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Pathomorphology of regional and mesenteric lymph nodes in acute and chronic alcoholic pancreatitis: a comparative autopsy study

Y.A. Musayeva [1], **A.E. Latibjonov** *[2]

[1] Neurology and medical psychiatry, Tashkent State Medical University, Tashkent, 100019, Uzbekistan
[2] Department of Traumatology and Orthopedics, Fergana Medical Institute of Public Health, Fergana, 150100, Uzbekistan
yulduz76m@gmail.com (Y.M.), latibjanov92@gmail.com (A.L.)
* Correspondence: latibjanov92@gmail.com; Tel.: +998 88 363 44 46

Abstract:

Aim. To characterise and compare the pathomorphological changes of peripancreatic (regional) and mesenteric lymph nodes in acute and chronic alcoholic pancreatitis, and to define the structural correlates of their impaired immunopoietic and barrier–filtration functions.

Materials and methods. Peripancreatic and mesenteric lymph nodes obtained at autopsy from decedents with a clinically and anamnestically confirmed history of chronic alcohol misuse were examined. Sections were stained with haematoxylin–eosin, van Gieson and alcian blue, and assessed semi-quantitatively across four morphofunctional compartments.

Results. Acute forms were dominated by massive interstitial oedema involving all compartments, subcapsular and intermediate sinus dilatation, capsular disorganisation with fibre destruction, and sequestration of cortical lymphoid follicles. Chronic forms showed parenchymal atrophy with reciprocal proliferation and sclerosis of stromal–vascular structures, capsular thickening, medullary neoangiogenesis, sinus histiocytosis with plasmacytic and fibroblastic accumulation, and reticulosclerosis. In both groups paracortical postcapillary venules lost their high-endothelial phenotype and converted to thin-walled congested veins without transmural lymphocyte migration, and the reticular cell–lymphocyte symbiosis was disrupted.

Conclusion. Alcoholic pancreatitis induces a stage-dependent, non-infectious lymphadenopathy that progresses from oedematous–destructive to atrophic–sclerotic remodelling, providing a structural basis for the impaired regional immune response and lymphatic drainage that accompany the disease.

Keyword: pancreatitis, alcoholic, lymph nodes, autopsy, fibrosis, immunity, cellular, pathology.

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Introduction

Acute pancreatitis remains one of the three leading causes of emergency admission for abdominal pathology worldwide, and its global burden continues to increase in absolute terms despite modest declines in age-standardised rates [1,2]. Analyses of the Global Burden of Disease 2021 dataset show that pancreatitis affected populations across all socio-demographic strata, with the alcohol-attributable fraction accounting for a substantial and geographically uneven share of the total burden [1,3]. Between 1990 and 2021 the disability-adjusted life years attributable to alcohol-related acute pancreatitis rose from approximately 401,671 to 699,335, and the number of deaths nearly doubled, from about 9,972 to 18,749; men carried a 9.3-fold higher DALY rate and a 7.6-fold higher mortality than women, and Eastern Europe showed both the highest burden and the fastest growth [3]. These figures place alcoholic pancreatitis firmly among the socially significant diseases of the working-age population, particularly in the post-Soviet region.

Alcohol is the second most frequent aetiology of acute pancreatitis after biliary disease and underlies up to one-third of cases in some series; among patients hospitalised with alcoholic acute pancreatitis, the 11-month readmission rate reaches 43.1%, and nearly one in five shows signs of evolving alcoholic chronic pancreatitis [4]. Contemporary work indicates that ethanol alone rarely suffices to initiate the disease: co-factors such as smoking, endotoxin exposure, and genetic

predisposition are required for progression [4,5]. The proximate mechanisms are well characterised at the acinar level and involve disturbed intracellular calcium signalling, premature intracellular trypsinogen activation, mitochondrial dysfunction and ATP depletion, impaired autophagic flux, and the release of damage-associated molecular patterns that recruit neutrophils and macrophages [6,7]. Persistent injury activates pancreatic stellate cells, which deposit extracellular matrix and drive the fibro-inflammatory remodelling that defines the chronic phase [8–10].

By contrast, the fate of the lymphoid compartment that drains the inflamed gland has received very little morphological attention. The pancreatic lymphatic network is extensive and follows an imperfect tripartite pattern: the head drains chiefly through pancreaticoduodenal nodes, the body through superior and inferior pancreatic nodes, and the tail through splenic hilar nodes, with all pathways ultimately converging on the coeliac and superior mesenteric groups [6]. This arrangement makes the peripancreatic and mesenteric nodes the obligatory first filter for the enzymes, lipolytic products, acetaldehyde adducts and damage-associated molecular patterns released from the injured gland, and simultaneously the site at which the regional adaptive immune response is generated. Experimental and translational data show that the lymph node is not a passive sieve: fibroblastic reticular cells build the conduit network and organise reactive myeloid niches [11]; subcapsular sinus macrophages capture particulate antigen and shape germinal-centre output [12]; and high endothelial venules of the paracortex control the recruitment of naive lymphocytes and are highly plastic under inflammatory stress [13,14]. Chronic alcohol exposure additionally compromises the intestinal barrier, raising portal and mesenteric lymphatic endotoxin load and imposing a continuous, non-infectious antigenic burden on the same node groups [15,16].

Despite this, we are not aware of any systematic morphological description of regional and mesenteric lymph nodes in human alcoholic pancreatitis. Existing pathological accounts of the disease concentrate on the gland itself — protein plugs, calcifications, perilobular and intralobular fibrosis, paraduodenal variants — and treat the nodes only as staging landmarks [5,17]. This gap is clinically relevant, because the transition of severe acute pancreatitis into a compensatory anti-inflammatory response syndrome with lymphocyte depletion and secondary infection is thought to originate in the secondary lymphoid organs [18,19].

