Case Report

Unusual "Subcutaneous Mass" in a Young Adult: A Case Report of Sclerosing Epitrochlear Lymph Node and Brief Review of the Literature

Liang Ding, MD, PhD;[1] Mahyar Khazaeli, MD;[1] Lin Lin, MD, PhD[1,2]*

1. Department of Pathology, State University of New York at Buffalo, Buffalo, NY
2. Department of Dermatology, Buffalo Medical Group, Buffalo, NY

Lymph nodes are specialized tissues that play an essential role in the immune system. Nodal hyalinization/sclerosis is often seen in the elderly, involving the mediastinum, pelvis, and other areas. Hyalinization of the lymph node might contribute to impaired filtration function of the node. Nevertheless, the clinical significance is still unclear. Here, we report a 35-year-old Caucasian female with an unremarkable past medical history, presented at the dermatology clinic with a subcutaneous mass in the forearm, and an excisional biopsy was performed. The histological findings are consistent with a lymph node with hyalinization and storiform sclerosis. The patient is doing well after the focal excision. Although deposition of hyaline material can be seen in the pelvic and inguinal lymph nodes of the elder, its histology is drastically different from the one seen in our case. In this case report and brief review, we compare and summarize several benign and malignant conditions associated with nodal hyalinization with or without a storiform pattern

[N A J Med Sci. 2022;15(1):001-007. DOI: 10.7156/najms.2022.1501001]

Key Words: *lymph node, hyalinization, sclerosis, storiform pattern*

INTRODUCTION

The lymph node, a secondary lymphoid organ, filters pathogens and tumor cells and produces an immune response against the trapped exogenous antigen. It is comprised of capsule, cortex, paracortex, medulla, follicles, sinuses, and hilus. Lymph nodes contain mainly lymphocytes and, to a lesser extent, plasma cells, macrophages/histiocytes, dendritic cells, and fibroblastic reticular cells.[1]

Lymph nodes distribute throughout the body, and there are an estimated 450-600 lymph nodes in adults.[2] The normal histology varies among lymph nodes from different locations and different age groups. For example, anthracotic pigments are commonly seen in hilar lymph nodes, and sinus histiocytosis is often seen in mesenteric lymph nodes. The numbers of germinal centers reduce with aging.[3] Peripheral lymph nodes are frequently replaced by adipose tissue due to minimal antigen exposures.[4]

Nodal hyalinization/sclerosis is often seen in the older person, involving the mediastinum, pelvis, neck, axilla, abdomen, and inguinal areas.[5] Sclerosis is associated with the deposition of thick hyalinized bands of connective tissue/collagen. Sclerosis of lymph nodes can occur under physiological or pathological conditions. With aging, the amount of hyaline material in lymph nodes usually increases.[1] Taniguchi et al. studied lymph nodes in elderly Japanese and white Americans ranging in age from 72 to 95 years old. They classified nodal hyalinization into two types: mediastinal-type hyalinization and pelvic-type hyalinization.[5] The former type displays onion-peel architecture associated with meshwork areas, and the latter demonstrates hyaline materials in B lymphocyte areas.[5] They also found the differences in collagen fibril diameters between the two types (50 nm in mediastinal-type vs. 150 nm in pelvic-type). It was proposed that the pelvic-type hyalinization in the older person was secondary to vascular degeneration in the cortex.[5] Besides aging, lymph node sclerosis is also seen in pathological conditions such as nodular sclerosing Hodgkin's lymphoma.

CASE REPORT

We report a case of a 35-year-old Caucasian female presenting to the dermatology clinic with a well-defined, firm, subcutaneous mass on the right forearm, measuring 1.1cm in the greatest dimension. The patient's past medical history was insignificant except for anemia, perineal laceration during delivery, and allergy to Clindamycin (rash and itching). An excisional biopsy was performed. Histological evaluation revealed a sclerosing lymph node in the subcutis **(Figure 1A)**. In the periphery, lymph node architecture was relatively

Received: 01/24/2022; Revised: 03/16/2022; Accepted: 03/23/2022
***Corresponding Author:** Department of Pathology, State University of New York at Buffalo, Buffalo, NY. Tel: 716-630-2582. (Email: llin@buffalomedicalgroup.com)

preserved **(Figure 1A)**. The central area of the lymph nodes was replaced mainly by storiform hyaline **materials (Figure 1B)** and scattered eosinophils **(Figure 1C)**, lymphocytes, and plasma cells. Focal vascular proliferation was noted **(Figure 1D)**. The immunostains showed CD3 positive small T-lymphocytes **(Figure 1E)** surrounding CD20 positive B-lymphocytes in the lymphoid follicle **(Figure 1F)**. The Bcl-6 labeled B cells in the germinal centers. Plasma cells were polytypic with both kappa and lambda light chain expression **(Figure 1G** and **1H)**. The pan-cytokeratin and Melan-A immunostains showed negative findings.

