

Pleural Effusion in Meigs' Syndrome—Transudate or Exudate?

Systematic Review of the Literature

Rafal Krenke, MD, PhD, Marta Maskey-Warzechowska, MD, PhD, Piotr Korczynski, MD, PhD, Monika Zielinska-Krawczyk, MD, Joanna Klimiuk, MD, PhD, Ryszarda Chazan, MD, PhD, and Richard W. Light, MD, FCCP

Abstract: Although Meigs' syndrome is regarded as a well-defined entity, contradictory data on pleural fluid characteristics have been presented, with some papers classifying it as a transudate, whereas others stating that it is an exudate.

The aims of the study were: (1) to evaluate pleural fluid characteristics in patients with Meigs' syndrome and (2) to analyze the prevalence of transudative and exudative pleural effusion in relation to the applied definition of the syndrome.

We performed a search through medical databases (MEDLINE, EMBASE, SCOPUS, and GOOGLE SCHOLAR) to identify papers on Meigs' syndrome published between 1940 and 2013. Two authors independently reviewed each paper searching for prespecified data: (1) signs and symptoms, (2) tumor characteristics, (3) clinical and laboratory data on ascites, (4) clinical, radiological, and laboratory data on pleural fluid, (5) clinical course after tumor removal. All case reports were reclassified according to a new unequivocal classification of Meigs' syndrome-related entities.

A total of 653 papers were initially identified, and 454 articles reporting 541 patients were included in the final analysis. After reclassification according to our case definitions, there were 196, 113, and 108 patients defined as classic Meigs' syndrome, nonclassic Meigs' syndrome, and pseudo-Meigs' syndrome, respectively. Significantly more patients presented with right-sided than left-sided and bilateral pleural effusions ($P < 0.001$). Median volume of withdrawn pleural fluid was 2950 (1500–6000) mL. The classification of pleural effusion with the use of Light's criteria was possible in only 7 patients. In 6 of these patients pleural effusion met the criteria for an exudate. When the protein concentration > 3.0 g/dL was applied as a criterion of pleural exudate, 88.8% (80/90) of effusions were classified as exudates. Increasing the cut-off level to 3.5 g/dL resulted in only a modest decrease in the percentage of exudative effusions (81%, 73/90).

Surprisingly few reports on Meigs' syndrome present data reliably defining the character of pleural effusion. The available data indicate,

however, that the majority of pleural effusions in patients with this entity are exudates. This finding may be a prerequisite for the verification of some earlier presented concepts.

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Abbreviations: BTS = British Thoracic Society, CA-125 = carbohydrate antigen 125 or cancer antigen 125, FGF = fibroblast growth factor, IL-6 = interleukin 6, LDH = lactate dehydrogenase, PE = pleural effusion, VEGF = vascular endothelial growth factor.

INTRODUCTION

Meigs' syndrome is regarded as a well-defined entity, yet certain aspects of this syndrome remain unresolved. Although the prevalence of the syndrome is low, it has an important clinical implication. The major message related to Meigs' syndrome is that abdominal tumor, ascites, and pleural effusion – symptoms strongly suggesting disseminated malignancy – do not necessarily mean advanced malignant disease and do not exclude curative treatment.

As dyspnea (due to large volume pleural effusion), fatigue and weight loss are common presenting symptoms, a significant proportion of the patients might be initially referred to general practitioners or chest physicians.^{1,2} Contradictory data regarding pleural effusion characteristics have been presented. The British Thoracic Society (BTS) statement on unilateral pleural effusion classifies pleural effusion in patients with Meigs' syndrome as a transudate.³ The same opinion can be found in other review papers.⁴ Conversely, according to other authors, Meigs' syndrome is associated with exudative pleural effusion.⁵ As our knowledge on Meigs' syndrome comes almost exclusively from case reports, the data on pleural fluid characteristics are scarce and dispersed throughout many different papers. Although several larger analyses on patients with Meigs' syndrome have been published, none of them focused on pleural effusion characteristics.^{6–13} Thus, we undertook the study whose primary goal was to evaluate the pleural effusion characteristics in patients with Meigs' syndrome. As some other Meigs' syndrome-related terms, including Demons–Meigs' syndrome, pseudo-Meigs' syndrome, pseudo–pseudo Meigs syndrome, and atypical and incomplete Meigs' syndrome have also been introduced,^{7,11,14–19} the secondary goal of our study was to analyze the prevalence of transudative and exudative pleural effusion in relation to the applied definition of the syndrome.

