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Follicular dendritic cells: origin, function, and different disease-associated patterns

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Summary Follicular dendritic cells (FDCs) are a specialized type of antigen-presenting dendritic cells that are largely restricted to lymphoid follicles. They form dense three-dimensional meshwork patterns within benign follicles, which maintain the follicular architecture. The FDC function is to bind and retain antigens by linking to complement and immune complexes and then present these antigens to germinal center B cells that start the secondary immune response. FDCs aid in the rescue of bound B cells from apoptosis, and induce the differentiation of B cells into long-term memory B cell clones or plasma cells. We will discuss the different patterns of the FDC meshwork observed in different types of reactive and neoplastic disorders, which may be due to underlying different roles that FDCs may play in these disorders and whether changes in the architecture of the FDC meshwork can be useful in routine diagnostic practice or have a prognostic value.

1. Introduction

Dendritic cells are a heterogeneous group of antigen-presenting cells that are present in lymph nodes and other organs. Within the lymph nodes, there are at least 4 types of dendritic cells that exist, which provide structural and functional stability for the nodal microenvironment [1]. The four cell types differ in their location, histology, ultrastructure, and function and they include: follicular dendritic cells (FDCs), interdigitating reticular cells, Langerhans cells, and fibroblastic/histiocytic cells [1]. A fifth type of dendritic cell named indeterminate cells (a presumed precursor of Langerhans cells) has been hypothesized to also

migrate to the paracortical area of the lymph node, especially in the context of paracortical hyperplasia [2]. Although FDCs are rarely detected ectopically within the follicles in the synovial tissues of patients with rheumatoid arthritis, they are usually restricted to the follicles of the secondary lymphoid tissue such as lymph nodes, spleen, tonsils, and follicles that occur at extranodal sites [3].

2. Origin of FDCs

The origin of FDCs has been the subject of heavy debates and speculations and remains unclear to date. Identifying a precursor cell for FDCs has proved to be extremely difficult due to the fact that FDCs rarely change their morphology or phenotype, are long-lived for periods of months or even

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years, and seldom proliferate or divide, as demonstrated by the long half-life of radiolabeled antigens on FDCs [4]. The ontogenic development of FDCs has been examined in rodents during the postnatal period, where the development of germinal centers was investigated at different time intervals following antigen administration, and the consensus was that FDC precursors probably result from mesenchymal cell differentiation followed by acquisition of the dendritic long fibers that are arranged in the form of dense meshworks capable of binding immune complexes during the germinal center reaction [5,6].

Moreover, the ultrastructure, cytology, and immunophenotype of FDCs do not support a hematopoietic origin but favor a mesenchymal origin and raise the issue whether they arise from further differentiation of a local fibroblastic reticular cell [7-9] or from a migratory mesenchymal cell, likely from the bone marrow [10,11]. Most ultrastructural studies point to a fibroblastic origin for FDCs in their less differentiated forms; however, the mature FDCs differ from fibroblasts in that they bear a complex network of long branching dendrites that retain an electron-dense material and possess desmosomal and adherent junctions [5].

Using enzyme histochemistry, a change in the enzymatic activity is noted during the presumed transformation of fibroblastic reticulum cells into mature FDCs where alkaline phosphate levels decrease and a positive α-naphthyl acetate reaction in mature FDCs can be detected [12]. The expression of other fibroblast surface markers, such as ICAM1, VCAM-1, 1B10, and 3C8, on the surface of FDCs has also been reported [3,13,14]. Another study has reported the detection of certain bone marrow stromal progenitor cell–related antigens in a subset of the population in FDC-like cell lines cultured from human tonsils cells, which, along with the identification of some contractile activity within the cells and their expression of α-smooth muscle actin (also expressed in bone marrow stromal cells, adipocytes, and osteoblasts), prompted the authors to conclude a possible origin for the FDCs from a migrating bone marrow mesenchymal cell [15]. Numerous other studies regarding the origin of FDCs have been performed that are beyond the scope of this article, but to date, most scholars believe that FDCs have a non-hematopoietic origin and presumably derive from a migrating mesenchymal cell from the bone marrow.

3. Function of FDCs

The function of FDCs is dependent on the development of a healthy FDC meshwork, which in turn is subject to the presence of the proper microenvironment within the germinal center. In mice, no FDC meshwork develops in severe combined immunodeficiency, where B and T cells are nonexistent; however it does develop following the reconstitution of B and T cells [14,16]. The activation of B cells by T cells appears to be particularly critical for the development

of the FDC meshwork, as demonstrated by defective germinal center formation in CD40-deficient mice [17]. Targeting of B cells or FDCs may therefore result in defective germinal center formation, which is seen in cases of rituximab therapy (an anti-CD20 immunoglobulin), where depletion of B cells leads to interruption of both germinal center and FDC development [18]. FDCs have the ability to retain antigen for a long duration (from months to years) trapped within their dendritic processes, which intertwine to form a three-dimensional dense meshwork [19]. They present intact antigen-antibody complexes on their cell surface without the need of major histocompatibility complex like other antigen-presenting cells usually do [14]. The immune complexes are held on the cell surface by Fc receptors such as CD23 (low affinity IgE receptor) and CD32 or by complement receptors such as CD21 (C3d) and CD35 (C3b) [14,20]. Thus, CD21, CD23, and CD35 are all useful as immunohistochemical markers for FDCs in addition to other markers recently reported to be highly sensitive but not specific to FDCs such as clusterin and podoplanin [21], although in the authors' experience, CD21 represents the most reliable and sensitive antibody for highlighting FDCs.

The germinal center B cells that have the highest affinity for binding to the immune complexes trapped within the FDCs survive programmed cell death (apoptosis). These B cells process the antigen, proliferate, and later differentiate into a plasma cell or a memory B cell. The initiation of proliferative activity leading to somatic hypermutation (the hallmark of germinal center cells) may also be dependent on FDC-trapped antigen [22]. FDC function and presentation differs between the light and dark zones of the germinal center. The light zone FDCs strongly express Fc receptors (CD23 and CD32) and complement receptors (CD21 and CD35) and are involved predominantly in immune-complex presentation and selection of B cells [23]. The exact function of dark zone FDCs is not well-defined but they exhibit reduced or no expression of CD23 and CD21, indicating that immune-complex presentation is not their main function and that they are involved predominantly in stimulating the proliferation of the expanding population of B cells that have cytologic features of centroblasts [23]. Some researchers have hypothesized that characterization of the effects of aging on FDCs and the ability of these cells to present antigen and interact with B cells in the development of new germinal centers may have significant implications for the future treatment of immunodeficiency, whether related to aging or disease [22].

4. Patterns of FDCs

The proliferation and transformation of FDCs into neoplastic cells is very rare and gives rise to FDC sarcoma, which typically has an indolent course. In contrast, FDCs are seen in variable numbers in many reactive and neoplastic disorders with different patterns of the FDC meshwork,

which may provide clues as to any possible role that the FDCs might play in these disorders, and further may provide diagnostic or prognostic utility. Six major patterns are usually associated with FDCs (Fig. 1): (1) typical tight/dense meshwork pattern; (2) polarized FDC meshwork pattern; (3) expanded FDC meshwork with extension into the mantle zones; (4) contracted FDC meshwork pattern; (5) distorted/disintegrated FDC meshwork pattern; and (6) nearly absent FDC meshwork with only few, thin, short strands of scattered or rare fibrillary fibers of the FDCs. Generally, FDCs appear to be increased in number in regressed, atrophic, or dismantled germinal centers since the other follicular center cells succumb to death by apoptosis and only FDCs persist as evident by the increased number of FDCs in conditions associated with regressed or dismantled germinal centers such as Castleman's disease and progressive transformation of germinal centers. On the other hand, in conditions such as angioimmunoblastic T-cell lymphoma in which there are often regressed follicles, the FDC proliferation appears to be mainly due to a real increase in the number of these cells, perhaps due to interleukin stimulation. In the pages that follow, we present the different types of

FDC meshwork patterns seen in common reactive and neoplastic disorders and in FDC sarcoma.