DISCUSSION

The hyalinized lymph node in this patient was from the forearm where the epitrochlear lymph nodes locate. The epitrochlear (or supraepitrochlear) lymph nodes are the superficial lymph nodes of the upper limb. Usually, one to four of those nodes filter the lymph from the hand and forearm and drain into the axillary lymph nodes.[6]

The storiform pattern of hyaline material deposition/sclerosis in a benign lymph node is uncommon, as it is different from the usual pattern of hyalinization in lymph nodes which is commonly seen in elderly patients.[5] The etiology is unclear since the patient is young and has an insignificant clinical history. Theoretically, hyalinization could diminish the filtration function of lymph nodes; however, clinical follow-up and evidence-based studies are needed to clarify its clinical significance.

Based on our observations, hyalinized lymph nodes are often seen in elderly patients' pelvis and inguinal areas. The hyalinization in these nodes was described as pelvic-type hyalinization.[5] It may be a result of degeneration of vessels in the nodal cortex.[5] As showed in **Figure 2**, a pelvic lymph node from a 61-year-old female shows hyaline deposition, replacing 80% of the lymphoid component **(Figure 2A)**. Under high power, these thick hyaline materials are thin collagen fibers arranged in a whirling pattern **(Figure 2B)**.

Apart from aging, nodal hyalinization can be seen in several benign and malignant conditions. Correct diagnosis is essential because the clinical managements are different among these conditions. The following is a list of differential diagnoses with a brief review.

Metastatic melanoma in lymph nodes with sclerosis: Epitrochlear lymph nodes are considered interval/ in-transit nodes between the primary melanoma and the axillary lymph node basin.[7] The interval nodes are reported to bear a similar metastatic risk as sentinel lymph nodes do.[8] Hunt et al. assessed 13,139 melanoma cases and found that 1.1% of patients with primary melanomas in the upper extremities were positive for metastasis in the epitrochlear node.[9] The metastatic melanoma cells are epithelioid, spindled, and mixed in morphology, and most of them are found in the subcapsular region of the node.[10] The cells can be highlighted by S100, melan-A/MART1, SOX-10, and HMB45 immunostains. In our case, the melanocytic marker failed to detect any melanoma cells.

Amyloidosis: Immunoglobulin-derived amyloidosis refers to a category of diseases caused by the deposition of misfolded insoluble immunoglobulin chains, most usually light (AL) chains but rarely heavy (AH) chains.[11] These diseases are associated with hematologic malignancies, which cause an excess of immunoglobulin chains to be produced.[12] The spectrum of immunoglobulin-derived amyloidosis can range from systemic illness with broad amyloid deposition in organs distant to the site of production, known as paraneoplastic, to a localized form of disease known as peritumoral, in which the amyloid stays at the site of production.[13] Amyloid deposits in lymph nodes cause lymph node hypertrophy.[14] Lymph node replaced with amorphous, eosinophilic extracellular material and Congo red stain displaying apple green birefringence, which is diagnostic of amyloid.[15] It is critical to distinguish between localized and systemic lymph node amyloidosis when making a diagnosis, as pateints with a limited presentation are likely to have a better prognosis.[13]

Fibrotic lymph node status post cancer treatment: Neoadjuvant therapy is commonly used in breast cancer. Depending on the response to neoadjuvant therapy, axillary lymph nodes demonstrate variable morphologies, including lymphocyte depletion, sinus histiocytosis, foamy macrophages, fat deposition, and scar.[16] In lymph nodes with metastatic breast cancer, complete response to neoadjuvant therapy usually results in hyaline scars. Sometimes, the lymph node may be entirely replaced by a fibrous scar.[16] In germ cell tumors, fibrosis also accounts for around 50% of histological findings during post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND).[17] Mano et al. reviewd the medical records of men who underwent PC-RPLND between 1989–2013 with histological findings of lymph node necrosis/fibrosis.[18] As neoadjuvant therapy is gaining popularity, we will encounter more and more post-neoadjuvant therapy sentinel lymph nodes with fibrosis/sclerosis, and careful review of the patient's medical history may aid in the diagnosis.

