# Lymph Nodes

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**Summary of Pearls and Pitfalls**

- Always attempt to get sufficient sample for flow cytometric study, molecular analysis, and cellblock preparation if a lymphoma is suspected.
- A final diagnosis of lymphoma should not be based on cytomorphology alone. Ancillary tests such as flow cytometric study, immunohistochemistry (IHC), and cytogenetic analysis/fluorescence in situ hybridization (FISH) should be performed.
- Cell block preparation for immunostains is highly recommended if large B-cell lymphoma (LBCL) is suspected, since a significant number of cases have an inconclusive diagnosis from flow cytometric analysis due to the breakdown of the cytoplasm of lymphoid cells.
- Incisional or excisional biopsy is recommended for all cases suspicious for Hodgkin lymphoma, T-cell lymphoma, T-cell-rich B-cell lymphoma, transformation from a low-grade lymphoma into a high-grade non-Hodgkin lymphoma and unusual types of lymphoma.
- Culture should be considered when acute inflammation and necrosis are present.
- Mycobacterial infection should be considered when a granulomatous process and necrosis are present.
- Cohesive sheets and groups of lymphoid cells are frequently seen in an LBCL that might be mistaken for metastatic carcinoma.
- Noncaseating granulomas are frequently seen in Hodgkin lymphoma and T-cell lymphoma, in addition to benign conditions and metastatic tumors, such as seminoma.
- In addition to Burkitt lymphoma (BL), cytoplasmic vacuoles can be seen in other high-grade lymphomas, rhabdomyosarcoma, seminoma, and carcinomas.
- Lymphoglandular bodies are less frequently present in plasmacytoma or myeloid sarcoma.
- HIV-associated follicular hyperplasia and mononucleosis are more likely to mimic a high-grade lymphoma.
- Collision tumors, such as metastatic small cell carcinoma or melanoma in the background of small lymphocytic lymphoma (SLL), are infrequent, but can be seen.
- Most low-grade lymphomas have a mindbomb homolog 1 (MIB-1, Ki-67) proliferative index less than 26%; in contrast, high-grade lymphoma usually has a MIB-1 proliferative index greater than 26%.

## 2017 WHO Classification of Mature Lymphoid, Histiocytic, and Dendritic Neoplasms[1]

### Mature B-Cell Neoplasms

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
Monoclonal B-cell lymphocytosis[2]
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma (MZL)
Hairy cell leukemia
*Splenic B-cell lymphoma/leukemia, unclassifiable*
*Splenic diffuse red pulp small B-cell lymphoma*

[1]Used with permission from Arber et al. (Arber et al. 2016); and from Swerdlow et al. (Swerdlow et al. 2016a).

[2]Changes from the 2008 classification.

Provisional entities are listed in italics.



F. Lin et al., *Handbook of Practical Fine Needle Aspiration and Small Tissue Biopsies*, DOI 10.1007/978-3-319-57386-1_4

*Hairy cell leukemia variant*
Lymphoplasmacytic lymphoma (LPL)
Waldenström macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM[2]
Mu heavy chain disease
Gamma heavy chain disease
Alpha heavy chain disease
MGUS, IgG/A[3]
Plasma cell myeloma
Solitary plasmacytoma of the bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases[3]
Extranodal MZL of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal MZL
*Pediatric nodal MZL*
Follicular lymphoma
In situ follicular neoplasia[3]
Duodenal-type follicular lymphoma[3]
Pediatric-type follicular lymphoma[3]
*LBCL with interferon regulatory factor 4 (IRF4) rearrangement*[3]
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma (MCL)
In situ mantle cell neoplasia[3]
Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS)
Germinal center B-cell type[3]
Activated B-cell (ABC) type[3]
T-cell/histiocyte-rich LBCL
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
Epstein-Barr virus (EBV)-positive DLBCL, NOS[4]
*EBV+ mucocutaneous ulcer*[4]
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) LBCL
Intravascular LBCL
ALK-positive LBCL
Plasmablastic lymphoma
Primary effusion lymphoma
*Human herpes virus 8 (HHV8)-positive DLBCL, NOS*[4]
Burkitt lymphoma
*Burkitt-like lymphoma with 11q aberration*[4]
High-grade B-cell lymphoma (HGBCL), with *MYC* and *BCL2* and/or *BCL6* rearrangements[4]
HGBCL, NOS[4]
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and CHL

## Mature T- and Natural Killer (NK)-Cell Neoplasms

T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
*Chronic lymphoproliferative disorder of NK cells*
Aggressive NK-cell leukemia
Systemic EBV+ T-cell lymphoma of childhood[5]
Hydroa vacciniforme-like lymphoproliferative disorder[5]
Adult T-cell leukemia/lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma[5]
*Indolent T-cell lymphoproliferative disorder of the gastrointestinal (GI) tract* [5]
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous gamma-delta T-cell lymphoma
*Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma*
*Primary cutaneous acral CD8-positive T-cell lymphoma*[5]
*Primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder*[5]
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma*[6]
*Nodal peripheral T-cell lymphoma with T follicular helper (TFH) phenotype*[6]
Anaplastic large cell lymphoma, ALK positive
Anaplastic large cell lymphoma, ALK negative[6]
*Breast implant-associated ALCL*[6]

## Hodgkin Lymphoma

Nodular lymphocyte-predominant Hodgkin lymphoma
Classical Hodgkin lymphoma (CHL)
Nodular sclerosis CHL
Lymphocyte-rich CHL
Mixed cellularity CHL
Lymphocyte-depleted CHL

[3] See footnote 2.
[4] See footnote 2.
[5] See footnote 2.
[6] See footnote 2.

## Posttransplant Lymphoproliferative Disorders (PTLD)

Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD[6]
Polymorphic PTLD
Monomorphic PTLD (B- and T-/NK-cell types)
CHL PTLD

## Histiocytic and Dendritic Cell Neoplasms

Histiocytic sarcoma
Langerhans cell histiocytosis (LCH)
Langerhans cell sarcoma
Indeterminate dendritic cell tumor
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Fibroblastic reticular cell tumor
Disseminated juvenile xanthogranuloma
Erdheim-Chester disease[7]

**B Lymphoblastic Leukemia/Lymphoma**

B lymphoblastic leukemia/lymphoma, NOS
B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); *BCR-ABL1*
B lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged
B lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B lymphoblastic leukemia/lymphoma with hyperdiploidy
B lymphoblastic leukemia/lymphoma with hypodiploidy
B lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*
Provisional entity: B lymphoblastic leukemia/lymphoma, *BCR-ABL1-like*
Provisional entity: B lymphoblastic leukemia/lymphoma with *iAMP21*

**T Lymphoblastic Leukemia/Lymphoma**

*Provisional entity: early T-cell precursor lymphoblastic leukemia*
*Provisional entity: NK-cell lymphoblastic leukemia/lymphoma*

## Nonneoplastic Lymph Nodes

**Cytological Features (Fig. 4.1a, b)**

- High cellularity
- Mixed population of lymphoid cells with small lymphocytes predominant
- Plasma cells, plasmacytoid cells, and immunoblasts
- Histiocytes and tingible-body macrophages

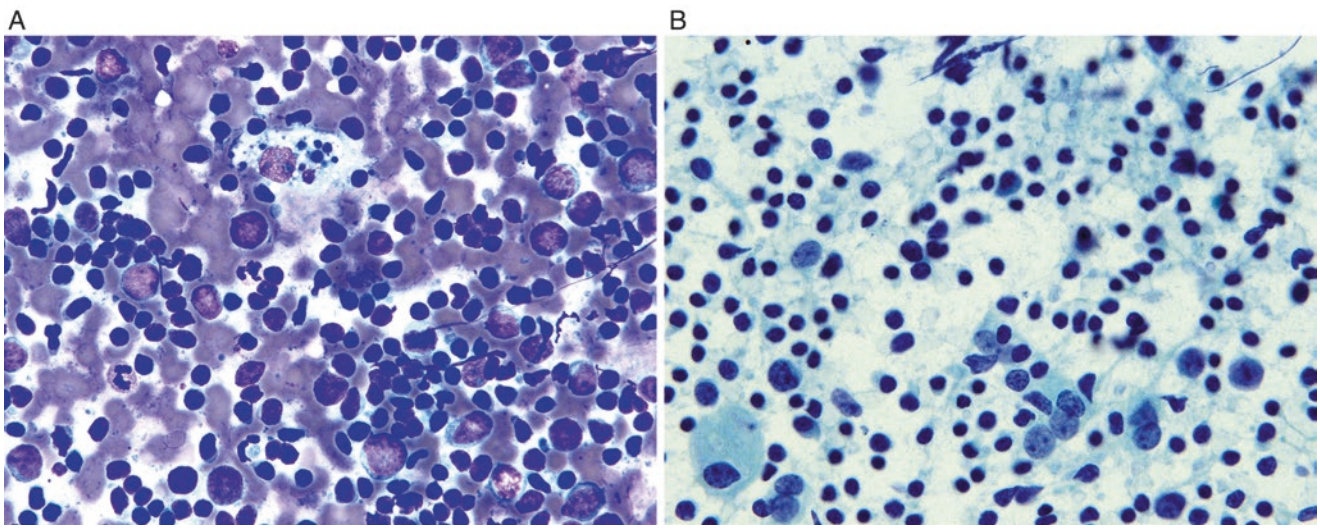


**Fig. 4.1** (**a**, **b**) Reactive lymph node with a mixed population of lymphoid cells with small lymphocytes predominant on Diff-Quik (**a**) and Pap stain (**b**)

[7]See footnote 2.

## Suppurative Lymphadenitis

### Cytological Features (Fig. 4.2a, b)

- Mixed population of lymphoid cells with a variable number of neutrophils.
- Degenerated lymphoid cells, histiocytes, neutrophils, and necrotic debris.
- Bacteria or fungus may be seen.
- Etiologies could include cat-scratch disease, bacterial infection, lupus, and less commonly Hodgkin lymphoma and metastatic carcinomas.

### Histologic Features

- Preserved nodal architecture with lymphoid follicular hyperplasia (Fig. 4.3).
- Hyperplastic lymphoid follicles show polarity with tingible-body macrophages (Fig. 4.4).
- Increased neutrophilic infiltrate, abscess formation, and perilymphadenitis (Fig. 4.5).

## Infectious Mononucleosis

### Cytological Features

- Highly cellular specimen
- Mixed population of lymphoid cells with many immunoblasts and plasmacytoid cells.
- Large atypical lymphoid cells are frequently present; some may mimic Hodgkin cells.
- Flow cytometry reveals an abundance of CD8-positive T cells and only a small population of B cells.

### Histologic Features

- Preserved nodal architecture with paracortical expansion composed of mixed mature lymphocytes, plasma cells, immunoblasts, and histiocytes in a mottled pattern (Figs. 4.6 and 4.7)
- Lymphoid follicular hyperplasia
- EBV-positive by in situ hybridization stain (Fig. 4.8)

### Differential Diagnosis

- HGBCL
- Hodgkin lymphoma

## Rosai-Dorfman Disease

### Cytological Features

- Mixed population of lymphoid cells.
- A large number of histiocytes with pale cytoplasm.
- Many histiocytes contain lymphoid cells or red blood cells.
- These histiocytes are positive for S100, but negative for CD1a.
- Tissue biopsy should be recommended for a final diagnosis.

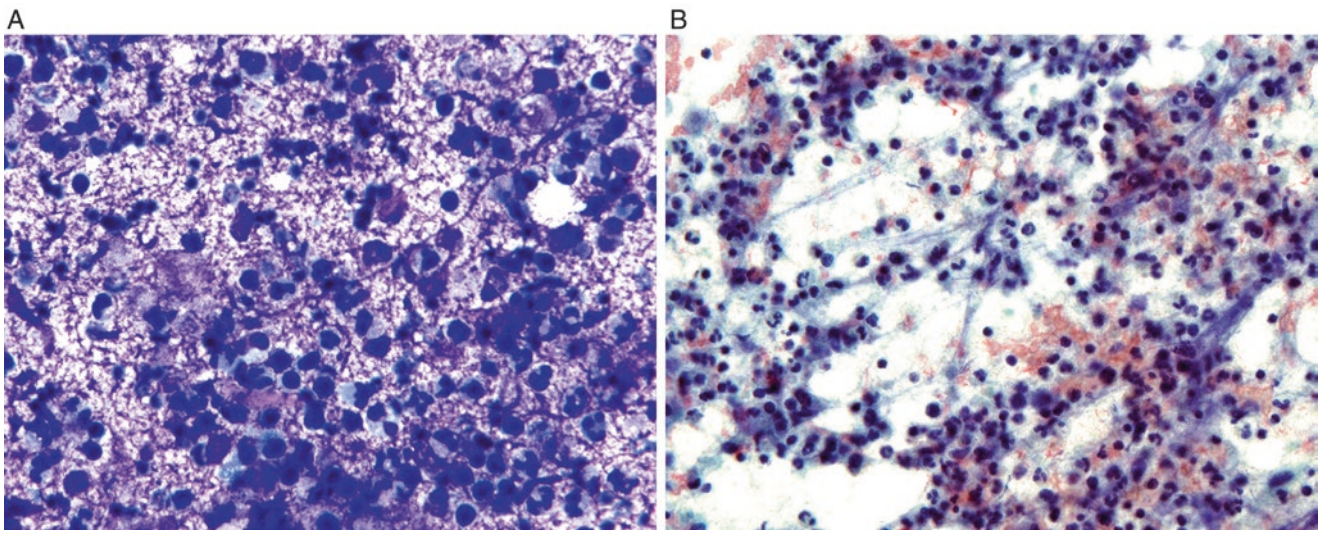


**Fig. 4.2** (**a**, **b**) Suppurative lymphadenitis with degenerated lymphoid cells, histiocytes, neutrophils, and necrotic debris on Diff-Quik (**a**) and Pap stain (**b**)

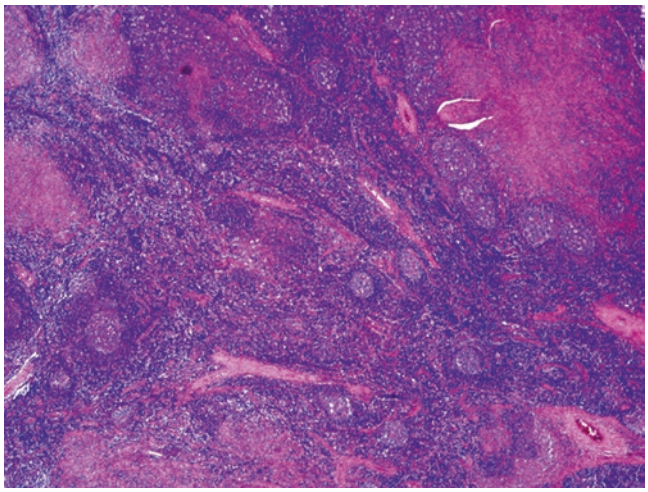

**Fig. 4.3** Suppurative lymphadenitis showing preserved nodal architecture with reactive lymphoid follicles and focal abscess formation

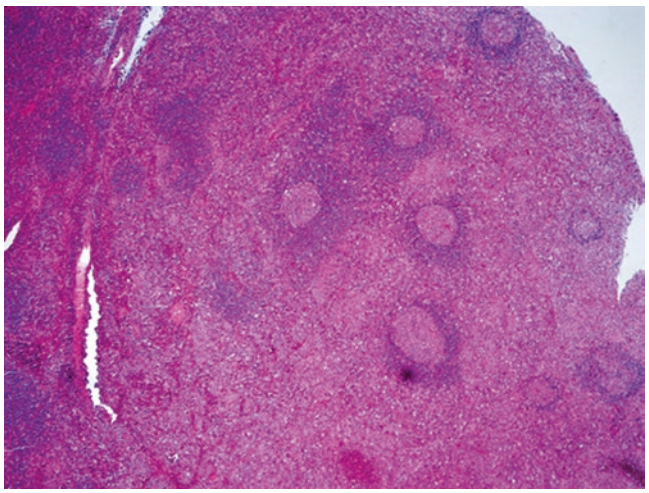

**Fig. 4.6** Infectious mononucleosis with reactive lymphoid follicles and perifollicular expansion

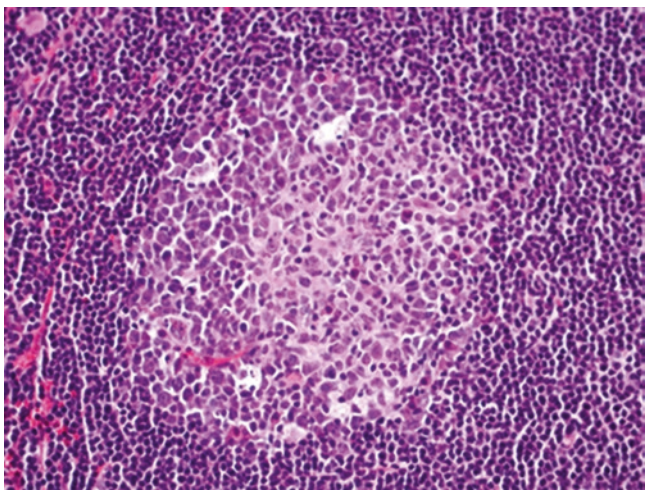

**Fig. 4.4** Reactive lymphoid follicles with polarity and tingible-body macrophages

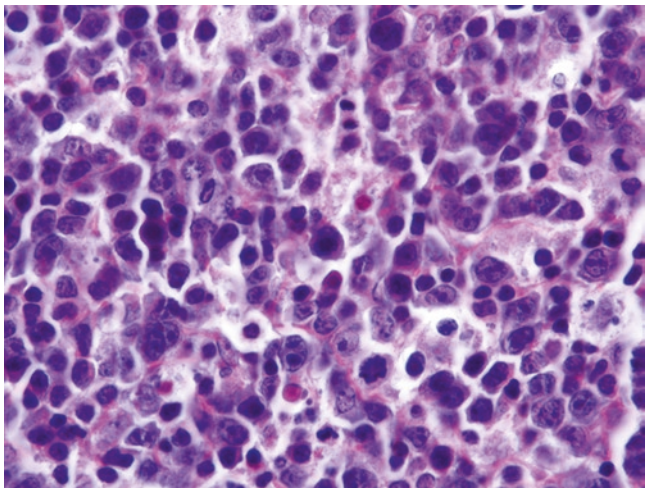

**Fig. 4.7** Infectious mononucleosis with lymphoblasts and immunoblasts showing prominent nucleoli

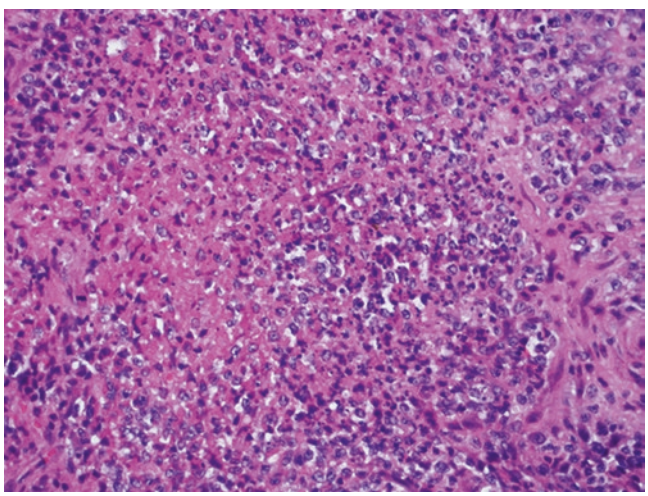

**Fig. 4.5** Suppurative lymphadenitis with focal abscess formation and necrosis

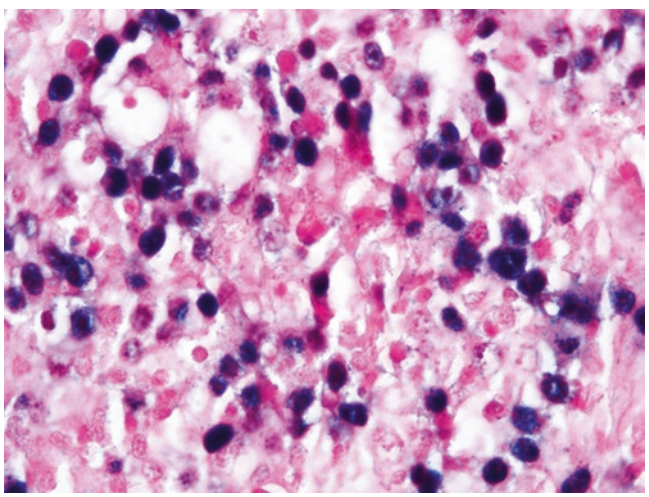

**Fig. 4.8** Infectious mononucleosis with positive EBV by in situ hybridization stain

### Histologic Features

- Marked sinus dilatation with sheets of foamy histiocytes (Figs. 4.9 and 4.10).
- Some histiocytes may contain lymphocytes, plasma cells, or red blood cells.

## Granulomatous Lymphadenitis

### Cytological Features (Fig. 4.11a–c)

- Mixed population of lymphoid cells.

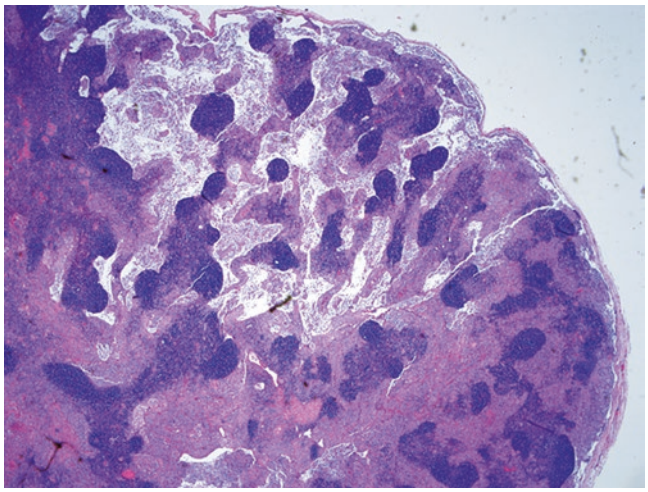

**Fig. 4.9** Lymph node with Rosai-Dorfman disease shows marked sinus dilation

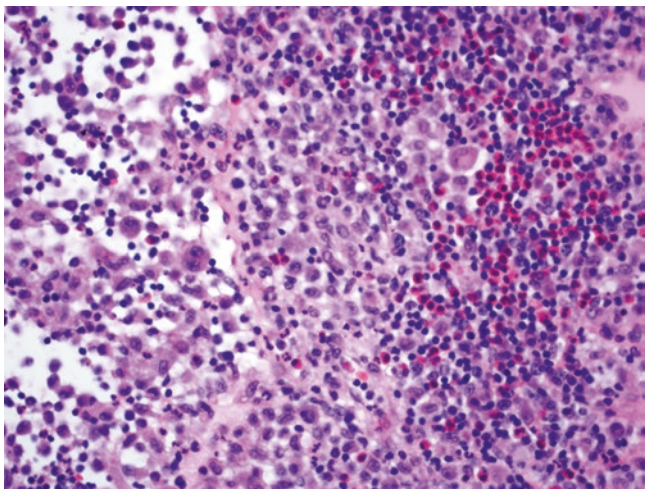

**Fig. 4.10** Lymph node with Rosai-Dorfman disease shows sheets of histiocytes

- Epithelioid histiocytes in aggregates with or without multinucleated giant cells.
- Necrotic debris and acute inflammatory cells may or may not be present.
- Etiologies could include foreign body reaction, sarcoidosis, fungus, mycobacteria, and toxoplasmic lymphadenitis.
- Culture should be submitted.

### Histologic Features

- Granulomas with necrosis in infection of mycobacteria (Figs. 4.12, 4.13, and 4.14)
- Granulomas surrounded by few or no lymphocytes (naked granuloma) in sarcoidosis (Figs. 4.15, 4.16, 4.17, and 4.18)
- Epithelioid granuloma and sheets of monocytoid lymphocytes in infection of Toxoplasma (Figs. 4.19 and 4.20)
- Multinucleated cells with foreign body in foreign body granuloma (Fig. 4.21)

## Non-Hodgkin Lymphomas

### Cytological Features

- Hypercellular specimen
- A relatively uniform population of lymphoid cells
- Can be divided into three groups
- Group 1 – small lymphoid cells (smaller than histiocytes), such as small lymphocytic lymphoma (SLL), grade I follicular lymphoma, MZL, LPL
- Group 2 –intermediate lymphoid cells (same size as histiocytes), such as MCL, grade II follicular lymphoma, BL, lymphoblastic lymphoma
- Group 3 – large lymphoid cells (larger than histiocytes), such as LBCL, grade III follicular lymphoma, ALCL, some T-cell lymphomas
- Immunophenotypes of B-cell lymphoma (Table 4.1) and frequent chromosomal translocations and gene mutations (Tables 4.2 and 4.3)

## Small Lymphocytic Lymphoma (SLL)

### Clinical Features

- Rare before 40 years of age
- General lymphadenopathy
- Bone marrow involvement

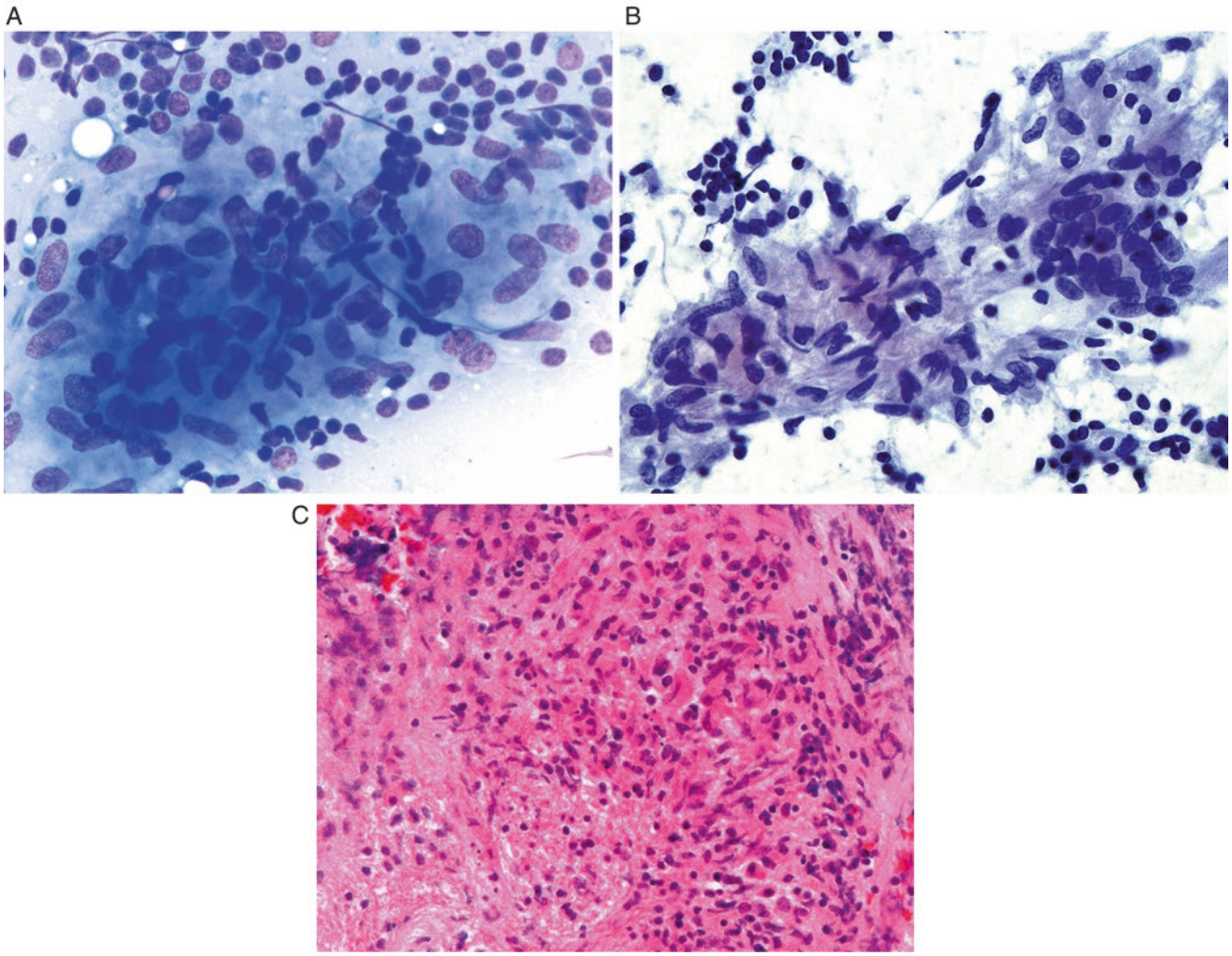


**Fig. 4.11** (**a**–**c**) Granulomatous lymphadenitis with epithelioid histiocytes in aggregates with or without multinucleated giant cells and a mixed population of lymphoid cells on Diff-Quik (**a**), Pap stain (**b**), and cellblock preparation (**c**)