MATERIAL AND METHODS

Data Sources and Search Strategy

Two authors performed an independent search of the electronic medical databases for papers on Meigs' syndrome

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From the Department of Internal Medicine, Pneumology and Allergology, Medical University of Warsaw, Poland (RK, MM-W, PK, M-ZK, JK, RC); and Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University, Nashville, TN.

Correspondence: Rafal Krenke, Department of Internal Medicine, Pneumology and Allergology, Medical University of Warsaw, Banacha 1A, Warsaw, Poland (e-mail: rafalkrenke@interia.pl; rkrenke@wum.edu.pl).

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TABLE 1. Classification and Diagnostic Criteria for Meigs' Syndrome-Related Terms Used in the Manuscript; Gray Rectangles in Each Column Show the Criteria that Had to be Met to Classify the Patient to the Appropriate Category of the Syndrome (Stated in Column Heading)

Diagnostic criteria		Meigs' syndrome related terms							
		Demons-Meigs' syndrome		Pseudo Meigs' syndrome		Incomplete Meigs' syndrome			Pseudo-pseudo Meigs' syndrome
		Classic Meigs' syndrome	Non-classic Meigs' syndrome	Benign pseudo Meigs' syndrome	Malignant pseudo Meigs' syndrome	Incomplete Demons Meigs' syndrome	Incomplete benign pseudo Meigs' syndrome	Incomplete malignant pseudo Meigs' syndrome	
TUMOR RELATED CRITERIA	Benign fibroma or fibroma-like ovarian tumor								
	Benign ovarian or broad ligament tumor other than fibroma or fibroma-like					OR			
	Benign extra-ovarian and extra broad ligament pelvic or abdominal tumor								
	Malignant pelvic or abdominal tumor								
NON-TUMOR RELATED CRITERIA	Ascites*					OR	OR	OR	
	Pleural effusion*								
	Resolution of ascites and pleural effusion after tumor removal								
	Systemic lupus erythematosus								
	Elevated serum CA-125 concentration								

*Without signs of malignant involvement. Please note that Demons–Meigs' syndrome includes all cases classified as classic Meigs' syndrome and nonclassic Meigs' syndrome, whereas incomplete Demons Meigs' syndrome combines all cases classified as incomplete classic Meigs' syndrome and incomplete nonclassic pseudo-Meigs' syndrome. Due to space limitations the subgroups of incomplete Demons–Meigs' syndrome were not presented on the diagram. CA-125 = carbohydrate antigen 125.

published between 1940 and 2013. MEDLINE, EMBASE, and SCOPUS were reviewed using the following search terms: "Meigs' syndrome," "Demons–Meigs' syndrome," "Demons' syndrome," "pseudo-Meigs' syndrome," "pseudo–pseudo Meigs' syndrome," "pleural effusion/pleurisy," and "ascites" or "peritoneal effusion" and "ovarian tumor" or "abdominal tumor." GOOGLE SCHOLAR search engine was also used to search for adequate articles. Reference lists from publications on Meigs' syndrome were then reviewed to find other relevant papers. No language restrictions were imposed during this study phase.

Study Selection

Titles and abstracts of initially selected papers were reviewed to exclude the articles which were not related to Meigs' syndrome or pseudo-Meigs' syndrome. Then, papers published in Japanese, Chinese, Korean, and Hebrew were excluded from the list due to limited access and the language barrier precluding a credible analysis. The remaining articles were collected and subjected for further analysis.

Data Extraction and Quality Assessment

Two authors independently reviewed each paper searching for prespecified data (see *Categories of data and statistical analysis*). Data collected by each author were then compared and verified. Articles which did not present new case reports as well as cases which were not consistent with the definition of Meigs' syndrome or pseudo-Meigs' syndrome (see *Case definitions*) were excluded from the analysis.

Classification and Case definitions

In order to unequivocally classify the analyzed case reports, we applied a modified classification of Meigs' syndrome and pseudo-Meigs' syndrome. This classification (Table 1) is based on historical determinants, but also reflects data from more recent case reports and review articles.^{7,11,12,14,20,21} Irrespective of the nomenclature used in the original case report, all patients were reclassified according to case definitions presented below.

Classic Meigs' Syndrome

Four criteria had to be met to classify a case as classic Meigs' syndrome (Table 1).^{7,14} These included: (1) benign fibroma or fibroma-like (thecoma, granulosa cell tumor, or Brenner tumor) ovarian tumor, (2) ascites, (3) pleural effusion, (4) resolution of ascites and pleural effusion after removal of the tumor.