IgG4-related lymphadenopathy: Immunoglobulin G4-related disease (IgG4-RD) is a benign fibro-inflammatory disease associated with increased IgG4 positive plasma cells in the affected tissues.[19] IgG4-RD could involve almost any tissue or organ, including the lymph nodes. The characteristic features are lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis. However, the histology of lgG4-RD is distinct from those of other organs. The histology of the lymph nodes could be categorized into three patterns, including the inflammatory pseudotumor (IPT)-like types.[20,21] In the IPT-like type, the lymph node is replaced by hyalinized fibrous tissue, mimicking the histology of our case. There are substantial plasma cell infiltrates in the dense sclerotic tissue,[21] which is lacking in our case. Besides histological features, the clinical findings are also different between our case and IgG4-RD (elderly males, generalized lymphadenopathy, increased serum IgG4).[19] The treatment includes glucocorticoids,

Rituximab, and methotrexate for recurrent or refractory cases.[22]

Nodular sclerosing Hodgkin lymphoma (NSHL): NSHL is the most common subtype of Hodgkin lymphoma in developed countries and constitutes up to 70% of classical Hodgkin lymphoma in Europe and the US.[23] NSHL is found most often in mediastinal lymph nodes.[24] Histologically, the sclerosing lymph node show thickened capsule, thick collagen bands surrounding the nodules, Reed/Sternberg (RS) cells, lacunar cells **(Figure 3A)**, which are the features of nodular sclerosing Hodgkin lymphoma. These features are not seen in our case. Furthermore, the hyaline materials arrange in layers around the nodules, and they are not in a storiform pattern **(Figure 3B)**. The treatment is stage-based and includes chemotherapy, radiation therapy, and, less commonly, stem-cell transplant.

Inflammatory pseudotumor of the lymph node (IPT): IPT is uncommon, benign lymphadenopathy due to the proliferation of fibroblasts and histiocytes. Moran et al. classified IPT into three stages (I - III) based on histological features.[25] Lymph nodes are focally involved in Stage I. As shown in **Figure 3C** and **3D**, the typical histology of stage II demonstrates proliferating fibroblasts or myofibroblasts in storiform pattern in fibrous stroma of node, often with extranodal extension and vascular proliferation. There are also mixed infiltrates of lymphoplamocytes, histiocytes, dendritic cells, and neutrophils. In stage III, the nodal architecture is largely effaced by diffuse sclerosis with scant residual inflammatory elements. The affected patients often have a fever, anemia, weight loss, fatigue, and elevated erythrocyte sedimentation rate,[25] which is not seen in our patient. Nevertheless, the hyalinized/sclerotic lymph node in our case could reflect the late-stage changes of inflammatory pseudotumor.[26] The mainstream therapy includes corticosteroids and surgical resection.[27]

The storiform pattern of hyaline material deposition/sclerosis can be seen in primary extranodal entities, such as desmoplastic melanoma **(Figure 4A, 4B)**, perineuroma (storiform perineural fibroma) **(Figure 4C)**, storiform collagenoma (sclerotic fibroma) **(Figure 4D)**, Type 1 autoimmune pancreatitis **(Figure 4E)**, and IgG4 related sialadenitis (Mikulicz disease) **(Figure 4F)**. The clinical and histological features are summarized in table1. Although it is nonspecific, getting familiar with this pattern could help narrow down the list of differential diagnoses.

In conclusion, our patient initially visited the dermatology clinic due to a superficial subcutaneous mass that is proven to be a sclerosing lymph node. A superficial lymph node of the forearm with diffuse storiforming sclerosis is unusual, especially in young patients. We review several benign and malignant conditions associated with lymph node hyalinization/sclerosis. Sclerosing lymph node is not routinely seen in the daily practice of dermatopathology. Increased awareness of this condition can help avoid misdiagnosis. Additional studies of more cases are warranted to further clarify the clinical significance of sclerosing lymph node in young individuals.

