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ORIGINAL ARTICLE

Comparison of biochemical, cellular and microbiological parameters of biological fluids with and without the presence of atypical cells

Comparação de parâmetros bioquímicos, citológicos e microbiológicos de fluidos biológicos com e sem presença de células atípicas

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ABSTRACT

Introduction: Biological/cavity fluids are liquids produced in different compartments of the body and have different functions. The definition of malignant cavity effusions is not simple and is very important to medical diagnosis and management. In this sense, this study sought to identify differential alterations on cavity fluids. **Objectives:** Comparing the biochemical, cellular and microbiological profiles of routine exams in biological fluids with presence of atypical/neoplastic cells (PAC) and without the presence of atypical/neoplastic cells (WPAC) and we show some morphology features of abnormal cells found during cytological analysis of different biological fluids. **Methods:** The data were obtained from online medical records of patients treated at a university hospital in Brazil. Physical aspects, cell counts, neoplastic cell research, biochemical analysis and Gram stain were evaluated in biological fluids. **Results:** It was evaluated a total of 170 specimens, 20 PAC and 150 WPAC being 43 WPAC and 5 PAC samples of peritoneal fluid, 47 WPAC and 8 PAC samples of CSF, 52 WPAC and 5 PAC samples of pleural fluid, 2 WPAC and 2 PAC samples of pericardial fluid and 6 WPAC of synovial fluid. Among the patients with PAC, 60.0% (12/20) had death as clinical outcome. All PAC samples showed a higher number of total leukocytes compared to WPAC. The peritoneal fluid PAC samples showed higher rate of macrophages and mesothelial cells than WPAC, while the cerebrospinal fluid PAC samples showed higher rate of lymphocyte and macrophage than WPAC. The PAC and WPAC samples showed differences in several biochemical dosages. **Conclusion:** The biochemical and cellular differences found between PAC and WPAC body fluids may help the diagnosis of presence of atypical/neoplastic cells.

Keywords: Neoplastic cells; Peritoneal fluid; Pleural fluid; Pericardial fluid; Cerebrospinal fluid.

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RESUMO

Introdução: Os fluidos biológicos/cavitários são líquidos produzidos em diferentes compartimentos do corpo e possuem diferentes funções. A definição de derrames cavitários malignos não é simples e é muito importante para o diagnóstico e manejo médico. Nesse sentido, este estudo buscou identificar alterações diferenciais nos fluidos cavitários. **Objetivos:** Comparar os perfis bioquímico, citológico e microbiológico de exames de rotina em fluidos biológicos com presença de células atípicas/neoplásicas (PAC) e sem presença de células atípicas/neoplásicas (WPAC). **Métodos:** Os dados foram obtidos de prontuários on-line de pacientes atendidos em hospital universitário do Brasil. Aspectos físicos, contagem celular, pesquisa de células neoplásicas, análise bioquímica e coloração de Gram foram avaliados nos fluidos biológicos. **Resultados:** Um total de 170 espécimes foram obtidos, sendo 20 PAC e 150 WPAC. Desses, 43 amostras WPAC e 5 PAC de líquido peritoneal, 47 amostras WPAC e 8 PAC de LCR, 52 amostras WPAC e 5 PAC de líquido pleural, 2 amostras WPAC e 2 PAC de líquido pericárdico e 6 amostras WPAC de líquido sinovial. Dentre os pacientes com PAC, 60,0% (12/20) tiveram óbito como desfecho clínico. Todas as amostras de PAC apresentaram maior número de leucócitos totais em comparação com WPAC. Amostras PAC do líquido cefalorraquidiano apresentaram maior taxa de macrófagos e células mesoteliais do que as WPAC, enquanto amostras PAC do líquido cefalorraquidiano apresentaram maior taxa de linfócitos e macrófagos do que as WPAC. As amostras de PAC e WPAC apresentaram diferenças em diversas dosagens bioquímicas. **Conclusão:** As diferenças bioquímicas e celulares encontradas entre os fluidos corporais PAC e WPAC podem auxiliar no diagnóstico da presença de células atípicas/neoplásicas.

Palavras-chave: Células neoplásicas; Líquido peritoneal; Líquido pleural; Líquido pericárdico; Líquido cefalorraquidiano.

Introduction

The routine of a clinical analysis unit from a hospital is complex and intense. Several biological materials are sent daily for analysis and medical request for biological fluids examination are usually urgent; thus, it must be performed as soon as possible[1]. In general, the studies of these body fluids are used to evaluate inflammatory, malignant, infectious and hemorrhagic processes[1-3].

Biological fluids are liquids delimited by an epithelium or mesothelium. Among them, the cerebrospinal fluid (CSF), synovial fluid, lymph, aqueous humor, peritoneal fluid (PEF), pleural fluid, pericardial fluid and others can be cited[4]. In the case of pleural, pericardial and peritoneal fluids, they are also classified as cavitary liquids because they are enclosed inside body cavities[1,2]. These fluids facilitate organ movement and confer mechanical protection to them[5], as well as help the organism to eliminate metabolites and provide nutrients to different parts of the body[1,2,6].