Nonclassic Meigs' Syndrome and Demons–Meigs' Syndrome

The term nonclassic Meigs' syndrome was applied for patients with ascites and pleural effusion associated with benign ovarian, Fallopian tube, or broad ligament tumors other than those included in the definition of classic Meigs' syndrome (Table 1). According to some authors, these cases, together with the cases meeting the classic criteria, should be included in a wider definition of the syndrome.²² This view is based on historical works of Albert Demons.¹¹ To be concordant with such a view, in our study all patients with typical features of the

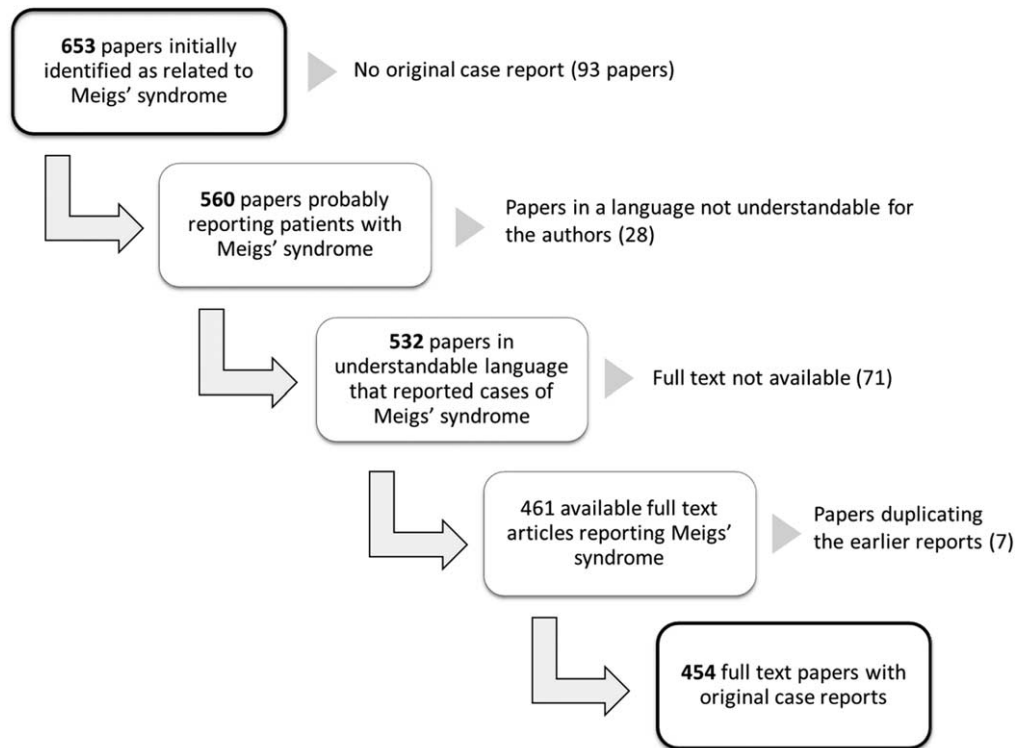


FIGURE 1. Flowchart presenting the selection process of papers subjected for analysis.

syndrome associated with any benign genital tumors, irrespective of its type and localization were combined in a larger group labeled as Demons–Meigs' syndrome (Table 1). This group did not include, however, patients with benign tumors of uterus.

Pseudo-Meigs' Syndrome

Pseudo-Meigs' syndrome refers to ascites and pleural fluid secondary to any other pelvic or abdominal tumors (not included in definition of Demons–Meigs' syndrome). This condition was further subclassified into 2 categories: (1) benign pseudo-Meigs' syndrome and (2) malignant pseudo-Meigs' syndrome (Table 1). The first term was used for patients with symptoms related to any benign pelvic or abdominal tumors localized outside of the ovaries, Fallopian tubes, and broad ligaments, whereas the second referred to patients with malignant pelvic or abdominal tumors (primary or metastatic). By definition, lack of evidence for peritoneal or pleural spread of the tumor must have been documented (negative pleural and peritoneal fluid cytology and/or no malignant involvement in biopsy samples) and both ascites and hydrothorax should have resolved after tumor removal.^{15,23,24}

Pseudo–Pseudo Meigs' Syndrome

Pseudo–pseudo Meigs' syndrome (or Tjalma syndrome) was defined as a combination of ascites, pleural effusion, and elevated serum carbohydrate antigen 125 (also known as cancer antigen 125, CA-125) concentration in a patient with systemic lupus erythematosus.^{17,18,25}