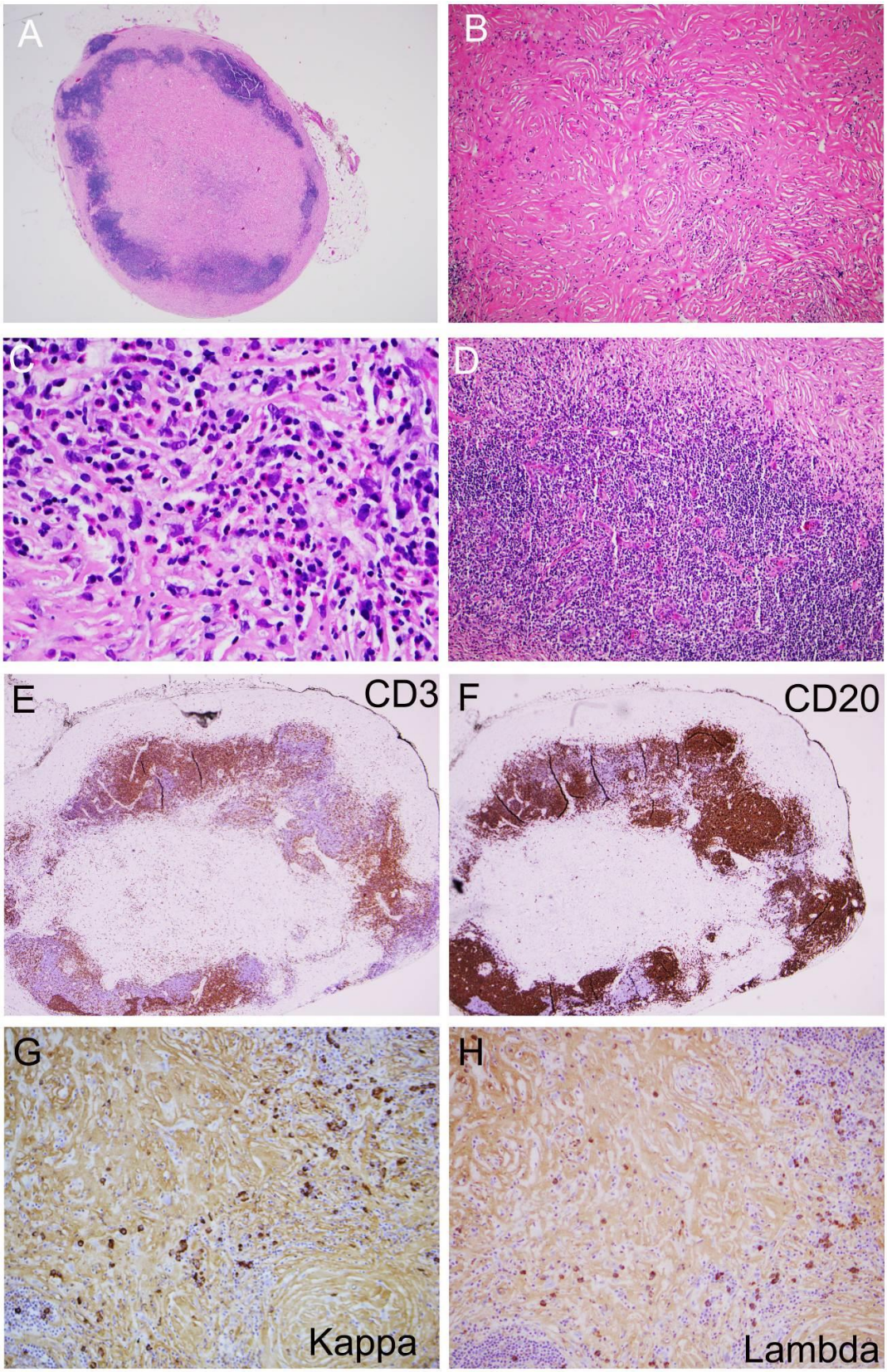

Figure 1: (**A**) A centrally sclerosing lymph node with thickened capsule surrounded by subcutis. The residual nodal architecture is relatively preserved in the periphery (2x, H&E). (**B**) The central area is replaced with storiform hyaline materials (10x, H&E). (**C**) Scarred eosinophils, lymphocytes, and plasma cells are noted in the sclerotic stroma (20x, H&E). (**D**) Focal vascular proliferation is present in the lymphoid follicle (10x, H&E). (**E**) CD3 highlights small T-lymphocytes in the lymphoid follicle. (**F**) CD20 positive small T-lymphocytes are surrounded by T cells. (**G-H**) The polytypic plasma cells express kappa and lambda light chains, with a kappa/lambda ratio of 1.8 (within the normal range).

