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Hematolymphoid Lesions of the Sinonasal Tract

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Summary

Various hematolymphoid lesions involve the sinonasal tract, including aggressive B, T, and NK-cell neoplasms; myeloid sarcoma; low grade lymphomas; indolent T-lymphoblastic proliferations; and Rosai-Dorfman disease. Differentiating aggressive lymphomas from non-hematopoietic neoplasms such as poorly differentiated squamous cell carcinoma, olfactory neuroblastoma, or sinonasal undifferentiated carcinoma may pose diagnostic challenges. In addition, the necrosis, vascular damage and inflammatory infiltrates which are associated with some hematolymphoid disorders can result in misdiagnosis as infectious, autoimmune or inflammatory conditions. Here, we review hematolymphoid disorders involving the sinonasal tract including their key clinical and histopathologic features.

Keywords

Diffuse large B-cell lymphoma; Extranodal NK/T-cell lymphoma; Rosai-Dorfman disease; sinonasal tract; Adult T-cell leukemia/lymphoma

Introduction

Hematolymphoid disorders that involve the nasal cavity and paranasal sinuses range from aggressive and rapidly fatal neoplasms to relatively indolent disease. Lymphomas are the most common hematolymphoid disorder of the sinonasal tract, with sinonasal disease comprising approximately 1% of all lymphomas in Western countries.^{1,2} The majority of sinonasal lymphomas diagnosed in Western countries are B-cell neoplasms, and the most common lymphoma involving the sinonasal area is diffuse large B-cell lymphoma (DLBCL).¹⁻³ Low grade B-cell neoplasms can also involve the sinonasal region, and often present with symptoms of congestion in adults or as difficulty breathing in children.^{1,2,4,5} T-cell lymphomas are far less frequent than B-cell lymphomas, although one of the best known sinonasal lymphomas is extranodal natural killer (NK)/T-cell lymphoma, nasal type, with its aggressive nature reflected in its former moniker “lethal midline granuloma.”^{5,7} The diversity

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of hematolymphoid disorders that may involve the sinonasal tract combined with the rarity of some these entities and potentially limited material in biopsy specimens can result in diagnostic challenges.

Aggressive B-Cell Neoplasms

Diffuse Large B-cell lymphoma

Diffuse large B-cell, not otherwise specified (DLBCL, NOS or DLBCL) is the most common type of sinonasal lymphoma seen in Western populations, and represents 33-58% of all sinonasal non-Hodgkin lymphomas and 42-94% of B-cell lymphomas involving the sinonasal tract.¹⁻⁵ In a large series described by Mian, et al., DLBCL affecting the sinonasal tract had a median age of onset of 61 (range 21-91) and a similar incidence in male and female patients.⁶ Unlike T-cell and NK/T-cell lymphomas, which often arise in the nasal cavity itself, DLBCLs tend to arise in the paranasal sinuses.^{3,5} Common symptoms at presentation include nasal congestion, soft tissue swelling, localizing pain, rhinorrhea and epiphora.³ Most patients with DLBCL involving the head and neck are treated with chemotherapy and/or radiation therapy. Patients in Mian, et al.'s series demonstrated a similar complete response rate, 5-year overall survival and 5-year event free survival when compared to patients with DLBCL involving other sites of the head and neck.⁶

DLBCL is a heterogeneous disease, but most present as sheets of large, atypical lymphocytes. The chromatin can range from fine to vesicular and the nucleoli may be prominent or inconspicuous. Apoptotic bodies and mitotic figures are often readily appreciated. DLBCLs characteristically express pan B-cell markers including CD19, CD20, CD22 and CD79a, and surface and/or cytoplasmic immunoglobulin can be demonstrated in most cases.⁷ The proliferative index as measured by Ki-67 immunostaining is high; it is often at least 50% and may exceed 90%. A subset of sinonasal DLBCLs are associated with Epstein-Barr virus (EBV) (Fig. 1), and rare cases of ALK-positive DLBCL involving the sinonasal tract have also been reported.^{5,8,9}