Atypical or Incomplete Meigs' Syndrome

The presence of either ascites or pleural effusion associated with a pelvic/abdominal tumor was regarded as incomplete

(atypical) Meigs', Demons–Meigs', or pseudo-Meigs' syndrome (depending on the nature and localization of the tumor).^{19,26,27}

Data Synthesis and Analysis

Five data categories were analyzed: (1) prediagnosis signs and symptoms, (2) tumor characteristics, (3) clinical and laboratory data on ascites, (4) clinical, radiological, and laboratory data on pleural fluid, (5) clinical course after tumor removal. As this was a retrospective analysis of previously published data no approval of the ethics committee was necessary.

Statistical analysis was performed using STATISTICA 10.0 (StatSoft Inc. USA) software. Quantitative variables are presented as median and interquartile range (IQR), whereas qualitative variables are presented as the number and the percentage. Nonparametric Kruskal–Wallis test, Mann–Whitney *U* test or Fisher exact test were used to assess the difference between different groups. Spearman's rank correlation coefficient was applied to test correlations between quantitative variables. The chi square test was used to assess the proportions of patients with various pleural fluid characteristics. A *P* value <0.05 was regarded significant.

RESULTS

The search of the medical databases revealed 597 publications. Another 42 articles were identified when searching through reference lists of papers found in databases. GOOGLE SCHOLAR engine discovered additional 14 papers. Thus, 653 articles, potentially related to Meigs' syndrome, were subjected for initial analysis. Figure 1 presents the process of the review and paper selection. Four hundred and fifty-four papers reporting 541 patients were available for final analysis. There were

288 papers in English and 166 papers in other languages. A single case was reported in 86% of the reviewed papers, and only 4 (0.9%) papers presented >3 cases.

We found that the terminology had been applied inconsistently, with the same term used to define different clinicopathological presentations and different terms used for the same clinicopathological entities. After reclassification there were 196 and 113 patients defined as classic and nonclassic Meigs' syndrome, respectively. These cases termed together as Demons–Meigs' syndrome ($n=309$) constituted 57% of all analyzed patients. Pseudo-Meigs' syndrome group included 33 patients with benign and 75 patients with malignant pseudo-Meigs' syndrome. Incomplete Meigs' syndrome was diagnosed in 56 patients (23 with pleural effusion and 33 with ascites) and pseudo–pseudo Meigs' syndrome in 7 patients.

Sixty-one patients had to be excluded from analysis: in 44 cases, data inconsistent with the syndrome (eg, malignant pleural or peritoneal involvement) were reported, whereas in the remaining 17 patients, the provided data were insufficient to confirm the diagnosis.

General data on patients with Meigs' syndrome are presented in Table 2.

Patients with benign pseudo-Meigs' syndrome were significantly younger than patients with classic, as well nonclassic Meigs' syndrome, $P=0.002$, and $P=0.03$, respectively. Significantly more patients presented with right-sided than left-sided and bilateral pleural effusions ($P<0.001$). In patients with right-sided pleural effusion, a larger volume of peritoneal fluid was removed than in patients with left-sided pleural effusion ($P=0.015$). There were no correlations between tumor dimensions or weight and the volume of withdrawn pleural or peritoneal effusion.

Biochemical characteristics of ascites and pleural fluid are summarized in Tables 3 and 4.

A significant correlation between the protein level in pleural fluid and ascites was found, $r=0.77$, $P<0.001$. There was also a significant negative correlation between the volume of withdrawn pleural effusion and serum protein concentration, $r=-0.62$, $P<0.001$.

We found that classification of pleural effusion with the use of Light's criteria was possible only in 7 of 447 (1.6%) patients in whom pleural effusion was reported. In 6 patients pleural fluid met the criteria for an exudate, whereas 1 patient had a transudative pleural effusion. One or two Light's criteria (pleural fluid protein/serum protein ratio, pleural fluid lactate dehydrogenase (LDH)/serum LDH ratio, or pleural fluid LDH level higher than 200 IU/l) could have been analyzed in additional 26 patients. Even when only 1 criterion was used, the test was sufficient to diagnose exudative pleural effusion in 21/26 (81%) of these patients.

