Serous fluid: Reactive conditions

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1. Introduction
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3. Approach to diagnostic cytopathology of serous effusions
4. Diagnostic pitfalls in effusion fluid cytology
5. Immunochemistry of effusion fluids: introduction to SCIP approach
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8. Mesothelioma
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10. Metastatic sarcomas, melanoma, and other non–epithelial neoplasms
11. Serous cavity metastasis: Evaluation of unknown primary
12. Hematolymphoid disorders
13. Flow cytometry, molecular analysis, and other special techniques
14. Appendix I: Collection and processing of effusion fluids for cytopathologic evaluation
15. Appendix II: Immunochemistry of effusions: processing and commonly used immunomarkers

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INTRODUCTION

Effusions of serous cavities (of the pleural space, peritoneal cavity, or pericardial space) are one of the more common manifestations of a systemic disease; however, in some instances they are reflections of regional pathology from altered homeostasis of fluid collection. It should also be noted that effusions are never ‘variations of normal’ but rather the result of an underlying pathologic process that needs to be accurately characterized both for diagnostic and for management purposes.

It is estimated that pleural effusions may affect approximately 1.3 million individuals each year in United States. Whereas most effusions are associated with reactive conditions, it is not infrequent to find malignancies as the underlying cause, which portends a very unfavorable prognosis for patients irrespective of the site. Cytologic evaluation of effusion samples plays a key role in distinguishing reactive conditions from malignancies.[1-3]

PATHOGENESIS IN BRIEF

The principal function of physiologic (submacroscopic) fluid in cavities (pleural, peritoneal, or pericardial spaces) is to provide a frictionless surface between two membranes. Altered homeostasis, including increased production, seepage from an adjacent structure or lack of absorption of accumulated fluid into or from these spaces, leads to abnormal collection of fluid.[1]

The following basic mechanisms may help better define the basic underlying pathogenesis for the accumulation of fluid in the serous cavities:

- Increased permeability of the membranes or capillaries (e.g., neoplastic disease, uremia, pancreatitis, pulmonary embolus)
- Altered pressures in a serous space whether associated with lack of expansion of an adjacent structure (e.g., lung from tumor) or marked increase in pleural surface area (e.g. extensive atelectasis, mesothelioma)
- Decreased lymphatic drainage or rupture of major lymphatic channels (e.g., chylosis, malignancy, trauma).

CLINICAL HISTORY

Predilections by gender

In general, the incidence is equal between both the sexes; however, effusions associated with certain systemic diseases show some sex predilection in parallel with the general distribution of these diseases in the population. For example, it is noted that effusions associated with systemic lupus erythematosus (SLE) are observed more frequently among women, whereas effusions associated with chronic pancreatitis and rheumatoid effusions are more frequently noted in men.

Table 1: Reactive conditions associated with Bloody Effusions.

| Condition | Description |
|-----------|-------------|
| Para pneumonic effusions | Post-traumatic effusions |
| Post-traumatic effusions | Post-cardiothoracic procedures and surgeries |
| | Thoracic cavity vascular damage |
| Pulmonary embolism | Acute aortic dissection |
| Pancreatitis | Endometriosis |
| Asbestos exposure associated pleural effusion | Sarcoidosis |
| Intralobar pulmonary sequestration | Some Infections – e.g. Bacillus anthracis |
Predilections of laterality with pleural effusions

Systemic diseases are often associated with bilateral pleural effusions, whereas isolated unilateral effusions occur more frequently with regional pathology. Isolated right-sided pleural effusions commonly occur with subphrenic or intrahepatic abscess formation, amebic liver abscess, Echinococcus infection, cirrhosis, liver transplantation, and Meigs’ syndrome. Isolated left-sided effusions are more frequently noted with esophageal rupture, pancreatic disease, especially pancreatitis, splenic abscess, splenic infarction, diaphragmatic hernia, pericardial disease, or following coronary artery bypass surgery.

EXAMINATION OF SEROUS FLUID: A SYSTEMATIC APPROACH TO DIAGNOSIS

It is recommended that at least 30–50 mL fluid (up to 1000 mL) should be sent for cytologic analysis. For patients with bilateral pleural effusions, thoracentesis of either side provides similar information.

Gross examination: type of fluid and possible etiology

Fluid appearances have been classified into many categories by various observers. Of these about eight different appearances have been well described with very good interobserver concordance. These eight gross appearances comprise: watery (light yellow), serous (yellow), blood-tinged (reddish), bloody (dark red, similar to blood), purulent (pus), milky (white and less thick than pus), turbid (yellow, but viscous or cloudy), and others (brownish, greenish, black, etc.). In daily practice, effusions can be classified into two major categories: non-bloody and bloody effusions.

