Enlarged Pericarotid Lymph Nodes Suggest Recent Ischemic Symptoms in Patients with Carotid Atherosclerosis

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Atherosclerosis is a chronic inflammatory disease closely associated with immunological activity. Lymph nodes (LNs) are essential secondary lymphoid organs, in which complex immune responses occur. Enlarged LNs are commonly observed around inflamed tissues or tumors; however, their role in atherosclerosis is not well understood. We hypothesized that enlarged pericarotid LNs would be present in symptomatic patients with carotid atherosclerosis. Therefore, we recorded the size of LNs around the carotid artery during surgery in patients undergoing carotid endarterectomy (CEA) for carotid atherosclerotic stenosis. Patients were stratified by enlarged LNs, defined as a diameter ≥ 10mm in the transverse diameters. Demographic and clinical data of participants were measured and analyzed. Hematoxylin and eosin (H&E), Sirius red, DAB-enhanced Perls’ Prussian blue, alizarin red, and immunohistochemistry (IHC) staining were performed for composition identification of plaques or LNs. Symptomatic patients were defined as those presenting with an ipsilateral cerebral ischemic event. Compared with patients with non-enlarged LNs, patients with enlarged LNs were more likely to be symptomatic (22/32, 68.8% versus 9/40, 22.5%, P < 0.001) and use calcium channel blocker drugs (17/32, 53.1% versus 10/40, 25%, P=0.014). In addition, they showed lower body mass index (mean ± SD: 24.00 ± 2.66 versus 25.34 ± 2.56 kg/m², P=0.034), lower weight (median [interquartile range]: 64 [60.00-76.00] versus 72.5 [65.00-77.50] Kg, P = 0.046) and higher diastolic blood pressure (mean ± SD: 78.94 ± 9.30 versus 73.93 ± 8.84 mmHg, P = 0.022). The plaque from patients with enlarged LNs exhibited a lower relative percentage of fibrous tissue (29.49 ± 10.73% versus 34.62 ± 10.33%, P = 0.041). The enlarged LNs remained oval-shaped by visual inspection. Compared to non-enlarged LNs, the predominant changes in enlarged LNs were atrophic lymphatic sinuses and dilated LNs parenchyma. Enlarged LNs contained more germinal centers and lymphocytes. In conclusion, symptomatic patients with carotid atherosclerosis have enlarged pericarotid LNs. The
INTRODUCTION

Atherosclerosis is a chronic inflammatory disease closely related to intense immunological activity (1, 2). Accumulation of lipids, vascular inflammation, immune cell activation, foam cell formation, cell apoptosis, and necrosis play important roles in both formation and development of atherosclerotic plaques (3). As the lesion progresses, unstable atherosclerotic plaques tend to rupture and cause ischemic stroke.

As early as 1980, Lemole et al. identified lymphstasis as a critical factor in the genesis of arteriosclerosis (4), but the role of the lymphatic network system, which carries a wide variety of immune cells, in the development of atherosclerosis has only recently been explored. Martel et al. introduced the concept of macrophage reverse cholesterol transport (mRCT) and identified the role of lymphatic vessels in reverse cholesterol transport (5). Subsequent studies have also shown that the lymphatic network is an important way of mobilizing cholesterol from the artery walls (6–8).

Lymph nodes (LNs) are essential secondary lymphoid organs that play an important role in immune responses (9). Enlarged LNs, which are commonly observed around inflamed tissues or tumors, usually indicate a strong inflammatory and immune responses (10, 11). Particular antigens, bacteria and viruses flowing through draining LNs can be effectively cleared, indicating that LNs are an effective filter (9, 12). LNs draining lymph from the arteries may play a more complex role in the course of atherosclerosis. Ox-low-density lipoproteins (LDLs) deposited in plaques can be taken up by DCs and then presented to T cells in draining LNs, thus initiating adaptive immune (2).

However, in a healthy artery wall, resident DCs usually exert immune tolerance by silencing T cells (13).