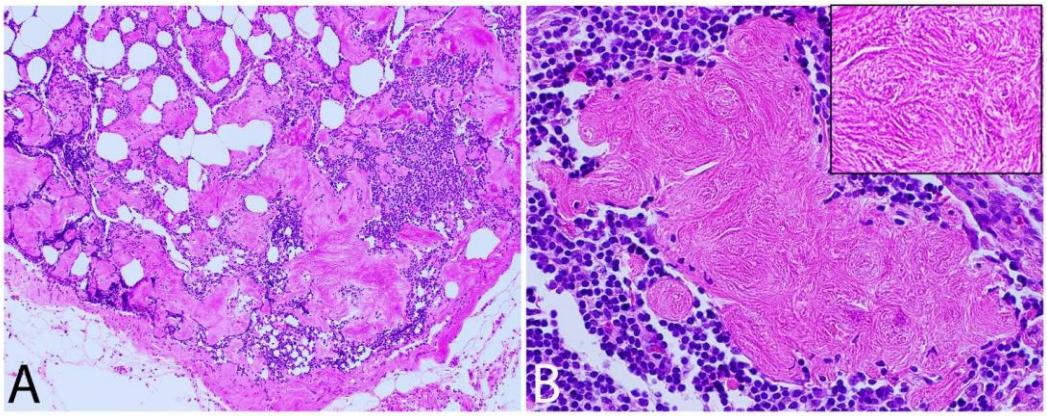

Figure 2. Pelvic lymph node of a 61-year-old female who underwent lymphadenectomy due to endometrial adenocarcinoma. The patient's lymph nodes are negative for metastatic carcinoma. (**A**) The lymph node shows replacement by hyaline materials and adipose tissue (20x, H&E). (**B**) The hyaline deposition is comprised of thin collagen fibers in a whirling pattern (40x, H&E). The insert shows more details of the collagen fibers.