Biological fluids production relies on three main factors: hydrostatic pressure, exerted by the physical presence of blood in the vessel lumen; oncotic pressure, generated by the plasma proteins; and lastly, capillary permeability[1,7]. If there is any imbalance between these forces, liquids can accumulate in the cavities, resulting in a process known as cavitary effusion[8-10].

Cavity effusions are pathological and are clinically classified as transudate or exudate[6,7]. Transudates are non-inflammatory effusions originated by the imbalance of hydrostatic and oncotic pressures, while exudates occur due to pathological conditions such as neoplasms, and infectious and inflammatory diseases, which damage mesothelial cells, increase vascular permeability, protein efflux and cellularity[4,6,8].

The occurrence of exudates is multifactorial and often secondary to benign or malignant neoplasms[11]. The most common benign effusions are caused by congestive heart failure, pneumonia, tuberculosis, pulmonary embolism, liver cirrhosis, nephrotic syndrome, kidney failure, pericarditis and pancreatic diseases[12,13]. On the other hand, metastatic solid tumors, such as breast cancer, lung, ovary, gastric system cancers and hematological neoplasms, such as lymphomas, are foremost the major causes of malignant effusions[7,9,14-16].

Malignant effusions are defined based on the presence of neoplastic cells in the cavity[2,7,15] and are frequently related to the terminal stage of several malignant diseases, since many patients rarely have a good prognosis in this scenario[17,18]. Due to its predictive value, the detection of neoplastic cells is very important, although difficult, because of the range of abnormalities on cell morphology. This is the reason cytological analysis must be associated with physical, biochemical and microbiological analyses, in order to establish a differential diagnosis or direct a therapeutic approach[4,17,19].

Kolte et al. (2022)[20] applied the International System for Reporting Serous Fluid Cytopathology (ISRSFC) to assess the risk of malignancy (ROM) in serous fluids obtained from a tertiary care hospital. They found that the ROM in suspicious for malignancy (SFM) and malignant-classified pleural effusions was 80.6% and 90%, respectively. The ROM in peritoneal fluids was 91.7% and 100%, respectively. In pericardial fluids the ROM was 100% for malignant-classified effusions. These results emphasize the role of cytological analysis to diagnose malignant conditions through serous effusions[20]. Although some categories such as "atypia of uncertain significance" and SFM classified effusions don't have well-established criteria, they may be important due their predictive value and must be used cautiously[20].

Furthermore, the medical literature is relatively limited in terms of biological fluids alterations directly related to the presence of neoplastic cells[4,6,8]. There are many studies around the world that have been assessing tumor markers in biological fluids, however, these require expensive laboratory techniques that are unfeasible for the Brazilian National Health System (SUS)[21].

Therefore, this study aims to compare the biochemical, cellular and microbiological profiles of routine exams in biological fluids with the presence of atypical/neoplastic cells (PAC) and without the presence of atypical/neoplastic cells (WPAC). In addition, we show some of the morphology features of abnormal cells found during the cytological analysis of different biological fluids. The results may contribute to a better understanding of how tumors affect the aspects of biological fluids and how these data correlate to each other.

Methods

This is a descriptive, longitudinal and retrospective study with a quantitative and qualitative approach. The data collection proceeded from records of biological fluids exams, from 2020 to 2022, stored on the Esmeralda System (laboratory information system) and Management Application for University Hospitals (AGHU), both used by the Clinical Analysis and Pathological Anatomy Unit of the Clinical Hospital of the Federal University of Triângulo Mineiro (UACAP HC-UFTM).

In UACAP HC-UFTM, the routine for biological fluids includes physical/macroscopical analysis, microscopical analysis and biochemical analysis (Abbott, model Architect). A cytocentrifuge (Cytopro, model 7620) to concentrate the fluids, which were stained with Giemsa and Gram techniques, was also used. The Giemsa-stained slide was used for cytological analysis (differential cell count and neoplastic cell research) and the Gram-stained one for microbiological examination. In the present study, photographs of the slides were captured in an optical microscope (Olympus, model BX41).

The parameters evaluated in cerebrospinal fluid (CSF) samples were volume, color, aspect, red blood cell count, total nucleated cell count (leukocytes), differential nucleated cell count, neoplastic cell research, dosage of glucose, total proteins, chloride and Gram stain. For the other biological fluids, all the previous parameters were evaluated plus pH, lactic dehydrogenase and amylase.

The comparison groups were samples with the presence of atypical/neoplastic cells (PAC) and samples without the presence of atypical/neoplastic cells (WPAC) from cerebrospinal, peritoneal, pericardial, pleural and synovial fluids. The total number of samples was 170.

Different criteria have been used to simplify the definition of exudate and transudate, the vast majority of them carried out in studies with Pleural Effusions[22,23], whereas the use of criteria defined for pleural effusions should be considered with caution for other biological fluids[24,25]. The criteria used to differentiate a biological fluid as an exudate were a global cell count greater than 1000 cells/uL and lactic dehydrogenase (LDH) dosage greater than 200 U/L[12,13].