4.1. FDCs in reactive follicular hyperplasia

Reactive follicular hyperplasia is caused by stimulation of the intrafollicular B cells by antigens of different types, as a part of the humoral immune response. It is more common in young adults and usually causes localized lymphadenopathy (mainly cervical, axillary, and inguinal areas) [24]. Morphologically, it is characterized by the presence of many large hyperplastic germinal centers that are variable in size and shape and are surrounded by thick to thin mantle zones. Many germinal centers show polarization, in which the densely packed, proliferating centroblasts are mainly confined to the dark zone admixed with tingible-body macrophages, mitotic figures, and rare to few intrafollicular T cells. In contrast, there are mainly centrocytes, intrafollicular CD4-positive T cells, FDCs, and occasional plasma cells located within the light zone. Also, tingible-body macrophages and mitotic figures are generally absent to few
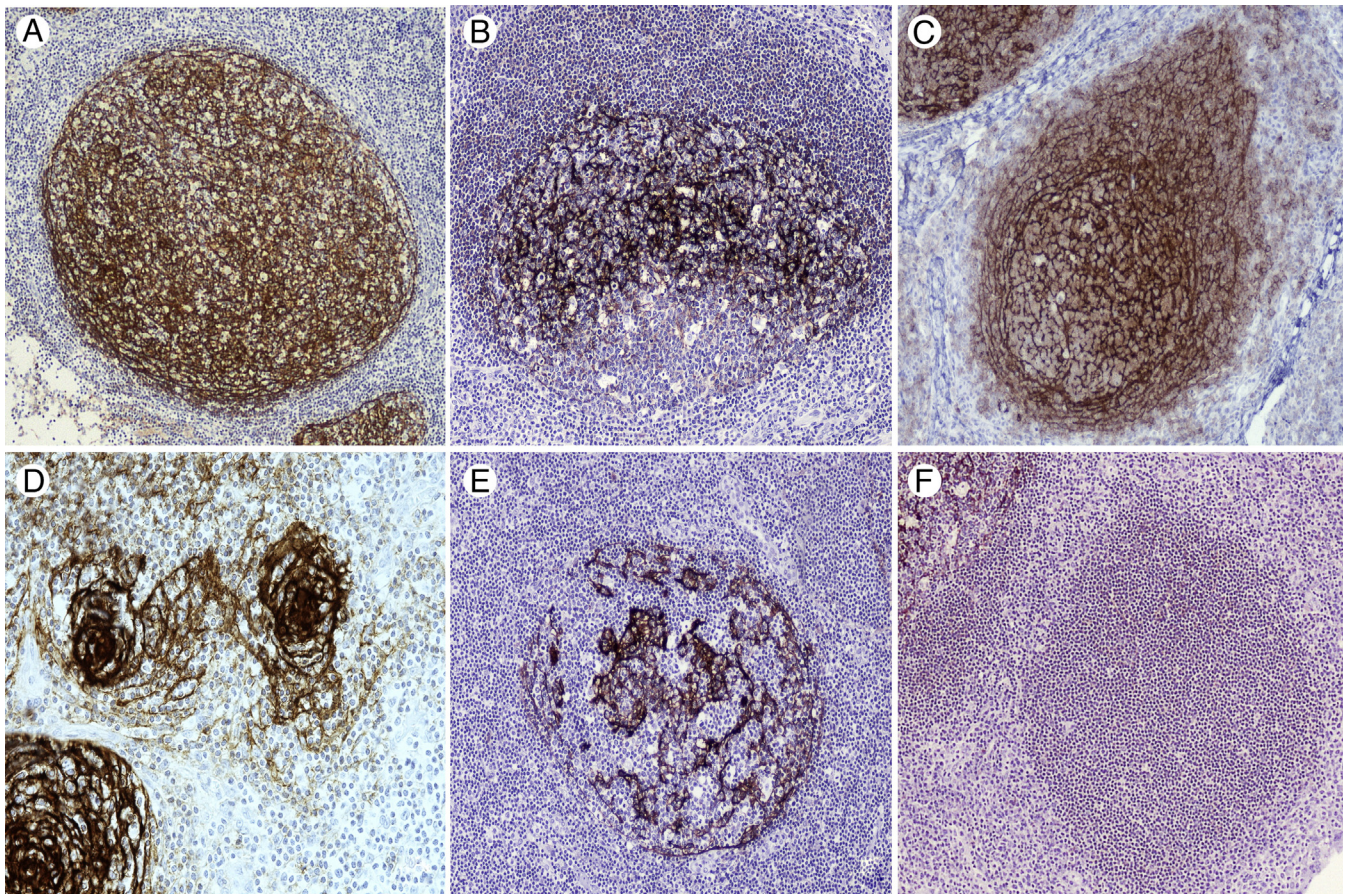
Fig. 1 The composite picture shows the different FDC patterns. A, Typical tight meshwork pattern. B, Polarized FDC meshwork pattern. C, Expanded FDC meshwork with extension into the mantle zones. D, Contracted FDC meshwork pattern. E, Distorted/disintegrated FDC meshwork pattern. F, Nearly absent FDC meshwork with only thin strands representing the presence of rare FDCs. A-F, original magnification ×10.

in the light zone [24]. Using the FDC immunostains such as CD21 and CD23, a characteristic arch-shaped FDC meshwork in the light zone is noted, whereas an absent or a less compact staining is noted in the dark zone (Fig. 2), which confirms the histologic presence of polarity seen in the hematoxylin and eosin (H&E) slides. This polarization is only seen in those follicles wherein a rapid proliferation of centroblasts is required to mount a vigorous immune response. However, in most cases of follicular hyperplasia, a typical tight FDC meshwork pattern is noted throughout the germinal center without evidence of polarization (Fig. 2).