Burkitt Lymphoma

Burkitt lymphoma (BL) is the second most common aggressive B-cell neoplasm affecting the sinonasal region after DLBCL, and accounted for 3-11% of the B-cell lymphomas that arose in the sinonasal tract in several large series.^{1,2,4,5} Variants of BL include endemic, sporadic and immunodeficiency-associated BL, any which may present with sinonasal involvement.⁹ Endemic BL is limited to equatorial Africa, but sporadic BL is seen worldwide and most commonly presents in children and young adults.⁷ Immunodeficiency-associated BL is predominantly seen in patients with HIV infection, and sinonasal BL has been reported in this context, including at least two reports of HIV+ adults who presented with symptoms of chronic sinusitis.^{10,11} BL is an aggressive neoplasm, but cure rates may reach as high as 60-90%.⁷

Morphologically, BL is characterized by sheets of medium-sized atypical lymphocytes with a high nuclear to cytoplasmic ratio, round nuclei with finely clumped chromatin, and multiple paracentrally located basophilic nucleoli. On touch preparations or smears, the neoplastic cells have deeply basophilic cytoplasm and often contain characteristic lipid

vacuoles. There are numerous apoptotic bodies, and the scattered tingible body macrophages that engulf the apoptotic debris give rise to the characteristic “starry sky” appearance of BL. Tumor cells are positive for CD19, CD20, CD10, Bcl-6, CD45 and surface light chain, but are typically negative for Bcl-2. Nearly 100% of nuclei label with Ki-67, reflecting the high proliferation index. Virtually all BLs demonstrate a translocation joining *MYC* to the immunoglobulin heavy or light chains.⁷ Of note, *MYC* rearrangements are not specific for BL, and can also be seen in DLBCL and plasmablastic lymphoma.^{7,12}

B-lymphoblastic Leukemia/Lymphoma

The differential diagnosis of BL includes B-lymphoblastic leukemia/lymphoma, which may also involve the nasal cavity.¹³ Both BL and B-ALL can form sheets of medium-sized atypical lymphoid cells with frequent admixed mitotic figures and apoptotic bodies, as well as occasional tingible body macrophages (Fig 2.). B-ALL is almost always positive for the B-cells markers CD19 and CD79a, and frequently co-expresses CD10. However, B-ALL characteristically shows dim or absent expression of CD45, CD20 and/or surface light chains, and is positive for a marker of immaturity such as TdT and/or CD34, allowing differentiation from BL.

Plasmablastic Lymphoma

Plasmablastic lymphoma (PBL) is an uncommon but aggressive variant of DLBCL first described in and frequently involving the oral cavity. It usually arises in the setting of immunosuppression, particularly in patients with HIV.^{7,14} The most commonly involved sites include the gingiva, floor of the mouth and palate, but involvement of the sinonasal cavity is not unusual.¹⁴⁻¹⁷ There is a strong male predominance, with a median age of 36 (range 5-86).¹⁵⁻¹⁸ A variant of PBL arising in elderly, HIV-negative patients has also been described, which has a median age at presentation of 68 years, also shows a male predominance, and has a predilection for the nasal cavity.¹⁷ The prognosis of PBL is poor, with most patients dying within a year following diagnosis.¹⁶

The tumor morphology in PBL is variable; some neoplasms have immunoblastic features while others have a more plasmacytoid appearance (Fig. 3, A-C).¹⁸ The tumor cells are characteristically CD138, CD38, and MUM-1 positive, and usually demonstrate light chain restriction. CD79a, CD30 and EMA are also frequently expressed, but the neoplastic cells are negative or only weakly positive for CD45, CD20 and PAX5. Ki-67 labeling is high, reflecting the high proliferation rate of this aggressive neoplasm. Approximately 60-75% of all PBL cases are EBV-associated.^{7,15,18}

