Review Article

A narrative review of malignant eosinophilic pleural effusion: incidence, etiology and prognostic significance

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Abstract: Eosinophilic pleural effusion (EPE) is defined as a pleural fluid with an eosinophilic count exceeding 10% and currently considered to be mainly caused by malignancy. However, the incidence, etiology and prognostic significance of malignant eosinophilic pleural effusion (MEPE) have not been studied extensively yet. Thus, the objective of this review was to summarize medical studies regarding MEPE to 2020 throughout an extensive search of PubMed. Overall, MEPE was a disease associated with multiple-cytokines-mediated immunity and varied from 4% to 92% of patients who had EPE. The discrepancy of the MEPE prevalence among studies could be explained by the development of diagnostic technology, disparity of study population, or various disease spectrum over time. Data summarized in this review demonstrated that the incidence of malignancy was lower in EPEs than in non-EPEs (29.7% *vs.* 32.9%). Additionally, MEPE could be a manifestation of a great variety of tumor subtypes, among which lung cancer was the most common cause and accounted for more than 34% of cases. The second common causes were non-Hodgkin lymphoma and metastatic cancers with unknown primary site which were observed in around 5% of cases, respectively. The presence of eosinophils in the pleural effusion may be associated with a positive prognosis of MEPE. Besides, the prognosis of MEPE may be related to the percentage of eosinophils in the pleural fluid. More extensive studies, however, are warranted to validate these findings.

Keywords: Malignant eosinophilic pleural effusion (MEPE); incidence; etiology; prognosis

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Introduction

Eosinophilic pleural effusion (EPE), a pleural effusion in which eosinophils account for ≥10% of the white blood cells (WBCs), was described firstly by Harmsen in 1894 (1). Since then, it has been of great interest to clinicians. EPEs account for 5–16% of exudative pleural effusions and can be a manifestation of an extreme variety of diseases, including infections, malignancies, drug reactions, autoimmune diseases, pulmonary embolism, chest trauma and many others (1). In light of literatures from recent four decades, the most common cause of EPE was malignancy followed by idiopathic and parapneumonic effusions (2). Nonetheless, most information about malignant eosinophilic pleural effusion (MEPE) came from small series and case reports. The incidence, etiology and prognosis of MEPE still remain largely unclear. An understanding of MEPE prevalence and etiology will contribute to the development of novel treatments. Thus, the overarching goal of our work is to summarize current literatures regarding incidence, etiology and prognosis significance of MEPE. We present the

following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1742).

Methods

PubMed was used to retrieve for clinical studies including prospective and retrospective studies regarding EPE. The publication date of searched literatures was from the inception of databases to 2020 and there were no restrictions on publication types, regions, or languages. The following MeSH terms and their combinations were used in [Tittle/abstract]: "eosinophilic pleural effusion" OR "malignant pleural effusion" OR "malignant eosinophilic pleural effusion" OR "incidence" OR "etiology" OR "prognostic". We also reviewed the related articles to broaden the scope of search. Studies enrolling adolescents (under 18 years of age) were excluded.

Definition and diagnosis of MEPE

MEPE is commonly considered as EPE ascribed to malignant etiology. Since malignancies were only observed in exudates, many studies took exudates pleural effusions into considerations and excluded transudates (1,3,4). Certain conditions were well-known to frequently produce EPE, including the bloody effusion, pneumothorax, chest trauma, previous pleural puncture or drug reaction (1,3). MEPE should be diagnosed after exclusion of above risk factors.

Studies involved clinical characteristics of MEPE are scare. Reechaipichitkul *et al.* (5) demonstrated that patients with malignant pleural effusion (MPE) had a significantly longer duration (>1 month) of clinical symptoms than those with benign EPE, including cough, dyspnea, chest discomfort, hemoptysis, pain, and weight loss. This may be proportional to the volume of pleural effusion (6). However, a quarter of patients were asymptomatic from a respiratory perspective. The pleural fluid profile, abnormal chest radiographs, and blood eosinophilia of MEPE were also not specific (6). Thus, histologic examinations should be required.