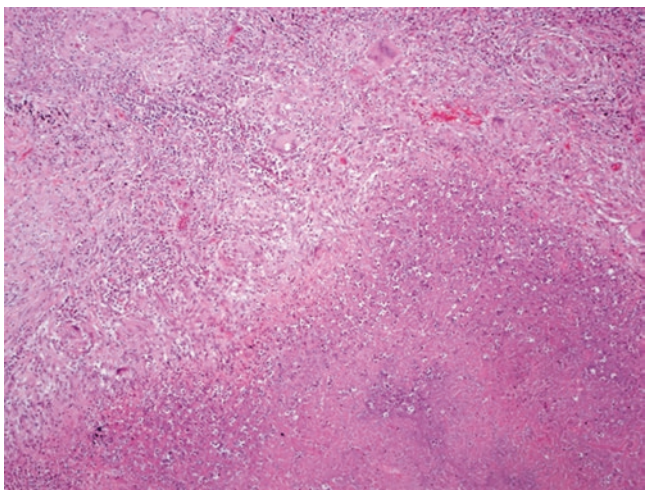

**Fig. 4.12** Lymph node with caseating granulomas in tuberculosis

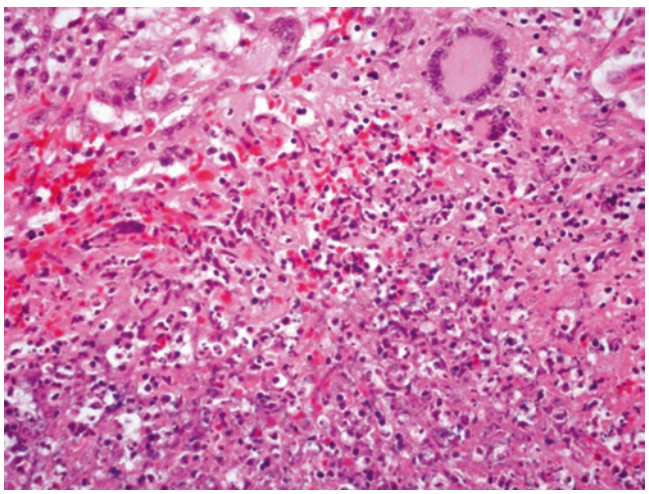

**Fig. 4.13** Lymph node with caseating granulomas showing necrosis and giant cells

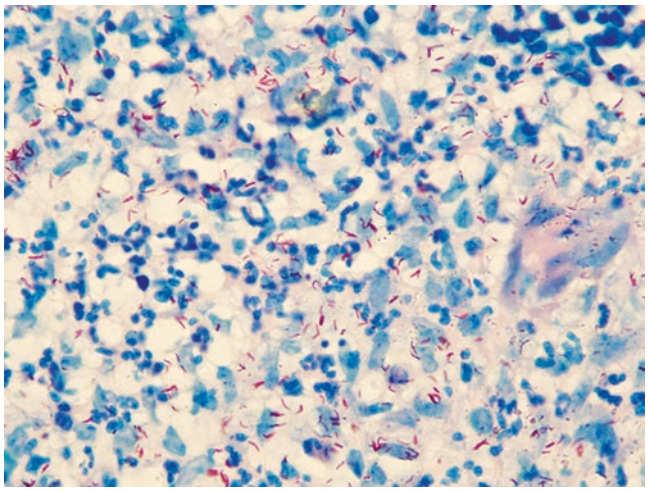

**Fig. 4.14** Special stain (acid-fast bacilli [AFB], acid-fast Fite) reveals mycobacteria in caseating granulomas

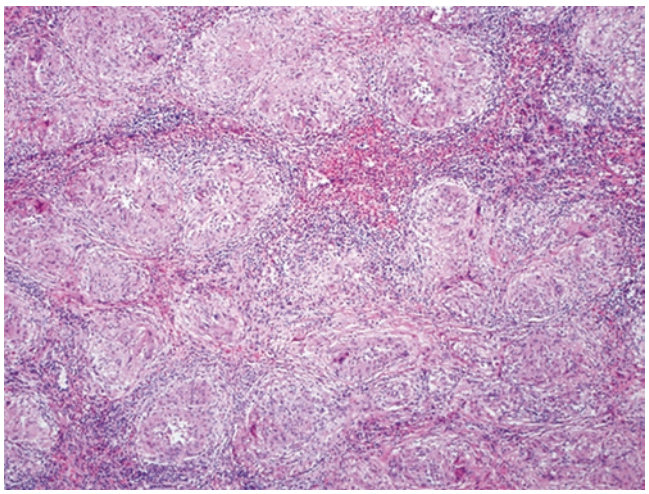

**Fig. 4.17** Sarcoidosis in the spleen with noncaseating granulomas

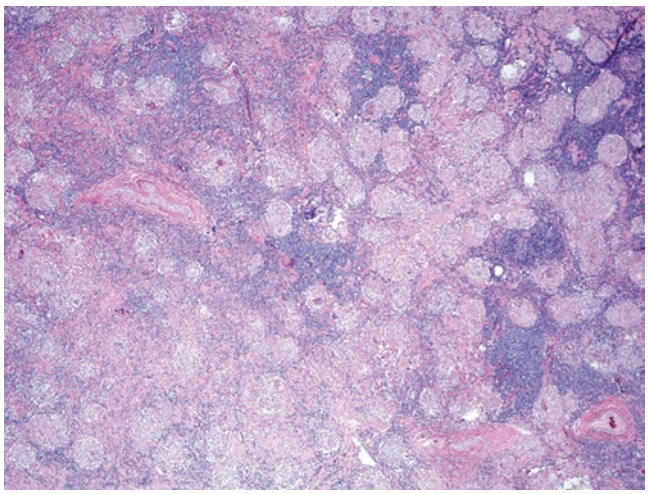

**Fig. 4.15** Sarcoidosis in lymph node with noncaseating granulomas

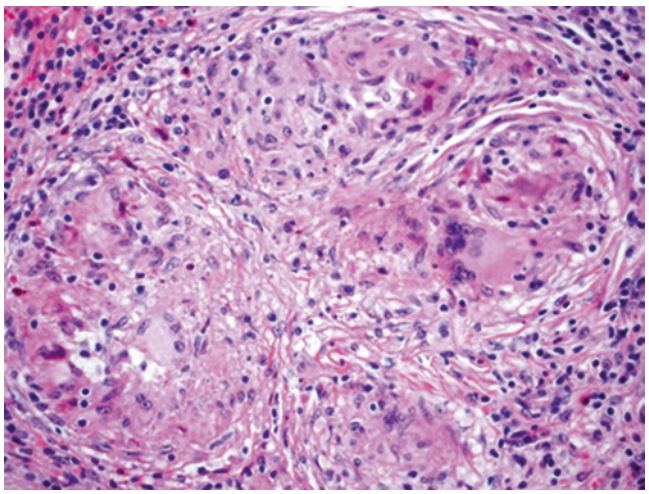

**Fig. 4.18** Sarcoidosis in the spleen with "naked" noncaseating granulomas

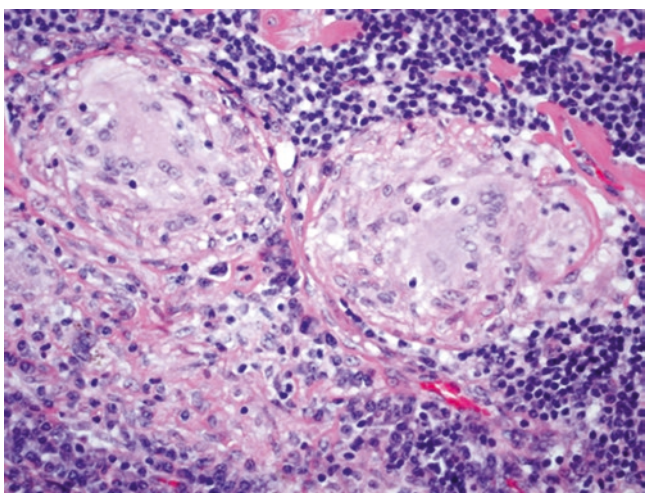

**Fig. 4.16** Sarcoidosis in lymph node with "naked" noncaseating granulomas

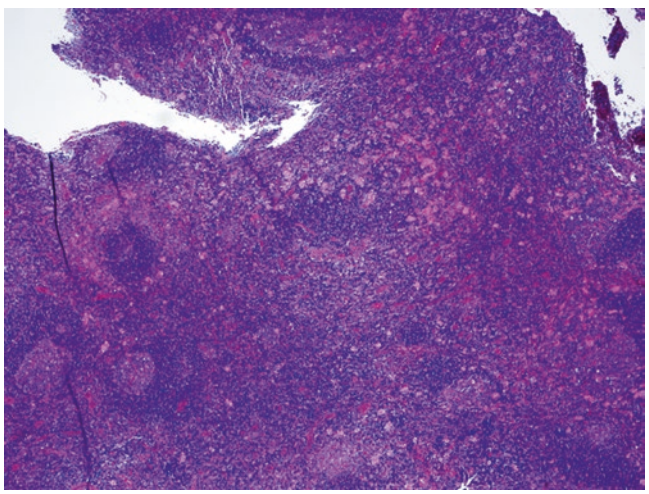

**Fig. 4.19** Lymph node with toxoplasma shows reactive lymphoid follicles and expanded perifollicular area in a "mottled" appearance

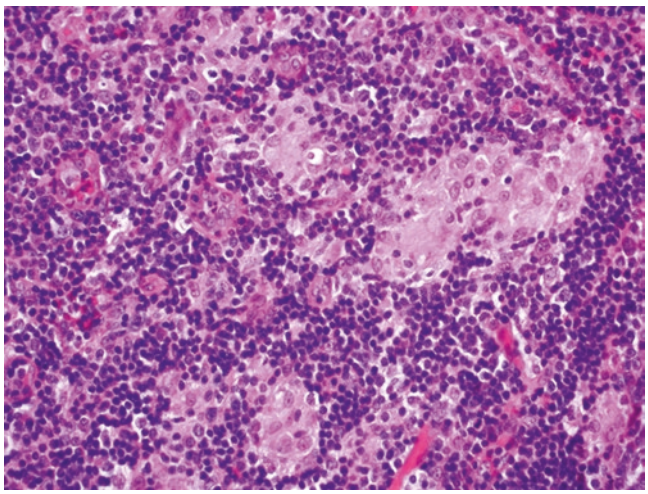

**Fig. 4.20** Lymph node with toxoplasma shows cluster of epithelioid histiocytes and monocytoid lymphocytes

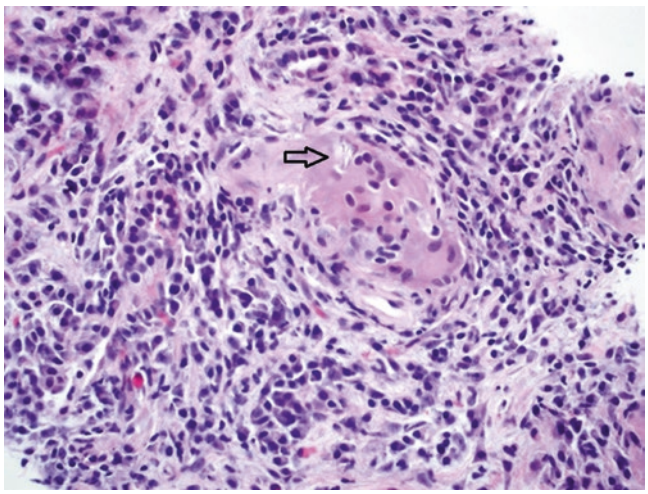

**Fig. 4.21** Foreign body granuloma with giant cells containing foreign body (arrow)

### Cytological Features (Fig. 4.22a, b)

- Highly cellular
- Monotonous population of small lymphocytes
- Smooth nuclear membrane, "clock face" nuclear chromatin, small to invisible nucleoli, and scant cytoplasm

### Histologic Features

- Effaced nodal architecture in a vaguely nodular (pseudofollicular) pattern (Fig. 4.23).
- Sheets of neoplastic lymphocytes with hypercondensed chromatin and round to slightly irregular nuclear contour (Fig. 4.24).
- Admixed with prolymphocytes.
- Adenopathy <1.5 cm by computed tomography (CT) scan is called tissue-based monoclonal B-cell lymphocytosis.

### Immunohistochemistry and Ancillary Studies

- Flow cytometry studies: CD19+, CD20+ (low intensity), CD5+, CD23+, CD43+, FMC7- (Fig. 4.25a–d); CD38 and zeta-chain-associated protein kinase 70 (ZAP-70) to evaluate the prognosis: both negative, most favorable; one positive and one negative, intermediate; and both positive, least favorable prognosis
- IHC: CD20+, PAX5+ (especially important after Rituxan treatment that cause CD20 negativity on IHC), CD5+, CD23+, lymphoid enhancer-binding factor 1 (LEF1)+ (Fig. 4.26)
- FISH: deletion of 13q14 in 50% of cases, trisomy 12 in 20% of cases (Figs. 4.27 and 4.28)

### Differential Diagnosis

- Reactive lymph node
- Other low-grade lymphoma

**Table 4.1** Immunophenotype of B-cell lymphomas

| Category | CD20 | CD5 | CD10 | CD23 | BCL1 | BCL2 | BCL6 | LEF1 | LMO2 | SOX11 |
|---|---|---|---|---|---|---|---|---|---|---|
| SLL | + | + | – | + | – | + | – | + | – | – |
| FL | + | – | + | – | – | + | + | – | + | – |
| MZL | + | – | – | – | – | + | – | – | – | – |
| MCL | + | + | – | – | + | + | – | – | – | + |

*CD* cluster of differentiation, *BCL* B-cell lymphoma, *LEF1* lymphoid enhancer-binding factor 1, *LMO2* LIM-only transcription factor 2, *SOX 11* sex-determining region Y box 11, *SLL* small lymphocytic lymphoma, *FL* follicular lymphoma, *MZL* marginal zone lymphoma, *MCL* mantle cell lymphoma

**Table 4.2** Summary of chromosomal translocation-associated lymphomas and the affected genes

| Chromosome | Lymphoma | Affected genes |
|---|---|---|
| t(8;14)(q24;q32) | BL | *c-MYC* and *IgH* |
| t(11;14)(q13;q32) | MCL | *Cyclin D1* and *IgH* |
| t(14;18)(q32;q21) | FL | *BCL2* and *IgH* |
| t(2;5)(p23;q35) | ALCL | *ALK* and *NPM* |

*BL* Burkitt lymphoma, *IgH* immunoglobulin heavy, *MCL* mantle cell lymphoma, *FL* follicular lymphoma, *BCL2* B-cell CLL lymphoma 2, *ALCL* anaplastic large cell lymphoma, *ALK* anaplastic lymphoma kinase, *NPM* nucleophosmin

**Table 4.3** Most common gene mutations in non-Hodgkin lymphomas

| Lymphoma | Affected genes |
|---|---|
| Hairy cell leukemia | *BRAF V600E* |
| LPL<br>Waldenström macroglobulinemia | *MYD88 L256P* |
| DLBCL, GC type | *EZH2, BCL2, GNA13* |
| DLBCL, ABC type | *MYD88, CD79A, CARD11, TNFAIP3* |
| Large granular lymphocyte leukemia | *STAT3* |

*BRAF* v-raf murine sarcoma viral oncogene homolog B1, *LPL* lymphoplasmacytic lymphoma, *MYD88* myeloid differentiation primary response gene 88, *L256P* leucine to proline mutation at amino acid position 256, *DLBCL* diffuse large B-cell lymphoma, *GC* germinal center, *EZH2* enhancer of zeste homolog 2, *BCL2* B-cell lymphoma 2, *GNA13* guanine nucleotide-binding protein subunit alpha-13, *ABC* activated B-cell, *CD79A* cluster of differentiation 79A, *CARD11* caspase recruitment domain-containing protein 11, *TNFAIP3* tumor necrosis factor, alpha-induced protein 3, *STAT3* signal transducer and activator of transcription 3

## Follicular Lymphoma

### Clinical Features

- Accounts for 35% of adult non-Hodgkin lymphomas in the USA and 22% worldwide.
- Accounts for 70% of "low-grade" lymphomas in the USA.
- Affecting mainly adults, median age of 59 years, rarely occurs before age 20 years.
- 40% of patients have bone marrow involvement at the initial diagnosis.

### Cytological Features (Fig. 4.29a–d)

- Usually cellular.
- Small lymphocytes with cleaved nuclei.
- Papanicolaou (Pap) stain better shows nuclear membrane irregularities.
- Small to inconspicuous nucleoli and scant cytoplasm.
- Increased numbers of large atypical lymphoid cells (centroblasts) in grade 2 and grade 3 follicular lymphoma.
- Grading of follicular lymphoma in a fine needle aspiration (FNA) specimen is similar to that of a histological specimen by counting the number of centroblasts at 40x high-power field (HPF); i.e., grade 1, 0–5 centroblasts/HPF; grade 2, 6–15 centroblasts/HPF; and grade 3, >15 centroblasts/HPF.

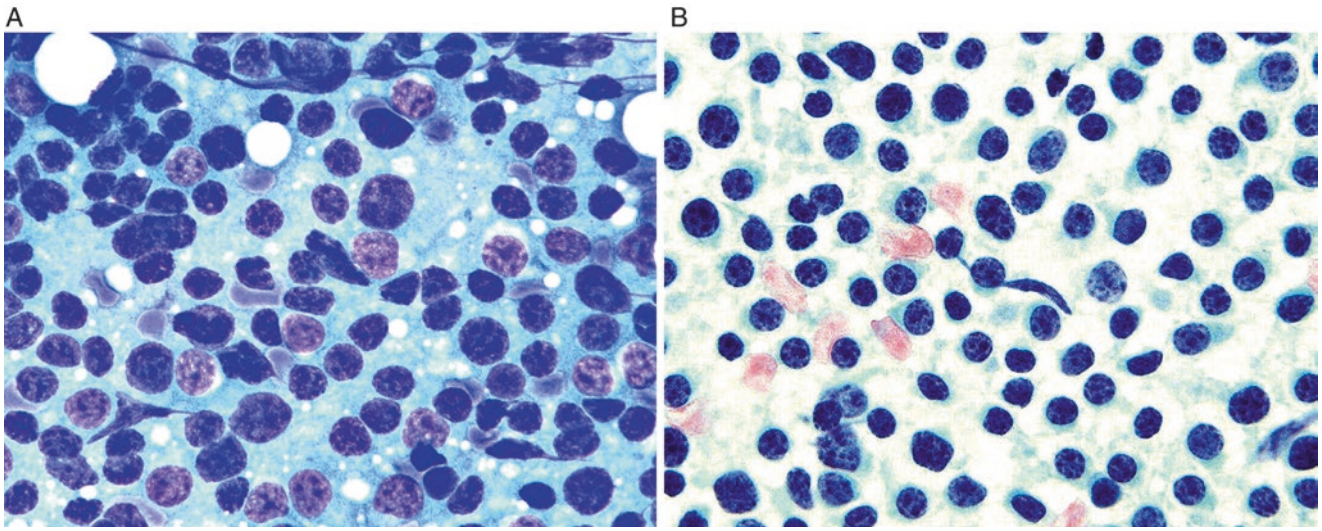


**Fig. 4.22** (**a**, **b**) Small lymphocytic lymphoma with monotonous population of small lymphocytes on Diff-Quik (**a**) and Pap stain (**b**)

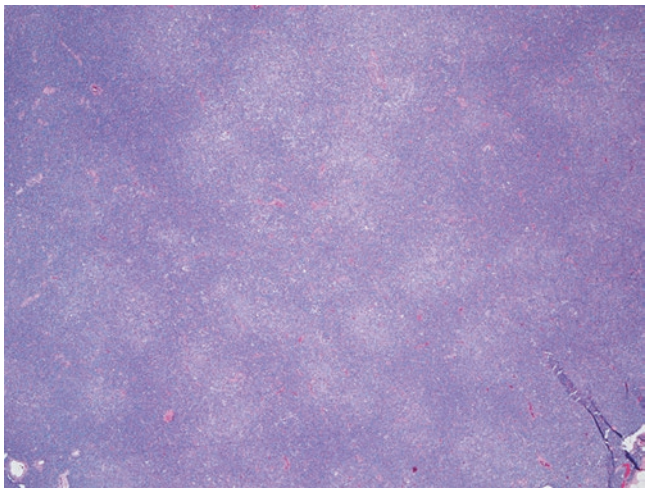

**Fig. 4.23** Small lymphocytic lymphoma with effaced nodal architecture in a vaguely nodular (pseudofollicular) pattern

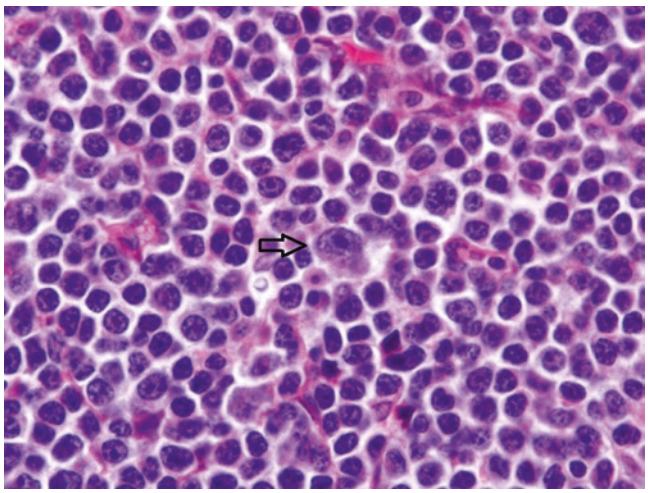

**Fig. 4.24** Small lymphocytic lymphoma cells with hypercondensed chromatin and round nuclear contour; admixed prolymphocytes (*arrow*) with nucleolus and larger in size

- MIB-1 (Ki-67) is a useful marker to differentiate most grade 1 and grade 2 from grade 3.
- In situ follicular neoplasia with a low rate of progression can be detected by flow cytometry studies in half of the cases. Careful interpretation of FNA specimens is recommended.

### Histologic Features

- Effaced nodal architecture in follicular pattern, follicles >75% (Fig. 4.30); in follicular and diffuse pattern, follicles 25–75%; in focally follicular pattern, follicles <25%; and in diffuse pattern, follicles 0%.
- Neoplastic follicles are usually round, surrounded by decreased mantle zone and composed of centrocytes and centroblasts without tingible-body macrophages.
- Centrocytes have mature chromatin and folded nuclear membrane; centroblasts show prominent nucleolus and round nuclear contour (Fig. 4.31).
- Grades 1–2 (low grade) with similar clinical prognosis
  - Grade 1: <5 centroblasts/HPF
  - Grade 2: 6–15 centroblasts/HPF
- Grade 3 (high grade): >15 centroblasts/HPF
  - Grade 3A: centroblasts separated by centrocytes
  - Grade 3B: sheets of centroblasts

### Immunohistochemistry and Ancillary Studies

- Flow cytometry: CD19+, CD20+, CD10+ (Fig. 4.32a–d)
- IHC: CD20+, CD10+, BCL2+, BCL6+ and LIM-only transcription factor-2 (LMO2)+ (Fig. 4.33)
- FISH: positive for t(14;18)(q32;q21) (IGH;BCL2) (Fig. 4.34)

### Differential Diagnosis

- Reactive lymph node
- Other low-grade lymphoma

## Marginal Zone Lymphoma (MZL)

### Clinical Features

- Involving nodal and extranodal sites
- Commonly in women
- Usually in the elderly

### Cytological Features (Fig. 4.35a–f)

- Cellular smear
- A heterogeneous population of cells, including plasmacytoid cells, plasma cells, scattered immunoblasts, centrocyte-like cells
- Monocytoid B cells

### Histologic Features

- Expanded marginal zone (Fig. 4.36)
- Neoplastic cells may appear as monocytoid, plasmacytoid, or centrocyte-like cells (Fig. 4.37).

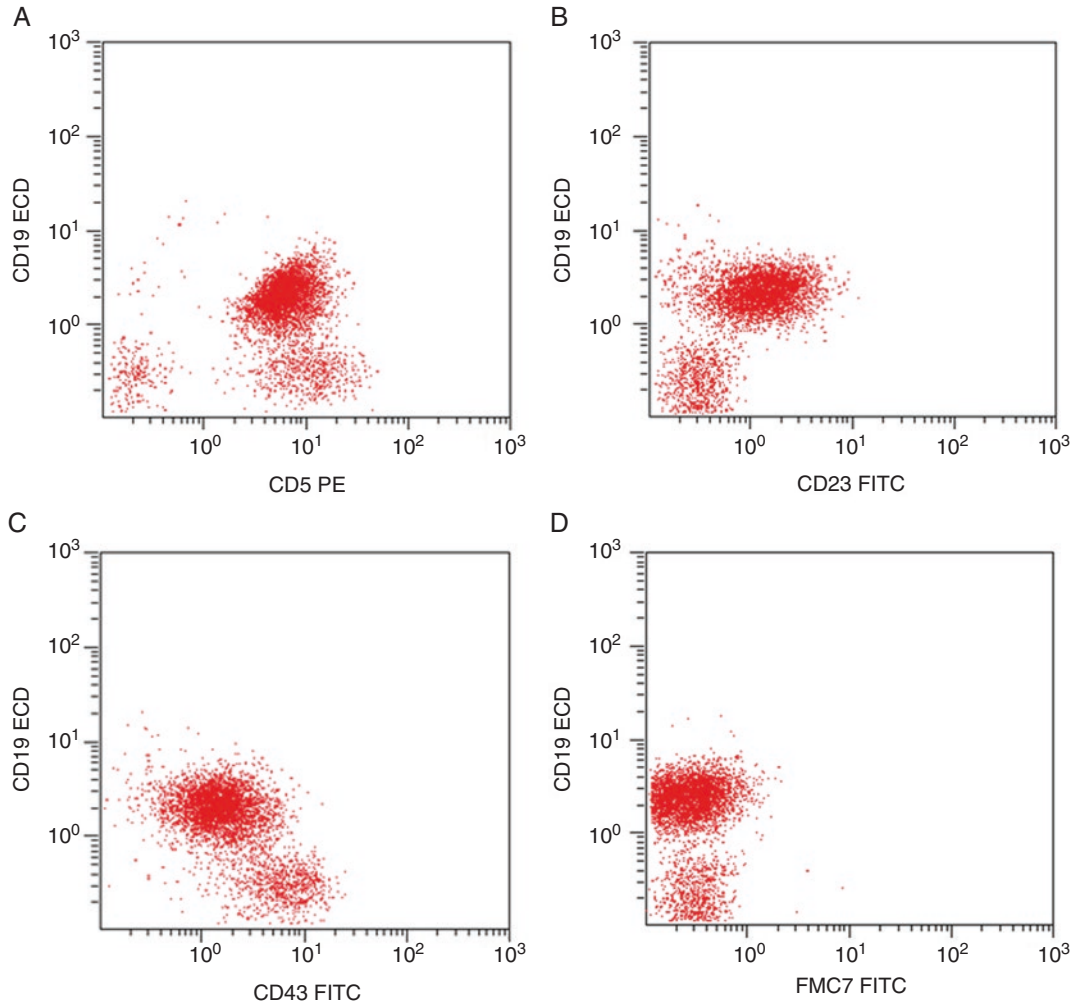


**Fig. 4.25** (**a**–**d**) Flow cytometry studies in small lymphocytic lymphoma shows CD19+ lymphoma cells with coexpression of CD5 and CD23, positive for CD43 and negative for FMC7

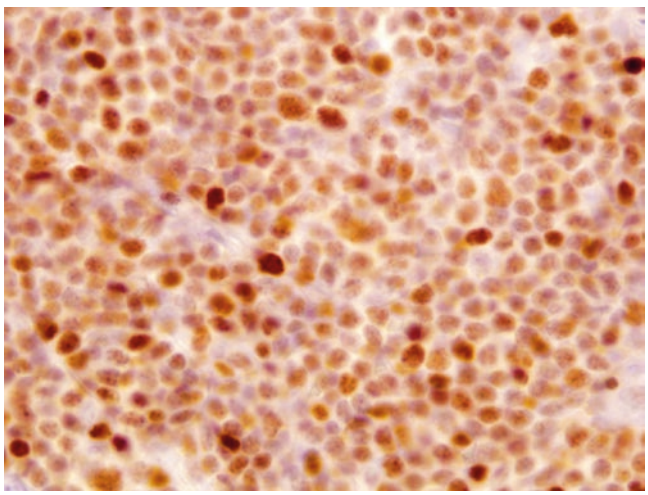

**Fig. 4.26** Small lymphocytic lymphoma positive for LEF1

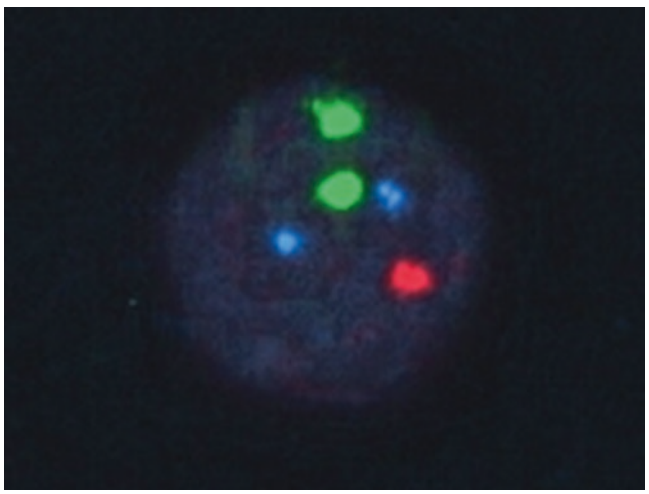

**Fig. 4.27** FISH in small lymphocytic lymphoma with deletion of 13q14 (IR2G2A) in 50% of cases

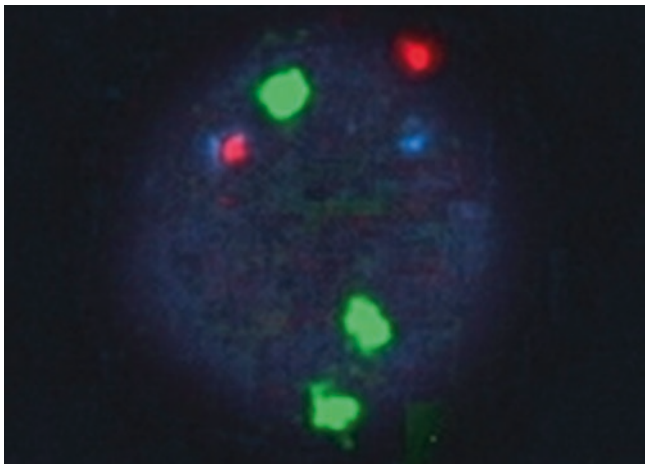

**Fig. 4.28** FISH in small lymphocytic lymphoma with trisomy 12 (2R3G2A) in 20% of cases

### Immunohistochemistry and Ancillary Studies

- Flow cytometry: CD19+, CD20+, CD5-, CD10-, CD23-
- IHC: CD20+, CD43+ (50% of cases), immunoglobulin superfamily receptor translocation associated 1(IRTA1)+ (Fig. 4.38)

### Differential Diagnosis

- Reactive lymph node
- Other low-grade lymphoma

## Mantle Cell Lymphoma (MCL)

### Clinical Features

- 3–10% of non-Hodgkin lymphomas.
- Median age of 60 and male predominance.