The differential diagnosis of PBL includes anaplastic plasmacytoma, primary effusion lymphoma (PEL), and EBV-positive DLBCL of the elderly. *In situ* hybridization for EBV encoded small RNA (EBER) is often helpful in distinguishing anaplastic plasmacytoma from PBL, since plasmacytomas are not EBV-associated. Additionally, expression of CD56 on the tumor cells suggests anaplastic plasmacytoma rather than PBL. Both PBL and PEL tend to arise in patients with HIV/AIDS; however, unlike PEL, PBL is not associated with human herpes virus-8.^{7,15} PBL arising in elderly, HIV-negative patients is EBV-associated, and in this patient population, the distinction between PBL and EBV-positive DLBCL of the

elderly can be challenging.¹⁷ Immunostains may be helpful since, unlike PBL, DLBCL tends to express CD20, Pax-5 and CD45.

Low Grade B-Cell Neoplasms

Normal mucosa in the nasal cavity and paranasal sinuses does not contain prominent lymphoid tissue, and it is relatively rare for low grade B-cell lymphomas to arise in this anatomic site.^{1,2,4} However, many low-grade lymphomas have circulating neoplastic cells, which may infiltrate the sinonasal tissue and can be sampled in biopsy specimens.

Chronic lymphocytic leukemia/small lymphocytic lymphoma

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a low grade lymphoma that typically has both circulating tumor cells and infiltration of lymph nodes. The mean age at diagnosis is 65 years, and there is a slight male predominance.⁷ The neoplastic cells can infiltrate the soft tissue or be found in association with inflammatory infiltrates in the sinonasal tract.²

CLL/SLL is predominantly composed of small lymphocytes with scant cytoplasm condensed chromatin and inconspicuous nucleoli (Fig 4.). Occasional admixed larger lymphocytes with open chromatin and conspicuous nucleoli ("prolymphocytes") are also seen. The tumor cells express B-cell antigens, although the expression of CD20 can be rather dim, and they characteristically express aberrant CD5 along with CD23. The differential diagnosis includes mantle cell lymphoma, which also shows co-expression of CD20 and CD5 but infrequently involves the sinonasal area. Mantle cell lymphoma is Cyclin D1-positive, allowing it to be readily distinguished from CLL/SLL.

Follicular lymphoma

Follicular lymphoma is an indolent lymphoma that predominantly affects older adults, is slightly more common in women, and often involves lymph nodes.⁷ Sinonasal involvement is rare.^{1,2,4} While follicular lymphoma generally has a slow progression with a good initial response to treatment, it ultimately becomes refractory to therapy and transformation to an aggressive lymphoma occurs in approximately 30% of cases.⁷

The tumors typically demonstrate closely packed atypical follicles that are not polarized, lack tingible body macrophages, and are composed of a mixture of centrocytes and larger centroblasts. Diffuse areas lacking follicles, often with sclerosis, may also be present. Grading is based on the number of centroblasts per high power field (HPF) in the atypical follicles, with grade 1-2 defined as having 15 or fewer centroblasts per HPF, and grade 3 having greater than 15 centroblasts per HPF. Grade 3 is further subdivided to distinguish grade 3A where admixed centrocytes are still present, and grade 3B where the follicles are entirely composed of centroblasts.⁷ Follicular lymphomas have a germinal center phenotype and are positive for CD19, CD20, CD79a, Bcl-6 and CD10 with aberrant expression of Bcl-2. Of note, a small percentage of FL are Bcl-2 negative, and this is more commonly seen in grade 3 lesions and pediatric follicular lymphoma.⁷

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is a low grade B-cell lymphoma. It is most commonly seen in adults and tends to arise within acquired lymphoid tissue, often secondary to chronic antigen stimulation or chronic inflammatory conditions.^{7,19,20} Sinonasal MALT lymphomas are exceedingly rare, but have been observed in acquired lymphoid tissue within the sinonasal mucosa and tend to be associated with chronic sinusitis.^{3,5,19,20}

