Body Fluids

9

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9.1 Introduction

The four main body cavities (left and right pleural, pericardial and peritoneal) are lined by parietal and visceral membranes, composed of blood and lymphatic vessels in loose connective tissue stroma covered by mesothelial cells, with a film of fluid in between for lubrication. Any accumulation of fluid within this potential space is termed an effusion and is always pathological. Effusions may be noninflammatory, inflammatory, infectious, or neoplastic, benign or malignant. Common causes of effusions in adults include cirrhosis, heart failure, pneumonia, and metastatic carcinoma, all of which are rare in children and adolescents. As a consequence, body cavity fluids from the pediatric population represent a small minority of all effusions sent for cytological evaluation and raise different diagnostic considerations than those from adults [1–6].

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9.2 Categorization of Body Fluids

- Effusions can be divided into transudates and exudates. Transudates are ultrafiltrates that are low in protein and typically accumulate due to physiological abnormalities, such as increased fluid pressures. Exudates imply damage to the serous membranes and leakage of protein, due to an underlying inflammatory or neoplastic process. Whereas the cause of a transudate is often known, the etiology of an exudate may be unknown or require confirmation to initiate appropriate therapy. Therefore, exudates are more likely to be sent for cytological evaluation.
- The vast majority of effusions in children are benign; however, they are not common cytological specimens and usually contain a smaller volume of fluid than those in adults. Although the primary purpose of effusion cytopathology is to identify a neoplastic effusion, it can be useful in the identification of inflammatory and other conditions.
- Parapneumonic effusions are pleural effusions that occur in patients with pneumonia, lung abscess, or bronchiectasis. Cardiac failure should also be ruled out in a child presenting with an effusion if there is no evidence of neoplasia or infection.

S.E. Monaco, L.A. Teot (eds.), *Pediatric Cytopathology*, DOI 10.1007/978-3-662-53441-0_9

9.3 Gross Appearance of Fluid

On receipt of an effusion, the laboratory should note the amount of fluid and the gross appearance. This includes the following descriptions, which can help in categorizing the fluid specimen [5]:

- *Clear straw colored*: The vast majority of effusions are serous in nature and appear clear or straw colored, even if some blood is present.
- *Milky white*: Chylous effusions are cloudy and milky in appearance. They may be due to the accumulation of chylomicrons which can be idiopathic or due to blockage or injury of the thoracic duct. Tuberculosis of a body cavity can also present with a chylous-appearing effusion, as can hematologic malignancies.
- *Metallic gold*: This implies a pseudochylous effusion due to the presence of cholesterol crystals. This color is associated with long-standing effusions, often in association with tuberculosis, rheumatoid lung disease, or myxedema.
- *Yellow purulent*: This is due to the presence of a marked acute inflammatory infiltrate, often secondary to an underlying pneumonia or perforated organ. When a purulent fluid is received in the cytology laboratory, a portion should be submitted for microbial cultures at the time of processing if that was not done at the point of collection.
- *Green*: Bile-stained effusions are usually due to a perforated bile duct or secondary to acute pancreatitis.
- *Bloody dark brown*: This may be due to trauma, infarction, endometriosis, or malignancy. As blood can be seen in both benign and malignant conditions, it is relatively nonspecific.

9.4 Benign Conditions

As previously mentioned, effusions in the pediatric population are most commonly due to non-neoplastic or benign causes.

9.4.1 Transudates

Common causes of transudates include congestive heart failure, cirrhosis, nephrotic syndrome, hypoalbuminemia due to malnutrition, and hypothyroidism. These are paucicellular specimens with scattered lymphocytes, histiocytes, and mesothelial cells. The mesothelial cells appear singly and in small clusters. Intercellular windows may be evident. The cells have well-defined cell borders with a peripheral cytoplasmic "lacy skirt," centrally situated nuclei with smooth nuclear borders, and finely granular chromatin.

9.4.2 Reactive Mesothelial Cells

Reactive mesothelial cells occur in the context of a wide variety of injuries, infections, and neoplasms. The fluid contains increased numbers of mesothelial cells appearing singly, in monolayered strips, and in sheets. The clusters have "knobby" borders, papillary-like structures, and "cell-in-cell" arrangements. The cells are round with dense cytoplasm and central to eccentrically situated nuclei. The nucleus has a well-defined membrane and uniform granular chromatin. Nucleoli may be apparent. Binucleation and multinucleation are not uncommon. Stimulation of the mesothelium by a variety of factors, including but not limited to uremia, dialysis, liver disease, and drugs, can cause exfoliation of markedly atypical mesothelial cells that may mimic malignancy. Immunocytochemistry may be required to make this distinction.

9.4.3 Inflammatory Effusions

The presence of inflammatory cells in effusions is due to a wide variety of infectious and noninfectious etiologies. Table 9.1 lists the most common causes of effusions associated with various types of inflammatory cells (Figs. 9.1, 9.2, 9.3, and 9.4).

9.4.3.1 Infectious Etiologies

Effusions result from a wide variety of infections. While cultures or clinical context may be needed for a specific diagnosis, the constituent inflammatory

Table 9.1 Differential diagnosis for inflammatory effusions based on the predominant type of cells identified

Predominantly neutrophils	Predominantly eosinophils
Acute pneumonia (empyema) Acute peritonitis Fungal infection Mycobacterial infection Penetrating injury Perforated viscera or intrathoracic rupture of esophagus Neoplasm Mimic: Karyorrhectic debris from high-grade lymphomas or other small round blue cell tumors involving a body cavity can mimic the multilobulated nuclei of neutrophils	Chest tubes Thoracotomy Pneumothorax Parasites Allergies Pneumonia Malignancy Autoimmune disease Pulmonary embolus Mimic: Eosinophils may be mistaken for neutrophils in an effusion, since the eosinophilic granules are not easily seen on Papanicolaou-stained slides
Predominantly lymphocytes	Predominantly plasma cells
Mycobacterial infection Autoimmune disease Trauma Peritoneal dialysis Chylous effusion Leukemia and lymphoma Other neoplasms Mimic: Karyorrhectic or apoptotic debris from small round blue cell tumors involving a body cavity can mimic lymphocytic effusions	Autoimmune disease Mycobacterial infection Neoplasia Mimic: Plasmacytoid neoplasms such as melanoma, and neuroendocrine neoplasm can mimic a plasmacytic effusion
Predominantly histiocytes	
Inflammation Mechanical irritation Histiocytic and mesothelial hyperplasia Neoplasia	

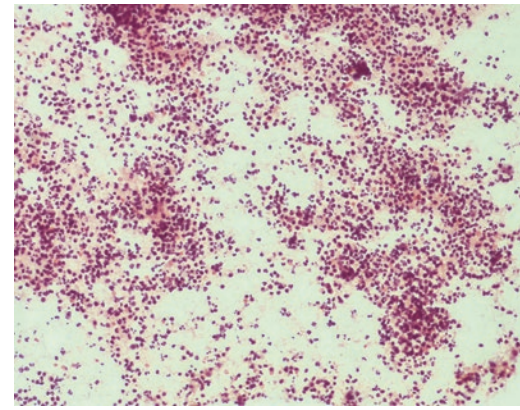

Fig. 9.1 In this pleural fluid from a child with pneumonia, there are numerous neutrophils, scattered lymphocytes, and histiocytes, consistent with an empyema (Papanicolaou stain, medium power).

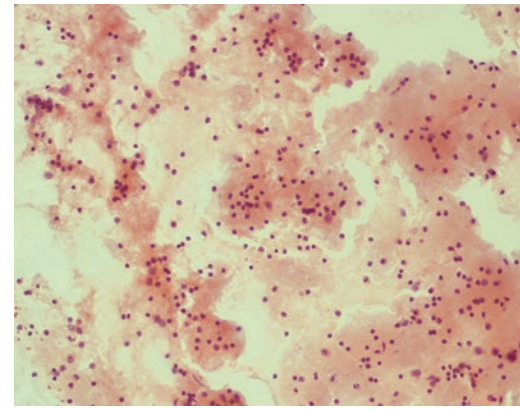

Fig. 9.2 In this pleural fluid from a 10-year-old boy with a mycobacterial infection, a moderate number of lymphocytes are present in a serous background (Papanicolaou stain, medium power). The culture grew *M. tuberculosis*.

cells provide an important clue to the differential diagnostic considerations:

- *Viral infection*: Many viral infections including, but not limited to, influenza, parainfluenza, adenovirus, respiratory syncytial, and mumps result in serous effusions. Variable numbers of chronic inflammatory cells are noted. Very occasionally, a viral cytopathic effect can be identified in mesothelial cells.
- *Bacterial infection*: Infection due to streptococci, staphylococci, haemophili, and other bacteria can lead to empyema, acute peritonitis or pericarditis. The fluid is macroscopically purulent, with numerous neutrophils and inflammatory debris noted microscopically (Fig. 9.1). Bacteria, within neutrophils and/or histiocytes or extracellularly, may be noted. Ancillary microbiological tests can help to identify the organism and to determine antimicrobial sensitivities.
- *Mycobacterial infection*: Fluid from a tuberculous serositis is typically shiny green macroscopically. Microscopically, there is a dearth of mesothelial cells with scattered to moderate numbers of lymphoid cells in a serous background [1, 2, 6]. Very occasionally, caseous necrosis and granulomas may be seen.