Special types of effusions

Bloody effusions

Bloody effusions (hemothorax, hemopericardium, and hemoperitoneum) are considered when the fluid is homogenously red or dark brown, shows hemosiderin pigment, and the hematocrit of the effusion is 10% or greater of the blood hematocrit. Occasional blood-tinged fluids may be noted as a result of trauma associated with a procedure. Recovery of such trauma-associated fluids shows a decreasing gradient of blood (hematocrit) as compared to a true ‘bloody effusion.’

Bloody effusions are more likely to be associated with an underlying malignancy. The most frequent benign causes of bloody pleural effusions include parapneumonic and post-traumatic pleural insults. Table 1 lists some of the more frequent causes for bloody effusions.

| Table 2: Conditions usually associated with Transudates. |
|---------------------------------------------------------|
| Congestive heart failure                                   |
| Cirrhosis                                                |
| Nephrotic syndrome                                        |
| Peritoneal dialysis                                       |
| Hyponatremia (e.g. severe starvation)                     |
| Superior vena cava obstruction                            |

| Table 3: Conditions Associated with Exudates. |
|------------------------------------------------|
| Malignancies                                   |
| Infectious diseases                            |
| Pancreatic diseases (acute or chronic pancreatitis, pseudocyst, pancreatic abscess), |
| Intra abdominal abscess (e.g. subphrenic, intrasplenic, intrahepatic) |
| Esophageal perforation (spontaneous/iatrogenic)   |
| Abdominal surgery                              |
| Collagen vascular diseases/immune-mediated diseases: |
| Rheumatoid arthritis                           |
| Systemic lupus erythematosus                   |
| Sjögren syndrome                               |
| Familial Mediterranean fever                   |
| Uremia                                        |
| Therapy-associated effusions–e.g. nitrofurantoin, dantrolene, methysergide, bromocriptine, amiodarone, procarbazine, methotrexate, ergonovine, ergotamine, oxprenolol, maleate, practolol, minoxidil, bleomycin, interleukin-2, propylthiouracil, isotretinoin, metronidazole, mitomycin |

| Table 4: Conditions demonstrating either exudative or transudative characteristics. |
|---------------------------------------------------------------|
| Pulmonary embolism                                            |
| Hypothyroidism                                                |
| Transudates in patients following diuretic therapy.          |
| Pericardial disease (inflammatory or constrictive)           |
| Atelectasis                                                   |
| Sarcoïdosis                                                   |
| Amyloidosis                                                   |

Chylos effusion

Chylothorax is the accumulation of lymphatic fluid (chyle) in the pleural space due to disruption of the thoracic duct or...
another major lymphatic vessel. It more commonly occurs in the pleural space rather than peritoneal or pericardial cavities. In post-traumatic cases, the fluid accumulates rapidly following injury (usually within 2–10 days), whereas those cases with gradual onset of the effusion often have a different pathologic cause, including malignancies, more specifically lymphoma. Chylous effusions should be distinguished from pseudochylous effusions since they suggest a different pathogenesis and could be observed in a myriad of other conditions, including infections such as tuberculosis.

**Causes**

Some of the more common causes of chylous effusions are trauma to the lymphatic vessels, occurring either from a surgical intervention (e.g., transplants, cardiac surgeries, thoracostomy tubes), thrombosis in a subclavian indwelling catheter or following non-surgical causes (e.g., 'boxer’s chest,' penetrating gunshots, stab wounds, blast and crush injuries). On many occasions, conditions associated with chylothorax are idiopathic. This, in fact, is one of the most common presentations associated with pleural effusion in the newborn. In adults, constrictive pericarditis, cirrhosis, and lymphangiomyomatosis have been reported to be associated with chylous effusions. They are also frequently noted with malignancies.

**TRANSUDATE VS EXUDATE**

Distinguishing whether a fluid is a transudate or an exudate is often the initial step in the analysis of effusions and may help define the basic underlying etiopathogenesis of the effusion [Tables 2-4]. A transudate is an ultrafiltrate of plasma associated with intact vasculature, and usually results from increased hydrostatic pressure and decreased oncotic pressure. In contradistinction, exudative fluids are generally a result of disruption of capillaries or actively altered capillary permeability. Thus, an exudative fluid more frequently parallels the plasma content. While there are many causes for exudative fluid as enumerated below, exudates are more frequently noted with malignancies and infectious/inflammatory processes [Table 3].

