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Lymph node or lymphoid aggregate? Impact on cancer resection quality, clinical prognosis, and tumor staging

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Summary. The clinical outcome of most cancer patients depends on the stage of the primary tumor, the lymph node status, and if distant metastases are present. According to the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC), the Tumor Node Metastasis (TNM) classification of malignant tumors requires the examination of a minimum number of regional lymph nodes for each type of cancer to fulfill the criteria of high-quality surgical oncology. Due to the daily challenge of collecting an appropriate number of lymph nodes and time constraints when processing and assessing tissue samples, pathologists may be tempted to identify every histological lymphoid structure mimicking a lymph node as a "true" lymph node.

Faced with this issue, we propose to resolve it by specifying histological characteristics to differentiate lymphoid aggregates from "true" lymph nodes. To find a minimum consensus, we suggest defining as lymph nodes only those lymphoid structures composed of lymphoid cells encapsulated by a complete or incomplete fibrous capsule.

Key words: Lymph node, Normal tissue, Quality of pathology, Quality management, Histology, Standard protocol, Oncology, Lymphoid aggregate, Tumor deposits, Tumor satellites

Introduction

When asked, 'What is a lymph node?', artificial intelligence (AI) specifies that "A lymph node is a small, bean-shaped organ that plays a crucial role in the lymphatic system, which is a part of the immune system" (GPT-3.5, OpenAI, https://chat.openai.com/, date of query 24th January 2024). In histology and microanatomy classes, photographs and schematic drawings of mature lymph nodes are presented, depicting idealistic organs with clearcut morphology in strictly plane-oriented tissue sections, allowing the identification of compartmentalized lymphoid cells encapsulated and embedded in a delicate meshwork of connective tissue, entering and exiting lymph vessels, and supplying blood vessels. Every day, pathologists encounter histological lymphoid structures that do not fulfill all morphological criteria of a "true" lymph node. The following proposed definitions serve to provide histological criteria that pathologists can use to classify questionable lymphoid formations.

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Morphology of the normal lymph node

The normal adult human is well equipped with numerous lymph nodes. The body contains roughly 450 to 800 lymph nodes, the majority of which are located within the abdomen and pelvis followed by the head and neck (up to 300 lymph nodes), and the thorax (about 100 lymph nodes) (George, 2016; Medeiros et al., 2017; Chaturvedi et al., 2022). During development, the lymph node rudiment consists of diffuse aggregates of lymphocytes, first detectable in the 10t^{h} week of gestation. In the 12th week, the differentiation of the nodal cortex and medulla begins (Bailey and Weiss, 1975; Markgraf et al., 1982; von Gaudecker, 1993) (Fig. 1). The mature lymph node microarchitecture with all subsets of cells, as known in adults, is developed during the second fetal trimester and the immunocompetence of a lymph node is acquired shortly after birth (Westerga and Timens, 1989; Drayton et al., 2006).

In standard textbooks of normal human anatomy (Lowe and Anderson, 2015; George, 2016; Medeiros et al., 2017; Gartner, 2021; Drake et al., 2022), a mature lymph node is morphologically described as a bean-shaped encapsulated lymphoid structure including a hilum with entering blood vessels and an efferent lymphatic vessel, as well as multiple afferent lymphatic vessels at the opposite and convex side of the capsule (Fig. 2). It is the capsule, which in routinely

Hematoxylin and Eosin (HE)-stained tissue sections, discriminates a lymph node from simple lymphoid aggregations (Fig. 4). These aggregations may be more highly organized than previously assumed at first inspection (see below under paragraph 4).

The lymph node capsule is subdivided into two zones: (1) a "floor" that contains lymphatic endothelial cells and (2) a "roof" that consists of fibers of extracellular matrix with embedded fibroblasts (Assen et al., 2022) (Fig. 3A). The capsule defines the compartment of the lymphatic sinuses, which transport the lymph fluid containing soluble antigens, pathogens and leukocytes including antigen-presenting cells (APC) into the lymph node. The adjacent subcapsular sinuses provide an exit route for activated and recirculating lymphocytes filtering into the efferent lymphatic vessel (Bekkhus et al., 2023).

The lymph node is subdivided into three zones: (1) Cortex, composed of the fibrous capsule, primary and secondary lymphatic follicles, and the interfollicular

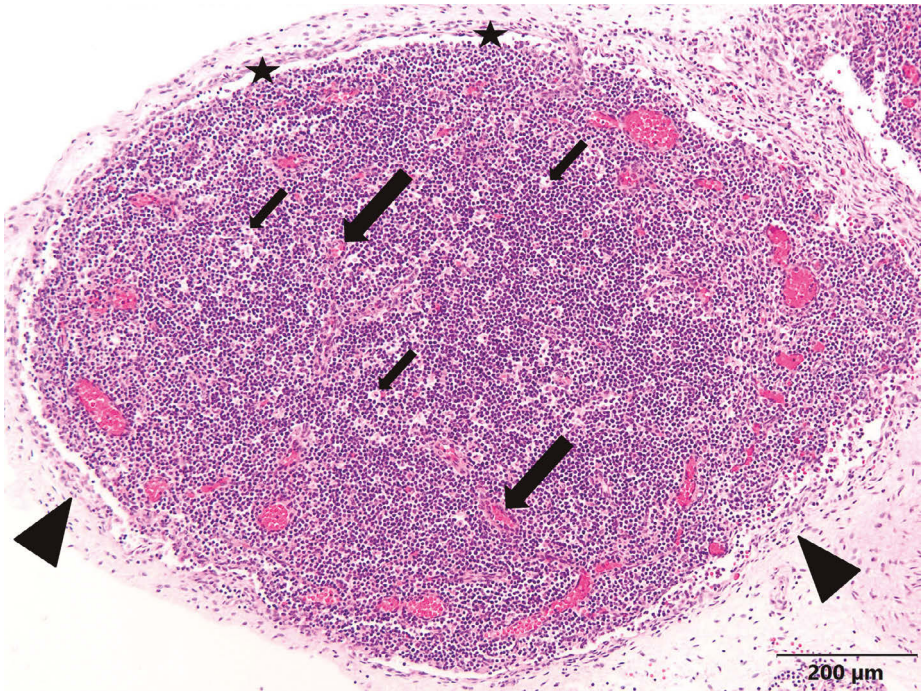

Fig. 1. Lymph node developing from the mesentery of the small intestine of a male fetus in the 20th week of gestation. The parenchyma consists of small lymphoid cells with scattered histiocytes (small arrows). In this example, the cortex and medulla cannot be clearly distinguished. Some high endothelial venules are already present (large arrows). Proliferating fibroblasts are condensed, forming the capsule (arrowheads) with a well-developed subcapsular sinus (stars).