In summary, based on the definition of EPE and MPE, MEPE was diagnosed in patients who had:

(I) EPE that is pleural fluid contains at least 10% of eosinophils among the WBCs in the first thoracentesis;
(II) Exudative pleural fluid/exudates;
(III) A positive pleural fluid cytology and/or positive histology pleural biopsy (proven malignant effusion) (7), or a known malignancy after excluding alternative causes of EPE.

Incidence of MEPE

According to past publications for decades, the prevalence of MEPE varied from 4% to 92% of patients who had EPE (*Table 1*). The diagnosis of MEPE is affected by various factors.

It was once believed that the finding of pleural fluid eosinophilia in an exudative effusion considerably reduced the probability of malignancy, and increased conversely the likelihood of an underlying benign disorder (13). It was even suggested that malignancy was not a cause of EPEs (13). The studies of Adelman *et al.* (13) and Kalomenidis *et al.* (1) reported that air/blood in the pleural space was the most common cause of EPE (29%). It was also found that a high percentage of idiopathic effusions were characterized by EPE (11,13). Nevertheless, the spectrum of EPEs has changed since 1960, and malignancy should no longer be considered uncommon among EPEs (2). The cumulative incidence of malignancy among EPEs has gradually increased from 7% to 25% over the last 4 decades (2). The current studies confirmed that malignancy was the most common etiology related to EPE (ranging from 22.7% to 40.1%) (2,7,13,18,22). The tendency may be explained by the development of diagnostic technology, improved diagnostic awareness, disparity of study population, or various disease spectrum over time. Additionally, idiopathic pleural effusions can be defined as non-specific pleuritis which is a diagnosis made after the pleural biopsy and without a definitive aetiology (23). Of note, more than 10% of these cases could be subsequently found to have malignancy during the follow-up periods (23).

The diagnostic criteria were somehow different from study to study. The diagnosis of malignancy required a pathological confirmation in some literatures but in others the diagnosis was conducted based on clinical findings. The prevalence of MEPE was significantly lower in patient cohorts that involved a pathological confirmation (2). Methods of pathological diagnosis were made up of pleural biopsy, pleural fluid cytology, thoracotomy and autopsy. Furthermore, the prevalence of MEPE was likely underestimated because of insufficient durations of follow-up for MEPE when an initial work was unrevealed.

Another reason for the difference of MEPE incidence

Table 1 The incidence of MEPE

Year	First author	Country	Type of study	Patients with PE, n	Patients with EPE, n	Patients with EPE/all patients with PE, %	Patients with MEPE, n	Patients with MEPE/patients with EPE, %
1967	Bower (8)	USA	Retro-	NA	21	NA	2	10
1973	Light (9)	USA	Pro-	182	8	4	1	13
1974	Kokkola (10)	Finland	Retro-	476	78	16	6	8
1979	Hirsch (11)	France	Pro-	270	23	9	8	35
1981	Pettersson (12)	Finland	Pro-	140	26	19	1	4
1984	Adelman (13)	USA	Review	NA	343	NA	27	8
1985	Wysenbeek (14)	Isreal	Retro-	NA	36	NA	7	19
1989	Kuhn (3)	Switzerland	Pro-	160	19	12	9	47
1989	Lakhotia (15)	NA	Pro-	NA	162	NA	32	20
1989	Kamel (16)	France	Pro-	NA	86	NA	6	7
1996	Rubins (17)	USA	Pro-	476	44	9.2	9	21
2000	Martínez-García (18)	Spain	Retro-	358	45	13	11	24
2003	Matthai (19)	India	Pro-	444	26	6	4	15
2003	Reechaipichitkul (5)	Thailand	Retro-	NA	50	NA	46	94
2003	Kalomenidis (1)	USA	Review	NA	53	NA	15	28
2007	Ozkara (20)	Turkey	Retro- and Pro-	697	60	9	22	37
2009	Krenke (7)	Poland	Retro-	1,868	135	7.2	47	35
2011	Ferreiro (21)	Spain	Pro-	605	50	8.3	15	30
2016	Chu (22)	Taiwan	Pro-	3,942	115	3	38	33
Total					1,380		306	22

Retro-, retrospective; Pro-, prospective; NA, not available; PE, pleural effusion; EPE, eosinophilic pleural effusion; MEPE, malignant eosinophilic pleural effusion.