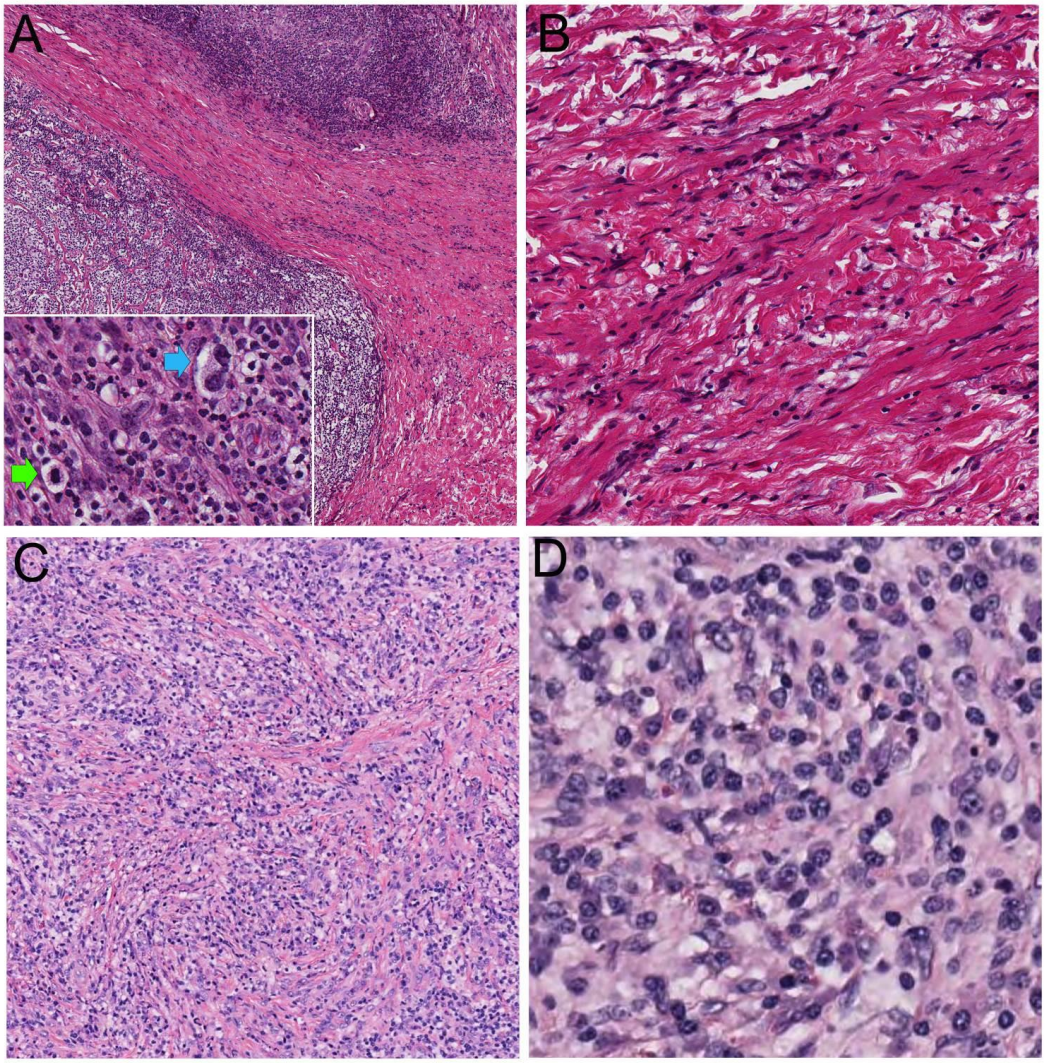

Figure 3. (**A-B**) Nodular sclerosing Hodgkin lymphoma (NSHL). The NSHL lymph node shows thick collagen bands surrounding the nodules (**A**, 5x, H&E). Insert: Reed-Sternberg cells- blue arrow, lacunar cells- green arrow, small lymphocytes, and eosinophils. The collagen bundles arrange in layers, and they are not in a storiform pattern (**B**, 40x, H&E). (**C-D**) Inflammatory pseudotumor of the lymph node**.** The fibroblasts or myofibroblasts proliferate in a storiform pattern (**C**, 10x, H&E). Mixed infiltrates of lymphocytes, plasma cells, histiocytes, and neutrophils are noted (**D**, 40x, H&E).