4.2. FDCs in progressive transformation of germinal centers and follicular lysis

After an exuberant germinal center cell proliferation has served its normal physiologic function, it must be terminated, and this usually occurs by dismantling the germinal center cell component for which the term progressive transforma-

tion of germinal centers (PTGC) is used. This sequential process of dismantling the germinal center compartment occurs by extensive inward migration of mostly mantle cells along with T cells leading to progressive fragmentation of the germinal center compartment into islands of centrocytes, centroblasts, and FDCs [25]. In the advanced stages of this process, there is absence of germinal center cells and the presence of mantle cells, scattered FDCs and few T cells. One of the theories about the cause of that inward migration is believed to be due to the redistribution of the germinal center T cells and the loss of their preferential location near the FDCs in the light zone, which likely induces subsequent B-cell migration [25]. Although PTGC has been linked to nodular lymphocyte predominant Hodgkin lymphoma in a small subset of the cases, it is more commonly seen in association with reactive follicular hyperplasia representing part of the spectrum of the reactive changes, where it has been reported that up to 10% of reactive nodes with non-specific lymphadenitis contain one or more areas of PTGC [26]. At the early stages of PTGC process, the FDC
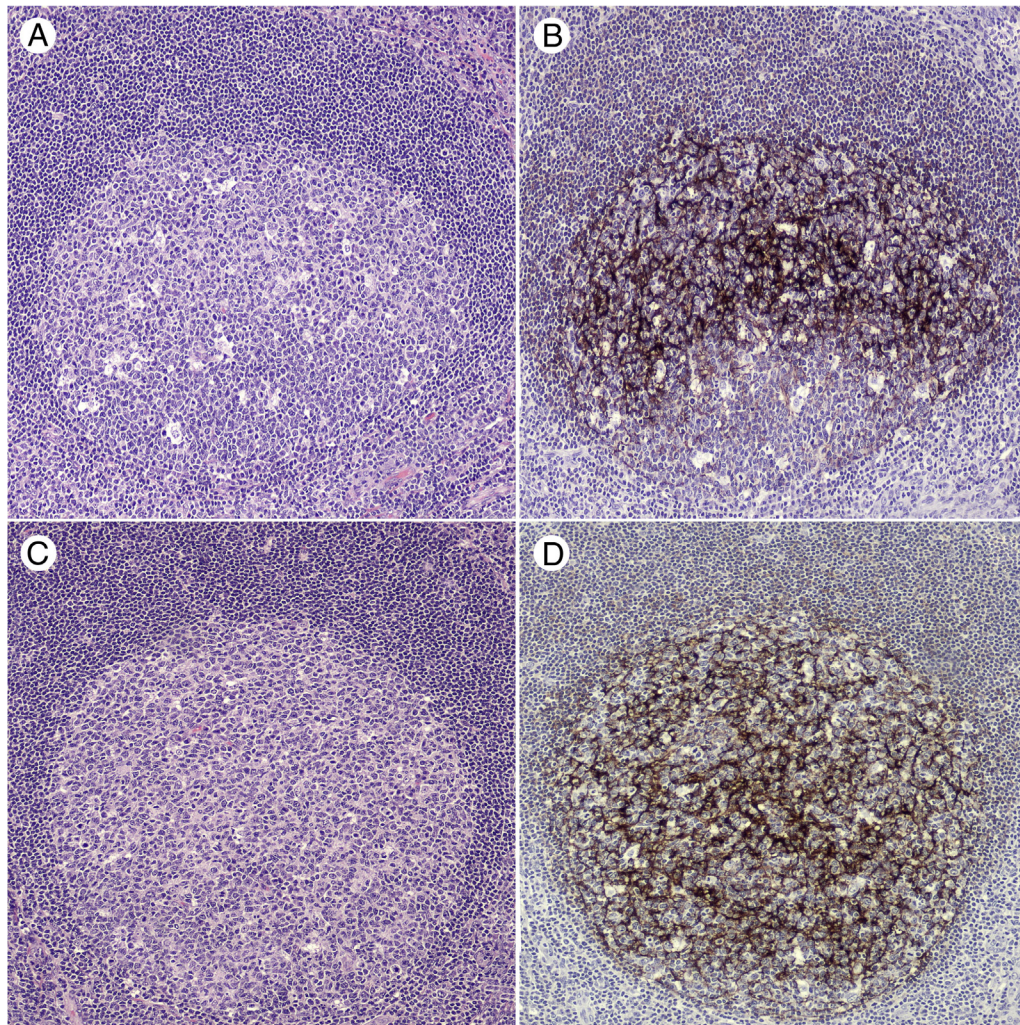
Fig. 2   The composite picture shows the difference between a polarized follicle with H&E staining (A) and CD21 staining (B) and a non-polarized follicle with H&E staining (C) and CD21 staining (D). All pictures were taken at 10× magnification.

meshworks show signs of disruption/disintegration that become more evident as the inward migration of mantle cells and T cells progresses (Fig. 3). Eventually, the germinal centers disappear and FDCs become shorter and thinner, and eventually completely disappear. For these reasons, we believe the best term to describe PTGC is progressive regression of germinal centers.

Follicular lysis is also a process of fragmentation of the germinal center cell compartment and morphologically, it is similar to the process seen in PTGC; however, the germinal center cell compartment shows extensive hemorrhage [25,27]. Follicular lysis is commonly associated with viral infections, especially HIV infection, where it is believed to represent an immune attack against the viral antigens captured by the FDC fibrillary processes leading to destruction of the FDCs with ensuing marked reduction or absence of FDCs in the light zone [27]. Similar to PTGC but more prominently, the FDC meshworks are disrupted/

disintegrated and eventually absent when complete dissolution of the germinal center occurs (Fig. 3).