Objective. To characterise and compare the pathomorphological changes of peripancreatic (regional) and mesenteric lymph nodes in acute and chronic alcoholic pancreatitis, and to define the structural correlates of their impaired immunopoietic and barrier–filtration functions.

Materials and Methods

Study design and material This was a retrospective, descriptive, autopsy-based pathomorphological study. The material comprised peripancreatic (regional) and mesenteric lymph nodes together with matched pancreatic tissue, sampled during routine forensic and clinical autopsies of decedents in whom chronic alcohol misuse had been documented in the clinical and anamnestic records. Alcoholic pancreatitis was accepted as present when a compatible clinical history was supported by macroscopic and microscopic findings in the gland (interstitial oedema, fat necrosis, aseptic non-suppurative pancreatonecrosis, intralobular and perilobular fibrosis, or ductal protein plugs) in the absence of biliary obstruction, hypertriglyceridaemia, or other identifiable aetiology.

Inclusion criteria were: (i) a documented history of regular alcohol consumption of at least five years; (ii) morphologically confirmed pancreatitis; and (iii) availability of at least two adequately preserved lymph nodes from the peripancreatic and/or mesenteric groups. Exclusion criteria were: haematolymphoid neoplasia; metastatic carcinoma involving the sampled nodes; documented septicaemia or purulent peritonitis; tuberculous or other granulomatous lymphadenitis; HIV infection; and post-mortem autolysis precluding interpretation. Cases were assigned to two groups: Group I — acute and severe (necrotising) forms, and Group II — chronic forms with a clinically indolent course, in which death resulted from competing or background disease (type 2 diabetes mellitus, hypertensive disease, ischaemic stroke).

Applying these criteria to the autopsy archive yielded a final study cohort of 42 decedents with alcoholic pancreatitis: 24 in Group I (acute and severe forms) and 18 in Group II (chronic forms). A total of 136 lymph nodes were examined, comprising 78 peripancreatic (regional) nodes (44 from Group I, 34 from Group II) and 58 mesenteric nodes (32 from Group I, 26 from Group II).

Histological and histochemical processing

Tissue blocks were fixed in 10% neutral buffered formalin for 24–48 h, dehydrated through graded alcohols, cleared in xylene, and embedded in paraffin. Serial sections of 4–5 μm were cut and stained with haematoxylin and eosin for general morphology, by the van Gieson method for the assessment of collagen and the degree of capsular, trabecular and perivascular sclerosis, and with alcian blue for acid glycosaminoglycans of the ground substance and sinus content. Semi-thin sections were additionally prepared from selected blocks to resolve the cytoplasmic and nuclear detail of medullary sinus endothelial and reticular cells. Slides were examined and photographed on a light microscope at objective magnifications of $\times$10 and $\times$40 (final magnifications $\times$100 and $\times$400); calibrated scale bars are reproduced on each micrograph.

Assessment of lymph node morphology

Each node was evaluated systematically in four morphofunctional compartments: (i) capsule, trabeculae and subcapsular/intermediate sinuses; (ii) cortex with its lymphoid follicles and germinal centres; (iii) paracortex with its postcapillary (high endothelial) venules; and (iv) medulla with its cords and sinuses. For each compartment the following features were graded semi-quantitatively on a four-point ordinal scale (0 = absent, + = mild, ++ = moderate, +++ = marked): interstitial oedema; sinus dilatation; capsular and trabecular sclerosis; follicular hyperplasia versus follicular depletion and sequestration; germinal-centre reactivity; paracortical expansion or denudation; conversion of high endothelial venules to ordinary venous channels with loss of transmural lymphocyte migration; sinus histiocytosis; plasmacytic, fibroblastic and reticulocytic proliferation; medullary neoangiogenesis; and lipomatosis. Grading was performed independently by two pathomorphologists blinded to group allocation; discordant scores were resolved by joint review at a double-headed microscope.

Ethics

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Ethics Committee of Fergana Medical Institute of Public Health (protocol code K29, approval date 08.26.2025). Only archival, de-identified post-mortem material was used.

Statistical analysis

Given the descriptive design and the ordinal nature of the grading scale, findings are presented as absolute counts and proportions of affected nodes per compartment. Between-group comparison of ordinal scores was performed with the Mann–Whitney U test, and comparison of proportions with Fisher's exact test; a two-sided $p < 0.05$ was regarded as significant. Inter-observer agreement was expressed as weighted Cohen's kappa. Calculations were performed in standard statistical software.

Results

Peripancreatic lymph nodes in the study material were consistently larger than nodes of other regions, reaching up to 20 mm in maximum dimension, which is consistent with their dual immunopoietic and barrier–filtration workload. Across both groups the nodes departed from the normal architectural template in a reproducible manner, and the pattern of departure differed systematically between acute and chronic forms. Findings are presented below by morphofunctional compartment; the semi-quantitative summary is given in Table 1.

Generalised interstitial oedema and sinus dilatation

The single most conspicuous feature of the acute forms was massive oedema affecting all morphofunctional zones simultaneously (Figure 1). The capsule and trabeculae were distended and frayed by transudate, their cells rarefied and their collagen bundles split and deformed. The subcapsular and intermediate sinuses were widely dilated, and the cellular and fibrillar structures within them were correspondingly sparse. Lymphoid follicles of the cortex were themselves oedematous, with reticular cells and lymphocytes pulled apart and loosely dispersed. Alcian blue staining showed increased ground-substance metachromasia in the widened interstitial spaces, in keeping with an exudative rather than a purely hydraulic process.

This degree of intranodal oedema is not simply a passive consequence of raised afferent lymph pressure. Because the pancreatic lymphatics carry activated proteases, free fatty acids released by lipolysis, and damage-associated molecular patterns directly into the subcapsular sinus, the node is

exposed to a chemically aggressive afferent stream, and the resulting rise in endothelial and conduit permeability is best interpreted as an active inflammatory response of the nodal microvasculature.