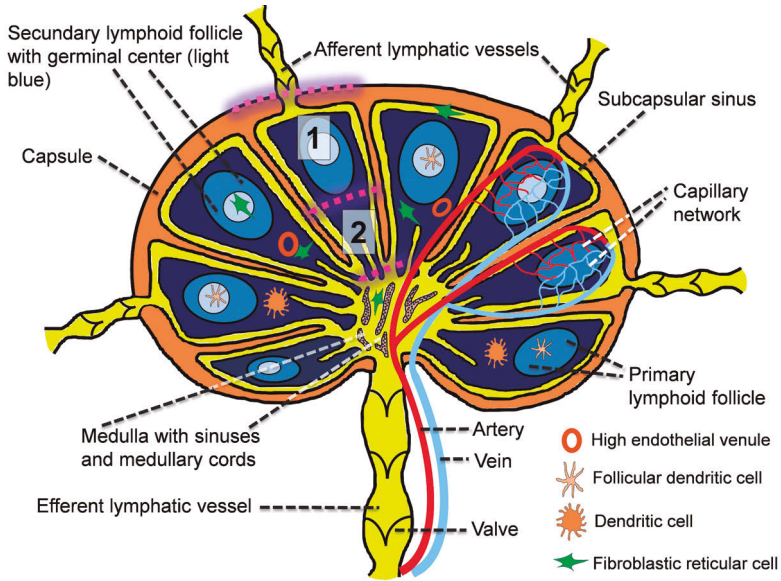

Fig. 2. Schematic drawing of a mature lymph node. The cartoon illustrates the basic histological structure of a lymph node with the most important cells involved in its composition. The pink dashed lines delineate the border between the cortex (1) and paracortex (2). The lymphatic fluid (yellow) is taken up through the afferent lymph vessels, passes through the parenchyma, where immunological processes take place, and exits the lymph node through the efferent vessel. Note that fibroblastic reticular cells include all subtypes, i.e., marginal, T-cell zone, CXCL12-producing, perivascular (around high endothelial venules), and medullary fibroblastic cells (Perez-Shibayama et al., 2019). The original cartoon of the lymph node comes from Cheng et al. (2022) (CC BY license is accessible at https://creativecommons.org/licenses/by/4.0/) and has been substantially modified by the authors of this article.

cortex; (2) Paracortex, composed of the "deep cortical unit" homed by peripheral T-lymphocytes interacting with dendritic cells (DC) as well as containing arterioles, high endothelial venules and paracortical sinuses; and (3) Medulla and sinuses, composed of paired arterioles and venules, fibroblastic reticular network, and lymphoid cells. The lymph node parenchyma is composed of T and B lymphocytes, APC, macrophages, DC, follicular dendritic cells (FDC), and stromal cells (Figs. 2, 3). Some of the stromal cells forming the lymph node meshwork perform special tasks and are named "fibroblastic reticular cells" (FRC). It is assumed that signals from lymphocytes induce FRC to form the meshwork that regulates the movement and interactions of immune cells within the lymph node (Katakai et al., 2004; Perez-Shibayama et al., 2019; Novkovic et al., 2020). FRC synthesize collagen type III fibrils, which they surround with slender cytoplasmic processes that prevent the interaction of these so-called reticular fibers with the lymphatic fluid (Kaldjian et al., 2001). This

