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Review

Follicular dendritic cell sarcoma

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Summary

Follicular dendritic cells (FDC) are mesenchymal-derived dendritic cells located in B-follicles where they play a pivotal role in triggering and maintaining B-cell adaptive immune response. In 1986 Dr. Juan Rosai first reported a series of neoplasms showing features of FDC and defined it as Follicular Dendritic Cell Tumor, subsequently renamed as "sarcoma" (FDCS). In its seminal and subsequent articles Rosai and colleagues highlighted the heterogeneous microscopic appearance of FDCS and its immunohistochemical and ultrastructural features.

FDCS mostly occurs in extranodal sites (79.4% of cases) and lymph nodes (15.1%); in about 7%-10% of cases it is associated with hyaline-vascular Castleman disease. Given its significant growth pattern and cytological variability, FDCS can be confused with various neoplasms and even inflammatory processes. The diagnosis requires the use of a broad spectrum of FDC markers (e.g. CD21, CD23, CD35, clusterin, CXCL13, podoplanin), particularly considering that tumor antigen-loss is frequent. The inflammatory-pseudotumor-like (IPT-like) variant of FDCS, in addition to its peculiar histopathological and clinical features, is characterized by positivity of tumor cells for Epstein-Barr virus, representing a diagnostic requisite.

No distinctive genetic and molecular anomalies have been identified in FDCS. It often carries an aberrant clonal karyotype and chromosomal structural alterations, frequently involving onco-suppressor genes. Direct or next generation sequencing showed alterations on genes belonging to the NF-κB regulatory pathway and cell-cycle regulators. In contrast to hematopoietic-derived histiocytic and dendritic cells tumors, FDCS typically lacks mutations in genes related to the MAPK pathway.

FDCS recurs locally in 28% and metastasizes in 27% of cases. Extent of the disease, surgical resectability and histopathological features are significantly associated with the outcome. IPT-like FDCS behaves as an indolent tumor, even if it often recurs locally over years.

Complete surgical excision is the gold standard of treatment. Data on targeted therapies (e.g.: tyrosine kinase inhibitors) or immune checkpoint inhibitors are very limited and responses are variable. A better understanding of the molecular drivers of this tumor may lead to potential new therapeutic strategies.

Key words: follicular dendritic cell sarcoma, diagnosis; mutations, personalized medicine

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Introduction

Primary malignant neoplasms showing features of follicular dendritic cells (FDC) were first recognized by Monda and Rosai in 1986 [1]. The four patients described had tumors involving cervical lymph nodes that had been variously diagnosed as lymphoma, lymphosarcoma, metastatic malignant fibrous histiocytoma, and metastatic hemangiopericytoma. This original report defined the distinctive light-microscopic appearance of this tumor, as well as its immunohistochemical and ultrastructural features. Additional details on this entity were provided in a report of 13 cases from Dr. Rosai's consultation [2,3]. In particular, the study highlighted the frequent extranodal location of the tumor, the primary role of complete surgical resection as

treatment of choice, the spectrum of neoplasms mimicking FDC tumor (nowadays redefined as "sarcoma"), and the relationship between histopathological features (e.g.: necrosis, nuclear pleomorphism, high mitotic activity) and aggressive clinical behavior. An extensive review on FDC tumor was subsequently published by Perez-Ordonez and Rosai in 1998 [3].

In this article we summarize data on normal FDC and their physiological functions, FDC abnormalities in some hematolymphoid disorders, and the clinical, histopathological, phenotypic and molecular features of FDC sarcoma.

Origin and functions of FDC

FDC are mesenchymal-derived cells located in the B follicles, where they capture, retain and present antigens to surrounding B cells [4,5]. These cells were originally described in human lymph node B follicles by Maximow in 1927 and defined as "embryonal non-phagocytic reticulum cells" [6]. On electron microscopy FDCs revealed extensions and interdigitations of their plasma membranes in close association with other cells of the germinal center [7-10], suggesting that they might play an important role in the germinal center reaction, as subsequently demonstrated by a series of experimental studies (reviewed in [4]).

Together with other members of the stromal compartment of secondary lymphoid organs (fibroblastic reticular cells and marginal reticular cells) FDC share a mesenchymal precursor located in the perivascular area [4,11]. FDC differentiation occurs in two steps, with initial development of pre-FDC triggered by lymphotoxin (LT) $\alpha\beta$ and leading to the expression of milk fat globule-EGF factor 8 (Mfge8*)* and chemokine (C-X-C motif) ligand (CXCL)13, and final maturation into complement receptor-positive FDC, mediated by both LT$\alpha\beta$ and Tumor Necrosis Factor (TNF) Receptor-1 [4].

FDC immune functions are mediated by interactions with other components of the B-cell follicle, particularly in the microenvironment of germinal centers (GC) [4,5] (Fig. 1). By CXCL13 FDC recruit C-X-C chemokine receptor (CXCR)4 and CXCR5-positive B and T lymphocytes within the follicles. Moreover, interactions of FDC with B cells are based on adhesion molecules (Vascular Cell Adhesion Molecule 1/VCAM1 and Intercellular Adhesion Molecule 1/ICAM1) that bind their ligands (integrins ITGA1 and ITGB2, respectively) on lymphocytes. These immunological synapses and their functional modulation establish the effectiveness of the adaptive immune response following antigen capture and presentation by FDC as immunocomplexes (IC) [12]. IC are shuttled to FDC from the marginal sinus and bound to FDC by either complement or Fc receptors (e.g. CR2/CD21, CR1/CD35, FCER2/CD23, FCGR2A/CD32). FDC retain IC in endosomes for a long period, periodically recycling them on the cell surface to enhance B-cell activation [13]. Through binding the antigen on FDC surface, B-cells receive pro-survival signals, including the B-cell activating factor (BAFF) secreted by FDC. In addition, FDC can modulate the adaptive response by sensing via toll-like receptor (TLR)4 environmental innate stimuli, and the activation of the TLR signaling induces expression of CXCL13, tumor growth factor β receptor and BAFF, which respectively mediate recruitment, class-switch recombination, and survival of B cells.

FDC express CD40 [14] from which depends the efficiency of the FDC network through CD40-CD40 ligand interaction with B cells and T follicular helper cells [14,15]; notably, CD40/CD40L deficiency causes lack of immunoglobulin class switch recombination and is associated with defective or absent FDC meshwork in the follicles [15,16]. During the GC reaction B-cells with low-affinity B-cell receptor undergo apoptosis and are phagocytized by tingible body macrophages; this process is mediated by Mfge8 secreted by FDC [17], and it has been shown to prevent the development of autoimmunity [17].