Recent single-cell sequencing has uncovered a new function of LN endothelial cells in scavenging LDLs (14); During the carotid endarterectomy (CEA), enlarged pericarotid LNs were observed in some patients (Figure 1B). In this study, we aimed to explore the relationship between enlarged LNs and recent ischemic symptoms, which helped us improve our understanding of the predictors of plaque vulnerability and better treat this high-risk group of patients with carotid atherosclerosis.

MATERIALS AND METHODS

Patients Selection

This study was approved by the ethics committee of our hospital. Informed consent was obtained from all patients prior to the procedure. Patients undergoing CEA for carotid atherosclerotic stenosis or occlusion in our department were enrolled consecutively in the study between December 2020 and January 2022. All patients were clearly diagnosed and other etiologies were excluded by Doppler ultrasound, computed tomography angiography (CTA), magnetic resonance imaging or angiography, and digital subtraction angiography (DSA). The minimum age limit was 18. Patients with neck tumors, a history of neck radiation, lymphoma, and lymph node tuberculosis were excluded. LN size around the carotid artery, including longitudinal and transversal diameters, was recorded during the operation. If there is more than one lymph node around the carotid artery, the largest one is recorded. Enlarged LNs were
defined as those with transverse diameters ≥ 10 mm (15, 16). Symptomatic patients had a history of amaurosis fugax, transient ischemic attack, or ischemic stroke ipsilateral to the extracted plaques within six months before the endarterectomy procedure. Conversely, asymptomatic patients did not have a history of cerebrovascular events (17). Data on venous blood samples, and the clinical and demographic characteristics of the participants were gathered from patients before CEA.

Plaque Specimens
For this study, 72 formalin-fixed paraffin-embedded blocks of carotid artery specimens met the inclusion criteria. All samples exhibited morphological characteristics of atherosclerotic plaques such as a necrotic core, connective tissue, and the presence of at least a portion of the fibrous cap in sectioned slides. Hematoxylin and eosin (H&E) staining was performed according to standard procedures (18). Macrophages were identified in consecutive sections by immunohistochemistry (IHC) using primary antibodies against CD68 (Cell Signaling Technology, 76437T) (19). Picosirius red staining was used to detect collagen fibers (19). DAB-enhanced Perls’ Prussian blue staining was used to evaluate the presence of intraplaque hemorrhage (19). Alizarin red staining was used to evaluate calcium deposition (19). Quantification of staining was documented as the threshold area divided by the lesion area using ImageJ software.

LN Specimens
H&E staining and IHC were performed on formalin-fixed and paraffin-embedded LNs, which included nine enlarged and five non-enlarged LNs. All LNs were dissected transversely in the middle of the longitudinal axis and serially sectioned. The primary antibodies used were anti-CD20 (Cell Signaling Technology, 48750T, 1: 100) for identifying B cells, anti-CD68 (Cell Signaling Technology, 76437T) for identifying macrophages, anti-CD3 (Servicebio, GB11014) for identifying T cells, and anti-Ki67 (Cell Signaling Technology, 9449T) for identifying proliferating cells (18). Diluents without primary antibodies were used as negative controls. Staining was visualized using the Dako REAL™ EnVision™ Detection System followed by counterstaining with hematoxylin. Images were captured using a digital camera under a light microscope (VS120; Olympus). The number of germinal centers (GCs) observed was counted in one HE-stained section. The proportions of CD68- and Ki67-positive cells in the LNs were calculated as positive cells versus total cells in at least five randomly selected areas under ×1000 magnification of microscopic fields.

Data Analysis
In this study, all statistical analyses were performed using the SPSS software version (version 25.0; SPSS, Inc., Chicago, IL, USA). Normally distributed continuous variables were expressed as the mean ± standard deviation, and were analyzed using the Student’s t-test. Abnormally distributed continuous variables were expressed as median (interquartile range [IQR]) and analyzed by the Mann-Whitney U test. Categorical variables were described as percentages, and were analyzed using the chi-square test or Fisher’s exact test. Statistical significance was set at P < 0.05.

