Pleural Effusions in Hematologic Diseases – A Narrative Review

Department of Pulmonology, S. Maria della Misericordia University Hospital, Italy

*Corresponding author: Alberto Fantin, Department of Pulmonology, Santa Maria della Misericordia University Hospital, Via Colugna, 33100 Udine, Italy, Tel: +39.0432.552926; Email: af@albertofantin.com

Abstract

Background: Pleural effusions frequently occur in hematologic disorders. The diagnosis of this entity is extremely challenging, as traditional techniques, such as pleural fluid cytology and pleural biopsy, have a low diagnostic yield. In addition, a growing number of evidence suggests that the appearance of a pleural effusion leads to a worse prognosis. The aim of this work is to provide a non-systematic review of haematological pathologies more frequently associated with a pleural effusion, the diagnostic challenges and treatment options.

Methodology: This revision work is the result of a critical analysis of the existing literature, carried out by collecting the main bibliographic entries in different languages present in international scientific databases relative to the topic of interest. All the arguments have been elaborated by the authors and critically re-proposed, in a non-systematic way (narrative revision).

Keywords: Pleura; Hematologic; Lymphoma; Leukaemia; Myeloma

Abbreviations: CLL: Chronic Lymphocytic Leukemia; HDs: Hematologic Diseases; HL: Hodgkin’s Lymphoma; L-MPE: Lymphoma Related Malignant Pleural Effusion; MM: Multiple Myeloma; MPE: Malignant Pleural Effusion; NHL: Non-Hodgkin’s Lymphoma; PE: Pleural Effusion.

Introduction

Pleural effusion (PE) is a common complication of hematologic diseases (HDs). Overall incidence of HD-associated PEs has not been established. According to the major case series, serous effusions occur from 20% up to 48% of all hematologic disorders, with lymphoma, leukaemia, and multiple myeloma (MM) being the most frequent associated disorders [1-3]. A large review evaluating 584 malignant PE (MPEs), found that 15.9% were due to HDs, in particular lymphoma/leukaemia [4]. In Valdes’ series, lymphomas and leukaemia were respectively the third (10.8) and the eighth (2%) cause of MPEs [5].

Although MEPs are generally associated to a bad prognosis and advanced disease during the course of solid tumour, implications of MEPs in HDs are not well defined. To date, the large part of available randomized clinical trials (RCT) and large reviews on PEs, generically focus on malignant MPEs or non-malignant PEs. Any revision has never focused on HD-associated malignant and non-malignant PEs in hematologic disorders. In the light of this, in this review we discuss the presentation, the treatment, and the prognostic significance of HD-related PEs.

Methods

This revision work is the result of a critical analysis of the existing literature, carried out by collecting the main bibliographic entries in English present in international scientific databases (Medline, PubMed, Scopus, Google Scholar), by keyword research (“hematologic”, “serous”, “pleural”, “effusion”, “lymphoma”, “leukaemia”). The full texts
of pertinent papers were retrieved. Additional bibliographic entries were added, although not initially identified through the keyword search, but which were cited within the manuscripts evaluated and were in our opinion particularly relevant. References were selected for inclusion according to the subjective evaluation of the authors.

Aetiology

Both malignant and non-malignant HDs have been described to be associated with PEs. A retrospective review including 172 haematological malignancy cases, found that MPEs accounts for 85.5% of all the PEs [6]. Another retrospective multicentre study by Gilbert CR included 91 cases of PEs in the setting of HD. In 96% of the collected cases, fluid contained malignant cells [2]. Malignant cells are more likely to be found in lymphoma and chronic leukaemia; non-malignant fluid is generally collected in the setting of acute leukaemia and multiple myeloma (MM) [6].

Overall lymphomas are the most frequent MPEs-associated hematologic malignancy in both adults and children [7]. Lymphoma related MPEs (L-MPE) have been reported in 30% of Hodgkin’s lymphoma (HL) and 20% of non-Hodgkin’s lymphoma (NHL) [2,8]. Nodular sclerosis type and large cell lymphomas are the most frequent types associated with MPEs respectively in HL and NHL group [8]. Noteworthy, 4% of all NHL present as primary lymphoma of body cavities (primary effusion lymphoma, PEL). Although PELs might present in every host, they principally occur in immunocompromised patients, especially in those infected with HIV. PELs manifests with massive MPEs of body serous cavities, without neoplastic masses [7].