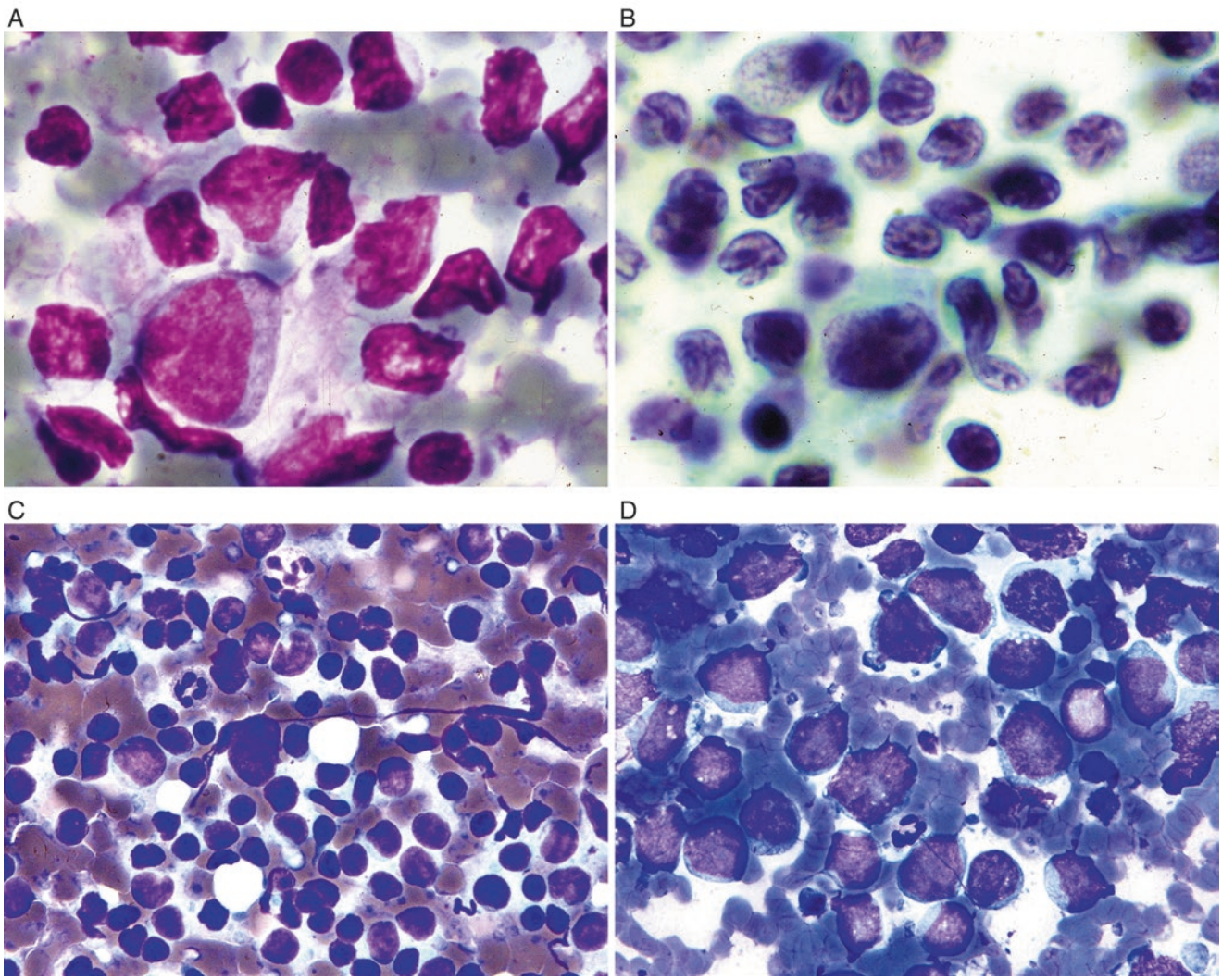


**Fig. 4.29** (**a**–**d**) Follicular lymphoma with increased numbers of large atypical lymphoid cells (centroblasts) in grade 1 (**a**, **b**), grade 2 (**c**), and grade 3 (**d**) follicular lymphoma

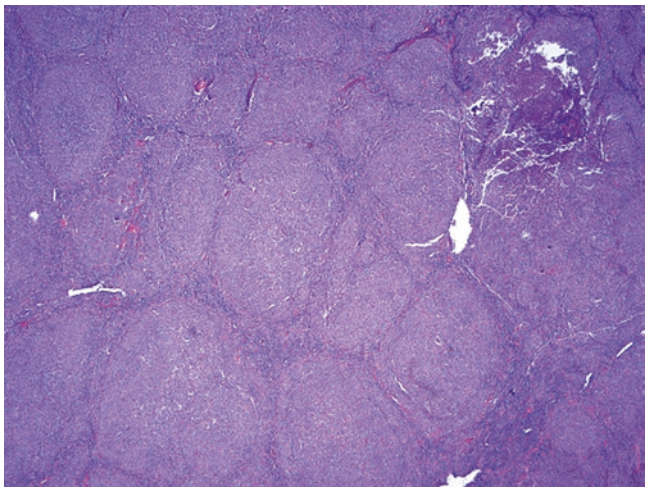

**Fig. 4.30** Follicular lymphoma with effaced nodal architecture in a follicular pattern as "balls in a bag"

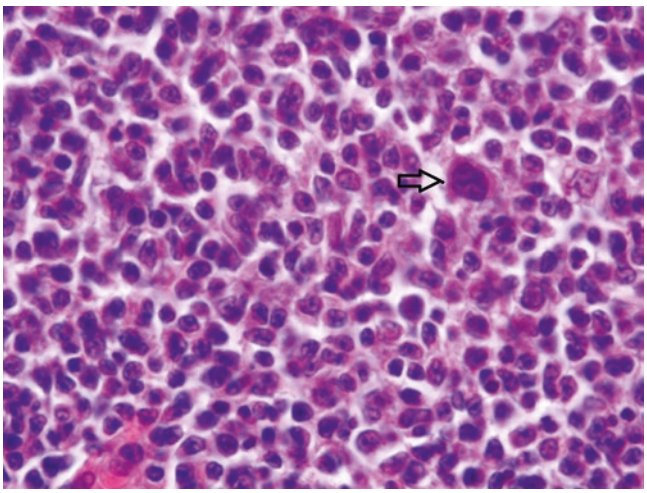

**Fig. 4.31** Neoplastic cells (centrocytes) with folded nuclear contour and mature chromatin; admixed centroblasts (*arrow*) with smooth nuclear membrane and vesicular chromatin

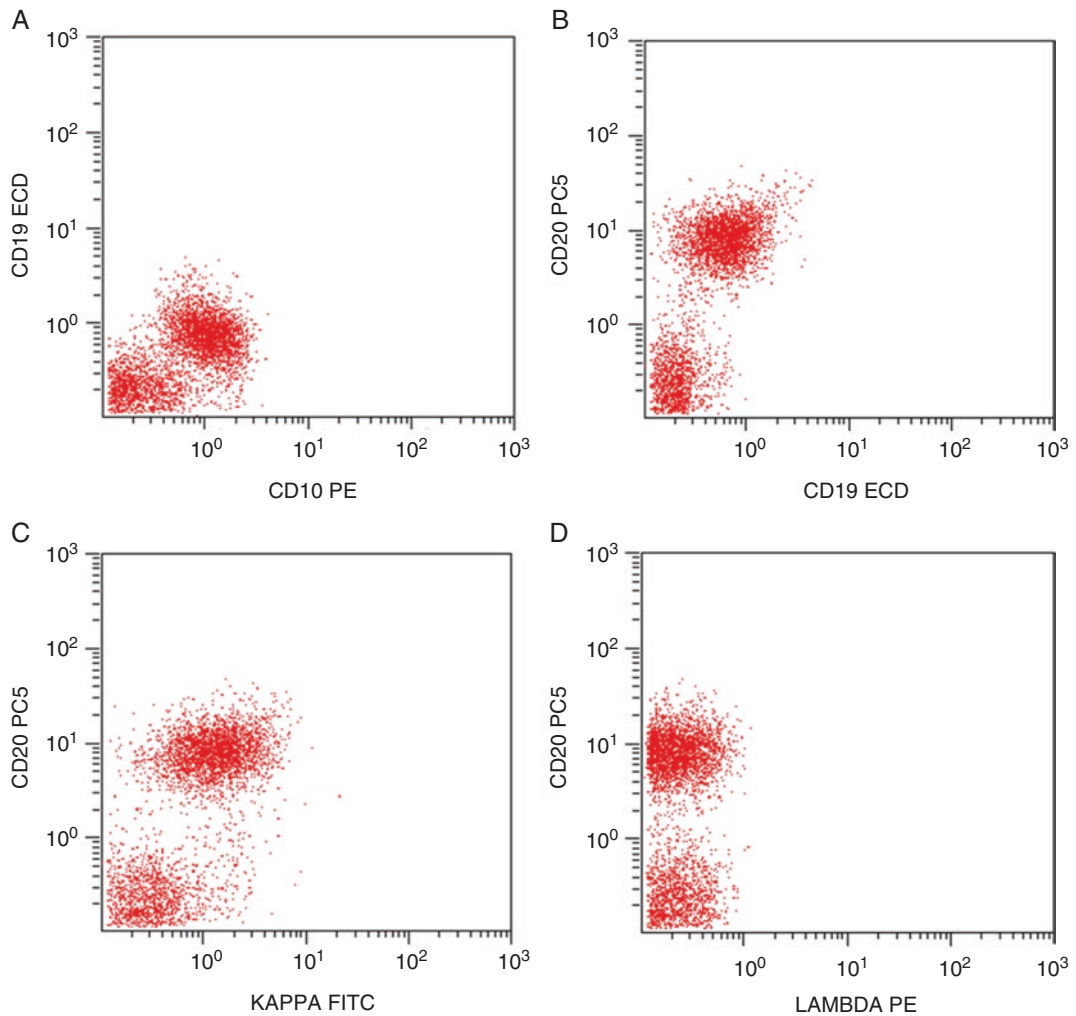


**Fig. 4.32** (**a**–**d**) Flow cytometry studies of follicular lymphoma with coexpression of CD10, high intensity of CD20, and immunoglobulin light chain restriction

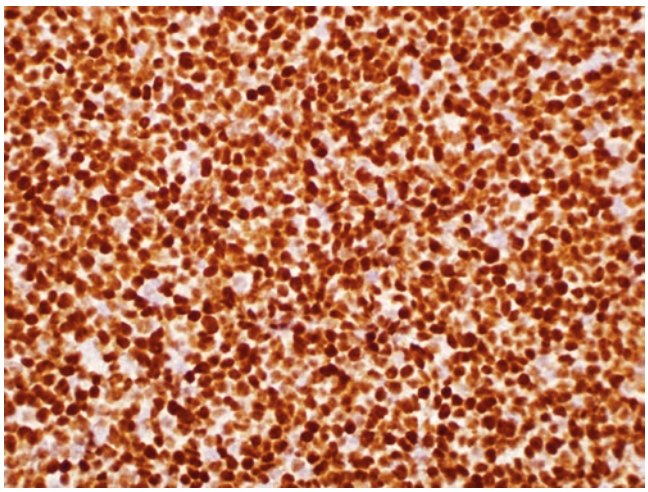

**Fig. 4.33** Follicular lymphoma with LMO2 positivity

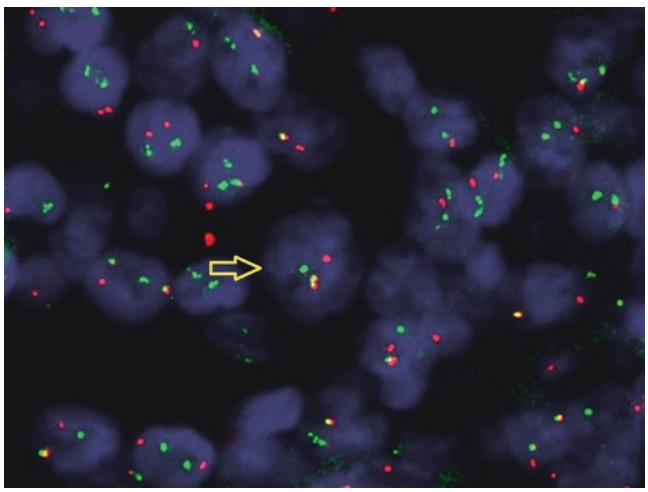

**Fig. 4.34** FISH in follicular lymphoma with t(14;18) (*IGH; BCL2*) (1R1G2A, arrow)

- Involvement of the lymph nodes, spleen, and bone marrow.
- Up to 30% with GI involvement.
- Up to 25% with peripheral blood involvement.
- Two types: sex-determining region Y box (SOX)11-positive/immunoglobulin heavy chain variable *(IGHV)*-unmutated MCL typically involves lymph nodes and other extranodal sites with an aggressive clinical behavior; SOX11-negative/*IGHV*-mutated MCL usually involves the peripheral blood, bone marrow, and spleen with an indolent clinical course.

### Cytological Features (Fig. 4.39a, b)

- Cellular smear.
- Homogeneous population of small- to intermediate-size lymphocytes
- Slightly cleft nuclear membrane.
- Condensed chromatin.
- Inconspicuous nucleoli.
- Many large cells are seen in a blastoid variant (resembling lymphoblasts) with a high mitotic index (>10/10 HPF).
- Positive for CD20, CD5, and negative for CD23 and CD10.
- FISH showing nearly 100% of cases with the t(11;14) translocation.
- Cyclin D1 overexpression by immunostain.

### Histologic Features

- Nodular pattern with expanded mantle zone and may show a diffuse pattern (Fig. 4.40).
- Neoplastic cells with mature chromatin and irregular nuclear contour (Fig. 4.41).
- Capillary proliferation (Fig. 4.42).
- Aggressive variants:
  - Blastoid variant with lymphoblasts
  - Pleomorphic variant with oval to irregular nuclear contour and prominent nucleolus
- Other variants:
  - Small cell variant mimicking SLL
  - Marginal zone-like variant with monocytoid cells
- In situ mantle cell neoplasia with a low rate of progression and indolent clinical course. Careful interpretation of FNA specimen is recommended.

### Immunohistochemistry and Ancillary Studies

- Flow cytometry: CD19+, CD20+, CD5+, FMC7+, CD43- (Fig. 4.43a–d)
- IHC: CD20+, CD5+, BCL1+, SOX11+ (Figs. 4.44 and 4.45)
- FISH: t(11;14) (CCND1;IGH) (Fig. 4.46)

### Differential Diagnosis

- Reactive lymph node
- Other low-grade lymphoma

## Plasmacytoma/Multiple Myeloma

### Cytological Features (Fig. 4.47a, b)

- Mature or immature plasma cells.
- Binucleation or multinucleation.
- Intranuclear bodies (Dutcher body) or intracytoplasmic bodies (Russell body).
- Positive for CD38 and CD138 and negative for CD20.
- May be positive for epithelial membrane antigen (EMA), but negative for cytokeratin.
- IgM MGUS is more closely related to LPL.

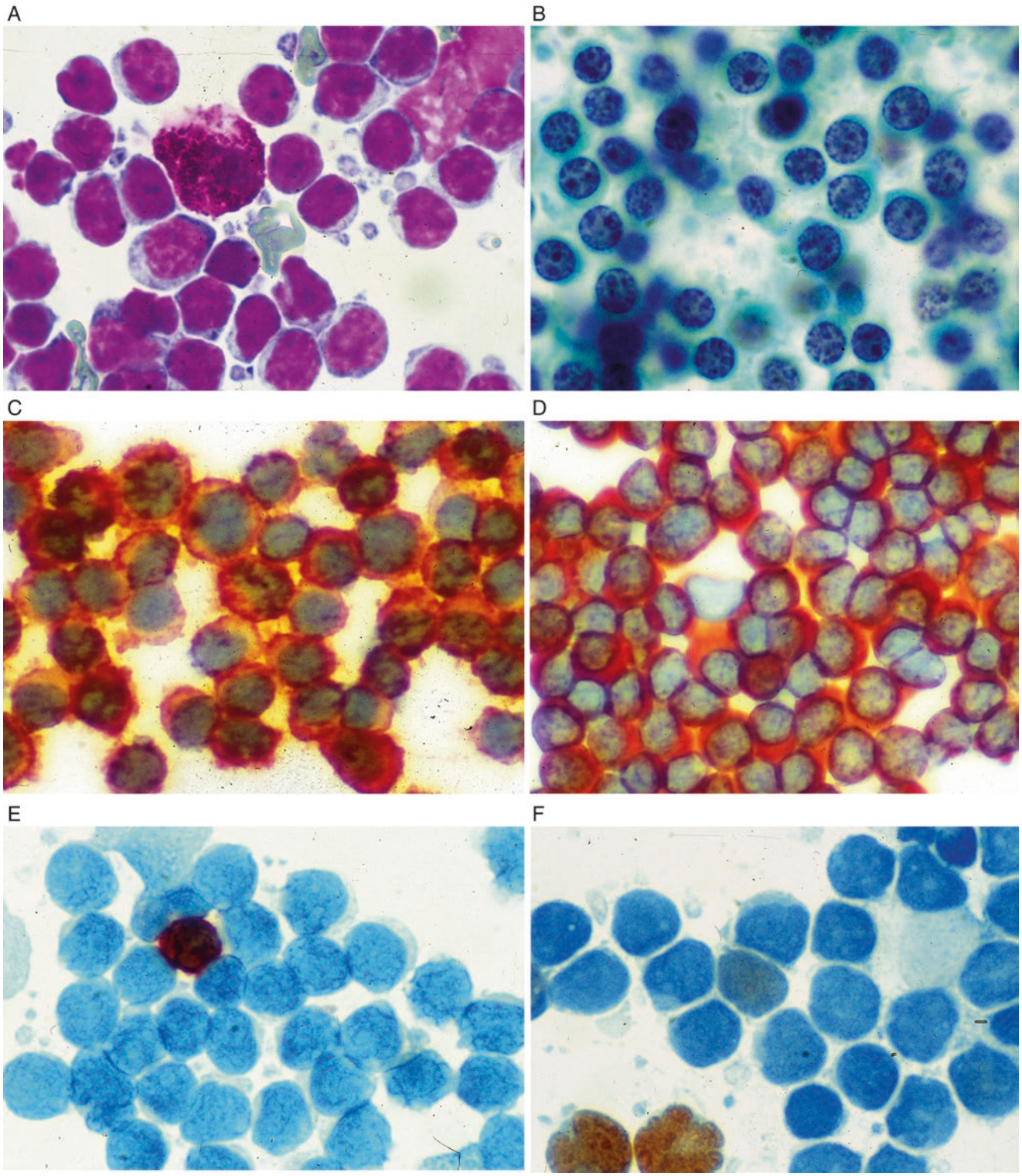


**Fig. 4.35** (**a**–**f**) Marginal zone lymphoma with a heterogeneous population of cells, including plasmacytoid cells, plasma cells, scattered immunoblasts, centrocyte-like cells on Diff-Quik (S), and Pap stain (**b**). Note that immunostain performed on the direct FNA smears showed CD20 positivity (**c**), Kappa light chain restriction (**d**), lack of Lambda light chain (**e**), and low Ki-67 proliferative index (**f**)

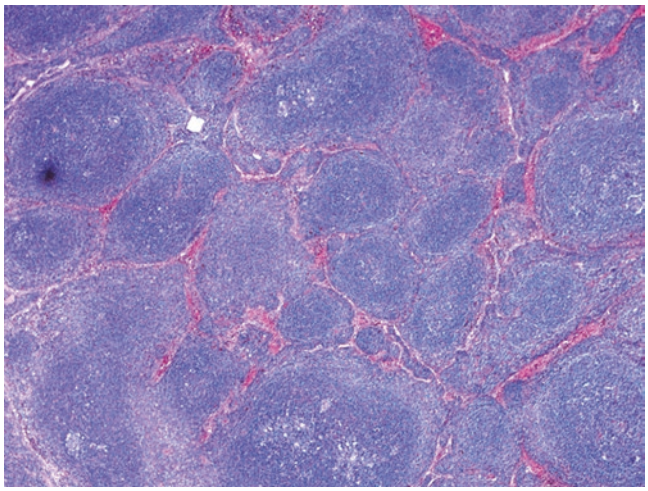

**Fig. 4.36** Marginal zone lymphoma with effaced nodal architecture and marked marginal zone expansion

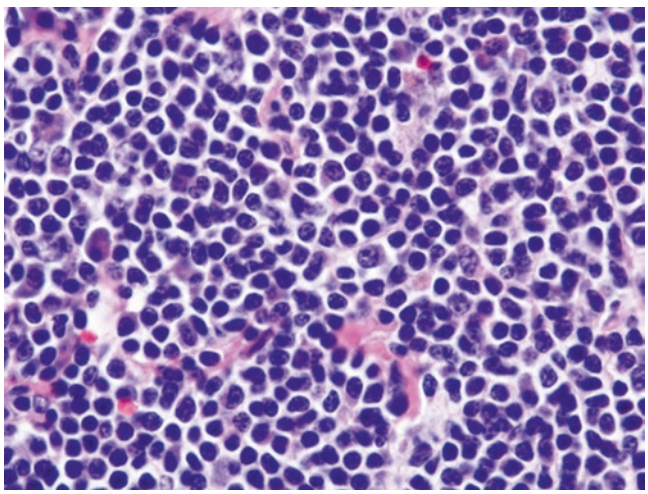

**Fig. 4.37** Neoplastic marginal zone cells show round nuclear contour and mature chromatin with monocytoid or plasmacytoid appearance

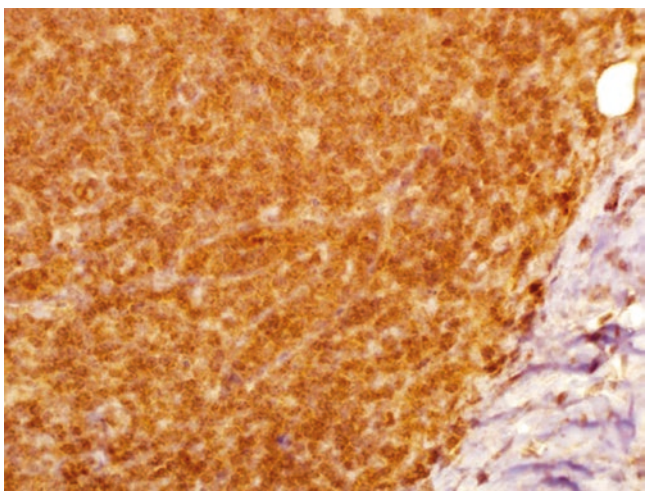

**Fig. 4.38** Neoplastic marginal zone cells positive for IRTA1

### Histologic Features

- Sheets of plasma cells in tissue or lymph node (Figs. 4.48 and 4.49).
- Multiple myeloma in bone marrow biopsy: monotypic plasma cells represent >30% of marrow cellularity.

### Immunohistochemistry and Ancillary Studies

- IHC: CD138+ (Fig. 4.50) used to evaluate volume of plasma cells and kappa and lambda for clonality; some neoplastic plasma cells show aberrant expression of CD56, BCL1, and CD117.

## Large B-Cell Lymphoma (LBCL)

### Clinical Features

- Accounts for 30%–40% of adult non-Hodgkin lymphomas in western countries.
- Nodal or extranodal disease.
- Forty percent with initial extranodal presentation, GI tract most common.
- HIV or other immunodeficiency is a risk factor.
- Many morphologic variants, including centroblastic, immunoblastic, and anaplastic, and subtypes, such as T-cell/histiocytes-rich, primary DLBCL of the CNS, primary cutaneous DLBCL leg type and EBV-positive DLBCL, NOS, et al.
- t(14;18) chromosomal translocation in 30% of cases.
- Two major patterns of gene expression in DLBCL: germinal center (GC)-B cell type DLBCL and activated B-cell (ABC)-type DLBCL. GC-type DLBCL has a much better prognosis than ABC-type DLBCL.

### Cytological Features (Fig. 4.51a–g)

- Highly cellular specimen.
- Dispersed large uniform to variable-size lymphoid cells.
- Numerous lymphoglandular bodies in the background.
- Large pleomorphic nuclei, irregular nuclear contour, and prominent nucleoli.
- Multinucleated giant cells can be seen.
- Variable nuclear-to-cytoplasmic ratio.
- Cohesive groups of large atypical lymphoid cells may mimic other malignant tumors, such as carcinoma, melanoma, and sarcoma.
- Tumor necrosis and mitosis are usually present.