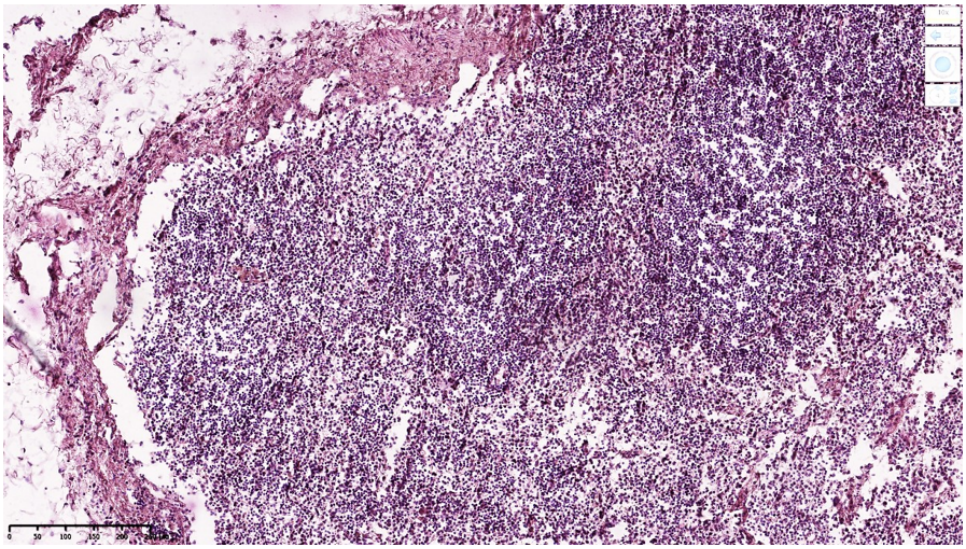

Figure 1. Regional lymph node in alcoholic pancreatitis: marked oedema of all morphofunctional zones, with fraying of the capsule and rarefaction of the cortical lymphoid tissue. Haematoxylin–eosin, ×100.

Sequestration and depletion of cortical lymphoid follicles

Where oedema was most severe, it disrupted the histotopographic organisation of the node itself. Lymphoid follicles lost their confluence with the surrounding cortex and became separated into discrete, sharply demarcated aggregates — a pattern best described as follicular sequestration (Figure 2). Within such sequestrated follicles the reticular framework was fragmented, and lymphocytes were detached from the reticular cells and distributed at random.

Germinal centres, when identifiable, lacked the polarised light-zone/dark-zone architecture and the tingible-body macrophages that mark an active humoral response. In several nodes the cortex showed follicles of markedly unequal size without reactive foci in the germinal centres, indicating that the follicular compartment had been structurally disorganised rather than functionally recruited. In the chronic group, by contrast, a subset of nodes retained secondary follicles with pale germinal centres and B-lymphoblastic populations of varying density, suggesting that a low-grade, non-infectious reactive response persists as long as the follicular scaffold is preserved.

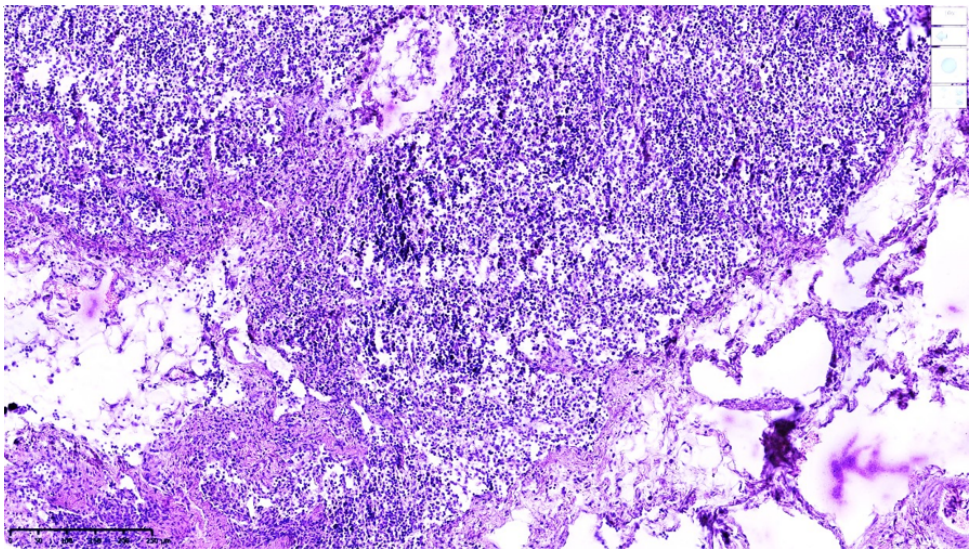

Figure 2. Regional lymph node in alcoholic pancreatitis: cortical lymphoid follicles are fragmented and sequestrated; the reticular framework is disrupted. Haematoxylin–eosin, ×100.

Capsular disorganisation and destruction

The connective-tissue structures of the capsule underwent frank disorganisation (Figure 3). Collagen bundles were split, fragmented and destroyed; capsular cells were disorderly arranged and showed necrobiotic change. The peripheral sinus beneath the capsule was sharply dilated, and the connective-tissue strands that normally anchor it to the cortex were disrupted. Van Gieson staining confirmed loss of the ordered fuchsinophilic architecture in these areas.

Within the sinus lumen, lymphocytes and macrophages lay in disarray. The portion of each cortical follicle abutting the subcapsular sinus was the most severely affected, with frayed borders and reduced lymphocyte density — an appearance consistent with loss of the subcapsular sinus macrophage layer that normally forms the immunological interface between afferent lymph and the follicle.

