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New biomarkers for the diagnosis of pleural effusion

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Abstract

Background: Persistent undiagnosed effusion is present in approximately 15% of all causes of exudative effusion. Pleural effusion caused by immunoglobulin G4 (IgG4) is a new type of pleural effusion. Tumor markers such as Carcinoembryonic antigen (CEA) may play a role in the diagnosis of malignant pleural effusion. This study aimed to evaluate the use of serum Immunoglobulin G4 and carcinoembryonic antigen in diagnosing pleural effusion.

Methods: This observational descriptive cross-sectional study comprised 89 individuals with exudative pleural effusion who visited the Assiut university hospital's chest department. All patients were examined and asked about their medical history. Also, chest X-ray, MSCT chest, transthoracic ultrasonography, pleural fluid analysis and cytology, serum level of carcinoembryonic antigen, and immunoglobulin G4 were performed. In addition, pleural biopsy, bronchoscopy, and thoracoscopy were performed when required.

Results: In comparison to another diagnosis, the level of serum IgG 4 was observed to be substantially greater in individuals with IgG4-associated effusion (725 ± 225.45). Patients with malignant mesothelioma (70 ± 16.24) and metastatic adenocarcinoma (93.52 ± 19.34) had lower levels of IgG4. In contrast, the serum level of CEA was significantly higher in individuals with malignant mesothelioma (79.50 ± 29.47) and metastatic adenocarcinoma (68.71 ± 28.98). Patients with para-pneumonic effusion had a minor serum level of CEA (0.36 ± 0.26). At cutoff point > 152 mg/dl serum IgG-4 had 100% sensitivity and 94% specificity in the diagnosis of IgG4 related pleural effusion with an overall accuracy of 95.3% and area under the curve of 0.97. At the cutoff point > 5 ng/ml serum CEA had 77% sensitivity and 100% specificity in diagnosing malignant pleural effusion with an overall accuracy of 91.1% and area under the curve of 0.88.

Conclusion: Serum IgG4 higher than 152 mg/dl has good diagnostic accuracy in cases of undiagnosed pleural effusion. Carcinoembryonic antigen aids in diagnosing malignant pleural effusion with a cutoff point higher than 5 ng/ml in serum.

Trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03260088) registration ID [NCT03260088](https://clinicaltrials.gov/ct2/show/study/NCT03260088)

Keywords: Pleural effusion, Malignant pleural effusion, Immunoglobulin G4 related effusion, Carcinoembryonic antigen

Background

Pleural effusion is the most prevalent pleural disease, with various etiologies as cardiac disorders, tuberculous effusion, and malignant diseases, all of which necessitate immediate examination and treatment [1].

Pleural fluid cytology, pleural biopsy, thoracoscopy, and computed tomography have all been employed to diagnose PE etiology (CT). These methods, however,

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have their own set of limitations, pleural biopsy has a limited diagnostic utility, and thoracoscopy, as an interventional surgery, is not available in many hospitals [2].

Diagnosis of malignant pleural effusion needs different modalities. Approximately one-fourth of all pleural effusion and 30–70% of exudative effusion in hospital settings are secondary to cancer [3]. Thoracoscopy could establish the diagnosis in approximately 92.6% of cases [4].

Tumor markers play a role in the diagnosis of malignant effusion [5]. Despite this, in some cases of exudative effusions, the etiology of the pleural effusion remains unknown despite of full history taking, physical examination, and pleural fluid biochemical and cytological investigations. After multiple investigations, up to 15% of patients were found to have no diagnosis. As a result, a novel strategy to detect the cause(s) of idiopathic pleural effusions is required [6].

IgG4-related disease (IgG4-RD), formerly known as IgG4-related systemic illness, is an inflammatory syndrome marked by tissue infiltration with lymphocytes and IgG4-secreting plasma cells, varying degrees of fibrosis (scarring), and a typically rapid response to oral steroids. During the acute phase of this condition, blood IgG4 values are high in 51–70% of patients [7].

It is critical to recognize IgG4-related disease early to avoid organ damage and failure [8].

Glucocorticoids cause a rapid and often significant improvement in clinical aspects, as well as the remission of symptoms [9].

IgG4-related pleural effusion affects 1.6% of IgG4-RD patients and 4.6% of IgG4-RD patients with intrathoracic lesions [9].

In roughly 40% of IgG4-RD patients, thoracic involvement can be observed. Pleural mass, pleuritis with fibrosis (nodular or widespread pleural thickening), and pleural effusion are all pleural symptoms of IgG4-RD. Although thoracic involvement in IgG4-RD is usually seen in conjunction with other organ disorders such as pancreatitis and sialadenitis, pleural effusions in IgG4-RD without other organ involvements are more prevalent [10].

Pleural effusions in IgG4-RD are exudative, with lymphocytes and plasma cells as major cellular elements. Fibrinous pleuritis with lymphoplasmacytic inflammation, including many IgG4-positive plasma cells and active fibrosis, is revealed by histopathological analysis of the biopsied pleura [11].