in different studies may be the discrepancy of the local prevalence of malignancy. Adelman *et al.* (13) estimated the probability of malignancy in an eosinophilic pleural fluid throughout Bayes' theorem. As a result, the likelihood of malignancy varied from 14% to 39%. However, the proportions were far below those observed by Kuhn *et al.* (3) who utilized the same approach and found that the probability of malignancy was 40% from 47%. Hence, when evaluating the results, the disease spectrum of the study population should be given serious consideration (5,22). Various outcomes of MEPE prevalence were mere reflections of the population investigated.

The confounding factors known to frequently cause EPE is difficult to be excluded. Chung *et al.* (24) reported that repeated thoracenteses might induce an increase in the number of pleural fluid eosinophils in patients with malignant PE. Conversely, Rubins *et al.* (17) concluded that repeated thoracenteses within 2 to 12 weeks reduced rather than produced EPE. However, accumulating work indicated that the prevalence of EPEs with a repeated thoracentesis was similar to that of EPEs with the first thoracentesis (7,18). Most studies failed to take it into consideration whether pleural fluid eosinophilia was found on the first or subsequent thoracenteses but others not. In short, this should be taken into account in future work. Moreover, other risk factors including blood or air in the pleural space, drug interaction and other obscure potential conditions (2). Wysenbeek *et al.* (14) demonstrated that the MEPE percentage decreased from 33% to 3.8% after ruling out all additional etiologies for EPE.

Table 2 The incidence of MEPE in EPE and non-EPE

First author, year	Total (EPE/non-EPE)	The number of MEPE in EPE (%)	The number of MEPE in non-EPE (%)	P value
Light, 1973 (9)	7/125	1 (14.3)	34 (27.2)	NS
Hirsch, 1979 (11)	23/246	8 (34.8)	109 (44.3)	NS
Pettersson, 1981 (12)	25/89	1 (4)	23 (25.8)	S
Mihailescu, 1985 (25)	10/126	3 (30)	73 (57.9)	NS
Kuhn, 1989 (3)	11/141	5 (45.5)	80 (56.7)	NS
Lakhotia, 1989 (15)	17/135	1 (5.9)	31 (23)	NS
Rubis,1996 (17)	44/432	10 (22.7)	118 (27.3)	NS
Riantawan,1998 (26)	31/363	24 (77.4)	135 (37.2)	S
Martínez-García, 2000 (18)	45/313	11 (24.4)	84 (26.8)	NS
Ferreiro, 2011 (21)	50/555	15 (30)	144 (25.9)	NS
Total	263/2,525	78 (29.7)	831 (32.9)	–

NS, not significant; S, significant; EPE, eosinophilic pleural effusion; MEPE, malignant eosinophilic pleural effusion.

Incidence of MEPE in EPE and Non-EPE

The majority of previous studies found that malignancy was as prevalent among eosinophilic as non-EPEs (*Table 2*). In a prospective cohort enrolling 476 consecutive patients with thoracentesis, malignancy was as frequent among eosinophilic as non-EPEs (20.5% *vs.* 20.1%) (17). Ferreiro *et al.* (21) illustrated that there were no significant differences in the incidence of neoplasm between the EPE and non-EPE (30% *vs.* 25.9%, P=0.533). Nevertheless, one more recent meta-analysis (2) of 8 studies suggested that the prevalence of malignancy was lower in EPEs than in non-EPEs (odds ratio: 0.51, 95% confidence interval: 0.32 to 0.78; P=0.001) except in one study (11). In accordance with the results of meta-analysis, this review summarized the latest articles and found that the incidence of malignancy was lower in EPEs than in non-EPEs (29.7% *vs.* 32.9%) (*Table 2*).

Spectrum of diseases associated with MEPE

In light of literature review, a vast majority of MEPE was associated with solid tumors and only a small group of patients with hematological malignancies developed EPE (7). The etiology of MEPE is clearly shown in *Table 3*.