4.3. FDCs in Castleman disease

Castleman disease was first described in 1956 in a group of patients with localized mediastinal lymph node enlargement and was reported as an indolent process confined to one node [28]. Since then, the definition has broadened to encompass cases with multiple nodal involvement, extranodal presentation, and cases associated with plasma cell hyperplasia. Several nomenclatures and classifications have been proposed for Castleman disease, but currently, the most frequently used includes: localized hyaline vascular type, localized plasma cell type, multicentric plasma cell type, and a mixed type containing features of both hyaline vascular and plasma cell types. The etiology of Castleman disease is
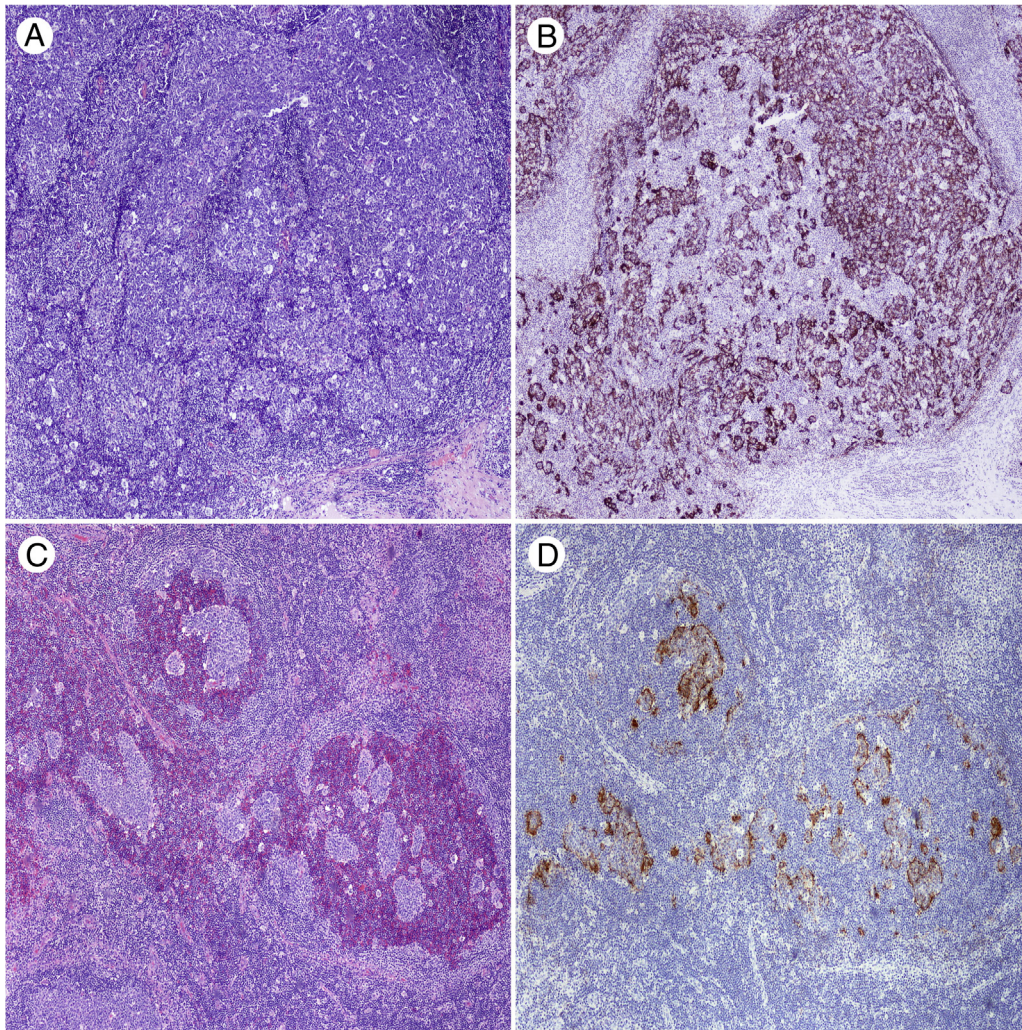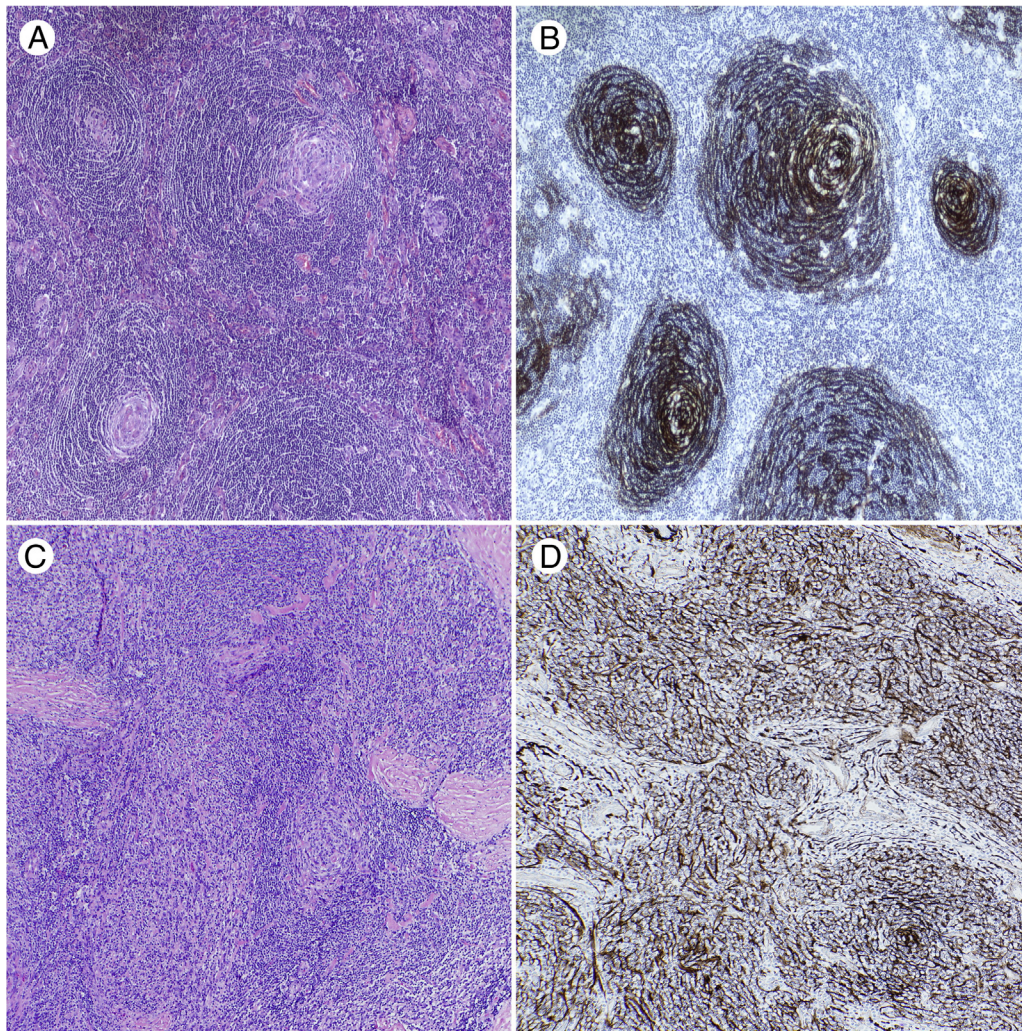

Fig. 3 The composite picture shows a case of PTGCs with H&E staining (A) and CD21 staining (B) and a case of follicular lysis with H&E staining (C) and CD21 staining (D). Note the disrupted/disintegrated FDC pattern seen in both cases. All pictures were taken at 4× magnification.

unknown; however, a possible role for human herpes virus-8 and interleukin-6 in the pathogenesis of the disease has been hypothesized in a subset of cases [24,29].

Morphologically, the hyaline-vascular type shows mainly small regressed germinal centers containing hyalinized small blood vessels that radially penetrate the follicles. The mantle zones are thick and expanded and are often arranged in concentric rings, for which the term "onion skin" pattern is used. The interfollicular areas show small-vessel proliferation [29,30]. FDCs are often prominent with preserved or distorted meshwork pattern, and they comprise the majority of cells within the regressed germinal centers, although thin fibrillary strands of FDCs can also be seen within the expanded mantle zones. A subset of FDCs may show nuclear atypia and can rarely give rise to bizarre hyperchromatic cells, and in some cases, these cells may have multilobated nuclei resembling the lymphocyte predominant (LP) cells of nodular lymphocyte predominant Hodgkin lymphoma [24].

By immunohistochemistry, most follicles show a tight contracted FDC meshwork, while a minority show expanded meshworks (Fig. 4). In some cases, known as the stromal-rich variant, FDCs may be significantly increased in number, have a diffuse pattern of infiltration, and show aberrant FDC meshworks by immunohistochemistry [24] (Fig. 4). The plasma cell type shows mostly hyperplastic instead of regressive germinal centers and a vascular interfollicular area that contains numerous plasma cells. Generally, a preserved FDC meshwork pattern is often noted within the germinal centers. Interestingly, a few cases in the literatures have reported the development of FDC sarcoma as a result of or in association with Castleman disease, exclusively the hyaline vascular type [31,32]. The consistent detection of epidermal growth factor receptor (EGFR) in FDC sarcoma as well as up-regulation of EGFR in the FDCs of Castleman disease has been reported, but not in the FDCs of reactive germinal centers or in the FDC meshworks associated with several

Fig. 4 The upper half of the composite picture shows a case of hyaline vascular Castleman's disease with H&E staining (A) and CD21 staining (B). Note the contracted FDC pattern with extension of the FDC processes into the surrounding thick mantle zones. The lower half shows a case of Castleman's disease, stromal-rich variant with H&E staining (C) and CD21 staining (D). Note that CD21 shows significantly increased number of FDCs that have a diffuse pattern of infiltration. All pictures were taken at 4× magnification.

lymphoma types, suggesting a common pathogenetic factor between the 2 entities [33].