The following diagnostic criteria for IgG4-related respiratory illness have been proposed:

1. An abnormal chest CT shadow
2. A serum IgG4 level > 135 mg/dL

3. Histopathologic characteristics that meet the full diagnostic criteria
4. Extrathoracic lesions (IgG4-related diseases can cause interstitial pneumonia, inflammatory nodules, and airway inflammation)

Pleural effusion caused by IgG4-related disease is predicted to be exudative pleural effusion due to inflammation, with unilateral or bilateral pleural effusion patterns. Pleural effusion in IgG4-related pleuritis has been described as a lymphocyte-dominated exudative pleural effusion with high level of ADA [12].

This study aimed to evaluate the accuracy of serum level of Ig G4 and CEA in the diagnosis of IgG4-related pleural effusion and malignant pleural effusion, respectively.

Patients and methods

Study design: an observational descriptive cross-sectional study

- Study settings: The Chest Diseases and Tuberculosis Department, Assiut University Hospital, Egypt.
- Study period: From October 2017 to October 2020.
- Ethical considerations: First, the study was approved by the Scientific Ethics Committee of the Faculty of Medicine of Assiut University and was registered at www.clinicaltrials.gov under ID: NCT03260088. Second, informed consent was obtained to deal with patient data.
- Inclusion criteria
Adult patients with exudative pleural effusion.
- Exclusion criteria
All patients with transudative effusion

All patients were subjected to full history taking and clinical examination, laboratory investigations, including complete blood count and coagulation profile, and imaging, including chest X-ray, MSCT chest, and chest ultrasonography; besides, pleural fluid aspiration analysis and cytology with the assessment of both serum CEA and IgG4. In addition, pleural biopsy, bronchoscopy, and thoracoscopy were performed when required.

Carcinoembryonic antigen (CEA)

CEA was measured in serum using Siemens Healthcare Diagnostic Inc., the ADVIA Centaur system according to the manufacturer's instructions.

Immunoglobulin G4 (Lot No. of Kits SG-10225)

Immunoglobulin G4 was measured in serum using (Sino-GeneClon Biotech Co., Ltd., Hangzhou, China) according to the manufacturer's instructions.

The final diagnosis was established according to the histopathological examination results of the pleural biopsy obtained either by ultrasound-guided closed pleural biopsy or medical thoracoscopy. Sections from paraffin blocks were cut at (3 to 5 μm thickness) and mounted over ordinary slides for hematoxylin and eosin staining. All slides were examined by pathologists who were blinded to the results of biochemical analysis. According to histopathological examination, the diagnosis was metastatic adenocarcinoma or malignant mesothelioma, caseating tuberculous granuloma, or lymphoplasmacytic infiltration.

Statistical analysis

The data was collected and analyzed by using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). The Shapiro test was used to determine compliance of the data to normal distribution. All quantitative data were expressed as a mean ± standard deviation (SD). In case of normally distributed data, it was compared by Student’s *t* test (two different means) or ANOVA (more than two means), while in case of not normally distributed data, it was compared by Mann-Whitney *U* test (two means) or Kruskal-Wallis test (more than two means).

Nominal data are given as number (*n*) and percentage (%). Chi² test was implemented on such data. Diagnostic accuracy of both IgG4 and CEA in serum was determined by receiver operator characteristics (ROC) curve in which the cutoff point was determined based in histopathological diagnosis.

In all statistical tests, *p*-value <0.05 was considered statistically significant.

Results

Baseline data of enrolled patients (n= 89)

The mean age of enrolled patients was 53.23 ± 14.98 years. Out of enrolled patients, 52 (58.4%) patients were males, and 37 (41.6%) patients were females. The majority (53.9%) of the patients came from urban areas, and also, the majority (85.4%) were married. Only two patients were opioid addicts.

A total of 17 (19.1%) patients were none smokers, and 20 (22.5%) patients were passive smokers. Thirty (33.7%) patients were smokers, and 22 (47.7%) patients were ex-smokers (Table 1).

Baseline clinical and laboratory data in enrolled patients (n= 89)

The most frequent presentations were chest pain (97.8%), cough (85.4%), and dyspnea (79.8%). Fever, expectoration, anorexia, and hemoptysis were found in 56 (62.9%), 52 (58.4%), 47 (52.8%), and 28 (31.5%) patients, respectively.

Table 1 The baseline data of enrolled patients

	N= 89
Age (years)	53.23 ± 14.98
Sex	
Male	52 (58.4%)
Female	37 (41.6%)
Residence	
Rural	41 (46.1%)
Urban	48 (53.9%)
Marital status	
Married	76 (85.4%)
Single	13 (14.6%)
Smoking status	
None	17 (19.1%)
Current smoker	30 (33.7%)
Ex-smoker	22 (24.7%)
Passive smoker	20 (22.5%)
Opioid addiction	2 (2.2%)

Data expressed as frequency (percentage) and mean (SD)

Table 2 The baseline of clinical and laboratory data of enrolled patients

	N= 89
Chest pain	87 (97.8%)
Cough	76 (85.4%)
Dyspnea	71 (79.8%)
Expectoration	52 (58.4%)
Hemoptysis	28 (31.5%)
Fever	56 (62.9%)
Anorexia	47 (52.8%)
Weight loss	19 (21.3%)
Pallor	20 (22.5%)
Jaundice	6 (6.7%)
Cyanosis	1 (1.1%)
Positive RF	2 (2.2%)
Positive ANA	2 (2.2%)
Positive anti-DsDNA	2 (2.2%)
CEA (ng/ml)	48.32 ± 12.22
IgG-4 (mg/dl)	417.68 ± 128.93

Data expressed as frequency (percentage). Data expressed as frequency (percentage) and mean (SD). RF rheumatoid factor, ANA antinuclear antibody, anti-DsDNA antidouble strand antibody, CEA carcinoembryonic antigen, IgG immunoglobulin G

The mean serum level of immunoglobulin G4 (IgG4) was 417.68 ± 128.93 (mg/dl). Other presentations and laboratory data are summarized in Table 2.