The summary of data demonstrated that lung cancer, especially the non-small-cell lung adenocarcinoma histocyte as well as metastatic cancer to lung (6,7), was the most leading cause of MEPE and accounts for more than 34% MEPE cases (n=23). Non-Hodgkin lymphoma and metastatic carcinomas with unknown primary site were the second most common causes for MEPE accounting for 5% of patients with MEPE. These results corroborated the previous findings illustrating that the percentage of MEPE with unknown primary site of cancer accounted for 5% to 10% (7). Pathological classification mainly included adenocarcinoma, squamous cell carcinoma, dysgerminoma (5,19). Other etiologies (thyroid carcinoma, prostate carcinoma, pancreatic carcinoma, and so forth) were relatively less common.

Pathogenesis

It is acknowledged that pleural effusion is attributed to the reason that cancer growth obstructs the lymphatic drainage (31). However, the differences in pathogeneses among EPE, MPE and MEPE are largely unknown. According to recent search progress, we propose herein some mechanisms accounting for the development of MEPE.

In general, the EPE formation is divided into two steps: accumulation and migration (32). Accumulation of eosinophils to tissues occurs in consequence of boosted eosinophil production in the bone marrow. Migration is followed by firm cytoadherence between eosinophils and endothelial cells. It should be addressed that the power of tumor-host cell interactions may become pronounced with the MEPE development (33). Eosinophils were known for

Table 3 The etiology of MEPE

Carcinoma types	The number of reported cases in the references (%)	References
Lung carcinoma	23 (34.3)	(7,20)
Pleural malignancy	2 (3.0)	(19,20)
Unknown primary site (metastatic carcinoma)	5 (7.5)	(7,20)
Breast carcinoma	3 (4.5)	(7)
Uterine corporeal carcinoma	2 (3.0)	(7)
Malignant mesothelioma	2 (3.0)	(7)
Hodgkin lymphoma	2 (3.0)	(7,20)
Non-Hodgkin lymphoma	5 (7.5)	(7,20,27,28)
Malignant lymphoma	2 (3.0)	(29,30)
Thyroid carcinoma	1 (1.5)	(7)
Pancreatic carcinoma	1 (1.5)	(7)
Prostate carcinoma	1 (1.5)	(7)
Urethelial carcinoma	1 (1.5)	(7)
Multiple myeloma	2 (3.0)	(7,30)
Chronic myeloid leukaemia	1 (1.5)	(7)
Malignant melanoma	1 (1.5)	(7)
Malignant fibrohistiocytoma	1 (1.5)	(7)
Ampulla of Vater carcinoma	1 (1.5)	(7)
Cholangiocarcinoma	1 (1.5)	(7)
Combined hepatocellular/cholangiocellular carcinoma	1 (1.5)	(7)
Cervical carcinoma	2 (3.0)	(5,19)
Osteosarcoma	1 (1.5)	(5)
Dysgerminoma	1 (1.5)	(19)
Wilms tumor	1 (1.5)	(20)
Papilla Vateri carcinoma	1 (1.5)	(20)
Colon carcinoma	1 (1.5)	(20)
Urinary bladder carcinoma	1 (1.5)	(20)
Testicular seminoma	1 (1.5)	(20)

allergies and parasites infections (34). However, many tumor cells were found to release chemokines that could recruit adhesion molecules and eosinophils (34). Hu *et al.* (35) found that the level of interleukin (IL)-33, acting as chemoattractant of eosinophils and other potent chemokines including IL-4 and IL-5 (35,36), was significantly higher in patients with non-small-cell lung cancer than those with benign lung diseases. Tumor necrosis factor (TNF)-alpha produced by tumor cells was also reported to regulate pleural microenvironment in the development of MPE and drastically stimulate eosinophils (37). Moreover, Ali *et al.* (38) expounded that breast carcinoma cell expressed vascular cell adhesion molecule-1 (VCAM-1), which could enhance adherence of eosinophils to endothelial cells.