MALT lymphomas are characterized by a heterogeneous chronic inflammatory infiltrate, and residual secondary follicles may be seen. The tumors contain a mixture of small and medium-sized lymphocytes with scattered immunoblasts, and plasma cell differentiation may be extensive. MALT lymphomas typically express B-cell antigens including CD19, CD20, CD79a, but are negative for CD10 and are usually negative for CD5. Some express aberrant CD43. Immunostains for kappa and lambda may help demonstrate clonality, particularly in cases with plasma cell differentiation, although in some cases confirmation of clonality may require molecular studies.

Extraosseus plasmacytoma

Extraosseus (extramedullary) plasmacytomas are localized monoclonal plasma cell neoplasms that present in the absence of an underlying plasma cell dyscrasia or myeloma (Fig. 3, C-F). Median age at diagnosis is 55 years, and they are more common in males.⁷ Plasmacytomas most commonly occur in the upper respiratory tract, including the nasopharynx and oropharynx, and have frequently been reported in the nasal sinuses where they typically present as a soft bleeding mass.^{1,4,21-24} Solitary plasmacytomas demonstrate an indolent course, progressing to plasma cell myeloma in only a minority of cases. Solitary plasmacytomas should be differentiated from reactive conditions, such as mucous membrane plasmacytosis, via immunostaining for kappa and lambda light chains.²⁵⁻²⁷ Differentiation of a plasmacytoma from a MALT lymphoma with extensive plasma cell differentiation may be difficult or impossible based on morphologic and immunophenotypic findings in a biopsy specimen.

Hodgkin Lymphoma

Classical and nodular lymphocyte-predominant Hodgkin lymphoma do not typically involve the sinonasal tract, although classical Hodgkin lymphoma has rarely been reported in Waldeyer's ring.^{28,29}

Aggressive T and NK-Cell Neoplasms

Extranodal NK/T-cell lymphoma

Extranodal NK/T-cell lymphoma, nasal type is relatively rare; however, it is more common in Asian countries and certain native American populations of Mexico, Central and South America.⁷ Extra-nodal NK/T-cell lymphoma, nasal type generally occurs in adults and is more common in males than females. The initial site of tumor formation is frequently the nasal cavity, paranasal sinuses, nasopharynx or palate.⁹ Patients may present clinically with nasal obstruction, rhinorrhea and epistaxis. Involved mucosal sites typically show extensive,

non-healing ulceration that progresses toward extensive midline destruction and nasal septal perforation.² Extranodal and disseminated disease is also observed. The prognosis of extranodal NK/T-cell lymphoma, nasal type is historically poor, with a median survival of approximately 30 months, although a more recent study demonstrates a 5-year survival closer to 50%.^{2,7,30,31}

The tumor may demonstrate an angiocentric growth pattern with fibrinoid necrosis of vessels, extensive apoptosis and areas of geographic, coagulative necrosis. The neoplastic cells range in size from small to large, but the cells are typically medium-sized with a moderate amount of pale to clear cytoplasm, irregularly folded or elongated nuclei, granular chromatin and inconspicuous nucleoli (Figure 5). Tumor cells may be accompanied by a variable inflammatory infiltrate including small lymphocytes, plasma cells, histiocytes and eosinophils, creating potential diagnostic confusion with reactive conditions or an inflammatory process, particularly granulomatosis with polyangiitis.^{7,14,32}

Extranodal NK/T-cell lymphomas are thought to predominantly arise from activated NK cells, and are typically positive for CD2, CD56 and cytoplasmic CD3, but negative for CD4, CD5, CD8 and CD3 surface antigen. Cytotoxic molecules such as granzyme, TIA-1 and perforin are also characteristically expressed.^{7,30,32,33} As suggested by the name, a smaller fraction of cases appears to be derived from a subset of cytotoxic T-cells rather than NK cells, and demonstrate monoclonal T-cell receptor gene rearrangement.^{7,30} The tumor is strongly associated with EBV, and *in situ* hybridization for EBV is positive in most of the lymphoma cells. While rare EBV-negative cases have been reported, care should be taken before making a diagnosis of EBV-negative extranodal NK/T-cell lymphoma.^{30,33}