4.4. FDCs in follicular lymphoma

Follicular lymphoma is a non-Hodgkin B-cell lymphoma that arises from and recapitulates germinal center cells (centrocytes and centroblasts), comprising about 20% of all lymphomas [34]. In contrast to marginal zone lymphoma, where it has been suggested that FDCs represent remnants of pre-existing germinal centers that have been colonized by lymphoma cells, the FDCs in follicular lymphoma are thought to represent newly generated cells arising during lymphoma growth and progression, although they remain non-neoplastic bystander cells [23]. Moreover, other investigators have identified two novel FDC-signaling molecules, 8D6 and 4G10/CD44, which are required for tumor formation in vivo as they provide the neoplastic cells with the needed microenvironment for growth, and as a result, lymphomagenesis is inhibited completely when inoculated with monoclonal antibodies against these 2 proteins [35,36]. Recent studies have also utilized gene expression data to suggest a role of the germinal center microenvironment, including FDCs, in predicting the clinical course and behavior of follicular lymphoma [34,37]. Given the presence of 2 populations of FDCs in the light and dark zones of the reactive germinal centers that differ in their immunophenotype and function, conflicting reports have emerged about whether the FDCs in follicular lymphoma recapitulate FDCs from the light zone or dark zone. The more recent studies have suggested an immunophenotype closer to dark zone FDCs, thus possessing a possible role in the stimulation and proliferation of the neoplastic B cells [23,38].

No specific morphologic pattern has been identified for the FDC meshwork in follicular lymphoma although in most cases, the FDC meshwork is either distorted or disintegrated and the fibrillary processes of the FDCs, in most cases, are fewer than in normal follicles, with variable expression of CD21 and CD23 [34]. In contrast, in the interfollicular and diffuse areas of follicular lymphoma, the FDCs are absent [34,39]. Such distinction is important because in follicular lymphoma, the follicles are sometimes large, very poorly defined, and do not have any mantle zones surrounding them, and therefore, they are very difficult to recognize, and such follicles appear as diffuse areas (diffuse pattern). Such examples can be really classified as a follicular and diffuse lymphoma or as a diffuse lymphoma. In fact, in follicular lymphoma grade 3, presence of diffuse areas has to be designated separately as a diffuse large B-cell lymphoma, and since this designation connotes aggressive clinical behavior requiring aggressive treatment, it is crucial to do a CD21 stain to demonstrate absence of FDCs in the areas that appear to be diffuse and, importantly, that these areas should not be interfollicular areas. In the areas that appear to have a diffuse pattern, presence of few, loose aggregates of thin fibrillary strands of FDCs represent follicular pattern and not diffuse pattern.

In addition, rare cases of diffuse large B-cell lymphoma that exhibit a very monomorphic diffuse population of large lymphoid cells, also display a very vague "follicular-like" pattern, but lacking mantle zones anywhere. Such cases exhibit scattered loose aggregates of short, thin strands of FDCs in the CD21 stain, and hence appear like malignant follicles probably representing follicular lymphoma and a diffuse large B-cell lymphoma. Notwithstanding the presence of these FDCs, we classify such cases as diffuse large B-cell lymphoma that has massively colonized benign germinal centers, and not a follicular and diffuse large B-cell lymphoma. The large cells in such cases are CD10 and bcl-6 negative, and MUM-1 positive, the phenotype of non-germinal center cells (activated B-cell phenotype), which further support that such lymphomas are not of a germinal center cell origin, and hence unlikely to be a follicular lymphoma. Moreover, such lymphomas are genetically much more closely related to diffuse large B-cell lymphomas, rather than a follicular lymphoma.

4.5. FDCs in mantle cell lymphoma

Mantle cell lymphoma (MCL) is a B-cell lymphoma comprised mainly of small- to medium-sized lymphoid cells with slightly irregular nuclear contours and scant cytoplasm. The neoplastic cells mostly correspond to naïve pre-germinal center B cells and carry the characteristic translocation involving the *CCND1* (cyclin D1) gene at the long arm of chromosome 11 and *IGH* at the long arm of chromosome 14 [40]. Several growth patterns have been described for MCL including: (1) nodular growth pattern with residual germinal centers (mantle zone pattern), (2) nodular growth pattern with no residual germinal centers (mantle cell nodular pattern), (3) nodular growth pattern due to colonization of reactive germinal centers (follicular colonization pattern), and (4) diffuse pattern with or without residual germinal centers [41,42]. MCL, in its initial stages usually has a mantle zone pattern, followed by mantle cell nodular and follicular colonization patterns. In advanced stages, the diffuse pattern predominates. When there is a mantle zone pattern, the reactive germinal centers have preserved tight FDC meshworks and are surrounded by the proliferating mantle cells, but as the expansion of the mantle zones continue outwards, a mantle cell nodular pattern is formed resulting in mantle cell nodules with absent FDC meshworks and negative staining for CD21. When the proliferating mantle zones extend inwards in the germinal center, the tight FDC meshwork gets disrupted/disintegrated progressively, and a follicular colonization pattern will be formed. With further histologic progression of the lymphoma, the mantle zones, mantle cell nodules, and the colonized follicles fuse together with an ensuing diffuse pattern. Germinal centers are absent although rarely, small residual germinal centers

may be seen. The FDC meshworks are generally absent, and the CD21 stain is negative except for residual scattered fibrillary FDC strands that can be occasionally seen. The different patterns also have prognostic relevance, where several clinical studies correlated the different growth patterns with survival, and it was reported that the mantle zone pattern (pattern 1) showed superior survival than the nodular (patterns 2 and 3) and the diffuse growth pattern (pattern 4) [43,44]. In addition, a more recent study concluded that cases with a nodular intact FDC meshwork showed a better overall survival time than cases with follicular colonization (disrupted FDC meshwork) or cases with no or diffuse FDC staining [45].

4.6. FDCs in marginal zone lymphomas

Marginal zone lymphoma is an indolent B-cell lymphoma corresponding to post-germinal center memory B cells that derive from and proliferate specifically in extranodal, nodal, and splenic tissue. As such, it was originally subclassified into nodal marginal zone lymphoma, splenic marginal zone lymphoma, and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma); however, in the most recent 2008 WHO classification, each entity is now considered a unique lymphoma subtype [46,47]. Despite the variable clinical presentation and the different genomic profiling results among the three entities, many histologic similarities exist; marginal zone pattern, inverse follicular pattern, follicular colonization, interfollicular and sinus patterns, as well as presence of plasma-cell differentiation, and cytologic features of the marginal zone cells. However, some of these features may be more predominant in one entity over the other [47,48]. Specifically, the organization of the marginal zone B cells in relation to the follicles has resulted in several distinctive morphologic patterns. When they surround naked germinal centers as an outer second layer or surround mantle cell nodules, they will produce an inverse follicular pattern, but when they surround normal follicles with benign mantle zones as a third outer layer, they will produce a marginal zone pattern [49]. As the marginal zone cells extend outwards into the interfollicular areas, they form confluent clusters resulting in an interfollicular pattern or a diffuse pattern in the absence of any follicles at later stages of the disease [49]. The marginal zone cells may also grow inwards into the follicles and produce either partial or complete follicular colonization (Fig. 5) [49]. The FDC meshwork is variably distorted and disintegrated in most cases in all three entities when there is follicular colonization and is more evident in cases with a nodular/follicular pattern [48,50,51]. In CD21 or CD23 immunostain slides that are counterstained with hematoxylin, which permits excellent visualization of nuclear details, small clusters of marginal zone cells are typically seen in the partially colonized follicles among the short FDC strands [51]. Moreover, in some cases, the FDC meshwork within the residual germinal centers may be completely absent, a situation in which some authors have speculated a possible evolution of tumor pattern that may be correlated with disease progression when compared with cases that contain intact or distorted FDC meshworks [51].