Morphology and phenotype of normal FDC

FDC are characterized by abundant poorly defined eosinophilic cytoplasm with long dendritiform processes. The nucleus is large, round to ovoid and contains a small eosinophilic nucleolus; chromatin is finely dispersed and the nuclear membrane is sharply defined. FDC are often bi- or multinucleated, with nuclear overlap and molding (so-called "kissing" pattern) [5] (Fig. 2); these features facilitate FDC recognition also in cytological smears. On electron microscopy, the cytoplasmic extensions of FDC form an intricate network connected through desmosomes and are coated by amorphous electron-dense material corresponding to immunocomplexes [7-8]. Markers originally used to identify FDC on frozen and paraffin sections such as DRC-1 (R4/25), recognizing the long form of CD21 (CD21L), CNA.42, Ki-FDC1p and Ki-M4p [5] have been replaced by CD21, CD23 and CD35. FDC are also positive for Clusterin [18], a secreted apolipoprotein acting as B-cell trophic factor [19] and CXCL13, with a peculiar dot-like Golgi pattern [20]. In keeping with their intercellular junctional apparatus, FDC express desmoplakins and Claudin 4 [21]. They are also positive for Podoplanin and for the low affinity NGFR, although little is known about their functions

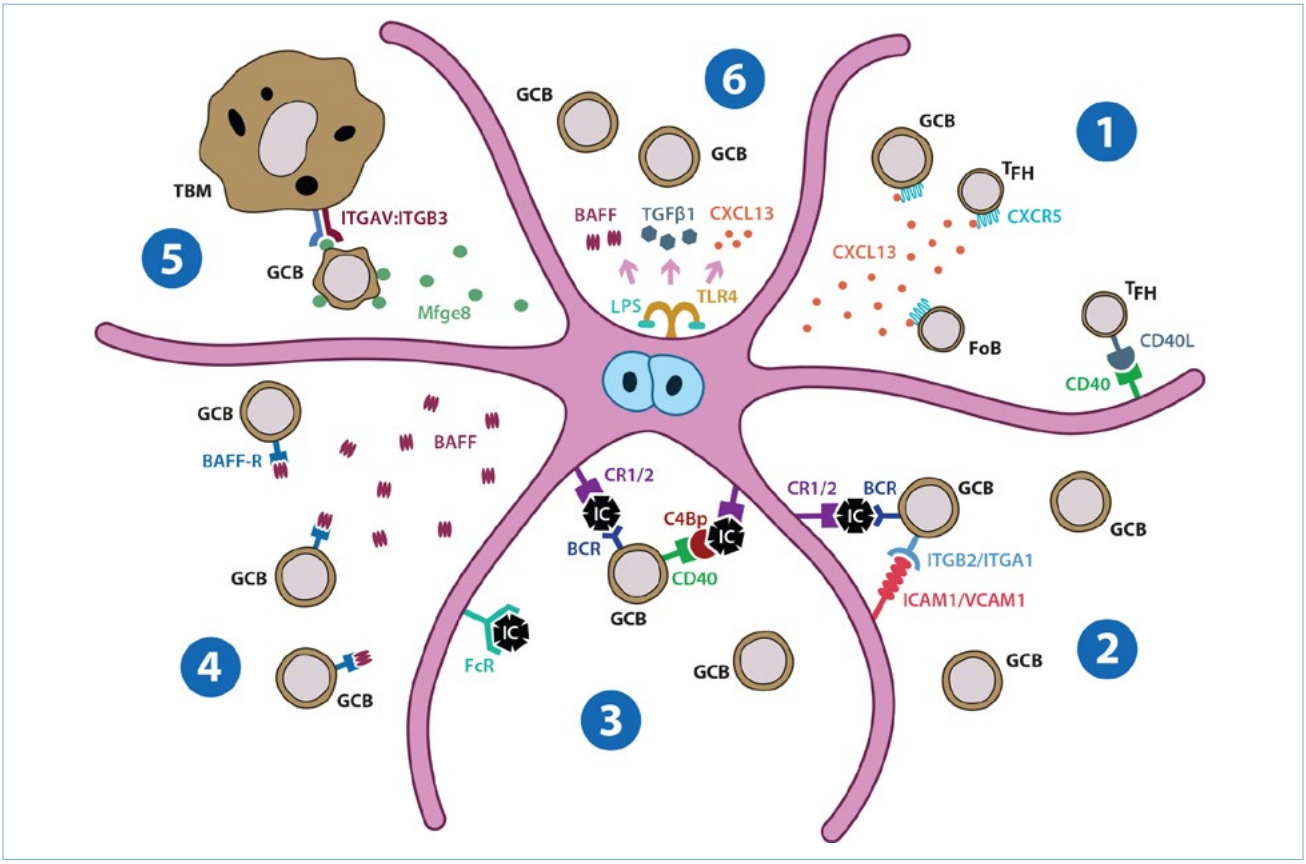

Figure 1. Follicular dendritic cell (FDC) functions in the germinal center. FDC plays a crucial role in the recruitment of B and T cells in B follicles, especially by secreting CXCL13 (1) and interacting with B cells by integrins and cognate receptors (2). FDC cell membrane is lined by immunocomplexes which are "exposed" to germinal center B-cells (2, 3). FDC promotes B-cell survival and maturation through secretion of various B-cell growth factors, especially BAFF (4). During the germinal center reaction, B-cells with low-affinity B-cell receptor undergo apoptosis and are phagocytized by tingible body macrophages, a process mediated by Mfge8 secreted by FDC (5). FDC can modulate the adaptive response by sensing, via TLR4, environmental innate stimuli (e.g. microbial lipopolysaccharides) resulting into TLR signaling that induces production of factors (CXCL13, TGFβ1 and BAFF), which contribute to recruitment, class-switch recombination and survival of B cells (6). For details see paragraph (Origin and functions of FDC). BAFF, B activating factor; BAFF-R, BAFF receptor; BCR, B-cell receptor; C4Bp, Complement component 4 binding protein; CD40L, CD40 Ligand; CR, Complement receptor; CXCL13, C-X-C motif chemokine ligand 13; CXCR5, C-X-C motif chemokine receptor 5; FcR, Fc receptor; FoB, Follicular B-cell; GCB, Germinal center B-cell; ICAM1, Intercellular adhesion molecule 1; IC, Immunocomplex; ITGA1, Integrin subunit alpha 1; ITGAV:ITGB3, Integrin subunit alpha V: beta 3; ITGB2, Integrin subunit beta 2; LPS, Lipopolysaccharide; Mfge8, Milk fat globule-EGF factor 8; TBM, Tingible body macrophage; TGFβ1, Transforming growth factor beta 1; $T_{FH,}$ T follicular helper cells; TLR4, Toll-like receptor 4; VCAM1, Vascular cell adhesion molecule 1.

in FDC [22,23]. Antigens expressed by FDC, but rarely used for diagnostic purposes are the epidermal growth factor receptor [24], estrogen receptor alpha [25] and gamma-synuclein [26].