### Histologic Features

- Effaced nodal architecture in a diffuse pattern by medium to large neoplastic lymphocytes

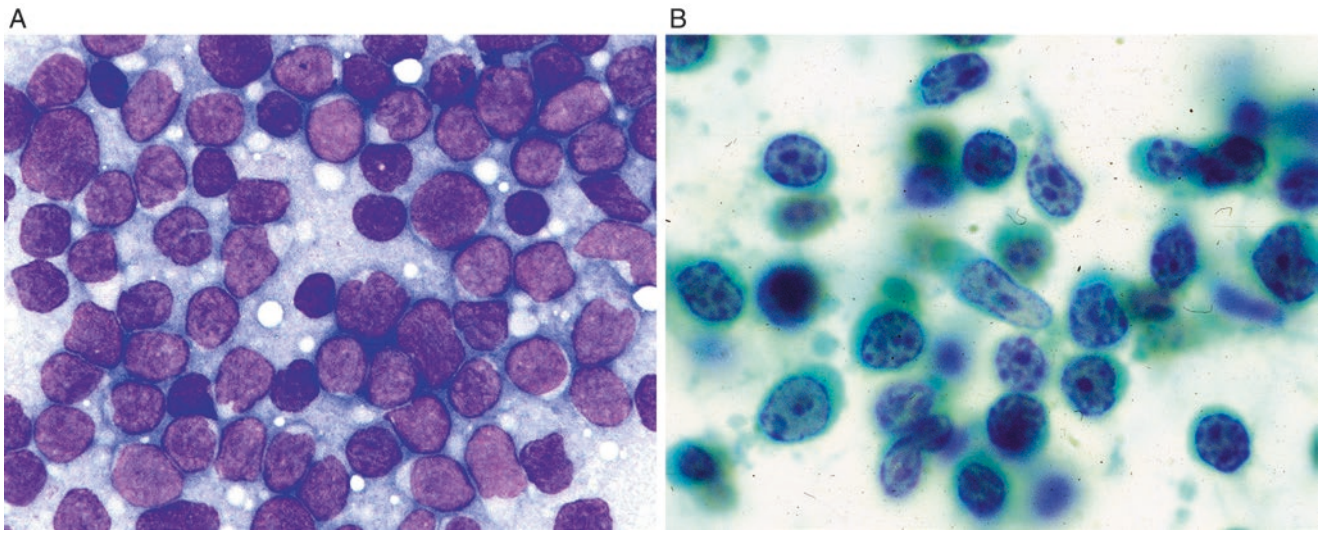


**Fig. 4.39** (**a**, **b**) Mantle cell lymphoma with a homogeneous population of small to intermediate-size lymphocytes with slightly cleft nuclear membranes on Diff-Quik (**a**) and Pap stain (**b**)

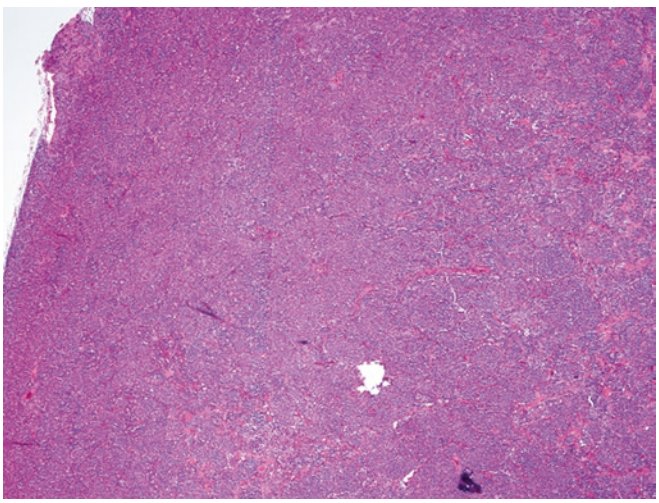

**Fig. 4.40** Mantle cell lymphoma with effaced nodal architecture and mantle zone expansion in a vaguely nodular pattern

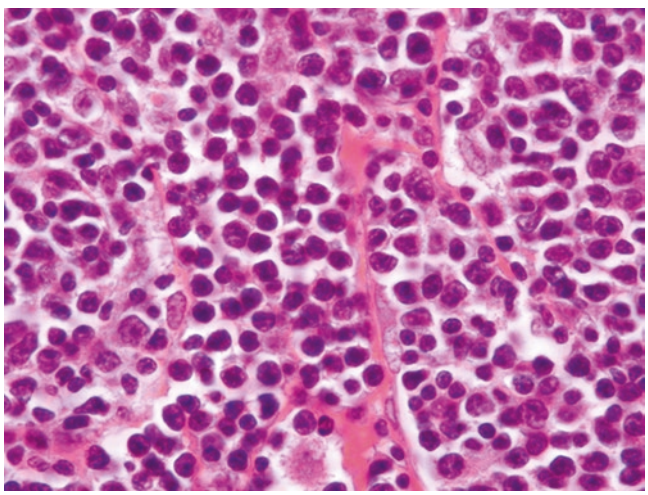

**Fig. 4.41** Neoplastic mantle cells with irregular nuclear contour and mature chromatin

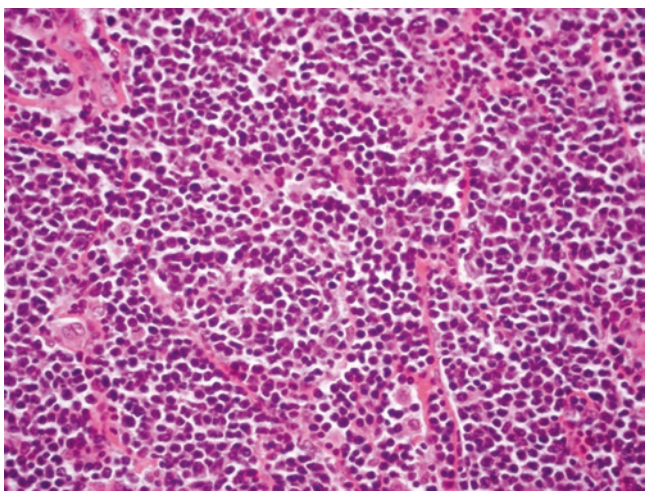

**Fig. 4.42** Mantle cell lymphoma with capillary proliferation

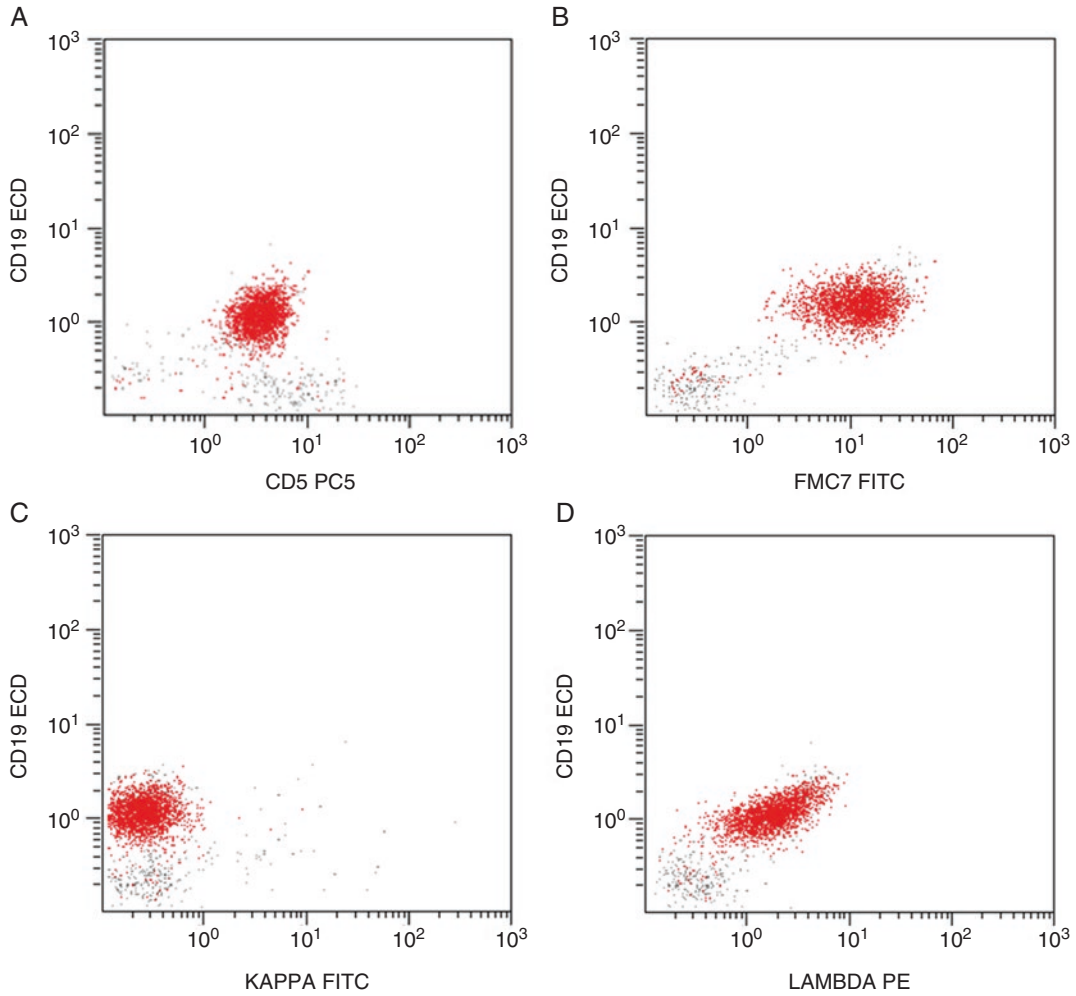


**Fig. 4.43** (**a**–**d**) Flow cytometry studies of mantle cell lymphoma with coexpression of CD5, positivity of FMC7, and immunoglobulin light chain restriction

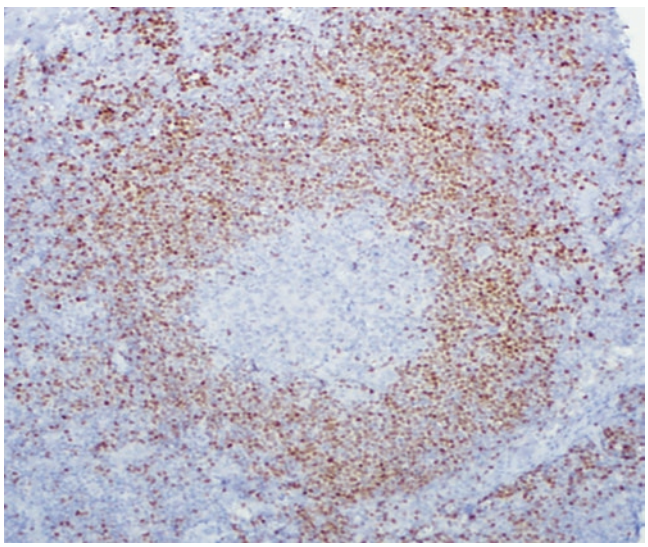

**Fig. 4.44** Immunohistochemical study of SOX11 in mantle cell lymphoma shows mantle zone expansion

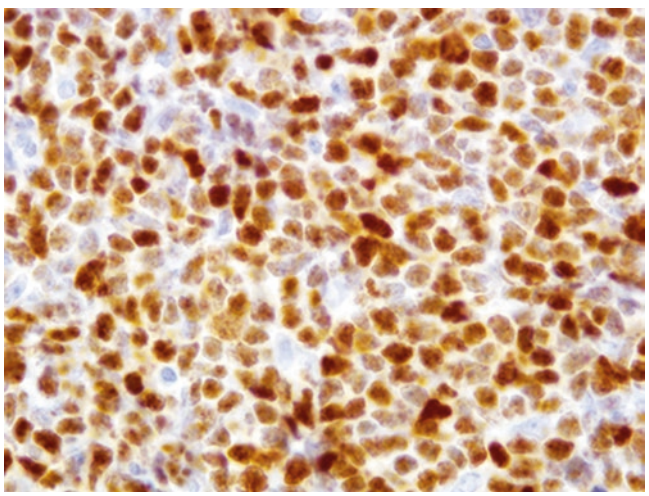

**Fig. 4.45** Immunohistochemical study in mantle cell lymphoma shows mantle cells positive for SOX11

- Neoplastic cells in sheets or a scattered pattern, depending on the subtype (Figs. 4.52 and 4.55)

### Immunohistochemistry and Ancillary Studies

- IHC: positive for the B-cell markers CD20 (Figs. 4.53 and 4.56), paired box gene (PAX)5 (Fig. 4.54), B-cell Oct binding protein 1 (BOB1), octamer-binding transcription factor 2 (Oct2); MIB evaluates the proliferation rate.
- Subclassification:
  - GCB-type DLBCL: CD10+, BCL6+, multiple myeloma 1 (MUM1)-
  - ABC-type DLBCL: CD10-, BCL6-, MUM1+
- Other types include double-hit or triple-hit HGBCL with rearrangements of *MYC* and *BCL2* and/or *BCL6*, and double-expresser HGBCL with immunostain of MYC (>40%) and BCL2 (>50%) but lack *MYC* and *BCL2* chromosomal alteration.

### Differential Diagnosis

- Reactive lymph node
- High-grade lymphoma and Hodgkin lymphoma
- Melanoma
- Carcinoma
- Sarcoma

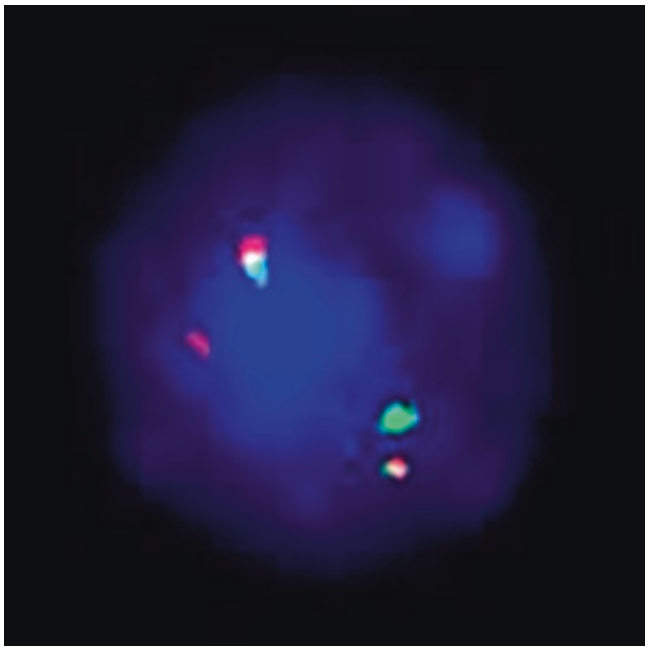

**Fig. 4.46** FISH in mantle cell lymphoma with t(14;18) (*CCND1;IGH*) (1R1G2F)

## Burkitt Lymphoma (BL)

### Clinical Features

- Endemic BL, sporadic BL, and immunodeficiency-related BL.
- Extranodal involvement frequent in the jaw, facial bone, abdominal organs, and breast.
- EBV plays an important role in endemic BL.
- Transcription factor 3 (*TCF3*) mutation in 40% of endemic BLs and 70% of sporadic BLs and immunodeficiency-related BLs.

### Cytological Features (Fig. 4.57)

- Cellular smear.
- Monotonous population of medium-size lymphoid cells.
- Usually smooth nuclear membrane, small notched or indented, may be seen.
- Finely stippled nuclear chromatin.

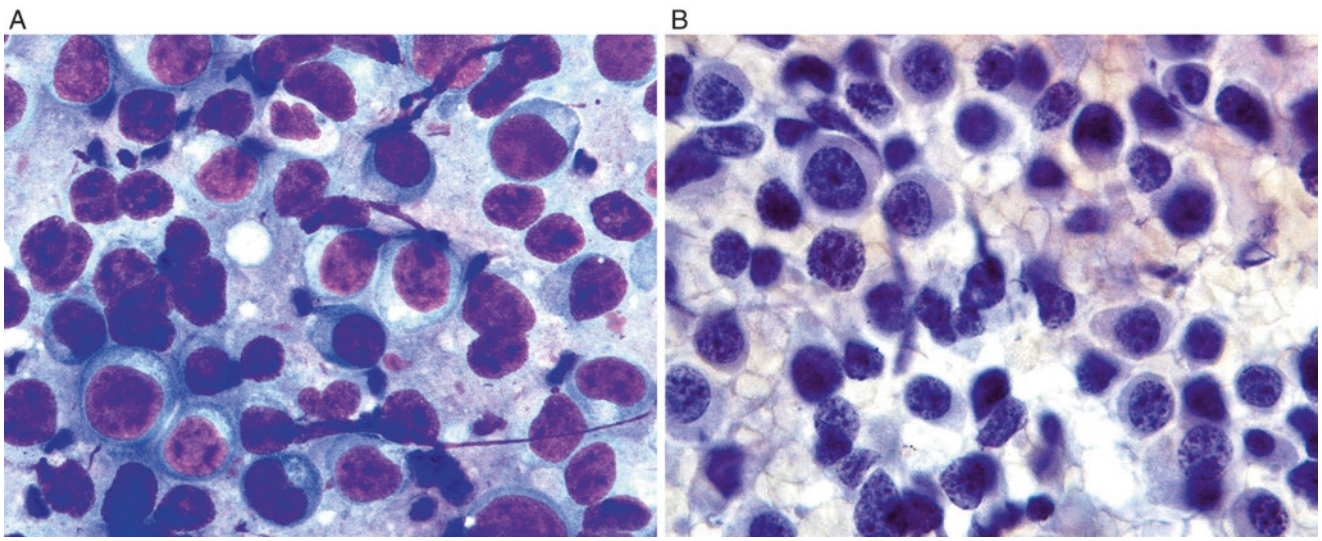


**Fig. 4.47** (**a**, **b**) Plasmacytoma on Diff-Quik (**a**) and Pap stain (**b**)

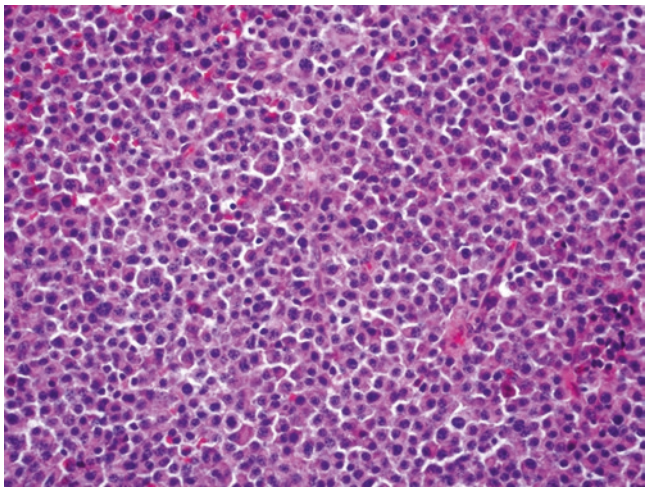

**Fig. 4.48** Plasmacytoma with sheets of plasma cells

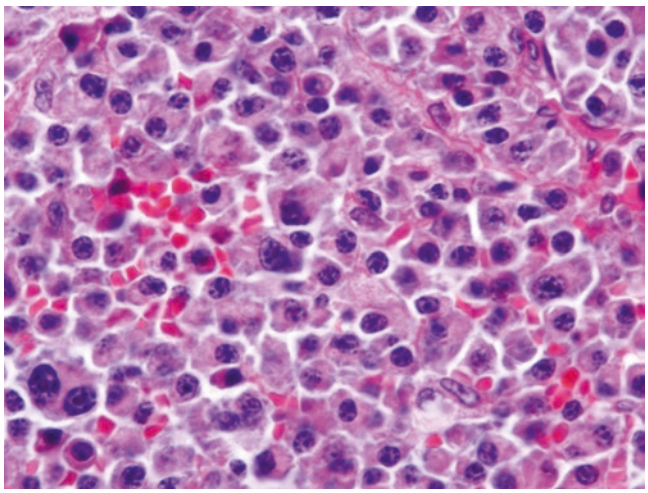

**Fig. 4.49** Neoplastic plasma cells with less mature chromatin, nucleolus, and scattered binucleation

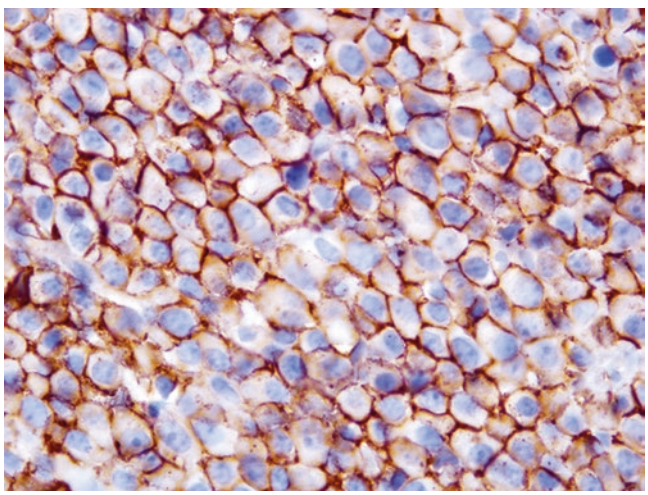

**Fig. 4.50** Plasmacytoma with sheets of CD138 positive plasma cells

- Multiple conspicuous nucleoli.
- Moderate amount, deeply basophilic cytoplasm with tiny vacuoles.
- CD20, CD10, BCL6 positive.
- All cases positive for the t(8;14) translocation, involving *MYC*.

### Histologic Features

- Effaced nodal architecture with a "starry sky" pattern and composed of sheets of neoplastic lymphocytes and scattered tingible-body histiocytes (Fig. 4.58)
- Neoplastic lymphocytes are medium in size with a round to slightly irregular nuclear contour and small nucleoli with a "snake head" appearance (Fig. 4.59).

### Immunohistochemistry and Ancillary Studies

- IHC: strongly positive for CD20, CD10, BCL6, c-MYC and negative for BCL2 with proliferation rate of 100% by MIB-1 stain (Fig. 4.60)
- FISH: MYC translocation (Fig. 4.61)
- A subset lacking *MYC* rearrangement called "Burkitt-like lymphoma with 11q aberration" shows the same morphology and similar clinical course.

### Differential Diagnosis

- LBCL
- Viral infection with reactive change
- Lymphoblastic lymphoma

## T-Cell Lymphoma

### Clinical Features

- Relatively uncommon lymphoid neoplasm, accounting for less than 12% of non-Hodgkin lymphomas, including peripheral T-cell lymphoma (PTCL), unspecified T-cell lymphoma, NK-cell lymphoma, ALCL, and nodal T-cell lymphoma with TFH phenotype
- More common in Asia

### Cytological Features (Fig. 4.62a, b)

- Polymorphous population of a spectrum of small, medium, and large lymphocytes.
- Convoluted nuclear membranes, vesicular or coarse chromatin, and prominent nucleoli.
- Binucleation and multinucleation can be seen.
- Cytoplasm ranging from scant to abundant, pale to basophilic.

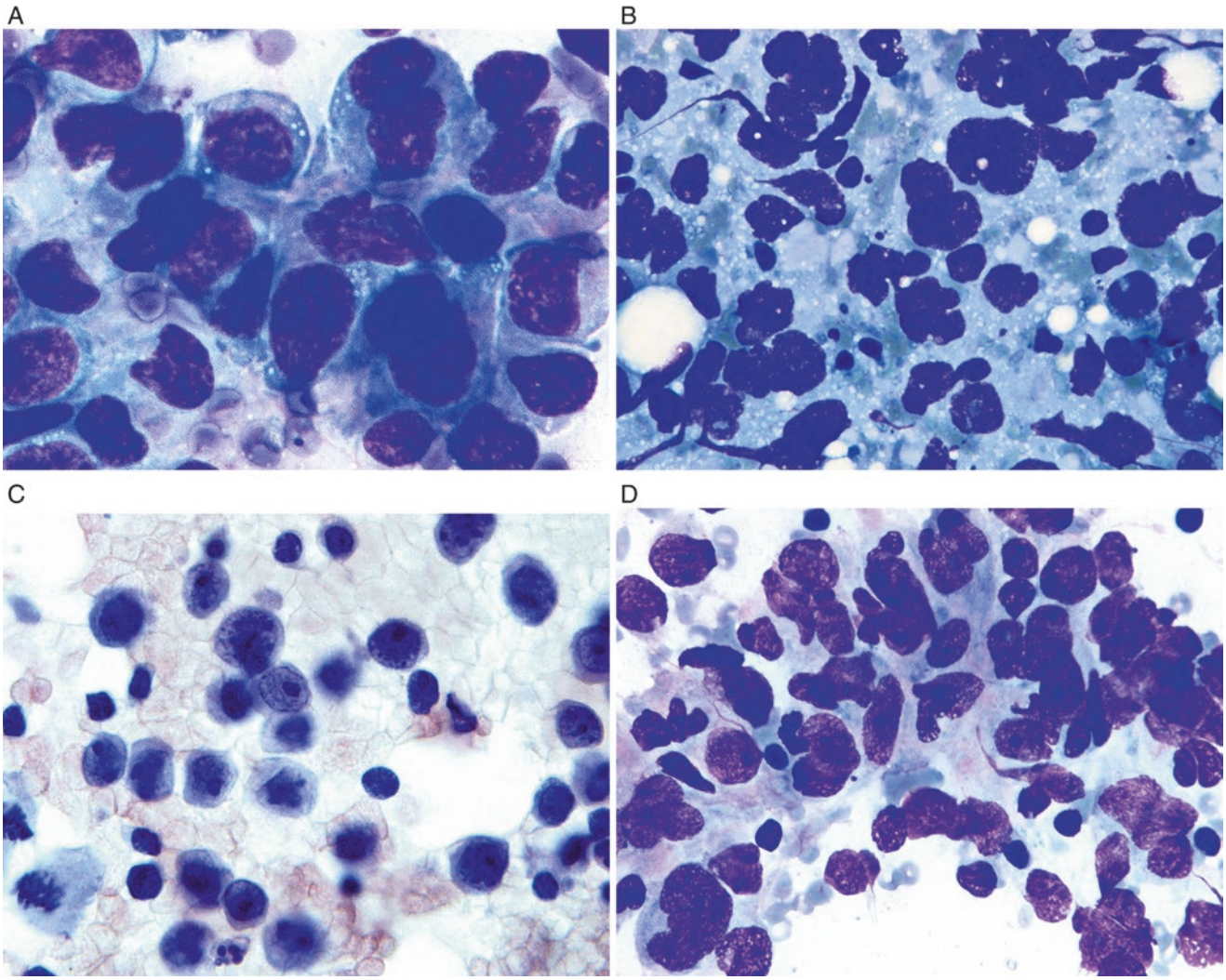


**Fig. 4.51** (**a**–**g**) Large B-cell lymphoma with large uniform to variable-size lymphoid cells on Diff-Quik (**a**, **b**) and Pap stain (**c**). Note that LBCL may mimic other malignant tumors, such as carcinoma, as shown in (**d**), on cellblock preparation (**e**), positive for CD20 (**f**) and increased Ki-67 proliferative index (**g**)

- Histiocytes, eosinophils, plasma cells and neutrophils can be seen.
- Granulomas can be seen.

### Histologic Features

- Effaced nodal architecture with perifollicular (T-cell zone) expansion (Fig. 4.63).
- Neoplastic lymphocytes are medium in size with irregular nuclear contour, vesicular chromatin, and prominent nucleoli; they form sheets or a scattered pattern (Fig. 4.64).

### Immunohistochemistry and Ancillary Studies

- Positive for, but often loss of one or more of, the T-cell markers CD2, CD3, CD5 and CD7 with either CD4 or CD8.
- Angioimmunoblastic T-cell lymphoma (Fig. 4.65) and two new subtypes – follicular center T-cell lymphoma and nodal PTCL with TFH type – show the follicular center markers CD279/programmed death 1 (PD1), CD10, BCL6, chemokine (C-X-C motif) ligand 13 (CXCL13), inducible T-cell co-stimulator (ICOS), serum amyloid P (SAP), and chemokine receptor type 5 (CCR5).

## Anaplastic Large Cell Lymphoma (ALCL)

### Clinical Features

- Three percent of adult non-Hodgkin lymphomas.
- ALK+ ALCL represents 10–20% of childhood lymphomas; ALK- ALCL peaks in adults (40–65 years).
- CD30-positve T-cell lymphoma.