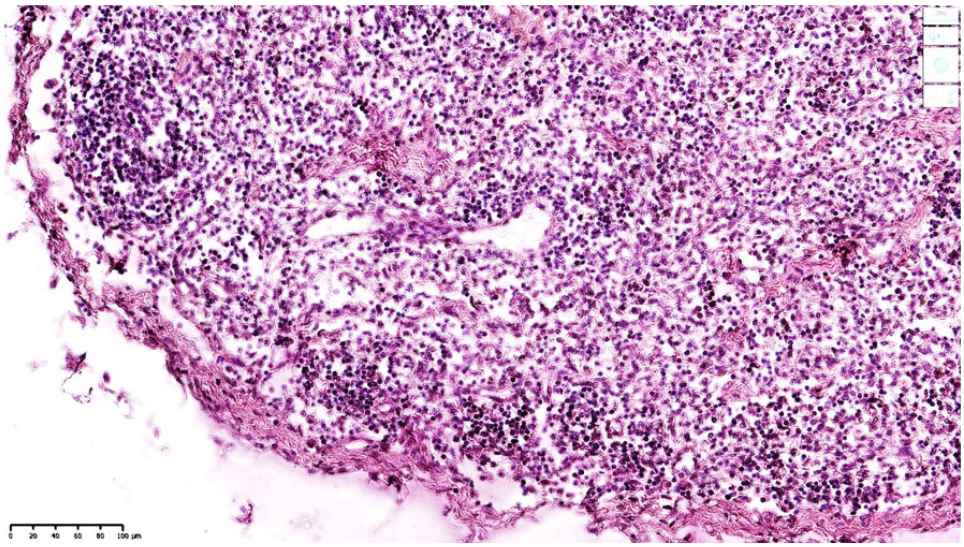

Figure 3. Regional lymph node in alcoholic pancreatitis: the capsule is frayed by oedema, sclerosis, destruction and disorganisation; cellular and fibrillar structures are destroyed. Haematoxylin–eosin, ×400.

Parenchymal atrophy and stromal–vascular proliferation in severe and chronic forms

In decedents with severe and long-standing disease the balance between parenchyma and stroma was inverted (Figure 4). The immunopoietic parenchyma was extensively atrophic, whereas the stromal–vascular structures responsible for the barrier–filtration function were proliferated and thickened. Between these structures, chiefly within the sinus lumina, accumulations of lymphocytes at various stages of destruction were identified.

This reciprocal relationship — parenchymal loss with stromal gain — is the morphological signature of a node that has been converted from an immunopoietic organ into a fibrous filter. It corresponds closely to the reticulosclerosis and reticulocytosis noted in the chronic group and provides a structural explanation for the reduced drainage capacity that predisposes to recurrent acute exacerbations.

Loss of the high endothelial venule phenotype in the paracortex

A consistent and, in our view, functionally decisive finding concerned the postcapillary venules of the paracortex (Figure 5). In both groups these vessels had lost their characteristic tall, cuboidal endothelium and had been converted into ordinary thin-walled veins with widened, blood-filled lumina. Critically, no transmural migration of lymphocytes was observed across the walls of these converted vessels.

Because entry of naive lymphocytes into a node occurs almost exclusively across high endothelial venules, their phenotypic conversion effectively closes the recruitment gate. Nodes showing this change must therefore be regarded as having ceased to perform their immunopoietic function, irrespective of the amount of residual lymphoid tissue.

The paracortical stroma itself showed oedema and haemorrhage, proliferation of macrophages containing abundant haematoxyphilic phagocytosed inclusions, and small to medium-sized lymphocytes confined to the inter-vascular territories. At high magnification the paracortex was rarefied

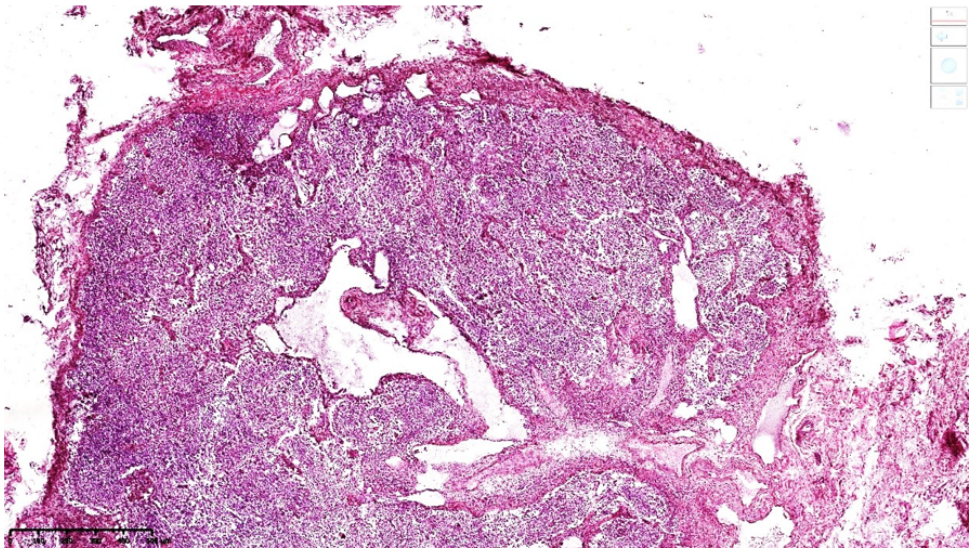

Figure 4. Regional lymph node in the chronic form of alcoholic pancreatitis: atrophy of the nodal parenchyma with proliferation of stromal–vascular structures. Haematoxylin–eosin, ×100.

and frayed; even the connective-tissue cells of the stroma were disrupted, with severed fibres lying as isolated fragments. Reticular cells were detached from one another, fragmented, and showed cytoplasmic dystrophy, so that the lymphocytes of this zone lay free in the interstitial space. Their weakly haematoxyphilic nuclei indicate a functionally passive state.