Adult T-cell Leukemia/Lymphoma

Adult T-cell leukemia/lymphoma (ATLL) is a mature T-cell neoplasm associated with human T-lymphotrophic virus-1 (HTLV-1), a retrovirus that is endemic to Southwestern Japan, the Caribbean, parts of Central Africa, the Middle East, Papua New Guinea, and South America.⁷ As suggested by the name, ATLL occurs only in adults, and it demonstrates a slight male predilection with a male to female ratio of 1.5:1. Acute, chronic, smoldering and lymphomatous subtypes have been characterized, but most patients present with hypercalcemia, rash, widespread involvement of lymph nodes and abnormal circulating T-cells that have distinctive polylobated nuclei ("flower cells").⁷ ATLL can involve the sinonasal tract, and most of these cases are described in patients who emigrated from endemic areas.^{3,5,34,35} The prognosis of ATLL is poor, but patients who presented with a localized mass or locally infiltrative disease in head and neck sites without evidence of significant peripheral blood involvement tend to have a more indolent disease course.^{7,34}

Due to the multiple morphologic variants, the diagnosis of ATLL can be challenging in the absence of clinical information. The typical pattern is medium to large lymphoid cells with pronounced nuclear pleomorphism, coarsely clumped chromatin and conspicuous nucleoli. The tumor cells typically express CD2, CD3, CD5 and CD25, and most cases are CD4-positive with loss of CD7.⁹ Tumor cells demonstrate monoclonal integration of HTLV-1 proviral DNA, which is absent from healthy carriers, as well as clonal T-cell receptor gene rearrangements.⁹

Anaplastic Large Cell Lymphoma

Anaplastic large cell lymphoma has only rarely been reported to involve the sinonasal tract, including one case that arose in the context of HIV/AIDS.^{2,5,36,37} Presenting symptoms included nasal congestion, epistaxis and loss of visual acuity.

The neoplastic cells in ALCL show considerable morphologic variability. While the characteristic feature of ALCL is the presence of large cells with eccentric horseshoe or kidney-shaped nuclei (“hallmark cells”), tumors may be comprised of a variable number of large and small cells. In addition, an abundant inflammatory background composed of histiocytes or neutrophils may obscure the tumor cells.^{38,39} The neoplastic cells in ALCL show strong and uniform expression of CD30 and CD25, and most are positive for CD43 and EMA. The tumor cells may lack expression of CD45. Additionally, ALCL variably expresses T-cell markers; CD2 and CD4 are most commonly positive, but CD3, CD5 and CD7 are often lost. CD8-positive cases are rare. Unlike Hodgkin/Reed-Sternberg cells, the neoplastic cells of ALCL usually lack expression of CD15 and Pax-5, are EBV-negative, and show clonal rearrangement of the T-cell receptor genes. ALCL is further sub-divided into ALK-positive and ALK-negative ALCL. The expression of ALK is associated with recurrent cytogenetic abnormalities, most commonly t(2;5)(p23;q35), which fuses the ALK and NPM genes. Both the t(2;5) translocation as well as numerous variant ALK translocations can be detected using an immunohistochemical stain directed against ALK. ALK-positive ALCL has a more favorable prognosis than ALK-negative ALCL.⁷

Peripheral T-cell Lymphoma, Not Otherwise Specified—Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS or PTCL) has been reported in the sinonasal tract, although its frequency in older studies is difficult to determine based on changes in classification systems.^{1-5,8} PTCL encompasses T-cell lymphomas that do not meet the criteria for a specific type of T-cell lymphoma. PTCL is a disease of older individuals, and the prognosis is poor.⁷