Table 3 The final diagnosis of enrolled patients

Diagnosis	N= 89
Metastatic adenocarcinoma	23 (25.80%)
Para-pneumonic effusion	22 (24.73%)
IgG4 related effusion	17 (19.10%)
Caseating tuberculous granuloma	15 (16.90%)
Malignant mesothelioma	9 (10.10%)
Pulmonary embolism	3 (3.37%)

Data expressed as frequency (percentage)

The final diagnosis of enrolled patients (n= 89)

Based on clinical, radiological, laboratory, and histopathological evaluation, the most frequent diagnoses were metastatic adenocarcinoma (25.80%), para-pneumonic effusion (24.73%), and IgG4-related effusion (19.10%). Caseating tuberculous granuloma was found in 15 (16.90%) patients. Nine (10.10%) and 3 (3.37%) patients had malignant mesothelioma and pulmonary embolism, respectively (Table 3).

Characteristics of patients with IgG4-related effusion (n= 17)

The mean age of those patients was 52.88 ± 16.24 years. Out of those patients, 10 (58.8%) patients were males. Three patients were smokers, and another three patients were ex-smokers. All patients had chest pain. The most frequent presentations were dyspnea (94.1%), cough (88.2%), and expectoration (58.8%). The mean serum level of IgG4 level among those patients was 725 ± 225.45 mg/dl (Table 4).

Radiological data and pleural fluid analysis of patients with IgG4 related effusion (n= 17)

The majority (58.8%) of IgG4 had right effusion. Also, all of them had complex effusion, either septated (11.8%) or non-septated (88.2%). The majority (47.1%) of those patients had predominant lymphocyte effusion. Six (35.3%) patients had consolidation, and 7 (41.2%) patients had mediastinal lymphadenopathy.

Only three patients had positive adenosine deaminase. The appearance of pleural fluid was serosanguinous in 13 (76.5%) patients, while each serous and hemorrhagic fluid were present in two patients (Table 5).

Serum level of IgG-4 and CEA based on final diagnosis (n= 89)

It was found that serum level of IgG4 was significantly higher among patients with IgG4-related effusion (725 ± 225.45) in comparison to other diagnoses. The low level of serum IgG4 was observed in patients with malignant

Table 4 The baseline data of patients with IgG4-related effusion

	N= 17
Age (years)	52.88 ± 16.24
Male sex	10 (58.8%)
Smoking status	
None	10 (58.8%)
Current smoker	3 (17.6%)
Ex-smoker	3 (17.6%)
Passive smoker	1 (5.9%)
Dyspnea	16 (94.1%)
Chest pain	17 (100%)
Cough	15 (88.2%)
Expectoration	10 (58.8%)
Hemoptysis	3 (17.6%)
Fever	6 (35.5%)
Anorexia	8 (47.1%)
Weight loss	8 (47.1%)
Pallor	4 (23.5%)
Jaundice	3 (17.6%)
Local chest examination	
Effusion alone	15 (88.2%)
Effusion with the underlying collapse	2 (11.8%)
Leucocytes (10 ³ /ul)	10.82 ± 6.27
Hemoglobin (mg/dl)	10.64 ± 1.79
Creatinine (mmol/l)	74.94 ± 33.97
Urea (mg/dl)	7.89 ± 4.84
Bilirubin (mmol/l)	16.78 ± 6.78
Aspartate transaminase (u/l)	33.45 ± 13.11
Albumin (g/dl)	3.65 ± 0.47
Protein (g/dl)	5.94 ± 0.49
CEA (ng/ml)	1.21 ± 0.67
IgG-4 (mg/dl)	725 ± 225.45

Data expressed as frequency (percentage) and mean (SD)

mesothelioma (70 ± 16.24) and metastatic adenocarcinoma (93.52 ± 19.34).

In contrast, the serum level of CEA was significantly higher among patients with malignant mesothelioma (79.50 ± 29.47) and metastatic adenocarcinoma (68.71 ± 28.98) in comparison to other diagnoses. Patients with para-pneumonic effusion had the least serum level of CEA (0.36 ± 0.26) (Table 6).