The most commonly reported pleural fluid laboratory parameter was protein concentration. This, however, was available in only 20.1% (90/447) of the patients. The median pleural fluid protein concentration was 4.4 (3.6–5.0) g/dL. We found no differences between pleural fluid protein concentration in patients with fully symptomatic forms of Meigs' syndrome, including its benign and malignant forms. However, pleural fluid protein concentration was significantly higher in patients with incomplete benign Meigs' syndrome than in patients with complete Meigs' syndrome ($P=0.007$). When pleural fluid protein concentration > 3.0 g/dL was applied as a criterion of pleural exudate, 88.8% (80/90) of effusions were classified as exudates. Increasing the cut-off level to 3.5 g/dL resulted in only

a modest decrease in the percentage of effusions classified as exudates to 81% (73/90).

DISCUSSION

Pleural fluid analysis plays an important role in diagnosing patients with pleural effusion.^{3–5,28} Measurement of various pleural fluid components provides reliable information on the fluid nature and the potential mechanisms involved in pleural fluid formation. Although different approaches to the interpretation of pleural fluid biochemical composition have been proposed, including Bayesian analysis estimating the likelihood ratio of exudative effusion,²⁹ the dichotomous differentiation between transudate and exudate is still the key point in the evaluation of pleural effusion.

In some diseases, data on pleural fluid characteristics are equivocal. This also refers to Meigs' syndrome. As Meigs' syndrome is uncommon, it would be extremely difficult to plan a prospective study designated to evaluate the features of pleural effusion in this entity. Therefore, retrospective data analysis was the only reasonable method to evaluate and clarify pleural fluid characteristics. We believe that the strength of our study lies in the systematic analysis of pleural fluid in this entity. The results of this analysis have an important practical application. As Meigs' syndrome is often associated with large volume pleural effusion, thoracentesis and pleural fluid analysis are important initial diagnostic steps. Our review showed that dyspnea and abdominal distension were the most common presenting symptoms reported in 32% (92/285) and 32.5% (93/285) of patients with Demons–Meigs' syndrome, respectively. We found that 77% (201/261) of patients with Demons–Meigs' syndrome and 95.4% (63/66) patients with malignant pseudo-Meigs' underwent at least 1 thoracentesis. As determination of pleural fluid laboratory characteristics plays a pivotal role for further diagnostic decision making, their interpretation based on unsupported data may be misleading and result in a misoriented diagnostic approach. Our analysis demonstrates that Meigs' syndrome should be included in the differential diagnosis in a female patient with a pleural exudate and, contrary to the statements presented in various papers,^{3,4,30} is less probable in a patient with a transudate.

Although our study provided reliable and unique data on various aspects of pleural effusion associated with Meigs' syndrome, it must be admitted that we had expected a significantly higher percentage of patients in whom differentiation between transudate and exudate could have been performed on the basis of currently used biochemical criteria. We were disappointed that despite reviewing 454 papers which included 541 case reports, data necessary to calculate Light's criteria were available only in 7 (1.6%) of patients of whom 6 had exudates. The high percentage of patients with exudative pleural effusion is confirmed by the observation that as many as 21/26 (81%) patients in whom only 1 Light's criterion was available met exudative criteria. As the criteria used to discriminate transudate and exudate have evolved over time, older tests, which were commonly applied in the past, were also included in our analysis. Surprisingly, the results of these tests, including pleural fluid specific gravity and Rivalta test, were only rarely reported (in 12.4% and 9.6% of patients, respectively). When specific gravity was applied to discriminate between transudate and exudate (cut-off level ≥ 1.016), 70.4% (38/54) of effusions were classified as exudates. The Rivalta test revealed a slightly higher percentage of exudates (76.7%, 33/42).

TABLE 2. Clinical characteristics of Patients With Different Categories of Meigs' Syndrome