**Figure 1:** Many apoptotic neutrophils are noted in the pleural effusion sample from a patient with empyema associated with bacterial infection. (Papanicolaou stain, 20×.)

**Figure 2:** In the same patient as Figure 1, the second day pleural effusion sample demonstrated many neutrophils with coccii within the cytoplasm (arrow) better highlighted in Diff-Quik stained preparation. In such patients, bacterial cultures would help to further speciate the bacteria. (Diff-Quik stain, 20×.)

**Figure 3:** Pleural effusion sample from the same patient also demonstrated macrophages (arrow) with intracellular coccii. (Diff-Quik stain, 40×.)
While most described criteria provide a working guideline, it is not always possible to characterize a fluid into an exudate or a transudate. In a patient with a transudative effusion, therapy with diuretics may lead to reduction in water content and may result in altered protein concentration. Further characterizing a fluid into one of the two types (transudate or exudate) provides only a general guideline for the possible underlying etiology.

**BIOCHEMICAL ANALYSIS**

The following tests may aid in arriving at etiologic possibilities.

**Glucose estimation**

Low glucose content in effusion samples is observed more frequently in patients with tuberculosis and rheumatoid arthritis-associated effusion.

**Amylase levels**

High amylase content is noted more frequently as a result of chronic pancreatitis or its sequelae.
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**BIOCHEMICAL ANALYSIS**

 Cultures should be performed in addition to morphologic assessment, combined with special stains for highlighting organisms to characterize infectious organisms in a suspected case or when derived from an immunocompromised host.[12]

**Morphology and histochemical stains**

 Bacteria [Figures 1-3], parasites (e.g., microfilariae), and fungal forms could be visualized by morphologic examination and may be further highlighted using appropriately selected silver stains, periodic acid–Schiff (PAS) stain, or other special stains (e.g., Ziehl–Neelsen stain). As a routine stain, the organisms are highlighted better in Diff-Quik stained preparations [Figure 2 (arrow)].

**Cultures**

 Use of appropriate culture media may help detect bacterial as well as fungal organisms and may further help to speciate the organism and its sensitivity to antimicrobial agents.

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**Figure 8:** Peritoneal fluid sample from a patient with cirrhosis demonstrates occasional mitosis (arrow). (Papanicolaou stain, 20×.)

**Figure 9:** Pleural effusion from a patient with pulmonary infarction shows macrophages, and some also demonstrate hemosiderin pigment (arrows) in the cytoplasm. (Diff-Quik stain, 40×.)

**Figure 10:** Pleural effusion sample from a patient with pulmonary infarction demonstrates areas with increased eosinophils. This example shows characteristic eosinophilic cytoplasmic granules and bilobed nuclei (arrows). (Diff-Quik stain, 20×.)

**Figure 11:** LE bodies (arrow) are noted in a neutrophil in this pleural effusion sample obtained from a patient with a history of systemic lupus erythematosus. (Diff-Quik stain, 40×.)
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Figure 12: LE bodies are seen in both neutrophils (1) as well as a macrophage (2) in pericardial effusion in a patient with a history of systemic lupus erythematosus. (Papanicolaou stain, 40×)

IMMUNOLOGIC TESTS

Immunophenotyping (immunohistochemistry or flow cytometry)

Demonstration of a polyclonal population of atypical lymphocytes noted in effusion samples may further help to confirm the reactive nature of lymphocytes.

Immunohistochemistry

A panel of immunohistochemical stains rather than one single immunostain performed on atypical cells in an effusion sample may be of additional help to distinguish reactive mesothelial cells from metastatic epithelial malignancies. Importance of these stains and their applications with the ‘subtractive coordinate immunoreactivity pattern’ (SCIP) approach is discussed in other reviews.[13,14] This is one of the more frequently utilized ancillary studies in serous fluid cytology practice.[10,15-18] Similar studies for microorganisms are also frequently used.

CYTOLOGY

Discussion related to the morphologic details of cells that can be seen in effusion samples is discussed in other reviews.[2,19-21]

REACTIVE CONDITIONS THAT HAVE CHARACTERISTIC FEATURES OF OR COULD MIMIC CARCINOMA

Liver cirrhosis with activity, uremia, and acute pancreatitis

Serous cavity effusions can develop in these conditions and deserve special recognition. In these conditions, reactive mesothelial cells could be present singly, in groups [Figure 4], may form pseudopapillary structures [Figure 5], or may form small gland-like formations. These cells could show extreme degrees of reactive atypia including multinucleation [Figure 6], enlarged nuclei, nuclear membrane irregularities, nuclear hyperchromasia, prominent nucleoli [Figure 7], and mitoses [Figure 8].