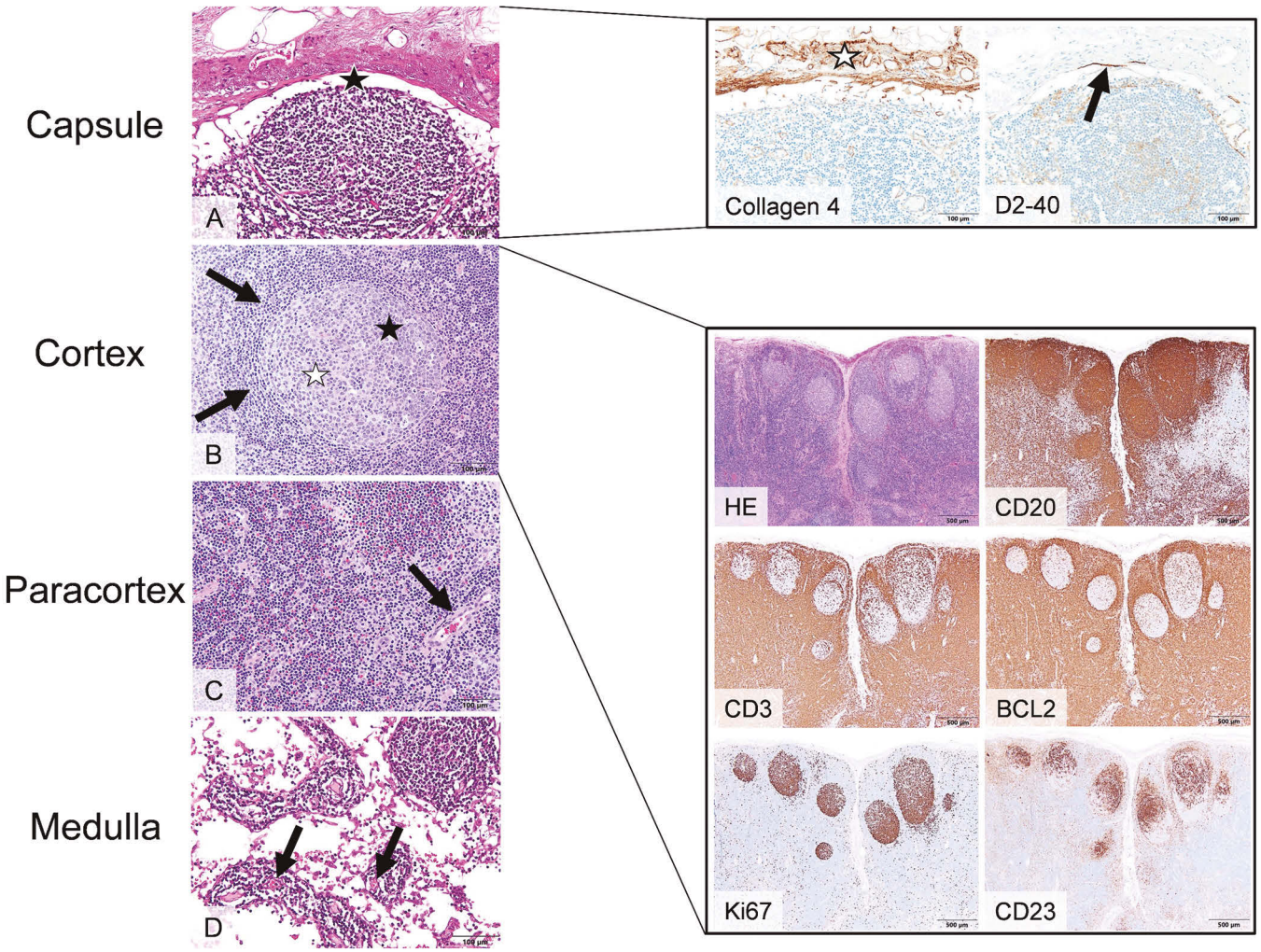

Fig. 3. Microphotographs depicting the zonal compartmentalization of a lymph node, i.e., in capsule **(A)**, cortex **(B)**, paracortex **(C)**, and medulla **(D)**. **A.** The capsule separates the subcapsular sinus (black star) from the parenchyma. The right upper box discloses immunohistochemical findings. The capsular stroma is intensively immunostained for collagen 4 (white star), representing the "roof". The "floor" is formed by lymphatic endothelial cells whose delicate processes are immunostained for D2-40 (podoplanin) (arrow). **B.** Lymph node cortex from the cervical region of a 24-year-old female. Depicted is a representative follicle containing a germinal center surrounded by the mantle zone (arrows). The germinal center (GC) is subdivided into light (white star) and dark zones (black star). The light zone contains centrocytic B cells, T follicular helper cells, and follicular dendritic cells. The dark zone consists of centroblastic B cells and CXCL12-expressing reticular cells. The GC B cells alternate between these zones to gain efficient antibody affinity maturation (Rodda et al., 2015). The right lower box depicts selected immunostaining of the cortex at lower magnifications. The marker antigens are commonly used to detect B cells (CD20), T cells (CD3), and follicular dendritic cells (CD23). The GCs contain numerous proliferating B cells staining for Ki67. The BCL2 protein blocks the apoptotic death of GC lymphocytes and is normally expressed by B cells in the mantle zone but not by those of the GC. **C.** The paracortex contains numerous T lymphocytes. The arrow points to a high endothelial venule. **D.** The medulla is composed of a fibroblastic reticular network with densely packed lymphocytes separated by largely spaced sinuses. Arrows point to high endothelial venules. HE stains in A-D.

coverage is necessary, otherwise the blood clotting system would be activated by the naked collagen fibers (Kuivaniemi and Tromp, 2019). Comprehensive, more detailed descriptions of the microarchitecture of lymph nodes, the compartmentalization of distinct cell types, and their functions are found in several original and review articles (Willard-Mack, 2006; Huang et al., 2018; Jalkanen and Salmi, 2020; Mercadante and Tadi, 2023; Pabst et al., 2023).

Normal adult lymph nodes vary in size from 0.1 cm to a maximum of 2 or 2.5 cm (Padhani, 2014; George, 2016; Bujoreanu and Gupta, 2023), depending on the age of the individual and the location in the body (Luscieti et al., 1980). As the human body ages, lymph nodes in several locations become smaller due to lymphocyte loss and progressive replacement with adipose tissue (Hadamitzky et al., 2010) (Fig. 5A,B). Small lymph nodes, less than 1 Millimeter in diameter, may also be found in younger individuals during dissection. Lymph nodes of this size are easily overlooked or are easily confused with simple lymphoid aggregates (Fig. 4). In their normal state, lymph nodes may present a wide spectrum of morphological characteristics, depending on age, localization, physiological adaption during immunocompetence, and persistent morphological changes following repeated occurrences of infections (Luscieti et al., 1980; Bontumasi et al., 2014; Jin et al., 2022) and chemo- and/or radiation-therapy (Shvero et al., 2001; O'Neil and Damjanov, 2009; Albano et al., 2021) (Figs. 5, 7).

Extensive fatty infiltration of lymph nodes, called "lipomatosis" or "lipomatous pseudohypertrophy" is a common presumably normal finding (Fig. 5A-D), particularly in adults older than 40 years (Pflieger et al., 1979; Bekkhus et al., 2023). However, it is not entirely clear whether such changes represent a genuine pathological condition or are normal age-related changes. Recently, Bekkhus et al. (2023) demonstrated that fatty changes in lymph nodes are an active cellular process with the transformation of lymph node fibroblasts into adipocytes (Fig. 6A,B). This process is associated with decreased levels of the lymphokine lymphotoxin beta, which is known to inhibit stromal cells from differentiating into adipocytes during normal lymph node development (Bénézech et al., 2012). Bekkhus et al. (2023) argue that this remodeling could contribute to decreased immune functions. The capsule in the fatty lymph node changes frequently and appears partially vanished (Fig. 5A,C,D) which may be caused by the transformation of capsule fibroblasts into adipocytes.

Lymph node metastases and clinical impact on cancer

In cancer patients, tumor stage is an important factor for prognosis and treatment planning (Brierley et al., 2019; Hanna et al., 2020; Pung et al., 2023). In most cancers, tumor stage is specified in the UICC (Union for International Cancer Control), TNM (Tumor Node Metastasis) and AJCC (American Joint Committee on Cancer) TNM classifications, which define the extension of the primary tumor, regional lymph node metastasis (Fig. 6A-C), and distant metastasis (Amin et al., 2017; Wittekind et al., 2019; Brierley et al., 2019; 2021; Wittekind, 2020). In these classifications, it is mandatory to investigate a minimum number of collected regional lymph nodes for the possible presence of lymph node metastasis; this minimum number to investigate is specifically defined for each affected organ. The required minimum number of collected lymph nodes in completely resected tributary lipolymphatic tissue strongly correlates with the clinical outcome and is specific for each cancer entity (Bilchik and Trocha, 2003; Parsons et al., 2011; Dudeja et al., 2012; Trepanier et al., 2019). Examining a minimum number of regional lymph nodes in cancer increases the likelihood of recognizing putative lymph node metastases, which affects the prospective therapeutic strategies and survival prediction, e.g., in cancers of the colon (Nelson, 2018; Chen et al., 2020), pancreas (Mirkin et al., 2017; Takagi et al., 2022), stomach (Cao et al., 2018), lung (He et al., 2021; Liang et al., 2023), kidney (Terrone et al., 2003), thyroid (Heng et al., 2020), head and neck (Roberts et al., 2016), and breast (Sun et al., 2020). Therefore, pathologists are requested to dissect as many lymph nodes as possible. It is noteworthy that lymph node dissections performed by biomedicine technicians in comparison with pathologists yielded significantly higher numbers of lymph nodes harvested, which has a critical impact on survival rates of colonic cancer patients through optimized treatment (Buchwald et al., 2011). However, some studies indicated, that in colon carcinoma, increasing the number of collected lymph nodes beyond the required minimum quantity, i.e., 12 lymph nodes does not improve the accuracy of nodal staging (Parsons et al., 2011; Budde et al., 2014). Not only the number of lymph nodes harboring metastases is of importance but also the structure of the lymph node capsule yields useful information. The clear histological identification of an intact lymph node capsule is important in many cancer entities. In certain cancers, metastatic tissue may breach the capsule and extend extranodally (Fig. 6C). This extranodal extension worsens the clinical outcome, and in some cancer types, an appropriate therapy, such as extensive lymph node sampling or chemoradiation therapy, may be recommended (Sergeant et al., 2009; Luchini and Veronese, 2017; Luchini et al., 2017; Hei et al., 2022; Mahajan et al., 2022; Sun et al., 2022; Yokota et al., 2023; Yoon et al., 2023).