Statistical analyses were performed using Bioestat v.5.0 available at https://www.mamiraua.org.br/pt-br, MS Excel (Microsoft Corporation) and GraphPad PRISM v. 6.0 available at https://www.graphpad.com. The normality of the data was evaluated using the D'Agostino Pearson test. The homogeneity of variances among groups was tested by Bartlett's test when the data presented normal distribution. The quantitative variables were evaluated by the Mann-Whitney test to compare two groups applying the Dunn's post-test if necessary. To compare categorical variables, the Fisher's exact test or chi-square test were used. *P*-values less than 5% ($p<0.05$) were considered statistically significant.

Ethics

This study was approved by the Committee for Ethics and Research on Human Beings (CEP) of HC-UFTM under protocol number 5.724.202 and follows the criteria of the Brazilian National Health Council Resolution (CNS) 466/12.

Results

In a total of 170 samples, 20 presented atypical/neoplastic cells (PAC) and 150 did not present atypical/neoplastic cells (WPAC). Table 1 depicts the cellular alterations observed on PAC samples. Table 2 shows the descriptive statistics of numerical variables. 43 WPAC and 5 PAC samples of peritoneal fluid, 47 WPAC and 8 PAC samples of CSF; 52 WPAC and 5 PAC samples of pleural fluid, 2 WPAC and 2 PAC samples of pericardial fluid and 6 WPAC of synovial fluid were obtained.

Most of the patients (60%, 12/20) with PAC samples evolved to death (Table 1). All PAC fluids (except pericardial fluid) showed a higher number of nucleated cells/leukocytes (Tables 2.1, 2.2 and 2.3). The mean values of peritoneal fluids were WPAC 411.6 cells/mm3 (± 664.8) versus PAC 4809 cells/mm3 (± 6587) (p=0.001)(Table 2.1), CSF WPAC 22.2 cells/mm3 (± 61.5) versus PAC 309.2 cells/mm3 (± 292.9) (p=0.001)(Table 2.2), pleural fluid WPAC 616.8 cells/mm3 (± 657.9) versus PAC 1832 cells/mm3 (± 922.8) (p=0.015) (Table 2.3) and the total sum of 170 samples, with the mean of WPAC 377.8 cells/mm3 (± 611.8) versus PAC 1768 cells/mm3 (± 3422) (p=0.014).

The cytological analysis (Table 2.1) showed WPAC 31.3% (± 19.4) × PAC 13% (± 8.1) (p=0.003) for number of macrophages in peritoneal fluid and WPAC 7.1% (± 10.9) × PAC 29.8% (± 38.5) for CSF macrophages (p=0.020) (Table 2.2). In addition, the mesothelial cell count in peritoneal fluid showed to be significantly higher on PAC 15% (± 18) × WPAC 4.1% (± 5.1) (p=0.006) (Table 2.1), while the number of lymphocytes in CSF was significantly higher on WPAC 80.5% (± 27.4) × PAC 57.2% (± 38.5) (p=0.042) (Table 2.2).

The biochemical analysis (Table 2.1) revealed that the PAC group had a lower glucose level (54.7 mg/dL ± 48.7) than WPAC (109.4 ± 41.1) in the peritoneal fluid. The CSF PAC group also showed lower a level of glucose (38.0 mg/dL ± 27.0) than WPAC (63.3 mg/dL ± 23.9) (Table 2.2). However, the glucose level of the pleural fluid PAC group was higher (198.8 mg/dL ± 139.2) than WPAC (88.9 mg/dL ± 49.5) (Table 2.3). All previous comparison sets displayed a significant difference.

Nevertheless, the biochemical analysis (Table 2.2) showed that lactate and total proteins (TP) were significantly higher in the CSF PAC group (34.5 mg/dL ± 32 and 124.2 mg/dL ± 62) than in the WPAC group (18.4 mg/dL ± 14.43 and 115.7 mg/dL ± 274.4). The chloride dosage showed the opposite results, WPAC (723 mmol/L ± 32.9) × PAC (690.4 mmol/L ± 35.4) (p=0.027).

Using the nucleated cell counts >1000 cells/uL as a parameter to define a biological fluid as exudate, 12.4% of the pleural fluid samples were exudate and 87.6% were transudate. For the peritoneal fluid, 6.97% were exudate and 93.03% transudate. The average value of LDH dosage for pleural fluid was 1526 U/L and for peritoneal fluid, 1930 U/L, both PAC samples (Table 2.3).

In the neoplastic cell research, cells with different malignant characteristics such as abnormal cytoplasmic vacuolization, presence of multiple nucleoli, over coarse or loosen chromatin, high nucleus/cytoplasm ratio, atypical mitotic figures, membrane projections, hyperchromasia and unusual cell aggregates (Figures 1 and 2) were observed. The clinical evolution and diagnosis definition of these patients was confirmed through electronic medical records (Table 1).