13% of the HDs presenting with PE are MM [2]. It has been estimated that 6% of patients suffering from MM will develop PE during the course of the disease. In this setting, MPEs represent 0.8-2.6% of all MM-related HD; the majority of this effusions are non-malignant, and generally related to MM-associated systemic complications (renal failure, heart failure, amyloidosis, infections) [9,10].

Leukaemia underlies 21% of the HD-associated MPEs, in particular in form of chronic lymphatic leukaemia (CLL), acute lymphatic leukaemia (ALL). In case of CLL, MPEs typically occur in more advanced stages than in acute disorders. Furthermore, it sometimes heralds a secondary malignancy [11,12]. Myelodysplastic syndrome (MDS) and myelofibrosis-related PEs are far more rare [2,13]. To note that in case of MDS and myelofibrosis, PEs is more frequently of non-malignant composition, as it is generally expression of intrapleural extramedullary haematopoiesis (EMH) or infections [14].

Intrathoracic EMH is the most frequent non-malignant cause of HD-associated PE. The majority of the pleural EMHs have been reported in myelofibrosis and haemolytic disorders, especially thalassemia [15]. In MDS, PEs have also been described to be associated with autoimmune manifestations [16]. PE may also occur in systemic IgG4-related disease. In rare cases, PE might also be the only sign of IgG4-related disease [17]. Usually, IgG4-related disease PEs occur in older population, and are far more frequently transudates [18]. Among children, the most frequent cause of MPEs are lymphoma and leukaemia (from 52% up to 81% of all MPEs) [19,20].

PEs Characteristics

A retrospective analysis conducted on 111 cases of acute leukaemia and myeloproliferative neoplasm undergoing pleural procedures, found that the majority presented as unilateral effusion (79%), with a light predominance for the left side (47 vs 40%). Mean age of the affected patients was 65 (range 17-85), and males were more affected than women (55 vs 50%) [21].

In a minority of the cases, PE is already present at the time of the diagnosis of the HD; however it most frequently also occur during the course of the disease and/or during disease relapses [2,22,23]. 25789576 As regards chemical composition, HDs associated PEs are mainly exudates (80-88%) [6,24]. In 12% up to 20% of the cases, HDs-related PEs are chylous. Chylothorax more frequently occur with lymphoma (19% of NHL-MPEs, 3% of HL); however, chronic lymphocytic leukaemia (CLL), HL, and MM can present with chylous effusion as well [6]. Chylous effusions have also been found to arise from malignant pleural infiltration, tumour spreading through pleural lymphatic vessels, and mass obstruction/compression of chest lymphatics [25]. In a minority of the cases, HDs-associated PEs are transudates. These forms have been either described to be reactive to HDs or to relate with other HDs-associated compliances, such as major vasa compression, congestive heart failure, hypoalbuminemia, and renal failure [26,27].

Diagnosis

Nature of the PEs needs to be carefully investigated. Differentiation between non-malignant hematologic PE, MPE, and PEs arising from non-haematologic causes (iatrogenic, infective, vascular, haemodynamic, autoimmune) can be really challenging.

Diagnostic work up of HDs-associated PEs should always include standard biochemical fluid analysis (lactate dehydrogenase, total protein, glucose, cholesterol and
triglycerides), cell count, and microbiological investigations. Malignant nature of the pleural effusion is mainly established by mean of cytology and flow cytometry. Overall, diagnostic yield of cytology on pleural effusion ranges from 60% up to 75%. Immunocytochemistry study slightly improves diagnostic yield [21,28]. In the aforementioned Gilbert CR’s multi-centre cohort, MPE diagnosis was confirmed by mean of pleural fluid cytology in 46% of the cases, and pleural biopsy in 9%. Combination of biochemical analysis of pleural fluid, cytology, flow cytometry, and pleural biopsy lead to a definitive diagnosis in 85.5% of the cases [2]. When no conclusive cytology has been found, pleuroscopy should be considered.