"True" lymph nodes *versus* lymphoid aggregates. Practical application in resected oncological tissues

To treat cancer patients with curative intent, the complete or partial surgical resection of the tumor-affected organ is one option. In most cases, the regional

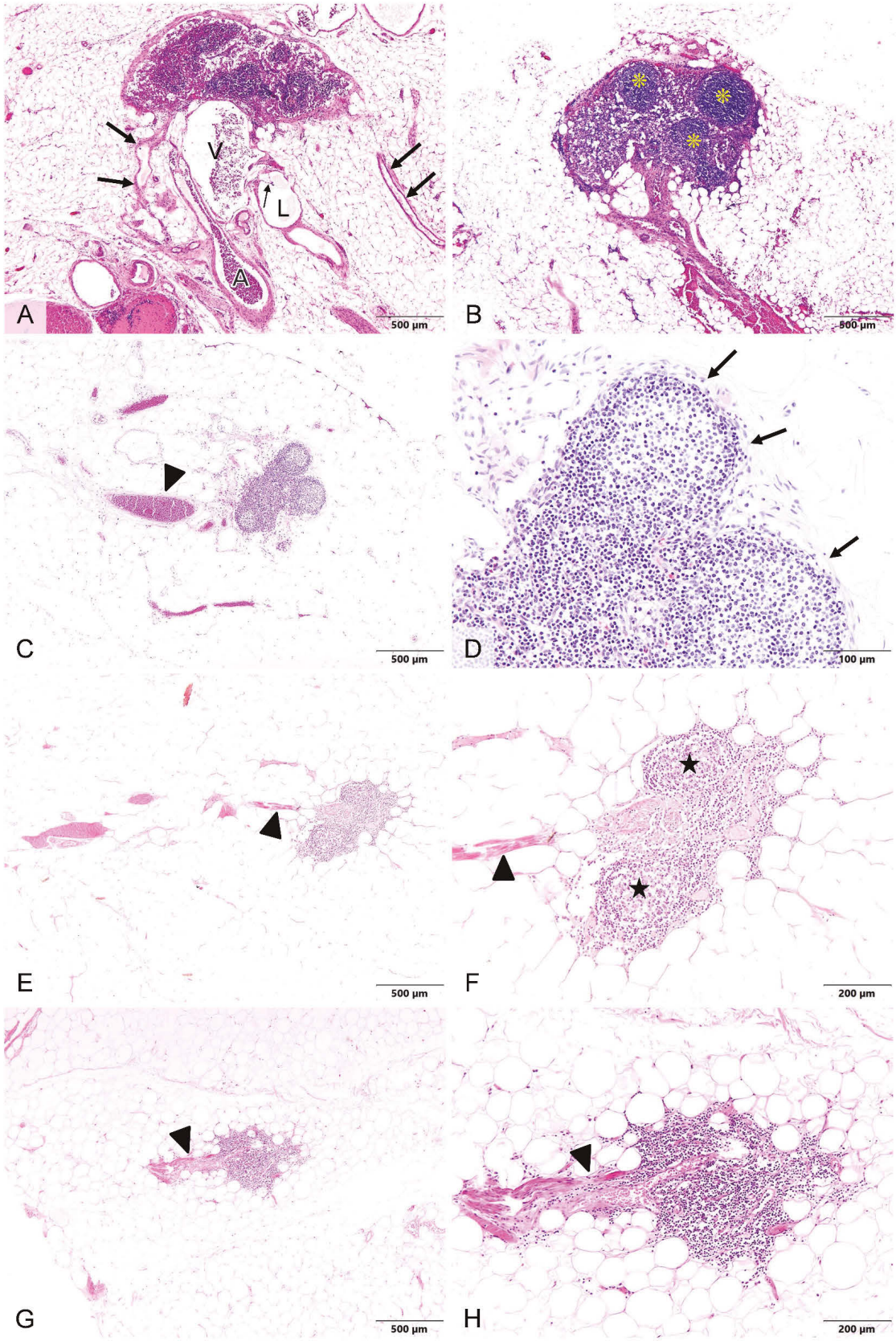

Fig. 4. A-D. Small lymph nodes measuring between 800 µm **(C, D)** and 1.8 mm **(A)**. The lymph node in **A** stems from pericolonic adipose tissue and presents all characteristic substructures of a normal lymph node, i.e., a capsule covering the parenchyma, afferent lymphatic vessels (arrows), as well as an efferent lymphatic vessel (L) accompanied by a vein (V) and an artery (A). The small arrow points to a lymphatic valve. **B.** Lymph node with three primary lymphoid follicles (asterisks). **C.** Tiny lymph node exhibiting a supplying blood vessel (arrowhead) and a fibrous capsule, clearly identifiable at the higher magnification in **D** (arrows). **E-H.** Lymphoid aggregates are depicted, presenting with supplying blood vessels (arrowheads) but lacking a lymph node capsule. The lymphoid aggregate in **E** and **F** resembles a tertiary lymphoid organ with two lymphoid follicles (stars).