FDC show diverse immunoreactive patterns depending on the follicle developmental stage. They are localized in the central region of primary B follicles and are particularly abundant in the light zone of secondary follicles, where they strongly express CD21, CD23 and CD35; in contrast, in the dark zone FDC are less abundant and CD23 and CD35 are downregulated, together with VCAM1 and ICAM1 [14, 27].

FDC in hematological disorders

As components of the microenvironment of several lymphoproliferative disorders FDC [28] may play a role

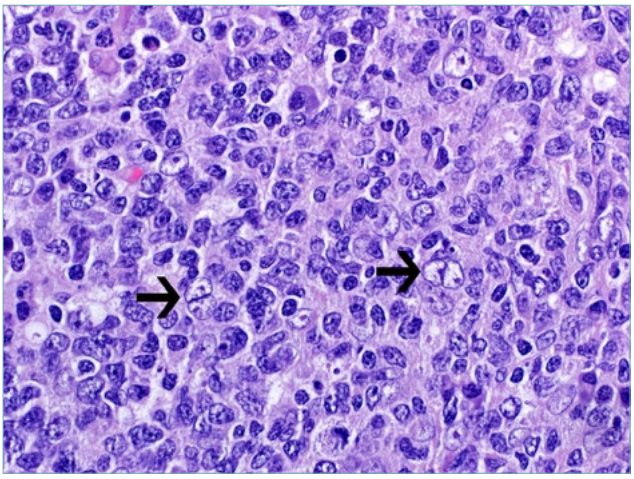

Figure 2. Follicular dendritic cells in a reactive germinal center are typically recognizable by their medium-sized nuclei, showing well demarcated membranes and single small nucleoli; paired nuclei often show membrane molding (arrows).

in their pathogenesis [29-31]. Moreover, the evaluation of FDC pattern of distribution is helpful in the overall interpretation of pathological processes, especially in Castleman's disease, follicular lymphome (FL), and angioimmunoblastic T-cell lymphoma (AILT).

Castleman disease is typically associated with abnormalities of FDC, especially in the hyaline-vascular histological subtype (HV-CD) and in the multicentric variant [32,33].

In HV-CD, large B follicles composed of small mantle B cells surround one or more regressing germinal centers. FDC form a dense concentric array in the mantle which displays an onion-skin pattern, while in the germinal centers they are admixed with hyalinized blood vessels and often show nuclear atypia [34]. Cytogenetic [35] and molecular studies [36] demonstrated the clonal nature of these FDC, accounting for the association of HV-CD with overt FDC sarcoma in some cases [37,38]. Notably, the evolution from HV-CD to FDC sarcoma is generally accompanied by enrichment of the interfollicular area of endothelial and myoid cells, and numerous atypical FDC [39]. In multicentric CD, B-follicles may have hyperplastic unremarkable features or can be associated with regressing germinal centers with abnormal FDC as in HV-CD. The degree of FDC prominence has been recently included in the histological criteria to identify idiopathic multicentric CD [40].

FL recapitulates the germinal center reaction where FDC may play an active role instead of merely representing bystander cells. It has been shown that FDC-dependent CXCL12/CXCR4 signaling fosters establishment of follicular B-cell proliferations and FDC sustain survival of therapy-resistant lymphoma stem cells; moreover, FDC-derived signals of angiogenesis, adhesion, migration and survival to neoplastic follicular B-cells have been detected by gene expression analysis of FL-FDC co-cultures. In FL, FDC phenotype recapitulates that observed in GC dark zone FDC, with positivity for CD21 and Clusterin, but weak or negative expression of CD23, CD35 and ICAM1 [5,27,32]. Recently, the expression of estrogen receptor in FDC in cases FL was found to be associated with low grade and good prognosis [41], while positivity of CD14 was an independent predictor of transformation into large B cell lymphoma [29].

In the early stages of AITL, including peripheral T-cell lymphoma with a follicular growth pattern, no significant FDC abnormalities are recognizable. In contrast, in full blown AITL an abnormal hyperplastic meshwork of FDC is intermingled with atypical T cells in the extrafollicular areas, representing an useful diagnostic feature, helping in the differential with other peripheral T cell lymphomas [5]. Notably, in some cases the FDC hyperplasia is prominent up to mimicking an incipient FDC sarcoma [42]. As in FL, FDC in AITL express CD21, while CD23 and CNA.42 are weak or negative [43]. In AITL, anti-CXCL13 stain is mainly useful to detect neoplastic follicular helper T-cells, and is often lost by FDC.

Follicular dendritic cell sarcoma

Follicular dendritic cell sarcoma (FDCS), previously known as "tumor", is a rare neoplasm composed of cells with morphological and immunophenotypic features of FDC. Since the original description in 1986 several cases of FDCS have been published as single case reports or small series, and the clinical and histopathological features are nowadays rather well defined. Nevertheless, FDCS remains an intriguing neoplasm, occurring at different body sites where it may simulate various tumors or even inflammatory processes; moreover, FDCS shows an unpredictable clinical course and an effective treatment for recurring or metastasizing cases is still lacking. Very recently new data on the mutational landscape and gene expression of FDCS have been provided, but specific and recurrent anomalies were not identified.

Clinical presentation

FDCS has no gender predilection [44,45], and mainly occurs during adulthood (median age 49 years; range 8-90) [44] with very few pediatric cases reported [46-51].

FDCS can involve any anatomical area (Tab. I). It predominantly occurs in extranodal sites (79.4%), particularly the liver, the spleen, and the gastrointestinal tract [44,52,53]. Nodal involvement occurs in about 15% of cases, and may be associated with extranodal tumors. FDCS mostly presents as a slow-growing mass, asymptomatic or painful. The inflammatory pseudotumor (IPT)-like variant is characterized by rather peculiar clinical features, such as female predilection, involvement of liver or spleen, frequent systemic symptoms like fever, malaise and weight loss [54] and EBV infection of tumor cells [53-56]. Recently the clinicopathological scenarios of this variant has been broadened by the observation of cases in extra-hepatosplenic involvement (e.g.: gastrointestinal tumors presenting as colonic polyps, mesocolon, palatine or nasopharyngeal tonsils) [51,57-60]. Moreover, tumors located in the colon occurred in individuals of Asian origin and did not show the typical female prevalence [51].