4.7. FDCs in angioimmunoblastic T-cell lymphoma

Angioimmunoblastic T-cell lymphoma is a systemic lymphoproliferative disorder that mainly affects older individuals, and is associated with various constitutional symptoms (fever, generalized lymphadenopathy, skin rash, hepatosplenomegaly, and polyclonal hypergammaglobulinemia) [52]. It was initially described as a non-neoplastic lymphoid proliferation representing an abnormal hyperimmune reaction of B cells [53], but subsequent identification of clonal T-cell gene rearrangements has revealed the neoplastic nature of the disease [54]. It has been recently hypothesized that depletion of regulatory T cells (T Regs) may play a role in the pathogenesis of the lymphoma [55]. Morphologically, clusters of clear cells and sheets of neoplastic T cells admixed with small lymphocytes, plasma cells, histiocytes, and immunoblasts are noted, accompanied by marked proliferation of high endothelial venules [52]. The neoplastic T cells exhibit an immunophenotype consistent with that of follicular helper T cells (T_{FH}), including positivity for CXCL-13, PD-1, CD10, Bcl-6, and CD4 [56,57]. Scattered regressed germinal centers are usually noted, although hyperplastic germinal centers are seen during the early stages of the disease. The FDC meshworks within the follicles are usually variably distorted and disintegrated. Also, there is an extra follicular proliferation of FDCs that are typically associated with and located around small blood vessels. The FDC vascular meshworks can be seen by morphology alone when prominent but are best highlighted by immunohistochemistry using the FDC markers CD21 and CD23 [58] (Fig. 6). Variable numbers of small B cells and polyclonal plasma cells are present in addition to a population of Epstein-Barr virus (EBV)–positive transformed large B-lymphocytes (immunoblasts) that are almost always distributed randomly in single cells or as small clusters in association with the FDC aggregates [58] (Fig. 6). Identifying the FDC clusters by immunohistochemistry, mainly in association with blood vessels, constitutes one of the most important criteria for establishing the diagnosis along with the other morphologic and immunophenotypic features, mainly the germinal center phenotype of the neoplastic T cells.

4.8. FDCs in nodular lymphocyte predominant Hodgkin lymphoma

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) comprises about 5% of all Hodgkin lymphoma
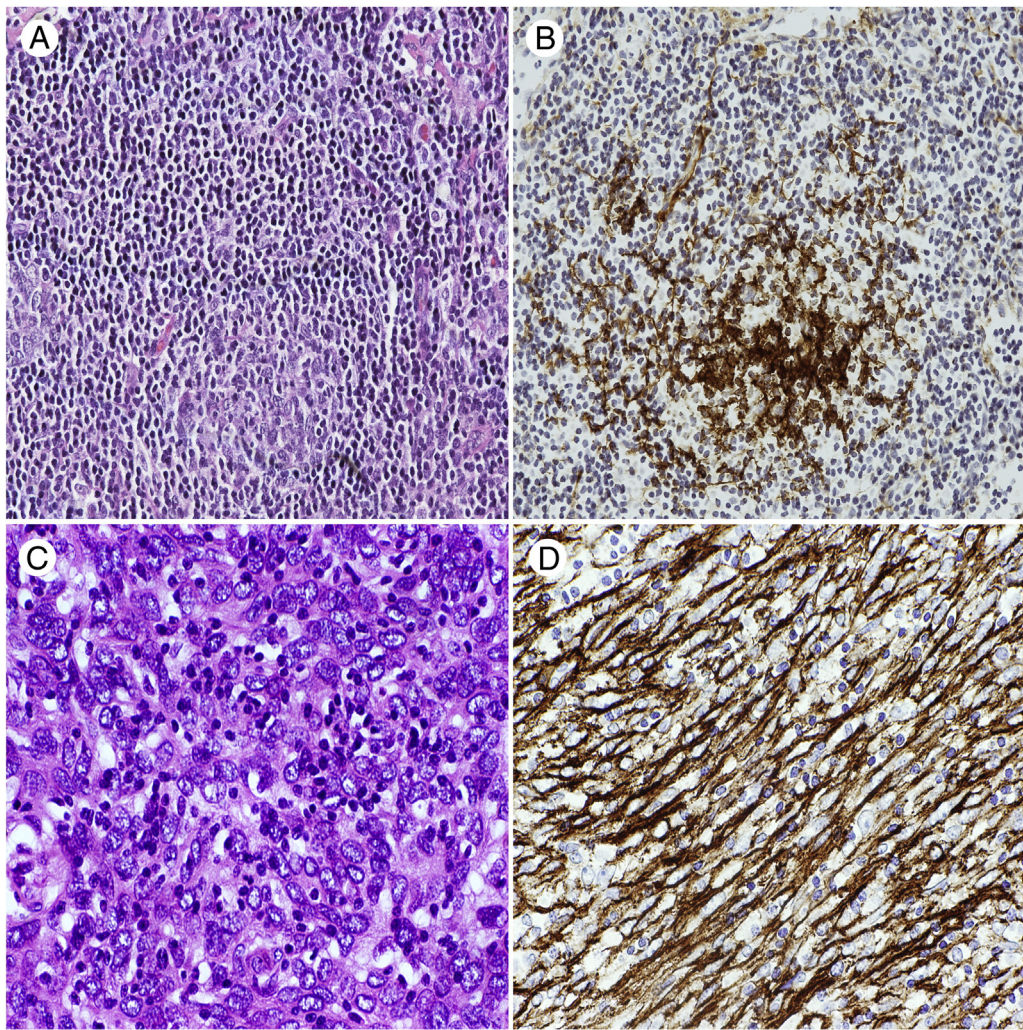
Fig. 5 The upper half of the composite picture shows a case of marginal zone lymphoma with follicular colonization. A, The H&E picture shows a small germinal center surrounded by expanding marginal zone cells, some of which are partially invading and colonizing the germinal center. B, CD21 highlights the disrupted FDC meshwork within the germinal center. The negatively staining marginal zone cells can be seen in between the positively staining fibrillary strands of the FDCs. The lower half of the composite picture shows a case of FDC sarcoma where the H&E stain (C) shows scattered small reactive lymphocytes interspersed between the clusters of neoplastic FDCs. D, The CD21 highlights the FDCs in a diffuse pattern. All pictures were taken at 40× magnification.