The total sum of 170 samples shows differences between the WPAC versus PAC groups in regard to parameters of total nucleated cell count, LDH, lactate and chlorides with values of 377.8 cells/mm3 (± 611.8) versus 1768 cells/mm3 (± 3422) (p=0.014), 1003 U/L (±4124) versus 1892 U/L (±4124) (p=0.048), 18.41 mg/dL (±14.43) versus 34.5 mg/dL (±32.02) (p=0.013) and 723 mmol/L (±32.96) versus 690.4 mmol/L (±7.41) (p=0.015), respectively.

The microbiological examination did not show a significant difference between PAC and WPAC groups in biological fluids.

Discussion

Recognizing neoplastic cells in cavity fluids depends on the cytologist's ability to identify abnormal cells and malignancy patterns[2,4]. Benign cells undergo morphological alterations due to multiple environmental stimuli becoming morphologically similar to malignant cells, hampering the diagnosis[26]. Despite the suggestive morphological findings, more expensive complementary tests are often required to complete the diagnosis of malignancy, such as immunocytochemistry, flow cytometry, cytogenetics or molecular techniques[21]. Furthermore, many tumor-derived effusions do not present neoplastic cells, just reactive mesothelial cells[26]. In the present study, we found (Figure 2) the presence of malignant-like cells in several patients. In this context, the search for tumor markers in biological fluids with atypical/neoplastic cells can be very relevant in clinical analysis laboratories.

Malignant pleural effusion is usually an exudate which occurs, among other reasons, due to increased vascular permeability[2]. However, Teixeira et al. (2006)[27] suggested that a small percentage of transudates may be derived from malignant processes. The authors state that in both cases, there is usually a significant increase in the number of cells

Table 1. Description of 20 biological fluids with the presence of atypical/neoplastic cells.

Sample type	Description of the cell morphology found	Diagnosis	Clinical outcome
1. CSF	Presence of atypical cells arranged in clusters and isolated, with loose chromatin and moderate nucleus/cytoplasm ratio.	Metastatic small cell neuroendocrine carcinoma	Death
2. CSF	Presence of atypical cells with average nucleus/cytoplasm ratio, irregular chromatin, basophilic cytoplasm and with some cells showing vacuolation.	Mantle cell B non-Hodgkin lymphoma (blastoid variant)	Death
3. CSF	Presence of lymphocytic atypia.	Bacterial meningitis; Convulsive crisis; Acute hydrocephalus; Gastroesophageal reflux	Hospital discharge
4. CSF	Presence of many destroyed and clustered cells.	Human immunodeficiency virus (HIV) disease	Hospital discharge
5. CSF	Presence of lymphocytic atypia.	Neuromyelitis optica	Hospital discharge
6. CSF	Numerous macrophages with hemosiderin inclusions.	Hydrocephalus	Hospital discharge
7. CSF	Presence of lymphocyte polymorphism.	Diffuse non-Hodgkin's lymphoma	Death
8. CSF	Presence of lymphocyte polymorphism, with some lymphocytes slightly enlarged and with less dense chromatin. Some lymphocytes had a lobulated nucleus.	Acute myeloid leukemia	Hospital discharge
9. PEF	Presence of atypical cells, arranged in clusters and isolated, with loose chromatin and presence of nucleoli, basophilic cytoplasm and presence of mitotic figures.	Liver nodules a/e (Primary neoplasm/ cholangiocarcinoma? Liver metastasis?)	Death
10. PEF	Presence of reactive mesothelial cells showing intense basophilia.	Erysipelas; Hepatic cirrhosis; cerebral vascular accident	Death
11. PEF	Presence of reactive mesothelial cells showing intense basophilia.	Liver disease not otherwise specified	Death
12. PEF	Enlarged cells apparently of hematological lineage, with a high nucleus/cytoplasm ratio, irregular chromatin tending to be loose, large and evident nucleoli. Irregular nuclei with indentations and invaginations, some cells presenting bipartite nuclei. Count: 42% of the total.	R/R follicular non-Hodgkin lymphoma with pancytopenia (lymphoma infiltration + hypersplenism)	Death
13. PEF	Differential counting not performed due to cellular deformation.	Unspecified heart failure, Unclassified pleural effusion, Acute respiratory failure	Hospital discharge
14. PCF	Presence of intensely basophilic giant cells, with eccentric nuclei of variable chromatin, intensely vacuolated, some arranged in clusters (hyperactivated mesothelial cells? Atypical cells?). Presence of vacuolation in neutrophils and macrophages	CA of lung, poorly differentiated, non-small cell	Death
15. PCF	Presence of atypical cells with loose chromatin and presence of nucleoli. Basophilic cytoplasm with vacuolation and membrane projections.	Malignant neoplasm of head, face and neck	Death
16. PF	Presence of cells with increase in size, very basophilic, often binucleated and with an increased nucleus/cytoplasm ratio.	Metastatic gastric adenocarcinoma	Death
17. PF	Presence of lymphocytic atypia.	Herpes zoster without complications	Hospital discharge
18. PF	Presence of numerous clusters of large, intensely basophilic cells with decentralized nuclei, medium nucleus-cytoplasm ratio, variable chromatin, containing large and sometimes multiple nucleoli. Some cells were multinucleated and some had numerous cytoplasmic vacuoles. Mitotic figures visualized. 74 suspicious cells were visualized out of 100 cells counted. // Presence of erythrophagocytosis // Presence of siderophages	Mesothelial hyperplasia, right residual pneumothorax + Small pleural effusion + Lung emphysema	Death
19. PF	Content rich in small lymphocytes and scarcity of mesothelial cells.	Undefined	Death
20. PF	Numerous figures of nuclear phagocytosis, suggestive of LE cells.	Chronic monocytic leukemia, Disseminated lupus erythematosus, Acute and subacute endocarditis	Hospital discharge

Legend: CSF = Cerebrospinal fluid; PEF = Peritoneal fluid; PF = Pleural fluid; PCF = Pericardial fluid.
Source: Prepared by the authors, 2024.