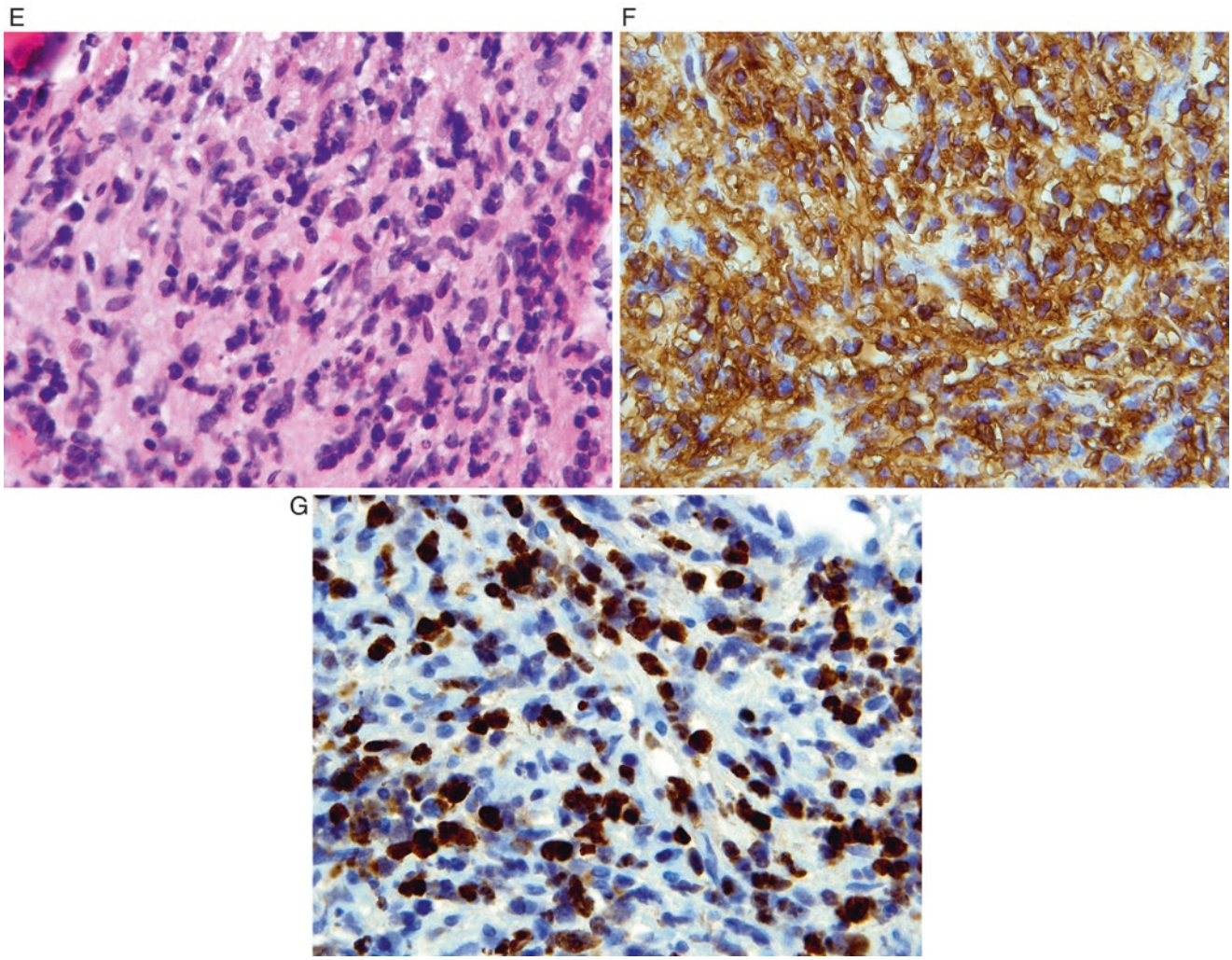


**Fig. 4.51** (continued)

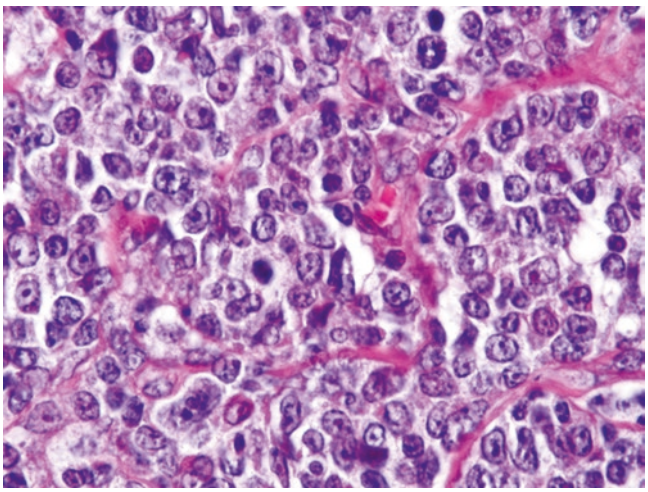

**Fig. 4.52** Diffuse large B-cell lymphoma with effaced nodal architecture in a diffuse pattern by sheets of large cells showing vesicular chromatin and prominent nucleolus

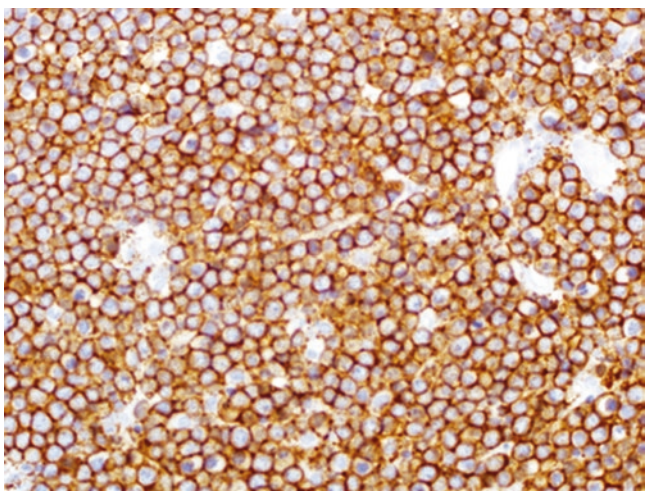

**Fig. 4.53** Diffuse large B-cell lymphoma with sheets of CD20-positive neoplastic cells

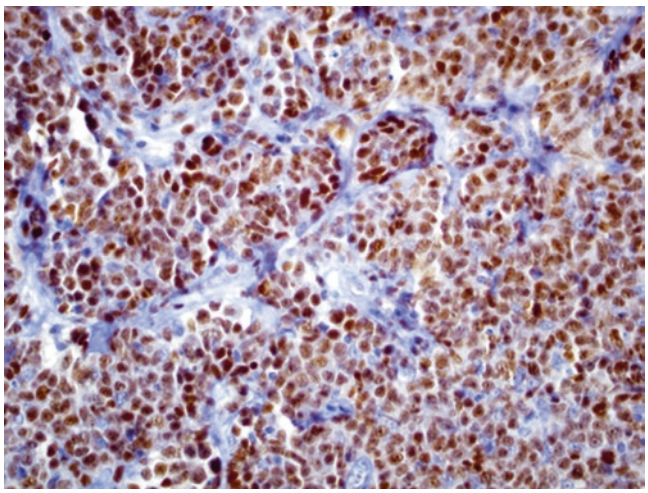

**Fig. 4.54** Diffuse large B-cell lymphoma with sheets of PAX5-positive neoplastic cells

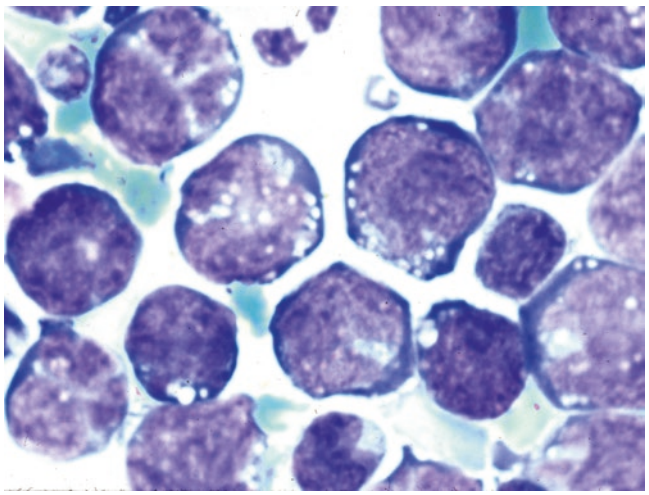

**Fig. 4.57** Burkitt lymphoma with a monotonous population of medium-size lymphoid cells. Note the deeply basophilic cytoplasm with tiny vacuoles

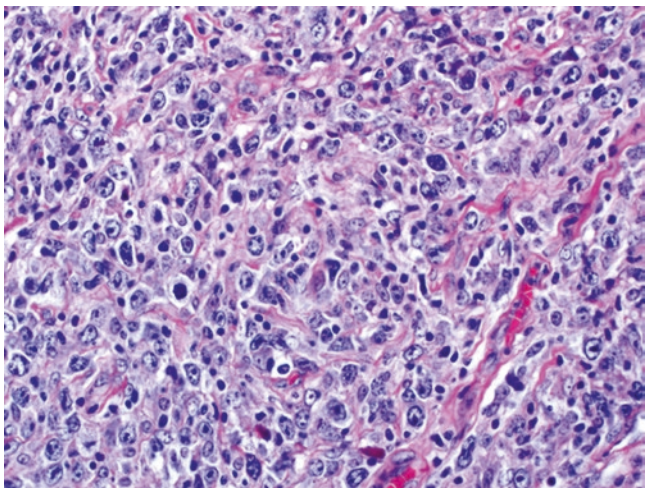

**Fig. 4.55** Diffuse large B-cell lymphoma with effaced nodal architecture in a diffuse pattern by scattered large cells showing pleomorphism

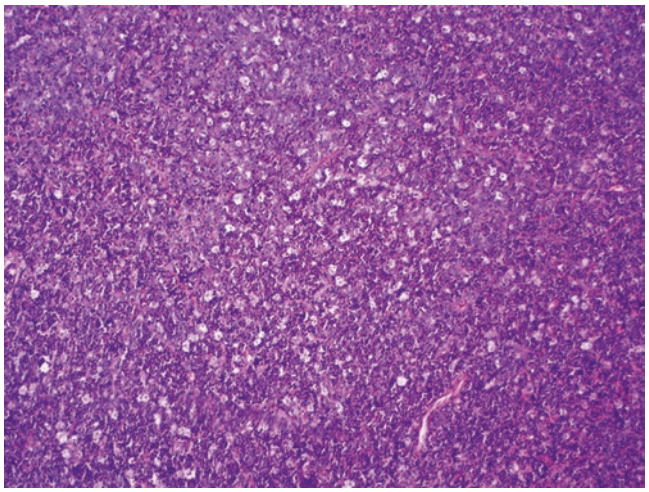

**Fig. 4.58** Burkitt lymphoma with sheets of lymphoma cells admixed with histiocytes as a "starry sky" pattern

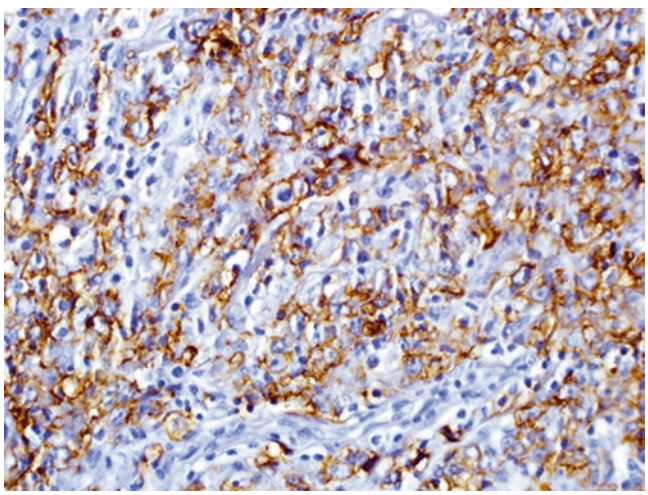

**Fig. 4.56** The large pleomorphic cells in diffuse large B-cell lymphoma with CD20 positivity

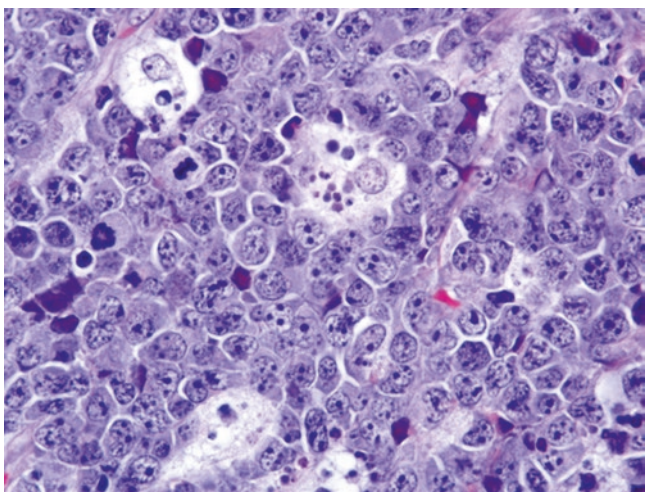

**Fig. 4.59** Burkitt lymphoma cells with round nuclear contour and small nucleoli as a "snake head" appearance

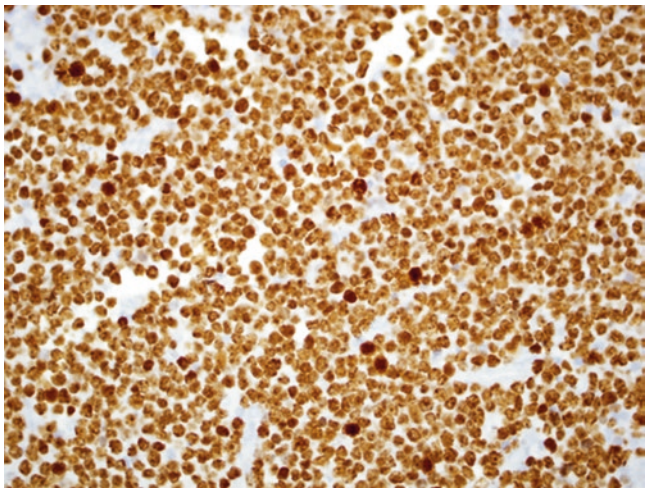

**Fig. 4.60** Burkitt lymphoma cells with 100% of proliferation rate by Ki67 (MIB) immunohistochemical stain

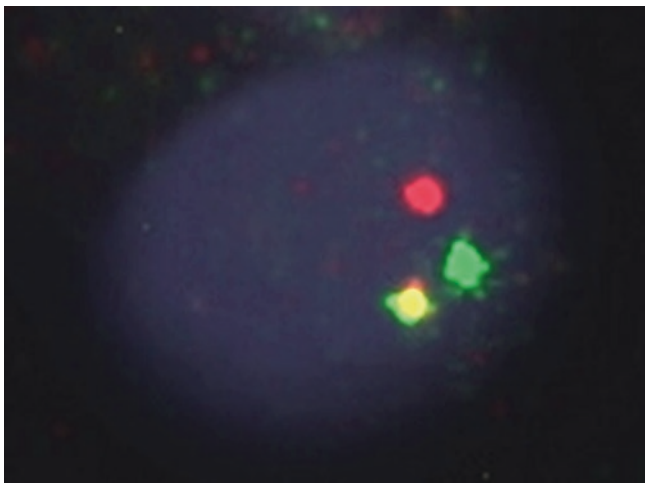

**Fig. 4.61** FISH in Burkitt lymphoma with *MYC* rearrangement (break-apart, 1R1G1F)

- 70–80% with t(2;5) translocation and ALK expression.
- ALK-positive cases frequently involve both nodal and extranodal sites and have a better prognosis.

### Cytological Features (Fig. 4.66a–d)

- Cellular smear.
- Pleomorphic cells with variable sizes.
- Binucleation or multinucleation or bizarre cells can be seen.
- Large nuclei with indentation and lobulation.
- Variable amount of cytoplasm.
- Heterogeneous population in the background, including small lymphoid cells, histiocytes, and plasma cells.
- CD2 and CD4 are the more sensitive markers.
- More than 75% of cases are negative for CD3.
- CD30 positive in all cases, usually in large lymphoid cells; most cases are positive for EMA.
- Seventy percent of cases show ALK expression (either nuclear or cytoplasmic staining).
- EBV is negative.

### Histologic Features

- Effaced nodal architecture with expanded perifollicular areas (Fig. 4.67).
- Neoplastic cells are pleomorphic and hallmark cells with horseshoe-like nucleus (Fig. 4.68).

### Immunohistochemistry and Ancillary Studies

- Positive for T-cell markers, CD30 (Fig. 4.69), and ALK1 (Fig. 4.70) and negative for CD15
- ALK1+ and ALK1- types share a similar molecular Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) pathway.

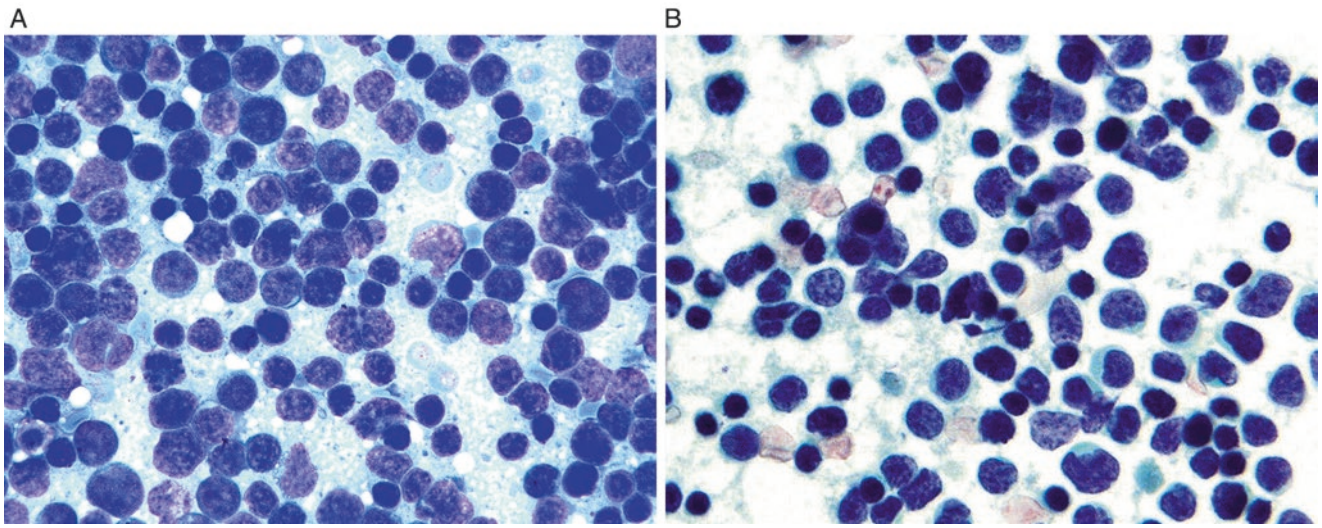


**Fig. 4.62** (**a**, **b**) T-cell lymphoma with a polymorphous population of a spectrum of small, medium, and large lymphocytes on Diff-Quik (**a**) and Pap stain (**b**)

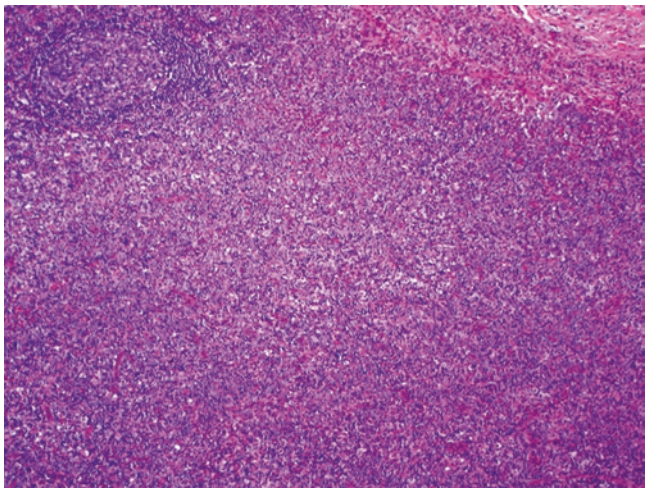

**Fig. 4.63** Peripheral T-cell lymphoma with effaced nodal architecture and perifollicular expansion

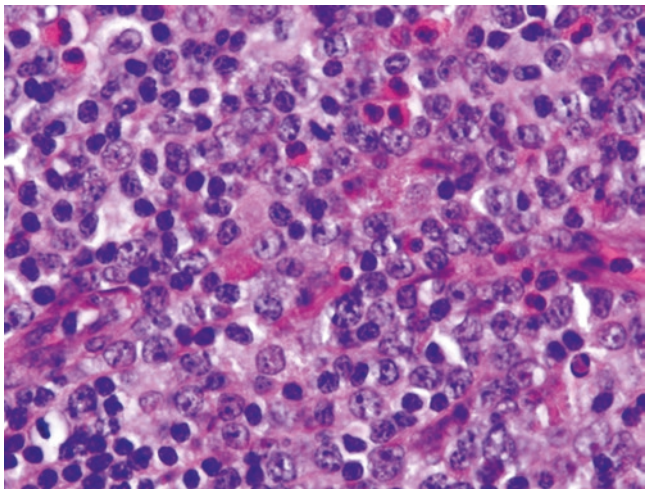

**Fig. 4.64** Neoplastic T cells are medium in size with vesicular chromatin and nucleolus; there is a background of mature lymphocyte and scattered eosinophils

- New type: ALK-negative ALCL arising in association with breast implants shows similar morphological features, but neoplastic cells are confined to the seroma fluid without invasion of the capsule. Treatment is removal of the implant and capsule.

### Differential Diagnosis

- Hodgkin lymphoma
- Other high-grade lymphoma
- Carcinoma
- Melanoma
- Sarcoma

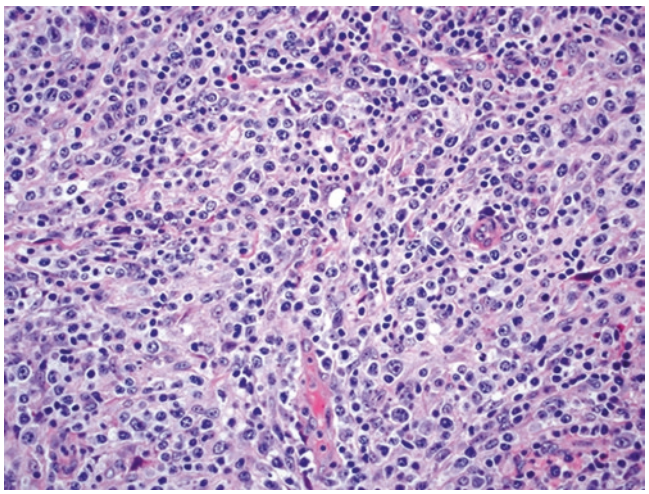

**Fig. 4.65** Angioimmunoblastic T-cell lymphoma with effaced nodal architecture and perifollicular expansion by monocytoid lymphocytes and capillary proliferation

## Hodgkin Lymphoma

### Clinical Features

- Cervical, mediastinal, or axillary mass
- Bimodal age curve with a peak in young adults (15–35 years) and a second in the elderly

### Cytological Features (Fig. 4.71a–h)

- Low to moderate cellularity.
- Polymorphous population of small lymphoid cells, plasma cells, histiocytes, and eosinophils.
- Classic multinucleated Reed-Sternberg cells and mononuclear Hodgkin cells.
- Fibrosis and crushed cellular components are frequently seen.
- Excisional biopsy should be suggested for further classification.

### Histologic Features

- Effaced nodal architecture in a nodular or diffuse pattern with two types: CHL (nodular sclerosis, mixed cellularity, lymphocyte rich, and lymphocyte depleted) (Figs. 4.72a–d and 4.73a–c) and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) (Figs. 4.74 and 4.75a–d)
- Large neoplastic cells including Reed-Sternberg cells, Hodgkin cells, lacunar cells, and popcorn cells (Fig. 4.76a–d)

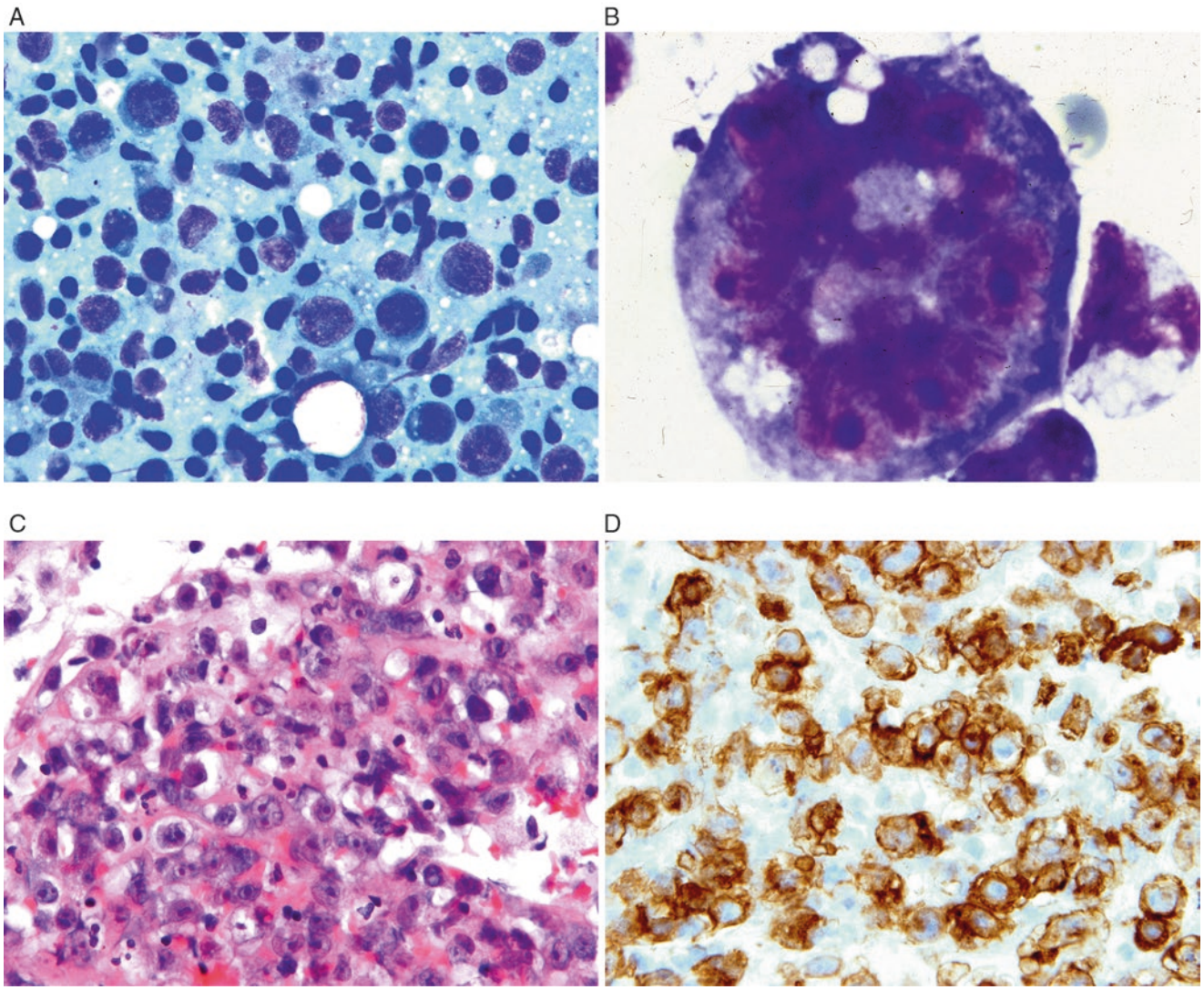


**Fig. 4.66** (**a**–**d**) Anaplastic large cell lymphoma with pleomorphic cells with variable sizes on Diff-Quik (**a**, **b**), cellblock (**c**), positive for CD30 (**d**)

### Immunohistochemistry and Ancillary Studies

- Reed-Sternberg cells in CHL are positive for CD15, CD30, and K homology domain-containing protein over-expressed in cancer 1 (KOC1) (Fig. 4.77a–c) and negative for CD3 and CD20.
- NLPHL is a monoclonal B-cell neoplasm that is CD45 positive, CD20 positive, PAX5 positive, CD15 negative, and CD30 negative (Fig. 4.78a–e).
- Lymphocyte-rich CHL has features intermediate between CHL and NLPHL.

#### Differential Diagnosis

- Poorly differentiated carcinoma
- Melanoma
- Sarcoma
- Reactive lymph node with many immunoblasts

## Others

### Langerhans Cell Histiocytosis (LCH)

#### Cytological Features (Fig. 4.79a–e)

- Langerhans histiocytes and eosinophils.
- Nuclear grooves or linear folds are seen in Langerhans cells.
- Immunostain shows positivity for both S100 and CD1a.
- Multinucleated giant cells may be present.
- Some of these neoplasms may have transdifferentiation to follicular lymphoma, CLL, B- or T-lymphoblastic

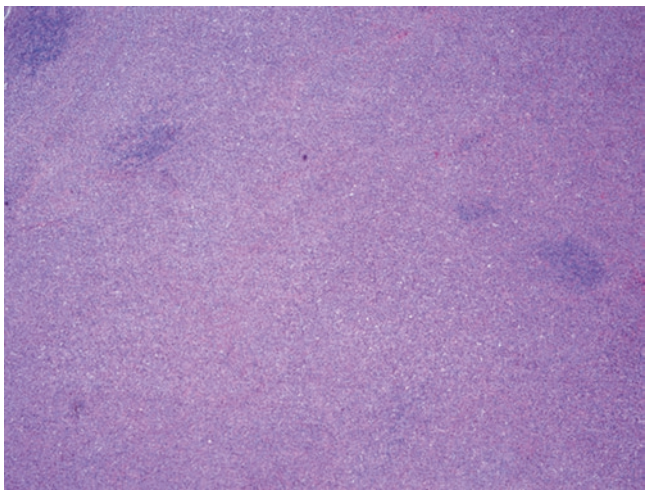

**Fig. 4.67** Anaplastic large cell lymphoma with effaced nodal architecture and perifollicular expansion

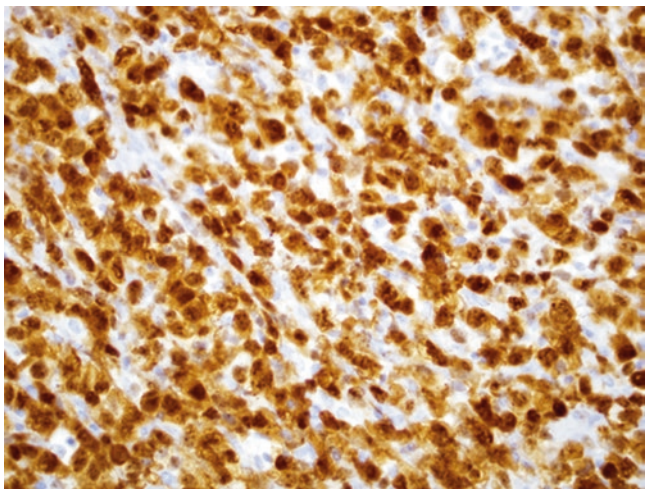

**Fig. 4.70** Neoplastic T cells positive for ALK1

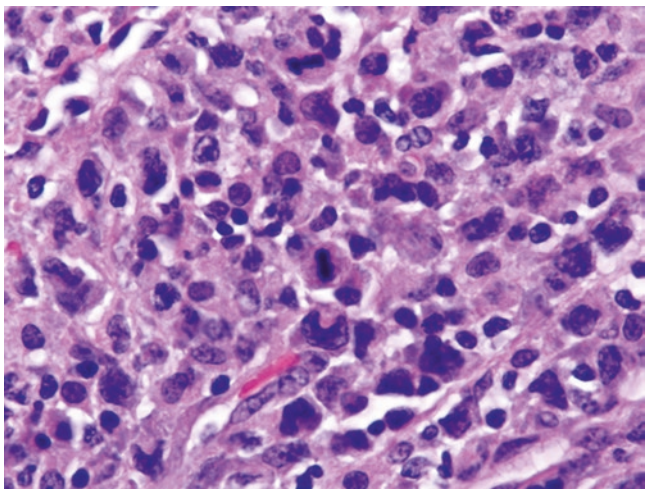

**Fig. 4.68** Neoplastic T cells are pleomorphic and some with horseshoe-like nucleus – hallmark cells

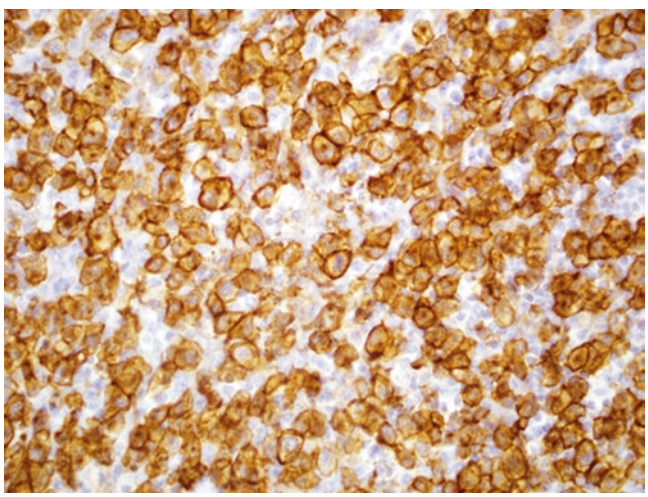

**Fig. 4.69** Neoplastic T cells positive for CD30

neoplasms carrying the same *IGHV*, or T-cell receptor (*TCR*) gene rearrangement.