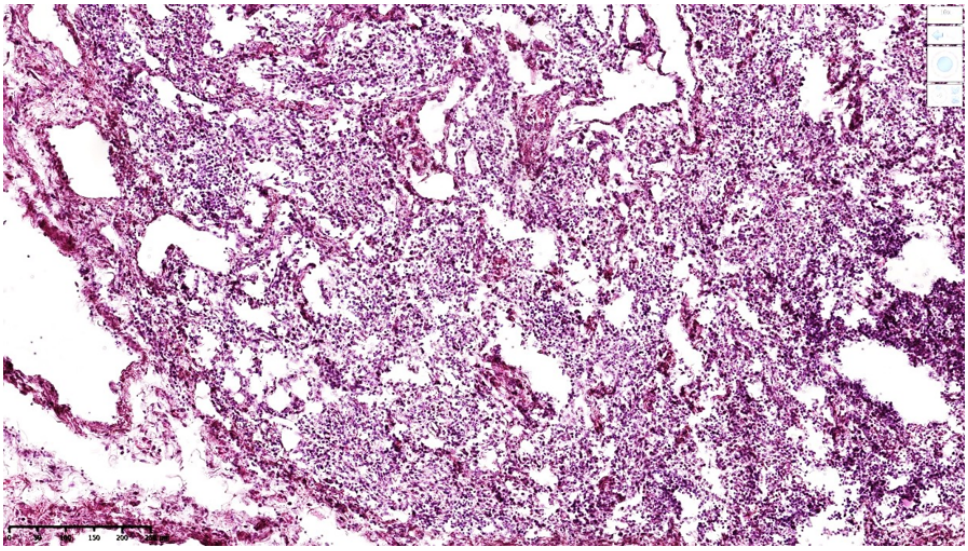

Figure 5. Paracortical zone of a regional lymph node in alcoholic pancreatitis: postcapillary venules have converted into ordinary veins; no transmural lymphocyte migration is present. Haematoxylin–eosin, ×100.

Medullary sinus dilatation and sinus histiocytosis in mesenteric nodes

Mesenteric nodes from middle-aged decedents showed pronounced dilatation of the medullary sinusoids, whose lumina were massively widened (Figure 6). Plasma cells and histiocytes were identified both within the sinus lumina and along the medullary cords. This sinus histiocytosis, combined with a plasmacytic component, is the expected reaction of a node receiving a continuous non-microbial particulate and lipid load — precisely what would be predicted from the transport of lipid-rich material and acetaldehyde–protein adducts from the interstitial spaces of the inflamed gland.

Notably, neutrophils were scarce in all sinuses examined, whereas macrophages were abundant around the reticular arcades of the corticomedullary zone. The combination of macrophage dominance

with paucity of neutrophils supports an aseptic, metabolically driven inflammation rather than a bacterial lymphadenitis.

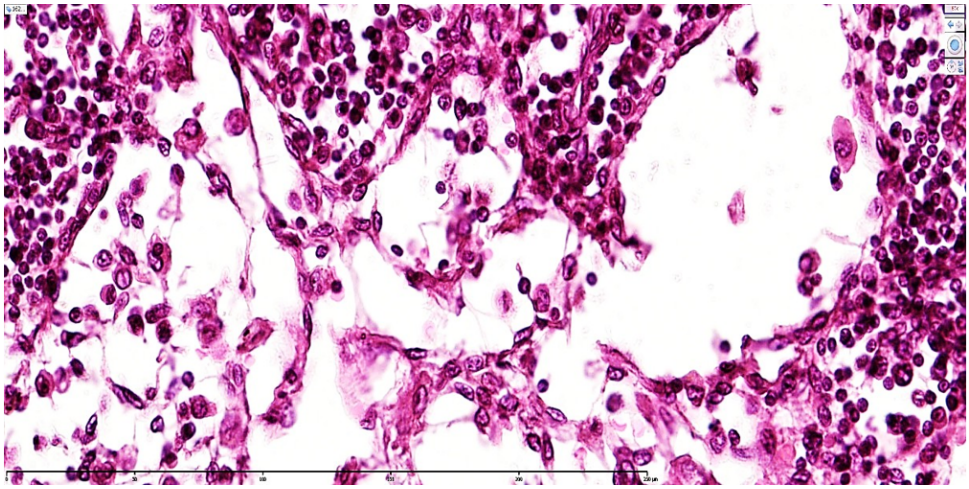

Figure 6. Mesenteric lymph node in alcoholic pancreatitis, middle-aged decedent: dilatation of the medullary sinusoids (1) with plasma cells and histiocytes in the lumina and medullary cords. Haematoxylin–eosin, ×400.

Corticomedullary remodelling and stromal fibrosis

Tangential sections along the medullary cords of the corticomedullary zone demonstrated sinusoidal spaces alternating with reticular bands (Figure 7). The lumina contained plasma cells and histiocytes, and the stroma showed fibrous tissue components at varying stages of maturation. In many areas the inter-sinus soft cords were sclerosed and had been converted into dense fibrous connective tissue; elsewhere they persisted as relatively thick bundles packed with lymphoid cells. Blood vessel walls within these cords were thickened by sclerosis and stood out from the surrounding lymphoid tissue.

Between the cortical and subcapsular zones the stroma formed coarse-fibred reticular meshes, an appearance indicative of chronic hypoxia and of an increased connective-tissue component in the node. Taken together with the maturational heterogeneity of the fibrous tissue, this indicates that the process is chronically evolving rather than acute.

In semi-thin sections of the medulla the endothelial cells lining the sinus walls were flattened and elongated, their cytoplasmic processes covering the vessel surface continuously. Beneath and beside them lay reticular cells with relatively large, delicate nuclei. These nuclei were deformed, with heterochromatin almost entirely absent from the karyoplasm — a sign of disturbed nuclear protein turnover — and with nucleoli displaced to the periphery or absent altogether. Their cytoplasm stained palely and organelles were poorly resolved, consistent with dystrophy and destruction. As a result, lymphocytes had moved away from the reticular cells and lay separately, so that the normal reticular cell–lymphocyte symbiosis was lost.

