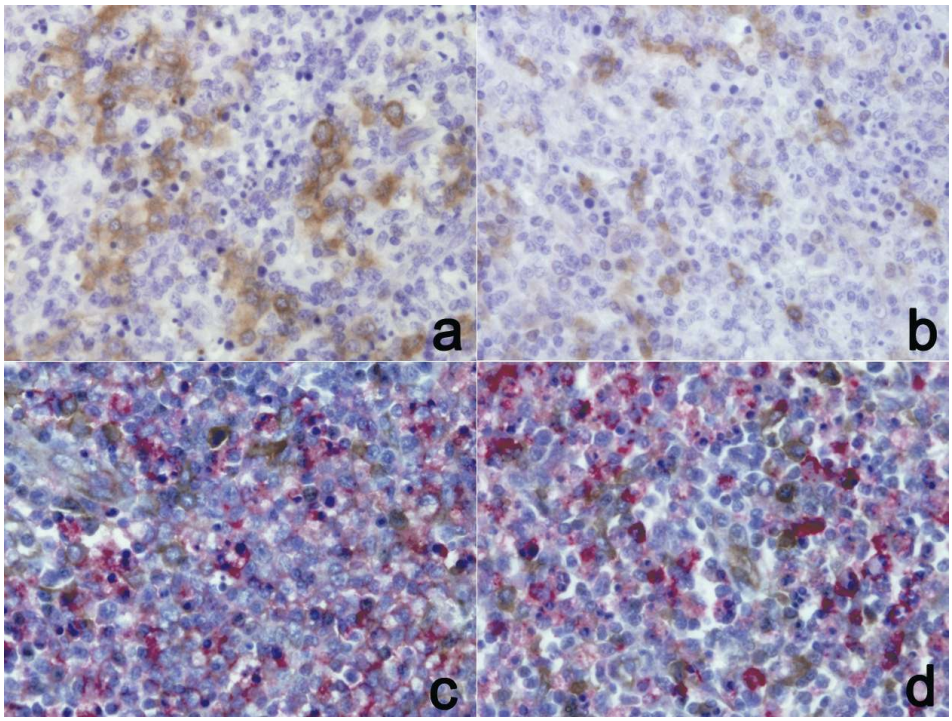

Figure 4. Clusters of (A) CD123-positive plasmacytoid dendritic cells (PDCs) and (B) CD303-positive PDCs by immunohistochemical staining at the border of the lesion of SNL are shown (×400). (C) Double immunohistochemical staining for CD123 (DAB, brown chromogen) followed by CD11c (Permanent red, red chromogen) shows CD123- positive PDCs (brown color) and CD11c-positive myeloid dendritic cells (red color) (×400). (D) Double immunohistochemical staining for CD123 (DAB, brown chromogen) followed by MPO (Permanent red, red chromogen) shows CD123-positive PDCs (brown color) and MPO-positive histiocytes (red color) (×400).

IV. DISCUSSION

The expression of MPO in the cytoplasm of lesional histiocytes was reported for the first time by Pileri et al.[6] in 2001. According to their report, 25% to 75% of lesional CD68+ histiocytes coexpress MPO. Normally, histiocytes do not express MPO in their cytoplasm and the expression of MPO in histiocytes is peculiar to SNL and LE lymphadenitis. Pileri et al.[6] hypothesized that MPO+/CD68+ blood monocytes may be recruited into tissues to supplement MPO for oxidative process. Thereafter, Nomura et al.[20] confirmed MPO expression in 23% (range, 5%–80%) of the lesional CD68+ histiocytes of SNL. They suggested that MPO was expressed in the cytoplasm of histiocytes by endocytosis because DNA released from nuclear debris during inflammation was reported to stimulate the release of MPO from neutrophils.[21,22] We performed immunohistochemical staining for albumin to explore the possibility of MPO expression in the macrophage cytoplasm by endocytosis as suggested by Nomura et al.[20] We observed faint cytoplasmic immunoreactivity for albumin in some lesional macrophages. However, MPO-expressing histiocytes were significantly more numerous than were histiocytes showing albumin expression in their cytoplasm, and the staining intensity was also significantly stronger. In accordance with the results of Pilichowska et al.[16] and Nomura et al.,[20] MPO-positive cells occupied 45.7% (range, 18.8–80.2%) of lesional areas in our study. The MPO expressed in the lesional histiocytes of SNL seems to play an important role in massive apoptosis of lymphoid cells in conjunction

with granzymes, and immunostaining for MPO can also be used as a valuable supportive diagnostic tool for the confirmatory diagnosis of SNL. Several recent studies demonstrated that lesional histiocytes of SNL were heterogeneous and immature dendritic cells were the most abundant lesional cells surpassing macrophages.[5,6,16,20] Although MPO- and CD68-positive histiocytes have been reported to be surprising in SNL, there has been no study to date exploring the specific lineage of MPO- and CD68-positive histiocytes.