Different procedures and serum levels of IgG-4 and CEA in IgG4-related effusion and malignant effusion

The serum level of immunoglobulin G-4 was significantly higher in patients with IgG4-related effusion (725 ± 225.45 vs. 86.90 ± 22.45 (mg/dl); *p* < 0.001), while the serum level CEA was significantly higher in

Table 5 The radiological data and pleural fluid analysis of patients with IgG4 related effusion

	N= 17
Site of effusion	
Right side	10 (58.8%)
Left side	6 (35.5%)
Bilateral	1 (5.9%)
Effusion	
Complex non-septated	15 (88.2%)
Complex septated	2 (11.8%)
Consolidation	6 (35.3%)
Pleura	
Normal	7 (41.2%)
Thick	8 (47.1%)
Irregular	2 (11.8%)
Mediastinal lymphadenopathy	7 (41.2%)
Appearance	
Serous	2 (11.8%)
Serosanguinous	13 (76.5%)
Hemorrhagic	2 (11.8%)
Protein (mg/dl)	42.47 ± 4.89
Albumin (mg/dl)	28.58 ± 6.06
SPAG	1.03 ± 0.32
Positive ADA	3 (17.6%)
Decreased glucose level	7 (41.2%)
Cytology	
Polymorph	3 (17.6%)
Lymphocytes	8 (47.1%)
Mesothelial cells	1 (5.9%)
Atypical cells	1 (5.9%)
Plasma cell	4 (23.5%)

Data expressed as frequency (percentage) and mean (SD). SPAG serum pleural albumin gradient, ADA adenosine deaminase

Table 6 The serum levels of immunoglobulin G-4 and CEA based on the final diagnosis

Diagnosis	Immunoglobulin G4	CEA
Metastatic adenocarcinoma	93.52 ± 19.34	68.71 ± 28.98
Para-pneumonic effusion	138.47 ± 67.98	0.36 ± 0.26
IgG4-related effusion	725 ± 225.45	1.21 ± 0.67
Caseating tuberculous granuloma	109.40 ± 22.67	0.43 ± 0.22
Malignant mesothelioma	70 ± 16.24	79.50 ± 29.47
Pulmonary embolism	103.33 ± 44.11	0.43 ± 0.29
P value	< 0.001	< 0.001

Data expressed as mean (SD). CEA carcinoembryonic antigen. P-value was significant if < 0.05

Table 7 The procedures and serum levels of IgG-4 and CEA in IgG4-related effusion and malignant effusion

	Final diagnosis		P-value
	IgG4-related effusion (n= 17)	Malignant effusion (n= 32)	
Pleural biopsy	3 (17.6%)	22 (68.8%)	< 0.001
Thoracoscopy	17 (100%)	9 (28.1%)	< 0.001
IgG-4 (mg/dl)	725 ± 225.45	86.90 ± 22.45	< 0.001
CEA (ng/ml)	1.21 ± 0.67	71.94 ± 15.87	< 0.001

Data expressed as mean (SD) and frequency (percentage). P-value was significant if < 0.05. CEA carcinoembryonic antigen, Ig-G immunoglobulin G

Table 8 The procedures and serum levels of IgG-4 and CEA in IgG4-related effusion and TB effusion

	Final diagnosis		P-value
	IgG4-related effusion (n= 17)	Tuberculous effusion (n= 15)	
Pleural biopsy	3 (17.6%)	10 (66.7%)	< 0.001
Thoracoscopy	17 (100%)	5 (33.3%)	< 0.001
IgG-4 (mg/dl)	725 ± 225.45	109.40 ± 22.67	< 0.001
CEA (ng/ml)	1.21 ± 0.67	0.43 ± 0.22	0.50

Data expressed as mean (SD) and frequency (percentage). P-value was significant if < 0.05. CEA carcinoembryonic antigen, Ig-G immunoglobulin G, TB tuberculous effusion

patients with malignant pleural effusion (71.94 ± 15.87 vs. 1.21 ± 0.67 (ng/ml); *p* < 0.001) (Table 7).

Different procedures and serum levels of IgG-4 and CEA in IgG4-related effusion infiltration and TB effusion

The serum level of immunoglobulin G-4 was significantly higher in patients with IgG4 related effusion (725 ± 225.45 vs. 109.40 ± 22.67 (mg/dl); *p* < 0.001), while serum level CEA showed no significant differences between both groups (0.43 ± 0.22 vs. 1.21 ± 0.67 (ng/ml); *p* = 0.50) (Table 8, Figs. 1 and 2).

Discussion

Pleural effusion is still one of the most critical issues in chest medicine despite the significant advances in diagnostic and therapeutic tools.

The study was performed in the Chest Department of Assiut University and included 89 pleural effusion patients. Of them, 17 were diagnosed with IgG4-related pleural effusion. On the other hand, 22 had para-pneumonic effusion, three had pulmonary embolisms, 23 were metastatic adenocarcinoma, nine had malignant mesotheliomas, and 15 had TB.