Capsular thickening, histiocytic proliferation and medullary neoangiogenesis

In an elderly decedent (58 years) with chronic alcoholic pancreatitis the mesenteric node showed a thickened capsule with massive histiocytic proliferation (Figure 8). Foci of neoangiogenesis, comprising dense networks of small-calibre and capillary vessels, were identified in the medulla. Plasma cells, histiocytes and fibroblasts were arranged along the margins of the sinusoidal spaces.

Medullary neoangiogenesis in a node whose high endothelial venules have been lost is a paradoxical but informative combination: vascular expansion is occurring, yet it is of a type that supports stromal and myeloid rather than lymphocytic traffic. In a proportion of nodes the medullary sinuses were deformed and of markedly unequal size and shape, and adipose tissue had extended into the nodal substance (lipomatosis), completing the picture of chronic involution.

Discussion

Two morphological programmes, one aetiology

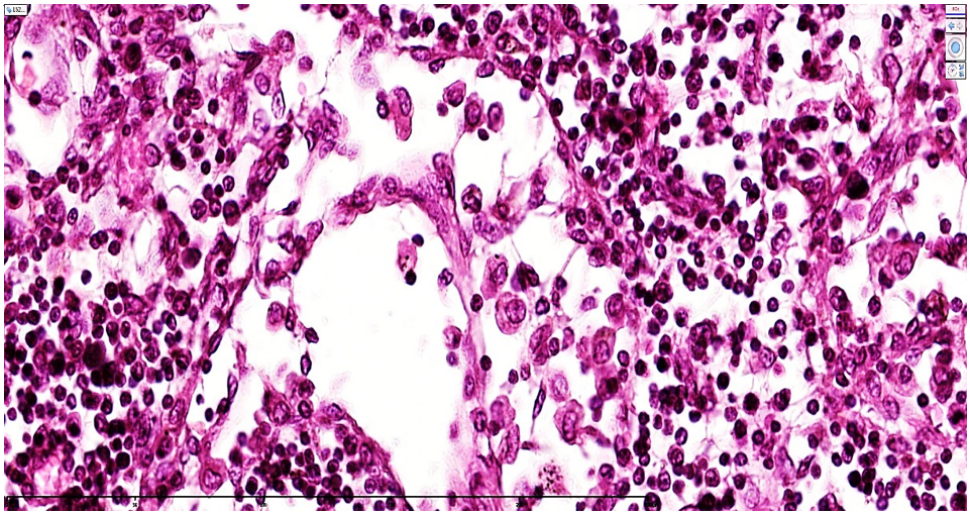

Figure 7. Corticomedullary zone of a mesenteric lymph node in alcoholic pancreatitis: tangential section along the medullary cords showing sinusoidal spaces and reticular bands (1) with plasma cells and histiocytes; fibrous tissue components of varying maturity are present in the stroma. Haematoxylin–eosin, ×400.

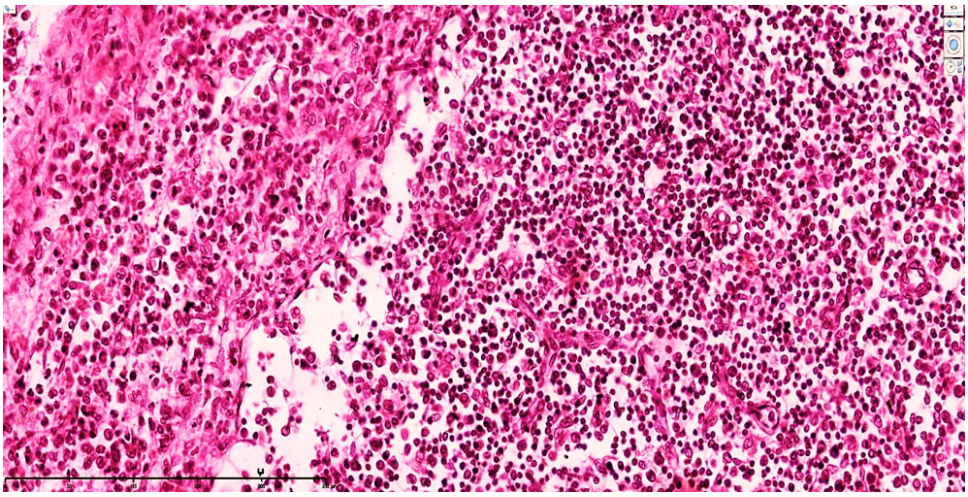

Figure 8. Mesenteric lymph node in chronic alcoholic pancreatitis, 58-year-old decedent: thickened capsule with massive histiocytic proliferation; foci of neoangiogenesis in the medulla; plasma cells, histiocytes and fibroblasts along the sinusoidal margins. Haematoxylin–eosin, ×100.

The principal finding of this study is that alcoholic pancreatitis does not produce a single lymph node lesion but two sequential morphological programmes. The first, dominating the acute and severe forms, is oedematous and destructive: transudation into every compartment, sinus dilatation, capsular disorganisation, and mechanical sequestration of cortical follicles. The second, dominating the chronic forms, is atrophic and sclerotic: loss of immunopoietic parenchyma with compensatory expansion and fibrosis of the stromal–vascular scaffold, sinus histiocytosis, reticulosclerosis, medullary neoangiogenesis and lipomatosis. Recognising these as stages of one process, rather than as separate entities, is important for interpreting nodal biopsies and intraoperative frozen sections in patients with an alcohol history, where the appearances may otherwise be mistaken for a lymphoproliferative or granulomatous disorder.

The paracortical venule as the functional bottleneck

The conversion of paracortical postcapillary venules into ordinary thin-walled veins, with complete absence of transmural lymphocyte migration, is the change with the clearest functional consequence. High endothelial venules are specialised vascular structures whose tall endothelium expresses the peripheral node addressin and chemokines required for L-selectin–mediated tethering and subsequent diapedesis of naive lymphocytes; they are the principal portal of lymphocyte entry

Table 1. Semi-quantitative comparison of pathomorphological changes in peripancreatic and mesenteric lymph nodes in acute and chronic alcoholic pancreatitis.