### Histologic Features

- Effaced nodal architecture with expanded sinus and pericortex by large neoplastic Langerhans cells
- In early stage, Langerhans cells prominent admixed with eosinophils and neutrophils; in late stage, the number of Langerhans cells is decreased with fibrosis and increased foamy macrophages.

## Myeloid Sarcoma

### Cytological Features (Fig. 4.80a–e)

- Myeloid cells in various stages of differentiation
- Can be mainly blasts or a mixed population of myeloid cells in different stages
- Eosinophilic myelocytes may be seen.

### Histologic Features

- Effaced nodal or tissue architecture with sheets of myeloblasts (Figs. 4.81 and 4.82), rarely, of erythroid precursors or megakaryoblasts
- May present de novo, with peripheral and bone marrow involvement, relapse of acute myeloid leukemia (AML) or progression of a prior myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), or MDS/MPN. Recommend clinical correlation.

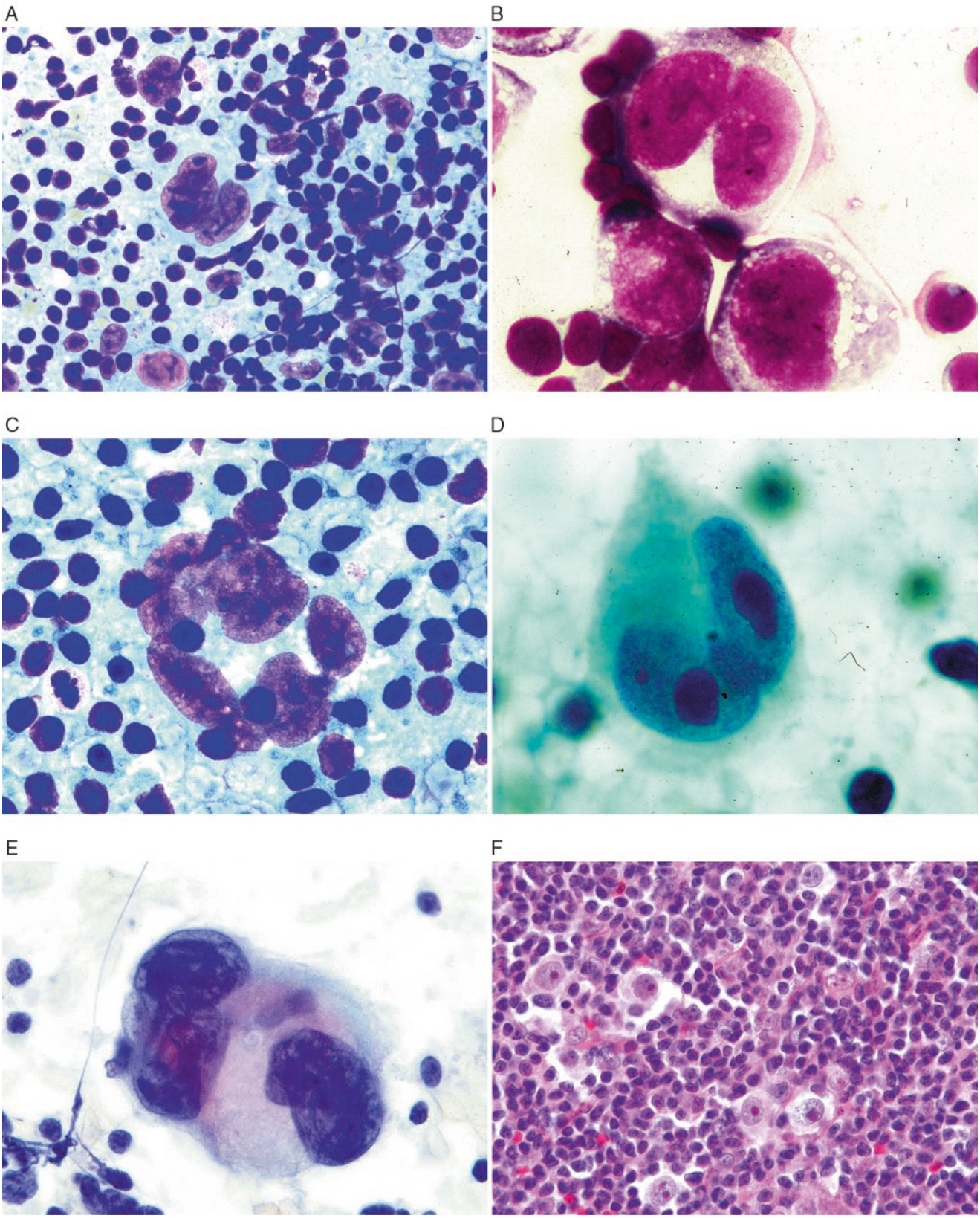


**Fig. 4.71** (**a**–**h**) Hodgkin lymphoma with classic Reed-Sternberg cells and mononuclear or multinucleated Hodgkin cells in the background of a polymorphous population of small lymphoid cells, plasma cells, histiocytes, and eosinophils (**a**–**e**), and small tissue section (**f**), Hodgkin cells positive for CD15 (**g**), and CD30 (**h**)

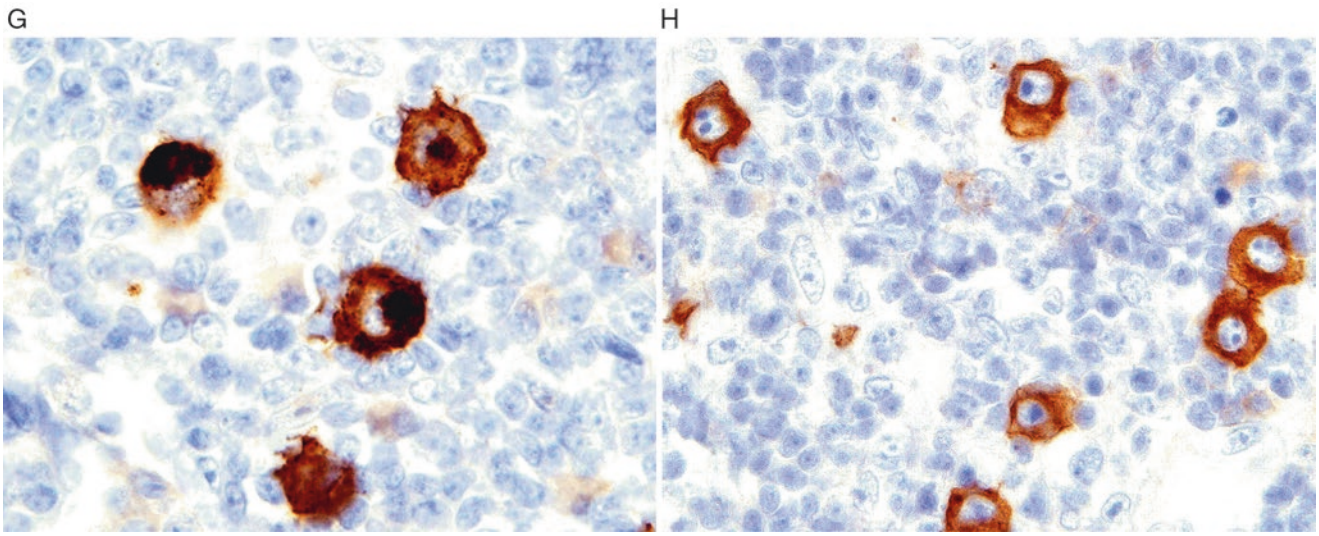


**Fig. 4.71** (continued)

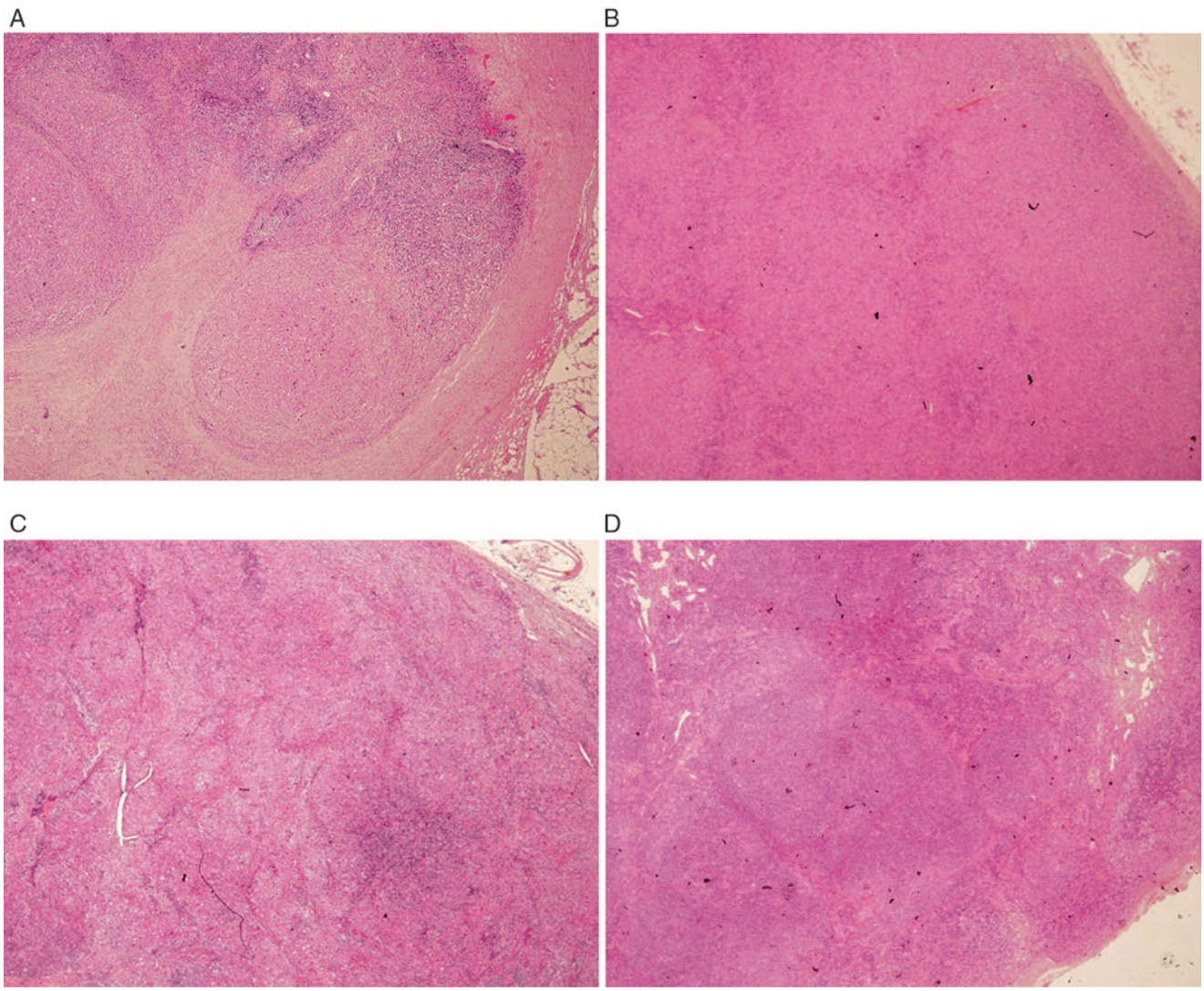


**Fig. 4.72** (**a**–**d**) Classical Hodgkin lymphoma with nodular sclerosis (**a**), mixed cellularity (**b**), lymphocyte rich (**c**), and lymphocyte depleted (**d**)

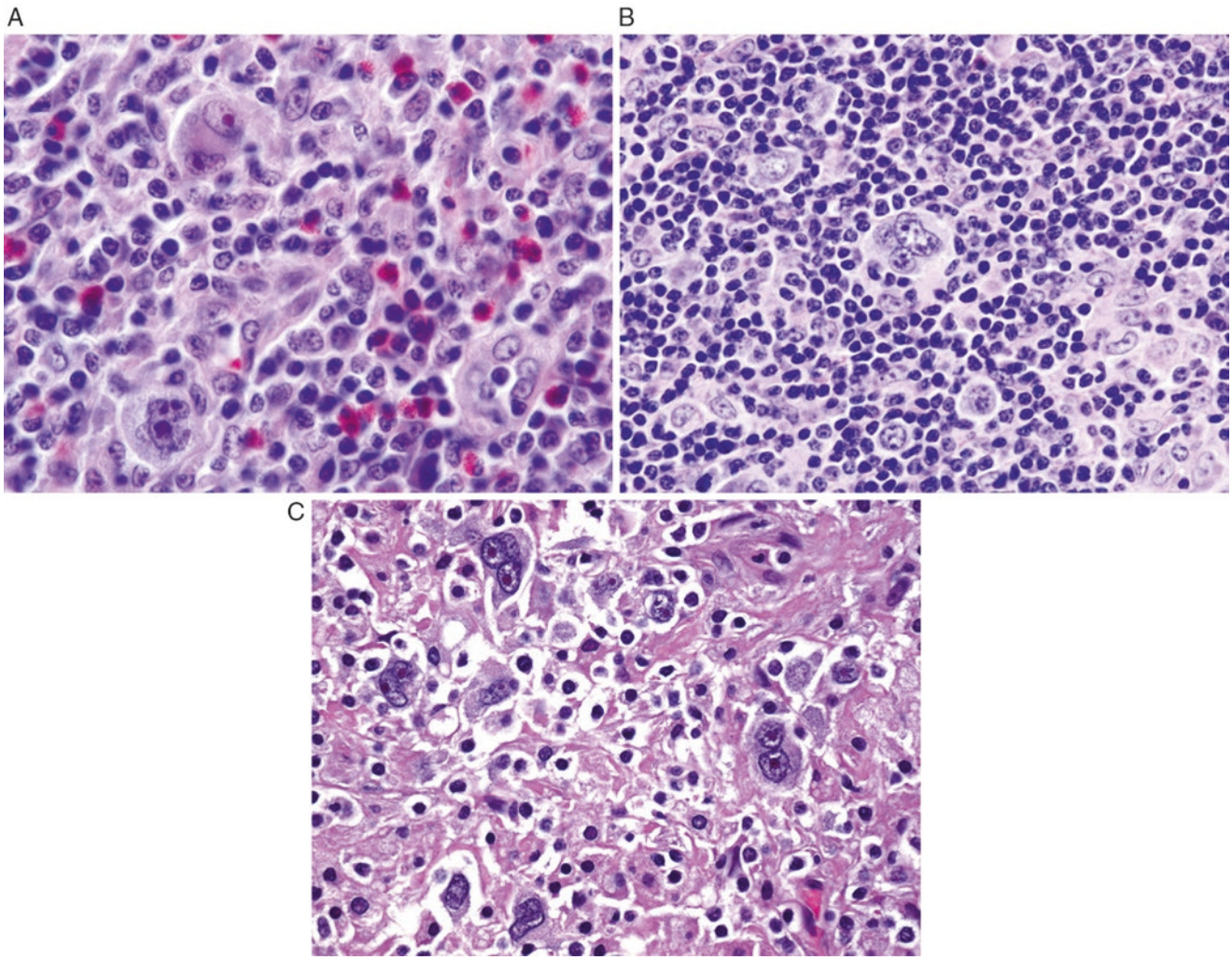


**Fig. 4.73** (**a**–**c**) High-power view of classical Hodgkin lymphoma with Reed-Stenberg cells in a background of mixed lymphocytes, plasma cells, and eosinophils in nodular sclerosis and mixed cellularity (**a**), neoplastic cells with background of lymphocytes in lymphocyte-rich (**b**) and neoplastic cells with background of hypocellularity in lymphocyte depleted (**c**)

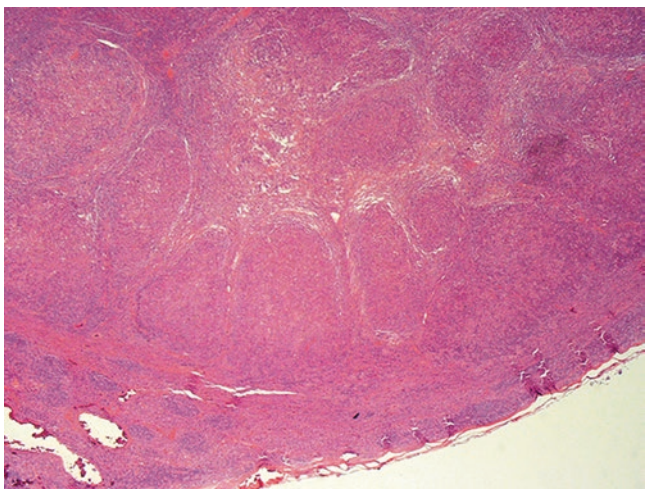

**Fig. 4.74** Nodular lymphocytic-predominant Hodgkin lymphoma with large nodular pattern

### Immunohistochemistry and Ancillary Studies

- Myeloblasts positive for myeloperoxidase (MPO, Fig. 4.83), CD117, lysozyme (Fig. 4.84), CD68, CD99, and CD34

## Lymphoblastic Lymphoma

### Clinical Features

- A childhood disease
- 90% precursor T-lymphoblastic cells and 10% precursor B lymphoblastic cells.
- A designation of lymphoma is given when a patient presents as a mass lesion and less than 25% blasts in bone marrow.
- T-lymphoblastic lymphoma frequently present with a mediastinal mass.

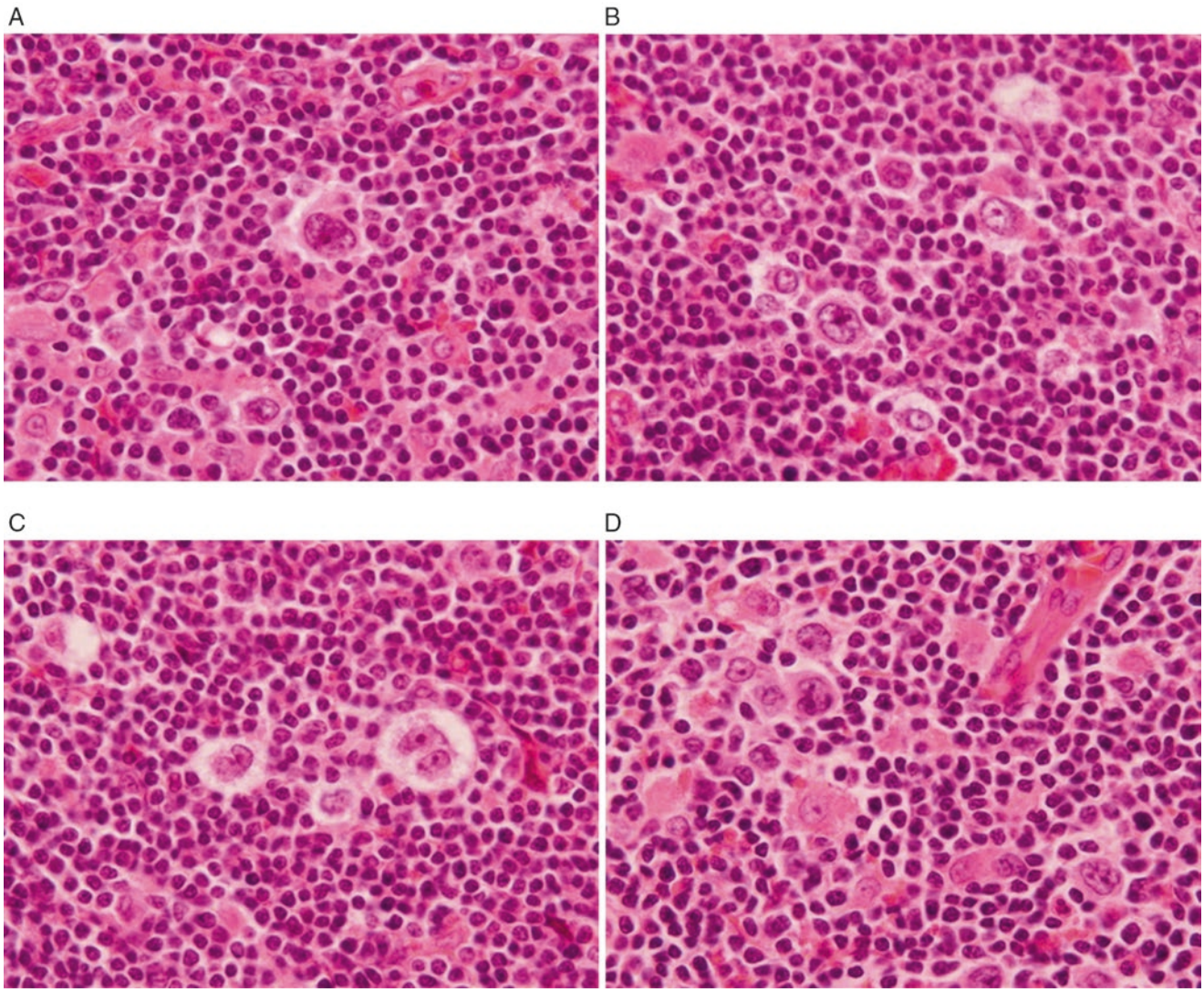


**Fig. 4.75** (**a**–**d**) Nodular lymphocytic-predominant Hodgkin lymphoma with scattered lymphocyte-predominant cells in a background of mature lymphocytes

- Indolent T-lymphoblastic proliferation may mimic T-lymphoblastic lymphoma. It typically involves lymphoid tissue of the upper aerodigestive tract without systemic dissemination and also no clonality detected.

**Cytological Features (Fig. 4.85a–c)**

- Cellular smear
- Relatively uniform population of medium-size lymphoid cells
- Fine, delicate, and powdery nuclear chromatin
- Small to conspicuous nucleoli
- Nuclear membrane variable from smooth to convoluted
- Scant to small amount of cytoplasm
- Cytoplasmic vacuoles can be seen

**Histologic Features**

- Effaced nodal architecture with sheets of blasts (Fig. 4.86) and may have a "starry sky" pattern.
- Neoplastic cells are medium in size with vesicular chromatin and small nucleolus (Fig. 4.87).
- New type: Early T-precursor (ETP) lymphoblastic leukemia shows blasts positive for CD2, CD7, cytoplasmic CD3, and CD4 and negative for CD1a, CD5 (or weak expression) and CD8 with one or more of the myeloid/stem cell markers CD34, CD117, CD13, CD33, CD11b, or CD65 (Figs. 4.88 and 4.89a, b). It has a very poor outcome.
- New provisional entity: Indolent T-lymphoblastic proliferation belongs to nonneoplastic entity and may mimic

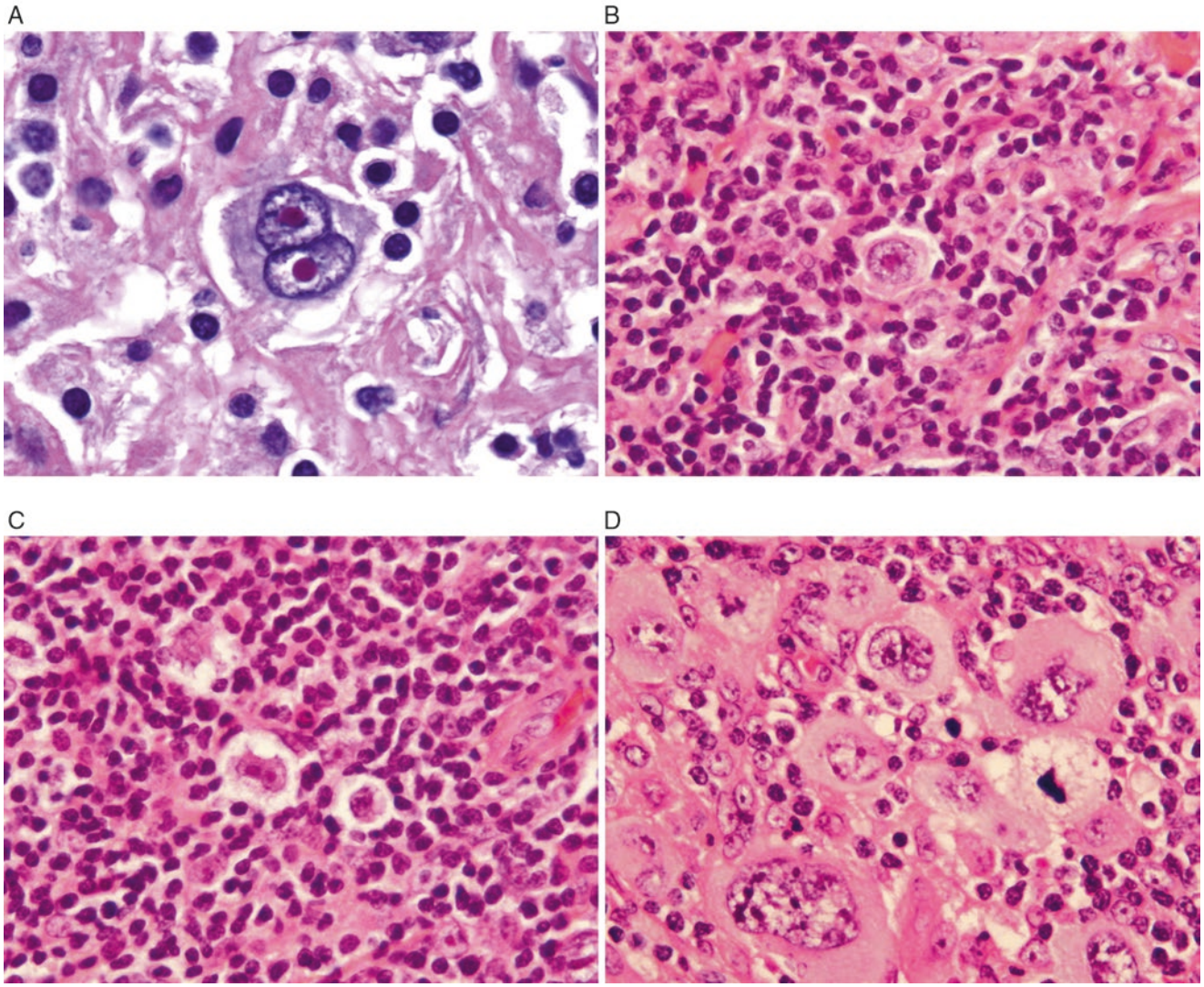


**Fig. 4.76** (**a**–**d**) Hodgkin lymphoma with Reed-Sternberg cells (**a**), Hodgkin cells (**b**), lacunar cells (**c**), and popcorn cells (**d**)

T-lymphoblastic lymphoma. IHC: TdT+, no aberrant phenotype, and not clonal. It mostly occurs in lymphoid tissue of upper aerodigestive tract with good prognosis.

### Immunohistochemistry and Ancillary Studies

- Terminal deoxynucleotidyl transferase (TdT)-positive in both T and B lymphoblasts.
- T lymphoblasts are positive for CD7 and cytoplasmic CD3 with coexpression of CD4 and CD8 and also positive for other T-cell markers, such as CD1a and CD2.
- B lymphoblasts are positive for CD19, CD79a, CD10, and CD34.