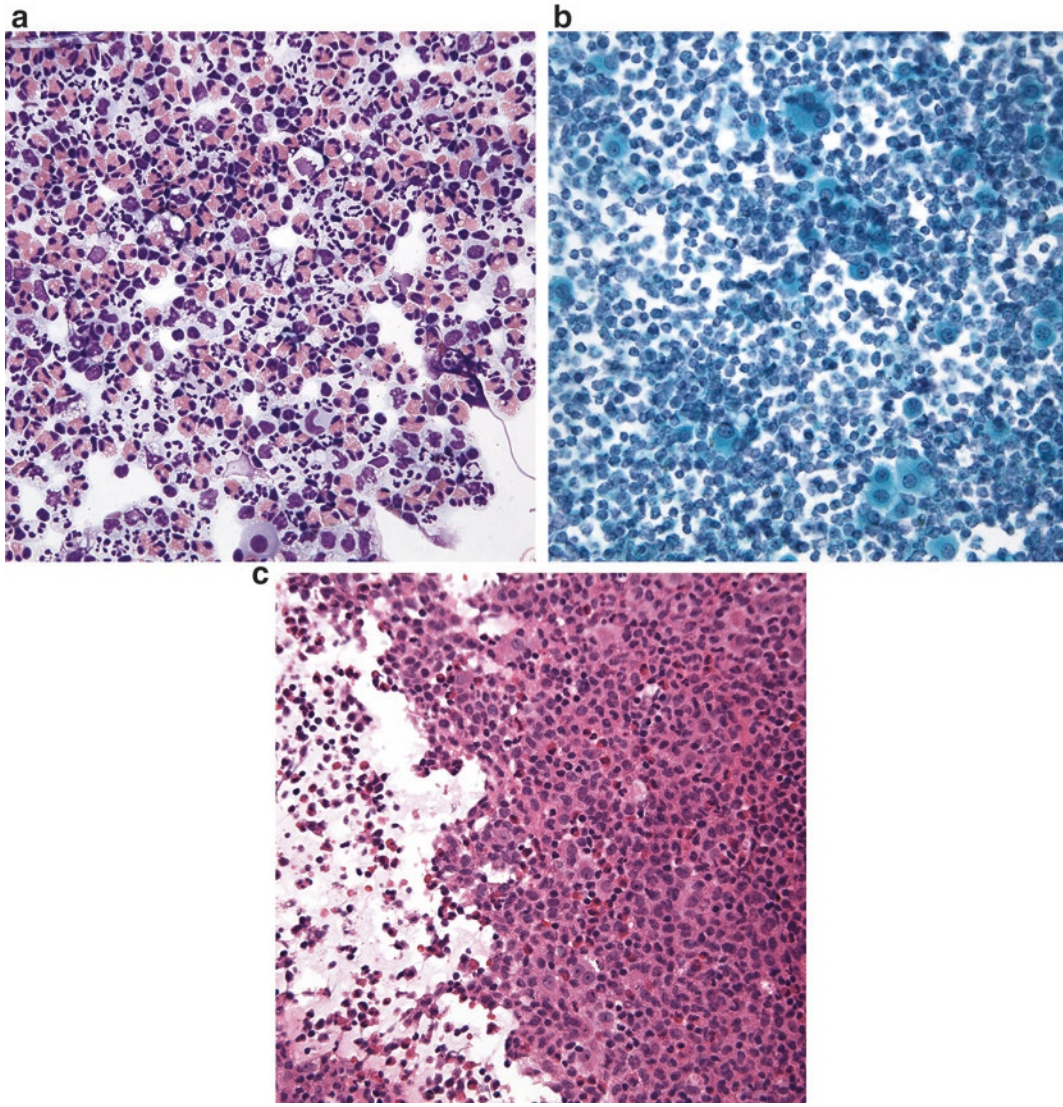

Fig. 9.3 This eosinophilic effusion taken after repeated chest tubes has numerous eosinophils with bilobed nuclei and cytoplasmic granularity (**a**. Diff-Quik stain, medium power; **b**. Papanicolaou stain, medium power; **c**. H&E stain, medium power). The eosinophilic granules are not as easily seen on the Papanicolaou stain, compared to Diff-Quik and H&E stains. (Images courtesy of Dr. Sara Monaco).

Mycobacterial infection can, on occasion, cause an acute inflammatory infiltrate (Fig. 9.2). Adenosine deaminase (ADA) and gamma-interferon (IFN) levels are raised. Routine acid fast stains can be used on direct smears made from the centrifuged 'pellet' of the fluid. A cell block can also be produced on which ancillary tests for mycobacterial infection can be performed.

- *Fungal infection*: Fungal serositis is encountered most frequently in immunosuppressed children. A predominance of neutrophils is seen with a varying amount of debris. The most common fungi in this regard are candida spp, cryptococcus spp, and *Pneumocystis jirovecii*. Special stains, such as PAS, GMS, and mucicarmine, highlight the morphologic features of the organisms and, thus, may aid in identification.
- *Parasitic infection*: Many parasites have been reported in serous effusions including paragonimiasis, amebiasis, echinococcosis, ascariasis, and schistosomiasis (Fig. 9.4).

9.4.3.2 Autoimmune and Rheumatologic Disease

Effusions are most often seen with systemic lupus erythematosus (SLE) and rheumatoid arthritis, but can be associated with other autoimmune and rheumatologic disorders.

Rheumatoid Arthritis

- Pleural effusions are most commonly seen, but peritoneal and pericardial effusions have been described. Arthritis is typically present before pleuritis develops.
- The fluid is yellow to green with a metallic shine (pseudochylous).
- The cytomorphology mimics that seen in a rheumatoid nodule. Variable amounts of granular debris and acute inflammatory cells are observed in the background. Mesothelial cells are sparse. Histiocytes are noted and can assume a variety of unusual shapes (e.g., spindled). These spindle cells have well-defined cell borders, dense cytoplasm, and pyknotic nuclei. Multinucleated histiocytes and cholesterol crystals can also be observed (Fig. 9.5).
- Biochemical analysis reveals an exudate with low glucose and pH levels, high lactic dehydrogenase levels (LDH), and high rheumatoid factor titers.

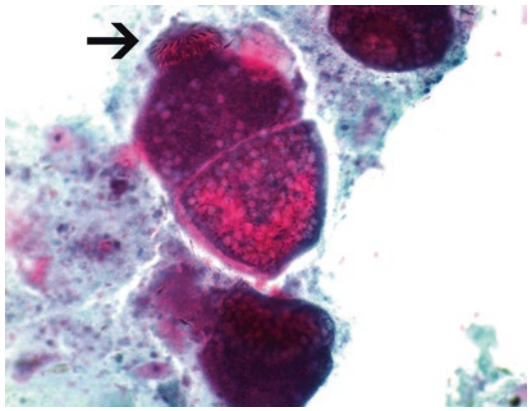

Fig. 9.4 Protoscolex of *Echinococcus* in a background of hydatid sand from an intra-abdominal cyst in an 11-year-old boy (Papanicolaou stain, medium power). An *arrow* indicates the collar of hooklets.

Systemic Lupus Erythematosus (SLE)

- An effusion is a very unusual presentation for SLE, but effusions often develop during the course of the disease. Pleural effusions are more often encountered, but peritoneal and pericardial serositis may be observed.
- Under the microscope, variable numbers of neutrophils and lymphocytes are noted. Two different cell types have been described in asso-

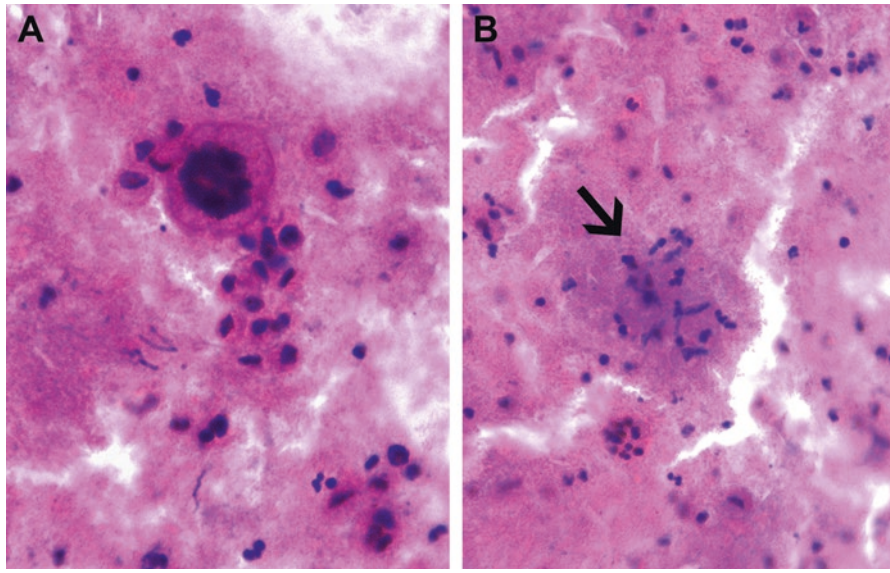

Fig. 9.5 This pleural fluid from a 17-year-old girl with rheumatoid arthritis shows multinucleated cells (**a**) in a granular, inflamed background with degenerating epithelioid histiocytes (**b**, *arrow*) (Papanicolaou stain, high power).

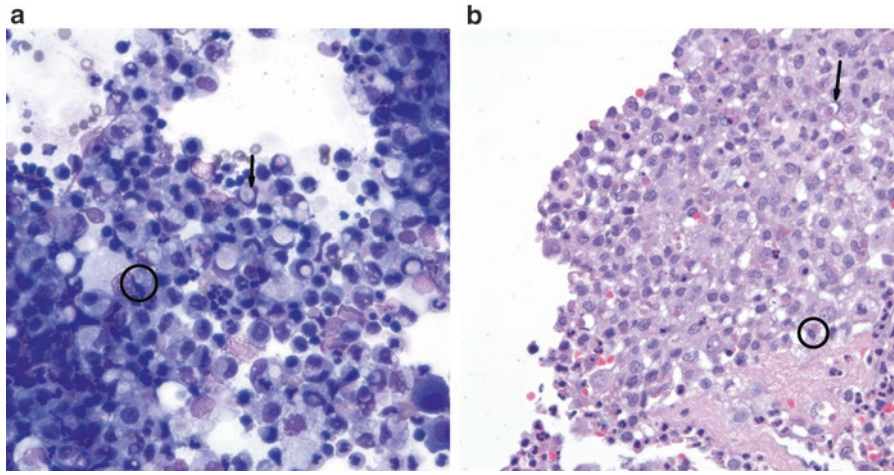

Fig. 9.6 A pleural effusion from a young woman with a history of systemic lupus erythematosus shows degenerating cells in various stages, including those within neutrophils and histiocytes (**a**. Diff-Quik stain, high power; **b**. H&E stain, medium power). The LE cells typically have completely degenerated cells with no discernible chromatin (*circles*), whereas the tart cells contain engulfed cells in various states of degeneration, but with intact chromatin visible (*arrow*). (Images courtesy of Dr. Sara Monaco).

ciation with effusions in SLE. The LE cell is a neutrophil or macrophage with a large, homogeneous cytoplasmic inclusion that pushes the nucleus to one side of the cell. The nucleus becomes crescentic in shape [7]. This inclusion, referred to as a hematoxylin body, represents the denatured nucleus of a phagocytosed cell. Tart cells have phagocytosed material that is smaller than a hematoxylin body, is nonhomogeneous, and does not displace the nucleus. Tart cells are thought to represent the initial stages of degeneration of the phagocytosed cell, when the nuclear morphology is still visible and precedes the completely denatured and homogenized form seen in LE cells (Fig. 9.6).