Table I. Site of disease of 809 Follicular dendritic cell sarcoma cases reported in the English literature from 1986 to June 2021.

Sites	
Extranodal	642 (79.4%)
Nodal	122 (15.1%)
Nodal and Extranodal	45 (5.5%)
Nodal	
Abdominal	31
Axillary	26
Cervical	29
Mediastinal	25
Inguinal	8
Not specified	3
Extranodal	
Liver	84
Spleen	84
Gastrointestinal tract	69
Tonsil/Adenoid	57
Mediastinum	42
Lung	40
Retroperitoneum	34
Soft tissues	30
Mesentery	30
Bone	15
Parapharyngeal space	15
Nasopharynx	14
Pancreas	11
Breast	11
Oral cavity	10
Chest wall	7
Thyroid	7
Porta hepatis	5
Female reproductive tract	4
Central Nervous System	3
Kidney	3
Parotid	3
Urinary bladder	2
Pleura	1
Larynx	1
Hypopharynx	1
Eye	1
Not specified	58

Paraneoplastic pemphigus associated or not with myasthenia gravis has been reported in several cases of FDCS; it can anticipate a diagnosis of FDCS and adversely influences the outcome [51]. Schizophrenia and FDCS are concomitant in rare cases [5,44]. In about 7% of cases, especially in extranodal sites, FDCS arises in the background of Castleman disease hyaline-vascular subtype (HV-CD) [37,38,46,61]. However, this association might be underestimated, since an extended FDCS might prevent recognition of a residual HV-CD component [37]. In contrast with tumors derived from Langerhans cells or histiocytes, FDCS is only exceptionally associated with lymphomas or leukemias [5]. Rare cases of FDCS occurred in patients with previous diagnosis of epithelial or melanocytic malignant neoplasms [44].

Morphology and immunophenotype

Grossly, FDCS does not have distinctive features, appearing as a well circumscribed, firm mass, exhibiting a gray-yellow surface; areas of necrosis can be present. On microscopy FDCS shows a wide range of architectural patterns, such as fascicular, storiform, whorled and diffuse (Figs. 3A, B). A reticular growth pattern mimicking a thymoma has been described and is best highlighted by immunostains (Figs. 3C, D); tumor forming small or large nodules associated with small lymphocytes have also been reported [62]. Rare growth patterns include the "folliculocentric", where FDC tumor cells form intrafollicular nodules, resembling high grade follicular lymphoma [49], and the "angiomatoid", with non-cohesive atypical cells delineating pseudovascular spaces mimicking angiosarcoma [63] (Figs. 3E, F). Cellularity may be dense or dissociated by myxoid, fibrovascular or hyaline stroma [5,62]. In nearly all cases of FDCS, small lymphocytes, with a variable composition of B- and T-cells are interspersed between tumor cells and may cluster around vessels [2,46].

Tumor cells can be spindled, oval or epithelioid, have a moderate amount of eosinophilic cytoplasm and the cell borders are rather indistinct, often with syncytial features. The nuclear details of tumor cells are reminiscent of those of normal FDC, and atypia is generally mild to moderate (Figs. 4A-C). Nuclei can be multiple and nuclear pseudoinclusions are frequent