- As a general rule, therefore, a diagnosis of malignancy should be made with extreme caution in patients who have a history of effusions noted in association with the abovementioned etiologies.

In these effusions all atypical cells will show similar features and will resemble mesothelial cells. Thus a ‘morphologic continuum’ and not two distinct cell populations is noted in these conditions. Immunophenotyping may further help in distinguishing reactive mesothelial cells from metastatic adenocarcinoma by the SCIP approach.[13,14]

Pulmonary Embolism and Infarction

Effusions associated with pulmonary infarction may show reactive mesothelial cells that may require them to be distinguished from adenocarcinoma. These effusions may also show increased hemosiderin-laden macrophages [Figure 9], neutrophils, and eosinophils [Figure 10].

Systemic Lupus Erythematosus[22-24]

Effusions associated with SLE are noted most frequently in the pleural cavity. Although less frequent, SLE-associated effusions may be noted in pericardial cavities. Effusions associated with SLE show characteristics of an exudate. On cytology, these effusions show predominance of inflammatory cells (neutrophils,
Rarely eosinophils or lymphocytes. One of the most characteristic features is the presence of LE cells. LE cells are inflammatory cells (usually a neutrophil but could be a macrophage) which contain a homogenous hematoxylin body [Figures 11, 12]. The number of LE cells noted in effusion samples can vary. Although the presence of LE cells is a characteristic feature of SLE, it is not pathognomonic of this condition. Other conditions, including drug-associated change, may also show similar features. It should also be recognized that LE cells may not be present consistently in SLE-associated effusions.

**Rheumatoid Effusions**[22-31]

Pleural effusion is a relatively uncommon but known complication of rheumatoid arthritis. It may be concurrent, or occur prior to, or after the development of joint manifestations of the disease. Rheumatoid effusions are exudative fluids and, as noted earlier, are more frequently noted in males with rheumatoid arthritis in comparison to females. These fluids have reduced glucose levels. On cytology, these effusions show many degenerated cells, necrotic debris, atypical spindled cells resembling spindled squamous cells, histiocytes, and round multinucleated giant cells [Figure 13] in addition to many lymphoplasmacytic cells. It has been suggested that the presence of necrosis in an effusion specimen is almost characteristic of a rheumatoid nodule. Spindled cells may show varying degrees of degeneration and are frequently pyknotic. Spindled cells in these effusions may raise the differential diagnosis of squamous cell carcinoma.

Such characteristic features may not always be seen in these effusions. These effusions may only show increased neutrophils, lymphocytes, and mononuclear cells. Mesothelial cells may either be absent or rare.

Other less-common causes of reactive effusions include fistulous-tract-associated effusions, endometriosis, asbestosexposure-associated effusions, and talc-associated effusions. Correlation with history and corroborative cytologic features are helpful to arrive at a correct interpretation.

### Table 5: Distinction between chylous and pseudochylous effusions.

| Characteristic                  | Chylous Effusion | Pseudochylous Effusion |
|--------------------------------|------------------|------------------------|
| Effusion Following Centrifugation | Turbid          | Turbid                 |
| Addition of 2ml . ethyl ether   | Clear fluid     | Turbid Fluid           |
| Triglyceride level              | >100 mg/dl      | Yes                    |
| 50-110 mg/dl                   | Presence of chylomicrons | Absence of Chylomicrons |
| <50 mg/dl                      | No               | Possible               |
| Effusion : Serum triglyceride   | >1.0             | <1.0                   |
| Effusion : Serum Cholesterol    | <1.0             | >1.0                   |

### STUDY CASES

#### Case 1

**History**

A 72-year-old male with a 30 pack-years cigarette smoking history presented with long-standing fever, weight loss, and non-productive cough. This week he noted blood in his sputum and feels he cannot climb two flights of stairs without developing shortness of breath. Imaging studies demonstrated a possible mass in the upper lobe of the right

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**Figure 14:** Many mature lymphocytes are noted in this patient with pleural effusion. (Diff-Quik stain, 40µ.)

**Figure 15:** Many mature lymphocytes were noted, with marked membrane irregularity, in this pleural effusion sample. (Papanicolaou stain, 20×.)
lung, mediastinal adenopathy, as well as a pleural effusion. The pleural effusion was tapped and sent for examination.