- Biochemically, lupus effusions are exudates with normal glucose levels. Antinuclear antibody titers are positive in both serum and effusion fluid.

9.4.3.3 Miscellaneous Lesions

- *Hepatitis and uremia*: Both of these conditions can cause reactive mesothelial cells that should not be confused with neoplasia. There are increased numbers of mesothelial cells lying singly, in monolayered sheets and in three-dimensional clusters with a knobby or flowerlike border. The cells are round with a well-defined cell border, dense cytoplasm, and central or eccentrically located nucleus. The cytoplasm has a peripheral "lacy skirt" appearance. The nuclei have smooth nuclear borders with fine to moderately coarse chromatin. Nucleoli can be prominent [1, 6].
- *Dialysis*: In children undergoing peritoneal dialysis, mesothelial cells ranging from mildly reactive to markedly atypical can be observed. Varying numbers of lymphocytes are seen, although eosinophilia has also been described.
- *Radiation and chemotherapy*: Increased numbers of mesothelial cells are noted in a hemorrhagic background. The mesothelial cells demonstrate enlargement of the nucleus and cytoplasm, but the overall nuclear-to-cytoplasmic (N/C) ratio is maintained. Other features include cytoplasmic vacuoles, nuclear hyperchromasia, and multinucleation. Degenerative changes in neoplastic cells include nuclear enlargement or reduction in size, karyorrhexis, karyolysis, and pyknosis, in addition to necrosis and apoptosis (Fig. 9.7).
- *Chylous effusion*: This is the accumulation of chyle within a serous cavity, most often the pleural cavity. It can occur in neonates with abnormal thoracic duct development, in children of all ages after surgery or trauma, or be idiopathic. Chylous fluid is a milky white. Numerous small lymphoid cells are seen on cytological evalua-

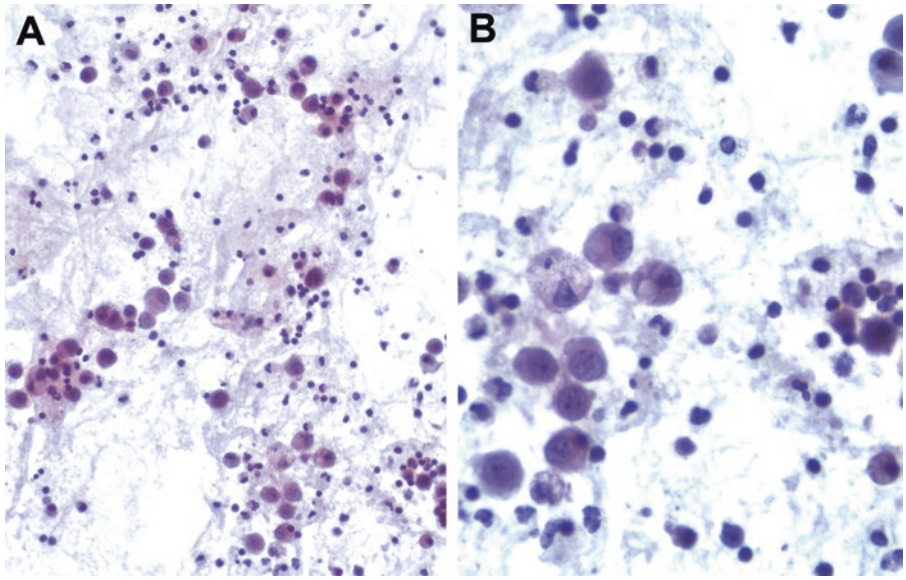

Fig. 9.7 Benign and reactive mesothelial cells from a pleural fluid in a 2-year old male who developed a pleural effusion while undergoing chemotherapy for retinoblastoma (**a**, **b**. Papanicolaou stain, low power and high power).

tion. Biochemistry reveals chylomicrons and high triglyceride levels. These effusions can have features similar to tuberculous effusions or effusions seen in autoimmune disorders.

- *Meconium peritonitis*: This is seen soon after birth and is caused by intestinal tract perforation and leaking of meconium into the peritoneum. Cytologically, debris, hemosiderin, anucleate squamous cells, and inflammation are observed [2].
- *Endometriosis and endosalpingiosis*: These entities are rare in fluid specimens. When present, they are usually seen in peritoneal washings in female adolescents, but are occasionally encountered in pleural fluids. In endometriosis, small clusters of endometrial cells are noted in a hemorrhagic background. The cells are tightly clustered and cuboidal with eccentrically situated nuclei. Hemosiderin-laden macrophages and stromal cells may, on occasion, be seen. CD10 immunochemistry may be used to indicate an endometrial stromal component. Endosalpingiosis presents with ciliated or non-ciliated columnar cells lying in clusters and papillary-like arrangements. Psammoma bodies may be seen in endosalpingiosis but hemosiderin-laden macrophages are lacking. Endosalpingiosis demonstrates B72.3, estrogen receptor and progesteron receptor positivity.
- *Extramedullary hematopoiesis*: While the myeloid precursor cells may be difficult to appreciate in effusion cytology, the presence of megakaryocytes should alert one to the diagnosis of extramedullary hematopoiesis. Megakaryocytes are large cells with multilobulated nuclei and granular chromatin.
- *Kawasaki disease*: This is a disease of unknown etiology that produces a systemic vasculitis. It is seen most often in children under the age of 5 years. It may, on occasion, be associated with hemorrhagic pleural or pericardial effusion. Cytology reveals a blood-stained effusion with scattered lymphoid cells.
- *Nodular mesothelial and histiocytic hyperplasia*: This is a benign hyperplasia of mesothelial cells and histiocytes that can mimic malignancy and potentially cause false-positive diagnoses in fluid cytology. Although it was originally described in hernia sacs and pericardial fluids, it can occur in the pleural or peritoneal cavities as well and is thought to be the result of focal irritation by trauma, tumor, or inflammation. Cytologically, there are distinct cellular clusters of mesothelial cells and histiocytes without pleomorphism, in addition to a background of chronic inflammation [8].

9.5 Malignancies in Fluid Cytology

Most effusions in the pediatric population have a benign etiology. However, primary and secondary malignancies need to be actively excluded when examining serous fluid from a child or adolescent. Most malignant effusions in the pediatric population are due to involvement by a hematolymphoid process. Other small round cell tumors, primary or metastatic, are the next most common cause of malignant effusion in this clinical setting. Although most of these patients have a known history of malignancy, in a subset of patients, the malignant effusion is the initial presentation, and in these cases, ancillary testing is important for arriving at an accurate and specific diagnosis [9].

9.5.1 Primary Malignancies

9.5.1.1 Desmoplastic Round Cell Tumor (DRCT)

Clinical features

DRCT is a rare but aggressive tumor, which is usually located intra-abdominally and in the pelvis but can be found in the retroperitoneum, thorax, and central nervous system. The tumor is most often seen in young males aged 8 to 38 years, but has been described in females. Patients typically present with abdominal pain or abdominal mass, and may have ascites. Prognosis is poor.

Cytological features

The specimen is often cellular with tumor cells in loosely cohesive groups or tighter clusters, without any distinct architecture. The presence of sphere-like clusters without a stromal core is a helpful feature, although this can morphologically mimic adenocarcinoma in fluids [9, 10]. Sporadic single cells and rosettes may also be seen. The cells have a high N/C ratio with minimal cytoplasm and occasional cytoplasmic vacuoles. The nuclei are round to oval with moderately granular chromatin and may show nuclear molding. Nucleoli can be prominent or inconspicuous. The background is typically hemorrhagic or necrotic. Despite the characteristic alternating round cell and stromal components observed on histology, metachromatic stromal fragments are seldom seen in the effusions, although scattered spindle cells may be present.

Triage

DRCT exhibits polyphenotypic immunostaining for epithelial (AE1/AE3, CK5/CK6, EMA, and/or others), muscle (desmin), and neural (NSE, synaptophysin, and/or others) markers. WT1 is usually positive, while FLI1 is negative. DRCT is characterized by a recurrent translocation t(11;22)(p13; q12) with fusion of the *EWSR* and *WT1* genes which can be demonstrated by cytogenetics or reverse transcriptase-polymerase chain reaction (RT-PCR). An *EWSR* translocation can also be identified by fluorescence in situ hybridization (FISH), although this is not specific for DRCT. Electron microscopy shows intermediate filaments located near the nucleus.