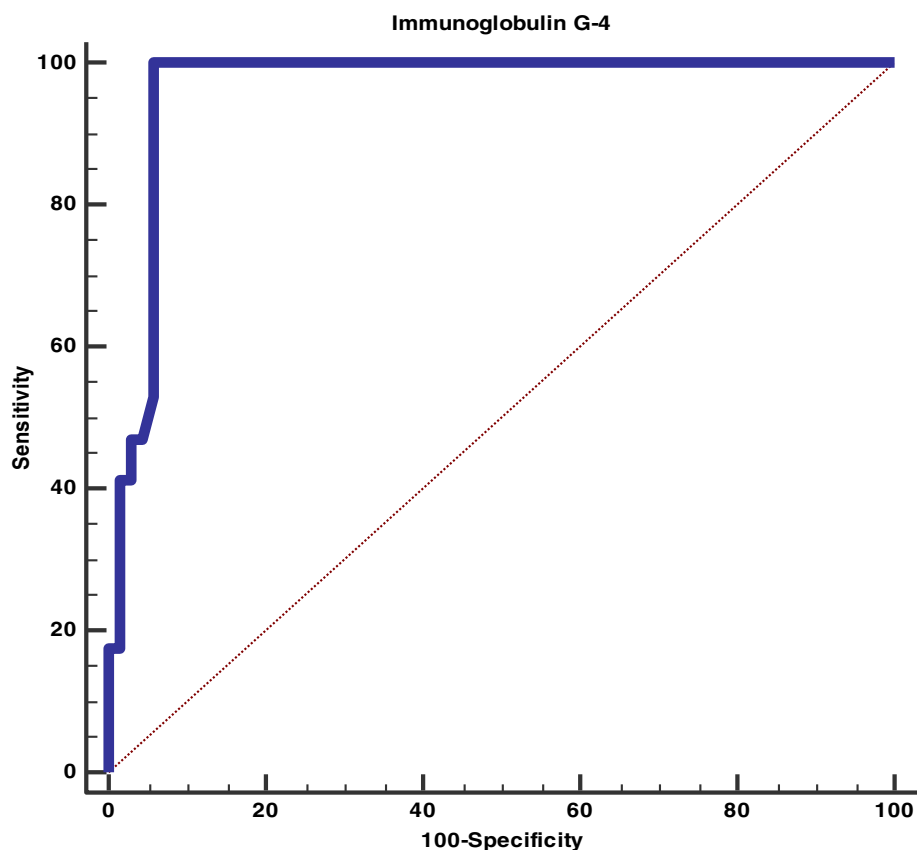


Fig. 1 Accuracy of serum level of IgG4 in diagnosis of pleural effusion secondary to lymphoplasmacytic infiltration. At cutoff point > 152 mg/dl; IgG-4 had 100% sensitivity, and 94% specificity in diagnosis of pleural effusion secondary to IgG 4-related effusion with overall accuracy was 95.3% and area under the curve

Pleural effusion is a common symptom of IgG4-RD and can occur in various conditions, including congestive heart failure and viral and malignant disorders. Even after a thorough examination, including a thorascopic biopsy, patients may have idiopathic exudative effusions [6].

Almost 19% of pleural effusion patients included in this study were diagnosed with IgG4-related disease. Due to the novelty of the diseases, to our knowledge, no consensus has been published to estimate its prevalence. However, a large study in Japan found that 34% of patients with idiopathic pleural effusion were associated with IgG4. The study screened 830 patients. Only 35 were undiagnosed [6].

In the current study, there was slight male predominance in patients with IgG4-related diseases (58,8%), which agreed with previous reports that IgG4-RD pleural disease occurred more frequently in men (78%) [13].

In the current study, the mean age of patients with IgG4-related pleural effusion was 52.88 years. Zen et al. (2009) reported that 63.5 years was the mean age of

their included patients. Generally, IgG4 RD is a disease of middle-aged to elderly patients, with an average age of 69 years [10].

There was no relation between smoking condition and IgG4-related disease in the current study. However, according to a large recent randomized controlled experiment, current smoking was linked to a higher risk of IgG4-RD, especially among women and those with normal IgG4 levels. The first known modifiable risk factor for IgG4-RD was current smoking. This disagreement might be because only the included patients were with manifested pleural effusion, not all cases of IgG4-related disease [14].

Our study revealed that 35% of patients with IgG4-related pleural effusion reported fever, and 47% reported anorexia and weight loss. Yamamoto et al. (2014) found that patients with IgG4-RD demonstrated symptoms, such as fever, malaise, night sweats, or weight loss [15].

In our study, the following findings were reported in combination with the effusion; consolidation in (35.3%)