Table 2.1. Descriptive statistics of numeric variables with presentation of mean and standard deviation of 48 peritoneal fluids evaluated in the period from 2020 to 2022.

Body fluid	Item	Mean (WPAC)	DP (WPAC)	Mean (PAC)	DP (PAC)	*p*
Peritoneal fluid = 48	Volume (mL)	11.5	1.8	11.75	2.3	0.999
	pH	7.48	0.21	7.09	0.33	0.067
	Red Cells* /mm³	19070	38213	14250	4924	0.120
	Nucleated cells /mm³	**411.6**	664.8	**4809**	6587	**0.001**
	Eosinophils %	0.20	0.70	0	0	0.615
	Neutrophils %	22.3	22.9	47.7	42.3	0.164
	Lymphocytes %	43.1	20.6	24.3	18.5	0.159
	Macrophages %	**31.3**	19.4	**13**	8.1	**0.003**
	Mesothelial cells %	**4.1**	5.1	**15**	18.0	**0.006**
	Glucose mg/dL	**109.4**	41.1	**54.7**	48.7	**0.003**
	Amylase U/L	100.7	274.6	40.5	53.1	0.276
	LDH U/L	445	1726	1930	3041	0.084
	TP mg/dL	2.12	1.11	1.8	1.5	0.409
	Albumin mg/dL	1.2	0.64	1.04	0.84	0.599

Legend: WPAC = without presence of atypical/neoplastic cells; PAC = with presence of atypical/neoplastic cells; * - Automated quantification, the minimum value reported is <10000 which was set to 10000 in the analyses; LDH = lactate dehydrogenase; TP = total proteins. The number of peritoneal fluid samples evaluated was 43 WPAC and 5 PAC.
Source: Prepared by the authors, 2024.

Table 2.2. Descriptive statistics of numeric variables with presentation of mean and standard deviation of 55 cerebrospinal fluids evaluated in the period from 2020 to 2022.

Body fluid	Item	Mean (WPAC)	DP (WPAC)	Mean (PAC)	DP (PAC)	*p*
Cerebrospinal fluid = 55	Volume (mL)	4.16	3.01	5.91	3.66	0.212
	Red Cells /mm³	285.9	1496	1403	2690	0.213
	Nucleated cells /mm³	**22.2**	61.5	**309.2**	292.9	**0.001**
	Eosinophils %	0	0	0.5	1.22	0.113
	Neutrophils %	12.8	25.1	10.8	10.5	0.324
	Lymphocytes %	**80.5**	27.4	**57.2**	38.5	**0.042**
	Macrophages %	**7.1**	10.9	**29.8**	38.5	**0.019**
	Glucose mg/dL	**63.3**	23.9	**38.0**	27.0	**0.020**
	TP mg/dL	**115.7**	274.4	**124.2**	66.0	**0.036**
	Lactate mg/dL	**18.4**	14.43	**34.5**	32.0	**0.019**
	Chlorides mmol/L	**723**	32.9	**690.4**	35.4	**0.027**

Legend: WPAC = without presence of atypical/neoplastic cells; PAC = with presence of atypical/neoplastic cells; LDH = lactate dehydrogenase; TP = total proteins. The number of cerebrospinal fluid samples evaluated was 47 WPAC and 8 PAC.
Source: Prepared by the authors, 2024.

being produced. Likewise, our results showed that PAC samples of pleural fluid had a higher number of nucleated cells than WPAC samples.

The total nucleated cell count of PAC was higher than WPAC in peritoneal fluid. Similarly, other studies observed that malignant peritoneal effusions have higher number of total leukocytes compared to benign peritoneal effusions, indicating that these tumors are active and producing a large number of cells[8,12].

The total leukocyte/nucleated cell count in the CSF represents one of the most sensitive indicators to characterize a central nervous system disease[28]. In inflammatory, malignant and hemorrhagic processes, the number of nucleated cells is much greater than under normal conditions[5,28]. Such results were found in the present study, where the total count of nucleated cells in the PAC group was significantly higher compared to the WPAC group for most biological fluids.

In the CSF samples, the dosage of total proteins (TP) in the PAC group was higher than in the WPAC group. This result could be explained due to an increase in the concentration of monoclonal proteins produced by atypical/neoplastic cells in the PAC group[27]. Increased TP is also commonly attributed to suspected disruption of blood-brain/nerve barriers by infectious or immunological

Table 2.3. Descriptive statistics of numeric variables with presentation of mean and standard deviation of 57 pleural fluids evaluated in the period from 2020 to 2022.