RESULTS

Clinical and Biochemical Characteristics of Patients
Baseline clinical, biochemical, and demographic characteristics of the study participants are shown in Table 1. No significant differences in age, sex, systolic blood pressure, pulse pressure, serum low-density lipoprotein cholesterol, cholesterol, or triglyceride levels were found between patients with enlarged and non-enlarged LNs (P > 0.05). Compared with patients without enlarged LNs, patients with enlarged LNs were more likely to be symptomatic (68.8% vs. 22.5%, P < 0.001) and more likely to use calcium channel blocker drugs (53.1% vs. 25%, P = 0.014). In addition, they showed lower BMI values (mean ± SD: 24.00 ± 2.66 versus 25.34 ± 2.56 kg/m², P = 0.034), lower weight (median [interquartile range]: 64 [60.00-76.00] versus 72.5 [65.00-77.50] Kg, P = 0.046), and higher diastolic blood pressure (mean ± SD: 78.94 ± 9.30 versus 73.93 ± 8.84 mmHg, P = 0.022).

Histological Characteristics of Plaque Samples
The plagues from patients with enlarged LNs exhibited a lower relative percentage of fibrous tissue (29.49 ± 10.73% vs. 34.62 ± 10.33%, P = 0.041, Table 2). There were no significant differences in incidences of intraplaque hemorrhage or plaque calcification between patients with enlarged and non-enlarged LNs (P > 0.05, Table 2). Macrophage infiltration was present in all plaques, mainly in the shoulder region (Figures 2I-L). No difference was observed in the relative percentage of the histological components of atherosclerosis including fibrosis, plaque hemorrhage, and calcium between the two groups (P > 0.05, Table 2).

Morphology and Histological Characteristics of LN Samples
Morphologically, the enlarged LNs were oval (transverse diameter, mean ± SD:13.12 ± 2.23 mm), whereas the non-enlarged LNs (transverse diameter, mean ± SD: 7.28 ± 1.34 mm) were round or oval (Figure 1). The predominant changes in enlarged LNs were atrophic lymphatic sinuses and dilated parenchyma (Figures 3A, B). Compared with non-enlarged LNs, enlarged LNs contained more and larger GCs (Figures 3A, B, K). The proportion of Ki67 positive cells was increased in the cortex of enlarged LNs compared with that of non-enlarged LNs (Figures 3C, D, L). The proportion of Ki67-positive cells was similar regarding GCs between the two (Figures 3C, D, M). CD68-positive macrophages were mainly infiltrated in the lymphoid sinus (Figures 3E, F). The proportion of CD68-positive macrophages showed no apparent changes in the cortex excluding sinus of enlarged LNs, but was increased...
slightly in the GCs (Figures 3E, F, N, O). The number of CD20-positive B cells and CD3-positive T cells increased in enlarged LNs (Figures 3G–J).

**DISCUSSION**

Ischemic stroke is a common cause of significant morbidity, mortality, and disability-adjusted life-years (DALYs) worldwide (20). The underlying pathological process is atherosclerosis, a chronic disorder of the intimal layer of large- and medium-sized arteries associated with inflammation and immunity (21). Significant stenosis of the carotid artery, rupture of unstable plaques, and subsequent thrombosis result in transient ischemic attacks (TIAs) or ischemic strokes (21, 22). Currently, the percentage of carotid stenosis based on angiographic measurements remains a major criterion for risk stratification in patients with carotid artery stenosis (23). This method has also been validated in randomized clinical trials (RCT) and meta-analyses, which demonstrated that CEAs reduce the risk of future stroke in symptomatic patients with carotid stenosis (24, 25). However, this method does not provide information about plaque composition, plaque stability, inflammation, intraplaque hemorrhage (IPH), ulceration, and calcification. It is widely recognized that plaque vulnerability is more important than degree of stenosis in evaluating the risk of