	Classic Meigs' Syndrome	Nonclassic Meigs' Syndrome	Benign Pseudo-Meigs' Syndrome	Malignant Pseudo-Meigs' Syndrome	Incomplete Syndrome With PE Due to Benign Tumors	Incomplete Syndrome With PE Due to Malignant Tumors	Pseudo-Pseudo Meigs' Syndrome
Number of patients	196	113	33	75	18	5	7
Age (years)	54 (44–63)	53 (40–63)	46 (38–47)	49 (41–57)	58 (51–67)	40 (35–48)	38 (38–42)
Primary tumor site	Ovary 196	Ovary 107 Fallopian tube/broad ligament 6	Uterus 32 Colon 1	Ovary 65		Breast (1), Ovary (1), Colon (2), Kidney (1)	
Tumor localization	83/76/24	42/49/11	32 tumors in uterus	23/27/28	6/4/2	3/0/2	–
right/left/bilateral							
Removed tumor weight (g)	1372 (806–2360)	930 (360–3240)	4000 (1350–7840)	2400 (1500–3010)	2170 (1225–3250)	NA	–
Follow-up duration (weeks)	12 (4–47)	26 (8–104)	31 (8–58)	28 (12–55)	40 (5–74)	40 (12–60)	10 (7–18)
Total volume of ascites removed (mL)	2250 (675–5000)	4050 (700–8500)	5500 (1900–10000)	3000 (1350–5150)	0	0	3000*
Site of pleural effusion, n (%)							
Right	128 (70.3%)	70 (64.8%)	16 (50%)	44 (59.5%)	12 (66.7%)	4 (80%)	2 (50%)
Left	19 (10.5%)	19 (17.6%)	11 (34.3%)	14 (18.9%)	3 (16.7%)	0	0
Bilateral	35 (19.2%)	19 (17.6%)	5 (15.6%)	16 (21.6%)	3 (16.7%)	1 (20%)	2 (50%)
Number of patients with different pleural fluid volume in chest radiograph, n (%)							
<1/3 of hemithorax	44 (36.1%)	19 (29.2%)	2 (15.4%)	11 (26.2%)	4 (40%)	0 (0%)	NA
1/3–2/3 of hemithorax	42 (34.4%)	25 (38.5%)	3 (23.1%)	19 (45.2%)	1 (10%)	3 (60%)	3 (60%)
>2/3 of hemithorax	36 (29.5%)	21 (32.3%)	8 (61.5%)	12 (28.6%)	5 (50%)	2 (40%)	2 (40%)
Total volume of pleural effusion removed	2500 (1500–4865)	3000 (1750–7150)	3800 (1800–4500)	2800 (1650–5450)	3500 (900–7500)	8250 (2250–21000)	NA

Since not all parameters were reported in all patients, the number of variables on tumor localization and pleural effusion localization may be different than the total number of patients with the respective syndrome. NA = data not available, PE = pleural effusion.

* Single data from 1 patient.

TABLE 3. Biochemical Characteristics of Ascitic Fluid in Patients With Different Forms of Meigs' Syndrome and Pseudo-Meigs' Syndrome

Categories of Meigs' and Pseudo-Meigs' Syndrome Ascitic Fluid Features	Classic Meigs' Syndrome (N = 192)	Nonclassic Meigs' Syndrome (N = 109)	Benign Pseudo-Meigs' Syndrome (N = 33)	Malignant Pseudo-Meigs' Syndrome (N = 74)	Incomplete Syndrome With Ascites Due to Benign Tumors (N = 32)	Incomplete Syndrome With Ascites Due to Malignant Tumors (N = 1)
Category of ascitic fluid as reported by the authors of original publications	(n = 15)	(n = 20)	(n = 2)	(n = 10)	(n = 3)	(n = 0)
Exudate	10 (66.7%)	17 (85%)	1 (50%)	6 (60%)	1 (33.3%)	
Transudate	5 (33.3%)	3 (15%)	1 (50%)	4 (40%)	2 (66.7%)	
Macroscopic appearance of ascitic fluid	(n = 115)	(n = 60)	(n = 20)	(n = 44)	(n = 20)	(n = 0)
Nonbloody	96 (83.5%)	51 (85%)	18 (90%)	27 (61.4%)	19 (95%)	
Bloody	19 (16.5%)	9 (15%)	2 (10%)	17 (38.6)	1 (5%)	
Specific gravity of ascitic fluid	(n = 5)	(n = 7)	(n = 0)	(n = 1)	(n = 1)	(n = 0)
	1010 (1010–1017)	1014 (1012–1020)		Result: 1015	Result: 1019	
Rivalta test in ascitic fluid	(n = 7)	(n = 7)	(n = 0)	(n = 2)	(n = 1)	(n = 0)
Positive	5 (71.4%)	5 (71.4%)		1 (50%)	1 (100%)	
Negative	2 (28.6%)	2 (28.6%)		1 (50%)	0 (0%)	
Total protein concentration in ascitic fluid (g/dL)	(n = 12)	(n = 19)	(n = 0)	(n = 7)	(n = 1)	(n = 0)
	4.6 (3.5–5.0)	4.0 (3.6–4.7)		4.1 (4.0–5.0)	Result: 4.9	
Ascitic fluid protein/serum protein	(n = 4)	(n = 6)	(n = 0)	(n = 4)	(n = 1)	(n = 0)
	0.74 (0.61–0.86)	0.62 (0.48–0.72)		0.74 (0.70–0.75)	Result: 0.69	