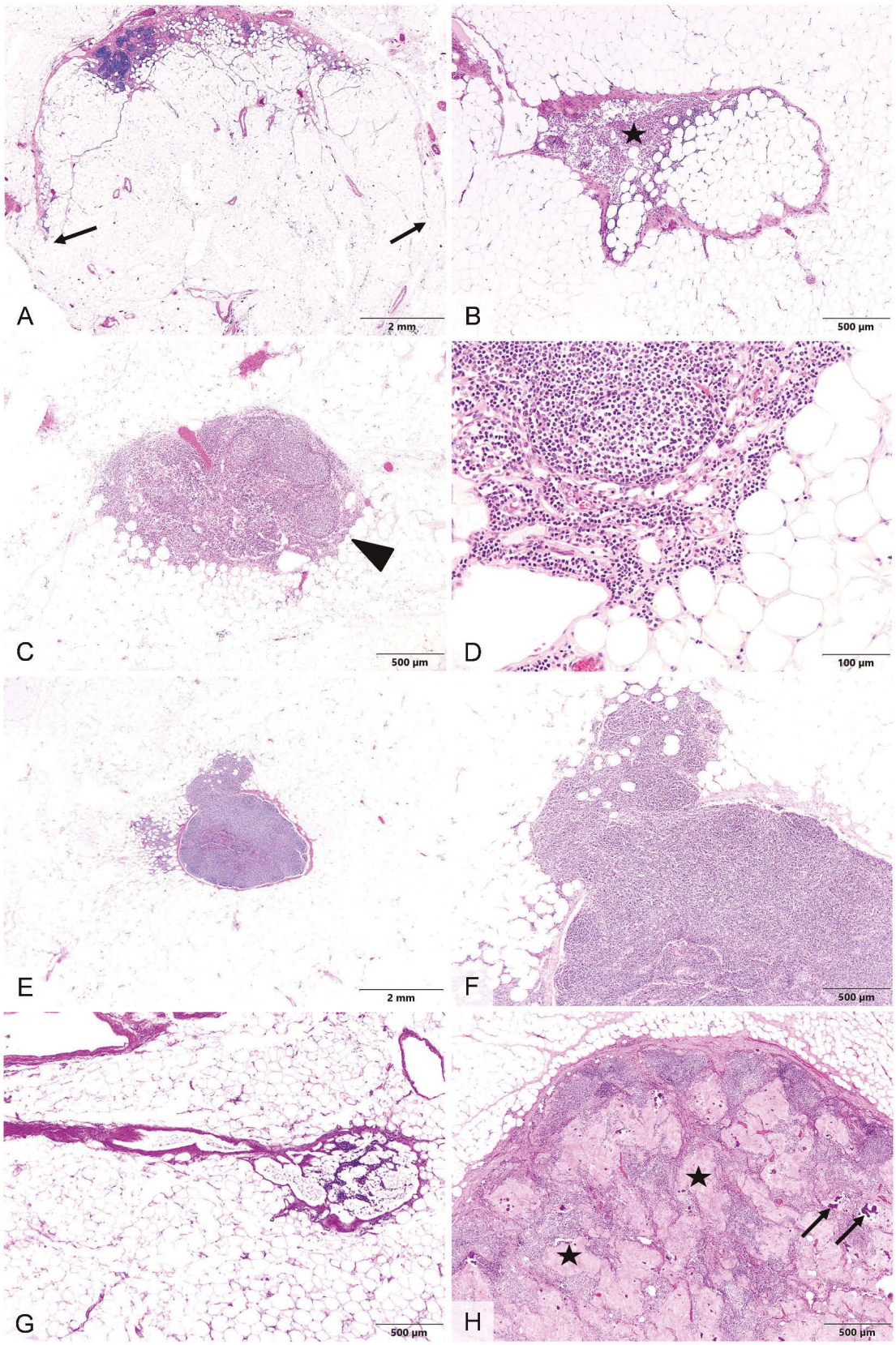

Fig. 5. Various physiological reactions of lymph nodes during aging. **A.** Fatty changes in a pelvic lymph node. The capsule has partially vanished (arrows). **B.** Lipoatrophic pelvic lymph node. The parenchyma is partially replaced by histiocytes (star) and adipocytes. **C, D.** Lymph node partially infiltrated by adipocytes and apparent loss of the capsule (arrowhead), clearly visible in **D**. **E, F.** Lymph node originating from pericolonic adipose tissue. This out-of-the-ordinary example comes from a 58-year-old male with a colonic adenocarcinoma, which presents without any indications of malignant lymphoma. The capsule is apparently penetrated by proliferating lymphocytes, the cause of which is unknown (possibly postinfectious). **G.** Atrophic lymph node from the pericolonic adipose tissue of a 93-year-old man. The lymphatic parenchyma is visibly reduced. **H.** Fibrotic pelvic lymph node showing broad collagen bundles (stars) with focal calcifications (arrows).