## Tumors Mimicking Lymphomas

### Melanoma

#### Cytological Features

- Loosely cohesive groups and single cells
- Binucleation and multinucleation
- Intranuclear inclusions
- Plasmacytoid cells with abundant cytoplasm
- Prominent nucleoli
- Dusty pigments

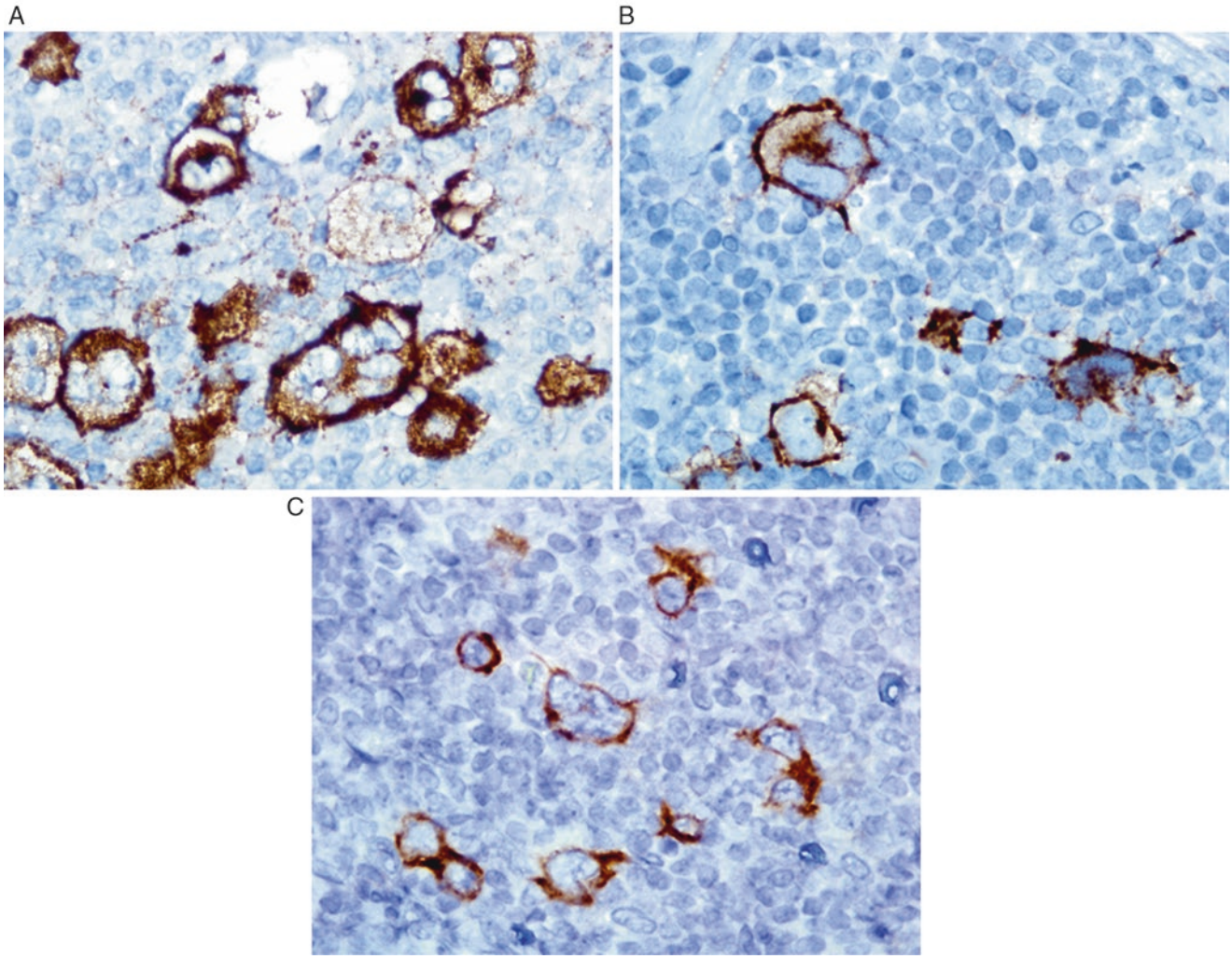


**Fig. 4.77** (**a**–**c**) Reed-Sternberg cells in classical Hodgkin lymphoma with positive CD15 (**a**), positive CD30 (**b**), and positive KOC1 (**c**)

## Small Cell Undifferentiated Carcinoma

### Cytological Features

- Cohesive and single neoplastic cells.
- Very high nuclear-to-cytoplasmic ratio.
- Neuroendocrine chromatin.
- Inconspicuous nucleoli.
- Single cell necrosis and many mitosis.
- Blue bodies in the background may resemble lymphoglandular bodies.

### Undifferentiated Carcinoma

- Nasopharyngeal carcinoma
- Poorly differentiated squamous cell carcinoma
- Basaloid squamous cell carcinoma
- Merkel cell carcinoma

### Small Round Cell Tumors

- Rhabdomyosarcoma
- Ewing's sarcoma/primitive neuroectodermal tumor (PNET)
- Neuroblastoma
- Desmoplastic small round cell tumor

## Seminoma

### Cytological Features

- Two populations of cells: large neoplastic tumor cells and small benign lymphoid cells.
- The neoplastic cells are large and relatively uniform in size.
- Single prominent nucleoli.
- Cytoplasmic vacuoles can be seen.

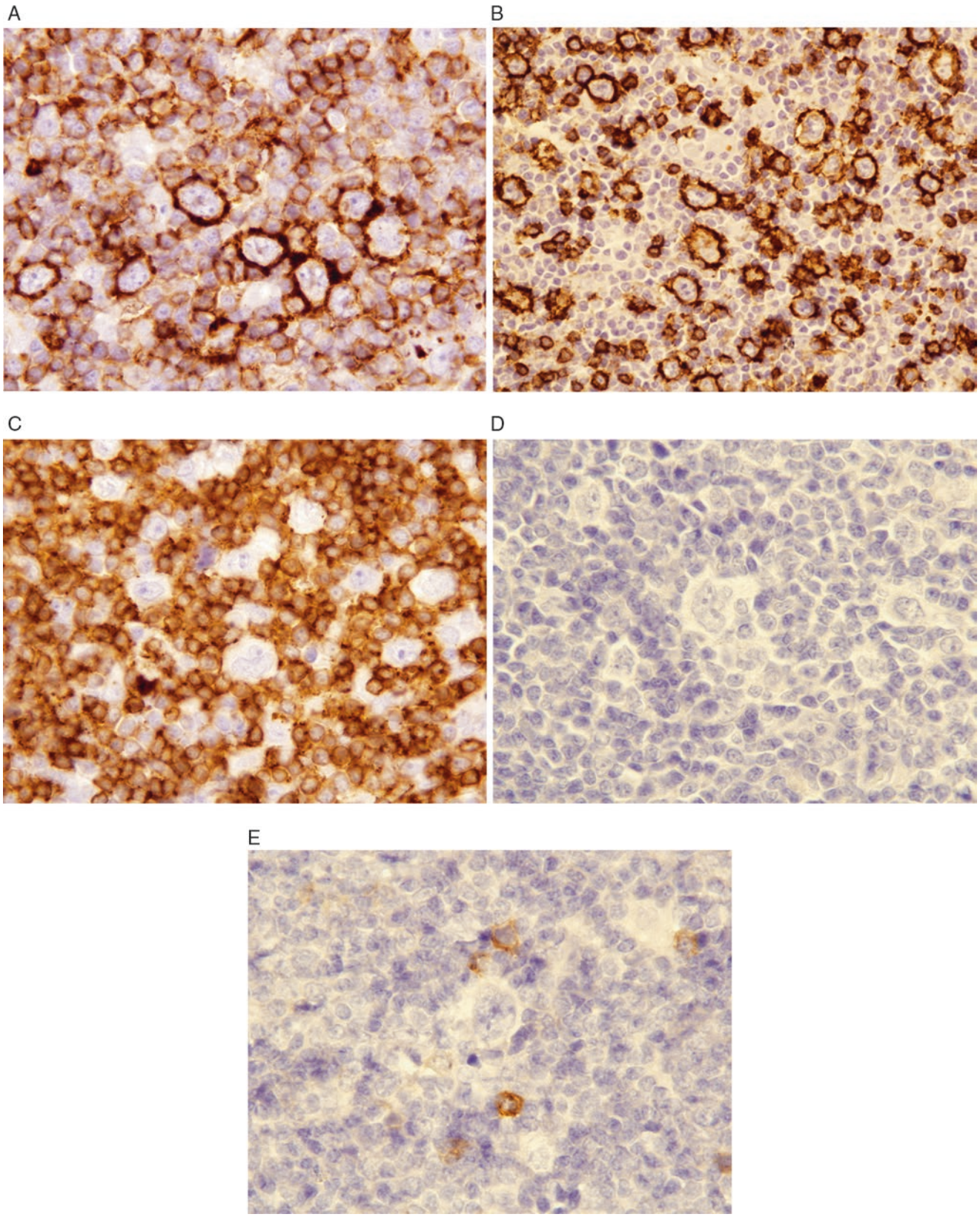


**Fig. 4.78** (**a**–**e**) Lymphocyte-predominant cells in nodular lymphocytic-predominant Hodgkin lymphoma with positive CD45 (**a**), positive CD20 (**b**), negative CD3 (**c**), negative CD15 (**d**), and negative CD30 (**e**)

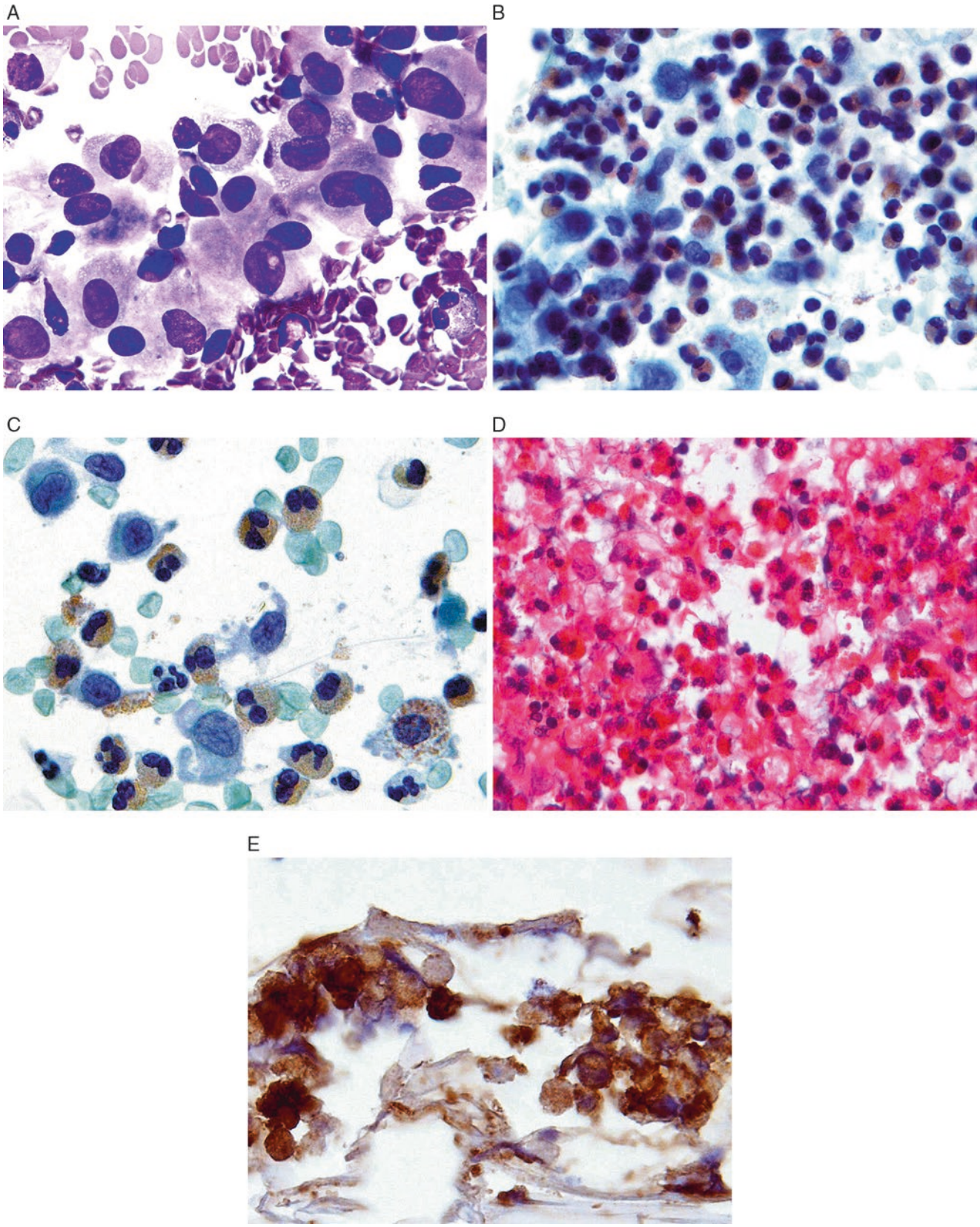


**Fig. 4.79** (**a**–**e**) Langerhans cell histiocytosis with Langerhans histiocytes and eosinophils in (**a**) and (**b**), prominent nuclear grooves or linear folds seen in Langerhans histiocytes (**c**), on cellblock (**d**) and positive for CD1a (**e**)

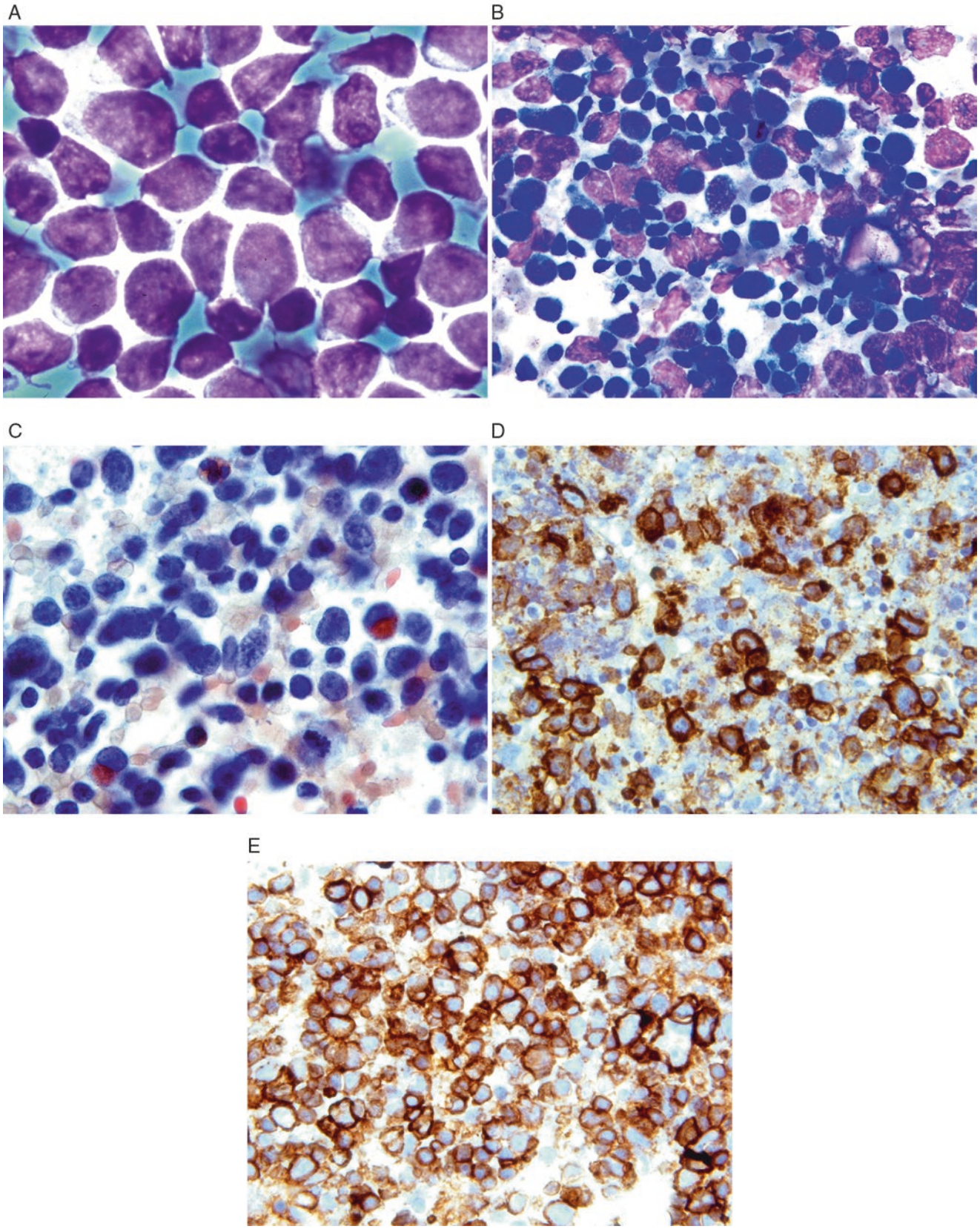


**Fig. 4.80** (**a**–**e**) Myeloid sarcoma on Diff-Quik (**a**, **b**), Pap stain (**c**), positive for CD34 (**d**) and CD43 (**e**) on cellblock sections

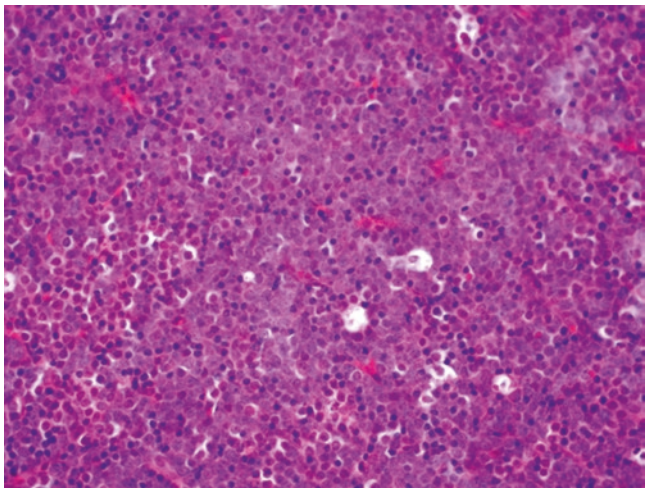

**Fig. 4.81** Myeloid sarcoma with sheets of blasts

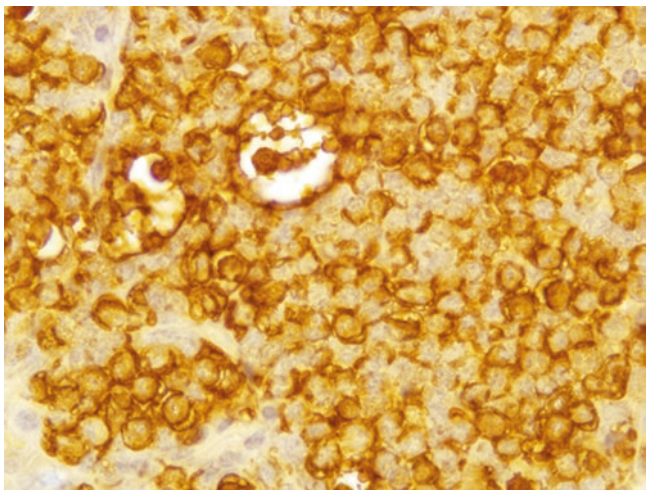

**Fig. 4.83** Myeloblasts with positive myeloperoxidase

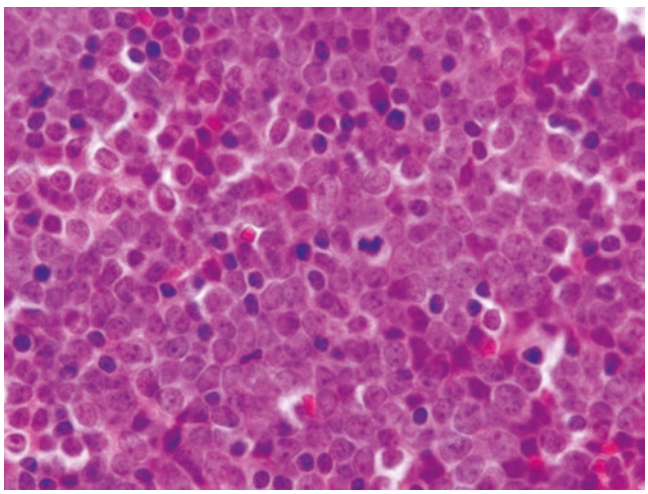

**Fig. 4.82** Myeloblasts with fine chromatin, round nuclear contour, and frequent mitotic figures

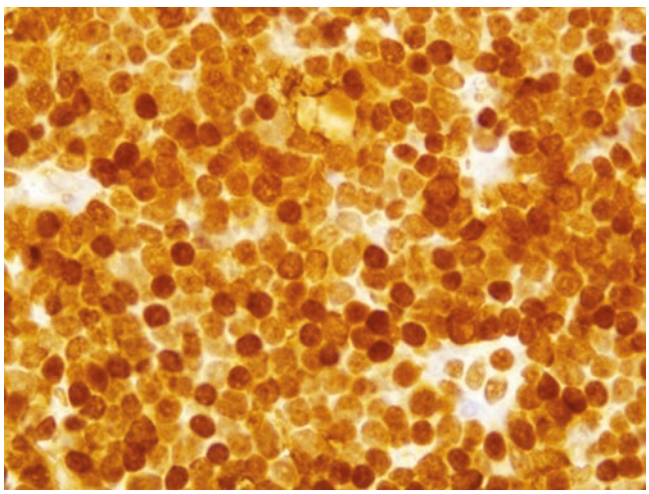

**Fig. 4.84** Myeloblasts with positive lysozyme

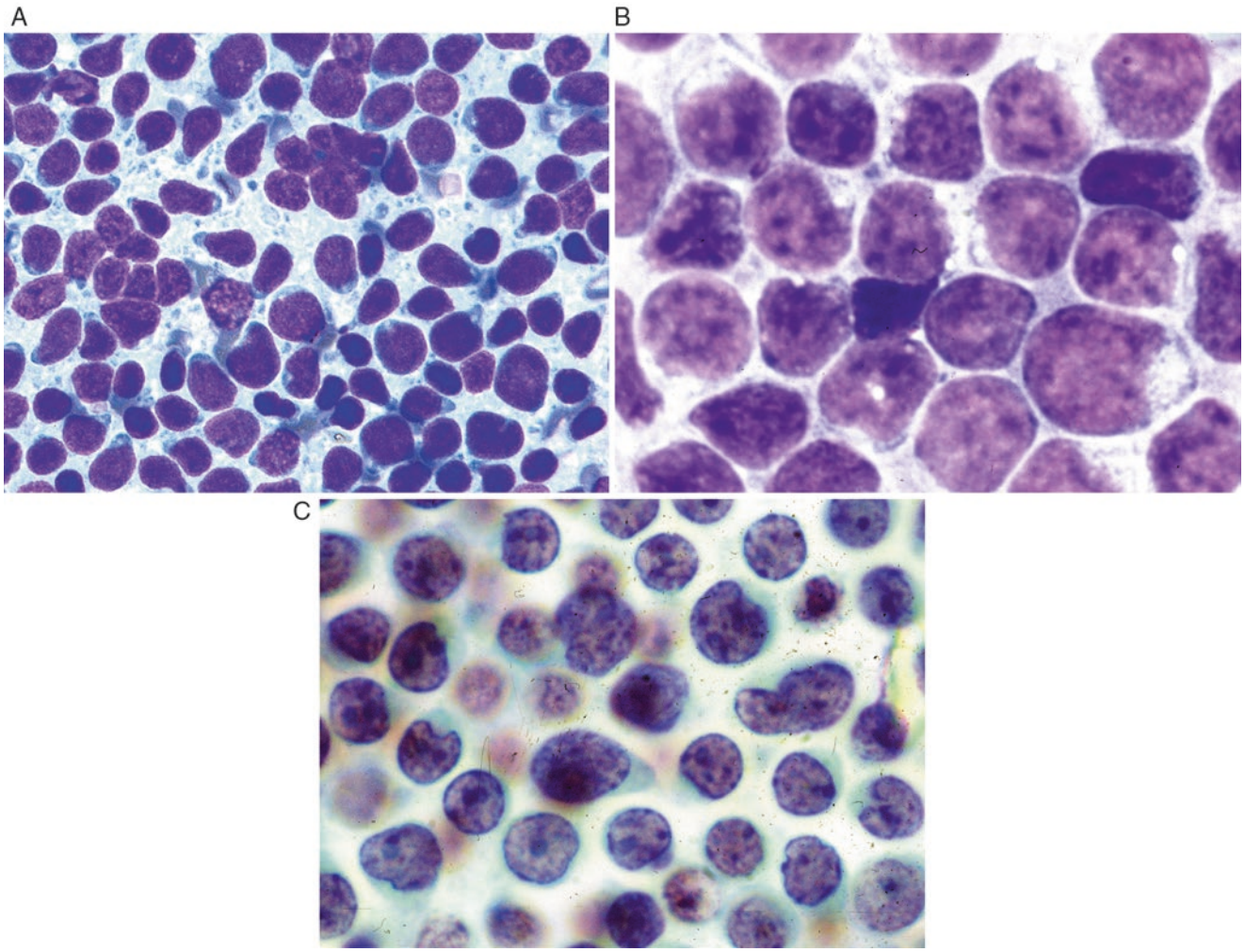


**Fig. 4.85** (**a**–**c**) Lymphoblastic lymphoma with relatively uniform population of medium-size lymphoid cells, with fine, delicate, and powdery nuclear chromatin on Diff-Quik (**a**, **b**) and Pap stain (**c**)

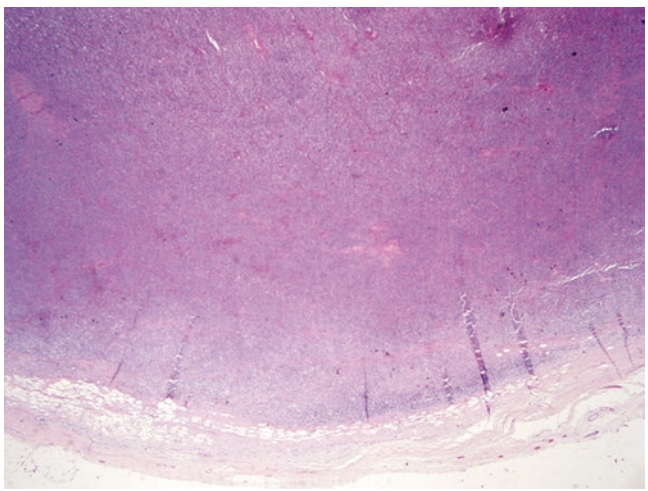

**Fig. 4.86** Lymphoblastic lymphoma with effaced nodal architecture in a diffuse pattern by sheets of neoplastic cells

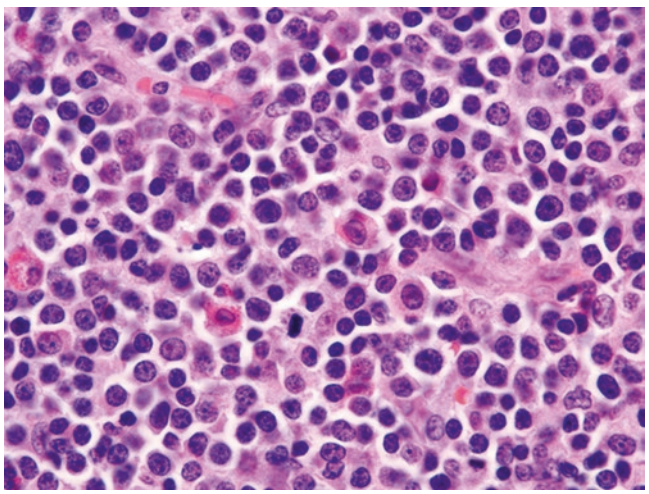

**Fig. 4.87** Neoplastic cells with round nuclear contour, vesicular chromatin, and small nucleoli; in a background of mature lymphocytes and eosinophils

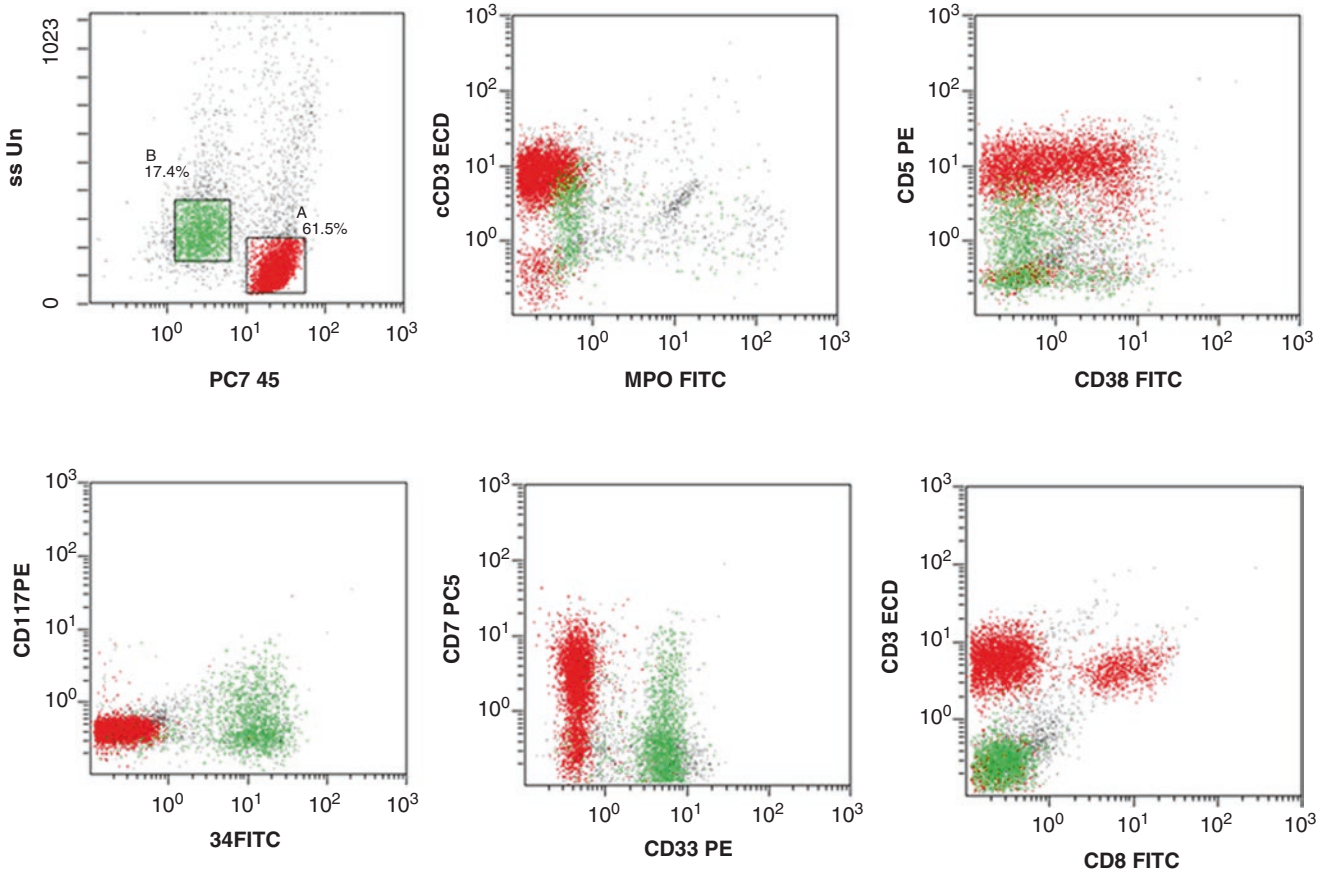


**Fig. 4.88** Flow cytometry studies of lymphoblast positive for cCD3 and CD34, and low intensity of CD5 and negative for sCD3, CD8, and MPO (a few blasts expressing MPO in low intensity) with aberrant expression of CD33

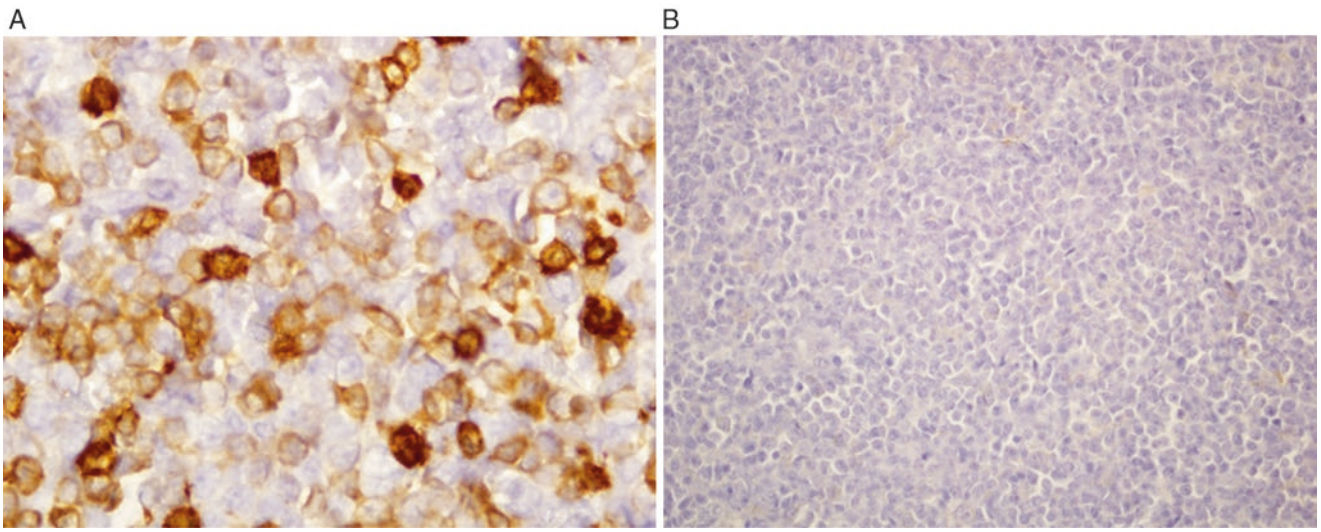


**Fig. 4.89** Neoplastic cells positive for cCD3 (**a**) and negative for CD1a (**b**)

## Thymoma

### Cytological Features

- Two populations of cells: epithelial cells and lymphoid cells.
- Can be predominately lymphoid cells.
- Lymphoid cells are CD3-positve and TdT-positive cortical thymocytes.
- Epithelial cells are positive for p63.