| TABLE 1 | Baseline Characteristics of Study Participants. |
| --- | --- | --- |
| No. patients, n | 32 | 40 |  |
| Age, y | 64.50 ± 7.39 | 65.70 ± 6.64 | 0.471 |
| Sex, male | 28 (87.5%) | 33 (82.5%) | 0.798 |
| Symptom, n | 22 (68.8%) | 9 (22.5%) | < 0.001 |
| BMI, kg/m² | 24.00 ± 2.86 | 25.34 ± 2.56 | 0.034 |
| Weight, kg | 64 (60.00-76.00) | 72.5 (65.00-77.50) | 0.046 |
| Systolic blood pressure, mmHg | 140.66 ± 18.10 | 139.95 ± 18.11 | 0.864 |
| Diastolic blood pressure, mmHg | 79.94 ± 9.30 | 73.93 ± 8.84 | 0.022 |
| Pulse pressure, mmHg | 61.72 ± 15.60 | 66.03 ± 18.11 | 0.290 |
| Total cholesterol, mmol/L | 3.58 ± 0.64 | 3.55 ± 0.86 | 0.891 |
| HDL-C, mmol/L | 1.07 (0.88-1.15) | 0.98 (0.82-1.16) | 0.264 |
| LDL-C, mmol/L | 1.98 ± 0.52 | 1.92 ± 0.60 | 0.648 |
| Triglyceride, mmol/L | 1.26 (0.96-1.55) | 1.26 (0.97-1.60) | 0.856 |
| hCY, µmol/L | 14.10 (11.00-17.53) | 12.15 (9.50-16.10) | 0.087 |
| Coronary heart disease, n | 11 (34.4%) | 10 (25.0%) | 0.282 |
| History of smoking, n | 19 (59.4%) | 15 (37.5%) | 0.287 |
| History of drinking, n | 16 (50.0%) | 15 (37.5%) | 0.287 |
| Use of aspirin, n | 9 (28.1%) | 10 (25.0%) | 0.765 |
| Use of clopidogrel, n | 5 (15.6%) | 3 (7.5%) | 0.276 |
| Use of beta-blockers, n | 2 (6.3%) | 7 (17.5%) | 0.282 |
| Use of calcium channel blockers, n | 17 (53.1%) | 10 (25.0%) | 0.014 |
| Use of ACEI or ARB, n | 5 (15.6%) | 10 (25.0%) | 0.154 |
| Use of statins, n | 9 (28.1%) | 10 (25.0%) | 0.765 |
| Stenosis of carotid artery, n (50-69%/70%-99%/100%) | 0/28/4 | 2/34/4 | 0.725 |

Data presented as mean ± standard deviation or median (IQR) based on normality of continuous variables. Data presented as n (%) for dichotomous or categorical variables. LN, lymph node; BMI, body mass index; IQR, interquartile range; HDL-C, high-density lipoproteins cholesterol; LDL-C, low density lipoprotein cholesterol; hCY, homocysteine; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

| TABLE 2 | Histological Characteristics of Plaques. |
| --- | --- | --- |
| Fibrous tissue relative percentage, % | 29.49 ± 10.73 | 34.62 ± 10.33 | 0.041 |
| Intraplaque hemorrhage, n (%) | 26 (66.7%) | 24 (60.0%) | 0.748 |
| Platelet aggregation, % | 0.15 (0.00-0.87) | 0.45 (0.00-1.00) | 0.467 |
| Calcium relative percentage, % | 6.65 (1.28-8.35) | 7.25 (2.30-11.38) | 0.284 |

Data presented as mean ± standard deviation or median (IQR) based on normality of continuous variables. Data presented as n (%) for dichotomous or categorical variables. LN, lymph node; IQR, interquartile range.
stroke. Many attempts have been made to identify patients with unstable atherosclerotic plaques to prevent stroke. Some researchers are developing advanced imaging systems that can identify plaque components, such as high-resolution magnetic resonance imaging, ultrasonography, and CT angiography (22, 23). Others search for plasma biomarkers such as C-reactive protein (CRP), interleukin-6 and P-selectin (26). Clinical studies and meta-analyses have confirmed the feasibility of these markers and their effectiveness in risk assessment. Nevertheless, peripheral carotid LNs, which are closely associated with plaque inflammation and immune responses, have received little attention. Our study focused on lymph nodes around the atherosclerotic carotid artery. We found that enlarged LNs around the carotid artery in patients with carotid atherosclerosis suggest recent ischemic symptoms.