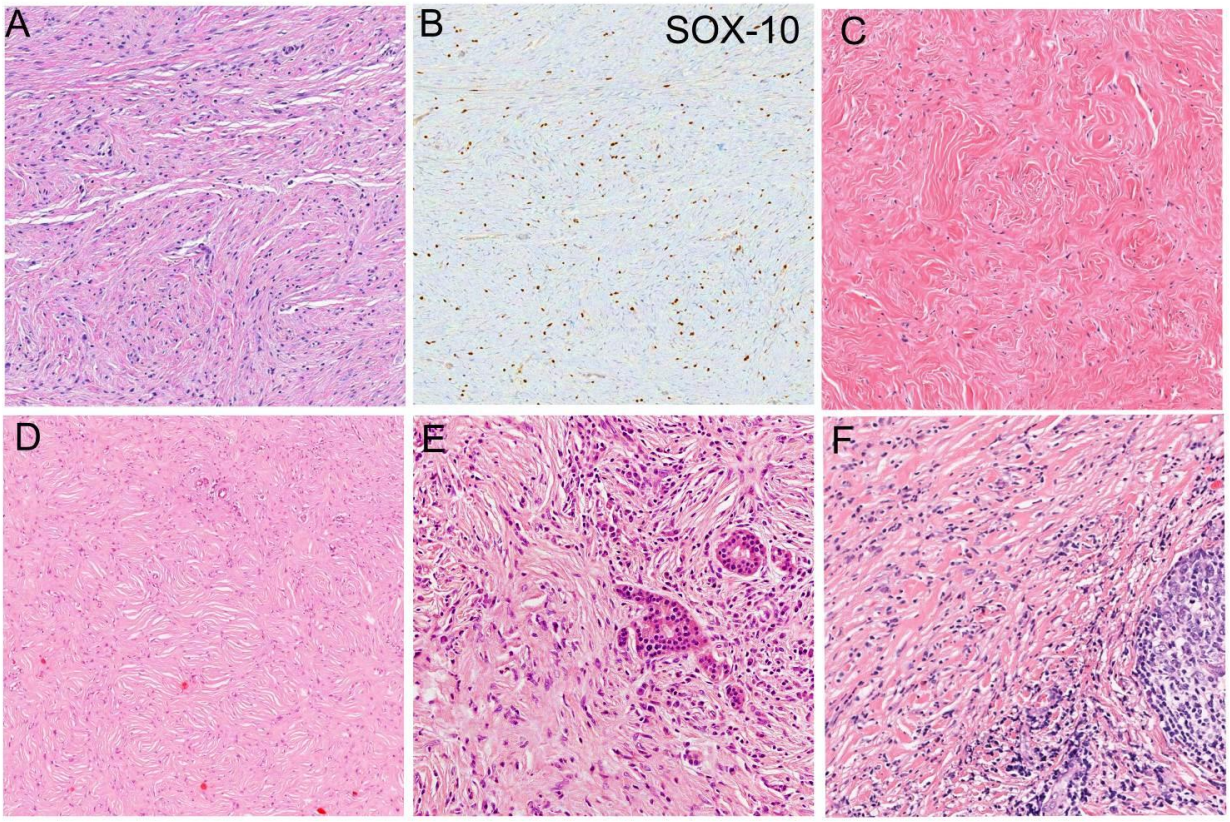

Figure 4. (A-B) Desmoplastic melanoma in the dermis. The densely fibrotic stroma contains abundant collagen deposition with a haphazard arrangement (**A**, 10x, H&E). SOX-10 immunostaining highlights melanocytic neoplastic cells (**B**). (**C**) Perineuroma (storiform perineural fibroma). The paucicellular, sclerotic stroma shows a whorled (storiform) growth pattern (10x, H&E). (**D**) Storiform collagenoma (sclerotic fibroma). The dermal nodule shows hyalinized collagen arranged in the storiform pattern (10x, H&E). (**E**) Type 1 autoimmune pancreatitis with dense plasmacytic infiltrates and storiform fibrosis (10x, H&E). Residual acini are present. (**F**) IgG4 related sialadenitis. Lymphoplasmacytic infiltrates surrounding epi-myoepithelial islands (10x, H&E). Storiform fibrosis is noted.

Table 1. Common extranodal entities with storiform hyalinization/sclerosis.

	Clinical features	Histology	Immunohistochemistry
Desmoplastic melanoma	Rare, less than 4% of primary cutaneous melanomas.28 Most common in the head and neck area in elders. M > F	Poorly circumscribed. Small foci of lymphoid aggregates. Two histological types:29 (1) pDM: pauci-cellular, with tumor cells dispersed in the fibrous stroma. Often amelanotic. (2) mDM: higher cell density.	Positive: SOX10 and S100. Negative: MelanA and HMB45.
Perineuroma (storiform perineural fibroma)	Benign peripheral nerve sheath tumor. More common in subcutis or deep soft tissues then dermis. F >= M	Well circumscribed. Collagenous stroma in whorled, storiform growth pattern. Thin spindle cells with serpentine nuclei. Low mitotic activities.	Positive: EMA, CD34, GLUT1, claudin1. Negative: GFAP, S100, SOX10, Neurofilament , melanA, HMB45.
Storiform collagenoma (sclerotic fibroma)	Benign; young to middle-aged adults. Possible association with Cowden's disease.	Circumscribed dermal nodule with hyalinized collagen showing storiform growth pattern and prominent clefting. Bland spindle or stellate cells	Positive: CD34. Negative: SMA, EMA, S100.
Type 1 autoimmune pancreatitis	Rare, associated with IgG4 related disease, elderly population. M > F. Good prognosis.	Heavy lymphoplasmacytic infiltrates; Storiform fibrosis. Obliterative phlebitis. IgG4+ plasma cells	IgG and IgG4 immunostains. IgG4/IgG ratio > 40%.
IgG4 related sialoadenitis	Painless, bilateral enlargement of salivary glands. Diffuse or local swelling of multiple organs. Serum IgG4 levels ≥ 135 mg/dL.	Lymphoplasmacytic infiltrates surrounding epi-myoepithelial islands. Scattered histiocytes and dendritic cells. Storiform fibrosis. Multiple germinal center formation.	IgG and IgG4 immunostains. >10 IgG4+ plasma cells/HPF. IgG4/IgG ratio > 40%.

ACKNOWLEDGMENTS
None.

CONFLICT OF INTEREST
None.

FUNDING
None.