When only one result was available in the group—a single variable was presented

TABLE 4. Biochemical Characteristics of Pleural Fluid in Patients With Different Forms of Meigs' Syndrome and Pseudo-Meigs' Syndrome

Categories of Meigs' and Pseudo-Meigs' Syndrome Pleural Fluid Features	Classic Meigs' Syndrome (N = 192)	Nonclassic Meigs' Syndrome (N = 109)	Benign Pseudo-Meigs' Syndrome (N = 33)	Malignant Pseudo-Meigs' Syndrome (N = 74)	Incomplete Syndrome With PE Due to Benign Tumors (N = 18)	Incomplete Syndrome With PE Due to Malignant Tumors (N = 5)
Category of pleural fluid as reported by the authors of original publications	(n = 39)	(n = 32)	(n = 6)	(n = 25)	(n = 6)	(n = 1)
Exudate	28 (72%)	25 (78%)	5 (83.3%)	20 (80%)	6 (100%)	1 (100%)
Transudate	11 (28%)	7 (22%)	1 (16.7%)	5 (20%)	0 (0%)	0 (0%)
Macroscopic appearance of pleural fluid	(n = 77)	(n = 37)	(n = 11)	(n = 43)	(n = 13)	(n = 3)
Nonbloody	61 (79%)	32 (86.5%)	8 (72.7%)	30 (69.8%)	7 (53.8%)	3 (100%)
Bloody	16 (21%)	5 (13.5%)	3 (17.3%)	13 (30.2%)	6 (46.2%)	0 (0%)
Specific gravity of pleural fluid	(n = 29)	(n = 14)	(n = 2)	(n = 5)	(n = 2)	(n = 2)
	1018 (101.5–1025)	1016 (101.5–1021)	Results: 1016, 1022	1018 (101.7–1020)	Results: 1019, 1029	Results: 1008, 1025
Rivalta test in pleural fluid	(n = 19)	(n = 11)	(n = 1)	(n = 8)	(n = 2)	(n = 1)
Positive	15 (79%)	10 (91%)	1 (100%)	4 (50%)	2 (100%)	1 (100%)
Negative	4 (21%)	1 (9%)	0 (0%)	4 (50%)	0 (0%)	0 (0%)
Total protein concentration in pleural fluid (g/dL)	(n = 36)	(n = 21)	(n = 5)	(n = 18)	(n = 8)	(n = 2)
	4.3 (3.7–4.9)	4.1 (3.6–4.7)	4.3 (2.5–5.1)	4.5 (3.5–5.3)	5.0–(4.6–5.4)	Results 3.4; 4.2
Pleural fluid protein/serum protein	(n = 5)	(n = 5)	(n = 4)	(n = 4)	(n = 1)	(n = 2)
	0.68 (0.0.59–0.75)	0.61 (0.6–0.7)	0.69 (0.57–0.72)	0.68 (0.61–0.74)	Result 0.61	Results 0.61; 0.79
Pleural fluid LDH activity in (IU/L)	(n = 7)	(n = 3)	(n = 1)	(n = 7)	(n = 1)	(n = 1)
	184 (95–330)	Results: 100; 101; 178	Result: 86	600 (436–620)	Result: 250	Result: 343
Pleural fluid LDH/ serum LDH	(n = 4)	(n = 1)	(n = 1)	(n = 1)	(n = 0)	(n = 1)
	0.83 (0.64–1.1)	Result: 0.3	Result 0.5	Result 1.5		Result 1.8

When 3 or less measurements were available all individual results were presented.

LDH = lactate dehydrogenase, n = number of patients in whom data on particular parameters were available, N = total number of patients analyzed within a respective group, PE = pleural effusion.

As Light's criteria could have been applied in only a very limited number of patients, we conducted a subsequent analysis on the relative prevalence of transudates and exudates taking the pleural fluid protein concentration as a discriminating criterion. The value of this parameter in the differentiation between transudates and exudates has been well documented. Heffner et al performed a meta-analysis of 8 studies including 1448 patients and found that, at the cut off level of 2.9 g/dL, pleural fluid protein showed 91.5% sensitivity and 83% specificity for detection of pleural exudates.³¹ Similar results (86.4% sensitivity and 83.2% specificity at the pleural fluid protein threshold of 3.0 g/dL) were reported by Porcel in a single center analysis of 2283 patients.³² When the same pleural fluid cut-off level was applied in our analysis, we found that 88.8% of pleural effusions associated with Meigs' syndrome should be classified as exudates. As Light's criteria are more sensitive but less specific than the pleural fluid protein level,³² we suppose that the only bias we could make using pleural fluid protein instead of Light's criteria is underestimation of the percentage of patients with exudative effusions. To further increase the specificity of the pleural fluid protein level criterion, we performed a second analysis with the cut-off level of 3.5 g/dL. This criterion was recommended in the earlier version of the BTS statement on investigation of unilateral pleural effusion.³³ We demonstrated, that at this cut-off level, the proportion of patients with exudative effusion still remained >80%. This supports the conclusion that Meigs' syndrome is associated with an exudate rather than a transudate. It should be emphasized, however, that a transudative pleural effusion does not rule out Meigs' syndrome. The scarcity and low quality of data available for retrospective analysis emphasizes the need for further prospective, multicenter studies on this field.