**Case Presentations**

There are three scenarios encountered in practice when evaluating an enlarged lymph node. Case Scenario 1 is how to make a diagnosis and classification of low-grade B-cell lymphoma based on morphology, flow cytometry, and molecular studies; Case Scenario 2 is how to work on a blast-looking lymphoma in a young patient and what immunophenotypic and molecular tests should be ordered; and Case Scenario 3 is how to deal with a T-cell lymphoma in an elderly patient and what immunophenotypic features need to be paid attention to.

## Case Scenario 1

### Learning Objective

1. To reiterate the diagnostic criteria for low-grade B-cell lymphomas on morphological, immunophenotypic, and molecular features (Table 4.4)

### Case

A 67-year-old female presented with a 2 x 1 cm left neck mass located in zone 5. She first noticed it 6 months ago and was not treated. She was otherwise healthy with no significant past medical history, no symptoms, and no weight loss. CT scan revealed a few tiny lymph nodes other than the enlarged lymph node mentioned above. Excisional biopsy was performed. The morphological features are shown in Figs. 4.90 and 4.91. Flow cytometry studies revealed a population of monotypic B cells positive for CD19 and CD20 and negative for CD5, CD10, and CD23 (Fig. 4.92a–d).

At this point, it is a low-grade B-cell lymphoma. Based on immunophenotypes, the differential diagnosis includes MZL, LPL, and other atypical B-cell lymphomas. Typically B-cell SLL coexpresses CD5 and CD23; MCL is positive for CD5 and FMC7; and follicular lymphoma is positive for CD10, but all the B-cell lymphomas can show an atypical immunophenotype with loss of one or more immunophenotypic marker(s). The morphological pattern showed perifollicular expansion by monotonous monocytoid/plasmacytoid cells, favoring LPL. Now the molecular test will be helpful to make the right classification of this low-grade B-cell lymphoma. Molecular testing showed MYD88 mutation (Fig. 4.93).

### Final Diagnosis

Lymphoplasmacytic lymphoma (LPL).

### What Are the Learning Points from This Case?

The learning points from this case include:

1. It is important to evaluate the pattern of effaced nodal architecture and cytological features of neoplastic cells, although there is overlapping in different low-grade B-cell lymphomas.
2. Every low-grade B-cell lymphoma has its typical immunophenotypic features, but it should be noted that any lymphomas could have atypical immunophenotypic features.
3. FISH and molecular tests, including specific translocation or mutation, would be helpful to make an accurate classification when immunophenotypic features are equivocal.

## Case Scenario 2

### Learning Objectives

1. To identify high-grade lymphomas, especially in young patients
2. To review the clinical, morphological, immunophenotypic, and molecular features of high-grade hematopoietic tumors (Table 4.5)

### Case

A previously heathy 14-year-old boy presented with new-onset dysphagia and snoring, followed by a change in his voice. Symptom started around the time when he and his family had upper respiratory infections. He visited his family doctor, who found him with right tonsillar hypertrophy and positive for *Streptococcus*. The boy was treated with multiple courses of antibiotics with minimal improvement in symptoms. A tonsillectomy was performed. The right tonsil was 4.0 x 3.5 x 1.5 cm and left tonsil 3.2 x 2.0 x 1.2 cm. Morphologically, the left tonsil showed lymphoid follicular hyperplasia; the right tonsil revealed focal effacement by sheets of blasts in a "starry sky" pattern (Fig. 4.58). High-power view showed neoplastic cells with round nuclear contour, small nucleoli, and frequent mitotic figures (Fig. 4.59).

At this point, a diagnosis of high-grade hematolymphoid tumor can be made. Differential diagnosis includes lymphoblastic lymphoma, DLBCL, BL, or myeloid sarcoma. A definite diagnosis cannot be rendered without immunophenotypic study.

(continued)

**Table 4.4** Summary of most common low-grade B-cell lymphomas

| Diagnosis | Clinical features | Cytological features | Histological features | IHC features | Molecular features |
|---|---|---|---|---|---|
| CLL/SLL | -Most common leukemia/ lymphoma in west countries<br>-Mostly occurs in adults >40 years<br>-M:F ratio - 1.5–2:1<br>-Involving PB, BM, and LN | Round nuclear contour and hypercondensed chromatin | -Vaguely nodular pattern<br>-Small lymphoma cells admixed with prolymphocytes | CD20+, CD5+, CD23+, LEF1+, CD38, and ZAP-70 to evaluate prognosis | 50%: del 13q, 20%:+12<br>Less common: del 11, del 17q, del 6q |
| FL | -20% of all lymphomas with highest incidence in the USA and Western Europe<br>-M:F – 1:1.7<br>-Involving LN, also BM, PB, and GI tract | Centrocytes with folded nuclear contour and mature chromatin<br>Centroblasts with round nuclear membrane, vesicular chromatin, and small nucleoli | Neoplastic follicles with neither polarity nor tingible-body macrophages<br>Pattern with follicular, diffuse and follicular, focally follicular, and diffuse<br>Grade with centroblasts:<br>1–2: <15/HPF<br>3:>15/HPF<br>3A: scattered centroblasts;<br>3B: sheets of centroblasts | CD20+<br>CD10+<br>BCL2+<br>BCL6+<br>LMO2+ | 80% with t(14;18)<br>20% with +7, +18<br>15% with abnormal 3q27–28, 6q23–26, 17p |
| MCL | –3–10% of non-Hodgkin lymphomas<br>-Adults of middle age to older<br>-M:F – > 2:1<br>-Involving the LN, spleen, BM, and GI | Irregular nuclear contour and mature chromatin | Mantle zone expansion to diffuse pattern<br>Vascular proliferation<br>In situ mantle cell neoplasia: limited to mantle zone | CD20+<br>CD5+<br>BCL1 (cyclinD1)+<br>SOX11+ | t(11;14) (*CCND1;IGH*)<br>Rare with *cyclinD2* or *D3* translocation |
| MZL | -10% of B-cell lymphomas<br>-Involving the GI, LN, spleen | Mature chromatin with monocytoid, plasmacytoid, or centrocytoid appearance | Expanded marginal zone | CD20+<br>CD5-<br>CD10-<br>CD23-<br>IRTA1+ | In GI MALT lymphoma: t(11;18) *(API2;MALT1)* |

*CLL/SLL* chronic lymphocytic leukemia/small lymphocytic lymphoma, *M:F* male to female ratio, *PB* peripheral blood, *BM* bone marrow, *LN* lymph node, *CD* cluster of differentiation, *LEF1* lymphoid enhancer-binding factor 1, *ZAP-70* zeta-chain-associated protein kinase 70, *FL* follicular lymphoma, *GI* gastrointestinal, *HPF* high-power field, *BCL* B-cell lymphoma, *LMO2* LIM-only transcription factor-2, *MCL* mantle cell lymphoma, *SOX11* sex-determining region Y box 11, *CCND1* cyclin D1, *IGH* immunoglobulin heavy, *MZL* marginal zone lymphoma, *IRTA1* immunoglobulin superfamily receptor translocation associated 1, *MALT* mucosa-associated lymphoid tissue, *API2* apoptosis inhibitor 2, *MALT1* mucosa-associated lymphoid tissue lymphoma translocation 1

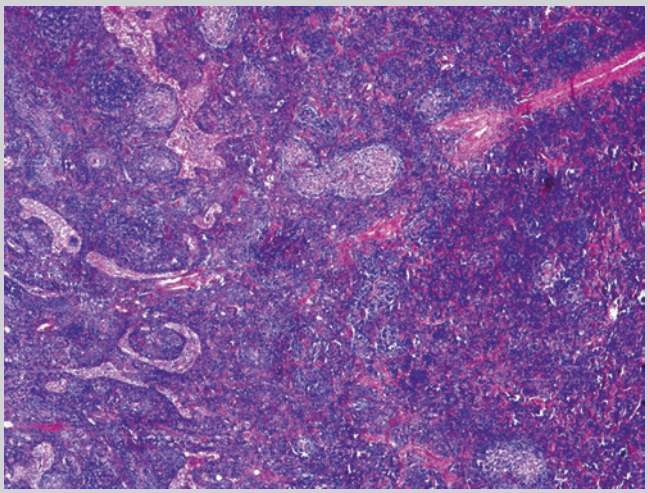

**Fig. 4.90** Lymphoplasmacytic lymphoma with effaced nodal architecture and perifollicular expansion

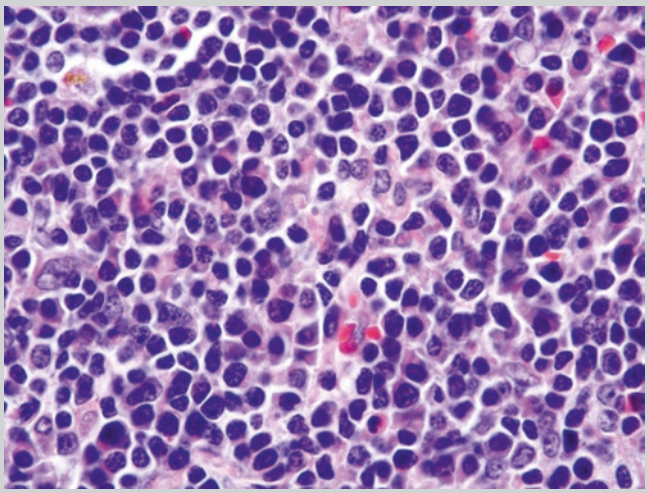

**Fig. 4.91** Neoplastic cells in lymphoplasmacytic lymphoma show round nuclear contour and mature chromatin with plasmacytoid appearance

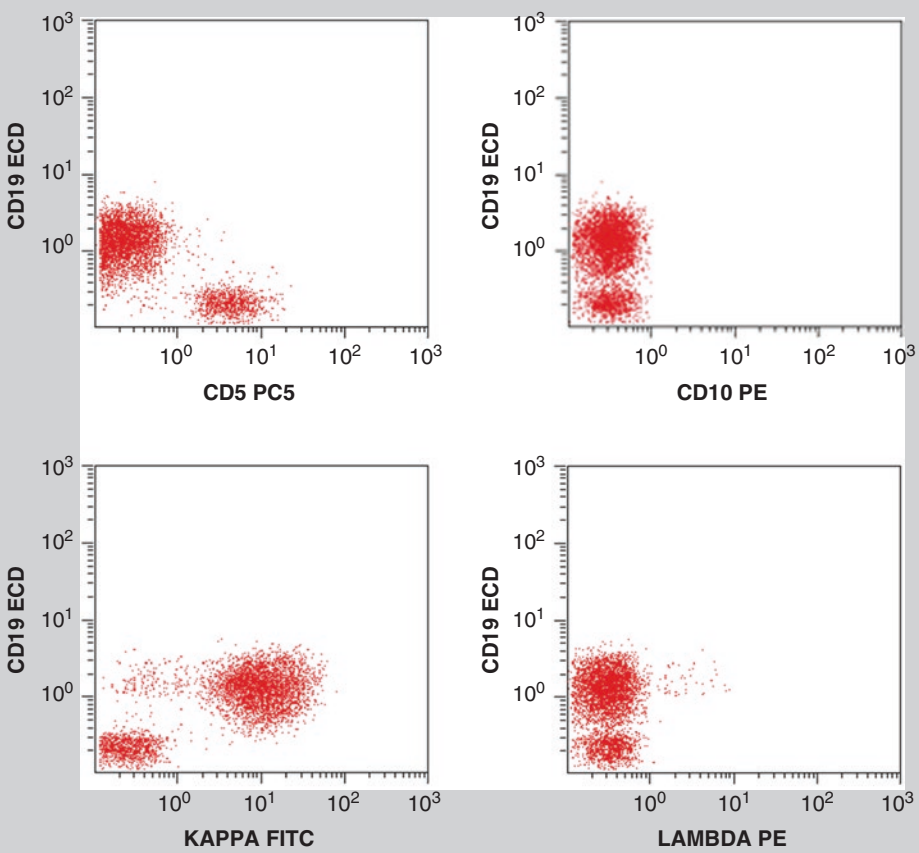


**Fig. 4.92** (**a**–**d**) Flow cytometry studies of lymphoplasmacytic lymphoma show lymphoma cells negative for CD5 (**a**) and CD10 (**b**) with immunoglobulin light chain restriction (**c**, **d**)


**Fig. 4.93** Molecular study of lymphoplasmacytic lymphoma with *MYD88 L265P* mutation: a mutation in chromosome 3p22 in a single nucleotide change, T to C (*inside frame*), in MYD88, resulting a switch of leucine to proline at amino acid position 265 (L265P)

Flow cytometry studies showed a population of monotypic B cells with coexpression of CD10 and negative for the blast markers of CD34 and TdT and T-cell or myelomonocytic markers. Immunohistochemical stains revealed the neoplastic cells to be positive for CD20, BCL6, and MYC and negative for BCL2 with a proliferation rate of 100% by Ki67 stain (Fig. 4.37). EBV was negative by in situ hybridization. FISH study was positive for MYC (8q24.1) rearrangement (Fig. 4.61).

**Final Diagnosis**
Burkitt lymphoma (BL)

**What Are the Learning Points from This Case?**
The learning points from the case include:

1. High-grade hematolymphoid tumor can partially involve lymphoid tissue in the early stage.
2. Immunophenotypic features by flow cytometry and immunohistochemical studies are useful to classify the tumor.
3. FISH or molecular studies are the gold standard to further confirm the diagnosis.

## Case Scenario 3

**Learning Objectives**
1. To review the T-cell leukemia/lymphomas
2. To pay attention to immunophenotypic features for classification and guided treatment

**Case**
A 60-year-old male presented with a rapidly progressive left axillary mass. He had night sweats and a 15-pound weight loss over the previous one to two months. His laboratory tests showed WBC of 7.3, hemoglobin of 11.9, and platelets of 248,000. CT scan revealed lymphadenopathy, including a left axillary lymph node of 3.0 x 3.4 cm with necrosis; periportal, retroperitoneal, bilateral iliac chain, and extensive mesenteric adenopathy, up to 2.4 cm; the enlarged spleen was 15 cm. There was no mediastinal or hilar mass. An excisional biopsy from left axillary lymph node was performed and showed an effaced nodal architecture in a diffuse pattern (Fig. 4.86). Neoplastic cells were medium in size with round nuclear contour, vesicular chromatin, and small nucleolus; there was a background of mature lymphocytes and eosinophils (Fig. 4.87).

(continued)

**Table 4.5** Summary of most common high-grade hematolymphoid tumors

| Diagnosis | Clinical features | Cytological features | Histological features | IHC features | Molecular features |
|---|---|---|---|---|---|
| DLBCL | -30% of adult non-Hodgkin lymphomas<br>-More in elderly adult<br>-Involving LN or extranodal areas<br>-May occur de novo or transform from any low-grade B-cell lymphomas | Medium to large in size with pleomorphic nuclei and vesicular chromatin | Effaced nodal architecture with a diffuse pattern | CD20+<br>PAX5+<br>ABC-type: CD10-, BCL6-, MUM1+<br>GCB type: CD10+, BCL6+, MUM1-.<br>BCL2, BCL6, and MYC to evaluate aggressive behavior | FISH for BCL2, BCL6, MYC for double-hit or triple-hit lymphoma that has worse prognosis and needs more intensive treatment |
| BL | Three clinical variants<br>-Endemic: mostly in Africa, in children, peak at 4–7 years, M:F – 2:1<br>-Sporadic: mainly in children and young adults, 30%–50% of all childhood lymphoma, M:F – 2–3:1<br>-Immunodeficiency-associated: occurs in HIV infection, transplant, or other immunodeficient patients | Medium in size with round nuclear contour, vesicular chromatin, and small nucleoli (snake head appearance) | Sheets of tumor cells with scattered tingible-body macrophages (starry sky pattern) | CD20+<br>CD10+<br>BCL6+<br>BCL2-<br>MYC+<br>EBV may+, mostly in endemic BL | *MYC* gene rearrangement<br>TCF3 mutation in up to 70% of cases |
| ALL | -Mostly in children<br>-B-ALL: 80–85% of all lymphoblastic leukemia<br>-T-ALL: 85–90% of all lymphoblastic lymphoma | Medium in size with round nuclear contour and blast-looking chromatin<br>Same in both B- or T-ALL | Same as BL | B-ALL: CD19+,<br>CD10+<br>CD22+<br>CD79a+<br>T-ALL:<br>CD1a+<br>CD2+<br>cCD3+<br>CD4 or/and CD8+<br>CD5+<br>CD7+<br>ALL:<br>CD34+, TdT+ | B-ALL:<br>clonal *IGH* gene rearrangement<br>t(9;22) (*BCR-ABL*) with worse prognosis:<br>p190kd-in childhood ALL;<br>p210kd in adult T-ALL: clonal *TCR* gene rearrangement |
| ALCL | -3% of adult non-Hodgkin lymphomas and 10–20% of childhood lymphomas<br>-M:F – 1.5:1<br>-Involving the LN, skin, bone, soft tissue, lung, and liver | Neoplastic cells are pleomorphic. Hallmark cells with horseshoe-like or kidney-like nucleus and eosinophilic cytoplasm | -Lymphohistiocytic pattern: hallmark cells and reactive histiocytes<br>-Small cell pattern: small to medium-size neoplastic cells admixed with hallmark cells;<br>-Hodgkin-like pattern: mimic CHL | CD30+<br>ALK+/-<br>CD2+<br>CD5+<br>CD4+<br>CD3+ in 25% of cases<br>TIA+<br>Granzyme+<br>EBV- | T(2;5) (*ALK;NPM*) or *ALK* translocation to other chromosomes 1, 2, 3, 17, 19, 2, and X |

(continued)

**Table 4.5** (continued)

| Diagnosis | Clinical features | Cytological features | Histological features | IHC features | Molecular features |
|---|---|---|---|---|---|
| Myeloid sarcoma | -mostly in adults<br>-M:F – 1.2:1<br>-involving any site<br>-may occur de novo, or proceed or coincide with AML or transformation of MDS and/or MPN | Myeloblasts with fine chromatin and high N/C ratio.<br>Rare case with erythroid precursors or megakaryoblasts | Sheets of blasts with frequent mitotic figures | MPO+<br>CD117+<br>Lysozyme+<br>CD68/KP1+<br>CD34+<br>TdT may + | 55% of cases:<br>+7, +8, *MLL*-rearrangement, inv.(16), +4, −16, 16q-, 5q-, 20q-, +1p |

*DLBCL* diffuse large B-cell lymphoma, *CD* cluster of differentiation, *PAX5* paired box gene 5, *ABC* activated B-cell, *BCL* B-cell lymphoma, *MUM1* multiple myeloma 1, *GC* germinal center, *FISH* fluorescence in situ hybridization, *BL* Burkitt lymphoma, *M:F* male to female ratio, *EBV* Epstein-Barr virus, *ALL* acute lymphoblastic leukemia, *B-ALL* B-cell acute lymphoblastic leukemia, *IGH* immunoglobulin heavy chain, *T-ALL* T-cell acute lymphoblastic leukemia, *TdT* terminal deoxynucleotidyl transferase, *BCR* breakpoint cluster region, *ABL* Abelson murine leukemia viral oncogene homolog 1, *TCR* T-cell receptor, *ALCL* anaplastic large cell lymphoma, *LN* lymph node, *CHL* classical Hodgkin lymphoma, *ALK* anaplastic lymphoma kinase, *TIA* T-cell intracellular antibody, *NPM* nucleophosmin, *AML* acute myeloid leukemia, *MDS* myelodysplastic syndrome, *MPN* myeloproliferative neoplasm, *N/C* nuclear to cytoplasmic, *MPO* myeloperoxidase, *TdT* terminal deoxynucleotidyl transferase, *MLL* mixed-lineage leukemia, *TCF3* transcription factor 3

At this point, a diagnosis of high-grade hematolymphoid tumor can be made. Differential diagnosis includes lymphoblastic lymphoma, myeloid sarcoma, or acute hematolymphoid tumor with bi-phenotypic features. A definite diagnosis cannot be rendered without immunophenotypic study.

Flow cytometry studies showed a population of blasts positive for cytoplasmic CD3 (cCD3) and CD34 and low intensity of CD5 and negative for surface CD3, CD8, and MPO (a few of blasts expressing MPO in low intensity) with aberrant expression of CD33 (Fig. 4.88). Immunohistochemical studies revealed neoplastic cells positive for cCD3 and negative for CD1a (Fig. 4.89a, b). Molecular test showed clonal TCR gene rearrangement.

### Final Diagnosis

Early T-cell precursor lymphoma

### What Are the Learning Points from This Case?

The learning points from the case include:

1. Lymphoblastic leukemia/lymphoma shares the same morphological features in B-cell acute lymphoblastic leukemia (B-ALL) and T-cell acute lymphoblastic leukemia (T-ALL).
2. Immunophenotype by flow cytometry and immunohistochemical studies are helpful to make a right diagnosis.
3. The aberrant immunophenotypes that would indicate the prognosis and guide the treatment should be carefully evaluated and mentioned.

## Abbreviations List

| Abbreviation | Full text |
|---|---|
| ABC | Activated B-cell |
| ABL | Abelson murine leukemia viral oncogene homolog 1 |
| ALCL | Anaplastic large cell lymphoma |
| ALK | Anaplastic lymphoma kinase |
| ALL | Acute lymphoblastic leukemia |
| AML | Acute myeloid leukemia |
| B-ALL | B-cell acute lymphoblastic leukemia |
| BCL | B-cell lymphoma (BCL1, BCL2, BCL6) |
| BCR | Breakpoint cluster region |
| BL | Burkitt lymphoma |
| BM | Bone marrow |
| BOB1 | B-cell Oct binding protein 1 |
| BRAF | v-raf murine sarcoma viral oncogene homolog B1 |
| CARD11 | Caspase recruitment domain-containing protein 11 |
| cCD3 | Cytoplasmic CD3 |
| CCND1 | Cyclin D1 |
| CCR5 | Chemokine receptor type 5 |
| CD | Cluster of differentiation |
| CHL | Classical Hodgkin lymphoma |
| CLL | Chronic lymphocytic leukemia |
| CNS | Central nervous system |
| CT | Computed tomography |
| CXCL13 | Chemokine (C-X-C motif) ligand 13 |
| DLBCL | Diffuse large B-cell lymphoma |
| EBV | Epstein-Barr virus |
| EMA | Epithelial membrane antigen |
| ETP | Early T precursor |
| ETV6 | ETS variant 6 |
| EZH2 | Enhancer of zeste homolog 2 |
| FISH | Fluorescence in situ hybridization |
| FL | Follicular lymphoma |
| FMC7 | A monoclonal antibody and an epitope of CD20 |
| FNA | Fine needle aspiration |
| GC | Germinal center |
| GI | Gastrointestinal |
| GNA13 | Guanine nucleotide-binding protein subunit alpha-13 |
| HGBCL | High-grade B-cell lymphoma |
| HHV8 | Human herpes virus 8 |
| HPF | High-power field |
| iAMP2 | Intrachromosomal amplification of chromosome 21 |
| ICOS | Inducible T-Cell co-stimulator |
| IgG/A | Immunoglobulin G/A |
| IGH | Immunoglobulin heavy chain |
| IGHV | Immunoglobulin heavy-chain variable |
| IgM | Immunoglobulin M |
| IHC | Immunohistochemistry |
| IL3 | Interleukin 3 |
| IRF4 | Interferon regulatory factor 4 |
| IRTA1 | Immunoglobulin superfamily receptor translocation associated 1 |
| JAK/STAT3 | Janus kinase/signal transducer and activator of transcription |
| KMT2A | Lysine methyltransferase 2A |
| KOC1 | K homology domain-containing protein overexpressed in cancer |
| L256P | Leucine to proline mutation at amino acid position 256 |
| LBCL | Large B-cell lymphoma |
| LCH | Langerhans cell histiocytosis |
| LEF1 | Lymphoid enhancer-binding factor 1 |
| LMO2 | LIM-only transcription factor-2 |

| Abbreviation | Full text |
|---|---|
| LN | Lymph node |
| LPL | Lymphoplasmacytic lymphoma |
| MALT | Mucosa-associated lymphoid tissue |
| MCL | Mantle cell lymphoma |
| MDS | Myelodysplastic syndrome |
| MGUS | Monoclonal gammopathy of undetermined significance |
| MIB-1 | Mindbomb homolog 1 |
| MLL | Mixed-lineage leukemia |
| MPN | Myeloproliferative neoplasm |
| MPO | Myeloperoxidase |
| MUM1 | Multiple myeloma 1 |
| MYC/c-MYC | A regulator gene that codes for a transcription factor |
| MYD88 | Myeloid differentiation primary response gene 88 |
| MZL | Marginal zone lymphoma |
| N/C | Nuclear to cytoplasmic |
| NK | Natural killer |
| NOS | Not otherwise specified |
| NPM | Nucleophosmin |
| Oct2 | Octamer-binding transcription factors |
| Pap | Papanicolaou |
| PAX | Paired box gene |
| PB | Peripheral blood |
| PBX1 | Pre-B-cell leukemia homeobox 1 |
| PD1 | Programmed death 1 |
| PNET | Primitive neuroectodermal tumor |
| PTCL | Peripheral T-cell lymphoma |
| PTLD | Posttransplant lymphoproliferative disorders |
| RUNX1 | Rnt-related transcription factor 1 |
| SAP | Serum amyloid P |
| sCD3 | Surface CD3 |
| SLL | Small lymphocytic lymphoma |
| SOX | Sex-determining region Y box |
| STAT3 | Signal transducer and activator of transcription 3 |
| T-ALL | T-cell acute lymphoblastic leukemia |
| TCF3 | Transcription factor 3 |
| TCR | T-cell receptor |
| TdT | Terminal deoxynucleotidyl transferase |
| TFH | T follicular helper |
| TIA | T-cell intracellular antibody |
| TNFAIP3 | Tumor necrosis factor, alpha-induced protein 3 |
| US, USA | United States (not spelled out in chapter) |
| WHO | World Health Organization |
| ZAP-70 | Zeta-chain-associated protein kinase 70 |

## References


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