REFERENCES

1. Elmore SA. Histopathology of the lymph nodes. Toxicol Pathol. 2006;34:425-454.
2. Moore JE, Bertram CD. Lymphatic System Flows. Annu Rev Fluid Mech. 2018;50:459-482.
3. Tsakraklides V, Tsakraklides E, Good RA. An autopsy study of human axillary lymph node histology. Am J Pathol. 1975;78:7-22.
4. Luscieti P, Hubschmid T, Cottier H, et al. Human lymph node morphology as a function of age and site. J Clin Pathol. 1980;33:454-461.
5. Taniguchi I, Murakami G, Sato A, et al. Lymph node hyalinization in elderly Japanese. Histol Histopathol. 2003;18:1169-1180.
6. Catalano O, Nunziata A, Saturnino PP, et al. Epitrochlear lymph nodes: Anatomy, clinical aspects, and sonography features. Pictorial essay. J Ultrasound. 2010;13:168-174.
7. Kidner T, Yoon J, Faries M, et al. Epitrochlear Sentinel Lymph Nodes in Melanoma: Interval or Independent? Am Surg. 2012;78:702-705.
8. Matter M, Lalonde MN, Allaoua M, et al. The Role of Interval Nodes in Sentinel Lymph Node Mapping and Dissection for Melanoma Patients. Journal of Nuclear Medicine. 2007;48:1607-1613.
9. Hunt JA, Thompson JF, Uren RF, et al. Epitrochlear lymph nodes as a site of melanoma metastasis. Ann Surg Oncol. 1998;5:248-252.
10. Murray CA, Leong WL, McCready DR, et al. Histopathological patterns of melanoma metastases in sentinel lymph nodes. J Clin Pathol. 2004;57:64-67.
11. Sipe JD, Benson MD, Buxbaum JN, et al. Amyloid fibril protein nomenclature: 2010 recommendations from the nomenclature committee of the International Society of Amyloidosis. Amyloid. 2010;17:101-104.
12. D'Souza A, Theis J, Quint P, et al. Exploring the amyloid proteome in immunoglobulin-derived lymph node amyloidosis using laser microdissection/tandem mass spectrometry. Am J Hematol. 2013;88:577-580.
13. Telio D, Bailey D, Chen C, et al. Two distinct syndromes of lymphoma-associated AL amyloidosis: a case series and review of the literature. Am J Hematol. 2010;85:805-808.
14. Leiro V, Fernández-Villar A, Bandrés R, et al. Primary amyloidosis involving mediastinal lymph nodes: diagnosis by transbronchial needle aspiration. Respiration. 2008;76:218-220.
15. Dhakal B, Harrington AM, Stadler ME, et al. Localized Lymph Node Light Chain Amyloidosis. Case Rep Hematol. 2015;2015:816565.
16. Mrkonjic M, Berman HK, Done SJ, et al. Breast specimen handling and reporting in the post-neoadjuvant setting: challenges and advances. J Clin Pathol. 2019;72:120-132.
17. Stephenson AJ, Sheinfeld J. The role of retroperitoneal lymph node dissection in the management of testicular cancer. Urol Oncol. 2004;22:225-233; discussion 234-235.
18. Mano R, Becerra MF, Carver BS, et al. Clinical Outcome of Patients with Fibrosis/Necrosis at Post-Chemotherapy Retroperitoneal Lymph Node Dissection for Advanced Germ Cell Tumors. J Urol. 2017;197:391-397.
19. Carruthers MN, Khosroshahi A, Augustin T, et al. The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. Ann Rheum Dis. 2015;74:14-18.
20. Cheuk W, Yuen HKL, Chu SYY, et al. Lymphadenopathy of IgG4-related sclerosing disease. Am J Surg Pathol. 2008;32:671-681.
21. Sato Y, Yoshino T. IgG4-Related Lymphadenopathy. Int J Rheumatol. 2012;2012:572539.
22. Pan Z, Zhou J. IgG4-related lymphadenopathy: a potentially under- and over-diagnosed entity. Int J Clin Exp Pathol. 2017;10:10153-10166.
23. Townsend W, Linch D. Hodgkin's lymphoma in adults. Lancet. 2012;380:836-847.
24. Medeiros LJ, Miranda RN. Diagnostic Pathology: Lymph Nodes and Extranodal Lymphomas. 2nd ed. Salt lake city, UT: Elsevier Health Sciences, Publishers; 2017.
25. Moran CA, Suster S, Abbondanzo SL. Inflammatory pseudotumor of lymph nodes: a study of 25 cases with emphasis on morphological heterogeneity. Hum Pathol. 1997;28:332-338.
26. Gandhi A, Malhotra KP, Sharma S. Inflammatory myofibroblastic tumor of inguinal lymph nodes, simulating lymphoma. J Cancer Res Ther. 2015;11:645.
27. Fayad FT, Bezerra MCT, da Rosa MRP, et al. Diagnosis, treatment, and rehabilitation of a patient with inflammatory pseudotumor. Eur J Dent. 2018;12:454-458.
28. Quinn MJ, Crotty KA, Thompson JF, et al. Desmoplastic and desmoplastic neurotropic melanoma: experience with 280 patients. Cancer. 1998;83:1128-1135.
29. Busam KJ, Mujumdar U, Hummer AJ, et al. Cutaneous desmoplastic melanoma: reappraisal of morphologic heterogeneity and prognostic factors. Am J Surg Pathol. 2004;28:1518-1525.