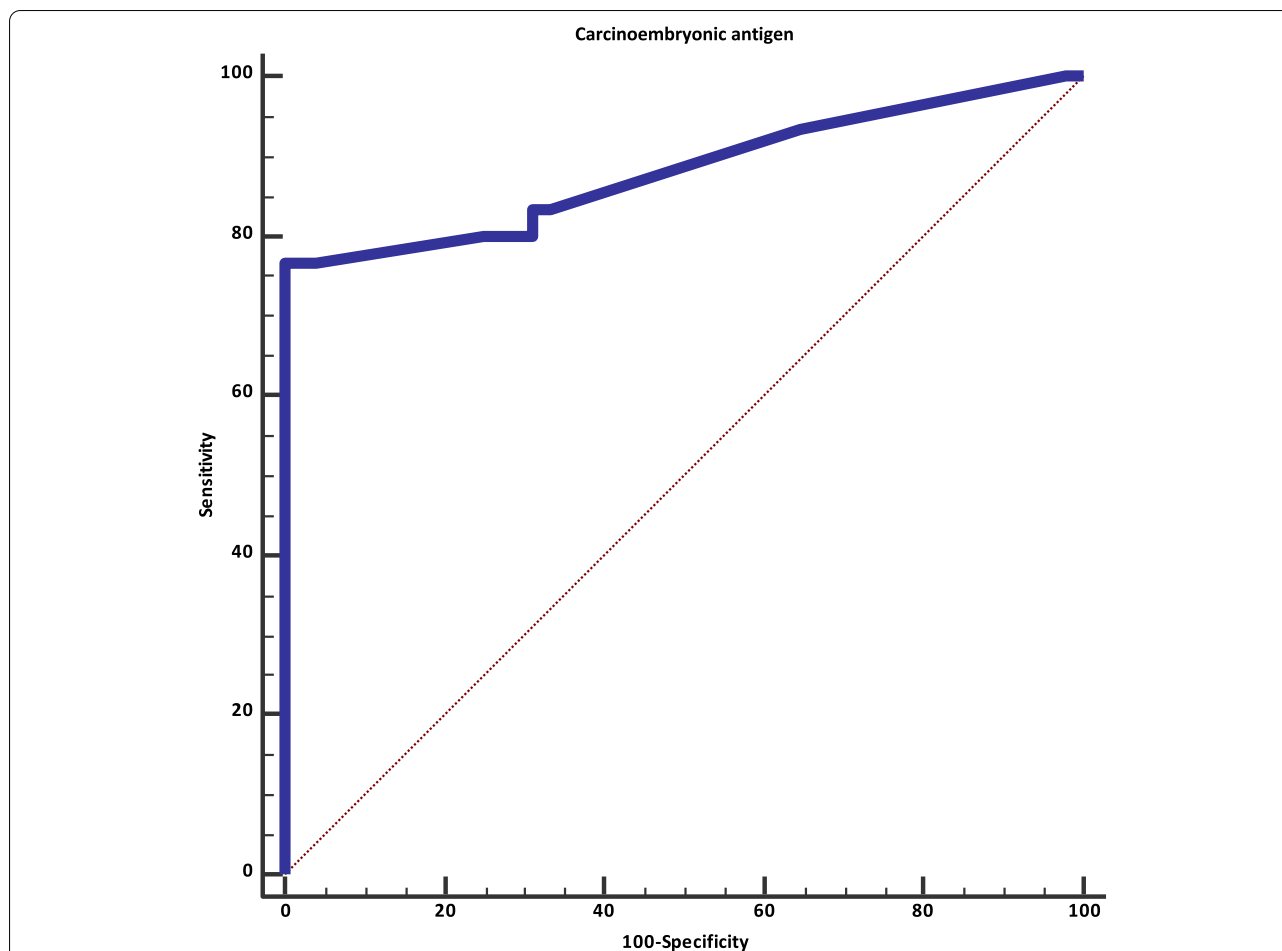


Fig. 2 The accuracy of serum level of CEA in diagnosis of malignant pleural effusion. At cutoff point > 5 ng/ml in serum; CEA had 77% sensitivity and 100% specificity in diagnosis of malignant pleural effusion with overall accuracy was 91.1% and area under curve was 0.88

and mediastinal lymphadenopathy (41.2%). The pleural effusion was predominantly the right side and complex non-septated with diffuse pleural thickening. According to Miyake et al. (2008), common radiological findings of IgG4-related lung disease included hilar and mediastinal lymphadenopathy, thickening of the perilymphatic interstitium with or without subpleural or peribronchovascular consolidation, and lymphoplasmacytic infiltration with fibrosis are correlated well with the radiological manifestations [16].

Laboratory diagnosis of IgG4 related diseases depends on serum IgG4 concentration greater than 135 mg/dl [17]. Our study reported that the mean level of IgG4 in patients with IgG4-related pleural effusion was 725 ± 225.45 mg/dl. The optimum cutoff point for diagnosing IgG4 RD in our study was 152 mg/dl, with 100% sensitivity and 94% specificity in the diagnosis of pleural effusion and overall accuracy of 95.3% and area under the curve 0.97. Inoue et al. (2009) reported that IgG4 serum concentration greater than 135 mg/dl was found to have

a 97% sensitivity and 79.6% specificity in the diagnosis of IgG4-RD. The higher level in our study might be explained by the inclusion of patients with only manifested pleural effusion, not all cases of IgG4 RD. [18]

Carruthers et al. (2015) showed that elevated serum IgG4 concentrations had a 60% specificity and a 34% positive predictive value, respectively [19].

In our study, all patients with IgG4-related disease had elevated IgG4 in serum. Lang et al. (2015) reported that elevated IgG4 levels were found in only 51% of patients. Another potential pitfall in detecting IgG4 levels was the so-called "Prozone effect," which occurred when too much antigen was in the test system, inhibiting agglutination and resulting in artificially low serum IgG4 levels. It could be avoided by diluting the material properly [20].

Another laboratory biomarker that might have a significant role in the diagnosis of IgG4-related diseases was the adenosine deaminase (ADA) level in pleural fluid. ADA is a lymphocyte-produced enzyme that participates

in purine degradation in the pathway from adenosine to inosine [21].

The presence of adenosine deaminase (ADA) in pleural fluid was linked to lymphocyte activation and was commonly employed in the supplementary diagnosis of tuberculous pleuritic effusion [12].

The most generally used pleural fluid ADA cutoff value for diagnosing tuberculous pleurisy is 40 U/L, with a sensitivity and specificity of 92% and 90%, respectively. As a result, a high pleural fluid ADA level can help diagnose tuberculous pleurisy [22].