cases, and is characterized by a nodular, or a nodular and diffuse proliferation of Hodgkin cells known as popcorn cells or lymphocyte-predominant cells (LP cells) [59]. NLPHL has distinctive morphologic, immunophenotypic, and molecular features that distinguish it from classical Hodgkin lymphoma. Although FDCs have not been implicated in the pathogenesis of NLPHL, the popcorn cells usually reside in nodules that have variably distorted and disintegrated FDC meshworks [59,60]. Most T cells within the nodules of NLPHL are germinal center–derived CD4, CD57, and PD-1 positive T cells that form rings or rosettes surrounding the popcorn cells. Fan et al subclassified NLPHL into 6 distinct immunoarchitectural patterns: (1) classical nodular pattern, (2) serpiginous/interconnected pattern, (3) nodular with prominent extranodular popcorn cells, (4) nodular with T-cell–rich background, (5) diffuse pattern "T-cell–rich B-cell lymphoma like," and (6) diffuse pattern "moth-eaten with B-cell rich background [61]. In patterns 1 and 2, scattered popcorn cells ringed by T cells are present within a nodular reactive background although the nodules may be serpiginous and connected in pattern 2. The FDC processes highlighted by CD21 stain usually sharply delineate the unstained popcorn cells and their T-cell rosettes [61,62] (Fig. 7). In pattern 3, the extranodular popcorn cells are present outside ill-defined nodules and are usually not associated with FDC meshworks or T-cell rosetting. In pattern 4, the popcorn cells are present in nodules with prominent T-cell–rich background and a lesser number of B cells. The FDC meshworks are usually retained although they often become more attenuated with fewer B cells. In pattern 5, the popcorn cells are present in a diffuse background of mainly T cells and a near absent FDC
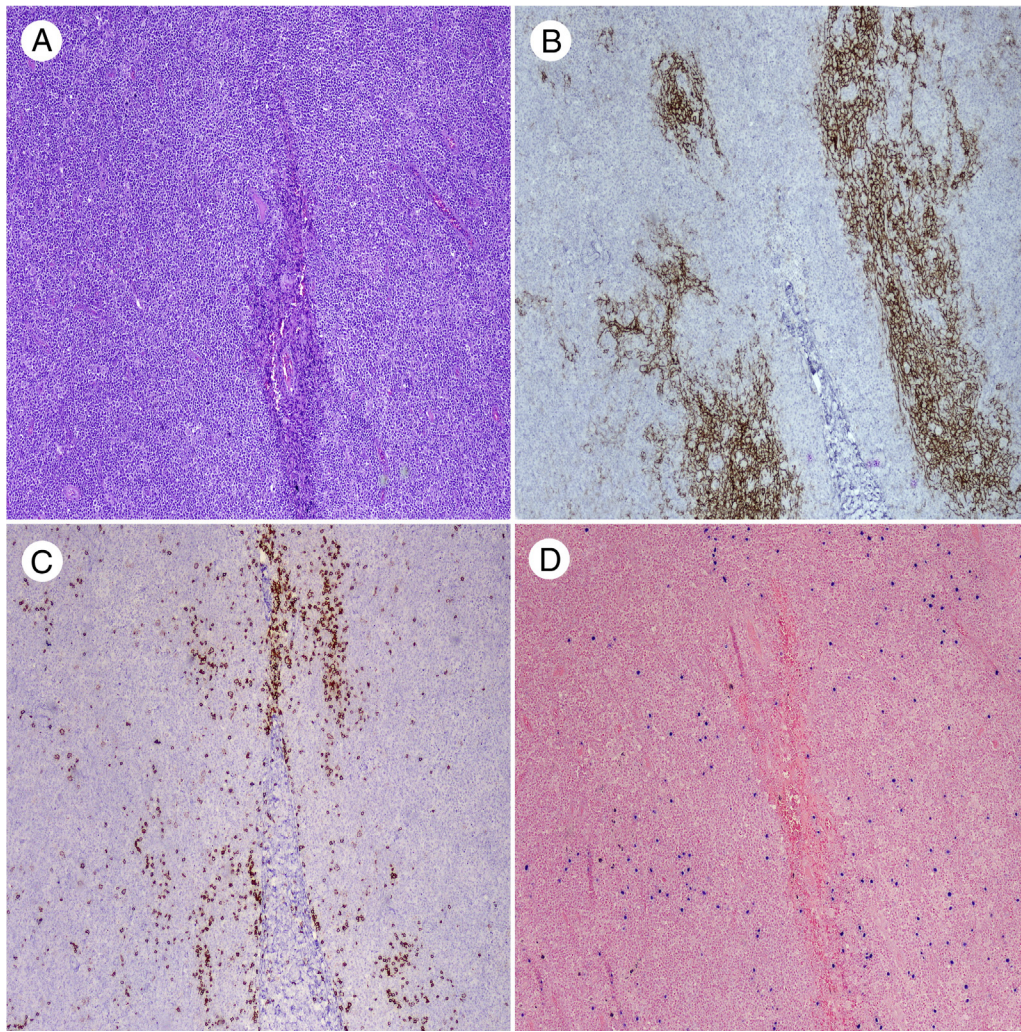
Fig. 6 The composite picture shows a case of angioimmunoblastic T-cell lymphoma (AITL). A, The H&E stain shows a diffuse lymphocytic infiltrate with mild vascular proliferation. B, CD21 highlights the dense extrafollicular FDC meshwork that is mainly surrounding the large blood vessel. C, CD20 highlights the scattered large B-immunoblasts around the blood vessel and in close proximity to the FDCs. D, The EBER stain highlights the scattered EBV positive immunoblasts. All pictures were taken at 4× magnification.

meshwork. Pattern 6 is similar to pattern 1 (classical nodular type) but lacks the formation of distinct nodules and is associated with a prominent FDC meshwork.

Cases that progress to diffuse large B-cell lymphoma tend to completely lose the FDC meshworks and may only contain scattered CD21-positive FDC cells by immunohistochemistry, where it has been hypothesized that the germinal center microenvironment containing FDCs may be needed for the survival of the popcorn cells and that their transformation into activated B cells may represent a module in which they can survive outside germinal center supportive environment [63]. Despite the similarities and the presence of some overlapping features between NLPHL and T-cell/histiocyte-rich B-cell lymphoma, the T cells in T-cell/histiocyte-rich B-cell lymphoma lack the CD10, Bcl-6, and PD-1 staining as they are not of a germinal center origin, and minimal or no FDC meshworks can be detected in such cases although results in large series of cases have not been reported [62].