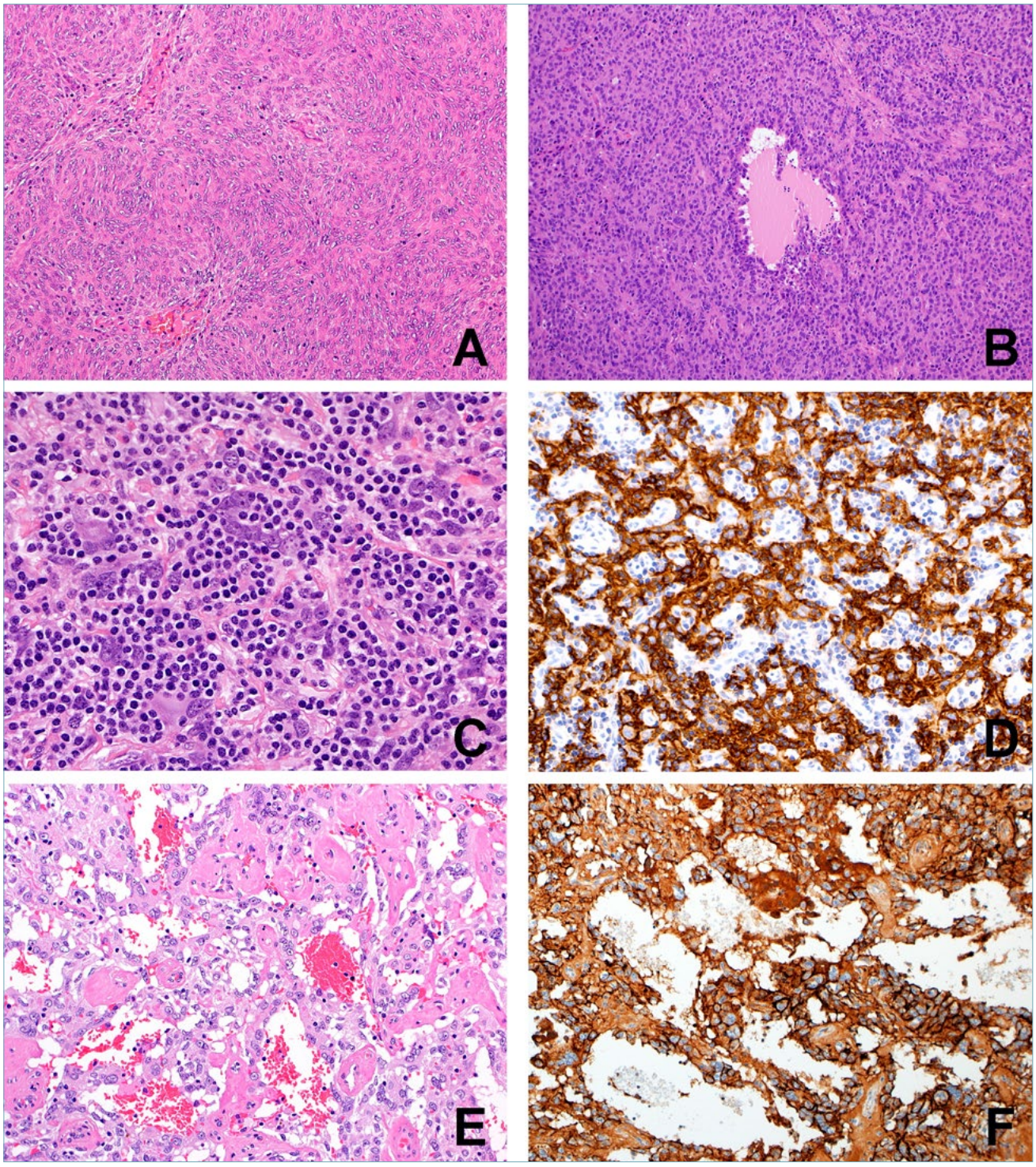

Figure 3. Variability of FDCS architectural growth patterns: whorled (A), diffuse (B), reticular and lymphocyte-rich mimicking a thymoma (C); this pattern, highlighted by immunostains as CD23 (D), is often observed in FDCS occurring in hyaline-vascular Castleman disease. An unusual "angiomatoid" pattern simulating angiosarcoma is shown in E, with strong immunoreactivity of tumor cells for CD21 (F).

(Figs. 4B, C). The tendency of nuclear clustering with uneven distribution is a rather unique feature of this tumor, although not always present (Fig. 4C). On fine needle aspiration cytology, the occurrence of single cells or syncytia showing FDC-like nuclear features should lead to suspicion of an FDCS (Fig. 4D).
Mitosis are generally rare; high mitotic rate, nuclear atypia, pleomorphism and necrosis are associated with aggressive clinical behavior [2,46] (Figs. 4E, F). The proliferation index (Ki-67) usually ranges from 1 to 25%, being higher in cases with frank atypia.
In the IPT-like variant, tumor cells may be hardly recognized since they are interspersed among a prevalent inflammatory infiltrate mainly composed of lymphocytes (including both B- and T-cells) and plasma cells [54]; rarely, numerous non-caseating epithelioid granulomas or eosinophils have been described [56]. Tumor cell identification requires immunostain for FDC markers or, even better, in situ hybridization for Epstein-Barr virus (Fig. 5) [51].
In FDCS associated with HV-CD a transition from HV-CD with FDC dysplasia to frank tumor proliferation can be observed; this may consist of a reticular network of bizarre cells, associated or not with solid areas [63] (Figs. 3C, D).
Non-clonal terminal deoxynucleotidyl transferase (TdT) positive T lymphocytes can be found in FDCS associated with HV-CD, either as scattered cells or as diffuse infiltrates. Interestingly, TdT+ T lymphocytes are also found in HV-CD and AITL, all conditions sharing abnormal FDC cell growth [5,64].
The diagnosis of FDCS is invariably supported by immunohistochemistry and multiple FDC markers are often necessary, since loss of antigens frequently occurs [5,62]. Neoplastic cells express one or more of the FDC-associated markers CD21, CD23, CD35, clusterin, CXCL13 and podoplanin, with highest sensitivity (> 80%) shown by CD21, CXCL13 and clusterin [65] (Figs. 3D, F; Figs. 6A-E). More recently, FDC secreted protein (FDCSP), Serglycin (SRGN) and SSTR2A have been reported as useful markers to identify FDCS [65,66] (Fig. 6F), while claudin 4, fascin, vimentin, and EGFR have low specificity. Reactivity of FDCS for EMA, S100, smooth muscle actin and CD68 has been occasionally reported. CD1a, langerin, CD34, CD45, lysozyme, CD163, myeloperoxidase, CD3, CD79a, cytokeratin, MART1 and HMB45 are negative [2,62,63].
Expression of CD30 has been found in a series of cases [63] representing a potential diagnostic pitfall. Notably, a high percentage of FDCS express PD-L1 and PD-L2 [67].
As pointed out by Rosai et al., FDCS shows quite distinctive electron microscopic features, with multiple thin cytoplasmic processes typically joined by scattered well-developed desmosomes [3].

Differential diagnosis

Given the variability of the sites where it can occur and its histopathological heterogeneity, FDCS can be confused with various neoplasms and even with inflammatory processes. It may mimic metastatic carcinoma, melanoma, ectopic meningiomas, ectopic or orthotopic thymomas, large cell lymphomas [2], and a variety of mesenchymal tumors, such as gastrointestinal stromal tumor, leiomyoma and solitary fibrous tumor. Generally, the immunophenotypic profile of these neoplasms and their negativity for classic FDCS markers allow an easy distinction from it. It has been shown that the gastrointestinal stromal tumor markers CD34, CD117 and DOG1, and STAT6 recognizing the solitary fibrous tumor are regularly negative in FDCS [5].
The IPT-like variant of FDCS is often overlooked at first examination, due to the prominent lympho-plasmacytic reactive component; diagnosis requires a high index of suspicion and is based on the identification of scattered, focal foci, or well-formed fascicles of cells showing nuclear FDC features, with variable atypia and, especially, positivity for EBV-RNA and FDC markers. A significant defective phenotype can be observed in the IPT-like variant of FDCS, and some cases do not express any FDC marker and/or variably express smooth muscle actin, thus raising the possibility of a differentiation towards fibroblastic reticular cells. The term “fibroblastic dendritic cell sarcoma” has been proposed for these tumors [62].
As pointed out by Juan Rosai in his seminal paper [2], FDCS must be distinguished from interdigitated dendritic cell sarcoma (IDCS), a rare neoplasm believed to derive from interdigitating dendritic cells of the nodal paracortex, usually occurring in lymph nodes and associated with aggressive behavior. Histologically IDCS may resemble FDC, but it generally shows a greater degree of atypia and lacks the fascicles and the whorl pattern of growth found in most FDCS. Moreover, IDCS regularly expresses S100 protein and often CD4, is variably positive for CD45, CD68 and lysozyme, and negative for FDC markers [63].