Although ADA levels were usually normal in IgG4-RD pleural effusions, some IgG4-RD patients showed increased ADA levels (>40 IU/l) in their pleural fluids [23].

Our study found positive ADA positive in 60% of tuberculous patients and 17% of IgG4-related effusion. Kasashima et al. (2019) found that pleural fluid ADA levels were modestly raised, with a median of 32.2 U/L (range 26.6–50.1), which was substantially higher than in non-IgG4-related cases without tuberculous pleurisy ($P = .05$) [24]. This result is consistent with Shimoda et al. (2021), who compared ADA level in IgG4 related effusion and tuberculous pleural effusion of 18 patients with IgG4-related pleural effusion, and 14 (77.8%) showed a high pleural fluid ADA of more than 40 U/L [17].

Considering the data above, we cannot depend on laboratory investigations alone to confirm the diagnosis of IgG4-related diseases. Cytological and histopathological examination is a cornerstone in the diagnosis. Two or more of the following features are required for the histopathologic diagnosis of IgG4-RD: (i) a dense lymphoplasmacytic infiltrate, (ii) fibrosis with a typical storiform pattern, (iii) obliterative phlebitis, (iv) an increased number of IgG4+ plasma cells/HPF, and (v) an IgG4+/IgG+ plasma cell ratio >40% [25, 26].

However, IgG4-related respiratory disease has distinct histology than IgG4-related solid organ diseases, such as the pancreas or kidney, and storiform fibrosis may not be a significant characteristic in thoracic IgG4-RD [27]. In the current study, the prominent pathological mark was the dense lymphoplasmacytic infiltrate with minimal fibrosis.

In our study, CEA was significantly higher among patients with malignant mesothelioma (79.50 ± 29.47) and metastatic adenocarcinoma (68.71 ± 28.98) in comparison to other diagnoses. By evaluating the accuracy of carcinogenic embryonic antigen in the diagnosis of malignant pleural effusion, we were able to detect a specificity of 77% and a sensitivity of 100% for a serum CEA level of 5ng/ml, which was the best eligible cutoff value according to ROC curve with an overall accuracy of 91.1% and area under the curve of 0.88. CEA showed

high specificity for malignancy in serum (97 %), with a serum sensitivity of 33% for CEA.

Another study estimated the optimum cutoff point to be 5.5 ng/ml. The isolated diagnostic performance (sensitivity, specificity, PPV, and NPV) of CEA in serum (cutoff 5.5 ng/ml) was as follows: 0.54, 0.89, 0.83, and 0.67 [28]. According to Hernández et al. The CEA serum level of 5 ng/ml showed 97% specificity and 33% sensitivity with area under the curve equal 0.66 in the diagnosis of malignant pleural effusion [29]. On the other hand, a lower cut off point was previously estimated (3.27 ng/ml) with lower sensitivity and specificity [30].

Conclusion

Serum IgG4 higher than 152 mg/dl has good diagnostic accuracy in cases of undiagnosed pleural effusion. Carcinoembryonic antigen aids in diagnosing malignant pleural effusion with a cutoff point higher than 5 ng/ml in serum.

Acknowledgements

None.

Authors' contributions

Raafat T. El-Sokkary and Nermen M. Abuelkassem: conception and design. Nermen M. Abuelkassem and Mohamed Ismail Seddik: data collection. Ahmed Metwally: statistical analysis. Nermen M. Abuelkassem: medical writing. The authors revised and approved the final manuscript.

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Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author when required.

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board and ethical committee of the Faculty of Medicine Assiut University in compliance with the Helsinki declaration.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

- Diaz-Guzman E, Dweik RA (2007) Diagnosis and management of pleural effusions: a practical approach. *Compr Ther*. 33(4):237–246
- Porcel JM, Vives M, Esquerda A, Salud A, Pérez B, Rodríguez-Panadero F (2004) Use of a panel of tumor markers (carcinoembryonic antigen,