**Gross examination**

A white (milky) odorless fluid (300 mL) was collected. The fluid was turbid and white, even after centrifugation. The effusion triglyceride level was 40 mg/dL.

**Biochemical studies**

The fluid had a high protein content, with increased effusion: serum lactate dehydrogenase ratio (>0.6).

**Cytology**

Evaluation of samples demonstrated many mature lymphocytes [Figure 14]. Many lymphocytes also demonstrated marked nuclear membrane irregularity [Figure 15]. Extensive review demonstrated only rare reactive mesothelial cells.

**Discussion**

The history suggests the need for additional studies to begin accurate management. Chief complaints and review of imaging studies suggest that the patient could have a malignancy (especially bronchogenic carcinoma) or an infectious condition (e.g., tuberculosis).

**Gross and biochemical examination [Table 5]**

Recovery of a milky and turbid fluid, even after centrifugation, is highly suggestive of pseudochoylous fluids.

**Cytology**

Cytology reveals predominantly small mature lymphocytes [see Figures 14, 15]. Conditions associated with predominant lymphocytes include congestive heart failure, spontaneous bacterial peritonitis, tuberculosis, cirrhosis, nephritic syndrome, sarcoidosis, and SLE.

In addition to lymphocytes, only rare mesothelial cells are noted. Lack of mesothelial cells in effusion samples with predominant lymphocytes is characteristically noted in
patients with tuberculosis. Cytology samples also shows cells with marked nuclear membrane irregularity. Such cells are most frequently an artifact result of centrifugation. Occasional activated lymphocytes and plasma cells may also be noted. In such a scenario, a possibility of chronic lymphocytic leukemia [Figure 16], primary effusion lymphoma, or a T-cell lymphoproliferative process should be excluded before considering a chronic inflammatory condition as a possibility. Ancillary studies such as immunophenotyping of lymphocytes either using flow cytometry or immunohistochemical studies on cell lock preparations could be useful.

### Table 6: Differentiating an Transudate from an Exudate.

| Characteristic                  | Transudate | Exudate |
|--------------------------------|------------|---------|
| Gross Appearance               | Clear      | Turbid  |
| Clotting capability            | Does not clot | May clot |
| Specific Gravity               | Usually 1 or less | >1.0 |
| Lactate dehydrogenase(LDH)     | <200u/l    | >200u/l |
| Effusion : Serum LDH ratio     | <0.6       | >0.6    |
| Effusion/:Serum Protein ratio  | <0.5       | >0.5    |
| Cellularity                    | Usually low | Usually high |

### Diagnosis

Negative for malignancy; chronic inflammatory cells are noted. A tuberculosis-associated pleural effusion is favored. Additional confirmatory studies are recommended.

### Follow-up

The patient had a positive tuberculin test. Transbronchial biopsy was positive for caseating granuloma that demonstrated acid-fast bacilli. Additional studies on an effusion sample revealed adenosine deaminase levels of 50 IU/L. Flow cytometry demonstrated lack of a monoclonal cell population, with increased T lymphocytes.

### Tuberculosis

This is one of the more common causes of effusion in countries where tuberculosis is endemic. The diagnosis of tuberculosis should be strongly suspected when a pleural fluid adenosine deaminase level is above 45 IU/L or a g-interferon level is above 3.7 U/mL. In the early stages of the disease, there may be predominantly neutrophils, which in later stages are replaced with mature small lymphocytes. Increased neutrophils with empyema are also noted with miliary tuberculosis. In later stages, patients with tuberculous effusion characteristically demonstrate absence of mesothelial cells, even upon repeated thoracocentesis.

- Some investigators have therefore suggested that in a suspected patient mesothelial count of greater than 5% in the effusion sample virtually eliminates the possibility of tuberculosis.