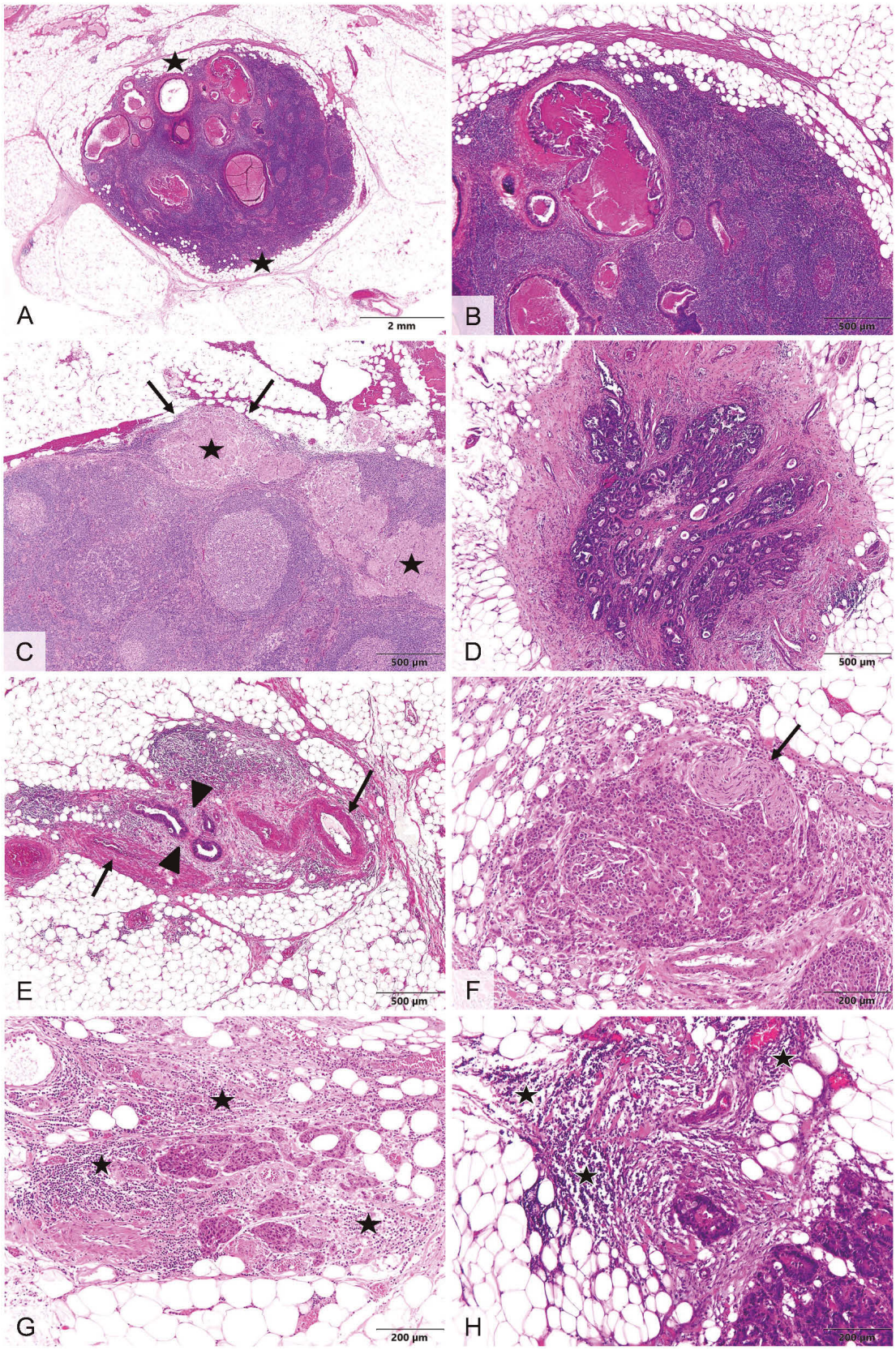

Fig. 6. Cancer manifestations in lymph nodes and tumor deposits (satellites). **A.** Regional lymph node metastasis in pericolonic adipose tissue originating from an adenocarcinoma of the colon. Note the subcapsular transdifferentiation of the stroma into adipocytes (stars). **B.** Higher magnification of **A**. **C.** Cervical lymph node metastasis of a squamous cell carcinoma of the base of the tongue. Tumor cells (stars) extend into the pericapsular adipose tissue (arrows). **D-H.** Tumor implants in the pericolic adipose tissue in a patient with an adenocarcinoma of the colon. **D.** Tumor deposit (satellite) with an irregular configuration with delicate spiculae infiltrating the surrounding tissue. **E.** These tumor glands (arrowheads) are located adjacent to a blood vessel (arrows) and thus are classified as venous infiltration. **F.** Tumor glands spread along a peripheral nerve (arrow) and thus this finding is classified as perineural invasion. **G, H.** Tumor deposits embedded in a lymphocyte-rich microenvironment (stars).

(tributary) lymph nodes are removed as well. The pathologist is then requested to examine the primary tumor as well as the attached or separately submitted lymph nodes. Gross inspection can be an arduous task as the lymph nodes can sometimes be hard to detect. This task can be impeded, for instance, by neoadjuvant therapy (Fig. 7). A simple but promising method to find lymph nodes is gently palpating the tributary adipose tissue using finger-pressing. All identified lymph nodes are embedded regardless of whether the minimum number required by guidelines has already been reached. In our laboratory lymph nodes are processed in accordance with established procedures (Vogel et al., 2008; Ganesan et al., 2019) as follows: lymph nodes less than 0.5 cm in size are embedded whole; lymph nodes measuring between 0.5 cm and 1 cm in diameter are bisected and both halves are embedded; nodes larger than 1 cm are sliced at 0.2 cm intervals, in a plane perpendicular to the longest axis; a maximum of 5 lymph nodes less than 0.5 cm in size are placed in one tissue cassette. Effective techniques were introduced to improve the yield of sufficient lymph nodes, such as fixation in picric acid (Lester, 2010), acetone or ethanol clearance of the fatty tissue (Vogel et al., 2008; Igali, 2012), and intra-arterial injection of methylene blue before fixation (Märkl et al., 2007). The fat-clearing methods have proven particularly effective in tissues rich in adipose tissue, e.g., axillary, pelvic, or mesenteric tissues, and can increase the yield of lymph nodes by 50 percent (Igali, 2012). Most commonly, standard fixation is followed by the fat-clearing procedure. Some laboratories prefer a two-step fixation, with fat-clearing occurring during the second fixation step (Iversen et al., 2008). According to this method, the tissue is initially fixed in buffered formal saline for 24 hours, which is followed by fixation for another 24 hours in a mixture of glacial acetic acid, ethanol, and formaldehyde. With all these methods, tiny lymph nodes particularly stand out from the translucent adipose tissue due to their yellowish-white or bright-white color. Care should be to seek the lymph nodes between the tumor and feeding vessels and it should be kept in mind that lymph node

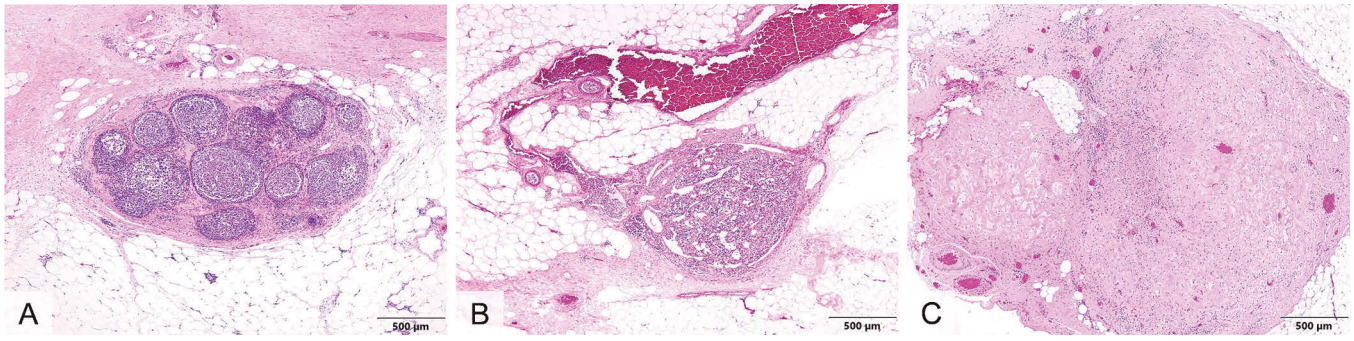

Fig. 7. Therapy-induced lymph node changes. **A.** Perigastric lymph node after chemotherapy for adenocarcinoma. The capsule is thickened due to fibrosis. **B.** Perirectal lymph node after combined chemoradiation therapy for rectal adenocarcinoma. The lymphatic cells are depleted and the capsule is fibrotic. **C.** Axillary lymph node of a breast cancer patient after chemotherapy. The original lymph node cellular structure is almost completely replaced by scar tissue, possibly after regression of a metastasis.