Prognosis and treatment

FDCS behaves like a low or an intermediate grade malignant neoplasm [3], with clinical evolution characterized by local recurrences in 28% and distant metastasis in 27% of cases [44,62,68]. Localized disease was associated with better outcome in a cohort of 31 FDCS cases treated in a single center [45]. Early localized or locally advanced tumors have a 2-year survival rates of 82% and 80% respectively, while metastatic

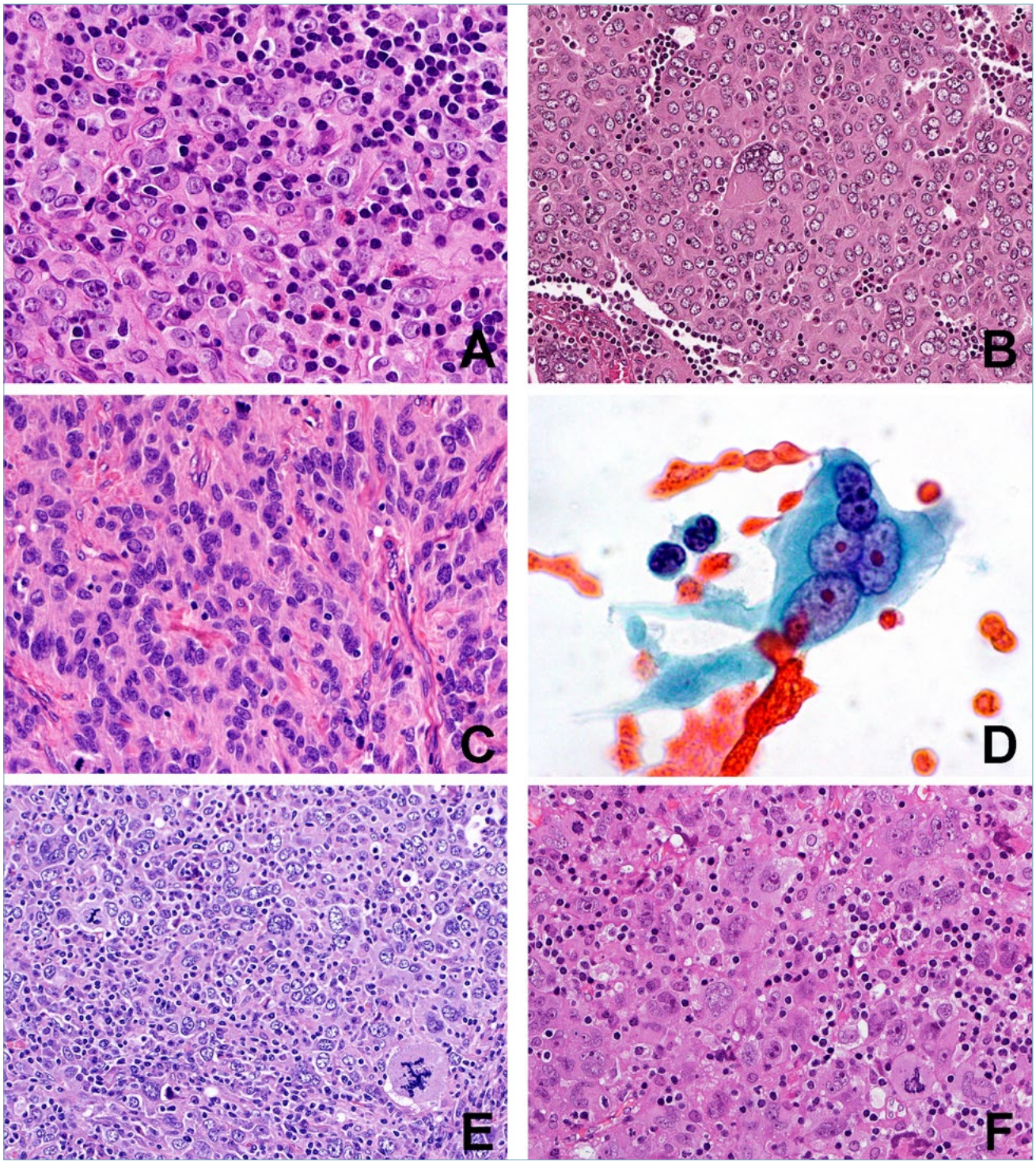

Figure 4. FDCS cytological details in three cases composed of epitheliod tumor cells (A, B, C). Note the delicate nuclear membrane and the single eosinophilic nucleolus, especially obvious in A, where tumor cells are associated with a rich lymphocytic infiltrate and rare eosinophils. B shows FDCS composed of mono- bi- and multinucleated cells, showing round nuclei with delicate membrane, small eosinophilic nucleoli and nuclear molding. C illustrates the tendency of clustering and uneven distribution of nuclei, as well as nuclear pseudoinclusions. In D, FDCS cytological details on fine needle aspiration (Papanicolau stain) is shown. Two examples of FDCS with atypical mitoses, significant pleomorphism and atypia (E and F), including Hodgkin-Sternberg-like cells (F).

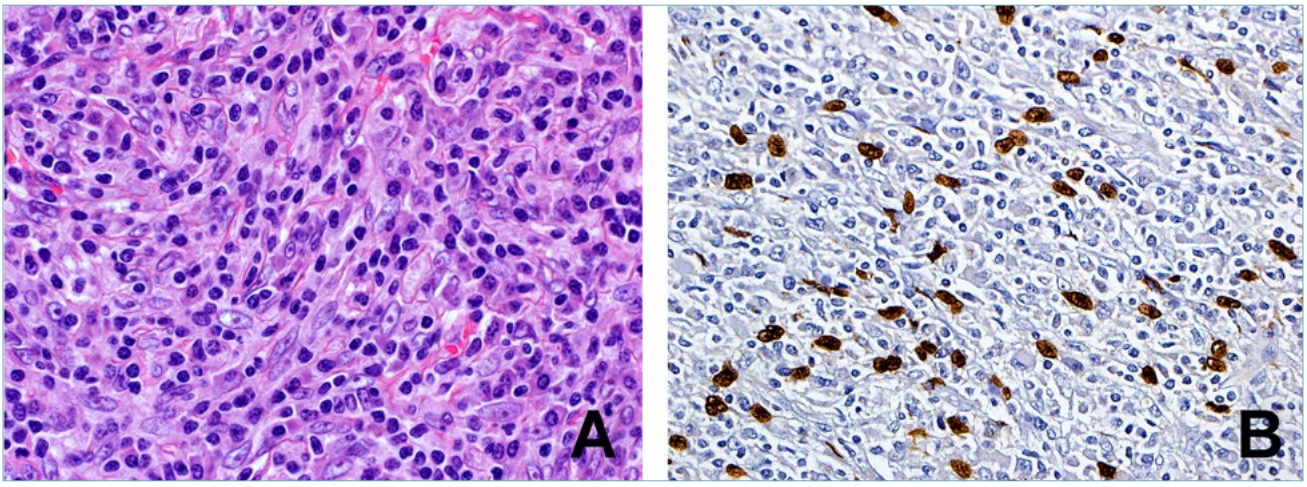

Figure 5. Inflammatory pseudotumor-like FDCS: tumor cells are hardly recognizable among the predominant inflammatory component mostly represented by lymphocytes and plasma cells (A). In situ hybridization for EBV prompts identification of the positive tumor cells (B).

disease survival drops to 42% [44]. The intra-abdominal involvement in young adults may be associated with poor prognosis; with rare exceptions [51], the IPT-like FDCS behaves as an indolent tumor, even of it often recurs locally over years [53,54].