- cancer antigen 125, carbohydrate antigen 15-3, and cytokeratin 19 fragments) in pleural fluid for the differential diagnosis of benign and malignant effusions. *Chest*. 126(6):1757–1763
3. Light RW (2000) Management of pleural effusions. *J Formos Med Assoc*. 99(7):523–531
 4. Maskell N (2010) British thoracic society pleural disease guidelines-2010 update. *Thorax* 65(8):667–669
 5. Riantawan P, Sangsayan P, Bangpattanasiri K, Rojanarawee Wong P (2000) Limited additive value of pleural fluid carcinoembryonic antigen level in malignant pleural effusion. *Respiration*. 67(1):24–29
 6. Murata Y, Aoe K, Mimura-Kimura Y, Murakami T, Oishi K, Matsumoto T et al (2017) Association of immunoglobulin G4 and free light chain with idiopathic pleural effusion. *Clin Exp Immunol*. 190(1):133–142
 7. Saito Z, Yoshida M, Kojima A, Tamura K, Kuwano K (2020) Characteristics of pleural effusion in IgG4-related pleuritis. *Respir Med Case Rep*. 29:101019
 8. Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN, Chari ST et al (2015) International consensus guidance statement on the management and treatment of IgG4-related disease. *Arthritis Rheumatol* 67(7):1688–1699
 9. Kamisawa T, Zen Y, Pillai S, Stone JH (2015) IgG4-related disease. *Lancet*. 385(9976):1460–1471
 10. Zen Y, Inoue D, Kitao A, Onodera M, Abo H, Miyayama S et al (2009) IgG4-related lung and pleural disease: a clinicopathologic study of 21 cases. *Am J Surg Pathol*. 33(12):1886–1893
 11. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T et al (2012) Consensus statement on the pathology of IgG4-related disease. *Mod Pathol*. 25(9):1181–1192
 12. Nagayasu A, Kubo S, Nakano K, Nakayama S, Iwata S, Miyagawa I et al (2018) IgG4-related pleuritis with elevated adenosine deaminase in pleural effusion. *Intern Med (Tokyo, Japan)*. 57(15):2251–2257
 13. Mei F, Mancini M, Maurizi G, Vecchione A, Zuccatosta L, Rendina EA et al (2021) Pleural involvement in IgG4-related disease: case report and review of the literature. *Diagnostics*. 11(12):2177
 14. Wallwork R, Perugino CA, Fu X, Harkness T, Zhang Y, Choi HK et al (2021) The association of smoking with immunoglobulin G4-related disease: a case-control study. *Rheumatology (Oxford)* 60(11):5310–5317
 15. Yamamoto M, Takahashi H, Shinomura Y (2014) Mechanisms and assessment of IgG4-related disease: lessons for the rheumatologist. *Nat Rev Rheumatol*. 10(3):148–159
 16. Miyake K, Moriyama M, Aizawa K, Nagano S, Inoue Y, Sadanaga A et al (2008) Peripheral CD4+ T cells showing a Th2 phenotype in a patient with Mikulicz's disease associated with lymphadenopathy and pleural effusion. *Mod Rheumatol*. 18(1):86–90
 17. Shimoda M, Tanaka Y, Morimoto K, Okumura M, Shimoda K, Takemura T et al (2021) IgG4-related pleural effusion with high adenosine deaminase levels: a case report and literature review. *Medicine (Baltimore)*. 100(11):e25162
 18. Inoue D, Zen Y, Abo H, Gabata T, Demachi H, Kobayashi T et al (2009) Immunoglobulin G4-related lung disease: CT findings with pathologic correlations. *Radiology*. 251(1):260–270
 19. Carruthers MN, Khosroshahi A, Augustin T, Deshpande V, Stone JH (2015) The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. *Ann Rheum Dis*. 74(1):14–18
 20. Lang D, Zwerina J, Pieringer H (2016) IgG4-related disease: current challenges and future prospects. *Ther Clin Risk Manag*. 12:189–199
 21. Aggarwal AN, Agarwal R, Sehgal IS, Dhooria S (2019) Adenosine deaminase for diagnosis of tuberculous pleural effusion: a systematic review and meta-analysis. *PLoS One*. 14(3):e0213728
 22. Liang QL, Shi HZ, Wang K, Qin SM, Qin XJ (2008) Diagnostic accuracy of adenosine deaminase in tuberculous pleurisy: a meta-analysis. *Respir Med*. 102(5):744–754
 23. Gajewska ME, Rychwicka-Kielek BA, Sørensen K, Kubik M, Hilberg O, Bendstrup E (2016) Immunoglobulin G4-related pleuritis - a case report. *Respir Med Case Rep*. 19:18–20
 24. Kasashima S, Kawashima A, Ozaki S, Kita T, Araya T, Ohta Y et al (2019) Clinicopathological features of immunoglobulin G4-related pleural lesions and diagnostic utility of pleural effusion cytology. *Cytopathology*. 30(3):285–294
 25. Detlefsen S (2019) IgG4-related disease: microscopic diagnosis and differential diagnosis. *Pathologie*. 40(6):619–626
 26. Bledsoe JR, Della-Torre E, Rovati L, Deshpande V (2018) IgG4-related disease: review of the histopathologic features, differential diagnosis, and therapeutic approach. *APMIS*. 126(6):459–476
 27. Corcoran JP, Culver EL, Anstey RM, Talwar A, Manganis CD, Cargill TN et al (2017) Thoracic involvement in IgG4-related disease in a UK-based patient cohort. *Respir Med*. 132:117–121
 28. Hackner K, Errhalt P, Handzhiev S (2019) Ratio of carcinoembryonic antigen in pleural fluid and serum for the diagnosis of malignant pleural effusion. *Ther Adv Med Oncol*. 11:1758835919850341
 29. Hernández L, Espasa A, Fernández C, Candela A, Martín C, Romero S (2002) CEA and CA 549 in serum and pleural fluid of patients with pleural effusion. *Lung Cancer*. 36(1):83–89. [https://doi.org/10.1016/s0169-5002\(01\)00474-3](https://doi.org/10.1016/s0169-5002(01)00474-3) PMID: 11891038
 30. Korczynski P, Krenke R, Safianowska A, Gorska K, Abou Chaz MB, Maskey-Warzechowska M, Kondracka A, Nasilowski J, Chazan R (2009) Diagnostic utility of pleural fluid and serum markers in differentiation between malignant and non-malignant pleural effusions. *Eur J Med Res* 14 Suppl 4(Suppl 4):128–133. <https://doi.org/10.1186/2047-783x-14-s4-128> PMID: 20156743; PMCID: PMC3521354

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