Management

According to European Respiratory Society (ERS) and American Thoracic Society (ATS) and ERS/ European Association for Cardio-Thoracic Surgery (EACTS) statements for management of MPEs, systemic chemotherapy should be the first line treatment for MPE [29,30]. In the setting of HDs, acute leukaemia and HD-related MPEs usually disappear with systemic chemotherapy.

When tumour is non-chemo-sensitive, and in case of refractory PEs, local pleural procedures such as radiation, medical or surgical drainage, pleurodesis, or intrapleural chemotherapy should be warranted [31]. Several randomized controlled trials (RCT) have investigated safety and efficacy of management of recurrent MPEs through indwelling pleural catheters (IPC), pleurodesis with a sclerosing agent or a combination of both, although none of these studies has been specifically conducted in the setting of hematologic disease. Overall, IPC positioning appears comparable to pleurodesis in terms of efficacy, safety, hospital stay and recurrence [32-35].

In non-malignant HDs-associated PEs treatment strongly varies according to the related disorders. In pleural EMH in myelofibrosis and thalassemia, PEs generally solves with hydroxyurea repeated transfusions. In refractory cases, the choice of an appropriate treatment remains controversial. Successful low dose irradiation, surgical resection, and pleurodesis have been reported [15]. In certain cases, palliative splenectomy and allogeneic hematopoietic cell transplant (HCT) have also been suggested [36,37].

Outcomes

It has been suggested that a PE emerging early after the diagnosis of a hematologic malignancy might correlate to a highly aggressive disease. However, prognostic implication of hematologic disease associated PEs are not well defined, apart from limited retrospective studies.

A case-controlled study was conducted to investigate the clinical significance of PEs in NHL. The analysis included 70 patients with PE at the diagnosis of NHL, matched with 23 controls. Overall, PEs at the time of NHL presentation did not result to correlate with worse significant difference in remission or survival rates between the groups. 9781955 Oppositely, a retrospective case series of 26 cases of NHL, found that the presence of PE, especially when MPE, would correlate with a poor prognosis. It has been estimated that 50% of the patients presenting with MPE in the context of NHL die within two years from the diagnosis. 3882444 Similarly, another retrospective reports of 57 high grade NHL found a strong association between early presentation of MPEs during the disease and worse outcomes [38].

According to Faiz S’s analysis, the predictor factors of longer survival in HDs-related MPEs were: younger age, type of hematologic disorders (with better prognosis for ALL), number of pleural procedures, and remission status [6]. A number of factors have been suggested to predict prognosis of HDs-associated PEs. In 2005, a multiparametric tool, named LENT score, was validated as a valuable risk stratification system to predict survival in patients suffering from MPE. Specifically, those with high pleural fluid lactate dehydrogenase (LDH), high Eastern Cooperative Oncology Group (ECOG) performance score (PS), high neutrophil-to-lymphocyte ratio, and highest risk tumour types are considered at high risk. Based on this analysis, hematologic malignancies are considered low risk tumor types (LENT score 0 – 1) [39]. However, Clive AO’s algorithm only included a small number of hematologic malignancies (principally lymphomas). Recently, a large retrospective review including almost 600 patient suffering from MPEs from hematologic malignancy has demonstrated that the LENT prognostic scoring system might not be useful for risk stratification and prognostication in this setting [40]. Nevertheless, no validated prediction score has been developed for hematologic disease related MPE.

Conclusion

In conclusion, PEs frequently occur in hematologic setting. Patients suffering from lymphomas have higher probability to develop a PE with respect to other HDs. HDs might affect pleural spaces in terms of direct infiltration or secondary involvement due to occurred complications. Diagnosis of HDs-associated PE and MPE is extremely challenging, as traditional techniques, such as pleural fluid cytology and pleural biopsy, have a low diagnostic yield. In case of systemic treatment-sensitive disease, PEs usually follows the course of the causative-disorder. However, in refractory cases, local invasive procedures may be necessary. Therapeutic decisions should be patient-targeted. The impact of PEs on prognosis of HD remains unclear, although a
growing number of evidence suggests that early appearance of PEs after HD diagnosis might reflect a more aggressive course of the disease.

References


24. Chen HJ, Huang KY, Tseng GC, Chen LH, Bai LY, et al. (2015) Diagnostic pitfalls of discriminating lymphoma-
associated effusions. Medicine (Baltimore) 94(17): e800.