LNs are mainly composed of the cortex, paracortical cortex and medulla. These are indispensable secondary lymphoid organs. They also generate a highly specialized microenvironment in response to effective immune responses and play an important role in immune initiation and efficacy (14, 27–29). In the body’s response to diseases, such as infections and tumors, enlarged LNs can be seen as a sign that the body’s immune function is activated or expanded. Pericarotid LNs, which drain lymph fluid from the plaque, are likely to indicate plaque inflammation and a strong immune response, thereby reflecting plaque instability. The results of our study support this hypothesis. Among patients with carotid atherosclerosis, we found that a majority of patients with recent ischemic symptoms, which suggest plaque vulnerability, had enlarged pericarotid LNs, and there was a strong statistical significance between the two (P < 0.001). Our analysis of plaque composition also supported this view. We found that plaques from patients with non-enlarged LNs were more likely to be fibrous (Table 2), suggesting that these plaques were more stable (30). Previous animal studies have reported the expansion of LNs draining the atherosclerotic aorta in aged atherosclerotic Apoe−/− mice (21). To the best of our knowledge, this is the first study to demonstrate this phenomenon in humans.
Through statistical analysis, we found that patients with enlarged LNs had lower BMI and lower body weight. Some scholars have conducted a retrospective study on female mammography (31) and found that the longitudinal and transverse diameters of axillary LN increased with increasing BMI. The author attributed the increase in LN size to expansion of the LN hilum caused by fat infiltration. This adds to the evidence that enlarged pericarotid LNs are associated with plaque formation rather than obesity. Meanwhile, lower systolic blood pressure in patients without enlarged LNs may partly explain the stiffer aorta in these patients (32); however, the differences in systolic blood pressure and pulse pressure were not statistically significant. Calcium channel blockers (CCB) are commonly used in patients with enlarged LNs. However, a literature review found no evidence of a relationship between CCB and enlarged LNs. Therefore, our result may not be of practical significance.

Macroscopic examination revealed that the non-enlarged LN was round or oval in shape, but the enlarged LN remained oval in shape, and the hilum was not obvious. Microscopic observation revealed that LN enlargement mainly result from an increase in the number of cells. First, an increase in the number of cells in the LNs may result from an increase in the influx of cells into the LNs. Lymphatic vessels carrying various types of immune cells

![FIGURE 3](image-url)
have been found in the adventitia of atherosclerotic arteries (33). The establishment and development of the lymphatic system can reduce the deposition of lipids and immune cells in arteries (34). These immune cells travel along the lymphatic vessels into the draining LNs, resulting in increased cell numbers in the LNs. Second, this may result from increased cell proliferation in LNs. We observed an increased proportion of Ki67-positive cells in the LN cortex. Although there was no difference in the proportion of Ki67-positive cells in the LN GCs, the number and volume of GCs increased. Finally, impairment of lymphocyte export also contributed to increased cell numbers in the LNs. Tay et al. suggested that disruption of lymphocyte export also contributed to increased cell numbers in the draining LNs, resulting in increased cell proliferation in LNs.

We observed an increased proportion of Ki67-positive cells in draining lymphatic vessels, or they may settle here themselves (9). Recent single-cell sequencing revealed an unanticipated function of LN endothelial cells in scavenging ox-LDL (14). Phagocytosis may occur in pericarotid LNs, in which lymphatic endothelial cells remove modified LDLs unloaded by the macrophages.

In conclusion, the current study demonstrated that enlarged pericarotid LNs suggest recent ischemic symptoms and may be a sign of plaque destabilization in patients with carotid atherosclerosis. Adaptive immune responses are activated and reinforced in enlarged pericarotid LNs that drain carotid plaque. Further studies are necessary to explore the potential mechanism between pericarotid LNs and plaque stability and to understand the lymphatic system as a potential therapeutic target in patients with carotid atherosclerosis.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Qilu Hospital, Shandong University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TS, XL and DW conceived and designed the study. TS, PZ, FW, YH, MH, HL and DW were responsible for patient care and treatment, clinical oversight, and clinical data collection. TS, HL and BM collected and characterized samples. TS and FW conducted data analysis. TS and DW wrote the manuscript. TS, XL and DW modified and revised the manuscript. PZ, XL, and DW...
supervised the study. All authors contributed to the article and approved the submitted version.

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