Differential diagnosis

The differential diagnosis includes other round cell tumors, and immunostains and FISH and/or RT-PCR studies are critical for establishing a correct diagnosis. Nephroblastoma or Wilms' tumor has cytological features of tubules, blastema, and stroma, which are more prominent than in DRCT, but both are positive for epithelial markers and WT1. DRCT stains with antibodies to the carboxy terminus of WT1, whereas dual immunoreactivity for the carboxy and amino terminuses is seen in Wilms tumor. Neuroblastoma occurs in a younger age group, has neuropil, and lacks metachromatically staining stromal fragments but similar to DRCT can demonstrate rosettes and positive immunostaining for neuroendocrine markers. Rhabdomyosarcomas tend to have dense cytoplasm and hyperchromatic nuclei, may show evidence of rhabdomyoblastic differentiation, such as more abundant eccentric cytoplasm or strap cells, and are immunoreactive for myogenin and myoD1, in addition to desmin. Of note, aberrant staining for epithelial and neuroendocrine markers occurs in a minority of rhabdomyosarcomas and may lead to diagnostic confusion; however, in contrast to DRCT, rhabdomyosarcomas lack *EWSR1* translocations. Ewing sarcoma/primitive neuroectodermal tumor (PNET) is typically negative for desmin, cytokeratin, EMA, and WT1, and has *EWSR1* translo-

cations that involve partners other than *WT1*. Lymphoid malignancies are characterized by lack of cellular cohesion, the presence of lymphoglandular bodies, and positivity for lymphoid markers. A less common tumor in the differential diagnosis includes extramedullary ependymoma of the myxopapillary type that may arise in the sacrum or abdominopelvic region and is positive for GFAP and S100. Small cell carcinomas and mesotheliomas are rare in the pediatric age group.

Pearls

DRCT overlaps cytomorphologically with other small round cell tumors of childhood. Thus, it is essential to use a panel of immunostains, in addition to FISH and/or RT-PCR to exclude other small round cell tumors of childhood and arrive at the correct diagnosis. RT-PCR has an advantage over the break-apart FISH probe for *EWSR1*, in that the *EWSR1-WT1* translocation detected by RT-PCR is specific for DRCT, whereas the break-apart probe for *EWSR1* is positive in a variety of tumors, including Ewing/PNET (*EWSR1-FLI1 and EWSR1-ERG*), extraskeletal myxoid chondrosarcoma (*CHN-EWSR1*), clear cell sarcoma (*EWSR1-ATF1*), and desmoplastic small round cell tumor (*EWSR1-WT1*) [6].

9.5.1.2 Pleuropulmonary Blastoma (PPB)

Clinical features

PPB is a rare intrathoracic neoplasm that occurs predominantly in children under the age of 4 years, but is the most common tumor seen in the cancer predisposition syndrome associated with germline *DICER1* mutations. It may be cystic, solid and cystic, or solid and, except for purely cystic tumors, follows an aggressive course. It is distinct from pulmonary blastoma. Patients present with respiratory symptoms, including cough, dyspnea, hemoptysis, and/or recurrent pneumonia, and some develop pleural effusions. Radiologically, these tumors can appear as low-attenuation masses in the pleural cavity with some high-attenuation areas, which can mimic an empyema [8].

Cytological features

PPB shows varying proportions of primitive blastema and sarcomatous elements and, in cystic lesions, benign epithelium. Lipoblastic, chondroblastic, and rhabdomyoblastic differentiation of the sarcomatous component has been described. The blastema is negative, on immunostaining, for CD99. Cytogenetic studies often show gains in chromosome 8q, and molecular studies reveal germline mutations in *DICER1* in approximately 50–70 % of patients with PPB.

Differential diagnosis

The differential diagnosis includes other small round cell tumors of childhood, malignant teratoma, synovial sarcoma, rhabdomyosarcoma, and infantile fibrosarcoma. Cases of pleuropulmonary blastoma can mimic an empyema of the pleural space on radiological imaging and thus awareness of this entity is important [11].

9.5.1.3 Primary Effusion Lymphoma

Clinical features

Primary effusion lymphoma (PEL) is a human herpesvirus 8 (HHV8)-positive lymphoma that manifests as an effusion, usually without a solid component. However, extracavitary or solid variants have been described. It is strongly linked to infection with HHV8 and variably related to infection with EBV. It usually occurs in young patients with advanced human immunodeficiency virus (HIV) disease or other immunocompromised patients, such as those with solid organ transplants, but has also been diagnosed in HIV-negative, elderly patients. Usually only one serous cavity is involved, mostly the pleura, and the prognosis is poor.

Cytological features

The specimen is usually cellular and composed of a pleomorphic, intermediate to large lymphoid population with features overlapping with immunoblastic diffuse large B-cell lymphoma, anaplastic lymphoma, and Burkitt lymphoma [12] (Fig. 9.8). The cytoplasm is basophilic and may be vacuolated or show perinuclear clearing. Nuclei are large and hyperchromatic with irregular nuclear contours and prominent nucleoli. Mitotic figures, bi- or multinucleation with Reed-Sternberg-like cells, and apoptosis are usually apparent.

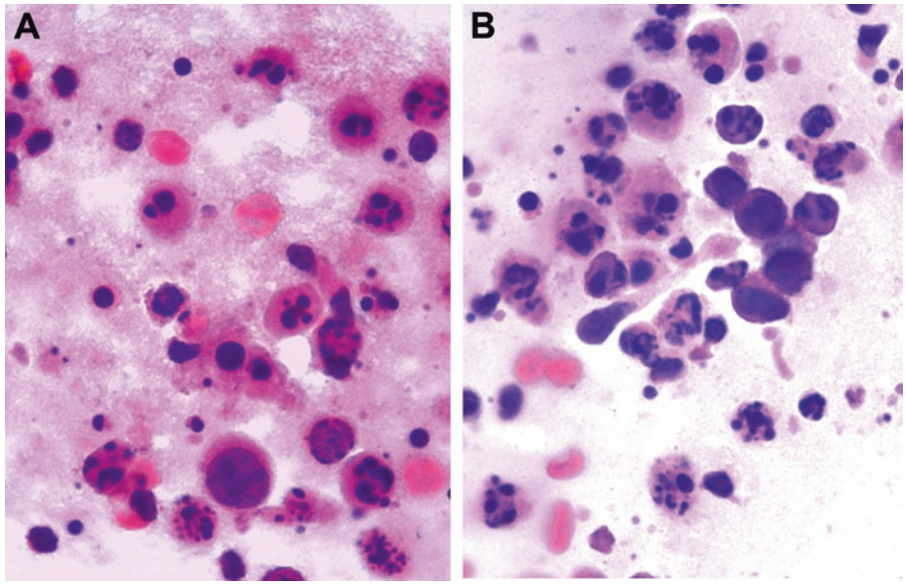

Fig. 9.8 Peritoneal fluid from an HIV-positive 17-year-old with primary effusion lymphoma (**a**, **b**. Papanicolaou stain, high power with oil magnification). Pleomorphic, malignant lymphoid cells are noted in an apoptotic background.

Triage

Fluid should be sent for flow cytometry, in addition to making a cell block for immunostains and in situ hybridization. This lymphoma generally does not express the usual B- and T-cell antigens, but usually expresses LCA, CD30, EMA, CD38, and CD138, while being negative for CD20, CD19, PAX5 and CD79a. The tumor cells show nuclear positivity for HHV8, and in situ hybridization sometimes reveals Epstein-Barr virus (EBV)-encoded RNA (EBER) nuclear positivity.

Differential diagnosis

The differential diagnosis includes other intermediate to large cell lymphomas or leukemias in children, including diffuse large B-cell, plasmablastic, and anaplastic large cell lymphomas, all of which are negative for HHV8. Burkitt lymphoma is positive for *C-MYC* gene rearrangement, and lymphoblastic lymphomas/leukemias are positive for TdT. Post-transplant lymphoproliferative disorders should also be considered in immunocompromised patients, but these are negative for HHV8 and positive for EBV. Other pediatric nonlymphoid large cell malignancies should also be considered, including metastatic malignant melanoma and poorly differentiated carcinoma.

Pearl

HHV8 infection is also associated with Kaposi sarcoma and multicentric Castleman's disease, but in lymphomas involving the body cavity, the presence of HHV8 is relatively specific for PEL. In the absence of HHV8 positivity, lymphomatous effusions are usually secondary to diffuse large B-cell lymphoma (including DLBCLs associated with chronic inflammation or pyothorax), anaplastic large cell lymphoma, or Burkitt lymphoma, depending on the immunophenotypic findings.

9.5.1.4 Malignant Mesothelioma

Clinical features

Malignant mesothelioma is extremely uncommon in children. Most appear to be unrelated to asbestos exposure. Table 9.2 lists features of malignant mesothelioma and compares them to those of metastatic epithelial and germ cell tumors, which comprise the major differential diagnostic considerations in the pediatric population [13].

Table 9.2 Comparison of malignant mesothelioma and metastatic epithelial and germ cell tumors

	Malignant mesothelioma	Metastatic epithelial and germ cell tumors Note: Morphology depends on the particular tumor
Frequency	Very uncommon	Uncommon but may be seen in children with germ cell tumors and adenocarcinoma of the breast, ovary, liver, colon, and other sites
Background	Cellular specimen, blood, necrosis, inflammation	Variable cellularity, blood, inflammation, necrosis, mucus (mucinous adenocarcinomas), tigroid (germ cell tumors with component of seminoma or dysgerminoma)
Architecture	Single-lying morula clusters with "knobby" borders, three-dimensional clusters, papillae, intercellular windows	Single-lying, two-dimensional, and three-dimensional clusters, acini, papillae
Cytoplasm	Round cells, dense two-tone cytoplasm, "lacy skirt," vacuoles usually multiple	Cuboidal to columnar shape, vacuolated or granular cytoplasm, single to multiple vacuoles
Nucleus	Centrally situated, bi- and multinucleation, irregular nuclear borders, granular chromatin, prominent nucleoli, normal-to-moderately increased N/C ratio	Central to eccentrically situated, irregular nuclear outlines, chromatin varies from hyperchromatic to vesicular, prominent nucleoli, moderate to marked increase in N/C ratio
Triage	*Immunostains*: calretinin+, CK5/CK6+, D2-40+, WT1+, CK7+, CK20−, CEA−, BerEP4−, B72.3−, MOC31− *Ultrastructure*: long microvilli *FISH*: *p16* deletion	*Immunostains*: BerEP4+, MOC31+, B72.3+, CEA+, CK profile depends on origin of carcinoma, calretinin−, CK5/CK6−, WT1−in metastatic carcinoma. Germ cell markers positive according to tumor type *Ultrastructure*: short microvilli, cytoplasmic mucin, or other secretory products
Pearl	Shows a spectrum from benign to atypical to malignant mesothelial cells	Look for two different cell populations—benign reactive mesothelial cells and a foreign population of malignant cells