Histological features associated with a worse prognosis include size (≥ 6 cm), necrosis, high mitotic count (≥ 5 mitoses per 10 high-power fields), and significant cytological atypia [44,46,62]. The main sites of metastasis are lung, liver, lymph nodes and bones.

To date there is no standard therapeutic protocol for FDCS, and different approaches have been applied including surgery, radiotherapy, chemotherapy and tyrosine-kinase inhibitors. Complete surgical excision is the gold standard of treatment; chemotherapy or radiotherapy can be associated, even if they have not shown a significant improvement in overall or disease free survival [5,62].

Kinase inhibitors have been used in few FDCS cases, showing durable partial response in one patient (treated with the mTOR inhibitor ridaforolimus) [69] and prolonged benefit in other five (after different protocols including pazopanib, sorafenib, sunitinib and sirolimus) [45,70]. On the basis of PD-L1 expression by tumor cells [67,71] immune checkpoint inhibitors have been applied with variable responses [72]. A better understanding of the molecular profile and drivers of this tumor may lead to new therapeutic strategies.

Genetics and molecular findings

The neoplastic nature of FDCS was originally supported by identification of aberrant clonal karyotype and EBV clonality in the IPT-like variant [73,74], and subsequently proven by the demonstration of chromosomal structural alterations, by classical karyotyping [75-78], inversion probe array [79] and RNA, massive or targeted, parallel sequencing [80-82]. Notably, loss-type structural alterations were recorded as the most common event in FDCS (including loss of arms or of entire chromosomes) [75,77,78], and often occur in regions encoding for important oncosuppressor genes [79].

Five different translocations leading to fusion proteins were identified in four cases TYK2-ATPAF2, MAP3K1-GCOM1, NTRK1-PDIA3, BPTF-WDR72 and HD-GRFP3-SHC4) [80,82]. Future studies are required to evaluate whether these translocations are recurrent and retain diagnostic specificity for FDCS; notably, some may represent molecular targets for treatment [80,82].

By direct or next generation sequencing, different authors found gene mutations and copy number variations on common pathways and the most frequently altered genes are shown in Figure 7.

In summary, FDCS is characterized by alterations on genes belonging to the NF-κB regulatory pathway (34/61 patients, 56%) [82-85], including copy number loss or missense mutations of *NFKBIA* [82,83,85], *CYLD* [83], *TRAF3* [82,85], *SOCS3* [82] and *TNFAIP3* [82,85]. Additionally, in line with the hypothesis of a tumor-suppressor driven biology, mutated cell-cycle regulators have been found in more than one study, and included the oncosuppressor genes *TP53* [80,82,83,85-87], *RB1* and *CDKN2A* [82,83] as well as the related genes *CDK4* and *MDM2* [83]. Notably, in a few additional cases, copy number gains or amplifications of the oncogenes *MYC* and *CCND2* were also reported [83,87].