4.9. FDCs in classical Hodgkin lymphoma

Classical Hodgkin lymphoma (CHL) is a monoclonal lymphoid neoplasm arising, in the vast majority of cases, from a mutated germinal center B cell [64]. Mononuclear Hodgkin cells and multinucleated Reed-Sternberg cells are present residing in an infiltrate comprised of a variable reactive inflammatory cells including small lymphocytes, eosinophils, plasma cells, histiocytes, and neutrophils [64]. CHL is subdivided into four subtypes: nodular sclerosis, lymphocyte rich, lymphocyte depleted, and mixed cellularity. In contrast to NLPHL, the relationship and distribution patterns of FDCs in the different subtypes of CHL have been infrequently studied. In the lymphocyte-rich subtype, two growth patterns are usually seen, a common nodular pattern and a rare diffuse pattern. The nodular pattern is similar to that seen in NLPHL in respect to the presence of small lymphocytes, but the malignant Hodgkin cells exhibit the
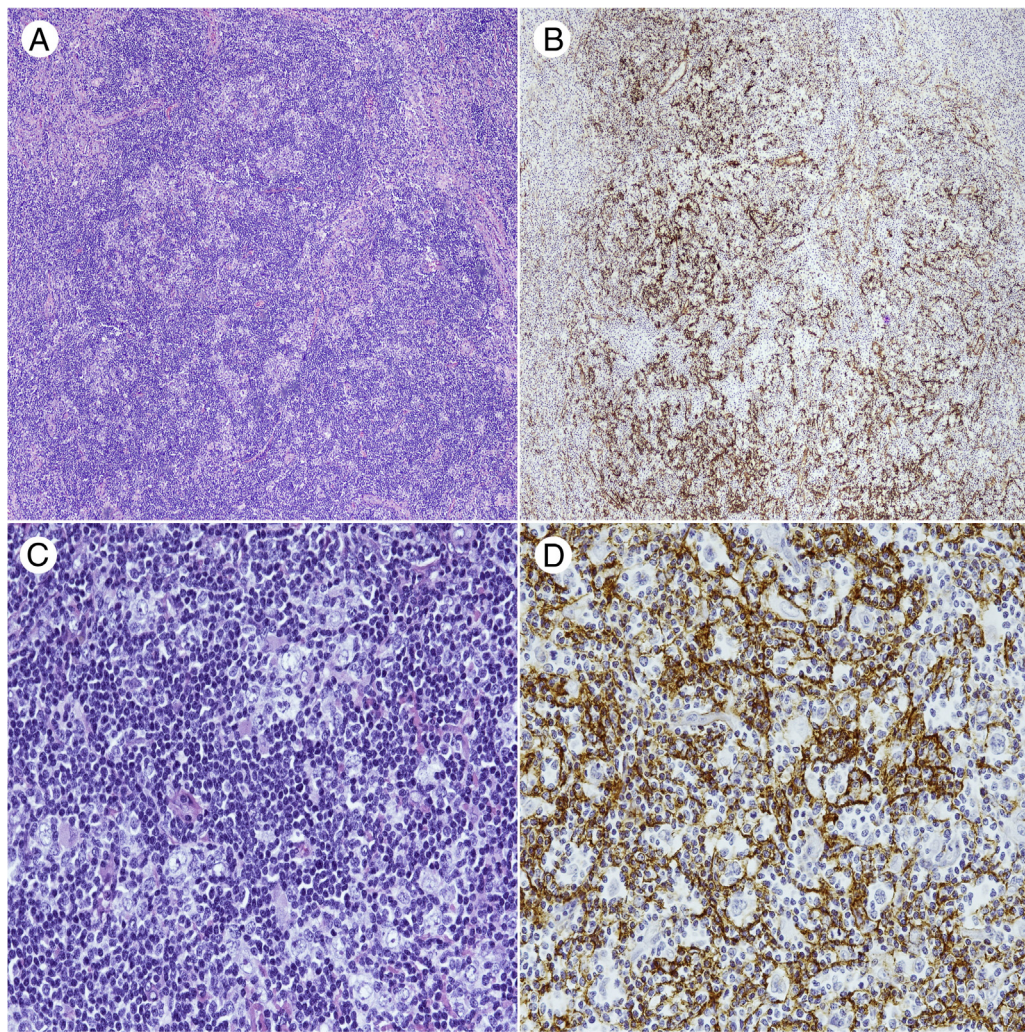
Fig. 7 The composite picture shows a case of nodular lymphocyte predominant Hodgkin lymphoma. At low magnification (4×), the H&E stain (A) shows a large nodule with the characteristic moth-eaten pattern, while CD21 stain (B) shows a mainly disrupted/disintegrated FDC meshwork. At high magnification (40×), the H&E (C) shows the characteristic popcorn cells interspersed in a background of small lymphocytes and scattered histiocytes, while CD21 (D) highlights the FDC processes that are delineating the unstained popcorn cells and their T cell rosettes.

phenotype of CHL (positive for CD15 and CD30, faintly positive for Pax-5, and negative for CD45 and CD20). In the authors' experience as well as in few reported studies, the FDC meshworks are usually present and are relatively intact in the nodules and sometimes may be distributed in a pattern similar to that seen in NLPHL [65,66].

In the nodular sclerosis and mixed cellularity subtypes, scattered reactive germinal centers are usually seen and they have a preserved FDC meshwork pattern. In addition, mantle cell nodules are frequently present, and the FDC meshworks in these nodules are disrupted or disintegrated, and sometimes loose and irregularly arranged dendritic processes can be seen surrounding Hodgkin cells. The borders of these mantle cell nodules are often scalloped, and in these areas Hodgkin cells are frequently present, sometimes forming small clusters. The meshworks may be disrupted in the mixed cellularity subtype, but usually completely absent in

the lymphocyte-depleted type [65,66]. The absence of the meshworks in the lymphocyte-depleted subtype is thought to be due to the loss of the ability of the Hodgkin cells to bind to the FDCs, which as discussed above, are needed for antigen presentation and for B- and T-cell survival, and as a result, progressive break-up of the FDC meshworks may partly be responsible for the lymphocytic depletion [66]. Earlier studies have examined the association of FDCs with the clinical outcome in patients with CHL, and an intermediate prognosis was reported in FDC-positive cases by immunohistochemistry (44% of the cases studied) compared to a guarded prognosis for the FDC-negative cases [67]. Similar results were reported in another study, although it was mainly confined to the nodular sclerosis subtype of CHL, where the authors reported the presence of FDC meshworks, whether intact or disrupted, in about 70% of their cases and that the cases with intact FDC meshworks exhibited

relatively better prognosis than those with disrupted meshworks and a much better prognosis than those with absent FDC staining by immunohistochemistry [66].

4.10. Follicular dendritic cell sarcoma

FDC sarcoma is a rare neoplasm characterized by proliferation of FDCs that usually exhibit the typical morphology and immunophenotype of non-neoplastic FDCs. The etiology of that neoplastic transformation is yet to be known, although it may evolve in situations in which there is FDC hyperplasia and overgrowth [68]. It usually occurs de novo; however, it can occur in association with Castleman disease (exclusively hyaline vascular type) in a small subset of the cases, whether simultaneously or as a succeeding event [68]. FDC sarcoma typically involves lymph nodes, mainly cervical nodes, in up to two-thirds of the cases but it can also involve extranodal sites such as the tonsils, spleen, gastrointestinal tract, skin, and breast [68-70]. Patients usually present with a slow-growing painless mass and no systemic symptoms.

The neoplastic cells can be spindled, polygonal, or ovoid in shape and tend to exhibit a storiform, whorled, trabecular, or a diffuse pattern of involvement (Fig. 5). Cytological atypia is present only in a subset of cases, and mitotic figures are common but highly variable in number. In both nodal and extranodal cases, interspersed reactive lymphoid cells and uninvolved lymphoid tissue are often seen. A recently described variant called the inflammatory pseudo-tumor-like variant has been reported to occur exclusively in the liver and spleen, exhibit a prominent lymphoplasmacytic infiltrate, and consistently express EBV by in situ hybridization [68]. By electron microscopy, the neoplastic cells show numerous interwoven long processes that are connected with desmosomes but with no cytoplasmic interdigitation or Birbeck granules [1]. Immunophenotypically, FDCs are positive for CD21, CD23, clusterin, and/or CD35, and they do not exhibit any characteristic staining pattern. In addition, they are usually positive for vimentin, fascin, HLA-DR, and epithelial membrane antigen (EMA) and variably positive for CD68, S-100, and CD45 [1,68]. The Ki-67 proliferation index is usually about 15%-25% [68]. No definitive EBV association has been established in any large study, except in the inflammatory pseudotumor variant [68,71,72]. The clinical course is typically indolent although local recurrences have been reported in up to 50% of the cases, and metastasis may occur in up to 25% of the cases; such events may occur many years after the initial diagnosis [68,71].

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