9.5.2 Secondary Malignancies

In adults, an important diagnostic quandary is to distinguish reactive mesothelial cells from metastatic adenocarcinoma, whereas in children, the challenge is differentiating small cell neoplasms from inflammatory cells. Many different tumors can spread to body cavities during the course of disease. It is important to distinguish a primary versus secondary neoplastic process as the treatment and prognosis differ. The most common tumors seen in the body cavities, particularly the pleural fluid, of young patients are hematolymphoid (Table 9.3), small round cell tumors of childhood, particularly neuroblastoma and nephroblastoma, and round and spindle cell sarcomas [2, 14]. Approximately 20–30 % of Hodgkin and non-Hodgkin lymphomas involve the pleural fluid, especially if there is mediastinal involvement [15]. In peritoneal fluid, hematolymphoid malignancies, neuroblastoma, and germ cell tumors, particularly those arising from the ovary, predominate (Table 9.3) [2]. In children with a nonlymphoid neoplasm aged less than 4-9 years, metastatic neuroblastoma or Wilm's tumor is the most common secondary malignancy while in those over 9 years of age, the metastasis is most likely to have arisen from a sarcoma or germ cell tumor [2]. Nonlymphoid neoplasms metastatic to the body cavities are usually distinguished based on the presence of a foreign population of cells that appear different to the background lymphocytes and mesothelial cells (Table 9.4). Sarcomas tend to round up in fluids, and the characteristic cell shapes (spindled, round, or pleomorphic) and architectural patterns, such as vascular arrangements, seen in fine needle aspirates of these lesions may not be apparent in the exfoliative cytological specimens [16]. In addition, sarcomas tend to exfoliate sparsely compared with lymphomas, small round cell tumors, and carcinomas. In rare cases, spindle cells may be observed, and these may be due to primary or metastatic neoplasms (Table 9.5).

Table 9.3 Most common malignancies in pediatric fluid cytology

Pleural fluid	Peritoneal fluid	Pericardial fluid
Hematolymphoid malignancies (lymphomas, leukemias)	Hematolymphoid malignancies (lymphomas, leukemias)	Hematolymphoid malignancies (lymphomas, leukemias)
Neuroblastoma	Neuroblastoma	
Sarcoma (rhabdomyosarcoma, osteosarcoma, Ewing sarcoma/PNET)	Nephroblastoma	
	Germ cell tumors	

Table 9.4 Hematolymphoid malignancies in serous fluids

Tumor	Cytomorphology	Triage
Acute leukemia	Blasts with immature powdery chromatin can be tightly packed together, especially in centrifuged preparations. Lymphoblastic leukemias tend to be round, intermediate-sized cells with scant cytoplasm, whereas myeloid leukemias usually have more lobulated nuclei and moderate amounts of granular cytoplasm.	Flow cytometry Immunohistochemical stains
Lymphoblastic leukemia/ lymphoma (Fig. 9.9)	Intermediate-sized cells with scant cytoplasm, irregular nuclear contours, and variable nucleoli. Ancillary studies reveal a T- or B-cell population with positive CD10 and TdT immunostaining (Fig. 9.10).	Flow cytometry Immunohistochemical stains
Burkitt lymphoma	Intermediate-sized cells with moderate amounts of vacuolated basophilic cytoplasm (best seen in Romanowsky-type preparations) and round monomorphic nuclei with immature chromatin. Abundant mitotic figures, apoptosis, karyorrhectic debris, and tingible body macrophages.	Flow cytometry Immunohistochemical stains FISH studies to confirm t(8;14) or variant translocations of *C-MYC* (t(2;8) and t(8;22))
Diffuse large B-cell lymphoma	Large cells with moderate to abundant cytoplasm, irregular nuclear outlines, and variable nucleoli. Karyorrhectic debris and mitotic figures may be apparent.	Flow cytometry Immunohistochemical stains
Primary effusion lymphoma (Fig. 9.8)	Large malignant cells with pleomorphism and a karyorrhectic background.	Flow cytometry Immunohistochemical stains
Hodgkin lymphoma	Reed-Sternberg (RS) cells with a mixed background including inflammatory cells, mesothelial cells, and histiocytes.	Immunohistochemical stains

One approach to the evaluation of tumors in body cavity fluids from children and adolescents is to determine whether the cells are small and round with minimal cytoplasm, larger with moderate to abundant cytoplasm, or spindled (Tables 9.4, 9.5, and 9.6). Based on the general morphology, the residual fluid can be triaged for flow cytometry and/or a cell block for immunostains, FISH, and/or RT-PCR.

9.5.2.1 Hematolymphoid Malignancies

Clinical features

Hematolymphoid malignancies are the most common tumors to be seen in body cavity fluids in the pediatric population. These tumors can be diagnostically challenging due to the morphological overlap with chronic inflammatory cells,

Table 9.5 Differential diagnosis of serous effusions in children comprising cells with moderate to abundant cytoplasm

Tumor	Cytomorphology	Triage
Germ cell tumor (Figs. 9.14, 9.16, and 9.17)	Single-lying and small clusters, high N/C ratio, ± vacuolated cytoplasm, round nucleus, and prominent nucleoli [17]	IHC: variable positivity for germ cell markers (PLAP, AFP, SALL4, HCG, CD117, OCT3/4, CD30)
Hepatocellular carcinoma (Fig. 9.18)	Single and clustered large malignant cells with eosinophilic cytoplasm, ± cytoplasmic bile pigment, prominent nucleoli, intranuclear cytoplasmic inclusions	IHC: positive for Hepar1, Glypican3, AFP; negative for CK7 and CK20
Papillary thyroid carcinoma	Papillary fragments, psammoma bodies; nuclear features of papillary thyroid carcinoma may not be apparent	IHC: positive for TTF1, PAX8, thyroglobulin, CK7
Serous tumors (ovary, peritoneum), mucinous tumors	Papillary fragments, psammoma bodies, ± mucin (mucinous tumors), large secretory vacuoles	HC: positive for WT1, PAX8, CA 125, CK7. Mucinous ovarian tumors can be CK7 negative, and CDX2, villin and CEA positive
Translocation-associated renal cell carcinoma (Fig. 9.19)	± Papillary fragments, hemosiderin, moderate to abundant dense to granular cytoplasm, ± prominent nucleoli	IHC: positive for vimentin, CD10, PAX8, TFE3; may be negative for MOC31 and BerEP4 FISH: *TFE3* gene rearrangements
Solid pseudopapillary tumor of pancreas	Papillae, round cuboidal shape, ± hyaline cytoplasmic granules, ± nuclear grooves, finely granular chromatin	IHC: positive for vimentin, synaptophysin, β-catenin, α1-antitrypsin, CD56, CD10
Rhabdomyosarcoma (Fig. 9.13)	Small round cells with minimal cytoplasm in addition to larger, more pleomorphic cells with moderate to abundant eosinophilic cytoplasm, spindle and strap cells, bi-and multinucleation	IHC: positive for desmin, myogenin, myoD1 FISH: Alveolar rhabdomyosarcoma has *FOXO1* translocations [t(1;13) or t(2;13)]
Ganglioneuroblastoma	Small round cell with minimal cytoplasm in addition to larger, more pleomorphic polygonal cells; abundant, granular cytoplasm; eccentrically to centrally situated nuclei; hyperchromatic, large nuclei; prominent nucleoli; bi- and multinucleation	IHC: positive for neuroendocrine markers FISH: to determine *N-MYC* amplification status
Osteosarcoma (Fig. 9.20)	Large pleomorphic cells, variable amount of eosinophilic cytoplasm, hyperchromatic, prominent nucleoli which may be multiple, giant cells. Osteoid is not usually seen in fluids.	IHC: No specific markers and cells may stain with multiple mesenchymal markers, confounding the diagnosis. Known history of osteosarcoma is helpful.
Sex cord/stromal tumor	Small, uniform cells, bland nuclear features, nuclear grooves. scanty cytoplasm. Call-Exner bodies rarely seen in effusions.	IHC: positive for inhibin, calretinin, pankeratin
Malignant mesothelioma	Morulae; clusters with "knobby" borders; intercellular windows; dense, biphasic cytoplasm with a "lacy skirt"; bi- and multinucleation; granular chromatin	IHC: positive for calretinin, CK5/CK6, D2-40, WT1, CK7; negative for CK20, CEA, BerEP4, B72.3. FISH for *p16* deletion
Multicystic mesothelioma	Single and clusters, monotonous-appearing mesothelial cells	IHC: positive for calretinin, CK5/CK6, D2-40, WT1, CK7; negative for CK20, CEA, BerEP4, B72.3
Hodgkin lymphoma	Very occasional Hodgkin Reed-Sternberg (HRS) cells, lymphocytes, plasma cells, neutrophils, ± eosinophils	IHC: HRS cells positive for CD15, CD30, ±CD20, ±BLIMP1; negative for LCA, TIA1, CD3
Epithelioid hemangioendothelioma	Round to oval cells, vacuolated eosinophilic cytoplasm, usually bland nuclear features, ± prominent nucleoli. Vascular architecture is not well seen in fluids.	IHC: positive for CD10, factor VIII, CD31, CD34, FLI1
Malignant melanoma (Fig. 9.21)	Single-lying and loose clusters, round to oval plasmacytoid to spindle, varying amounts of cytoplasm, ± melanin pigment, central to eccentric nucleus, granular chromatin, prominent nucleoli, intranuclear cytoplasmic inclusions	IHC: positive for HMB-45, MelanA, S100, MiTF, tyrosinase

Table 9.6 Differential diagnosis of serous effusions in children comprising spindled cells