Compartment	Morphological feature	Group I: grade, n/N (%)	Group II: grade, n/N (%)	p-value
Capsule and trabeculae	Oedema and fibre fraying	+++, 66/76 (86.8%)	+, 9/60 (15.0%)	< 0.001
	Sclerosis and thickening	+, 12/76 (15.8%)	+++, 54/60 (90.0%)	< 0.001
	Necrobiosis of capsular cells	++, 38/76 (50.0%)	+, 14/60 (23.3%)	0.002
Sinuses	Subcapsular / intermediate sinus dilatation	+++, 64/76 (84.2%)	++, 33/60 (55.0%)	< 0.001
	Sinus histiocytosis	+, 10/76 (13.2%)	+++, 51/60 (85.0%)	< 0.001
	Plasmacytic accumulation	+, 13/76 (17.1%)	++, 30/60 (50.0%)	< 0.001
Cortex	Follicular oedema and sequestration	+++, 61/76 (80.3%)	+, 8/60 (13.3%)	< 0.001
	Follicular hyperplasia with secondary follicles	0/+, 6/76 (7.9%)	++, 29/60 (48.3%)	< 0.001
	Reactive germinal centres	0, 0/76 (0.0%)	+, 11/60 (18.3%)	< 0.001
Paracortex	Oedema and haemorrhage	+++, 63/76 (82.9%)	+, 10/60 (16.7%)	< 0.001
	Conversion of HEV to ordinary veins	+++, 71/76 (93.4%)	+++, 55/60 (91.7%)	0.76
	Transmural lymphocyte migration	0, 0/76 (0.0%)	0, 0/60 (0.0%)	n.a.
	Macrophage proliferation with phagocytosed inclusions	++, 35/76 (46.1%)	+++, 52/60 (86.7%)	< 0.001
Medulla	Sinus deformation and unequal calibre	++, 32/76 (42.1%)	+++, 50/60 (83.3%)	< 0.001
	Reticulosclerosis of medullary cords	+, 11/76 (14.5%)	+++, 49/60 (81.7%)	< 0.001
	Neoangiogenesis	+, 9/76 (11.8%)	++, 26/60 (43.3%)	< 0.001
	Lipomatosis	0, 0/76 (0.0%)	++, 22/60 (36.7%)	< 0.001
Global	Parenchymal atrophy	+, 14/76 (18.4%)	+++, 53/60 (88.3%)	< 0.001
	Stromal–vascular proliferation	+, 13/76 (17.1%)	+++, 55/60 (91.7%)	< 0.001
	Loss of reticular cell–lymphocyte symbiosis	++, 40/76 (52.6%)	+++, 54/60 (90.0%)	< 0.001

0 = absent; + = mild; ++ = moderate; +++ = marked (modal score per group). n/N (%) — number and proportion of nodes in the group showing the feature at the stated grade or above. HEV — high endothelial venule. p-values from Fisher's exact test (proportions) / Mann–Whitney U test (ordinal grade comparison); n.a. — not applicable (identical, null, distribution in both groups). Inter-observer agreement for grading: weighted Cohen's κ=0.82 (95% CI, 0.76–0.88).

into a node and are known to be highly plastic, dedifferentiating rapidly when the local signals that maintain them are withdrawn [13,14]. The dedifferentiated phenotype we observed therefore represents a physical interruption of lymphocyte recruitment.

This finding integrates well with clinical observations in severe acute pancreatitis, where an early pro-inflammatory phase is followed by a compensatory anti-inflammatory response syndrome characterised by lymphocyte depletion, impaired antigen presentation and a high risk of secondary infection of pancreatic necrosis [18]. Much attention has been paid to circulating lymphocyte apoptosis as the source of this immunoparalysis; our data suggest that failure of lymphocyte recruitment into the draining node is an equally plausible, and structurally demonstrable, contributor.

Disruption of the reticular scaffold and its immunological cost

The dissociation of lymphocytes from reticular cells that we observed in both the paracortex and the medulla is more than a descriptive detail. Fibroblastic reticular cells generate the conduit system, provide the survival factors IL-7 and CCL19/CCL21 that retain T cells in the paracortex, and organise reactive myeloid niches within human nodes [11]. Loss of the reticular cell–lymphocyte symbiosis therefore implies loss of the trophic and positional cues on which lymphocyte survival and antigen encounter depend. The nuclear findings in semi-thin sections — deformed nuclei, near-total loss of heterochromatin, marginated or absent nucleoli, pale organelle-poor cytoplasm — indicate that the reticular cells themselves are dystrophic, so the defect is intrinsic to the stroma rather than secondary to lymphocyte loss.

In parallel, the fraying of the subcapsular region and the disorderly distribution of macrophages within the dilated sinus point to disturbance of the subcapsular sinus macrophage layer, which normally captures particulate antigen from afferent lymph and delivers it to follicular B cells; experi-

mental disruption of this layer reduces germinal centre output [12]. The absence of reactive germinal centres in the acute group is consistent with such a mechanism.

An aseptic, metabolically driven lymphadenitis

The cytological composition of the reaction — abundant macrophages and histiocytes, plasmacytic and fibroblastic accumulation, and conspicuously few neutrophils — argues that the nodal inflammation in alcoholic pancreatitis is aseptic and metabolically driven rather than microbial. Neutrophils do enter secondary lymphoid organs and modulate the adaptive response during infection [19]; their paucity here therefore carries positive diagnostic weight. The focal T-lymphocytic hyperplasia observed in some paracortical zones of the chronic group likewise indicates a non-infectious inflammatory response driven by metabolic injury.