### Case 2

#### Clinical history

A 53-year-old male with a history of status post right upper lobe lung resection with adjuvant therapy for non-small-cell lung resection with carcinoma 3 years ago, presented with a pericardial effusion.
Table 7: Features that differentiate reactive mesothelial cells from adenocarcinoma.

| Cytologic Features         | Mesothelial Cells                                                                 | Adenocarcinoma                                                                 |
|----------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Cell Types                 | Single cell population (spectrum of mesothelial cells)                              | Dual cell population (mesothelial cells and epithelial cells)                |
| Borders of cell groups     | Hobnail appearance                                                                 | Smooth, community borders                                                   |
| Intercellular windows      | Present                                                                           | Absent                                                                       |
| Cell-in-cell pattern       | Present                                                                           | Rare                                                                         |
| Vakuolated cells           | Absence of mucin in cells                                                          | ‘Mucin droplet’ present                                                     |
| (signet ring appearance)   | Nuclear borders are intact                                                         | Vacuole distorts cell nucleus                                                |
| Cytoplasm                  | Ecto- and endoplasm could be identified                                             | Usually homogenous                                                           |
| Cytoplasmic blebs          | Present                                                                           | Absent                                                                       |
| Immunohistochemistry       | Mesothelial markers +ve                                                            | Epithelial markers +ve                                                       |
| Microvilli (electron microscopy appearance) | Long and slender                                                                   | Short and stubby                                                            |

Gross Examination

- Bloody: Most likely Malignant, Inflammatory
- Non-Bloody Effusions: Most likely Non-neoplastic
- Exudate: Most likely Malignant, Trauma
- Transudate: Most likely Reactive, Malignant, Inflammatory

Additional studies
- Cytology with ancillary studies, e.g. stains for infections, immunohistochemistry, or immunophenotyping
- Specific biochemical estimations
- Microbiologic cultures

Figure 21: Systemic algorithmic approach to diagnosis.

Gross appearance and biochemical estimations

A turbid blood-tinged fluid was recovered that demonstrated increased protein content. Lactate dehydrogenase levels were >200 U/L in the effusion sample.

Cytology

The effusion sample demonstrated increased cellularity at lower magnification. This cellularity was a result of many neutrophils [Figure 17], clearly identifiable mesothelial cells, and atypical cell groups. The latter group of cells demonstrated either hobnailing or cells with community borders [Figure 18]. Individual cells demonstrated centrally placed nuclei with conspicuous nucleoli and moderate granular cytoplasm with endoand ectocytoplasm [Figure 19]. In addition, few multinucleated cells [Figure 20] and cells with nuclear hyperchromasia were also identified.

A diagnosis of atypical cells with possibility of metastatic adenocarcinoma was raised.

Immunophenotype

Immunohistochemical stains performed on the cell block were positive for calretinin and were negative for carcinoembryonic antigen, BerEP4, Leu-M1, cytokeratin 7 and 20, and thyroid transcription factor-1, and supported lack of a second population and confirmed the mesothelial nature of these atypical cells.

Diagnosis

Reactive mesothelial cells: favor therapy-associated changes.

Discussion

A new pericardial effusion in a patient with history of resected non-small-cell carcinoma of lung raises a possibility of metastatic carcinoma.

Evaluation of gross and biochemical estimations suggests this to be an exudate rather than a transudate [Table 6]. An exudate is usually associated with either malignancy or inflammatory/infectious etiology. In this context, this feature does not help distinguish the two.

Cytology also reveals a dual cell population with increased neutrophils. In addition, many of the cell groups reveal groups with hobnail appearance as well as occasional groups with community borders. Most of the cells show features associated with mesothelial cells. Table 7 summarizes some of the salient features that distinguish reactive mesothelial cells from metastatic cells. An immunohistochemical
staining pattern supports the mesothelial nature of these cells.

**Features associated with chemotherapy or radiation therapy-induced reactive mesothelial cells**

With cancer chemotherapy and radiation, there may not be a large effusion but when the effusion samples are evaluated they may present a significant diagnostic challenge for the pathologist. These samples are often cellular, hemorrhagic, and show increased protein concentration. The cellular composition may include highly reactive mesothelial cells with degenerative changes, occasional ‘community’ borders, and cytoplasmic vacuolation. In addition, histiocytes and bizarre cells may also be noted. A clear two-cell population, a cytologic clue to malignancy, is not identified in these samples. In addition, the cells may show features of a radiation therapy effect, including cytomegaly, multinucleation, smudging of chromatin, cytoplasmic vacuolation, and two-toned staining of cytoplasm.

**SUMMARY**

In summary, this review highlights that a systematic algorithmic approach [Figure 21] would facilitate appropriate processing of effusion samples for improved diagnostic accuracy. The reporting for cytopathology of serous fluids is comparable to that with other cytopathology specimens.

**ABBREVIATIONS** (In alphabetic order)

- **LE** = Lupus erythematosus
- **PAS** = Periodic Acid-Schiff
- **SCIP** = Subtractive Coordinate Immunoreactivity Pattern
- **SLE** = Systemic lupus erythematosus

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