Tumor	Cytomorphology	Triage
Embryonal or spindle cell rhabdomyosarcoma (Fig. 9.13)	Small round cells with minimal cytoplasm in addition to larger, more pleomorphic cells with moderate to abundant eosinophilic cytoplasm, spindled and strap cells, bi- and multinucleation	IHC: positive for desmin, myogenin, and myoD1; usually negative for cytokeratins and neuroendocrine markers
Desmoplastic round cell tumor	Small round cells with minimal cytoplasm in addition to sporadic spindle cells, ± stromal fragments	IHC: positive for desmin, neural markers, cytokeratins, EMA, vimentin, MOC31, WT1; myoD1 may be positive after treatment with chemotherapy FISH: *EWSR1* translocation RT-PCR: *EWSR1-WT1* fusion [t(11;22)(p13; q12)]
Nephroblastoma	Spindle cells as part of the stromal component, unusual for all three cells types to be seen when metastatic to serous cavity	IHC: Staining profile of stroma according to morphologic appearance (e.g., positive for desmin and myogenin in rhabdomyoblastic differentiation)
Pleuropulmonary blastoma	Primitive blastema and sarcomatous elements. ± lipoblastic, chondroblastic, and rhabdomyoblastic differentiation	IHC: Negative for CD99 Cytogenetics: ± gains in chromosome 8q Molecular: ± germline *DICER1* mutations
Synovial sarcoma	Monophasic/biphasic, sparse cytoplasm, irregular nuclear borders, prominent nucleoli	IHC: positive for EMA (may be weak in spindle cells), bcl-2+ (spindle cells), CD99+ FISH: *SS18* translocation [t(X:18)]
Angiosarcoma	Bloodstained fluid, single cells and loose clusters, ill-defined cell borders, finely vacuolated cytoplasm, irregular nuclear borders, hyperchromatic, prominent nucleoli. May also present with more abundant cytoplasm resembling metastatic carcinoma	IHC: positive for factor VIII, CD31, CD34, VEGF, FLI1
Malignant peripheral nerve sheath tumor	Wavy nuclei, hyperchromatic	IHC: positive or negative for S100 (not well demonstrated in alcohol-fixed smears)
Kaposi sarcoma	Bloodstained fluid, single and small clusters, bland spindle cells, scanty cytoplasm	IHC: positive for CD31, CD34, D2-40, HHV8
Malignant melanoma (Fig. 9.21)	Single-lying and loose clusters, round to oval to plasmacytoid to spindled, varying amounts of cytoplasm, ± melanin pigment, central to eccentric nucleus, granular chromatin, prominent nucleoli, intranuclear cytoplasmic inclusions	IHC: positive for HMB-45, MelanA, MiTF, S100, tyrosinase; negative for cytokeratins and LCA
Leiomyosarcoma	Single-lying, round, dense cytoplasm, bi-and multinucleation, coarse chromatin	IHC: positive for SMA, desmin, calponin, caldesmon

which are normally present in effusions. However, non-Hodgkin lymphomas (NHLs), excluding primary effusion lymphoma, and leukemias rarely present as an effusion without a prior history of malignancy. In addition, small cell lymphomas, which are difficult to distinguish from lymphocytic inflammation without ancillary studies, are uncommon in children, in contrast to the adult population.

Cytological features

The key features of a malignant hematolymphoid proliferation is the presence of a uniform population of discohesive cells with slight to marked nuclear enlargement, abnormal chromatin, which varies with the type malignancy, lymphoglandular bodies, and karyorrhectic debris. Although malignant lymphoid cells may artifactually clump, there is less cellular cohesion as com-

pared to other small round cell tumors of childhood. Immersion in a fluid medium can cause cytoplasmic vacuoles, and thus, the presence of cytoplasmic vacuoles alone should not lead to a diagnosis of Burkitt lymphoma. Blasts and immature myeloid precursors can also be seen when a leukemia involves the fluid, and in these scenarios, it is important to correlate with the amount of peripheral blood dilution and the peripheral blood blast count to determine if the blasts are from true fluid involvement or peripheral blood contamination (Figs. 9.8, 9.9, 9.10, and 9.11). Hodgkin lymphomas can also be present in pleural fluids, particularly if there is mediastinal involvement, and typically show HRS cells in a heterogeneous background mixed with mesothelial cells and histiocytes [15]. A summary of the hematolymphoid malignancies to consider in a fluid specimen is seen in Table 9.4.

Triage

Triage for flow cytometry, immunohistochemical stains, in situ hybridization or PCR is recommended for accurate immunophenotyping of the cells and to confirm malignancy. These studies are used to prove clonality, assess proliferative activity, and arrive at a differential and definitive diagnosis.

Differential diagnosis

Non-Hodgkin lymphoma must be distinguished from other small round cell tumors of childhood and from benign causes of a lymphocytosis, such

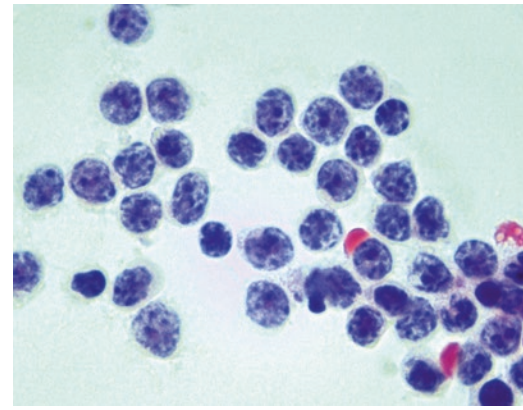

Fig. 9.9 This pleural fluid from a 16-year-old girl with T-lymphoblastic lymphoma shows numerous malignant lymphocytes with high nuclear-to-cytoplasmic ratios, irregular nuclear contours, and finely granular chromatin (Papanicolaou stain, high power with oil magnification).

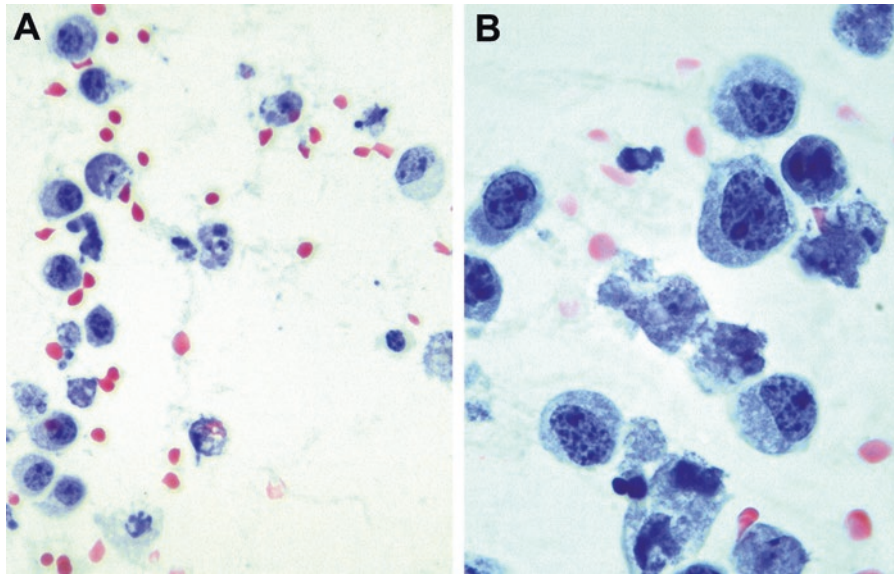

Fig. 9.10 This pleural fluid from an HIV-infected, 8-year-old boy with plasmablastic lymphoma shows pleomorphic, single-lying cells with eccentric nuclei, coarsely clumped chromatin, and moderate amounts of basophilic cytoplasm (**a**. Papanicolaou stain, medium power; **b**. Papanicolaou stain, high power with oil magnification).

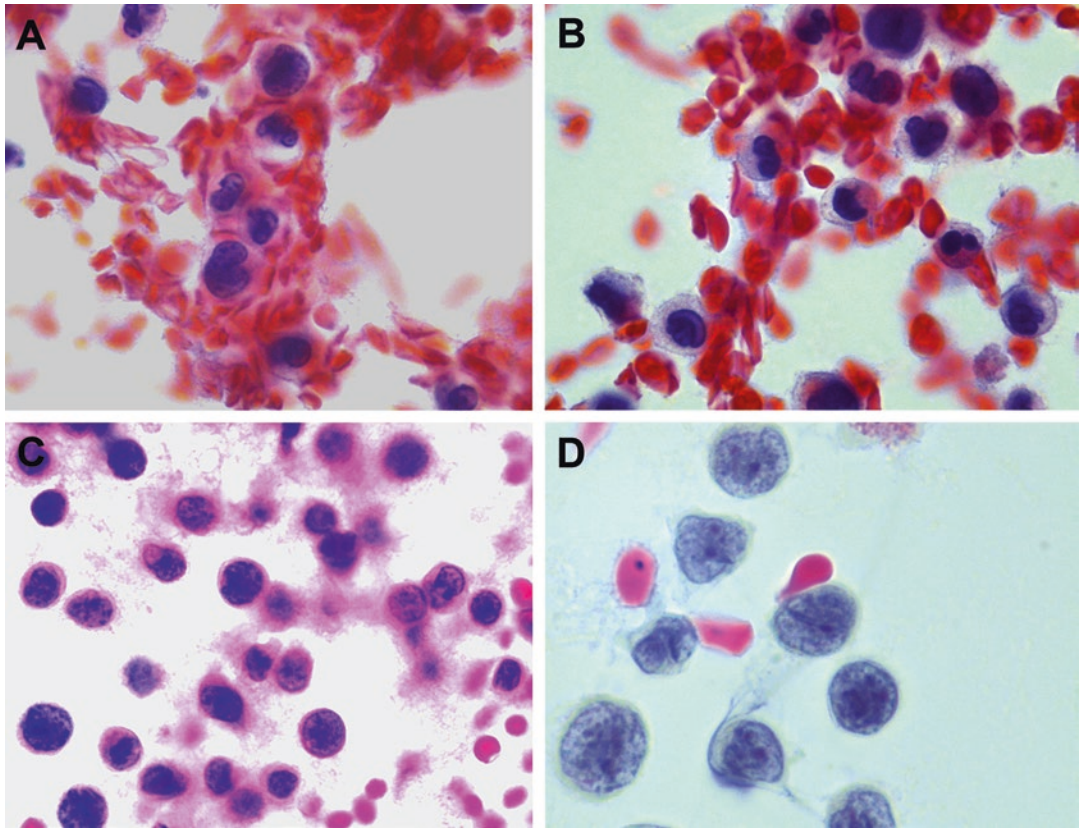

Fig. 9.11 (**a**, **b**) A pleural fluid from an 11-year-old girl with chronic myeloid leukemia showing myeloid precursor cells in a bloodstained background. (**c**, **d**) A pleural fluid from a 4-year-old girl with acute myeloid leukemia (**a**, **b**, **d**. Papanicolaou stain, high power; **c**. H&E stain, high power). Blasts are characterized by very high nuclear-to-cytoplasmic ratios, vesicular chromatin, and prominent nucleoli.

as tuberculous effusion or chylothorax. Although small lymphocytes may predominate, reactive lymphocytosis shows a polymorphous population of lymphoid cells, ranging from small, mature lymphocytes to immunoblasts, whereas malignant lymphoid populations tend to be monomorphic, such as Burkitt and lymphoblastic lymphomas, or highly pleomorphic, such as anaplastic large cell lymphoma or primary effusion lymphoma. Malignant lymphoid cells also tend to have more nuclear contour and chromatin irregularities compared to benign lymphoid cells. However, ancillary tests, including flow cytometry, immunocytochemistry, and molecular studies, may be required to accurately make this distinction in challenging cases. Acute and chronic leukemia has also been described in effusions.