Increasing work demonstrated that eosinophils were not bystander cells in tumorigenesis due to pleiotropic

effects. Eosinophils were able to secrete a range of anti-cancer molecules, including lipid mediators, cytotoxic granules, cytokines, growth factors and chemokines (34). These factors were shown to be cytotoxic in human cancer cell lines both in vivo and vitro. For example, eosinophil cytotoxic granules were shown to serve as a chemoattractant for T cells, neutrophils as well as dendritic cells and possess strong cytotoxic activity against human tumor cell lines (39,40). Tumor-homing eosinophils could also excrete a range of cytokines (such as, TNF-α, IL-4, and IL-5) which were associated with T cells (40) and chemokines which attracted T cells to the carcinoma microenvironment, leading to tumor eradication (41). Besides, eosinophils enhanced dendritic cell maturation throughout the increased expression of cell surface activation markers (42). Dendritic cells potentially overcame tumor tolerance and were related to good prognosis in carcinoma patients (43). Eosinophils were also able to serve as antigen presenting cells, migrate to local lymph nodes with antigen, and subsequently stimulate the expansion of T lymphocytes (44). Of note, eosinophils had the tumoricidal effects of various cancer cells throughout stable close contacts with target cells, expressing the same receptors and mediators as cytotoxic T lymphocytes (45).

Treatment and management of MEPE

Unfortunately, most existing MEPE management strategies fail to result in prolonged survival, and the primary purpose of management of patients with MEPE is to control symptoms and prevent recurrence of pleural effusions (46). Systemic radiotherapy, chemotherapy, or hormone therapy are available to control the MPE, particularly in small cell lung cancer (46). Strategies including chest-tube thoracostomy, needle drainage with thoracentesis, indwelling pleural catheter, or thoracoscopy with pleurodesis may alleviate patient symptoms (47,48). Achieving pleurodesis may impart a survival benefit in patients (48). Additionally, it has been reported that patients treated with pleurodesis at video-assisted thoracoscopy may have longer survival (49).

Prognostic significance of MEPE

As stated above, eosinophils may be established as prognostic markers given their role in cancer progression. They have been shown to be associated with a beneficial prognosis in most cases. For example, high eosinophilic infiltration of the colorectal cancer was associated with a beneficial 5-year overall survival rate (50). A reduced risk of tumor recurrence was present in breast cancer cases with a high peripheral eosinophil count (51). Furthermore, a previous study illustrated a correlation between an increased overall survival as well as disease-free survival and the intensity of tumor-associated tissue eosinophilia (52). Especially, overall survival would increase in intratumoral tumor-associated tissue eosinophilia when compared with other sites (53). In addition, a prospective cohort study found that patients with EPEs had a significantly better survival than those with non-EPEs (a median survival of 16.8 months compared with 7.7 months) (17). To date no evidence has revealed the difference of survival between MEPE and MPE. Evidence showed that survival of MPE may be depended on tumor subtypes, range from 50 days to almost a year (54). We assumed that eosinophils may contribute to a more favourable prognosis for MEPE based on current publications, and further studies in this regard are warranted to verify this assumption.

The association between eosinophil counts and survival was also assessed in carcinoma entities. High levels of eosinophils resulted in an improved survival rate in gastric carcinoma (55) and hepatobiliary cancer (56). Moreover, the possibility of malignancy was inversely related to the pleural eosinophil counts (2). The likelihood of malignancy was only 7% when an eosinophil count was more than 32% (2). Similarly, Chu *et al.* (22) found that eosinophil count in pleural effusion was a speculative negative predictor for malignancy in patients with EPE when eosinophils exceeded 15%. The analysis of Krenke *et al.* (7) revealed that an eosinophil percentage of 40% was the most accurate cut-off level to differentiate between malignant and non-malignant EPE, which supported the study by Kuhn *et al.* (3) who suggested that eosinophils exceeded 50% in the pleural fluid possessed the strongest negative predictability towards malignancy. Furthermore, a high eosinophil count at baseline was potentially associated with an improved overall survival in participants treated with immune checkpoint inhibitors (57).

Conclusions

Malignancy is the most common etiology related to EPE. Of note, the incidence of MEPE is affected by many variables, including the population investigated, diagnostic criteria or other risk factors of EPE. Unfortunately, most therapy strategies for MEPE to date are unavailable to

prolong survival. The presence of eosinophil in the pleural effusion may denote a positive prognosis of MEPE. The percentage of eosinophils may be an interesting predictor of MEPE prognosis which needs further researches.

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