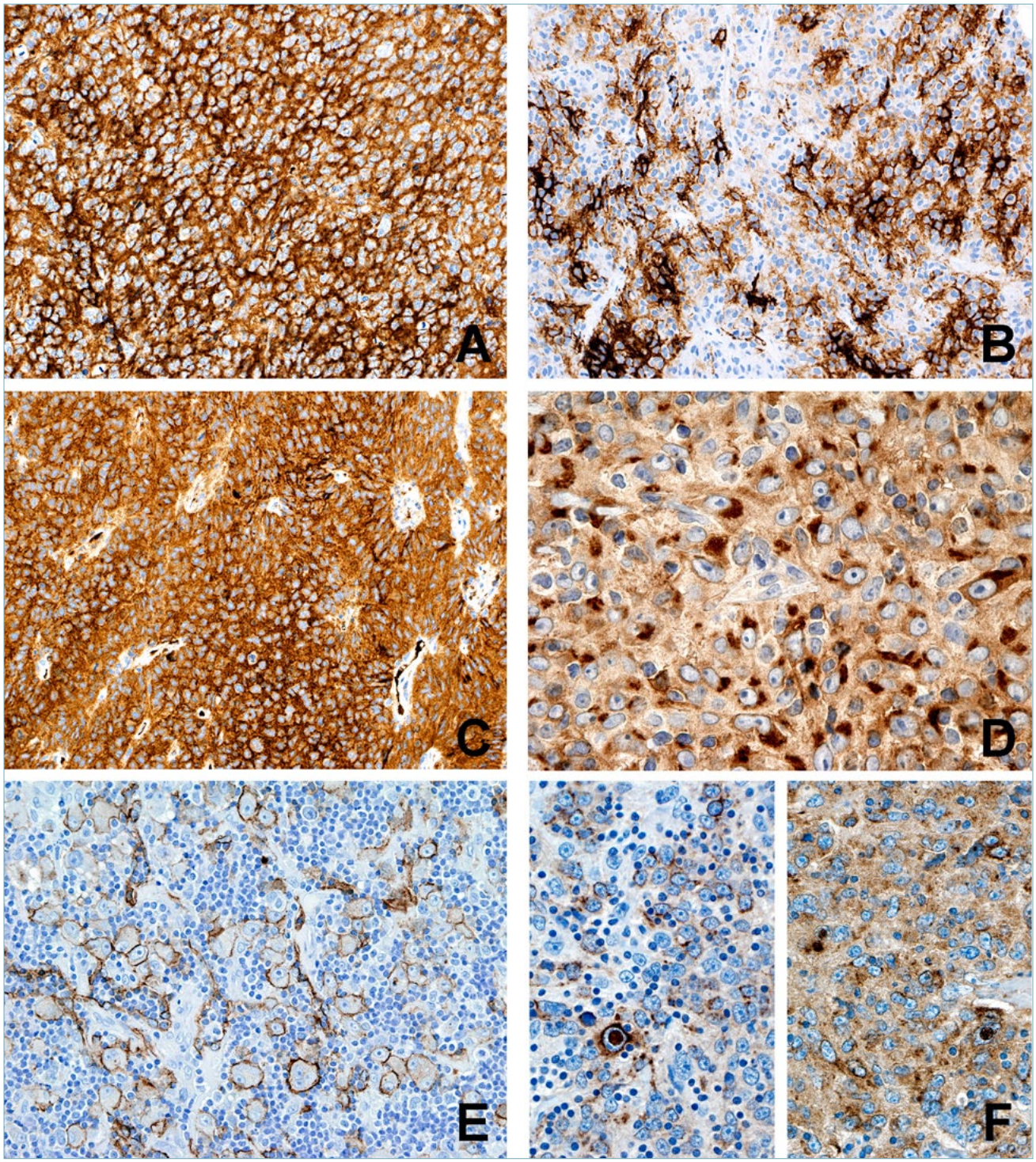

Figure 6. FDCS expression of classical and novel markers. A (CD21), B (CD23) and C (Clusterin) are from the same tumor and are heterogeneously expressed, particularly with partial loss of CD23. D and E are from the same FDCS case illustrated in Fig. 4A: note the peculiar Golgi-dot pattern of positivity for CXCL13 (D) and the delicate cell membrane expression of podoplanin (E). The novel FDC markers FDC secreted protein (FDCSP)(left) and Serglycin (right) are shown in F.

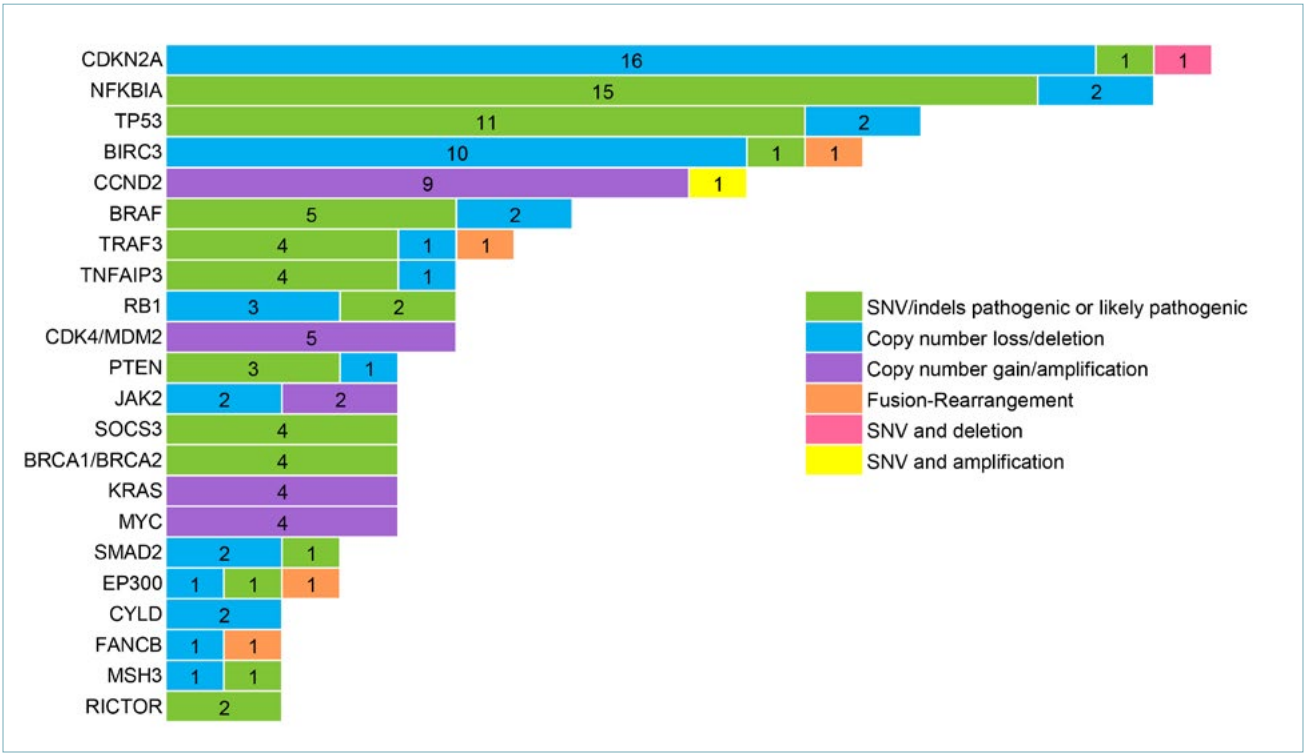

Figure 7. Plot of the most commonly affected genes in FDCS. The colors of the bars identify different types of alterations, and numbers refer to cases reported in the literature. Data obtained from references [80-87,89,97]. SNV, single nucleotide variation.

While the mitogen activated protein kinase (MAPK) pathway has been shown to be pivotal in the pathogenesis of hematopoietic-derived histiocytic and dendritic cells tumors [63,88], FDCS typically lacks mutations of genes such as *KRAS, NRAS* and *MAP2K1* [82]. Data on *BRAF* are more controversial, since *BRAF* V600E mutation was found in 5 of 27 cases in a single study [89], *BRAF* copy number loss reported in one additional case [84], but no anomalies on this gene were detected in at least 95 FDCS collected from different studies [24,63,82,83,90,91].

Notably, the *PDGFRB* N666S mutation often occurring in HV-CD [92,93], was detected in a case of FDCS with history of Castleman disease [82], further strengthening the biological relationship between these two diseases. In contrast to histiocytic and hematopoietic dendritic cell derived tumors, the occurrence of immunoglobulin or T-cell receptor clonality in FDCS is exceptionally reported [94,95], and its significance is unknown, especially considering that the "transdifferentiation" hypothesis is unlikely, given the mesenchymal derivation of the cell of origin of this tumor [5].

Despite the common expression of PD-L1 in FDCS [63,90,96] a low mutational burden (< 6 mutations/megabase) was detected in the majority of cases in a large series (41/44) [82] thus questioning the potential efficacy of an immunotherapy-based treatment for this neoplasm.

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Authors' contributions

F.F. designed the study; F.F., S.M. and L.L. performed data collection, data interpretation and drafted the manuscript. All authors read and approved the final version of the manuscript.

Ethical consideration

Histological images included in the manuscript are anonymized and privacy of the presented cases is maintained.

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