	Item	Mean (WPAC)	DP (WPAC)	Mean (PAC)	DP (PAC)	*p*
Pleural fluid = 57	Volume (mL)	11.35	3.49	9.75	6.0	0.844
	pH	7.4	0.24	7.37	0.22	0.558
	Red Cells* /mm³	61404	123656	10000	0	0.520
	Nucleated cells /mm³	**616.8**	657.9	**1832**	922.8	**0.015**
	Eosinophils %	0.57	1.87	0.25	0.5	0.731
	Neutrophils %	42.56	30.4	42	31.0	0.848
	Lymphocytes %	32.2	27.8	27.5	31.2	0.673
	Macrophages %	21.5	22.1	22.2	15.1	0.544
	Mesothelial cells %	3.0	5.2	8.0	8.4	0.056
	Glucose mg/dL	**88.9**	49.5	**198.8**	139.2	**0.006**
	Amylase U/L	97.0	411.9	25.7	12.3	0.628
	LDH U/L	1431	5560	1526	2153	0.287
	TP mg/dL	2.82	1.40	3.0	1.19	0.585

Legend: WPAC = without presence of atypical/neoplastic cells; PAC = with presence of atypical/neoplastic cells; * - Automated quantification, the minimum value reported is <10000 which was set to 10000 in the analyses; LDH = lactate dehydrogenase; TP = total proteins. The number of pleural fluid samples evaluated was 52 WPAC and 5 PAC.
Source: Prepared by the authors, 2024.

Table 2.4. Descriptive statistics of numeric variables with presentation of mean and standard deviation of 4 pericardial fluids evaluated in the period from 2020 to 2022.

	Item	Mean (WPAC)	DP (WPAC)	Mean (PAC)	DP (PAC)	*p*
Pericardial fluid = 4	Volume (mL)	18	0	16	5,6	0.667
	pH	7.48	0.25	#	0.0	@
	Red Cells* /mm³	279555	395195	1535000	849942	0.1987
	Nucleated cells /mm³	1820	523.3	3774	3548	0.5216
	Eosinophils %	0	0	0.5	0.7	0.4226
	Neutrophils %	49.5	40.31	23	8.48	0.4589
	Lymphocytes %	37.5	36.06	46.5	45.96	0.8477
	Macrophages %	8	2.82	25.0	31.11	0.5220
	Mesothelial cells %	5	7.07	4.5	6.36	0.9475
	Glucose mg/dL	66.5	10.61	46.5	47.38	0.6191
	Amylase U/L	14	15.6	61	0.0	@
	LDH U/L	2001	2361	2327	1235	0.8784
	TP mg/dL	3008	4246	4.85	0.21	0.4222

Legend: WPAC = without presence of atypical/neoplastic cells; PAC = with presence of atypical/neoplastic cells; * - Automated quantification, the minimum value reported is <10000 which was set to 10000 in the analyses; LDH = lactate dehydrogenase; TP = total proteins; # - Not evaluated, only one sample of pericardial fluids PAC presented this value; @ = It was not possible to make comparisons due to having only one sample in one of groups. The number of pericardial fluid samples evaluated was 2 WPAC and 2 PAC.
Source: Prepared by the authors, 2024.

disorders of the central/peripheral nervous system[29,30] that increase intrathecal antibody production[31], impaired CSF reabsorption and spinal sequestration[32].

According to Comar et al. (2011)[12], malignant cells in effusions are frequently associated with increased macrophages and mesothelial cell populations. This partially helps to explain our findings regarding these cell lineages in some PAC fluids evaluated in the present study. Sharma, Asotra and Asotra (2023)[33] reported peritoneal fluid accounted for the most frequent malignant effusion (51.16%) found in their study, followed by pleural fluid (46.51%) and CSF (2.32%).

Our results showed that the glucose level in pleural fluids was higher in the PAC group (198.8 mg/dL ± 139.2) compared to the WPAC group (88.9 mg/dL ± 49.5). According to Sahn (1982)[34], a glucose concentration greater than 60mg/dL in the pleural fluid has been accepted in the literature to differentiate exudates from transudates. In this

Table 2.5. Descriptive statistics of numeric variables with presentation of mean and standard deviation of 6 synovial fluids evaluated in the period from 2020 to 2022.

	Item	Mean (WPAC)	DP (WPAC)	Mean (PAC)	DP (PAC)	*p*
Synovial fluid = 6	Volume (mL)	9.91	6.03	-	-	-
	Red Cells* /mm³	11317	16737	-	-	-
	Nucleated cells /mm³	368	559.9	-	-	-
	Eosinophils %	0.5	1.22	-	-	-
	Neutrophils %	71.67	31.23	-	-	-
	Lymphocytes %	23.5	27.95	-	-	-
	Macrophages %	4.33	3.83	-	-	-
	Glucose mg/dL	83.33	48.23	-	-	-
	LDH U/L	955.8	696.9	-	-	-
	TP mg/dL	3.4	0.91	-	-	-

Legend: WPAC = without presence of atypical/neoplastic cells; PAC = with presence of atypical/neoplastic cells; * - Automated quantification, the minimum value reported is <10000 which was set to 10000 in the analyses; LDH = lactate dehydrogenase; TP = total proteins. The number of synovial fluid samples evaluated was 6 WPAC and 0 PAC.
Source: Prepared by the authors, 2024.