The morphologic and immunophenotypic characteristics of PTCLs are heterogeneous. In general, the neoplastic cells in PTCL are medium-to-large and show morphologic atypia including irregular nuclear borders or prominent nucleoli. There may be occasional large, anaplastic cells as well as admixed inflammatory cells including clusters of epithelioid histiocytes. The neoplastic cells in PTCL are positive for CD3 and CD45RO, and most express CD4, although occasional cases may be CD8-positive.⁷ Expression of CD5 and/or CD7 is often lost on the tumor cells, and PTCL is not strongly associated with EBV. While there may be dim or variable expression of CD30 in PTCL, bright or uniform CD30 expression should prompt consideration for ALCL.

T-Lymphoblastic leukemia/lymphoma

As with B-ALL, T lymphoblastic leukemia/lymphoma (T-ALL) can rarely involve the sinonasal tract.⁴⁰⁻⁴² T-ALL expresses the T-cell antigens CD3 and CD7 with concurrent expression of one or more markers of immaturity including CD34, TdT, CD99, CD10 and/or CD1a. The expression of CD4 and CD8 is variable, with some “single positive” cases (i.e. CD4 or CD8-positive), “double positive” cases (CD4 and CD8-positive) and “double

negative” cases (CD4 and CD8-negative). Sinonasal T-ALL can occasionally demonstrate aberrant CD56 expression suggesting a possible natural killer cell lineage.^{40,42} The expression of CD56 in these immature lymphoid neoplasms may create diagnostic confusion with other small round blue cell tumors that express CD56 including olfactory neuroblastoma, primitive neuroectodermal tumor and rhabdomyosarcoma.⁴¹

Indolent T-Lymphoblastic Proliferation

An important mimicker of T-ALL is the recently described indolent T-lymphoblastic proliferation (iT-LBP). These lesions are composed of sheets or aggregates of immature T-cells without associated tissue destruction, and have been described in lymph nodes and the upper aerodigestive tract, including sinuses. The cytologic features and immunophenotype of iT-LBP are similar to T-ALL, but iT-LBP is indolent in nature and requires no treatment.^{43,44}

The lesions demonstrate relative preservation of normal lymphoid architecture, and are composed of morphologically and immunophenotypically unremarkable immature T-cells that express CD3, CD5, CD7, CD99 and TdT, with variable expression of CD4 and CD8, and a high Ki-67 proliferation index (Figure 6). Thymic epithelium is absent. Flow cytometry demonstrates a heterogeneous population of T cell precursors with a normal pattern of maturation, and molecular studies for the T-cell receptor are consistent with polyclonality.

Other Hematopoietic Disorders

Myeloid Sarcoma

Myeloid sarcoma, also known as extramedullary myeloid tumor, granulocytic sarcoma or chloroma, is a tumor mass consisting of myeloid blasts that effaces tissue architecture and occurs at any site other than the bone marrow.⁷ Myeloid sarcomas are often identified in patients who have frank leukemia, but can rarely be seen as the presenting symptom of acute myeloid leukemia in the absence of marrow involvement. Myeloid sarcoma can occur at almost any location in the body, including multiple, although rare, reports in the sinonasal tract.⁴⁵⁻⁴⁷ Myeloid sarcomas are usually composed of sheets of mononuclear cells with a high nuclear:cytoplasmic ratio, and may mimic lymphoma or other poorly-differentiated malignant neoplasms of the sinonasal tract. Immunostains are critical for the diagnosis, and most myeloid sarcomas express CD43 and CD68, with variable expression of CD45, CD34, CD117, CD99, TdT, CD33, myeloperoxidase, CD4 and/or lysozyme.