Pearls

Flow cytometry is best performed on the residual, fresh fluid specimen as soon as possible to minimize degeneration. Ideally, the laboratories that receive body cavity fluid specimens should work together to ensure that aliquots of the specimen are sent to the appropriate laboratories for the requested tests, such as cell counts, chemical analysis, morphological assessment, flow cytometry, and/or microbial cultures. When patients are on chemotherapy at the time of fluid collection, marked degenerative changes and/or cytologic atypia may be present.

9.5.2.2 Metastatic Nonlymphoid Small Round Blue Cell Tumors of Childhood

Clinical features

Body cavity fluids are not usually the presenting site of non-hematolymphoid small round cell tumors, and, in addition, these tumors are less common in effusions than hematolymphoid malignancies. The age and gender of the patient may provide helpful clues to the differential diagnosis, as certain small round cell tumors are seen more often in effusions from patients of particular ages and/or genders (e.g., neuroblastoma in children under the age of 4 years, desmoplastic round cell tumors in adolescent and young adult males).

Cytological features

The key features of a nonlymphoid malignant small round cell tumor include more conspicuous cohesion and an absence of lymphoglandular bodies. In nephroblastoma metastatic to serous cavities, it is very unusual for all three cell types to be observed. Occasional rosettes may be seen in metastatic neuroblastoma (Fig. 9.12), while rhabdomyosarcoma may contain small round cells with minimal cytoplasm, binucleated cells, and cells with more abundant orangeophilic cytoplasm, with variable nuclear pleomorphism (Fig. 9.13). A checkerboard appearance of light and dark cells with a tigroid background on air-dried, Diff-Quik-stained material is observed in Ewing sarcoma/PNET, while papillary groups, rosettes, and myxoid material are more common in myxopapillary ependymoma. The immature neuroblastic elements of an immature teratoma also resembles a small round cell tumor (Fig. 9.14). Judicious use of ancillary investigations can help to confirm metastases from a known malignancy or establish an accurate, specific diagnosis in metastases of unknown primary origin.

Triage

Based on cytomorphology alone, it is usually not possible to distinguish the various types of small round cell tumors; however, prior history and/or ancillary studies are helpful for arriving at an accurate diagnosis. Triaging material for immunohistochemical stains is helpful for confirming the type of tumor. Due to the expected or aberrant immunoreactivity of multiple tumors to the same antibody (e.g., CD99), a panel of antibodies is usually employed.

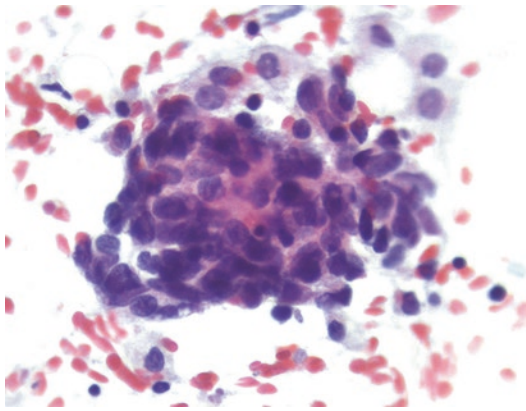

Fig. 9.12 Peritoneal fluid from a 4-year-old girl with neuroblastoma (Papanicolaou stain, high power). An ill-defined rosette with a suggestion of neuropil in the center is noted within this cohesive cluster of small round to oval dark cells with scant cytoplasm.

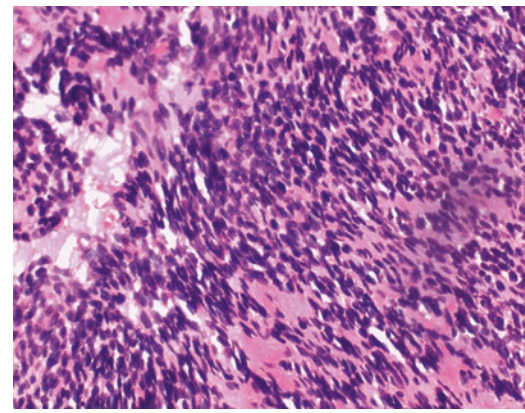

Fig. 9.13 A cell block from the peritoneal fluid in a 7-year-old girl with embryonal rhabdomyosarcoma (H&E, medium power). Spindled nuclei, some with moderate amounts of dense cytoplasm, are noted.

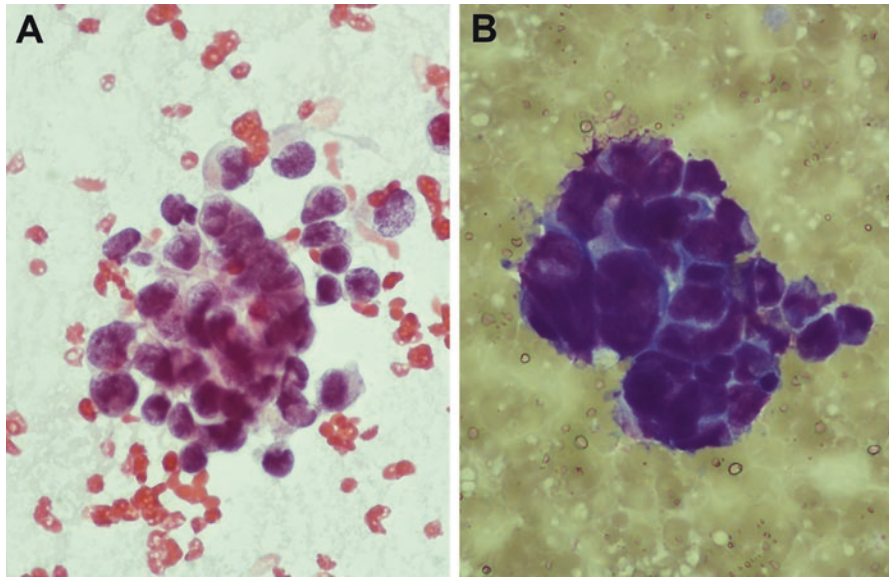

Fig. 9.14 Clusters of poorly differentiated cells with elevated nuclear-to-cytoplasmic ratios are present in this peritoneal fluid from a 19-year-old female with an immature teratoma (**a**. Papanicolaou stain, high power; **b**. Diff-Quik stain, high power).

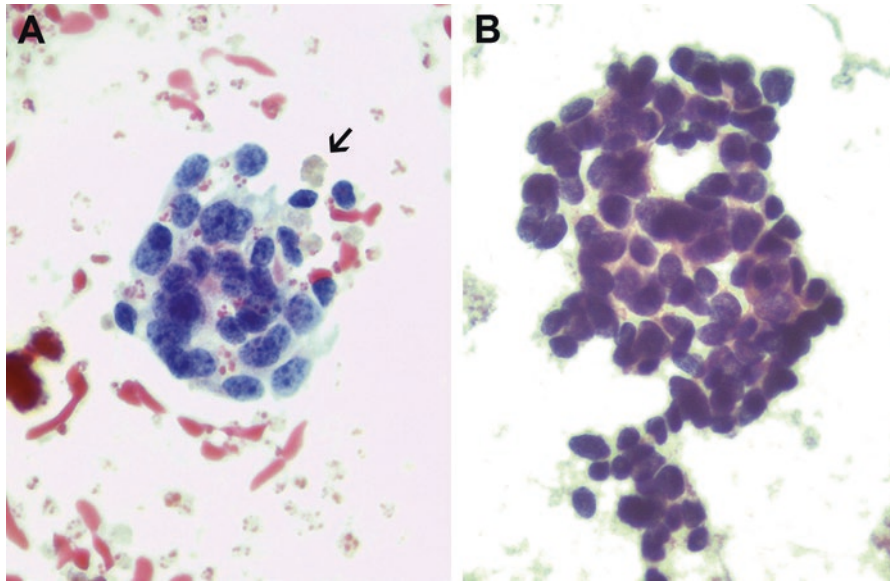

Fig. 9.15 The differential diagnosis of small round cell tumors in serous effusions includes endometriosis (**a**) in the peritoneal washings from a young female, where clusters of epithelial cells are observed in a bloodstained background with hemosiderin (*arrow*) (Papanicolaou stain, high power). In addition, it includes metastatic neuroendocrine carcinomas (**b**), particularly well-to-moderately differentiated neuroendocrine carcinomas of the pancreas, lung, or other origins, whereby there are clusters of cells with increased nuclear-to-cytoplasmic ratios and nuclear molding.