The likely afferent load is threefold. First, activated proteases and lipolytic products reach the node directly through the pancreatic lymphatics, whose tripartite drainage converges on precisely the coeliac and superior mesenteric groups examined here [6]. Second, chronic ethanol exposure disrupts intestinal tight and adherens junctions and produces gut leakiness and endotoxaemia, so that the mesenteric nodes receive a continuous lipopolysaccharide burden [15,16,20]. Third, the non-active transport of lipid-rich material from the intercellular spaces of the gland into the lymphatics contributes to pancreatolipomatosis and, we would argue, to the nodal lipomatosis observed in the chronic group.

Relationship to fibrogenesis in the gland

The sclerosis we documented in the nodal capsule, trabeculae, medullary cords and perivascular tissue mirrors the fibro-inflammatory remodelling of the gland itself. Pancreatic stellate cells are the principal effectors of pancreatic fibrosis, activated by ethanol metabolites, oxidative stress, cytokines and acinar-derived mediators such as sphingosine-1-phosphate, which promotes stellate cell autophagy and activation [8–10]. Whether the same signalling axes act on nodal fibroblastic reticular cells is not established, but the parallel timing and the shared afferent milieu make it a testable hypothesis. If confirmed, nodal fibrosis would qualify as an accessible surrogate of the fibrogenic activity of the disease.

Medullary neoangiogenesis fits the same framework. Lymph node angiogenesis is tightly coupled to the immune response and to stromal expansion [14], and lymphatic and vascular remodelling modulate the resolution of chronic inflammation in other organs [21]. The coexistence, in our material, of new small-calibre vessels with dedifferentiated high endothelial venules suggests that vascular expansion in these nodes serves stromal and myeloid, rather than lymphocytic, traffic.

Clinical implications

Three practical points follow. First, in decedents and patients with an alcohol history, peripancreatic and mesenteric nodal enlargement should not be interpreted as evidence of infection or neoplasia without histological confirmation; the appearances described here are reactive and aetiologically specific in context. Second, the combination of parenchymal atrophy, reticulosclerosis and loss of high endothelial venules provides a structural rationale for the reduced lymphatic drainage capacity of the peripancreatic basin, which may predispose to the acute exacerbations, oedematous crises and pancreatonecrosis that punctuate the chronic course. Third, if failure of lymphocyte recruitment into the draining node contributes to the immunoparalysis of severe acute pancreatitis, then strategies aimed at preserving nodal stromal integrity deserve exploration alongside the systemic immunomodulatory approaches currently under study [18,22].

Limitations

This study has several limitations. It is a descriptive autopsy series without a matched control group of nodes from decedents free of alcohol misuse, so the specificity of the changes to alcoholic pancreatitis, as opposed to chronic alcoholism in general or to agonal and terminal events, cannot be established definitively. Post-mortem interval and terminal hypoxia may accentuate oedema and cellular dissociation, and some of the fine cytological changes described in semi-thin sections must be interpreted with this in mind. The grading scale is ordinal and observer-dependent, and morphometric quantification of follicle number, paracortical area and vessel density was not performed. Finally, and most importantly, immunohistochemical phenotyping — CD3, CD20, CD21, CD68, PNAd/MECA-79, D2-40, α-smooth muscle actin and Ki-67 — was not available for the present series; the assignment

of lymphocyte subsets and of the high endothelial venule phenotype therefore rests on morphology alone. Prospective immunohistochemical and morphometric confirmation is the logical next step.

Conclusions

In this autopsy series, alcoholic pancreatitis was morphologically associated with a stage-dependent, non-infectious lymphadenopathy of the regional peripancreatic and mesenteric lymph nodes, which appeared to progress from an oedematous–destructive pattern in acute and severe forms to an atrophic–sclerotic pattern in chronic forms.

Acute and severe forms were characterised by massive oedema of all morphofunctional zones, dilatation of the subcapsular and intermediate sinuses, disorganisation and destruction of the capsule, and sequestration of cortical lymphoid follicles with absent germinal-centre reactivity.

Chronic forms were characterised by atrophy of the immunopoietic parenchyma with reciprocal proliferation and sclerosis of stromal–vascular structures, capsular thickening, sinus histiocytosis with plasmacytic and fibroblastic accumulation, reticulosclerosis of the medullary cords, medullary neoangiogenesis and lipomatosis.

In both groups the paracortical postcapillary venules lost their high endothelial phenotype and converted into thin-walled congested veins devoid of transmural lymphocyte migration, and the symbiosis between reticular cells and lymphocytes appeared disrupted. These findings are morphologically consistent with impairment of nodal immunopoietic function, although this functional interpretation could not be verified directly in autopsy material and requires confirmation by immunohistochemical and functional studies.

The predominance of macrophages and histiocytes with a paucity of neutrophils is more consistent with an aseptic, metabolically driven lymphadenitis than with a bacterial process. In the absence of a non-alcoholic control group, however, this interpretation, together with the apparent predominance of the chronic over the acute morphological programme in the natural history of the disease, should be regarded as a hypothesis-generating observation rather than a definitive conclusion.

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Ethics approval The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Fergana Medical Institute of Public Health (protocol code K29, approval date 08.26.2025). Only archival, de-identified post-mortem material was used.

Consent for publication. Patient consent was waived because the study used only de-identified archival autopsy material and no individual can be identified from the data or images presented.

Data Availability Statement The histological slides, digital micrographs and anonymised grading datasets that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly archived because of institutional restrictions on post-mortem material.

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Abbreviations

AP acute pancreatitis

DALY	disability-adjusted life year
AP	acute pancreatitis
DALY	disability-adjusted life year
DAMP	damage-associated molecular pattern
FRC	fibroblastic reticular cell
GBD	Global Burden of Disease
HEV	high endothelial venule
H&E	haematoxylin and eosin
LPS	lipopolysaccharide
PSC	pancreatic stellate cell

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