Exudative effusion in patients with Meigs' syndrome seems to be consistent with the mechanisms involved in pleural fluid accumulation. It is believed that the direct cause of pleural fluid formation is the translocation of ascites via diaphragmatic pores. In this context, Meigs' syndrome can be regarded as a form of porous diaphragm syndrome.^{34,35} Although the mechanism of peritoneal fluid formation has not been fully explained, several observations provide evidence that it may be linked to inflammatory cytokines and growth factor release, resulting in increased vascular permeability and capillary leakage. Abramov et al found extremely elevated serum, ascitic, and pleural fluid levels of vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and interleukin-6 (IL-6) in a patient with Meigs' syndrome.³⁶ Serum levels of VEGF, FGF, and IL-6 declined after removal of the ovarian tumor, along with resolution of ascites and hydrothorax. A high level of VEGF in serum, peritoneal, and pleural fluid was also reported by Ishiko et al.³⁷ The source of VEGF remains unclear. Strong expression of VEGF in tumor cells as well as significantly higher VEGF level in peritoneal than pleural fluid suggest its local production by the tumor. On the other hand, a reverse relationship between the peritoneal and pleural fluid levels of VEGF has been reported.³⁷ Still, Okuchi et al demonstrated an almost undetectable VEGF expression in primary tumor cells and metastatic ovarian tumor in a patient with malignant pseudo-Meigs' syndrome.³⁸ These authors suggested that pseudo-Meigs' syndrome may be attributable to hypersecretion of VEGF from extra-tumor sources, possibly stimulated by ovarian metastasis. Increased serum levels of other inflammatory cytokines were also reported in Meigs' syndrome.³⁹

Other hypotheses on the mechanism of ascitic fluid accumulation have also been formulated. Some suggest that

ascites results from stromal tumor edema and transudation of interstitial fluid. This concept was discussed by Joe V. Meigs in his extensive review published in 1954.⁷ Tumor edema may be at least partially related to the disproportion of arterial blood supply to a large mass and its venous and lymphatic drainage. The surface lymphatics located just beneath the single-layered cuboidal epithelium covering the tumor may play an important role in the escape of the transudative fluid into the peritoneal cavity.³⁶ It seems very likely that the pathogenesis of ascites in Meigs' syndrome may be related to both discussed mechanisms and the features of the ascitic and pleural fluid depend on the relative contribution of each mechanism. Our results suggest that increased vascular permeability plays a major role.

A significant problem we had to face in the study was the heterogeneous terminology used by different authors. To obtain reliable and unequivocal data on different clinicopathological entities, we proposed our own classification based on precise case definitions. We realize that this classification may seem complicated, mainly because we attempted to reconcile current data on pathology and pathogenesis of Meigs' syndrome with the previously developed terminology. Introducing this modified classification allowed us to perform our analysis in well-defined and relatively uniform groups.

We are aware of the limitations of our study. First, due to article unavailability and language barrier we were not able to review all publications which could have included case reports on Meigs' syndrome. As our analysis included >80% of initially selected articles, we suppose the inclusion of the remaining papers would not affect the results significantly. Second, it must be admitted that the quality of the papers was highly variable with some articles presenting only very limited data. Third, papers on Meigs' syndrome were published over a long period of time, and thus included different parameters used to discriminate transudates and exudates. Moreover, the currently recommended parameters were available in only very few papers. Despite these limitations, to our knowledge, this is the only study performed to date specifically aimed at evaluating the features of pleural effusion in Meigs' syndrome.

We conclude that surprisingly few reports on Meigs' syndrome present data reliably defining the character of pleural effusion. The available data indicate, however, that the majority of pleural effusions in patients with this entity are exudates. This finding may be a prerequisite for the verification of some earlier presented concepts.

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