Histiocytes have been recognized as the main lesional cells in SNL and can be classified morphologically as non-phagocytosing mononuclear histiocytes, crescentic macrophages, or phagocytosing macrophages, which include xanthomatous macrophages and PDCs.[5,6] SNL is known as a prototype of lymphadenopathy with PDC proliferation, especially in the early stages of the disease.[12-16] Pilichowska et al.[16] in a study of fresh-frozen tissue sections from 6 patients with SNL, disclosed that nearly all lesional cells were CD303 immunoreactive PDCs. Nomura et al.[20] in a study of 20 cases of SNL, reported that 43% (range, 5%–80%) of lesional CD68+ histiocytes were PDCs coexpressing CD123. However, CLA/HECA425 immunoreactive PDCs represented a minor proportion of lesional cells in the study by Pileri et al.[6] Our results showed that CD123+ dendritic cells occupied 3.2% (range, 0–10.5%) and CD303-expressing dendritic cells occupied 3.5% (range, 0–11.4%) of lesional areas. Our results are in agreement with those of Pileri et al.[6] because, here, PDCs represented a minor proportion of lesional cells in SNL. We think

this discrepancy in the prevalence of PDCs in lesional areas of SNL may be due to the different types of antibodies applied and due to the technical factors of immunohistochemical staining. The highest number of PDCs was reported in the study that used fresh-frozen sections and antibodies for CD123 and CD303.[11] Double staining for CD123 (DAB, brown chromogen) followed by CD11c (Permanent red, red chromogen) or MPO (Permanent red, red chromogen) showed no cell expression of both markers (Figure 4C and 4D). We therefore confirmed that PDCs do not express either MPO or CD11c.

Recently, CD11c-positive MDCs were reported to be the main lesional cells of SNL.[16] Our results also showed that CD11c-positive histiocytes occupy 50.1% (range, 26.9–77.6%) of lesional areas, and are the most prevalent lesional cells of SNL, surpassing CD163-positive histiocytes. Lesional cells expressing CD13 were much less numerous than lesional cells expressing CD11c, and exhibited less intense staining. Double immunohistochemical staining for CD11c and MPO showed many lesional histiocytes coexpressing both CD11c and MPO and some lesional histiocytes expressing only MPO in their cytoplasm.

Another population of cells comprising lesional histiocytes of SNL is macrophages. Macrophages are classified into 2 types according to their membrane expression of receptors, cytokines, and chemokines. M1 macrophages represent the interleukin (IL)–12^{high}, IL-23^{high}, IL-10^{low} phenotype and are involved in Th1 responses. Their main role is to kill intracellular

parasites and tumor cells via the release of reactive oxygen species, nitrogen intermediates, and inflammatory cytokines. In contrast, the more diverse M2 macrophages are involved in Th2 responses, immunoregulation, tissue repair and remodeling, and tumor progression.[20,23-25] Nomura et al.[20] analyzed 20 patients with SNL and reported a high rate of expression of the M2 macrophage markers, CD163 and CCL22, among lesional macrophages of SNL. Our results showed that CD163-positive macrophages occupied 32.0% (range, 11.4–53.8%) of lesional areas, which is in agreement with the results of Nomura et al.[20] Double immunohistochemical staining for CD163 and MPO showed many lesional histiocytes coexpressing both CD163 and MPO and some lesional histiocytes expressing only MPO in their cytoplasm. Lesional CD11c+/MPO+ cells were more numerous than were CD163+/MPO+ cells. Many CD11c-positive lesional histiocytes also coexpressed CD163 and MPO. The expression of CD11c was reported in alveolar macrophages, and these findings indicate the versatility of histiocyte lineage cells.[26]