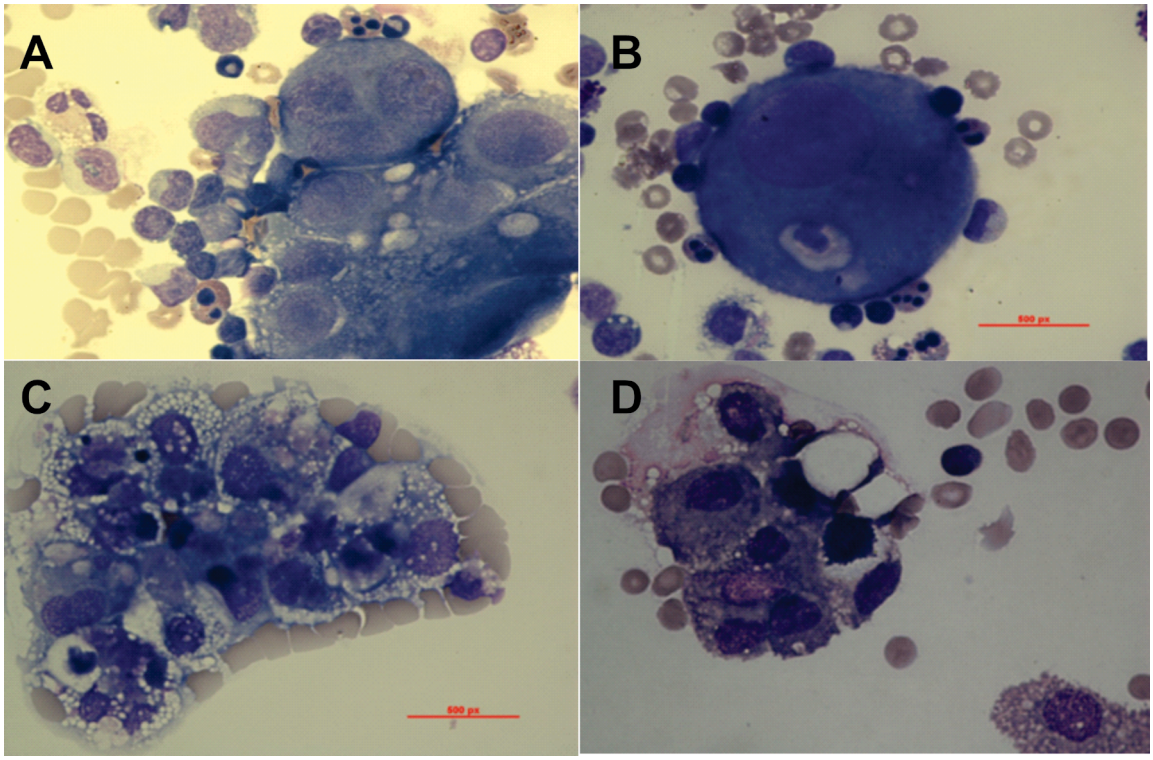

Figure 1. Neoplastic cells. **A.** Pleural fluid with atypical cells, arranged in lumps, nucleus with loose chromatin, evident nucleoli, increased nucleus/cytoplasm ratio, basophilic cytoplasm and cytoplasmic vacuoles. Some apoptotic cells; **B.** Pleural fluid with sole atypical cell, nucleus with loose chromatin, evident nucleoli, increased nucleus/cytoplasm ratio, abundant basophilic cytoplasm and hyperchromasia; **C.** Cerebrospinal fluid with atypical cells, arranged in clusters/aggregates, nucleus with loose chromatin, presence of nucleoli, increased nucleus/cytoplasm ratio, basophilic cytoplasm and high cytoplasmic vacuolization; **D.** Peritoneal fluid with cohesive cells arranged in clusters, loose chromatin, moderate nucleus/cytoplasm ratio, highly basophilic cytoplasm and cytoplasmic vacuoles. Images 1000x magnified. Giemsa-staining.
Source: Elaborated by the authors, 2024.