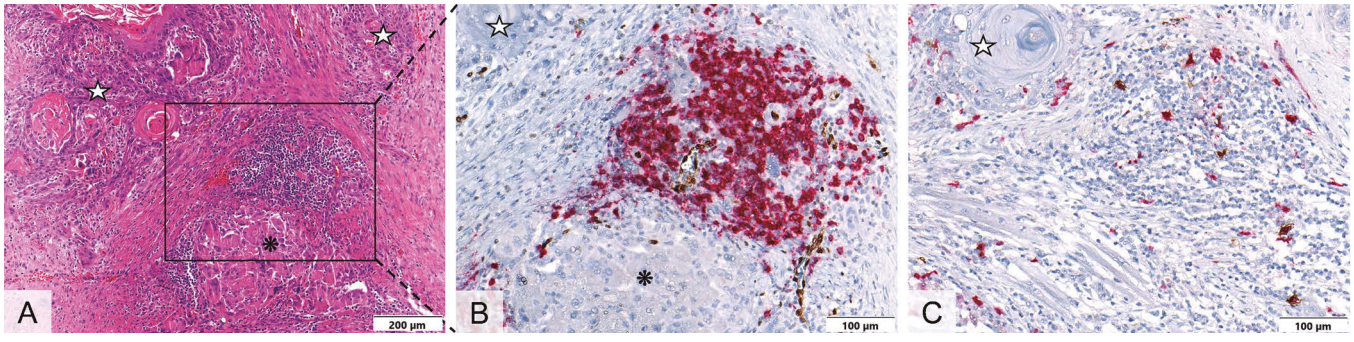

Fig. 8. Tertiary lymphoid tissue (TLT) in a patient with laryngeal squamous cell carcinoma. Immunohistological staining visualizes characteristic substructures of the TLT. **A-C.** Solid tumor cell aggregates are visible (white stars), which have induced a TLT with densely packed lymphocytes. Focal tumor cell necrosis is evident with reactive multinucleated macrophages (black asterisk). **A.** In the routinely HE-stained section, keratinization is distinctly visible (left upper corner). One TLT is framed by a black rectangle. From this area, immunostaining is shown at higher magnifications. **B.** Double immunostaining of B cells (CD20) and blood vessels (ERG). The TLT is composed of aggregates of B lymphocytes (red color) and supplying venules (brown nuclear staining). **C.** Double immunostaining (CD1a, S100 protein) for visualization of dendritic cells. The TLT contains several immature CD1a-positive dendritic cells (dark brown color). Antibodies against S100 protein label both immature and mature dendritic cells (red color).

collecting areas follow the directions of arterial distribution, not venous (Clapham et al., 2010; Igali, 2012).

Subsequently, the pathologist counts the lymph nodes and evaluates whether they contain metastatic tissue under the microscope.

In a 2017 web-based questionnaire published by the European Network of Uropathology (ENUP) (Prendeville et al., 2019), members were asked how they defined a lymph node in prostate and bladder resections. The following choices were available as possible answers: 1) Any aggregate of lymphocytes exceeding a certain size; 2) Any aggregate of lymphocytes surrounded by a fibrous capsule; 3) Any bean-shaped/oval aggregate of lymphocytes surrounded by a fibrous capsule; 4) Any bean-shaped/oval aggregate of lymphocytes surrounded by a fibrous capsule with a subcapsular sinus; 5) Seriously – I do not know.

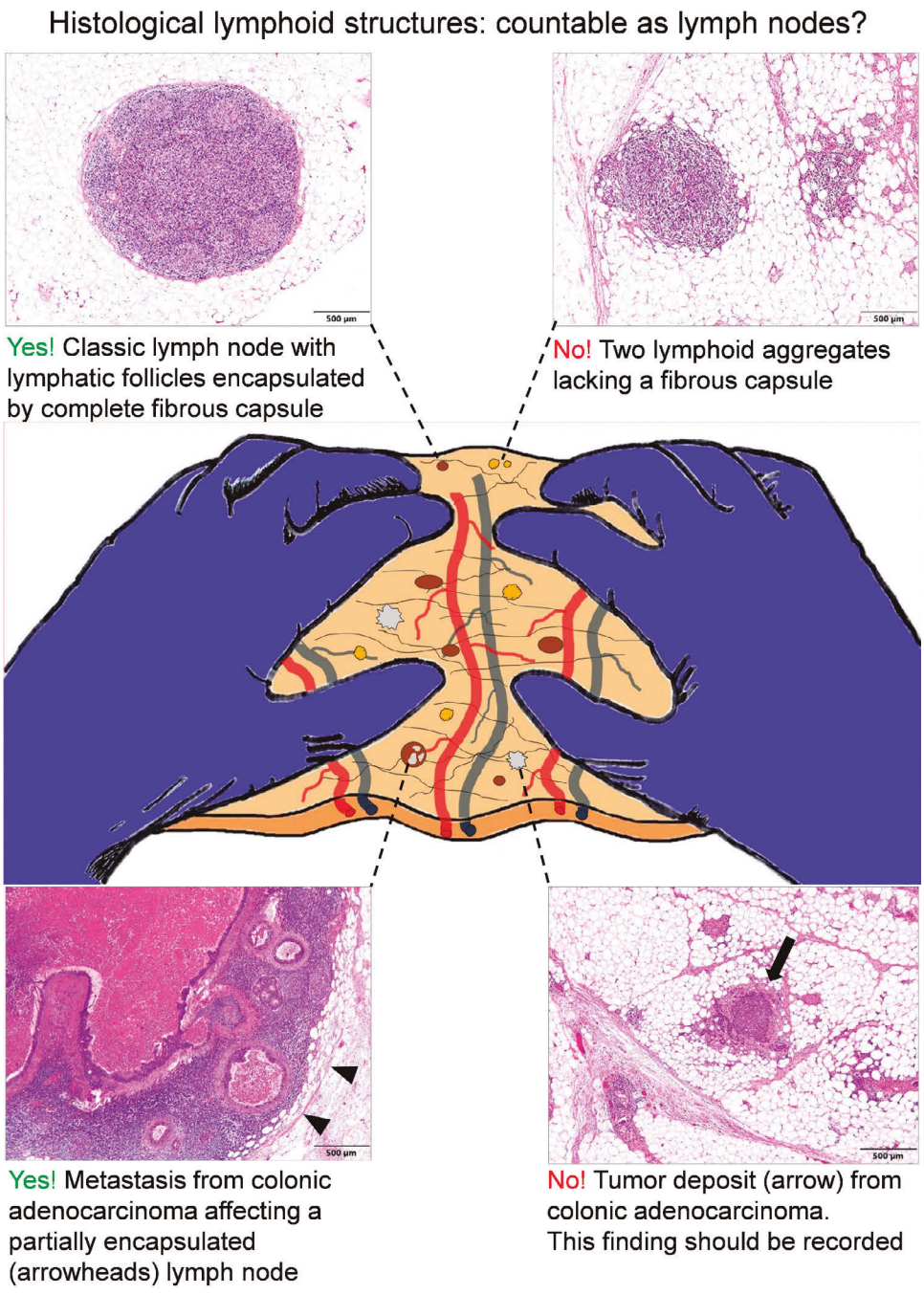

Fig. 9. Simplified approach to interpreting various lymphoid structures in pathological routine diagnostics using the example of pericolonic adipose tissue, taken from a patient with colonic adenocarcinoma. The tissue is carefully palpated for hardened or elastic-firm structures, which are all embedded for histological evaluation. Whether these structures correspond to "true" lymph nodes can only be determined microscopically. Note that during grossing, lymphoid aggregates are neither palpable nor visible, representing an incidental finding. Cartoon made by the authors.

Depends on my shape (sic!); 6) Other (please specify).

Most of the participating pathologists (91%) required a capsule and/or subcapsular sinus surrounding lymphocytic aggregates to designate a lymph node microscopically. However, 7.1% of pathologists still selected answer no. 1 "Any aggregate of lymphocytes exceeding a certain size".