The functional role of immature dendritic cells in SNL has not been clearly elucidated. The microscopic findings of SNL overlap with that of LE lymphadenitis, and there have been several reports of the association of SNL with systemic lupus erythematosus (SLE).[27-29] Moreover, the presence of MPO-expressing histiocytes both in SNL and LE lymphadenitis suggests a shared mechanism of necrosis in both diseases. PDCs are the major source of INF-α, which promotes the differentiation of monocytes into MDCs. MDCs

capture circulating DNA-containing bodies and activate lymphoid cells in autoimmune diseases including SLE.[30-34] According to the report by Pilichowska et al.,[16] lesional PDCs and MDCs in SNL strongly express MxA, an IFN-α inducible protein. Therefore, immature dendritic cells seem to play a pivotal role in the pathogenesis of SNL by sensing an unknown causative agent and augmenting the immune response.

The results of study elucidate that the main lesional histiocytes of SNL are MDCs expressing CD11c, and a significant proportion of lesional CD11c+ dendritic cells coexpress CD163 and MPO, indicating phenotypic plasticity and functional versatility of histiocyte lineage cells.

V. CONCLUSION

Although SNL has been reported as a prototype of lymphadenopathy and several studies analyzing lesional cells of SNL suggested a possible role of dendritic cells in SNL, this issue is not completely resolved. This study is to do analysis whether MPO-expressing lesional histiocytes of SNL also express immunophenotypic markers of dendritic cells.

1. The most common lesional cells in the 26 cases of SNL were CD11c-expressing histiocytes.
2. CD123- and CD303-positive PDCs were not the most abundant lesional histiocytes and, in some cases, they were found as small clusters mainly at the borders of the lesion.
3. Double staining for CD11c (DAB, brown chromogen) followed by MPO (Permanent red, red chromogen) revealed a significant proportion of CD11c-positive histiocytes coexpressing MPO.
4. CD163-positive histiocytes occupied less lesional area than did CD11c-positive histiocytes ($p < 0.001$).
5. Double immunostaining revealed that most CD163-positive lesional histiocytes also coexpressed CD11c
6. Double staining for CD163 (DAB, brown chromogen) followed by MPO (Permanent red, red chromogen) also revealed that a significant proportion

of CD163-positive histiocytes coexpressed MPO.

The results of study elucidate that the main lesional histiocytes of SNL are MDCs expressing CD11c, and a significant proportion of lesional CD11c+ dendritic cells coexpress CD163 and MPO, indicating phenotypic plasticity and functional versatility of histiocyte lineage cells.

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ABSTRACT(IN KOREAN)

아급성 괴사성 림프절염에서 Myeloperoxidase 양성 조직구의 CD11c과 CD163 면역염색 발현

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장 선 정

아급성 괴사성 림프절염에서 병변의 조직구에 대한 면역화학 분석에서 예상외의 결과들이 있었다. 하나는 조직구가 myeloperoxidase을 발현한다는 것이며, 또한 병변을 차지하는 다수의 세포가 immature dendritic cell이라는 점이다. 그러나 MPO를 발현하는 조직구가 immature dendritic cell의 immunophenotypic marker를 발현하는 지는 아직 알려진 바 없다.

아급성 괴사성 림프절로 진단된 26 사례의 파라핀 포매 조직을

이용하여 dendritic cell과 macrophage marker를 이용하여 병변을 차지하는 조직구에 대한 immunophenotype을 분석하였다.

CD11c을 표현하는 조직구가 주요한 병변 세포 (병변 면적의 평균 50.1%) 이며 CD163 양성 조직구 (병변 면적의 평균 32%)보다 우세하였다. Double immunohistochemical staining 결과 CD11c 양성 조직구의 대부분은 CD163뿐만 아니라 MPO도 같이 발현하였다. CD123 양성 plasmacytoid dendritic cell을 소수 (병변 면적의 평균 3.2%) 였으며, fascin 양성 mature dendritic cell은 병변에서는 관찰되지 않았다.

이러한 결과는 아급성 괴사성 림프절염의 주요 병변 세포가 MPO 뿐만 아니라 myeloid dendritic cell과 macrophage marker를 발현함을 나타내고 이것은 조직구 계열 세포에 있어서의 표현형의 가소성과 기능적인 다양성이 있다는 것을 의미한다.

핵심 되는 말: myeloid dendritic cell, myeloperoxidase, 아급성 괴사성 림프절염, plasmacytoid dendritic cell, 조직구

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