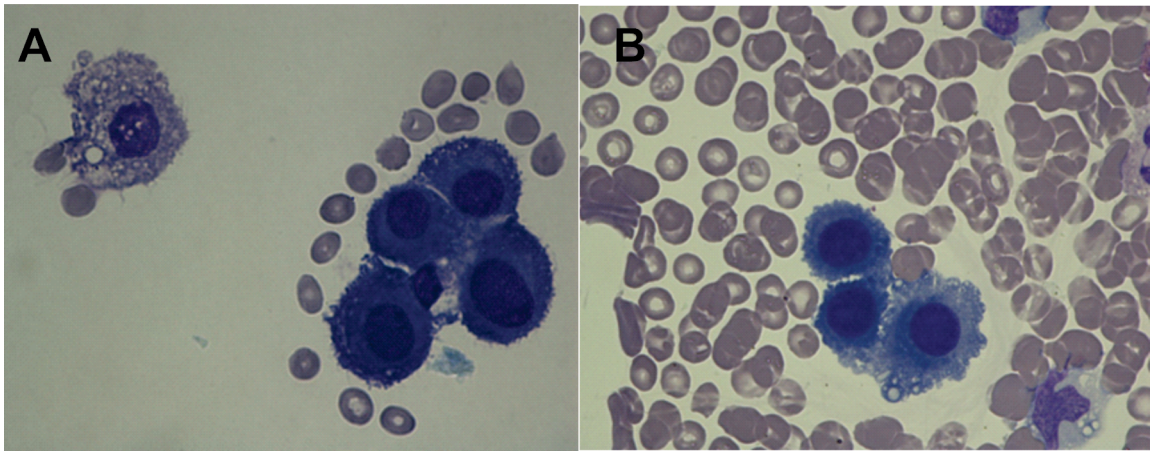

Figure 2. Reactive mesothelial cells. Peritoneal fluid with reactive and clump-disposed cohesive mesothelial cells with membrane projections and highly basophilic cytoplasm. Images 1000x magnified. Giemsa-staining.
Source: Elaborated by the authors, 2024.

sense, most of both of PAC and WPAC samples could be classified as exudates.

In addition, Dixit et al. (2017)[35] pondered that pleural malignant-exudative effusions with pH <7.2, glucose <60 mg/dL, LDH greater than two-fold of serum values, Karnofsky performance scale <30 and thoracoscopy, are likely to reflect greater tumor burden and a worse prognosis[35]. Even though our pH and glucose results differed, some PAC patients had death as an outcome (Table 1 and 2.3). Pleural effusions may lead to various complications such as empyema or pleural thickening, necessitating aggressive antibiotic therapy, drainage procedures or even surgical intervention in severe cases.[36] It is a potential indicator of increased mortality withal[35,37,38].

On the other hand, the PAC samples of peritoneal fluid (54.7 mg/dL ± 48.7) and cerebrospinal fluid (38.0 mg/dL ± 27.0) revealed a decreased glucose level in relation to WPAC samples. Other authors have reported that approximately one third of neoplastic effusions presents low glucose levels (<60 mg/dL)[8,39]. The decrease in glucose levels may be related to different factors, including the high consumption of glucose by malignant cells[4,27]. Besides that, decreased levels of glucose in CSF and peritoneal fluid may be caused by alterations in the transport mechanism of the molecule across the blood-brain barrier[14,21,39].

Several authors have reported that the most common malignancies in pleural fluids were hematolymphoid, lung and breast neoplasms[40-43] and, in the case of pericardial effusions, breast (44.4%) and lung cancers (36.1%) were the most frequent malignancies[20,44-48]. Gastrointestinal (48%) and ovarian cancers (30%) were the most frequent malignancies in peritoneal effusions[49]. The methods and the inclusion criteria explain the varying occurrence of the serous fluids malignancies reported in the literature[20].

Sharma, Asotra and Asotra (2023)[33] reported that metastatic ovary and lung adenocarcinomas corresponded to 67.44% of cases, thus being the most common malignancy in peritoneal and pleural effusions, followed by squamous cell carcinoma, small cell carcinoma, and Non-Hodgkin lymphoma, which corresponded to 23.25%, 4.6% and 2.3%, respectively. In addition, Jeffus et al. (2024)[50] elaborated a multi-institutional retrospective review where it was found that hematolymphoid malignancies were the most common neoplasms in cerebrospinal fluids from adults.

Biological fluid analysis is essential to understand physiological or pathological condition, and the clinical laboratory is responsible for carrying out diagnostic screenings and providing accurate information to help clinical staff assess the patient's health[51]. In this sense, the criteria for defining exudate and transudate in different biological fluids still needs further studies and standardization, since some authors indicate that the classical Light's criteria should only be used for pleural effusions[24,25,52]. Notwithstanding, we have indicated some distinctive biochemical and cytological alterations according to biological fluids source with atypical cells.

Conclusion

Our initial analyses revealed important differences on analytes evaluated in the biological fluids routine. These differences can help medical staff to define whether biological fluids are exudates or transudates. Even if most of the patients with PAC specimens are deceased, it is still of clinical interest to clarify the biochemical and cellular changes that are indicative of the presence of atypical/neoplastic cells in multiple biological fluids in order to enhance diagnosis, decision-making about therapeutic options or oncologic follow-up.

Author's Contribution

We describe contributions to the papers using the taxanomy (CRediT) provided above:

Conceptualization, Investigation, Methodology, Visualization & Writing – review & editing: MFM; JLMR; MLSV; LEAS. Project administration, Supervision & Writing – original draft: LEAS; MFM; JLMR. Validation & Software: MLSV; LEAS. Resources & Funding acquisition: LEAS; MFM; JLMR. Data curation & Formal Analysis: LEAS.

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