The term "aggregates of lymphocytes" in the above questionnaire is more appropriate than an experienced pathologist might assume. Recently, new types of lymphoid structures have been described, which resemble miniature lymph nodes lacking a capsule. These structures were given various names, such as "tertiary lymphoid tissues (TLT)", "tertiary lymphoid organs (TLO)", "tertiary lymphoid structures (TLS)" or "isolated lymphoid follicles (ILF)" (Eberl, 2005; Bery et al., 2022; Esparcia-Pinedo et al., 2023; Yoshikawa et al., 2023) (Fig. 8). TLT consist of similar cells as lymph nodes, comprising an inner zone of B cells surrounded by T cells, and contains FDC, high endothelial venules (HEV)-like vessels, lymphatic vessels, and some other cell types (Eberl, 2005; Mustapha et al., 2021; Schumacher and Thommen, 2022; Esparcia-Pinedo et al., 2023; Sato et al., 2023). TLT are distinguished from primary lymphoid tissues, such as bone marrow and thymus as well as secondary lymphoid tissues (e.g., lymph nodes, spleen, tonsils, and mucosa-associated lymphoid tissues (MALT)) (Eberl, 2005; Drayton et al., 2006; Ruddle, 2016). TLT show different degrees of organization, ranging from an immature stage as dense lymphoid aggregates without a network of FDC, to fully mature TLT with the segregation of T and B cells arranged into two distinct areas (Mitsdoerffer and Peters, 2016; Domblides et al., 2021; Werner et al., 2021; Zhang and Wu, 2023).

TLT do not exist under physiological conditions (Zhang and Wu, 2023) and form ectopic lymphoid structures outside lymphoid organs because of chronic inflammation. Examples include inflammatory bowel diseases (Bery et al., 2022), kidney diseases (Yoshikawa et al., 2023), rheumatic autoimmune diseases (Bombardieri et al., 2017), degenerative diseases such as chronic obstructive pulmonary disease (Briend et al., 2017) and atherosclerosis (Akhavanpoor et al., 2018), as well as cancer (Mustapha et al., 2021; Sautès-Fridman et al., 2022). TLT are frequently encountered in cancer resection specimens (Fig. 8) and could easily be mistaken for lymph nodes if not carefully inspected under higher magnification. The presence of TLT in cancer is associated with improved survival and sensitivity to immune checkpoint inhibitors (Watermann et al., 2021; Vanhersecke et al., 2023). On the other hand, as part of the tumor lymphatic pathway, TLT vasculature can provide alternative routes for the establishment of a pre-metastatic niche and cancer dissemination (Mustapha et al., 2021). As outlined above, one major morphological difference between a "true" lymph node and TLT is the absence of a capsule in TLT, which allows the direct exposure of lymphatic cells and specialized DC to diverse stimuli from the microenvironment (Sato et al., 2023). This may result in distinct immunological responses, e.g., a fast and efficacious antipathogen reaction (Mitsdoerffer and Peters, 2016). Additionally, TLT are transient structures that often disintegrate upon clearance of the antigen (Mitsdoerffer and Peters, 2016). From these standpoints, TLT and lymph nodes are quite different structures, which may exert different functions.

Sometimes, pathologists encounter structures within the lymph drainage area of certain cancers (e.g., primary carcinoma of the colon, appendix, pancreas, stomach, breast, small intestine) that are distant from the primary tumor and exhibit an unusual, irregularly shaped formation that, upon closer examination, contains clusters of tumor cells (Fig. 6D,G,H) (Jass and Morson, 1987; Puppa et al., 2007; Fujikawa et al., 2023; Liang et al., 2023; Ueno et al., 2023). These structures are called tumor deposits or satellites. Whether these tumor manifestations represent former lymph nodes, completely replaced by tumor growth, or are disseminations of tumor cells via blood or lymph vessels is still the subject of debate (Puppa et al. 2007; Ueno et al., 2023). However, pathology guidelines recommend a pragmatic approach: a tumor deposit is present if no residual tissue of a lymph node (usually without a smooth contour as seen in lymph nodes) or no identifiable vascular or neural structure is evident (Fig. 6E,F) (Wittekind et al., 2019; Wittekind, 2020). In some cases, tumor deposits may be infiltrated by a variable number of lymphocytes, resembling metastatic cells within TLT (Fig. 6G,H). Some authors suggest that, in such lymphocyte-containing tumor deposits, the de novo formation of TLT may have been tumor-induced, which facilitates tumor metastatic spread via the associated lymph and blood vessels (Puppa et al., 2007). These same authors could demonstrate that lymphocyte-containing tumor deposits are associated with a shorter survival time than those without lymphocytes. In contrast, and to our knowledge, TLT have never been shown to be a site of metastasis.

Conclusions

Understanding normal lymph node architecture is essential in pathology for cancer staging and should, therefore, be taught early in the medical curriculum. In oncological patients, harvesting a minimum number of regional lymph nodes, and draining a defined area of surgically resected tumor tissue, is a prerequisite for predicting the clinical outcome and choosing adequate therapy. Consequently, discriminating "true" lymph nodes from lymphoid aggregates, particularly TLT is essential (Fig. 9). In accordance with pathological guidelines, lymph nodes should be defined histologically as a collection of lymphocytes and other mesodermal cells (e.g., DC, fibroblasts or fibroblastic reticulum cells which synthesize the reticular meshwork of lymph nodes and blood and lymphatic vessels) invested with a fibrous

capsule, which may be complete or incomplete. Depending on the histological section plane, afferent lymph vessels penetrating the capsule and an efferent lymphatic vessel at the hilum, along with accompanying blood vessels, may be recognizable. In medical schools, students should be made aware that lymph node morphology can be quite diverse and may deviate from the ideal image of a bean-shaped structure with well-developed follicles, as well as clearly visible incoming and outgoing blood and lymph vessels. In addition, as regards correct classification and terminology, we propose that a non-encapsulated accumulation of lymphocytes, e.g., in chronic inflammatory diseases, should be referred to as a lymphoid aggregate or, if more organized with unambiguously recognizable lymph and blood vessels, as TLT. For pathologists, harvesting sufficient lymph nodes and detecting even tiny nodes is challenging. For economic reasons and time constraints, technically simple procedures are required. As a minimum standard, the following approach may be suitable (Fig. 9): 1) Embed all palpable suspected lymph node structures; 2) Do not stop your harvest just because you have collected the required number of lymph nodes according to guidelines; 3) If you have found too few lymph nodes (e.g., often after adjuvant therapy), embed 10 more randomly selected areas of adipose tissue in the second round. If the number is still too low, repeat the embeddings with 10 tissue cassettes per round; and 4) Tumor deposits (satellites) should be recorded since they may influence the lymph node status.

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Ethics approval statement. This work did not involve human participants or personal data. The use of microscopic photographs of human material was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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