Rosai-Dorfman Disease/Sinus Histiocytosis with Massive Lymphadenopathy

Approximately 10% of patients with Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, may present with sinonasal involvement.^{48,49} Most patients have evidence of RDD in other sites (Figure 7; A,B), although disease limited to the sinonasal cavity has also been described (Figure 7; C,D).⁴⁸⁻⁵⁰ Patients with RDD may be treated with endoscopic surgery for symptomatic control, and in many cases the disease is benign and self-limiting, particularly if the lesion can be excised in its entirety.⁴⁹

Histologically, this disorder is characterized by S100-positive macrophages that demonstrate emperipolesis, the engulfment of intact lymphocytes.⁵¹

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Fig. 1. EBV-positive Diffuse Large B-cell Lymphoma of the elderly

A nasopharyngeal biopsy of a mass in a 60 year old woman shows sheets of large atypical lymphoid cells with abundant clear cytoplasm and irregular nuclear borders with variably prominent nucleoli (A, H&E). The tumor cells express CD20 (B) and have a high Ki-67 proliferation index (C). An *in situ* hybridization for EBV encoded small RNA (EBER) is positive in the neoplastic cells (D). All images, 400 $\times$.

Figure 2. B lymphoblastic lymphoma

A nasal mass in a 29 month old demonstrates a sheet of B-lymphoblasts with scant cytoplasm and fine chromatin. There are scattered apoptotic bodies (A, H&E). The neoplastic cells are positive for CD79a (B), CD10 (C) and TdT (D), but largely negative for CD20 (E). CD3 (F) highlights rare admixed T-cells. All images, 500×

Fig. 3. Plasmacytic lesions of the sinonasal tract

Plasmablastic lymphoma arising as a nasal mass in a 74 year old HIV+ man (A, H&E). Tumor cells are positive for CD138 (B) and EBV (C; EBER). In contrast, plasmacytomas are composed of sheets of mature plasma cells (D) with clonal light chain restriction (B and C, kappa and lambda, respectively). All images, 400 $\times$.

Figure 4. CLL/SLL

The sinus contents of a 76 year old man with chronic sinusitis show involvement by CLL/SLL. The submucosa contains sheets of small lymphocytes with mature chromatin (A, H&E, 100 $\times$; B, H&E, 400 $\times$) that are positive for CD79a (C), CD5 (D) and CD23 (not shown). CD3 highlights scattered T-cells (E) and a Cyclin D1 immunostain is negative in the lymphocytes (F). All immunostains, 400 $\times$.

Fig. 5. Extranodal NK/T-cell lymphoma

Histologic sections of a nasal cavity lesion in a 66 year old man demonstrate a diffuse submucosal infiltrate (A, H&E, 200×) of atypical lymphoid cells (B, H&E, 500×) with abundant associated necrotic material (not shown). The tumor cells are positive for CD3 (C; 500×) as well as CD56 (not shown). They express cytotoxic markers including TIA-1 (D, 500×), and a Ki-67 immunostain labels the majority of tumor cells (E, 500×). An *in situ* hybridization for EBV encoded small RNA is positive in many of the cells (F, EBER, 500×).

Fig. 6. Indolent T-lymphoblastic proliferation

Lymphoid tissue in a nasopharyngeal biopsy from a 25 year old woman with persistent nasal congestion and post nasal drip (A, H&E, 100×). The majority of the lymphocytes are T-cells (B, CD3, 100×), although scattered follicles contain B-cells (C, CD20, 100×). The immature T-cells do not show overt morphologic atypia (D, H&E, 1000×), and are positive for CD99 (E, 500×) and TdT (F, 500×).

Fig. 7. Rosai-Dorfman Disease

An enlarged cervical node from a 2 year old girl with a nasal mass showed sinus histiocytosis with prominent emperipolesis (H&E: A, 100 $\times$; B 400 $\times$). Isolated nasal Rosai-Dorfman disease in a 48 year old woman demonstrates scattered lymphoid infiltrates in a loose fibroinflammatory background with subtle emperipolesis (H&E: C, 100 $\times$; D 400 $\times$).