Differential diagnosis

Benign chronic effusions and malignant hematolymphoid tumors are the main differential diagnostic considerations from nonlymphoid small round cell malignancies (Table 9.4). Other entities with cohesive small cells with minimal cyto-

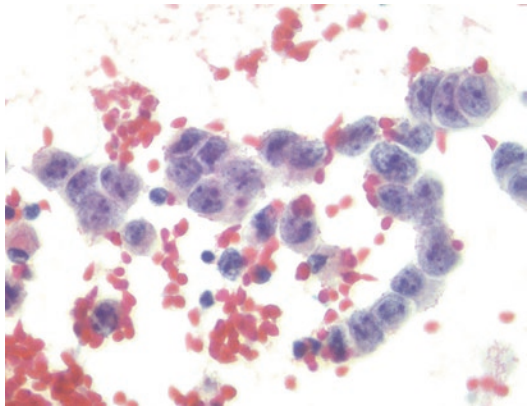

Fig. 9.16 Loosely cohesive cells with moderate amounts of vacuolated cytoplasm, large round nuclei, vesicular chromatin, and prominent nucleoli are observed in this peritoneal fluid from a 15-year-old female with dysgerminoma (Papanicolaou stain, high power).

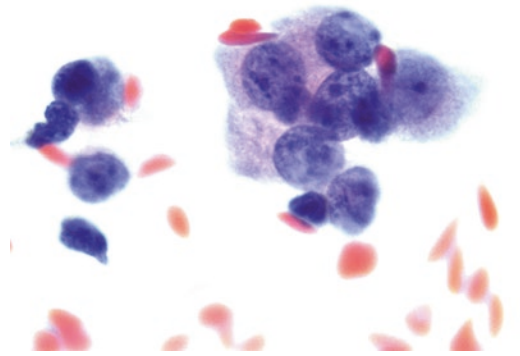

Fig. 9.17 A cluster of cells with moderate amounts of vacuolated cytoplasm, vesicular chromatin, and multiple nucleoli are present in this peritoneal fluid from a 5-year-old boy with a history of metastatic yolk sac tumor involving the liver (Papanicolaou stain, high power).

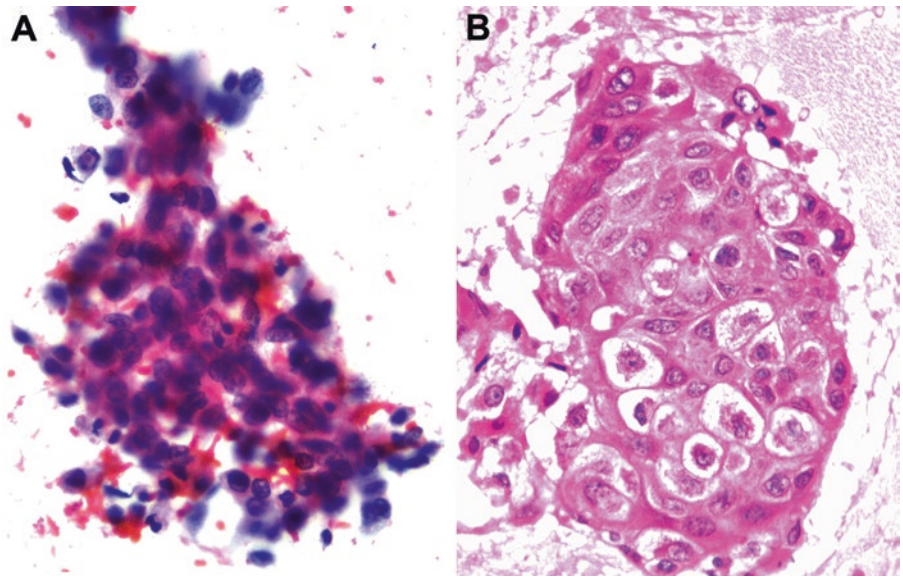

Fig. 9.18 This peritoneal fluid from a 19-year-old male with metastatic hepatocellular carcinoma shows hepatocytes arranged in a crowded trabecular arrangement with moderate amounts of granular cytoplasm and malignant nuclei (**a**). The cell block shows malignant cells with eosinophilic granular cytoplasm within thickened trabeculae lined by some endothelial cells (endothelial wrapping) (**b**) (**a**. Papanicolaou stain, high power; **b**. H&E stain, medium power).

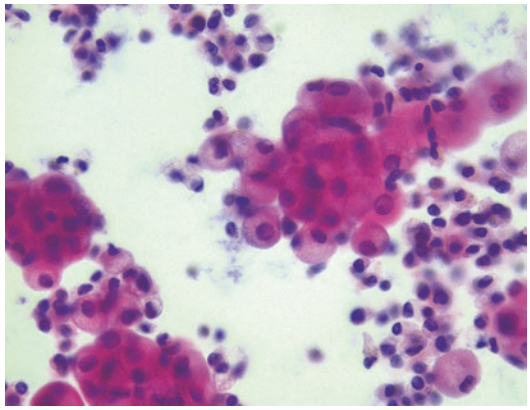

Fig. 9.19 Bland-appearing tumor cells with a low nuclear-to-cytoplasmic ratios and abundant vacuolated cytoplasm are seen in cohesive groups within an inflamed background in this peritoneal fluid from a young woman with renal cell carcinoma (Papanicolaou stain, high power).

plasm, such as endometriosis in young females, and neuroendocrine carcinomas can also mimic small round cell tumors (Fig. 9.15). The differential diagnosis for effusions with epithelioid cells having more abundant cytoplasm is presented in Table 9.5 (Figs. 9.16, 9.17, 9.18, 9.19, 9.20, and 9.21), and that for effusions with a predominance of spindle cell are seen in Table 9.6.

Pearl

Clinical history is helpful in evaluation of these effusions, particularly for determining how to triage residual fluid from limited specimens most appropriately for ancillary studies.

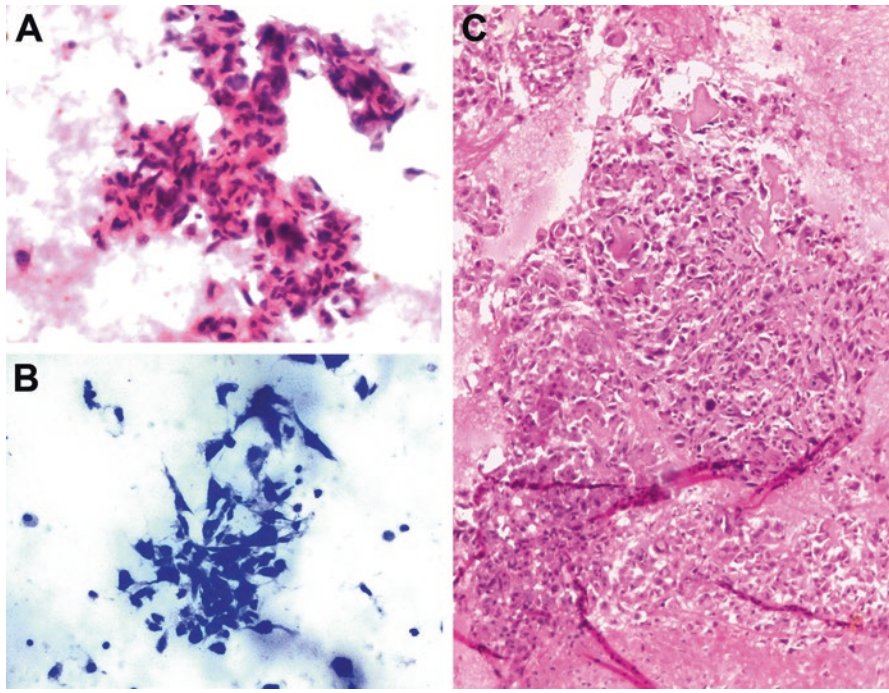

Fig. 9.20 This is a peritoneal fluid from a young girl who had undergone amputation of her left leg 1 year previously for osteosarcoma. The fluid shows loose clusters of spindle cells with moderate amounts of wispy cytoplasm and hyperchromatic nuclei (**a**, **b**). The cell block shows pleomorphic spindled cells with moderate to abundant cytoplasm, giant cells, and osteoid (**c**) (**a**. Papanicolaou stain, high power; **b**. Diff-Quik stain, high power; **c**. H&E stain, medium power).

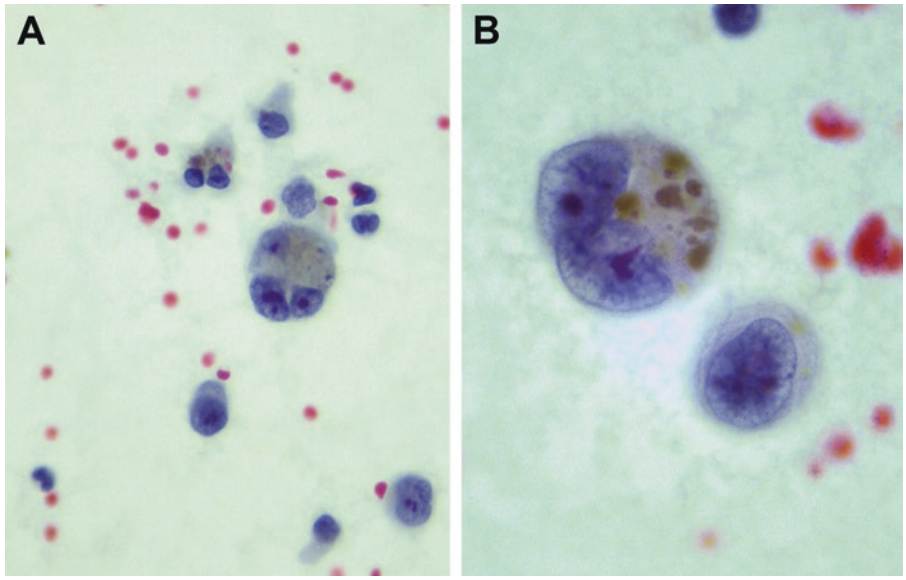

Fig. 9.21 In this pericardial fluid from a 21-year-old female with metastatic malignant melanoma, there are discohesive cells with eccentrically located, pleomorphic nuclei with prominent nucleoli and cytoplasm showing melanin pigment (**a**. Papanicolaou stain, medium power; **b**. Papanicolaou stain, high power).

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